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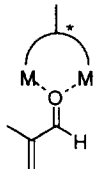
Complexes Containing a Lewis Acid and Brønsted Acid for the Catalytic Asymmetric Diels-Alder Reaction

Varinder K. Aggarwal,[a]* Emma Anderson,[a] Robert Giles,[b] Anne Zaparucha.[a]

[a]Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK.
[b]SmithKline Beecham, Old Powder Mills, Tonbridge, Kent TN11 9AN, UK.

Abstract: Complexes containing a Lewis acid and a Brønsted acid have been prepared by the reaction of an amino alcohol and a trihaloborane. The structures of the complexes were determined by ^{11}B, ^{1}H, and ^{13}C analysis and shown to be the acyclic structures **5** rather than the possible cyclic structures **6** which only contain the single Lewis acid. A variety of amino alcohols were combined with BBr_3 and BCl_3 and tested in Diels Alder reactions between methacrolein and cyclopentadiene. Whilst very high exo selectivity was observed, enantioselectivity was variable depending on the amino alcohol used. Prolinol **4** gave the highest ee (97%) but quinidine gave the highest ee (64%) for a naturally occurring amino alcohol.

The use of chiral Lewis acids for the asymmetric catalysis of Diels-Alder reactions is well established.[1-4] However, high selectivity is only obtained in those systems in which there is little conformational freedom in the Lewis acid-dienophile complex and this is commonly achieved through either bidentate chelation of the ligand to the metal[5-11] or through bidentate chelation of the dienophile to the Lewis acid complex[12] or both.[13-16] As an extension of this strategy we considered the possibility of a single carbonyl group complexing to *two* Lewis acids as in **1** and thereby restricting the conformational freedom of the Lewis acid-dienophile complex. Whilst double activation of a carbonyl group by two metals is very rare,[17-22] examples of carbonyl groups forming two hydrogen bonds to Brønsted acids are much more common.[23-26] We therefore considered the possibility of developing systems bearing one Lewis acid and one Brønsted acid to potentially activate a dienophile for Diels-Alder reactions. The recent finding that for Diels-Alder reactions activated through hydrogen bonding, the strength of the hydrogen bond in the transition state is ~1-2 kcalmol^{-1} stronger compared to the ground state hydrogen bond[27-29] suggested that even if the second mode of activation of the dienophile-metal complex by hydrogen bonding was not observed in the ground state it may still take place during the course of the reaction. Yamamoto has recently described a catalyst for Diels-Alder reactions bearing both one Lewis and one Brønsted acid and obtained very high enantioselectivities.[30]



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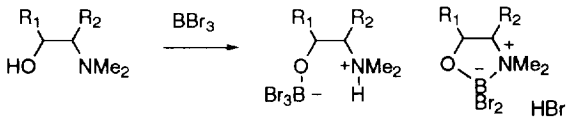
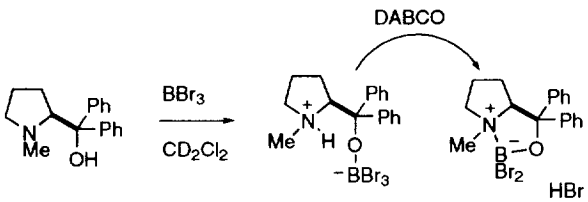
Careful juxtaposition of the Lewis and Brønsted acids is essential to ensure the possibility of chelation of both groups to a single carbonyl group and should be ideally 1,4 or 1,5 related but in any case not more than 1,6 related . We considered the possibility of simply combining a haloborane with a chiral amino alcohol and hoped that complex **2** rather than complex **3** would be formed. Complex **2** retains the Lewis acidity at boron due to the labile bromide groups, possesses a Brønsted acid and the two acid groups are 1,6 related. Complexes analogous to **2** have been reported (specifically the Lewis acid derived from prolinol **4** and BBr_3) and used to catalyse the Diels-Alder reaction. Good enantioselectivity was obtained and it was suggested that the structure of the complex was **5** but without proof.[31] In this paper we provide evidence for the structure of **5** and further examples of amino alcohol-haloborane complexes for the asymmetric catalysis of Diels-Alder reactions.



