Summer Scholar Report

Activation of β-amidoaldeydes Toward Diastereoselective Nucleophilic Addition

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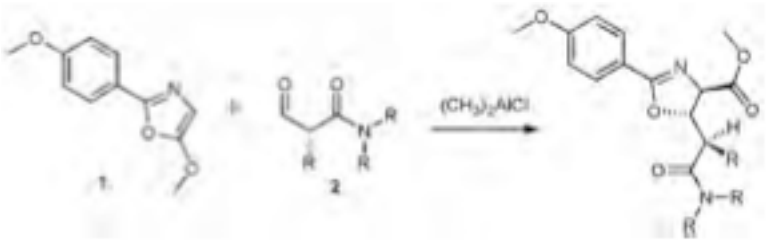
Background:

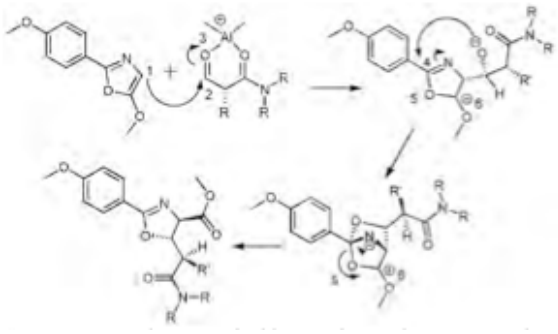
Our work on amino acid analogs, and the biological effects of their incorporation into biologically active species, has led us to investigate the preparation of a series of α-hydroxy amino acid analogs. While there are a variety of methodologies that allow the preparation of such species, we were intrigued by the application of metallic Lewis acids to the stereospecific addition of aldehydes to activated methoxyoxazoles. Some methods, such as Evans'[1] use of a salen-Al to catalyze the addition of benzaldehyde to 2-(4- methoxyphenyl)-5-methoxyoxazole, generate the stereoselectivity from the ligands attached to the metal. We, on the other hand, have studied the stereoselective addition of an aldehyde to an activated oxazole, using chirality within the aldehyde to generate high diastereoselectivity. Because chirality in a ligand may operate against the chirality of the aldehyde, and because the Evans salen-Al worked well for aromatic aldehydes, but not well for aliphatic aldehydes, we chose to begin our work with the achiral dimethylaluminum chloride. We have utilized the dialkyl aluminum catalyst for the addition of chiral amidoaldehydes to activated aryl oxazoles. The catalyst is a divalent Lewis acid, allowing it to complex to the bidentate amidoaldehyde and enforce conformational rigidity of the aldehyde. The reaction results in a diastereoselective addition to achieve an oxazoline product.



Scheme 1. *Reaction of oxazole with an aldehyde activated by an aluminum catalyst*

In the mechanism of the addition of the aldehyde to the oxazole (**Scheme 2**), carbon 1 acts as a nucleophile on aldehyde carbon 2, pushing electron density to oxygen 3 and leaving carbon 6 positively charged. The electron density from oxygen 3 attacks carbon 4, pushing the pi electrons toward the nitrogen. The pi electrons reform the double bond between carbon 4 and nitrogen, causing the bond between carbon 4 and oxygen 5 to break and forming a carbonyl between oxygen 5 and carbon 6. In this rearrangement, a new five membered ring is formed.

The aluminum catalyst is effective for the stereospecific addition of chiral amidoaldehydes to activated oxazoles because it is a divalent Lewis acid, thereby constraining the conformation of the bidentate amidoaldehyde and increasing the aldehyde's electrophilicity (**Figure 1**).[5,6] The aldehyde **2** may have variable R groups bonded to the amide nitrogen



