CATALYTIC ENANTIOSELECTIVE APPROACHES TO PYRROLIDINES

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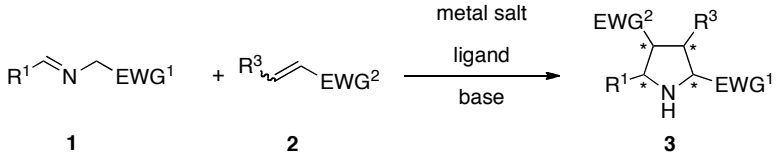
INTRODUCTION

Pyrrolidine derivatives are common in both natural products and pharmaceutical applications.[1] Catalytic methods that provide access to highly substituted pyrrolidines with control of stereochemistry in a single ring-forming step would build molecular complexity in an efficient manner. This seminar details advances in two catalytic asymmetric approaches to enantioenriched pyrrolidines: 1,3-dipolar cycloadditions of azomethine ylides[1b] and (3+2) annulations of donor–acceptor cyclopropanes.[2]

CATALYTIC ENANTIOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF AZOMETHINE YLIDES

Synthesis of pyrrolidines **3** using the 1,3-dipolar cycloaddition of azomethine ylides from precursor **1** with electron deficient alkenes **2** has potential to create up to four stereogenic centers (eq 1).

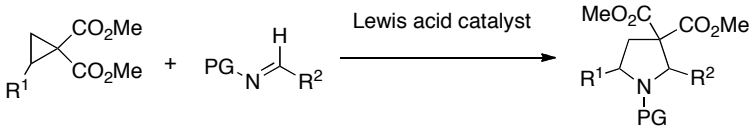


1 **2** **3** (1)

Asymmetric versions utilize *in situ* generated metalloazomethine ylides with a chiral Lewis acid. This was first demonstrated by Grigg using a stoichiometric amount of cobalt (II) chloride with an ephedrine ligand.[3] The first catalytic methods were independently pioneered by Zhang, using AgOAc and a chiral bisphosphine ligand, and Jorgensen using $Zn(OTf)_2$ and a bisoxazoline ligand, to isolate the *endo* disastereomer in high enantiomeric excess.[4] Alternative chiral ligands have been used with α-branched azomethine ylides to generate quaternary stereocenters at the 2-position.[5] Further work has expanded the dipolarophile scope to include nitroalkenes,[6a] vinyl sulfones,[6b] and enones.[6c] A catalytic system using a Cu(II) catalyst allows for isolation of the *exo* isomer.[7] Tuning the electronics of the chiral ligand can result in a reversal of diastereoselectivity.[8] Creative catalyst design can switch which enantiomer of the product is obtained. Oh demonstrated this by merely changing the Lewis acid from Ag(I) to Cu(I) while using the same chiral amino alcohol ligand.[9] Zhou reported similar reversal in enantioselectivity by altering the hydrogen bonding ability of the nitrogen moiety in a chiral P,N-ligand with AgOAc.[9,10]

(3 + 2) ANNULATIONS OF DONOR – ACCEPTOR CYCLOPROPANES

An alternative approach to the construction of pyrrolidines of structure **6** is the ring expansion annulation of donor-acceptor cyclopropanes **4** with aldimine dipolarophiles **5** (eq 2).



4 **5** **6** (2)

Diastereoselective Lewis acid-catalyzed annulations were first reported by Kerr and Tang using $Yb(OTf)_3$ and $Sc(OTf)_3$ respectively.[11] In both cases, the 2,5-*cis* pyrrolidine product was obtained in high dr and the aldimine component was limited to aromatic imines. Kerr expanded this scope to include aliphatic substitutents by using an oxime nucleophile, unfortunately this required tethering the cyclopropanediester to the oxime oxygen.[12] This system gave both 2,5-*cis* and 2,5-*trans* pyrrolidines by varying the order of addition of Lewis acid catalyst. Recently, Johnson reported a dynamic kinetic asymmetric transformation to give 2,5-*cis* pyrrolidines by using a chiral (pybox)MgI_2 catalyst.[13]

CONCLUSION

The catalytic enantioselective 1,3-dipolar cycloaddition provides access to a variety of 2,5-*cis* pyrrolidines, however is limited by aromatic and electron-withdrawing groups needed to stabilize the metalloazomethine ylide. In contrast, aliphatic substitutions and 2,5-*trans* pyrrolidines have been accessed using chiral donor–acceptor cyclopropanes and recent work as shown catalytic variants of these reactions to be possible.

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