2 **3**

Prolinol **4**[32] was reacted with BBr_3 in CD_2Cl_2 as solvent (the complex shows poor solubility in $CDCl_3$) and the product was analysed by ^{11}B, ^{1}H, and ^{13}C NMR. The ^{11}B NMR showed one peak at -24.6 (relative to $BF_3.OEt_2$ = 0 ppm) indicative of tetravalent borate.[33] The ^{13}C NMR did not show very significant differences between the free amino alcohol and the complex but the ^{1}H NMR did. Prolinol **4** showed a methyl singlet at 1.81 ppm whereas in the complex this changed to 2.48 and was now a doublet (J 6.5 Hz). Evidently, the complex is protonated on nitrogen and this results in additional coupling to the neighbouring protons. These data are consistent with the complex having structure represented by **5** rather than **6**. The methyl group of structure **6** would be expected to be a broad singlet due to coupling to boron (vicinal couplings of protons to boron are broadened due to the quadrupole moment at boron and if spin relaxation at boron (spin 3/2) was slow a quartet would be expected[34]). To confirm the structure of the complex, the mixture was treated with a strong base (DABCO[35]) in order to form the boracycle and the ^{1}H NMR revealed a broad singlet at δ 2.35.[36] This is consistent with formation of the boracycle **6**. This series of NMR experiments showed that reaction of boron halides with an amino alcohol did indeed give complex **5** bearing both a Lewis acid and a Brønsted acid rather than complex **6**. Attempts to determine the structure of the Lewis acid-methacrolein complex by NMR were unsuccessful due to the low equilibrium concentration of this complex.



4 **5** **6**

NMe δ 1.81, s δ 2.48, d, J 6.5Hz δ 2.35, s

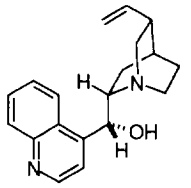
To determine the potential for this class of Lewis acids in Diels-Alder reactions between cyclopentadiene and methacrolein a variety of amino alcohols were tested as ligands with both BBr_3 and BCl_3 and the best

results are summarised in Table 1.[37] It is clear from Table 1 that yields and diastereoselectivities are high (in all cases the exo adduct was the major diastereoisomer) but enantioselectivities are variable. The highest enantioselectivity was obtained with prolinol **4** (Mukaiyama's results[31]), although quinidine provided the highest enantioselectivity for a naturally occurring (therefore more readily available) amino alcohol.[38] This result represents one of the highest enantioselectivities obtained in a Diels-Alder reaction using readily available commercial reagents.

Table 1: Diels-Alder reaction between methacrolein and cyclopentadiene at -78°C

Amino alcohol	Boron Reagent	Yield	de	ee[a]
Prolinol **4**	BBr_3	84%	>99:1	97% (R)
Prolinol **4**	BCl_3	90%	94:6	23% (R)
cinchonidine **7**	BBr_3	75%	83:17	0%
cinchonidine **7**	BCl_3	67%	96:4	47% (S)
quinidine **8**	BBr_3	85%	97:3	64% (R)
quinidine **8**	BCl_3	74%	94:6	0%

[a] Ee determined by ^1H NMR using $Eu(hfc)_3$ shift reagent. Absolute stereochemistry determined by comparison of rotation with the literature [for carbon bearing aldehyde group, (R) has negative rotation[39]].



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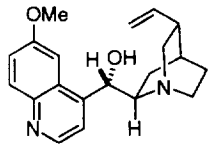

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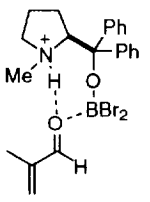

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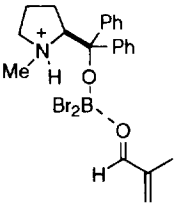

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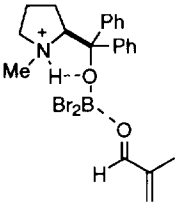

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As it was not possible to determine the structure of the Lewis acid-dienophile complex it is not possible to say whether Diels-Alder reactions occur via the cyclic complex **9** or via the acyclic complex **10**. In addition to the conformational freedom of the Lewis acid-dienophile complex **10** (both **9** and **11** are more constrained) there is also conformational freedom in the dienophile conformation (*s-cis* versus *s-trans*) and whilst there are indications that the *s-trans* is preferred in the ground state there is no evidence that this is also the reactive conformer[40] and therefore both conformations would need to be considered. It is difficult to reconcile the high selectivity observed with such conformationally mobile systems as there is also still the question of facial selectivity. However, if reactions are occurring through the acyclic complex it is possible that its conformation is constrained through hydrogen bonding **11** and this would reduce the number of available conformations and

lead to higher selectivity. In that case and in complex **9** both the Lewis acid and the Brønsted acid are contributing to the overall enantioselectivity of the process.

Acknowledgements
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EXPERIMENTAL

All syringes, pipettes and NMR tubes were oven dried, then stored in a dessicator. Manipulations were carried out in an argon filled glove bag or a nitrogen filled glove box. A 2M solution of BBr_3 (0.95 ml) was made up in 5 ml CD_2Cl_2. All spectra were run in CD_2Cl_2.

