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Asymmetric Bisboranes as Bidentate Catalysts for Carbonyl Substrates

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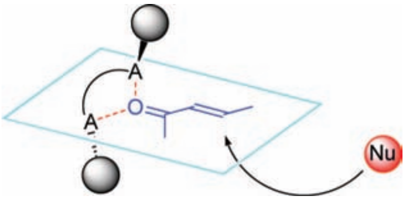
ABSTRACT



A new class of C_2 symmetric bisoxazaborolidinone compounds is described which exhibits bidentate binding to carbonyl substrates. Using the Diels−Alder reaction as a model system, the catalytic activity of these bis-Lewis acids is probed. Reaction rates and selectivities are observed that are higher than the corresponding mono-Lewis acids. This novel system offers a potentially powerful new approach to asymmetric Lewis acid catalysis.

Bimetallic catalysts have received considerable attention in recent years.[1] Drawing inspiration from bimetallic enzymes,[2] these catalysts incorporate two metal atoms positioned to act cooperatively on substrate molecules. Bimetallic catalysts are grouped in two major subsets: (i) bifunctional compounds that activate both the electrophile and nucleophile of a reaction[3] and (ii) bis-Lewis acids (BLA) that strongly activate electrophiles through cooperative binding.[4,5] Although considerable progress has been made in the former category, examples of the latter are less common,[4] and asymmetric examples of BLA catalysts remain rare.[5]

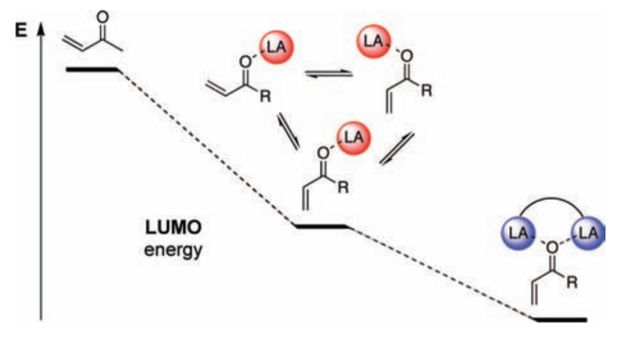


Figure 1. Bidentate interaction achieves greater organization than monodentate and lowers substrate LUMO to a greater extent.

Asymmetric Lewis acid catalysts are commonly employed to activate carbonyl substrates such as aldehydes, ketones, and esters by binding one of the carbonyl oxygen's lone pair electrons while creating a chiral microenvironment for the substrate. Since, in most cases, the carbonyl oxygen has two nonequivalent lone pair electrons, preorganization of the

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(3) (a) Matsunaga, S.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60–75. (b) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583.

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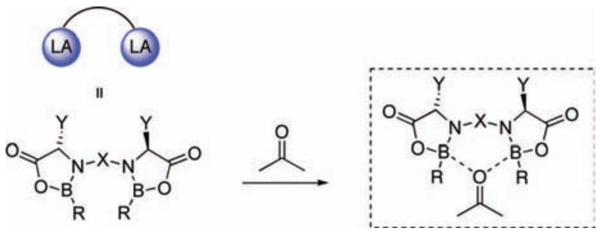
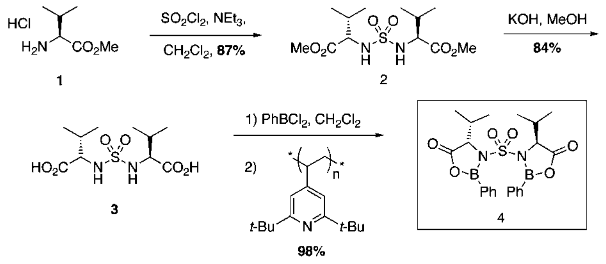


Figure 2. Modular bisoxazaborolidinone design.

catalyst and substrate often requires the use of modified substrates that incorporate auxiliaries to chelate the Lewis acid (i.e., oxazolidinones)[6] or secondary interactions as proposed in oxazaborolidinone catalysts.[7] Both strategies can add steps to a reaction sequence and/or limit substrate scope. An approach that does not rely on these constraints could offer a more general method for controlling product stereochemistry even for the most challenging substrates such as internal carbonyl groups.[8]

