PL1

Exploration of New Chemical Reactivities for Synthetic Efficiency

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The efficient making of new molecules is central to any new product in the pharmaceutical and fine chemical industries. It is equally useful to modify existing biomolecules directly in their natural states. However, state-of-the-art synthetic methods rely extensively on protection-deprotection, halogenation-dehalogenation, oxidation-reduction, and functionalization-defunctionalization. To address these challenges, our laboratory is exploring novel chemical reactivities for synthesizing chemical products in three aspects: (1) explore highly efficient chemistry to utilize the current chemical feedstock more efficiently: to avoid protection-deprotection, halogenation-dehalogenation, and allow direct CH/CH coupling; and (2) explore new chemistry that can utilize renewable resources readily. In many cases, the use of water plays the key role for the success of such reactions. This talk will focus our laboratory's efforts on developing C-C bond formations, with a special attention on the catalytic nucleophilic additions of alkynes in water and their applications in the direct modification of biomolecules such as carbohydrates and peptides under physiological ambient conditions in water (Figure 1).

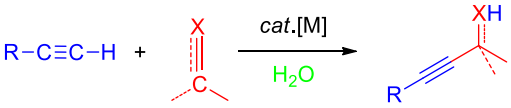

Figure 1

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Enantioselective Cooperative Catalysis and Complexity Building Reaction Cascades in Library and Natural Product Synthesis

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Enantiomerically pure compounds with the capacity to activate simultaneously electrophilic substrates and pro-nucleophilic reagents towards one another, offer numerous opportunities for the discovery of powerful new catalytic asymmetric carbon-carbon and carbon-heteroatom bond forming reactions. In this presentation, new families of bifunctional catalysts and their use in highly enantioselective Michael addition reactions, Mannich reactions, aldol reactions and alkylation reaction as well as other synthetically relevant transformations, will be described.[1-3] The application of these and other catalysts, separately and in concert, to the discovery of new one-pot reaction cascade processes to generate novel, multifunctional stereochemically defined scaffolds and architectures useful for library and target synthesis will also be discussed.

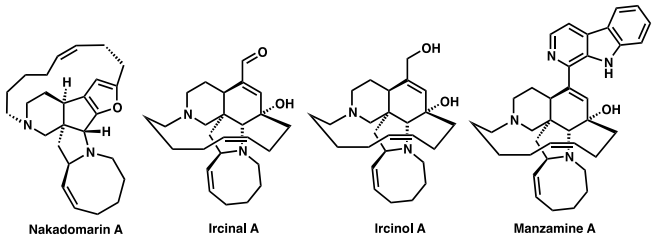

Figure 1: Manzamine alkaloid natural products.

Further application of selected methodologies as pivotal carbon-carbon bond forming steps in the total synthesis of a range of manzamine and daphniphyllum alkaloids[4-6] will then be discussed (Figure 1). These syntheses serve to illustrate how complex natural product targets can be rapidly accessed when combinations of catalyst-controlled reactions, one-pot multistep procedures and powerful route-shortening cascades are designed into the overall synthetic sequence.

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PL3

Chemical Protein Synthesis with the KAHA Ligation

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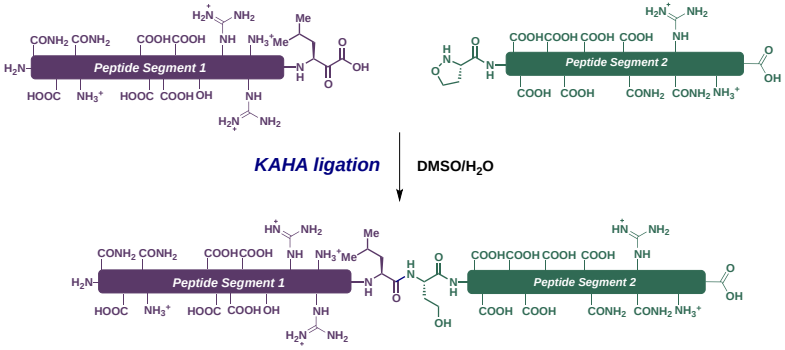
The chemical synthesis of proteins is critical to the understanding of biological function of proteins, particularly those containing posttranslational modifications or involved in covalent protein–protein conjugates. In order to expand the scope of chemical protein synthesis and to improve the ease with which proteins can be chemically synthesis, our group has sought to identify new ligation reactions that give native peptide bonds under mild, chemoselective conditions. This work has led to the discovery of the *α*-ketoacid–hydroxylamine amide-forming (KAHA) ligation, which operates in the presence of unprotected functional groups, requires no reagents or catalysts, and proceeds under aqueous conditions.



This talk will describe the development of the KAHA ligation, the reaction mechanism, methods to prepare peptide segments containing the key functional groups, and the application of this reaction to the chemical synthesis of proteins, including challenging targets such as membrane associated proteins. Ongoing efforts at multiple segment ligations to prepare larger peptides will also be discussed. Finally, we will discuss possible solutions to the still unsolved problem of ligating large, unprotected molecules at submillimolar concentrations with equimolar stoichiometry.