Scheme 2. *Mechanism of addition of oxazole to activated aldehyde.*

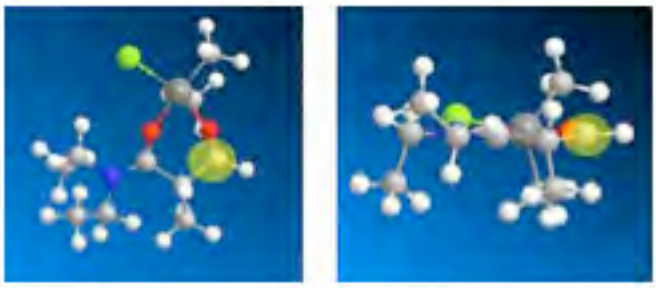
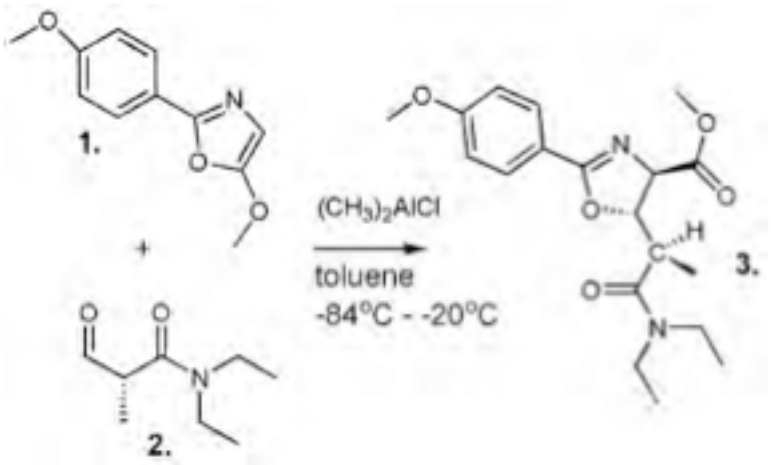


Figure 1. *Aluminum catalyst complexed to the carbonyls of the amidoaldehyde, with the spot of nucleophilic attack circled.*

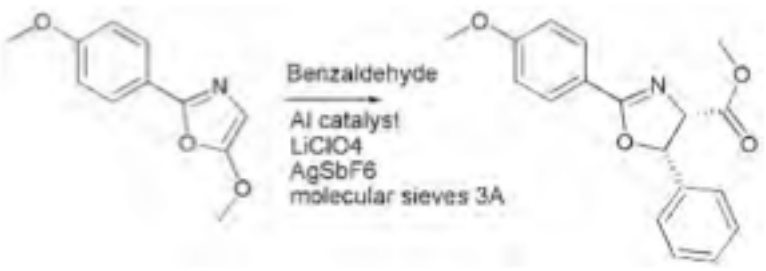


Scheme 3. *Reaction of oxazole with aldehyde.*

that will be removed later in the synthesis, and either a hydrogen or methyl group can be bonded to the carbon alpha to both carbonyls.

Synthetic Methods:
All glassware was oven dried. The 2-(4-methoxyphenyl)-5- methoxyoxazole **1** (0.218 g, 0.001 moles, 1.0 eq) was dis- solved in anhydrous toluene and the reaction flask was flushed with Ar. The mixture was cooled to -85o C, stirred for 10 minutes, and $(CH_3)_2AlCl$ (0.135 mL, 0.134 g, 0.0015 mol, 1.5 eq) was added. 2R-N,N-diethyl-2-methyl-3-oxo-propionamide (0.15 g, 0.001 mol, 1.0 eq) was added in 2 mL toluene. The reaction was stirred and warmed to room temperature over 24 hours, after which MS showed the desired product. The product was purified by silica gel chromatography in 1:1 to 3:1 ethyl acetate:hexanes. 1H NMR (300 MHz, CDCl3) δ 6.89 (d, J=6.9 Hz, 2 H), 7.89 (d, J=6.9 Hz, 2 H), 5.15 (dd, J=6.6 Hz and J=7.8 Hz, 1 H), 4.74 (d, J=6.6 Hz, 1 H), 3.63-2.99 (series of complex multiplets, 11 H), 1.9-1.1 (series of multiplets, 9 H, 3 methyl groups).

Results and Discussion:
The addition of **1** to **2** generated a single adduct as seen
by 'H NMR, demonstrating that the reaction was stereospecific. The relative stereochemistry of the two protons on the five-membered ring has not been fully elucidated, but can



Scheme 4. *Reaction of oxazole with benzaldehyde.*[1]

be predicted based on molecular modeling and a similar reaction done by Evans (**Scheme 4**).[6]

In the Evans reaction, a salen-aluminum catalyst was used to stereospecifically add benzaldehyde to the oxazole, resulting in the two protons on the five-membered ring being cis. The coupling constant for the two protons in our reaction of **1** and **2** is 6.6 Hz, while that of the two protons in the Evans reaction is 10.8 Hz. Based on the differing coupling constants, as well as modeling the interaction of **1** and **2**, we predict the stereochemistry of the two protons on the five-membered ring in our product to be trans. The results of this reaction suggest that the divalent nature of the catalyst and its ability to act as a Lewis acid are important to achieving stereospecificity.

