STEREODIVERGENCE VIA DUAL CATALYSIS

Reported by Tyler Smolczyk 11/13/18

INTRODUCTION

Asymmetric catalysis has been the subject of intense research over the last few decades. In general, these methods produce only a select few of the possible stereoisomers, leaving the remaining stereoisomers inaccessible. Stereodivergent catalysis, where each stereoisomer possible in a transformation can be accessed from the same starting materials, has emerged as a powerful tool to address this issue. Sequential catalysis performs this process in an iterative fashion, where after one stereocenter in the molecule has been set, the intermediate is then subjected to another asymmetric transformation. Dual catalysis achieves this goal with two independent catalytic systems allowing complete stereocontrol in a one step process. These systems have been studied to produce scaffolds present in biologically active molecules and used in the context of total synthesis.

SEQUENTIAL CATALYSIS

An early example of a stereodivergent sequential catalytic system was reported by MacMillan in 2005 (Figure 1).[1] Through an iminium-enamine protocol, a range of nucleophiles with a Cl^+ electrophile surrogate were added across α,β-unsaturated aldehydes. Importantly, the stereocenter set in the initial iminium step did not have any control over the stereoselectivity in the second enamine step, showcasing exquisite catalyst control. In 2016, Buchwald and coworkers demonstrated that the production of stereo-defined 1,3-amino alcohols can be accomplished by an enantioselective hydrosilyation of an α,β-unsaturated aldehyde followed by a syn-hydroamination procedure (Figure 2).[2] This example is extraordinary in that three contiguous stereocenters are set in the process, and by selecting the appropriate Z or E alkene in combination with the correct enantiomers of the ligand, all eight possible stereoisomers can be isolated.

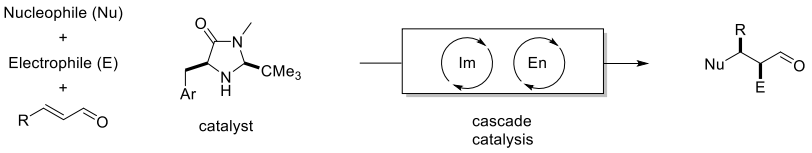

Figure 1: Cascade catalysis via dual iminium/enamine catalysis

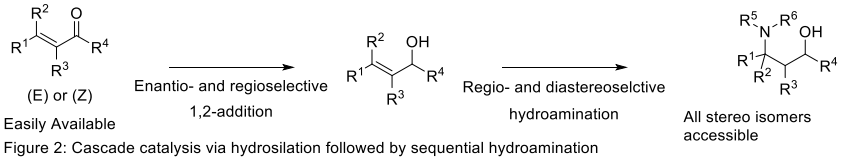

Figure 2: Cascade catalysis via hydrosilation followed by sequential hydroamination

METAL-ORGANO DUAL CATALYSIS

The Carreira group published the first stereodivergent dual catalytic system in 2013 where the enantioselective α-allylation of branched aldehydes was achieved via iridium-catalyzed allylic substitution of allylic alcohols with chiral enamines.[3] The authors proposed a single outer sphere transition state where the stereochemical information of each catalyst is transposed to their respective center, minimizing any matched/mismatched interactions. The proposed transition state model was studied computationally by Sunoj in 2015 and corroborated experimental results.[4] Carriera and coworkers expanded scope of this reaction to linear aldehydes in 2014 and used this reaction in the total synthesis of (-)paroxetine (Figure 3).[5]

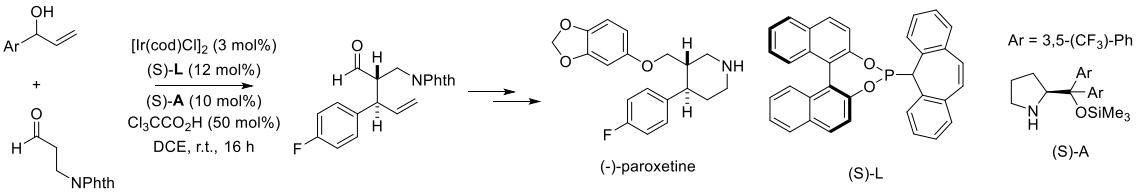

Figure 3: Total synthesis of (-)paroxetine

METAL-METAL DUAL CATALYSIS

The first report of a dual metal stereodivergent catalytic system was reported by Zhang in 2016.[6] This system employs a Zn/Ir system for the stereodivergent α-allylation of α-hydroxyketones (Figure 4). This reaction shows a broad substrate scope and can be performed on gram scale. The Hartwig group in 2018 expanded the metal-metal strategy to an Ir/Cu system in a stereodivergent allylation of azaaryl azetamides and acetates.[7] Given that azaarenes are ubiquitous in natural products and pharmaceuticals, this method allows for a streamlined approach into stereochemically defined azaarene structures which can be assessed for studies on structure-activity relationships.

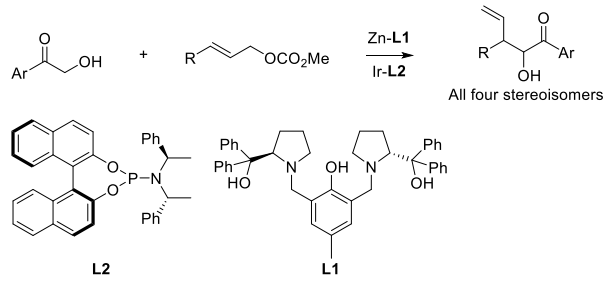

Figure 4: Dual metal sterodivergent a-allylation of a-hydroxyketones

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