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EDITORIAL

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Organocatalysis in Organic Synthesis

Although examples of organocatalysis—the use of small organic molecules to catalyze organic reactions—had been sporadically reported in the literature for decades, it was only recently realized that organocatalysis represents a fundamental *concept*, the development of which could provide catalysts for a wide array of important organic transformations which relied on neither transition metals nor enzymes. Early applications of organocatalysis relied on achiral compounds to promote the desired reaction, leading to achiral or racemic products.The realization that the use of enantiomerically pure compounds as catalysts could not only promote the desired reaction but also induce high enantioselectivity resulted in the dramatic expansion of the area in recent years.

Organocatalysis offers many advantages for synthetic organic chemistry. In contrast to many transition metal catalysts, most organocatalysts are stable to air and water, easily handled experimentally, relatively nontoxic, and readily separated from the crude reaction mixture. Many enantiomerically pure organocatalysts are readily available from natural sources or easily prepared in a few simple steps, and often both enantiomers are available, providing ready access to both enantiomers of the desired product.

Organocatalysts fall into four major classes: Lewis bases, Lewis acids, Bronsted bases, and Bronsted acids. Within each class, several modes of activation are available, and a number of organocatalysts utilize a combination of these properties to achieve the desired transformation. The 20 publications presented in this issue of *JACS* Select illustrate some of the many ways in which organocatalysts function. They provide a "snapshot" of this very active field for the period from mid-2008 to mid-2009, and illustrate the scope and potential of organocatalysis in synthetic organic chemistry.

Activation of conjugated enones by reaction with primary amines to form iminium ions is one of the earliest modes of organocatalysis developed. Utilizing a cinchona alkaloid-derived primary amine to activate the enone, and to induce enantioselectivity as well as to suppress epoxide formation, **Deng**[1] achieved the enantioselective catalytic peroxidation of conjugated enones. By increasing the temperature, the reaction could be directed to produce epoxides. Both classes of products are of biological interest, and this chemistry provides one of the very few approaches to chiral peroxides.

Enamine formation by the reaction of secondary amines with aldehydes or ketones provides another mode of organocatalysis. Utilizing a proline-derived secondary amine catalyst, **Jorgensen**[2] achieved the direct asymmetric catalytic synthesis of both chiral propargylic and allylic fluorides using *N*-fluoro-dibenzene-sulfonamide as the fluorine source and in situ conversion of the resulting α-fluoroaldehydes to the target compounds. **Maruoka**[3] synthesized (*S*)-2-tritylpyrrolidine as a catalyst for the direct asymmetric α-benzoyloxylation of aldehydes with benzoyl peroxide as the electrophile, when existing proline-derived catalysts proved ineffective. Both sets of compounds are important building blocks for organic synthesis, while fluorinated compounds are of substantial interest to medicinal chemists.

A third mode of organocatalysis involves asymmetric phase-transfer catalysis. The catalysts are usually chiral quaternary ammonium salts, with those derived from cinchona alkaloids being among the most utilized. Hydrogen bonding is thought to play a key role in the process. A very diverse range of organic reactions can be effected under phase-transfer catalysis, and the process serves as an important synthetic method. **Dixon**[4] developed an adamantyl-containing cinchona-based catalyst for the enantio- and diastereoselective ring-opening of aziridines by cyclic β-ketoesters to produce γ-butyric acid derivatives. **Fini** and **Bernardi**[5] used a quinine-derived phase-transfer catalyst to promote the asymmetric [3+2] cycloaddition of nitrones to conjugated esters, producing isoxazolidines with three contiguous stereocenters. These heterocycles can serve as precursors to useful compounds such as aminoalcohols, amino acids,

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(4) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076–10077.
(5) Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614–9615.

and azasugars. **Palomo**[6] utilized a related quinine-derived phase-transfer catalyst with a free hydroxyl group at the benzylic position to develop a highly efficient asymmetric addition of nitroalkanes to in situ generated N-Boc imines (aza-Henry reaction) to produce β-nitroamines, valuable precursors to 1,2-diamine and α-amino carbonyl compounds. Theoretical studies indicated that the free hydroxyl group in the catalyst interacted with the nitro group of the nitroalkane.

