INTRODUCTION

Tertiary stereocenters containing a C-H bond are found in many biologically active molecules such as pharmaceuticals and agrochemicals. The syntheses of many of these compounds involve the enantioselective hydrogenation of olefins, ketones, and imines by chiral transition metal complexes. In the last decade, organocatalysis has emerged as a powerful alternative for the enantioselective synthesis of chiral compounds. The lower costs and toxicity of the organocatalysts employed as well as the operational simplicity of the reactions are often presented as the main advantages of organocatalysts over transition metal catalysts. However, it is the different activation modes of organocatalysts that can provide real synthetic advantage. This seminar will focus on the recent developments of chiral iminium and Brønsted acid catalysts for the asymmetric transfer hydrogenation of C=C and C=N bonds with Hantzsch esters as a mild, organic source of hydrogen.

IMINIUM-CATALYZED 1,4-REDUCTION OF α,β-UNSATURATED ALDEHYDES

As an alternative to enantioselective conjugate addition reactions, the enantioselective conjugate reduction of α,β-unsaturated carbonyls offers a complementary approach to creating a stereocenter at the β-position. The metal-mediated enantioselective conjugate reduction of α,β-unsaturated aldehydes, unlike that of other unsaturated carbonyl compounds, lacks broad scope. In particular, the conjugate reduction of α,β-unsaturated aldehydes often suffers from competitive 1,2-reduction. Inspired by nature’s use of NADH and enzymes, List found that several ammonium salts catalyze the conjugate reduction of β-monosubstituted- and β,β-disubstituted-α,β-unsaturated aldehydes utilizing a Hantzsch ester as the hydrogen source. This iminium-catalyzed process lowers the LUMO of the unsaturated aldehyde to enable conjugate hydride delivery with no observed 1,2-reduction. In 2005, List and MacMillan independently reported the asymmetric 1,4-reduction of β,β-disubstituted-α,β-unsaturated aldehydes. A chiral imidazolidinone catalyst with a Hantzsch ester as the hydrogen source gave the saturated aldehydes in high yields with excellent enantioselectivities. List and coworkers reported an alternative approach with the ammonium salt of a sterically hindered chiral Brønsted acid that resulted in improved enantioselectivity and expanded the scope to unhindered aliphatic aldehydes. In stark contrast to most metal-mediated hydrogenations, E- and Z- olefin substrates converge to the same enantiomer upon hydrogenation. The enantioselective reduction of α,β-unsaturated aldehydes, a previously difficult reaction, can now be performed with a Hantzsch ester and an iminium catalyst.
CHIRAL BRØNSTED ACID-CATALYZED HYDROGENATION OF QUINOLINES

The enantioselective hydrogenation of substituted quinolines can provide a direct and efficient route to biologically interesting chiral tetrahydroquinolines. The metal-mediated asymmetric hydrogenation of quinolines is difficult because of the high energetic barrier to dearomatization as well as the ability of the substrate and product to act as a ligand. Current methods for the enantioselective hydrogenation of quinolines are limited in scope to those substituted at the 2-position, along with a few 2,3-disubstituted examples. Motivated by List and MacMillan’s biomimetic transfer hydrogenation of α,β-unsaturated aldehydes, Rueping and coworkers developed a chiral Brønsted acid-catalyzed transfer hydrogenation of ketimines with a Hantzsch ester as a hydrogen source. Encouraged by the success of this process, they expanded the scope of this method to the asymmetric hydrogenation of 2-substituted and 3-substituted quinolines. This is the first example of an enantioselective hydrogenation of 3-substituted quinolines. Du and coworkers developed double axially chiral phosphoric acids to enantioselectively reduce 2-substituted and 2,3-disubstituted quinolines with lower catalyst loading and higher enantioselectivity than Rueping’s system. The application of chiral Brønsted acid-catalysts and Hantzsch esters has led to highly enantioselective hydrogenations of substituted quinolines, including the first enantioselective hydrogenation of 3-substituted quinolines.

SUMMARY

Hantzsch esters have reduced both α,β-unsaturated aldehydes and quinolines by biomimetic, organocatalytic transfer hydrogenation. These methods have complementary scope to transition metal-mediated hydrogenations. Additionally, the Hantzsch esters offer a stable, operationally simple alternative to the direct use of hydrogen gas. However, hydrogen gas is cheap and plentiful compared to the more expensive Hantzsch ester; thus, catalytic regeneration of the Hantzsch ester in-situ would improve the practicality of these hydrogenation methods.

REFERENCES