Communication

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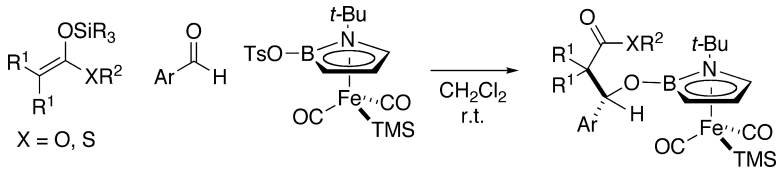

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Synthesis, Resolution, and Aldol Reactions of a Planar-Chiral Lewis Acid Complex

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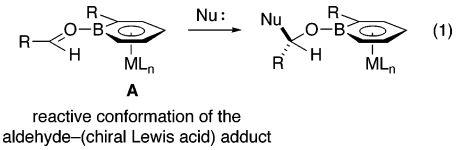
Chiral Lewis acids serve as useful catalysts for a wide variety of powerful transformations, particularly addition reactions to aldehydes.[2,3] Several years ago, we outlined a new approach to the design of a chiral Lewis acid, the distinguishing feature of which was a π interaction between the Lewis acid and the carbonyl group (Figure 1). Since maximizing this overlap should enhance the electrophilicity of the aldehyde, this interaction could define the most reactive conformation of the Lewis acid−aldehyde complex.[4] Because this design does not require a second functional group on the substrate in order to achieve conformational control of the complex,[5−7] we anticipated that this approach might furnish an unusually versatile catalyst.

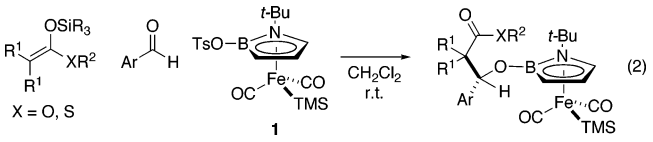
We speculated that a planar-chiral boron heterocycle (e.g., see **A** in eq 1) might serve as a suitable framework for this π-activation strategy, with the aromatic system of the boracycle functioning as the π acceptor. Consideration of steric interactions leads to the



(1)

prediction that the depicted conformation should be favored for nucleophilic addition reactions, which would therefore generate the illustrated stereoisomer (eq 1; Nu adds opposite to the face blocked by ML$_n$).[8,9]

In an earlier study, we described crystallographic and spectroscopic evidence for the suggested π overlap in the case of an electron-rich aldehyde and an (η^6-borabenzene)Cr(CO)$_3$ moiety.[4a] Although this initial investigation provided proof-of-principle for a critical aspect of our design, we were not able to achieve addition reactions with this system. We therefore turned our attention to other frameworks, including (η^5-1,2-azaborolyl)iron derivatives. In this Communication, we report the generation of an enantiopure (η^5-1,2-azaborolyl)iron adduct,[10] and we establish that it promotes highly stereoselective aldol reactions in which the sense of asymmetric induction is that predicted by our design (eq 2 versus eq 1).



(2)

The synthesis of our target complex (**1**) began with previously described (η^5-1,2-azaborolyl)iron adduct **2** (Figure 2).[10c] Selective reduction of the Fe−I bond with sodium amalgam, followed by quenching with TMSCl, furnishes chloroborane **3**. Hydrolysis of the B−Cl bond generates **4**, the enantiomers of which can be separated by preparative chiral HPLC.[11] The hydroxy group is then converted into a better leaving group by sequential reaction with oxalyl chloride and AgOTs,[12] thereby producing the desired enantiopure Lewis acid, (+)-**1**.

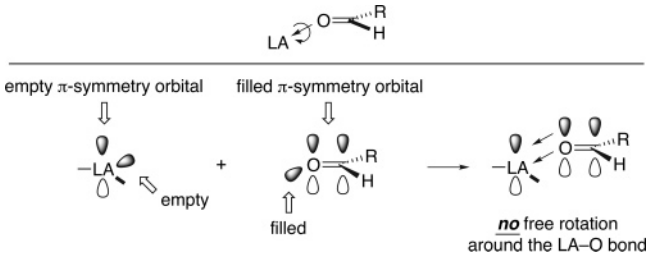


Figure 1. (top) The challenge: Controlling the conformational preference of a Lewis acid−aldehyde complex. (bottom) A possible solution: A Lewis acid that can accept electron density from a σ *and* a π orbital of the aldehyde.

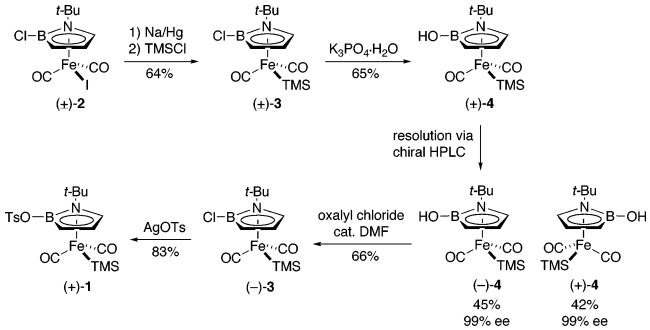
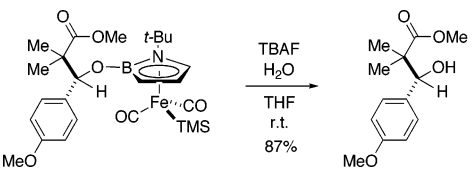


Figure 2. Synthesis of an enantiopure planar-chiral Lewis acid.

