Lecture 1: Rh(III)- and Co(III)-catalyzed C-H bond additions to polarized π-bonds

Transition metal-catalyzed C-H bond functionalization can enable the rapid and highly functional group compatible assembly of drug relevant architectures from simple and readily available inputs. In this first lecture, catalytic C-H bond additions to imines, aldehydes and electron deficient alkenes will be presented for the convergent asymmetric synthesis of amines and for cascade reaction sequences to heterocycles found in pharmaceuticals. Mechanistic studies on the aforementioned transformations, including X-ray structural characterization of a number of metallocycle intermediates, will also be discussed. Catalytic three-component sequential additions to two different electrophiles with simultaneous formation of two C-C bonds with high regio- and stereoselectivity will also be described.

Lecture 2: Rh(I)-catalyzed C-H functionalization cascades for the synthesis of nitrogen heterocycles

Practical and convergent routes to substituted 1,2-dihydropyridines from imines and alkynes by a Rh(I)-catalyzed C-H bond alkenylation/electrocyclization sequence will be presented. The regio- and stereoselective elaboration of these 1,2-dihydropyridines to provide rapid entry to densely substituted piperidines will then be detailed. Strategies will also be described for achieving unexpected rearrangements and cycloadditions upon silyl substituted 1,2-dihydropyridines to give multicyclic products, including tropanes, indolizidine and tricyclic nitrogen heterocycles with as many as five contiguous stereocenters. The utility of the presented methods will also be illustrated by short and efficient syntheses of important pharmaceutical agents.

Lecture 3: Adventures in small molecule enzyme inhibitor development

Substrate Activity Screening (SAS) is a fragment-based method for the rapid development of novel, small molecule enzyme inhibitors. The method consists of three steps: (1) a diverse library of low molecular weight substrates is screened against an enzyme target to identify lead fragments, (2) the identified fragments are rapidly optimized by subsequent rounds of analogue synthesis and evaluation, and (3) the optimized substrates are converted to inhibitors by direct incorporation of mechanism-based inhibitor pharmacophores. Because the assay requires productive substrate binding and turnover, false positives often seen in traditional high-throughput inhibitor screens are eliminated. Additionally, catalytic substrate turnover results in signal amplification enabling the identification of very weakly active lead fragments. The successful application of this and other approaches to the rapid identification of potent and selective inhibitors of therapeutically relevant proteases, phosphatases and protein arginine deiminases will be presented.

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