Scheme 1. Synthesis of Bisoxazaborolidinone **4**



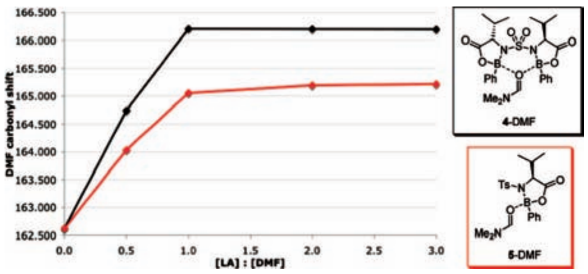


Figure 3. Plot of DMF carbonyl carbon ^{13}C NMR shift vs relative Lewis acid concentration.

The chelation of both carbonyl lone pair electrons with a BLA offers a potential solution to this challenge. Simultaneous coordination enforces the s-*trans* conformation, and it has been proposed that BLA coordination of carbonyl compounds results in enhanced activation compared to mono-Lewis acids (Figure 1).[9,10] Support for this has come from computational[9] and experimental studies.[10] We describe a new family of asymmetric BLAs prepared from readily available starting materials. The molecules are designed to bind carbonyl substrates by simultaneous binding to both electron lone pairs. The bisoxazaborolidinone design positions two Lewis acidic boron atoms to form a six-membered ring chelate with carbonyl substrates (Figure 2). Asymmetry is derived from α-amino acids and is transmitted to the boron atoms upon complexation to a carbonyl substrate. The Lewis acidity of the structure can be fine-tuned by choice of the tether “X” and boron substituent “R”. The steric environment can be optimized by choice of substituents “Y” and “R”.

The L-valine derivative **4** incorporating a sulfone one-atom linker and phenyl substituent on boron is a representative of this catalyst family. Its synthesis is illustrated in Scheme 1. Condensation of 2 equiv of L-valine methyl ester **1** with sulfuryl chloride gave diester **2**. Alkaline hydrolysis afforded diacid **3**. Two equivalents of phenyldichloroborane followed by treatment with polymer-bound hindered base furnished bisoxazaborolidinone **4** in nearly quantitative yield.

The coordination behavior of BLA **4** with carbonyl substrates was studied by NMR spectroscopy. Monooxazaborolidinone **5** was used[11] for comparison. Following a modified form of Maruoka’s procedure,[4a] the carbonyl carbon of dimethylformamide (DMF) was monitored by ^{13}C NMR in the presence of varying amounts of each Lewis acid. The data (Figure 3) show a steady downfield shift of the carbonyl signal that plateaus at 1:1 equivalency in both cases. Additional Lewis acid had no further effect on the carbonyl shift. Importantly, there was a larger downfield shift for bisoxazaborolidinone **4** compared to monooxazaborolidinone **5**, supporting a bidentate mode of binding for the former.

With evidence of bidentate binding by BLA **4**, a computational study was performed to determine the preferred binding configuration. There are four possible bidentate binding geometries for a C_2-symmetric BLA with a carbonyl substrate, two *anti* modes and two *syn* modes (Figure 4a). Formaldehyde was chosen as a carbonyl donor to simplify the system by merging both *syn* modes. The *antiexo*, *antiendo*, and *syn* conformations of the **4**−formaldehyde complex were modeled and the ground-state energies deter-

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(6) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

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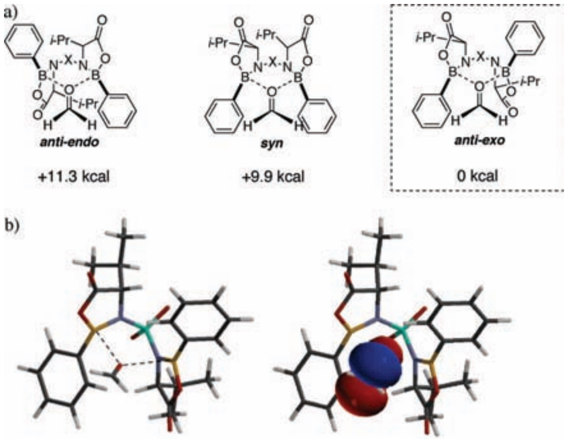
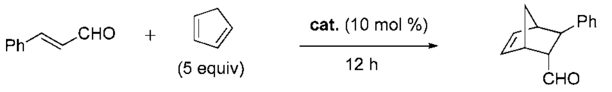