We next turned our attention to the application of azaborolyl complex **1** in a stereoselective process, specifically the Mukaiyama aldol reaction.[13] We were pleased to establish that, in the presence of **1**, silyl ketene acetals react with aldehydes to generate the desired aldol product with excellent stereoselectivity (Table 1, entries 1−3).[14] Somewhat lower selectivity is observed when a less sterically demanding nucleophile derived from a thioester is employed (entry 4).[15] To date, attempts to achieve turnover have not been successful, presumably due to the stability of the B−O bond of the aldol product.

We have established that the sense of stereoselection is as predicted by the general model illustrated (for a borabenzene complex) in eq 1. Thus, for the boron aldolate product of entry 1 of Table 1, hydrolysis of the B−O bond leads to the formation of a β-hydroxyester of known absolute configuration (eq 3).[16] For the



(3)

aldol adducts of the reactions depicted in entries 3 and 4, X-ray crystallographic analysis confirms that the relative stereochemistry is as anticipated (Figure 3).

Our current working hypothesis is that these aldol reactions proceed through the pathway illustrated in Figure 4. For the addition depicted in entry 4 of Table 1, we have determined that the rate

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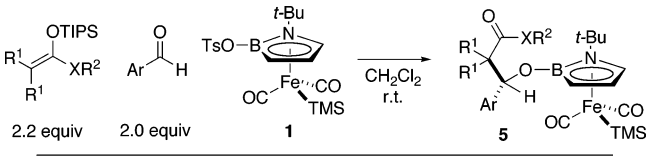
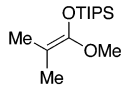
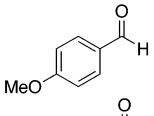
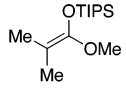
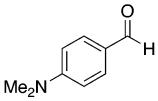
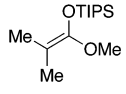
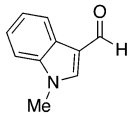
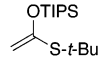
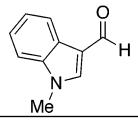
Table 1. Stereoselective Aldol Reactions in the Presence of Planar-Chiral Lewis Acid **1**



2.2 equiv 2.0 equiv **1** **5**

entry	nucleophile	aldehyde	yield of **5** (%)[a]	de of **5** (%)[b]
1			74	>95 (96)
2			70	>95 (99)
3			85[c]	>95
4			72[c,d]	74

[a] Isolated yield of the major diastereomer. [b] Determined by ^{1}H NMR. The value in parentheses is the ee determined after hydrolysis of the B–O bond. [c] Racemic **1** was used. [d] Acetonitrile was employed as the solvent. TIPS = triisopropylsilyl.

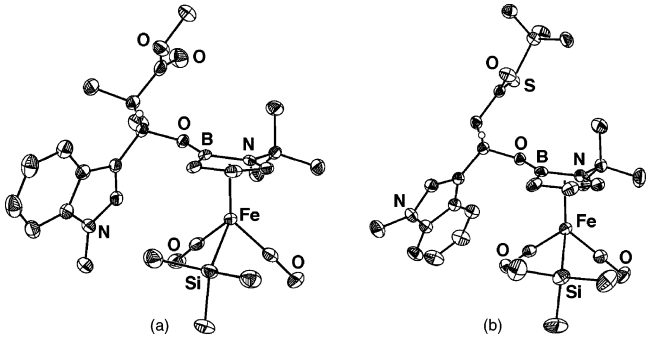


Figure 3. ORTEP illustrations, with thermal ellipsoids drawn at the 35% probability level, of two products from Table 1: (a) entry 3 and (b) entry 4.

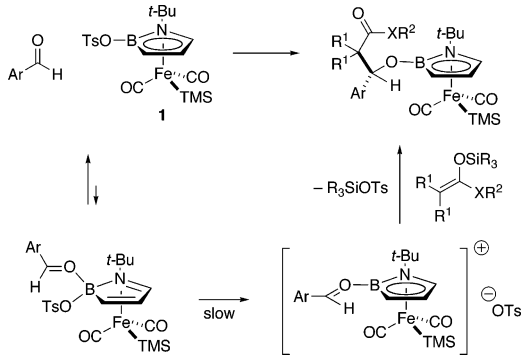


Figure 4. Possible mechanism for aldol reactions in the presence of Lewis acid **1**.

law is first-order in the aldehyde, first-order in **1**, and zero-order in the nucleophile. Furthermore, the rate is higher in solvents with higher dielectric constants (CH_3CN > CH_2Cl_2 > THF, benzene), consistent with greater charge separation in the transition state than in the ground state. Finally, the addition of $[Bu_4N]OTs$ leads to a slower reaction.[17] All of these observations are accommodated by the proposed mechanism (Figure 4).

In summary, we have presented evidence that a new chiral Lewis acid design, based on a π interaction with the substrate that simultaneously provides activation and organization, can furnish high stereoselectivity in addition reactions to aldehydes. Current efforts are directed at second-generation designs that will lead to catalyst turnover.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Notes: (a) We were not able to resolve (±)-**3** by preparative chiral HPLC. (b) The absolute configuration of (−)-**4** was determined by X-ray crystallography (for details, see the Supporting Information).
(12) For a related example of halide abstraction by a silver salt, see ref 10c.
(13) For a review, see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 29.1.
(14) If the aldehyde is not electron-rich, the aldol reaction is either slow or does not proceed at all, presumably due to difficulty in displacing the tosylate group from **1** (for our proposed mechanism for these aldol reactions, see Figure 4).
(15) This reaction also proceeds in CH_2Cl_2, but with somewhat lower stereoselectivity.
(16) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403–5404.
(17) Other observations: (a) When we monitor an aldol reaction by ^{1}H NMR, we do not detect the build-up of any intermediates. (b) In the absence of any one of the three reaction components, there is no detectable reaction/interaction between the other two species.

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