Development of Highly Selective Synthetic Reactions and Synthesis of Biologically Active Compounds

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Synthetic organic chemistry is a pillar behind pharmaceuticals. The research program in our group has encompassed both the development of highly selective synthetic reactions and the synthesis of complex molecular targets.

1. Catalytic Asymmetric Reactions Mediated by Chiral Dirhodium(II) Complexes

Asymmetric catalysis is one of the frontiers of research in organic chemistry as the demand for enantiomerically pure compounds continues to increase. It is well documented that dirhodium(II) catalysts have the advantage of allowing a broad spectrum of diazo carbonyl compound transformations under much milder conditions than can be achieved with any other catalyst. Consequently, a great deal of effort is being devoted to the design, synthesis, and evaluation of chiral dirhodium(II) catalysts. Our efforts in this area have led to the development of dirhodium(II) catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused-phthaloyl-(*S*)-amino acid derivatives as bridging ligands. These catalysts mediate intramolecular C–H insertions of a structurally diverse array of diazo carbonyl compounds, intermolecular 1,3-dipolar cycloadditions via the generation of an carbonyl ylide, and [2,3]-sigmatropic rearrangements via the intramolecular formation of allylic or propargylic oxonium ylides with high levels of enantioselectivities up to 99%. In addition, our catalysts have recently been found to be well suited not only for a variety of enantioselective nitrene transfer reactions but also for enantio- and diastereoselective hetero-Diels–Alder reactions.

2. Total Synthesis of Biologically Active Natural Products

The evolution of the drug discovery and development process parallels closely that of natural product total synthesis. The zaragozic acids have been shown to be picomolar competitive inhibitors of the enzyme squalene synthase. Their biomedical significance as intriguing lead compounds for the development of new serum cholesterol-lowering drugs coupled with the novel molecular architecture has provided a powerful incentive for numerous synthetic chemists to embark on the synthesis of zaragozic acids and their analogues. We have completed the total synthesis of zaragozic acid C by a convergent strategy, wherein the key feature is a simultaneous creation of contiguous, oxygen-atom substituted quaternary stereocenters C4 and C5 by $Sn(OTf)_2$-promoted aldol coupling reaction between an a-keto ester and a silyl ketene thioacetal derived from L-and D-tartaric acids, respectively. We have also accomplished a highly convergent and stereocontrolled total synthesis of zaragozic acids A and C by exploiting a tandem rhodium(II)-catalyzed carbonyl ylide formation/1,3-dipolar cycloaddition to assemble the core structure and an olefin cross-metathesis to construct the C1 alkyl side chain. The power of the carbonyl ylide cycloaddition strategy has also been demonstrated by the first total synthesis of polygalolides A and B. Very recently, the total synthesis of pinnatoxin A has been achieved, wherein the key steps involve a highly stereoselective construction of the dispiroketal system via an intramolecular hetero-Michael reaction of a reversibly formed hemiketal alkoxide, an *exo*-selective intermolecular Diels–Alder reaction, Ru-catalyzed cycloisomerization to fashion the 27-membered carbocyclic ring, and a smooth formation of the seven-membered cyclic imine by self-catalyzed dehydration of ketoamino acid.

3. Oligosaccharide Synthesis Based on New Glycosidation Method

Owing to the growing biological significance of saccharide residues of carbohydrate-containing biomolecules, the rational design and development of stereocontrolled glycosidation reactions are of paramount importance not only in carbohydrate chemistry but also in medicinal chemistry. Considering that the leaving group of glycosyl donors is one of the most fundamental parameters responsible for the selectivity and yield of glycosidation reactions, our efforts have led to the development of glycosyl donors incorporating diphenyl phosphate, *N*,*N*,*N*',*N*'-tetramethylphosphoroamidate, or diethyl phosphite as leaving groups, the glycosidations of which constitute mild and efficient methods for the highly stereocontrolled construction of various glycosidic linkages. Furthermore, we have developed chemoselective glycosidation strategies for oligosaccharide synthesis (Gb_3 and GM_3) based on the difference in anomeric reactivities of glycosyl donors and acceptors carrying phosphorus-containing leaving groups.