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Chiral Lewis Acids Derived from 1,8-Naphthalenediylbis(dichloroborane)

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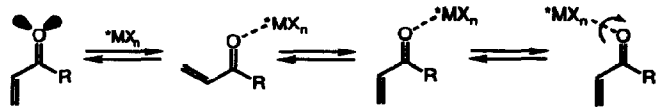
Abstract: Chiral Lewis acids derived from 1,8-Naphthalenediylbis(dichloroborane), a novel bidentate Lewis acid, have been found to be active catalysts for the asymmetric Diels-Alder reaction. Utilizing chiral ligands derived from amino acids and diols, a range of enantioselectivities have been achieved with cyclopentadiene and various α,β-unsaturated aldehydes.

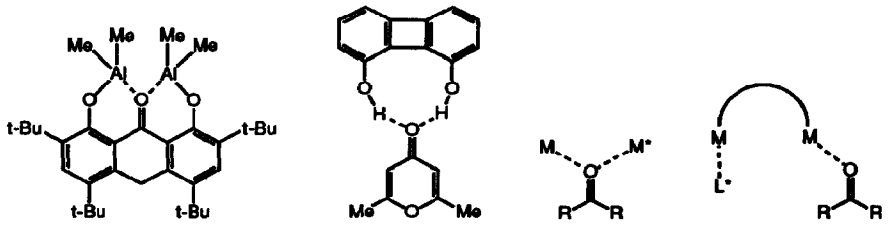
Lewis acid complexation to carbonyl compounds is known to have a dramatic effect on reactivity and selectivity in a variety of reactions.[1] One recent development has been in the area of asymmetric catalysis by chiral Lewis acids.[2] There are two major variables that influence highly selective Lewis acid catalyzed reactions such as the Diels-Alder reaction. The first is the strength of the Lewis acid, which must match the specific functional group and the reaction at hand, and the second is the highly ordered transition state assembly. While the strength of the Lewis acid can be controlled through the proper choice of chiral ligand, the conformation and the transition state assembly often can not be controlled predictably with current monodentate Lewis acids. The application of chiral bimetallic Lewis acids to the asymmetric Diels-Alder reaction promises to offer excellent control over both of these aspects.

As part of the development of chiral Lewis acids, Lewis acid-carbonyl group interactions have been under continued investigation. Equation 1 illustrates some of the parameters which need to be addressed. For example, in a conjugated enone-Lewis acid complex, there are two nonbonded lone pair Lewis basic sites available for coordination to Lewis acids. Solution NMR studies have shown that chelation to one of the nonbonded lone pairs of electrons by a Lewis acid affects the molecule distinctly differently than if the Lewis acid is chelated to the other nonbonded electron pair.[3] Rotomers around the coordination site can also affect the reactivity and selectivity of the reaction depending on the ligands around the Lewis acid. The conformation of the dienophile (*s-cis*, *s-trans*) is another factor which must be addressed. Simultaneous coordination of a carbonyl group by two Lewis acidic metal centers is a potential way to increase the organizational role played by the Lewis acid as well as doubly activate the substrate.[4,5] In a recent investigation, Wuest has shown that in an intramolecular case, where the carbonyl group was tethered by two aluminum Lewis acids, both Lewis acids coordinated simultaneously and symmetrically to the central ketone (Structure 1, Figure).[6,7] Hine has reported that the two hydroxyl groups of biphenylenediol can simultaneously hydrogen bond to a carbonyl group (Structure 2).[8] Kelly has also shown that biphenylenediol promotes Diels-Alder reactions.[9] Our investigation into this area focuses on the perceived ability of a bimetallic chiral Lewis acid to simultaneously coordinate to a carbonyl group (Structure 3) or play an organizational role in coordinating a chiral ligand and a carbonyl group (Structure 4) with each Lewis acidic metal center. This behavior should lessen the degree of conformational ambiguity found in the Diels-Alder transition state and eventually lead to the development of highly efficient asymmetric catalysts for this important transformation.



