CATALYTIC, ENANTIOSELECTIVE HETERO-DIELS-ALDER REACTIONS OF ALDEHYDES

Reported by Dustin Covell November 6, 2006

INTRODUCTION

The Diels-Alder reaction is widely known as a powerful reaction, especially in its asymmetric variants, for the construction of six membered rings with excellent regio- and stereocontrol.[1] The Hetero-Diels-Alder (HDA) reaction is somewhat less well known but is extremely useful for the construction of heterocycles.[2] In 1982 the HDA was extended to unactivated aldehyde heterodienophiles by Danishefsky and co-workers through the use of Lewis acid catalysis.[3] Since that time, the reaction has received much attention because of the ease with which the dihydropyranone products of the reaction of an aldehyde with Danishefsky's diene (**1**) (Figure 2) can be elaborated to numerous pyran containing natural products. This review will summarize the major advances in the development of practical Lewis acid catalyzed variants, with an emphasis on the state-of-the-art, for accomplishing the catalytic, enantioselective HDA of aldehydes. In addition, the application of these methods in synthesis will be highlighted.

Background

The HDA transformation is powerful because two new sigma bonds are formed in the reaction with the potential for stereocontrol at up to three sites. There are two main types of HDA reactions, those of dienes with aldehyde heterodienophiles, which proceed through a normal electron demand HDA, and those of enal dienes with electron rich dienophiles, which occur through an inverse electron demand HDA. Frontier Molecular Orbital (FMO) analysis of the normal electron demand HDA reveals that the HOMO of the diene and LUMO of the dienophile are the controlling orbitals. The polarity of the aldehyde carbonyl, the hetero-dienophile, strongly desymmetrizes the orbital coefficients of the LUMO leading to a bias in the head-to-tail orientation of the aldehyde relative to the diene. From a selectively standpoint, endo and exo orientations of the aldehyde in the transition state structure of the HDA remain a concern as well as which face of the aldehyde approaches the diene. However, early recognition of the acceleration of the HDA reaction in the presence of a Lewis acid provides a mechanism for overcoming these selectivity concerns. Theoretical studies of the HDA reaction catalyzed by various Lewis acids have shown that binding of the Lewis acid lowers the LUMO of the dienophile, accounting for the rate enhancement, while providing steric bulk that influences exo/endo selectivity.[4] A chiral ligand environment around the Lewis acid allows for preferential reaction at one of the enantiotopic faces of the aldehyde.

Similarly, in the inverse electron demand HDA reaction between enals and electron deficient dienophiles, the HOMO of the dienophile and the LUMO of the diene are the controlling orbitals. As in the normal electron demand HDA, Lewis acid coordination, in this case to the diene, leads to a rate enhancement by decreasing the HOMO-LUMO gap for the reaction, while providing an opportunity for biasing the selectivity of the reaction. A summary of these FMO considerations is presented in Figure 1.

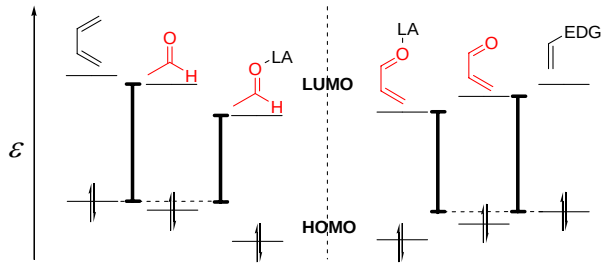


Figure 1. A FMO diagram of the uncatalyzed and Lewis acid catalyzed normal electron HDA (left) and inverse electron demand HDA (right).[2]

The mechanism of the Lewis acid catalyzed HDA of aldehydes with activated dienes has been examined both experimentally and theoretically for several systems.[5] From these studies, two reaction manifolds have emerged. In the first, the reaction proceeds through a Mukiyama-type aldol addition step, with subsequent cyclization occurring under acidic conditions to give the HDA product. The remaining documented HDA reactions seem to take place through a concerted, asynchronous [4+2] cycloaddition (Figure 2). Molecular modeling suggests that for the cycloaddition pathway the transition state structure with Lewis acid coordination to the carbonyl syn to the aldehyde hydrogen is the lowest in energy. This catalyst orientation forces the aldehydes non-hydrogen substituent into an endo orientation. The Lewis acid catalyzed HDA is calculated to have an activation energy ~12 kcal/mol lower than that for the uncatalyzed process, which is in accord with the dramatic rate increases empirically observed. Additionally, the transition state structure was found to be unsymmetrical with the C-O bond significantly less formed than the C-C bond.

