

Synthesis of a Family of Chiral Asymmetric Schiff Base Ligands

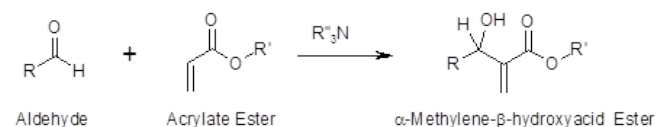
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Introduction

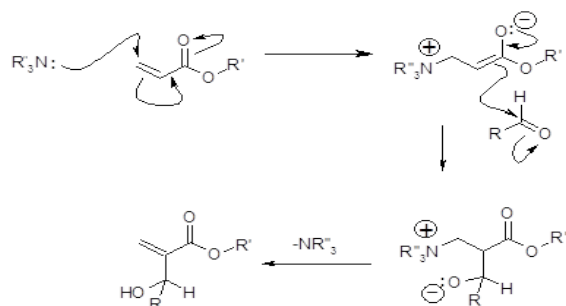
Carbon-Carbon bond-forming reactions are essential synthetic methods for organic chemists. Condensation reactions of carbonyl compounds are an important class of such reactions. Chiral organometallic compounds have been shown in some cases to act as catalysts to give condensation products in high yields and with high stereospecificity.¹ In this project we will synthesize some novel chiral ligands and test the effectiveness of metal complexes of these ligands as catalysts for condensation reactions.

The Baylis-Hillman reaction, patented in 1972, is a novel condensation of an acrylate ester and an aldehyde resulting in a β -hydroxy- α -methylene ester. This reaction is particularly interesting to synthetic chemists because the product is densely functionalized and the reaction can be stereospecific in some cases where a chiral catalyst is used. Every known example of this reaction requires a catalyst, usually a tertiary amine or phosphine. The object of this project is to prepare a set of peptide-based metal complexes and test them as chiral catalysts for the Baylis-Hillman reaction.



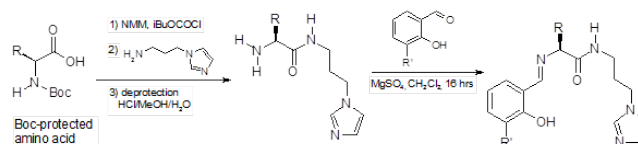
Scheme 1. The Baylis-Hillman Reaction

The overall mechanism of the Baylis-Hillman reaction is important in the context of this project because it provides the rationale for the design of our catalyst. The mechanism begins with a Michael addition by a tertiary amine on an α,β -unsaturated carbonyl. The resulting zwitterion, which serves as an activated enolate nucleophile, then attacks the carbonyl carbon of an aldehyde. After the formation of this carbon-carbon bond and a subsequent proton transfer, the catalytic amine is eliminated to reform the double bond.¹



Scheme 2. The Baylis-Hillman Mechanism. Initial Michael addition of the amine to the acrylate ester creates an enolate zwitterion that in turn attacks the aldehyde.

The goal of this research project was to synthesize potentially catalytic metal complexes of the following family of ligands based off of research of Hoveyda's group at Boston College.²



Scheme 3. Project scheme of ligand synthesis

Materials and Methods

Reagents and solvents were used without prior purification or manipulation. THF was first brought to -15°C . NMM and isobutylchloroformate were then added using slow addition. The mixture was allowed to mix for 45 minutes before the imidazole was added to the flask. The mixture was allowed to stir for a minimum of 3 hours. The mixture was then filtered through silica gel and eluted with ethyl acetate. Products were obtained by rotary vaporization and vacuum filtration.

Tests for chromatography were run using a chromatography chamber with silica test strips.³

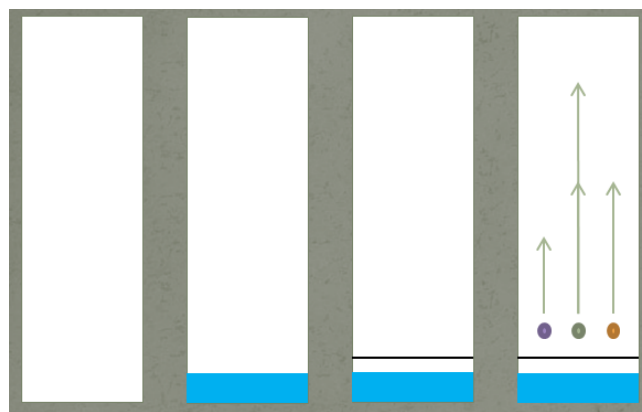


Figure 1: Outlined process for Thin-Layer Chromatography.

Solvents of 80/20, 60/40, and 50/50 hexane/ethyl acetate were used to determine the rate of movement of impurities in separation. 80/20 was determined to be used for column chromatography. A column was set up using silica gel, and the mixtures were filtered through using slow addition of eluent. Sections of solutions were captured using test tubes.

Products were once again obtained through rotary vaporization and vacuum filtration.

A 1:1 mixture of 1 M methanol and 3 M hydrochloric acid was brought to 0°C. The imidazole addition product was dissolved in the mixture and was allowed to stir for at least 3 hours. The methanol was then removed by rotary vaporization. The solution was brought back to 0°C. Sodium hydroxide was slowly added until the pH of the mixture reached 12. The product was extracted with methylene chloride and dried with potassium carbonate before rotary vaporization.

Results and Conclusion

After the addition of imidazole to the BOC-protected amino acid, oil was formed instead of the intended solid. Several trials were then performed leading to the following results:

Trial	Variable	Result
1	N/A	Oil
2	K ₂ CO ₃ Catalyst	Oil
3	Cu(NO ₃) ₂ Catalyst	N/A
4	Ether Solvent	Oil

For trial three, no product came out of solution after rotary vaporization. After the first trial resulted in oil, chromatography was performed on the first product. This yielded in sections of separations of solutions. Interestingly, the separations fluoresced under UV light, something not before catalogued in terms of chromatography. This led to the belief that clear separation had occurred, leading to rotary vaporization of the separate substances.

However, characterization of the separation yielded inconclusive spectra. Thus, the BOC deprotection step was proceeded on the product from trial two. Deprotection yielded spectra that plausibly matched chemical shifts for the intended molecule, even though the product remained an oil.

The initial target reaction was not straight out of literature but was rather inspired by work done by Hoveyda's group. Thus, the target compound, under the same conditions as those laid out by Hoveyda, may not be a direct possibility. This could be proved by the results of the first and third trials. However, after BOC deprotection of the second product, spectroscopy shows a possibility of the synthesis being a success. Thus, future work on this project is to attempt the BOC deprotection step on the fourth

product and then possibly continue the synthesis on the those two products. If the synthesis can be completed, then metal complexing can be attempted on the product. The main target of this complexing will be to examine the complexes as catalysts in the Baylis-Hillman reaction.

References

1. Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. J. Am. Chem. Soc., 2001, 123, 11594-11599.
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