This aluminum-catalyzed reaction results in the desired stereospecificity of the adduct, but in low yield, with the major side product being a result of interactions of the catalyst with aldehyde **2**. The methyl groups on the catalyst are fairly nucleophilic and react with the aldehyde to form 2R, 3?-N,N-diethyl-3-hydroxy-2-methylpropionamide: ^{1}H NMR (300 MHz, CDCl3) δ 4.15 (d, 1 H, J=5.1, -OH), 3.81 (complex multiplet, 1 H, proton on alcohol carbon), 3.35 (4 H, overlapping -CH_2's on nitrogen), 2.59 (doublet of quartets, 1 H, J=6.3 and J=5.1, proton alpha to carbonyl), 1.42- 1.0 (series of doublets and triplets, 12 H, 4 methyl groups). The spectrum shows a clean doublet of quartets for the proton alpha to the carbonyl, which suggests that the reaction resulted in a single diastereomer. The coupling constant of 5.1 suggests that the two protons are either 60^o or 120^o from one another, based on the Karplus relationship.[7] The favored conformation of the aldehyde will change by 180^0 between the aluminum complexed aldehyde and the uncomplexed aldehyde, leading us to predict that nucleophilic attack in these two states would lead to differing diastereomers. Molecular modeling of the products of the addition of the methyl group to the amidoaldehyde in both the catalyst con- strained conformation and the unconstrained conformation, shows that the protons will exist gauche to each other in the energy minimized (MM2) conformation in either case. In conclusion, the side product from this reaction shows stere- ospecific addition of the methyl group, but the application of coupling constants in the NMR is inadequate to allow us to determine the absolute stereoisomerism of the addition, and therefore we cannot claim with certainty the mechanism by which the methyl addition product is generated.

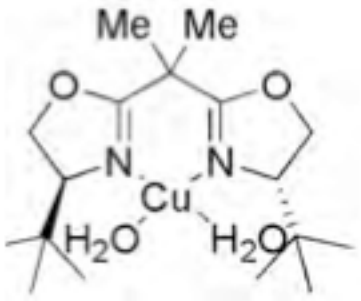


Figure 2. *Bis(oxazoline) copper(II) catalyst.*[8]

Future Directions:
An effective catalyst for this reaction must be relatively stable and show bidentate complexation to amidoaldehydes similar to **2**. A bis(oxazoline) (box) cop- per(II) catalyst (**Figure 2**) is a promising alternative to the aluminum catalyst because it has shown activation of aldehydes for stereospecific addition of nucleophiles weaker than the oxazole (**Table 1**) and it is a divalent Lewis acid.[8]

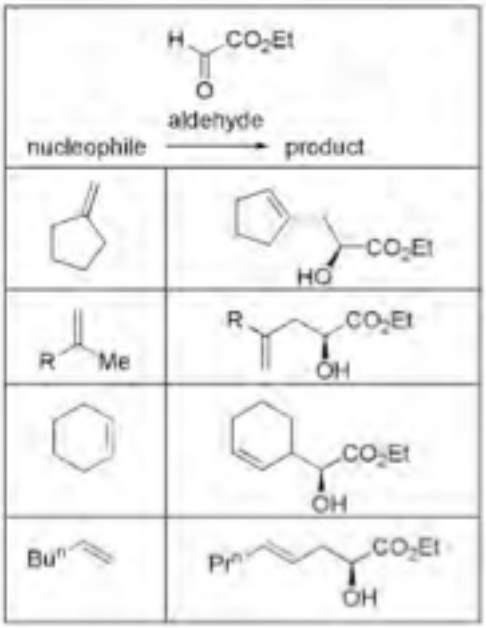


Table 1. *Nucleophiles used for addition to aldehydes activated by box catalyst.*[8]

We have synthesized a chiral box-copper catalyst that will be tested on a variety of ami-doaldehydes **2**. The chiral catalyst is predicted to be effective when used with achiral aldehyde **2A (Figure 3),** but introducing chiral catalyst may cause unintended stereointeractions. An achiral catalyst is also being synthesized, that may be effective in activating chiral amidoaldehydes **2B** such that the chirality of the aldehyde produces the desired stereoselectivity in the product, as was seen with

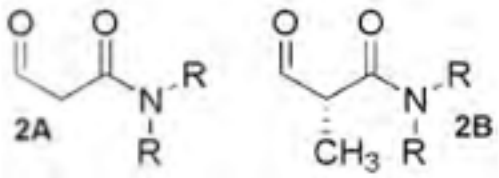


Figure 3. *Possible amidoaldehydes for addition to oxazoles activiated by box catalyst*

the aluminum catalysis. When the coupling of the aldehyde to the oxazole has been optimized, we will use this reaction to prepare a series of stereospecific α-hydroxy amino acid derivatives.

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