ORGANIC AND BIOLOGICAL CHEMISTRY/CHEMICAL BIOLOGY

The interest of this group is on design and discovery of reactions and mechanisms in chemical and biological systems. New reactions and mechanisms are fundamental to our ability to discover new chemical space and construct novel tools to ask and answer questions important to life sciences. Reaction and synthesis development, coupled with modern biochemical/biological techniques, is envisioned to be the driving force for not only refined understanding of chemical reactivity but also creative discovery in modern biology.

ASYMMETRIC ORGANOCATALYSIS: ENZYME-INSPIRED CHEMICAL COOPERATIVITY DESIGN

Asymmetric organocatalysis has seen tremendous growth in the past decade and is now standard operation in chemical, pharmaceutical, and materials industries worldwide (Nature 2012, 489, 278). Continuing on the theme of developing green and sustainable catalytic methods, this area of research currently focuses on new catalytic strategies that are highly proficient with enzyme-like control of both reaction rate and enantioselectivity. Such proficiency control has been one of the most difficult problems in organocatalysis and will require new mechanistic insight in reaction design. Furthermore, the ability to control more than one catalytic cycle at a time is a new exciting direction in organocatalysis of complex chemical systems (Angew. Chem. Int. Ed. 2007, 46, 1570).

Our group has pioneered in new catalytic mechanism design for achieving proficient asymmetric organocatalysis in carbon-carbon bond forming reactions. In particular, we reported the first trifunctional, enantioselective organocatalytic system for the Morita-Baylis-Hillman (MBH, Scheme 1) reaction with regulation (Advanced Synthesis & Catalysis 2009, 331. Highlighted by Synfacts, 009,447). Cooperative counteranion regulation is built into the catalytic cycle for high enantioselectivity with concurrent rate enhancement. We continue to elucidate the mechanistic details behind this unusual catalysis by using a combination of techniques such as kinetics, NMR spectroscopy, mass spectrometry, and computational chemistry. The key question here is to understand the reaction with complex transfer steps may lead to first the proton is the understanding of are critical to finding ultimately be tunability of our catalytic systems metal centers Highlighted by JOC catalytic centers will transfer characteristics in this multi-step rate determining factors (Scheme 2). Such proton-resemble those observed in isomerase enzymes and organocatalytic mimics of this natural system. As smallest and simplest catalyst, in-depth asymmetric and catalytic proton-transfer reactions new and efficient transformations that could developed in water. The multifunctionality and catalysts also offer the opportunity to design hybrid involving other co-catalytic factors, ligands, and (Journal of Organic Chemistry 2007, 331. 2007). These hybrid catalytic systems with multiple be used in domino reactions.

Scheme 1. a) The MBH mechanism. b) A regulated, enantioselective trifunctional organocatalyst.

Scheme 2
A proton-transfer model
ISOZYME SPECIFICITY: TARGETING CONFORMATIONAL FLEXIBILITY IN DRUG DISCOVERY

Enzymes are major drug targets, and their conformational flexibility is known to be a major factor in designing drug leads with isozyme specificity (Nature Review Drug Discovery, 2003, 527). This is exemplified by the discovery of Gleevec as the first CML drug that specifically induces a particular conformational state of the Bcr-Abl kinase domain, which is the molecular driver behind chronic myelogenous leukemia (CML). Protein flexibility is difficult to predict or model thus presenting considerable challenges in rational drug design. Our group has used a semi-targeted approach, using natural products as leads, to access derivatives that can induce specific conformational change in the protein target for achieving isozyme specific recognition. In particular, we are using nucleotide mimics such as the K252 family and balanol to construct libraries of compounds using a fragment based approach (Journal of Organic Chemistry 2009, 254; Organic Letter 2007, 195). Subsite targeting motifs and conformational tuners are assembled using diversity-oriented synthesis. Activity- and binding-based SAR profiles are then established to guide the next cycle of library synthesis to improve specificity and potency.

ACTIVITY-BASED PROTEOMICS: FINDING THE MOLECULAR SIGNATURE OF CANCER

The long history of research in covalent modification of enzymes serves as a rich source for developing activity probes for functional proteomics (Annu. Rev. Biochem., 1984, 53, 493-535). We have developed highly specific labeling techniques for tagging protein active sites (Journal of the American Chemical Society 2004, 7754. Highlighted by the Chemistry & Engineering News of the American Chemical Society). These techniques have allowed analysis of protein function and their mechanistic role in a complex environment. One of the most important applications of ABPs is in drug discovery (Curr. Opin. Chem. Biol., 2011, 57). In addition, this approach has been successfully used to clarify molecular mechanisms that drive disease onset and progression (Mol. Cell. Proteomics, 2008, 1887-2006).

Our group, in collaboration with the Australian Proteomics Analysis Activity Activity-based proteomics Facility is investigating the role of signaling enzymes in cancer by designing and synthesizing activity probes for membrane signaling enzymes (Proteomics, 2011, 2683). The elucidation of signaling networks and mechanisms responsible for cancer progression will lead to identification of more effective drug targets.

Selected recent publications