(1)

Figure

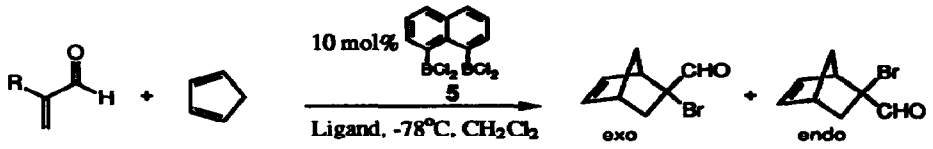


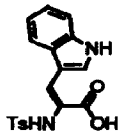
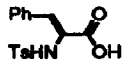
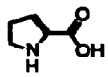
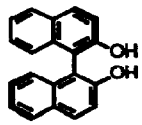
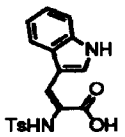
1 2 3 4

Our initial investigation consisted of screening ligands and dienophiles in the Diels-Alder reaction catalyzed by chiral Lewis acids derived from 1,8-naphthalenediylbis(dichloroborane), (5).[10] The following procedures were typical: The catalysts were prepared by adding a solution of the Lewis acid (5) in dichloromethane to a solution of the chiral ligand in dichloromethane at room temperature. The mixture was allowed to stir for 30 minutes and the solvent and HCl were removed under vacuum to give an oily solid which was used without further manipulations. To a solution of the above catalyst in dichloromethane at -78°C was added the dienophile dropwise followed by cyclopentadiene. The solution was stirred for several hours at this temperature and after the usual work-up procedures, afforded the desired Diels-Alder adducts. Table I summarizes the results obtained with various ligands in our screening with α-bromoacrolein as the dienophile and cyclopentadiene. In all cases, the catalysts were active as indicated by the reaction temperatures, time, and yields. Of the three amino acids we have screened, N-toluenesulfonylated tryptophan gave the highest enantiomeric excess of the exo-adduct (entries 1-3) and of the two diols, R(+)-binaphthol gave 36% and 28% ee (entries 5 and 6) while R,R-hydrobenzoin gave a disappointing 0% ee (entry 4). It is interesting to note that when an equimolar amount of binaphthol to bidentate Lewis acid was utilized, 36% ee was obtained for (+)-enantiomer while the use of two equivalents of binaphthol to Lewis acid produces the complimentary (-)-enantiomer with an ee of 28%. *The potential therefore exists to select the desired enantiomer by controlling the equivalence of the same binaphthol ligand.*

We have screened further the tryptophan-derived ligand with methacrolein and acrolein dienophiles and have noted some interesting outcomes (entries7-11). In the case of methacrolein, with one or two equivalents of ligand to Lewis acid, low ee's were observed for the exo-isomers. However, only one enantiomer was observed for the endo isomer (entries 7 and 8). Also, the exo-endo ratio was not as high as expected from the literature precedent. This Lewis acid, in conjunction with methacrolein at least, tends to be more selective for the endo-isomer as indicated by the high enantioselectivity for the endo-isomer and low enantioselectivity for the exo-isomer. The selectivity for the endo isomer in the reaction of acrolein with cyclopentadiene was high and gave moderate enantiomeric excess (entries 9 and 10). Addition of 4Å molecular sieves was detrimental to the enantioselectivity (entry 11).

Table . Diels-Alder Reactions Catalyzed by Chiral Ligand-5 complex.



Entry	R	Equivalents[a]	Ligand	exo:endo[b]	%ee exo:endo[c]	yield(%)[d]
1	Br	1.0		92:8	44: -	84
2	Br	2.0		89:11	8: -	83
3	Br	2.0		88:12	0: -	98
4	Br	2.0		80:20	0: -	83
5	Br	1.0		86:14	36(+): -	81
6	Br	2.0		80:20	28(-): -	81
7	CH_3	1.0		63:37	20:100	46
8	CH_3	2.0		68:32	24:100	50
9	H	1.0		6:94	- : 62	53
10	H	2.0		8:92	- : 50	60
11	H	1.0	+4Å MS	6:94	- : 0	68

a. Equivalents of Ligand to 5. b. The ratios were obtained by integration of the aldehyde ^1H NMR resonance.
c. ee's were determined by (+)-Eu(hfc)$_3$ shift reagent. d. isolated yields of Diels-Alder adducts.

The structure of the substrate-catalyst complex and its mode of coordination are not known at the present time. There is some evidence that **5** can simultaneously coordinate through both metal centers to strongly Lewis basic carbonyl groups; however, it is not known whether this mode of coordination plays an important role in the present case.[11] Optimization of the present catalytic system to the Diels-Alder reaction and attempts to elucidate the actual solution structure of the active catalyst are currently in progress.

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