BBr_3

For the initial boron NMR, 325 µl of 2M BBr_3 in CD_2Cl_2 was added to 3 ml CD_2Cl_2 in a 10 mm NMR tube. δ_B (80.25 MHz) +38.5 (relative to $BF_3.OEt_2 = 0$).

(S)-α,α-Diphenyl(1-methylpyrrolidin-2-yl)methanol (4)

δ_H (400 MHz) 1.55-1.72 (m, 3H), 1.81 (s, 3H), 1.82-1.94 (m, 1H), 2.45 (q, *J* = 9Hz, 1H), 3.08 (dt, *J* = 4, 6Hz, 1H), 3.64 (dd, *J* = 4.5, 9Hz, 1H), 4.76 (bs, 1H), 7.15 (dt, *J* 1.5, 5Hz, 2H), 7.28 (dt, *J* 1.5, 5Hz, 4H), 7.59 (dd, *J* 1.5, 7.5Hz, 2H), 7.66 (dd, *J* = 1.5, 7.5Hz, 2H).

δ_C (100 MHz) 24.5, 30.4, 43.3, 59.6, 72.3, 77.8, 126.0, 126.7, 128.5, 137.3, 139.1.

(S)-α,α-Diphenyl(1-methylpyrrolidin-2-yl)methanol (4) + BBr_3

In order to simulate the concentration of the reaction, the following quantities were used. To a 10 mm NMR tube was carefully added previously weighed out **4** (69.5 mg, 2.60×10^{-4} mol). CD_2Cl_2 (3.0 ml) was added and the tube shaken. BBr_3 (2M, 130 µl, 2.60×10^{-4} mol) was added slowly to give a yellow solution.

δ_B (80.25 MHz) -24.6.

δ_H (250 MHz) 1.93-2.27 (m, 4H), 2.48 (d, *J* = 6.5Hz, 3H), 2.92-3.07 (m, 1H), 3.86 (sext, *J* = 7.5Hz, 1H), 4.67 (q, *J* = 9Hz, 1H), 7.14-7.43 (m, 6H), 7.49-7.77 (m, 4H), 10.26 (bs, 1H).

δ_C (62.9 MHz) 23.7, 29.1, 43.5, 60.2, 76.9, 79.3, 125.5, 126.4, 128.9, 143.0, 145.1. A smaller second species was visible in the aromatic region : 127.6, 128.3, 129.3, 129.7, 130.0.

(S)-α,α-Diphenyl(1-methylpyrrolidin-2-yl)methanol (4) + BBr_3 + DABCO

To a 3 mm NMR tube was carefully added previously weighed out **4** (69.5 mg, 2.60×10^{-4} mol) in CD_2Cl_2 (0.6 ml) and the tube shaken. BBr_3 (2M, 130 µl, 2.60×10^{-4} mol) was added slowly to give a yellow solution. DABCO (29 mg, 2.60×10^{-4} mol) was added to the NMR tube and this caused th solution to turn pink and a precipitate to form. The mixture was therefore filtered into another tube, washing with a small amount of CD_2Cl_2. The pink solution remained cloudy, but NMR spectra were recorded.

δ_B (128.4 MHz) -5.7 (29%), -4.4 (71%). Two small broad peaks: 5.8 and 9.3.

δ_H (400 MHz) 1.96-2.08 (m, 4H), 2.35 (bs, 3H), 2.86-3.00 (m, 1H), 3.67 (bm, 1H), 4.71 (bm, 1H), 7-7.8 (m, 10H).

General Method for Diels-Alder Reactions

The amino alcohol (1.01 eq) was added to a flask under nitrogen and dissolved in 8 ml CH_2Cl_2. The boron reagent (1 eq) was added dropwise and the catalyst allowed to form by stirring at ambient temperature for 1 h. The mixture was cooled to -78°C before addition of methacrolein (5 eq) and cyclopentadiene (15eq), both freshly distilled. The reaction was carried out for the time indicated in the Table, then quenched at -78°C with saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, dried and the solvent evaporated under reduced pressure to leave a clear oil as a mixture of *exo* and *endo* adducts. Data were consistent with literature values.[41]

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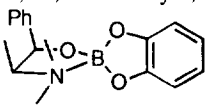

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(37) Other amino alcohols tested were (-)-N-methyl ephedrine, (+)-N-dimethyl pseudoephedrine, (-)-3-*exo*-(dimethylamino)isoborneol, (-)-3-*exo*aminoisoborneol, quinine and cinchonine. They all gave either low yields or low enantioselectivities.

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