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Enantioselective Diels-Alder Reactions of Enals: Fighting Species Multiplicity of the Catalyst with Donor Solvents

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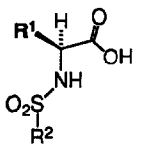
Abstract: Chiral Lewis acids obtained from reactions of N-arylsulphonylamino acids with borane adducts effectively catalyze Diels-Alder additions of α,β-unsaturated aldehydes. Maximum enantioselectivity (methacrylaldehyde: 86 %ee, crotonaldehyde: 81 %ee) was achieved in donor solvents. The first results with new chiral Lewis acids derived from C_2-symmetric N-sulphonyl derivatives of 2,2'-diamino-1,1'-binaphthyl are also presented.

In recent years spectacular advances have been achieved in catalysis with chiral Lewis acids[1]. Our first contribution, simultaneously announced with the very similar work of H. Yamamoto's group[2], was the introduction of a new class of chiral Lewis acids derived from N-sulphonylamino acids by reactions with borane-THF, Et_2AlCl or $TiCl_4$[3]. Of these catalysts, presumed to be metallacycles, boranes **2** were found most useful for the promotion of Diels-Alder (DA) reactions of α,β-unsaturated aldehydes **4** with cyclopentadiene.



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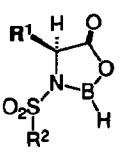

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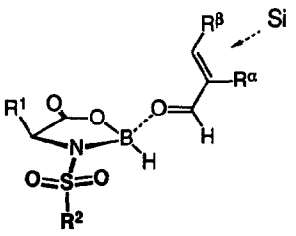


3

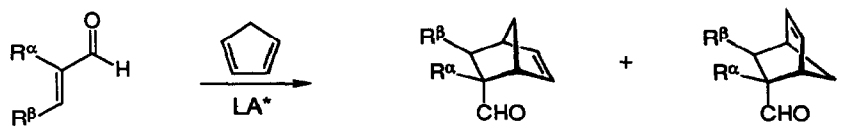
(transition state model)

a R^1 = i-Pr, R^2 = 4-$(CH_3)C_6H_4$

b R^1 = i-Pr, R^2 = 2,4,6-$(CH_3)C_6H_2$

c R^1 = tBu, R^2 = 4-$(CH_3)C_6H_4$

In the meantime we have extended these studies and propose the transition state model **3** which allows rationalisation of configurational relationships. This model is based on the following arguments: a) Group R^1 directs the steric bulk of the group R^2SO_2 to the opposite face of the ring[4]; b) The R^2SO_2 group in turn controls the coordination site and thus defines the configuration of the boron chirality centre[5]; c) For the enal, coordination of boron to the lone pair *syn* to H is preferred[6]; d) Coordinated as well as free acrolein prefers the *s-trans* conformation; however, according to recent calculations[7], in the transition state of the reaction between the acrolein-BH_3 complex and butadiene the *s-cis* conformation is preferred[8]; e) Finally, the *syn-planar* disposition of the B-H and the C=O bond[7] leads to the transition state model **3** with preferred attack of the diene at the C_α-*Si* enal face. This prediction was found to hold for all examples.



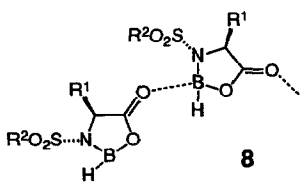
4 5n 5x

	R^{α}	R^{β}
a	CH_3	H
b	H	CH_3
c	H	H

Structures of the preferentially formed enantiomers

Recent developments in asymmetric catalysis demonstrate[9] that consideration of only the structural aspect of a catalyst may be misleading. The number and nature of the catalytically active species must also be taken into account. We call this aspect species multiplicity[10]. The importance of species multiplicity in a given system is best examined from the response to reaction variables. In the present case, these variables are the concentration of the catalyst, solvent, age and enantiomeric purity of the catalyst, structure of the starting material (R^1, R^2) and mode of catalyst preparation.

Initially following a procedure of H. Yamamoto[11], we prepared the catalyst by adding BH_3-THF (1 equiv, in THF)[12] to a suspension of **1** in CH_2Cl_2 at room temperature. A rapid reaction occurred[13]. This procedure introduces *ca.* 12 equiv of THF. The importance of this additive became apparent when we used BH_3-SMe_2 as a precursor for the catalyst, or removed THF by evaporation: almost complete loss of selectivity resulted. Further results displayed in the Table clearly demonstrate that donor additives are necessary for high selectivity. THF as solvent or even acetonitrile are tolerated by the system[14].



8

Most likely these effects are caused by association of the catalyst, *i.e.* a special case of species multiplicity. Association *via* the carbonyl group as in **8** and in similar higher oligomers, possessing one catalytically active site, leads to increased shielding of the C_{α}-*Si* enal face and thus to a decrease in enantioselectivity according to our model.