A wide range of organocatalysts that function via hydrogen bonding, often with additional functionality, has been developed. Thioureas, having two hydrogen-bonding NH's, have found extensive application in organocatalyzed reactions. **List**[7] utilized a chiral thiourea to activate β-nitro acrylates to undergo asymmetric transfer hydrogenation (via two hydrogen bonds to the nitro group) by the Hantzsch ester, producing β^2-amino acids. **Barbas**[8] developed a highly enantio- and stereoselective addition of oxindoles to nitroolefins catalyzed by a bifunctional thiourea, with the thiourea activating the nitro group through two hydrogen bonds and an appended tertiary amine aiding in the abstraction of the oxindole α-proton. This chemistry was used in a formal synthesis of (+)-physostigmine. Direct Michael addition of nitroalkanes to nitroalkenes is normally complicated by further reaction of the initial product, producing oligomers. **Wulff**[9] overcame this problem by designing a chiral scaffold incorporating a thiourea to activate the nitroalkene and a dimethylaminopyridine to deprotonate the nitroalkane and bind the resulting nitronate via hydrogen bonds. 1,3-Dinitro compounds were formed in good yield and with high enantioselectivity, without competing oligomerization. Chiral thiourea catalysis was used by **Jacobsen**[10] to generate oxocarbenium ions from glycosyl chlorides via hydrogen bonding to the chloride anion, allowing enantioselective addition of a range of nucleophiles. A bifunctional cinchona-derived catalyst was used by **Seidel**[11] in the enantioselective addition of isocyanoimides to imines, to produce α,β-diamino acid derivatives. In this case, the phenolic OH group in the catalyst activated the imine by hydrogen bonding, while the tricyclic amino group aided in deprotonation of the carbonyl substrate. A very unusual example of hydrogen-bonding organocatalysis was provided by **Rebek**,[12] who synthesized a cavitand receptor to bind and position an epoxyalcohol to undergo cyclization assisted by hydrogen bonding to an inward-directed carboxylic acid group.

Chiral BINOL-derived phosphoric acids exemplify a class of organocatalysts that contain both a strong Bronsted acid site (P—OH) and a Lewis base site (P═O). This class of bifunctional organocatalyst has found very broad application to a wide variety of reactions. **Goodman**[13] studied the BINOL-phosphoric acid-catalyzed addition of HCN to benzyl imine (Strecker reaction) by theoretical methods and concluded that the process involved activation of the imine by the acidic proton and activation of the HCN by the basic P═O group. The reverse in selectivity observed with benzyl amines versus aryl imines was attributed to a switch in the preference from a *Z*-imine to an *E*-imine. **Antilla**[14] prepared chiral *N*,*O*-aminals by the BINOL-phosphoric acid-catalyzed enantioselective addition of alcohols to *N*-benzoyl imines. By combining the nickel-catalyzed rearrangement of hemiaminal allyl ethers to the corresponding enol ethers with the BIONOL-phosphoric acid-catalyzed aza-Petasis−Ferrier rearrangement, **Terada**[15] produced an efficient route to enantioenriched *anti*-β-amino aldehydes. An even more complex process utilizing this same class of organocatalyst was developed by **Zhu**,[16] who reported a highly enantioselective three-component condensation of anilines, aldehydes, and *N*-vinyl carbamates (Povarov reaction) to produce *cis*-2,4-disubstituted tetrahydroquinolines. This chemistry was used to synthesize torcetrapib, a cholesterol-lowering drug. Because phosphoric acids are relatively weak, they fail to catalyze reactions of less basic substrates such as ketones. To catalyze the enantioselective protonation of silyl enol ethers, **Yamamoto**[17] replaced the P═O of the phosphoric acid with a P═S and the acidic OH with an *N*-trifluoromethanesulfonyl group. The resulting *N*-triflyl thiophosphoramide catalyst, in the presence of phenol, was effective even at very low loading (0.05%).

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Miller[18] incorporated a pyridylalanine residue into a β-turn tetrapeptide to catalyze the enantioselective α-alkylation of allenoates with aldimines. The pyridyl group acted as a Lewis base catalyst for the addition, while the peptide provided the platform to induce enantioselectivity. Multifunctional organization of the transition state for the enantioselective reaction of 2-trimethylsiloxy furan with Morita−Baylis−Hillman acetates, catalyzed by BINAP containing a Ph_2P group on one ring and an acetamide group on the other, was invoked by **Shi**[19] in a Lewis base-catalyzed synthesis of γ-butenolides.

All of the above organocatalytic processes involve activation of either the HOMO or the LUMO of the participant(s). In a distinct departure from this trend, **MacMillan**[20] implemented a fundamentally new strategy in organocatalysis (SOMO catalysis) involving the oxidative generation of a transient three-electron radical cation species to react with a variety of SOMOphiles. In this instance, a chiral imidazolidinone catalyst was used to generate the enamine of an aldehyde which, in the presence of a nitronate and ceric ammonium nitrate as the oxidizing agent, underwent enantioselective α-nitroalkylation.

The publications included in this issue of *JACS* Select provide examples of the wide range of reactions that can be promoted by organocatalysis and the diverse processes by which these catalysts function. Much remains to be understood about detailed mechanisms of action, and many new applications and catalysts are anticipated.

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