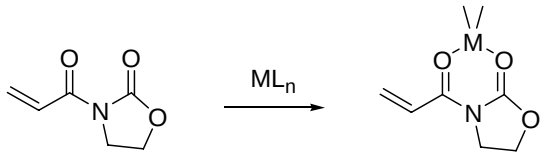
Asymmetric bis-Boron Compounds as Enantioselective Catalysts

Background

Therapeutic compounds for the treatment of disease are becoming increasingly complex as targeted processes (e.g. neural, metabolic) and structures (e.g. receptors) become more selective. Such selectivity is aimed at increasing therapeutic efficacy while simultaneously reducing side effects. To meet such requirements, the ability to synthesize such compounds must correspondingly increase. Carbon-based therapeutic compounds like Merck's protease inhibitor Indinivar[1] present especially challenging synthesis requirements because of their multiple chiral centers. These drugs must be enantiopure because other stereoisomers will not have the same pharmacological activity and one or more forms may cause significant side effects or toxicity risks. However, extra steps and materials required for making a single form (or "enantiomer") result in increased production costs. In the case of Indinivar, the high cost of production has even prompted foreign governments to threaten Merck with patent denials. Clearly, new, more efficient methods of synthesizing a single enantiomer of a given compound will result in reduced costs for patients and reduced side effects.

One promising approach to synthesizing non-racemic therapeutic compounds is through utilization of chiral Lewis acids.[2] Herein, we propose a novel chiral Lewis acid methodology based on amino acids which would comprise a vital subset of asymmetric catalysis.

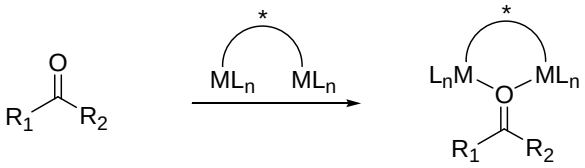
Though catalysts with chiral Lewis acids have been developed, these catalysts have notable drawbacks and limitations. One strategy involves a chiral Lewis acid binding to one of the electron lone pairs on a carbonyl functional group as well as to a lone pair on a nearby functional group (Scheme 1).[3]



Scheme 1. *Standard chiral Lewis acid design*

The resulting chelate structure is fixed in a rigid cyclic geometry, a general requirement for enantioselectivity,[4] and activated as an electrophile. This method is severely limited because the second electron donor is necessary to organize the substrate structure for enantiospecific reaction. Without the second donor, the catalysts are ineffective.

We seek to eliminate the limitation inherent in the previous asymmetric Lewis acids through an alternative approach: a *bis*-Lewis acid would be synthesized so that both of the electron lone pairs on the carbonyl oxygen would bind the catalyst to form a rigid chelate structure (Scheme 2).

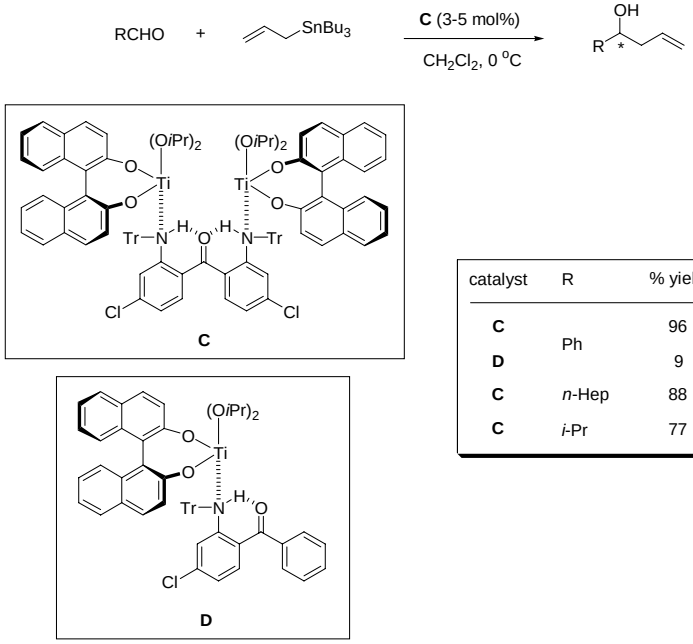


Scheme 2. *Proposed* bis-*Lewis acid catalyst*

This would eliminate the drawbacks faced in the previous system. Through the use of carefully selected ligands (particularly those with C_2 symmetry), the activated structure would be desymmetrized. Importantly, no target molecule feature other than the carbonyl group is required to produce an organized activated species.