Figure 4. (a) Computed bidentate adducts **4**/CH_2O at the B3LYP 6-31g* level of theory. (b) Lowest-energy conformer (*antiexo*) shown in 3-D without and with LUMO.

mined at the B3LYP 6-31g* level of theory.[12] Of the three, the *antiexo* mode, was found to have the most stable conformation by 9.9 kcal/mol. Further analysis revealed the lowest (most electrophilic) LUMO is associated with this *antiexo* isomer (Figure 4b) and that the orbital is localized on the carbonyl π* orbital. Taken together, the computational data indicate that the *antiexo* adduct is the most stable isomer and imparts the strongest activation of a carbonyl substrate.

Table 1. Optimization of Diels−Alder Reaction Conditions



entry	cat.	solvent	emp.	yield[a]	*endo*:*exo*	ee[b]
1	**4**	CH_2Cl_2	−78 °C	11%	94:6	73%
2	**4**	CH_2Cl_2	−34 °C	54%	85:15	31%
3	**4**	CH_2Cl_2	0 °C	91%	83:17	13%
4	**4**	Et_2O	−78 °C	32%	92:8	33%
5	**4**	toluene	−78 °C	96%	95:5	76%
6	**5**	toluene	−78 °C	21%	91:9	31%

[a] Yields were determined by ^1H NMR using naphthalene asan internal standard. [b] ee's determined by $NaBH_4$ reduction of aldehyde products to the corresponding alcohol and analysis by chiral HPLC.

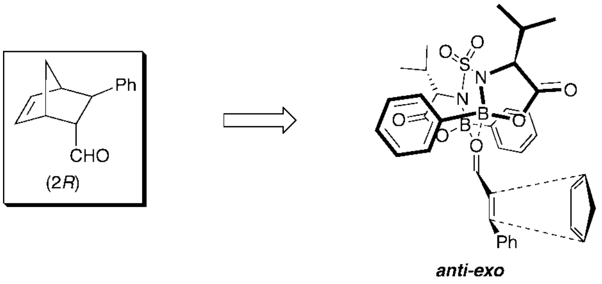


Figure 5. Proposed transition state model to explain enantioselectivity for the Diels−Alder reaction of cinnamaldehyde and cyclopentadiene catalyzed by BLA **4**. The model incorporates the *antiexo* structure.

The catalytic activity of BLA **4** was evaluated for the Diels−Alder cycloaddition of cinnamaldehyde and cyclopentadiene (Table 1). This choice was influenced in part by the absence of thermal reaction under the conditions studied.[13] At −78 °C in methylene chloride, 10 mol % of BLA **4** resulted in 11% conversion, indicating the absence of turnover. Increasing the temperature to −34 or 0 °C led to the onset of turnover (up to 91% yield) but at the expense of both *endo*:*exo* selectivity and ee (down to 83:17 and 13%, respectively). Returning to low temperature, the use of ether as solvent increased the yield somewhat but with lowered selectivity. In toluene, BLA **4** provided high conversion and moderate ee. In contrast, under these optimized conditions, monoborane **5** resulted in only 21% conversion and poor selectivity.

In all cases, the *endo* cycloadduct predominated, and one enantiomer was formed in excess. The absolute configuration of this enantiomer was established to be *endo*-2R by comparison with a known enantioenriched sample.[14] Importantly, the *endo*-2R enantiomer would be expected to arise from the *antiexo* binding mode between catalyst and substrate, as shown in Figure 5. In the proposed interaction, the boronic phenyl ring positioned above the substrate alkyl group blocks the Si-face of the dienophile, allowing approach of the diene only from the Re-face. This finding lends further support to the *antiexo* bidentate binding mode proposed previously.

These studies provide the first example of a new class of bisoxazaborolidinone catalyst. Computational and experimental results have shown that these BLAs, represented by **4**, form bidentate complexes with carbonyl substrates and that a single isomeric catalyst−substrate complex is strongly favored. The catalyst displays greater activity than the corresponding mono-Lewis acid and leads to products with predictable stereochemistry. It works as designed.

Current efforts are focused on modifying the catalyst structure and optimizing its performance as well as expanding the substrate scope. Further results will be presented in due course.

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Supporting Information Available: Experimental procedures, computational data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for all complete computational data.

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