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Asymmetric Counteranion Directed Catalysis (ACDC): A General Approach to Enantioselective Synthesis

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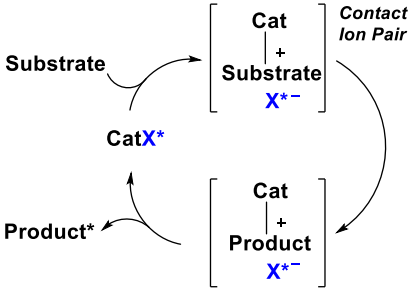
Most chemical reactions proceed via charged intermediates or transition states. Such “polar reactions” can be influenced by the counterion, especially if conducted in organic solvents, where ion pairs are inefficiently separated by the solvent. Although asymmetric catalytic transformations involving anionic intermediates with chiral, cationic catalysts have been realized, analogous versions of inverted polarity with reasonable enantioselectivity, despite attempts, only recently became a reality. In my lecture I will present the development of this concept, which is termed asymmetric counteranion-directed catalysis (ACDC) and illustrate its generality with examples from organocatalysis, transition metal catalysis, and Lewis acid catalysis.



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Mahlau M.; List B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518-533.

PL5

Addressing the Real Brain Drain: Nerve Regeneration by Synthetic Natural Products

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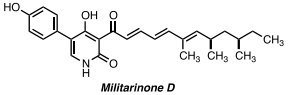
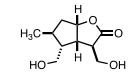
The reconstitution of neuronal networks by neurotrophins has been demonstrated as a viable strategy for addressing neuritic atrophy with regard to neurodegenerative diseases or spinal cord lesions.[1] However, limited efficacy was found for these proteins, due to poor bioavailability and the difficulty of reaching the central nervous system ('the blood/brain barrier'). Small molecule neurotrophins could overcome many of these problems and present thus a promising chemical alternative.[2] In addition, with regard to applications such as autologous nerve grafting for the treatment of spinal cord lesions, immobilized small molecules could offer unique advantages when compared to their protein counterparts.



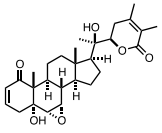
Militarinone D

Angew. Chem. Int. Ed. Engl. **2011,** *50*, 4222



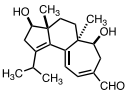
Gelsemiol

Chem. Eur. J **2013,** *19*, 2589



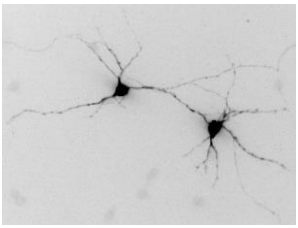
Withanolide A

Angew. Chem. Int. Ed. Engl. **2011**, *50*, 8407



Cyrneine A

Angew. Chem. Int. Ed. Engl. **2012**, *51*, 4071



In this communication, we will report (1) on the development of a versatile molecular platform for the generation of biologically active surfaces[3] and (2) on the total synthesis and biological evaluation of a series of small molecule neurotrophin mimics.[4] Both lines of research have converged,[5] and the design and biological evaluation of natural product functionalized surfaces for nerve regeneration is presented. Potential applications with regard to nerve grafting and guiding or the man/machine interface are discussed.

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Enantioselective Catalysis with Cations and Anions

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The past decade has witnessed remarkable development in the use of cationic gold(I) complexes as homogenous catalysts for the transformation of carbon-carbon π-bonds.[1] Several years ago, we demonstrated that the reactivity of these complexes could be controlled by modification of the counter anion to these cationic transition metal complexes.[2] This discovery provided a general platform for inducing enantioselectivity in reaction not only using cationic transition metal complexes, but also with reactive cationic reagents and intermediates. For example, we have applied this concept towards the development of enantioselective electrophilic fluorination under chiral anion phase transfer conditions (Figure 1).[3] The use of these ionic interactions to control selectivity of cationic species has generally relied on small molecular anions.[4] As an extension of this concept, we have been exploring the use of supramolecular assemblies as the anionic component in reactions catalyzed by cationic transition metal complexes. For example, cationic phosphinegold(I) complexes encapsulated by an anionic Ga_4L_6 tetrahedral demonstrated higher turnover numbers, rate acceleration, produced different products and are well-tolerated by the enzymes compared to the unencapsulated catalysts.[5]

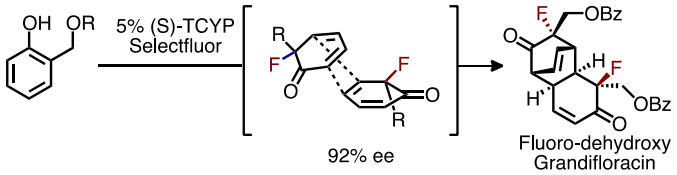

Figure 1: Enantioselective Fluorination of Phenols by Chiral Anion Phase Transfer Catalysis.

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