The identity of the Lewis acid plays a crucial role in determining both the mechanism by which the reaction proceeds and the selectivity. For example, early work on the HDA of benzaldehyde with trans-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene (**2**) (Figure 2) by Danishefsky and co-workers identified a preference for the trans-substituted dihydropyranone in the presence of BF_3 as the Lewis acid catalyst and a preference for the cis-substituted dihydropyranone when $ZnCl_2$ was the catalyst.[6] The cycloaddition mechanism for the $ZnCl_2$-catalyzed case was supported by ^1H NMR analysis of rapidly quenched aliquots from the reaction mixture. However, the product mixture obtained

from aliquots from the BF_3-catalyzed reactions was much more complex, suggesting a delicate balance between the Mukiayama-aldol type pathway and the cycloaddition pathway.

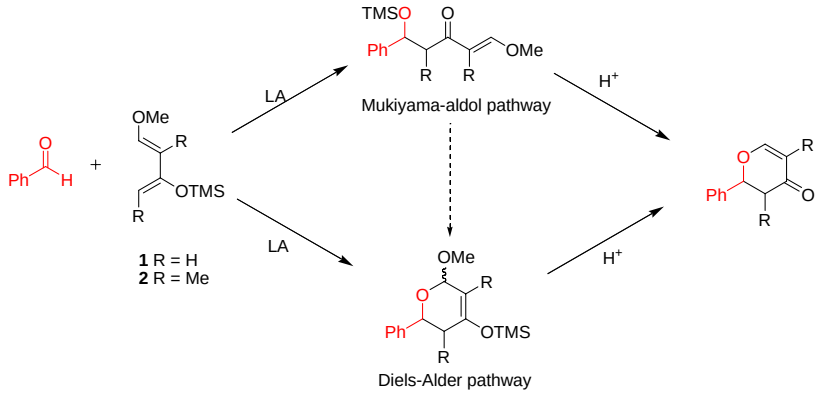
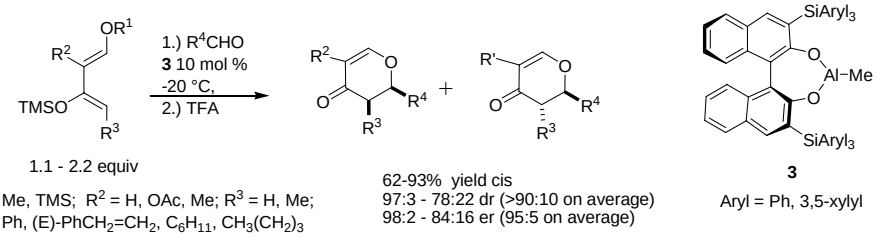


Figure 2. Mukiyama aldol vs. Diels-Alder pathway for the reaction of benzaldehyde with Danishefsky's diene (**1**).[2]

EARLY WORK ON THE LEWIS ACID CATALYZED, ENANTIOSELECTIVE HDA

A wide range of Lewis acids based on Al, B, Ti, Zr, Cu, and Co were developed in the 1980's and early 1990's as catalysts for the enantioselective HDA reaction. Following Danishefsky's discovery that Lewis acids catalyze the reaction between aromatic aldehydes and activated dienes, Yamamoto and co-workers demonstrated the first example of a catalytic, enantioselective variant of the transformation using an Al-BINOL complex (**3**) with large substituents at the 3 and 3' positions of the BINOL backbone.[7] This catalyst showed good to excellent yields and selectivities for a wide range of aldehydes and activated silyloxydienes, though the parent diene **1** was a poor substrate (Scheme 1). The reaction shows a preference for the cis–dihydropyranone products. Molecular modeling suggests that the reaction proceeds through the step-wise Mukaiyama-aldol like mechanism.

Scheme 1. Scope and Selectivities of Catalyst 3 for the HDA Reaction.

