INTRODUCTION

Enzymes are well-known to be multi-functional and the synergistic cooperation of the multiple acids and bases in the active site of the enzyme is the hallmark of enzyme catalysis. However, the principle of cooperative catalysis in enzymes has been slow to translate to small-molecule catalysis until recent years. Bifunctional catalysis has emerged as an important strategy in expanding the types of catalytic asymmetric reactions and in improving reactions that have been explored with monofunctional catalysts. This presentation will focus on the different types of bifunctional catalysis that have been developed, and some methods to study the reaction mechanisms involving bifunctional catalysis.

LEWIS ACID-LEWIS BASE CATALYSIS

Bifunctional or cooperative catalysis involves the simultaneous binding and activation of two reacting partners at defined positions in a catalyst complex, allowing bond formation to take place intramolecularly. This leads to enhanced rates and/or stereodifferentiation. Bifunctional catalytic systems typically involve the incorporation of at least two different Lewis or Bronsted acids and bases within the same catalyst. Several key developments in bifunctional catalysis centered around the goal of achieving high enantioselectivities for the addition of a cyanide nucleophile into carbonyl compounds or imines to give α-hydroxynitriles or α-aminonitriles respectively. The products are useful intermediates en route to α-hydroxy acids or α-amino acids which are common components of pharmaceuticals. Shibasaki and co-workers first explored the combination of a Lewis acidic Al metal center with BINOL ligands modified with Lewis basic phosphine oxide groups to achieve the highly enantioselective cyanosilylation of aldehydes. The combination of a Lewis acid and a Lewis base bridged by a chiral backbone has been explored for other reactions, including the Reissert and Reissert-type reactions, and the synthesis of β-lactams.

LEWIS ACID-BRONSTED BASE CATALYSIS

The Shibasaki group also developed a rare earth-BINOL complex for the first catalytic, asymmetric aldol and nitroaldol reactions. This class of complex also catalyzed hydrophosphonylation and Michael reactions. Although the structural complexity of these metal complexes has made it difficult to obtain...
precise mechanistic data, much of the data suggests the involvement of two metals, and Shibasaki and co-workers has, therefore, laid the groundwork for future research in heterometallic catalysis.

**BIFUNCTIONAL ORGANOCATALYSIS**

In another key development in bifunctional catalysis, the Jacobsen group developed thiourea-based organocatalysts for the cyanation of ketones and imines. The same group showed further that non-covalent, hydrogen-bonding interactions can attenuate the reactivity of cationic intermediates to achieve high enantioselectivity in the Povarov reaction. Detailed experimental and computational analyses of these reactions have revealed the likely mechanisms and the basis for enantioselectivity in these reactions.

**CONCLUSION**

Numerous catalysts that combine various Lewis and Bronsted acids and bases for different modes of activation have been reported since the early work in bifunctional catalysis carried out by the Jacobsen and Shibasaki groups. However, there are few reports that test the assertion that these catalysts operate by a cooperative mechanism. A clear mechanistic understanding of how these catalysts work should aid the design of improved catalysts with high turnover frequencies and high enantioselectivities for synthetic applications in both academic and industrial settings.

**KEY REFERENCES**