

Organocatalysis Symposium

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The Scripps Research Institute, La Jolla, CA, USA

Discovery and Design in Organocatalysis

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Tokyo University of Science, Japan

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Catalytic Asymmetric Synthesis with Chiral Designer Phase Transfer Catalysts

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Chiral Pyrrolidine Sulfonamide Promoted Enantioselective organic Reactions

Discovery and Design in Organocatalysis

ICOS-OCS-1

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One of the ultimate goals in organic chemistry is the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically complex products. As chemists, we often turn to nature for inspiration concerning stereochemically complex, diverse, and functional molecules. Indeed, the directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules has long been the purview of nature's enzymes. Our approach to this problem began in 1997 when we embarked upon studies exploring the similarity between proline and a novel class of aldolase antibodies we had developed earlier. Recently, these studies have allowed us to describe a variety of powerful organocatalytic asymmetric ketone and aldehyde additions in aldol, Michael, Mannich, and Diels-Alder reaction manifolds. Significantly, these studies were originally designed for antibody catalysis years before. This lecture will summarize the contributions of this laboratory to creating and converting enzymatic enamines, and in some cases imines, into a versatile catalytic asymmetric strategy powered by small organic molecules. A focus of the lecture will be on the design of novel catalysts that provide reactivities and selectivities that go beyond those of proline and its derivatives that we have previously documented.

Enantioselective Michael Reaction Catalyzed by Organocatalysis

ICOS-OCS-2

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Michael reaction is one of the most important carbon-carbon bond forming reactions. Usually asymmetric catalytic Michael reactions have been promoted by the use of chiral metal catalysts. In recent years several excellent, direct, asymmetric, catalytic Michael reactions have been reported by the use of organocatalysts. One of the aims of our research group is to develop a novel and effective organocatalyst, which is effective for the inter- and intra-molecular Michael reaction. In the intermolecular reaction, we have found that diphenylprolinol silyl ether is an excellent catalyst for the Michael reaction of nitroalkenes and aldehydes to afford the products with very high optical purity. On the other hand, newly developed organocatalyst derived from cysteine is an effective chiral catalyst, promoting the intramolecular Michael reaction to provide disubstituted cyclopentane derivatives with excellent enantioselectivity. In this lecture, we will also describe our recent results concerning the asymmetric aldol reaction in the presence of water.

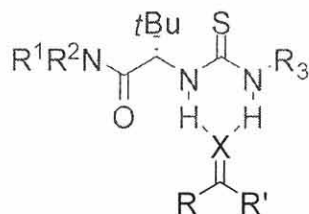
Thioureas as General Acid Asymmetric Catalysts

ICOS-OCS-3

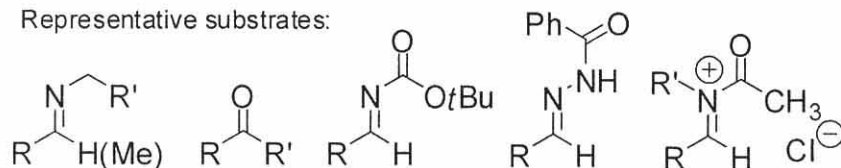
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In addition to its crucial role as a structural determinant, hydrogen bonding plays an important functional role in catalysis. H-bonding is one of the principal mechanisms by which enzymes promote a wide range of chemical processes, and organic chemists have begun to appreciate the tremendous potential offered by hydrogen bonding as a mechanism for electrophile activation in small-molecule, synthetic catalyst systems. In particular, chiral hydrogen bond donors have emerged recently as a broadly applicable class of catalysts for enantioselective synthesis. This lecture will provide an analysis of the structural and mechanistic features that contribute to high enantioselectivity in hydrogen bond-mediated catalytic processes, with examples provided from our own work with thiourea-based general acid catalysts.



Representative substrates:



Bifunctional Thiourea Catalysts for Asymmetric Nucleophilic Reactions

ICOS-OCS-4

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The catalytic asymmetric formation of C-C and C-N bonds is one of the most challenging fields in organic chemistry. From the viewpoints of the availability of substrates, high atom-economy, and simple manipulation, direct catalytic asymmetric Michael additions of active methylene compounds such as 1,3-dicarbonyl compounds to α,β -unsaturated carbonyl acceptors bearing a C=C, C=N or N=N bond attract considerable attention. However, the acceptors used in these Michael additions generally have been limited to enones and nitroalkenes and there have been no reports on their application to α,β -unsaturated acid derivatives without a metallic catalyst. Therefore, the development of general and highly enantioselective versions with α,β -unsaturated acid derivatives still remains a challenging goal. This lecture will summarize our recent results of the organocatalyzed asymmetric Michael reaction of several active methylene compounds to α,β -unsaturated imides, *N*-Boc imines, and azodicarboxylates as well as their application to asymmetric synthesis. The high enantioselectivity of these reactions is attributed to the simultaneous activation mechanism of both nucleophiles and electrophiles by a bifunctional amino-thiourea catalyst

Catalytic Asymmetric Synthesis with Chiral Designer Phase Transfer Catalysts ICOS-OCS-5

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Since the pioneering work of Dolling *et al.* in 1984, asymmetric synthesis by chiral phase transfer catalysis has provided an attractive method of preparing a variety of optically active compounds. However, most of the elaborated chiral phase transfer catalysts reported so far have been restricted to *cinchona* alkaloid derivatives, which unfortunately constitutes a major difficulty in rationally designing and fine-tuning of catalysts to attain sufficient reactivity and selectivity for various asymmetric transformations under phase transfer catalyzed conditions. Accordingly, structurally rigid, chiral spiro-type ammonium salts derived from commercially available (*R*)- or (*S*)-binaphthol have been prepared and commercialized as new C_2 -Symmetric chiral phase transfer catalysts. These organocatalysts can be applied to the highly efficient, catalytic enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base under mild phase transfer conditions. Quite recently, we have successfully designed simplified, yet very active chiral phase transfer catalysts for practical asymmetric synthesis of α -alkyl- and $\alpha\alpha$ -dialkylamino acids. In addition, we newly designed chiral, helical-type phase transfer catalysts for effecting asymmetric Strecker reaction for large-scale production of sterically hindered α -alkylamino acids.

Chiral Pyrrolidine Sulfonamide Promoted Enantioselective Organic Reactions

ICOS-OCS-6

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The amino acid L-proline is perhaps the most successful organocatalysts studied to date. However, in many cases, it shows poor catalytic activity and stereoselectivity toward reactions. As part of our recent efforts to uncover novel organocatalysts that are superior to L-proline, we have found that (*S*)-pyrrolidine trifluoromethanesulfonamide catalyzes various asymmetric organic transformations, such as the Mannich and α -aminoxylation reactions with excellent levels of enantioselectivities. In some cases, (*S*)-pyrrolidine sulfonamide displays superior catalytic activity to L-proline. For example, much higher enantioselectivities are observed in promoting asymmetric aldol reactions of α , α -dialkyl aldehydes with aromatic aldehydes, the Michael addition reactions of aldehydes and ketones to nitroolefins, and the conjugate addition of ketones to α,β -unsaturated ketones. Moreover, it also effectively catalyzes α -selenenylation and α -sulfenylation reactions, where L-proline exhibits poor catalytic activity and generates more side products. More recently, we have designed a fluorous version of the catalyst, which can efficiently catalyze enantioselective Michael reaction of aldehydes and ketones with nitroolefins in pure water. The fluorous catalyst can be conveniently recovered by fluorous solid phase extraction and subsequently reused up to 6 cycles. The detail of these studies will be presented in the talk.