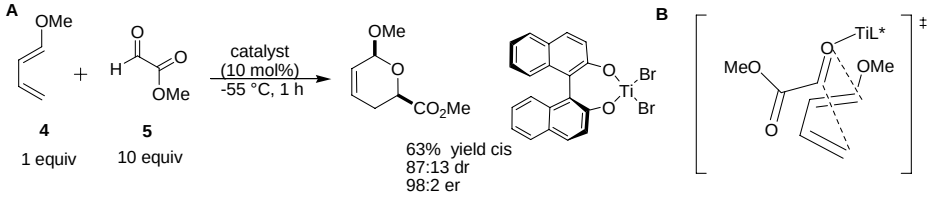


A Ti-BINOL complex for the catalytic, enantioselective HDA reaction of unactivated dienes with methyl glyoxylate gives the HDA product in reasonable yields and moderate to good selectivity (Scheme 2A).[8] The cis selectivity of the reaction suggests a cycloaddition transition structure in which

the titanium is bound in an anti-monodentate fashion to the glyoxylate formyl group and wherein the ester group adopts an endo orientation (Scheme 2B).

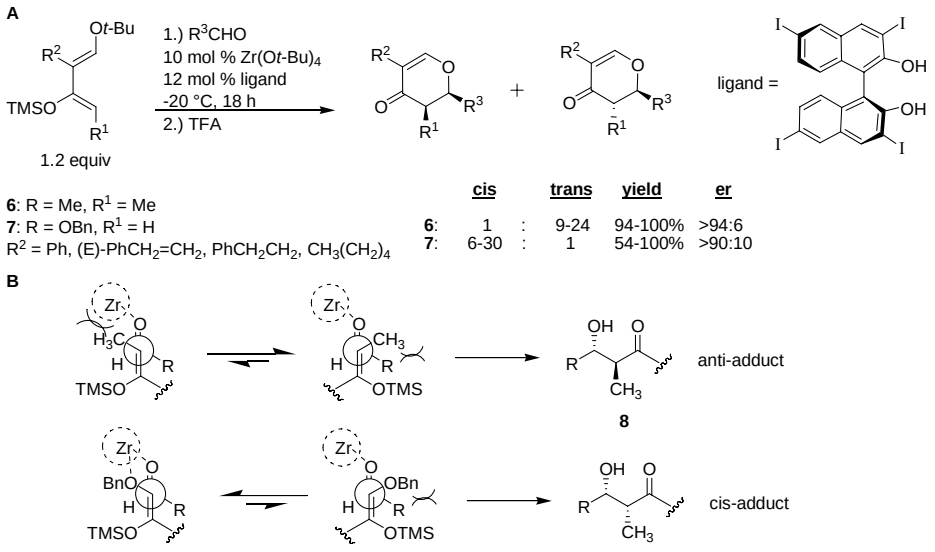
Jørgenson and co-workers reported additional studies toward the HDA reaction of glyoxylates with unactivated dienes (eg. cyclohexadiene, butadiene, and isoprene) with copper-bis(oxazoline) (Cu-BOX) catalysts. Good enantioselectivities (92:8 er on average) are obtainable with this catalyst, but in low to moderate yields (30-72%) and with significant loss of material to a competitive ene reaction of the starting materials.[9]

Scheme 2. Ti-BINOL HDA reaction of 4 with 5 and the Proposed Transition Sructure.



A zirconium(IV) complex containing an electron deficient BINOL derivative as the ligand, developed by Kobayashi and co-workers, displays remarkable reactivity in the HDA for a wide range of dienes and aldehydes.[10] Interestingly, this catalyst gives a highly trans selective HDA of diene **6** and a highly cis selective HDA of diene **7** (Scheme 3A). Careful purification of the reaction mixture of the HDA reaction of benzaldehyde with **6** prior to the addition of acid gave a single product; the anti-aldol adduct **8** (Scheme 3b).

Scheme 3. Zr-BINOL Catalyzed HDA Leading to Cis or Trans Configured Product.

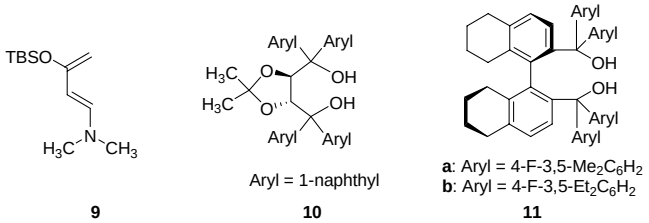


Treatment of **8** with acid gives the trans-dihydropyranone product rapidly, indicating that the reaction proceeds through the Mukiyama-aldol pathway. This product may arise from an anti-selective aldol addition in which the methyl group and the zirconium catalyst adopt positions on opposite sides of the forming bond between the diene and the aldehyde to minimize steric interactions. Conversely, replacing the terminal methyl group of diene **6** with an oxygen substituent, such as in diene **7**, affords a cis-selective aldol reaction, most likely through coordination of the ether oxygen with zirconium (Scheme 3B).