Table. Influence of solvents/additives on Diels-Alder reactions of aldehydes **4**[a].

aldehyde	solvent	catalyst	ratio of 2 : 4	endo-exo ratio	% ee	yield [%]
4a	CH_2Cl_2	2a[b]	0.6	2 :98	20	72
4a	CH_2Cl_2/12 eq THF	2a[c]	0.6	1 :99	86	84
4a	CH_2Cl_2/CH_3CN 2:3	2a[c]	0.6	1 :99	70	93
4a	THF	2a[c]	0.6	5 :95	82	79
4b	CH_2Cl_2/ 2 eq THF	2b[b]	0.2	95: 5	12	70
4b	CH_2Cl_2/12 eq THF	2b[b]	0.2	93: 7	59	65
4b	THF	2b	0.2	94: 6	76	60

(a) Reaction temperature: -78 °C; conc.: 0.2 mol/L; det. of ee: ref. 11.
(b) The catalyst was prepared at room temp. from BH_3-SMe_2 (1 M in CH_2Cl_2).
(c) The catalyst was prepared at room temp. from BH_3-THF (*ca.* 1 M in THF).

Another clear indication of species multiplicity is demonstrated by the dependence of enantioselectivity on the concentration of the catalyst (Fig. 1A). The very pronounced variation, particularly for the reaction of crotonaldehyde, indicates a complicated system. However, when the catalysts were prepared from BH_3-THF or BH_3-SMe_2 in THF, the enantioselectivities were found to be almost independent of the amount of catalyst present (Fig. 1B). According to our model, enlargement of R^1 should increase shielding of the carbonyl oxygen and inhibit association. Indeed, the catalyst **2c**, R^1 = tBu, shows the least degree of dependence of enantioselectivity on reaction conditions (Fig. 1A).

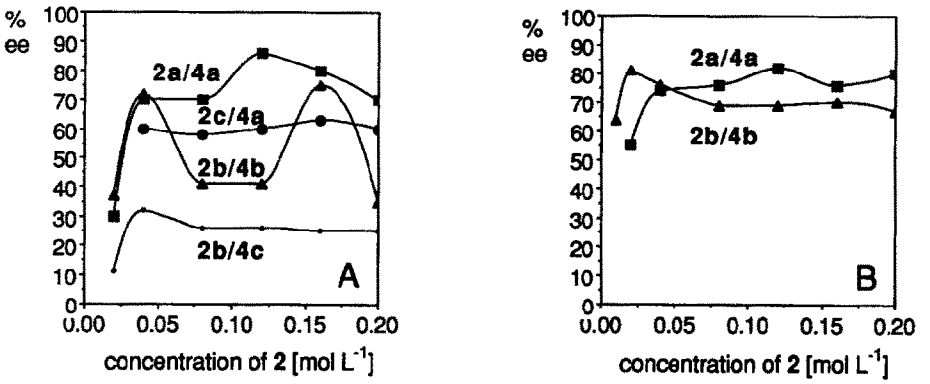
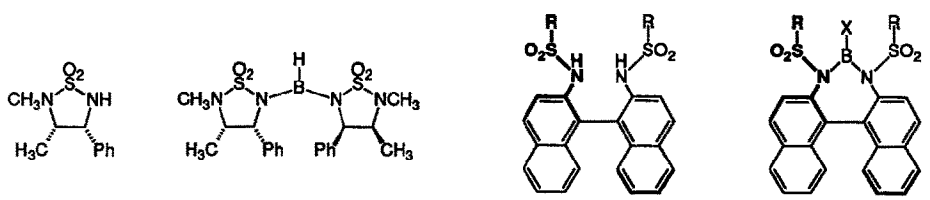


Fig. 1. Dependence of enantioselectivities of the DA reactions of aldehydes **4** on the concentration of the catalysts **2** (numbers at the curves designate dienophile/catalyst combinations).
A: The catalyst was prepared by reacting THF-BH_3 (1 M in THF) and **1** (molar ratio 1:1) in CH_2Cl_2; subsequent DA reaction by adddition of pure **4** and cyclopentadiene.
B: As A, but solvent THF; catalyst **2b** was prepared from BH_3-SMe_2 (1 M in CH_2Cl_2).



9 **10** **11** **12**

The reactivity of a Lewis acid is of great practical importance. It is known that acyloxyboranes are fairly active catalysts for Diels-Alder reactions[15]. However, little is known about N-arylsulphonylaminoboranes. Chiral bis-N-arylsulphonylaminoboron and aluminum halides seem to be weak Lewis acids that were only used in conjunction with the particularly reactive N-enoyloxazolidin-2-ones[16]. In order to address this issue we treated a CH_2Cl_2 solution of the sulphamide **9**, recently introduced by this group as chiral auxiliary[17], with BH_3-THF at room temperature. Slow evolution of H_2 occurred but the resultant product, presumed to be **10**, displayed a low degree of activity with crotonaldehyde. In order to decrease electron density at nitrogen we next investigated a variety of sulphonamides **11**[18], easily prepared from (*R*)-2,2'-diamino-1,1'-binaphthyl. Treatment of **11** (R = p-Tol) with BH_3-THF in THF resulted in slow evolution of H_2 and a new species (NMR)[19] was formed (**12**, X = H ?) which displayed catalytic activity at -78 °C in the DA reaction of **4a** with cyclopentadiene to give **5xa** in moderate yield

with 64 % ee and exo-endo ratio of 97:3. These initial results are sufficiently intriguing to further study this catalyst system. An investigation into the use of a range of sulphonamides **11** as ligands of chiral catalysts is currently in progress.

ACKNOWLEDGEMENTS

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6 This assumption is supported by a large body of experimental as well as theoretical (ref. 7) work, *cf.* Reetz, M.T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.
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