Shriver and Biallas demonstrated in 1967 that a base has a stronger affinity towards a *bis*-Lewis acid than a *mono*-Lewis acid.[5] Further study by Maruoka supports that his *bis*-Lewis acid catalyst produces superior yield than the corresponding *mono*-acid.[6] He demonstrated that his

titanium bis-Lewis acid can catalyze allylation of a variety of aldehydes by allyltributyltin in good yields and with excellent ee's (Scheme 3).[7]



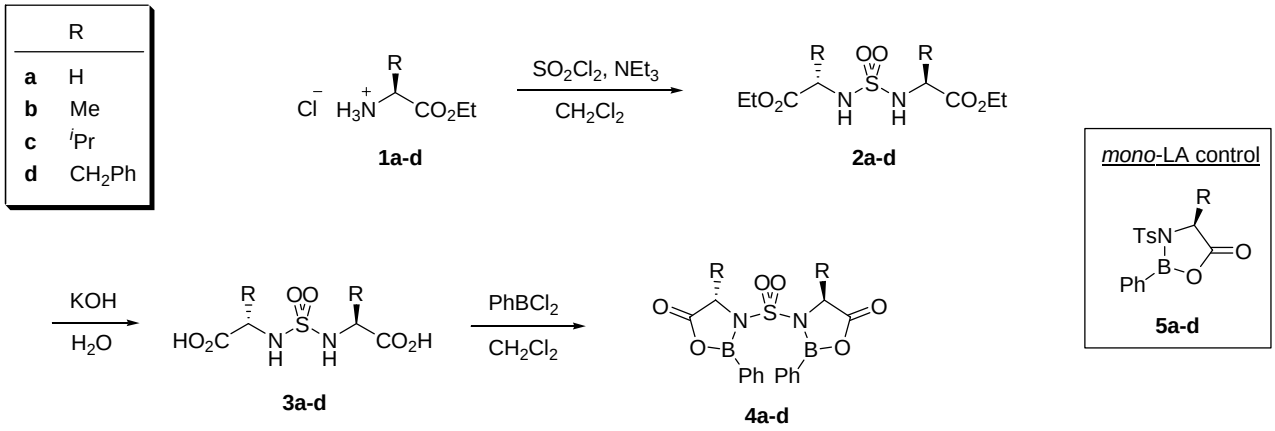
catalyst	R	% yield	% ee
C	Ph	96	98
D		9	90
C	*n*-Hep	88	99
C	*i*-Pr	77	99

Scheme 3. *Maruoka's proposed asymmetric* bis-*Lewis acid catalyst*

This yield enhancement suggests that the bidentate complex is formed *in situ* and that this adduct activates the carbonyl more strongly than a monodentate complex. Although the results show great potential for asymmetric bidentate Lewis acid catalysts, no direct information was reported concerning the structure of the proposed activated carbonyl complex. This presents an opportunity for catalytic development in asymmetric synthesis.

Research Plan

The first phase of this project will focus on the synthesis of *bis*-Boron catalysts **4a-d** (Scheme 4).



Scheme 4. *Proposed* bis-*Lewis acid design*

A selected amino acid **1** is obtained as the ethyl ester hydrochloride salt. Coupling with sulfuryl chloride produces **2**. Subsequent ester hydrolysis yields the *bis*-carboxylic acid **3**, and reaction with two equivalents of dichlorophenylborane can provide *bis*-Lewis acid **4**. With compound **4** in hand, adducts will be formed with dimethylformamide and crotonaldehyde. Infrared as well as ^{1}H and ^{13}C NMR analysis will be carried out to determine if bidentate interactions occur and to what extent they occur.[8] Although equilibrium typically exists between mono- and bidentate adducts,[9] it is anticipated that the bidentate structure will predominate due to the favorable six-membered ring formation. *Mono*-Boron catalysts **5a-d** will be prepared[10] as controls to compare with the *bis*-Lewis acids.

If possible, crystal structures will be obtained of the carbonyl adducts. X-ray crystallography can be used to verify the conclusions drawn from NMR spectra. If sufficient proof is collected of the bidentate binding ability of catalyst **4**, it will be used in comparison with the *mono*-boron catalyst **5** in a number of reactions. Some reactions that we propose to explore are the Diels-Alder reaction, aldehyde allylation, and ketone reduction. Increased reaction rates and yields for the *bis*-boron system will further indicate that the bidentate intermediate structure

is at work. Future experiments will involve a systematic study to determine the asymmetric synthetic utility of this class of catalyst.

Conclusion

The ultimate goal of this project is to synthesize a bidentate Lewis acid that will result in asymmetric selective synthesis. The chiral *bis*-boron Lewis acid catalysts are expected to serve as bidentate ligands that will bond with carbonyl substrates to activate the carbonyl and provide asymmetric induction. Great specificity comes from cheap, readily accessible starting materials with great potential for structural modification. Success in this project will provide a new powerful tool for asymmetric organic synthesis and the potential to outperform current *mono*-

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