RECENT ADVANCES IN THE CATALYTIC, ENANTIOSELECTIVE HDA REACTION

Chiral Hydrogen Bonding Catalysts

In their pursuit of more reactive dienes for the Diels-Alder reaction, Rawal and co-workers developed reactive diene **9**, which is readily prepared on a large scale from acetaldehyde dimethyl acetal (eq. 1). This diene is sufficiently activated to participate in HDA reactions at room temperature without the need for high pressure or a Lewis acid catalyst.[11] Aldehydes can be converted to dihydropyranones through a HDA reaction with subsequent unmasking effected by acetyl chloride. Performing the reaction in a solvent that could act as a hydrogen bond donor dramatically accelerated the rate of HDA reactions with **9**.[12] For example, the reaction of p-anisaldehyde with **9** proceeds 630 times faster in isopropyl alcohol-D_8 than in THF-D_8, which corresponds to a $\Delta\Delta G^{\ddagger}$ of -3.77 kcal/mol. On the basis of this dramatic rate enhancement, Rawal and co-workers investigated the use of chiral alcohols as catalysts. TADDOL (**10**) catalyzes the HDA of **9** with 2 equivalents of aromatic aldehydes to afford moderate to good yields (68-97%) and excellent enantioselectivities (96:4->99:1 er).[13,14] Aliphatic and vinyl aldehydes also react, but with poorer yields and diminished selectivities.



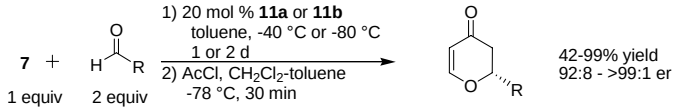
9 **10** **11** (eq. 1)

X-ray crystal structure analysis of a TADDOL-DMF complex obtained by Ding and co-workers reveals a potential model for the mode of catalysis by TADDOL. The X-ray crystal structure shows an intramolecular hydrogen bond that adds rigidity to the TADDOL backbone and an intermolecular hydrogen bond to the oxygen of DMF.[15] Using this crystal structure as a starting point, Ding and co-workers pursued additional experimental and theoretical studies of the TADDOL-catalyzed HDA of **1** with benzaldehyde. ^{1}H NMR analysis of the crude reaction mixture prior to the addition of TFA revealed no aldol-like products, suggesting that the reaction proceeds through a concerted, [4+2]

cycloaddition mechanism.[16] This conclusion was further supported by the absence of any zwitterionic or Mukiyama aldol-like intermediates along the reaction pathway by computational analysis.[16] Additional computational studies show a clear preference of the TADDOL-catalyzed reaction for the endo transition structure geometry, which places the bulky catalyst in an exo orientation to minimize steric interactions with the approaching diene. The two endo transition structures, corresponding to approach of the diene to the enantiotopic faces of the aldehyde, differ in energy by 2.6 kcal/mol, with a preference for the transition structure that leads to the experimentally observed enantiomer. Additionally, it was shown that the intramolecular hydrogen bond in the catalyst strengthens in the transition state, increasing the donor ability of the hydroxyl group participating in the intermolecular hydrogen bond, thereby enhancing the interaction of the catalyst with the aldehyde carbonyl group.

Further investigations by Rawal and co-workers led to the development of BAMOL derivatives **11a** and **11b.**[17] The tetrahydronapthalene groups of BAMOL cause a significantly more varied chiral environment around the reactive site than the isopropylidene ketal of the TADDOL catalyst leading to enhanced selectivities. This complex was found to catalyze the HDA of **9** with a variety of aliphatic, vinylic, alkynylic, and aromatic aldehydes in moderate to excellent yields with high enantioselectivities (Scheme 4). An X-ray crystal structure of a BAMMOL-benzaldehyde complex reveals an intramolecular hydrogen bond between the two hydroxyl groups of the catalyst and an intermolecular hydrogen bond between the catalyst and benzaldehyde.

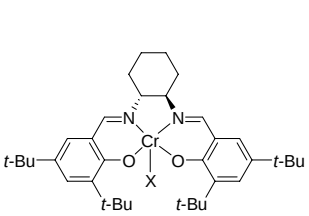
Scheme 4. Scope and Selectivities for the Chiral BAMOL Catalyzed HDA.



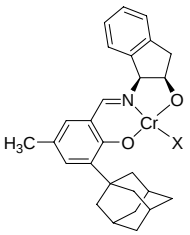
R = Me, n-propyl, $Ph(CH_2)_2$, $PhS(CH_2)_2$, $Phth(CH_2)_2$, 1-propynyl, *i*-butyl, C_6H_{11}, Ph, 3-(MeO)-C_6H_4, 2-(NO_2)-C_6H_4, 1-naphthyl, 2-furyl

Jacobsen Chromium HDA Catalysts

After the initial development of cobalt- and chromium-salen complexes as efficient catalysts for the enantioselective opening of epoxides, Jacobsen and co-workers investigated the Lewis acid catalyzed HDA reaction of benzaldehyde with **1**. Chromium(III) salen complexes (**12a** and **12b)** catalyze the addition of **1** to selected aliphatic, vinylic, and aromatic aldehydes in good yields (65-98%) and good enantioselectivities (85:15 – 96:4 er).[18] Mechanistic studies suggest that the reaction occurs through a synchronous HDA pathway. To rule out the involvement of the Mukiyama-aldol pathway the appropriate intermediate was independently synthesized and subjected to the standard reaction conditions. No cyclization product was observed, lending further support for the [4+2] mechanism.



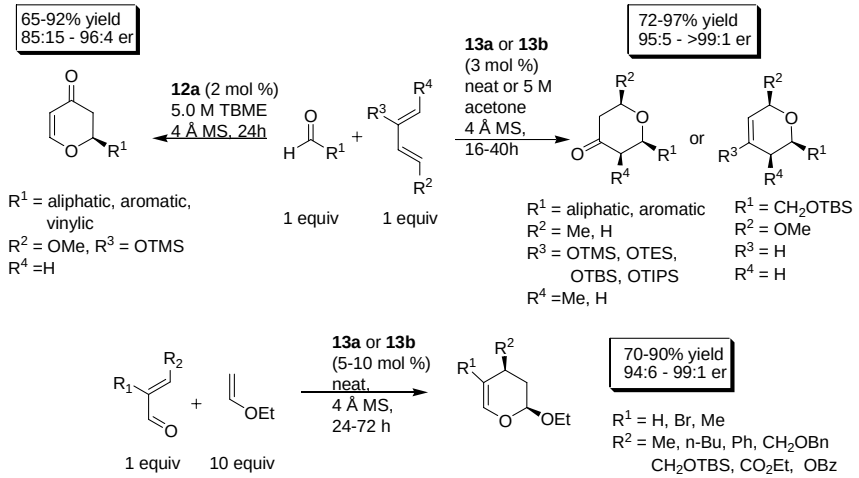
12a X = Cl
12b X = BF_4



13a X = Cl
13b X = SbF_6

Although the Cr-salen complexes are effective catalysts for the HDA of numerous aldehydes, enantiomeric ratios greater than 92:8 are seldom observed. Exploration of tridentate Schiff base complexes led to the discovery of complexes **13a** and **13b** which are highly selective catalysts for the HDA of numerous aliphatic and aromatic aldehydes with both activated and unactivated dienes.[19] Complex **13a** is also a competent catalyst for the inverse electron demand HDA of α,β-unsaturated aldehydes with ethyl vinyl ether to afford substituted pyrans (Scheme 5).[20]

Scheme 5. Summary of Reactivity for the Jacobsen Cr-HDA Catalysts 12a, 13a and 13b.



The Jacobsen HDA catalysts also effect catalyst-controlled diastereoselective reactions in both the normal (81-99% yield, 99:1 er, 1.4:1 - 33:1 dr),[21] and inverse-electron-demand HDA ((85% yield, 99:1 er, 7:1 - 97:3 dr).[22] The utility of the Jacobsen HDA method has been demonstrated through extensive application in natural product synthesis, including such targets as fostriecin, (+)-ambruticin, FR901464, several iridoid natural products,[23] (–)-dactylolide,[24] and gambierol.[25]

SUMMARY

Lewis acids are extremely useful catalysts for the Hetero-Diels-Alder reaction of aldehydes. Chiral Lewis acids are effective for catalyzing the HDA with modest to excellent stereocontrol. Early

work with aluminum-, titanium-, copper-, and zirconium-based Lewis acids has given way to more modern methods using Bronsted acids and chromium complexes. The scope of these modern catalysts is broad, allowing for highly enantioselective reactions of numerous heteroatom-containing dienes and dienophiles to give many interesting heterocycles. These heterocycles are extremely common subunits and have, therefore, been used as starting points for the synthesis of many natural products and pharmaceutically interesting compounds.

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