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Asymmetric Diels-Alder Reactions Catalyzed by Chiral Oxazaborolidines. Effect of the Position of an Electron-Donor Functionality in the α-Side Chain Substituent on the Enantioselectivity

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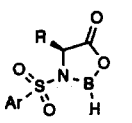
Abstract : *Asymmetric Diels-Alder reactions of cyclopentadiene with methacrolein and 2-bromoacrolein catalyzed by chiral oxazaborolidines* **1** *derived from N-tosyl-L-α-amino acids afforded cycloadducts in quantitative yield. Variation in the position of an electron donor atom in the α-side chain substituent shows that enantioselectivity is controlled by the presence of electron donor atoms in position 2 and 4.*

The development of chiral Lewis acids that mediate catalytic asymmetric reactions has been a challenging goal in synthetic organic chemistry[1]. Many efforts have been focused on the asymmetric Diels-Alder reaction[2]. Recently, chiral oxazaborolidines **1** derived from α-amino acids have been used as chiral Lewis acid catalyst in the asymmetric Diels-Alder reaction of α,β–enals with simple dienes. Transition state models **2** and **3**, respectively based on steric repulsion[3] and attractive donor-acceptor interactions[4], have been proposed to explain the configurational relationships and were confirmed by physical studies. For future design of efficient chiral Lewis acid catalysts the detailed understanding of the mechanism of enantioselectivity is important. Until now the exact location of the functionalities for donor-acceptor interactions is still not clear[5].



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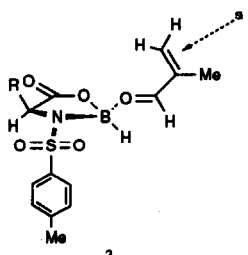

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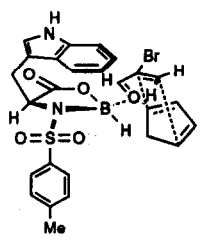


3[4]

In our study towards asymmetric Diels-Alder reactions catalyzed by chiral Lewis acids of type **1** we varied the *position* of an electron donor functionality in the substituent R, thereby influencing steric repulsion and/or electronic attractive interactions[6]. We expected that this could lead to a more detailed insight in the *position* of the donor-acceptor functionalities which direct the enantioselectivity. The reaction of cyclopentadiene with methacrolein catalyzed by new chiral oxazaborolidines **1** derived from N-(*p*-toluenesulfonyl)-*L*-α-amino acids[7] was chosen as a model (*Scheme 1*). The catalyst **1** is prepared *in situ* by adding BH_3.THF (1M in THF) to a suspension of the corresponding crystalline sulfonamide in CH_2Cl_2 or THF at 0°C for 30 min. (prep. method 1)[3] or at room temperature for 10 min. (prep. method 2)[4] under nitrogen atmosphere. Freshly distilled methacrolein and cyclopentadiene (3 eq.) were successively introduced at -78 °C. After overnight reaction and usual work-up the obtained product **4** was analyzed by GC and ^{1}H-NMR.

Scheme 1

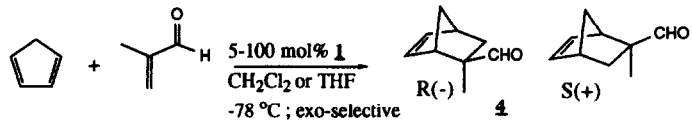


Table 1. Enantioselective Diels-Alder reaction of methacrolein and cyclopentadiene catalyzed by chiral boron catalysts 1[a]

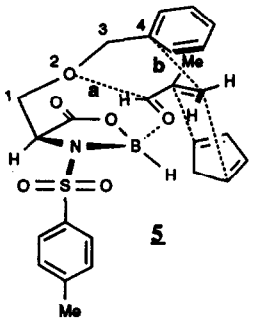
				solvent CH_2Cl_2		solvent THF		
entry	1 : R =	prep. meth.	mol% cat.[b]	exo/ endo[c]	e.e. (%)[d]	exo/ endo	e.e. (%)	exo-conf.[e]
1a	Me	1	20	91/9	20	98/2	53	R(-)
1b	*i*-Bu	1	20	96/4	22			R(-)
		1	50	97/3	60	98/2	71	R(-)
		1	100	98/2	41			R(-)
1c	Ph	1	20	95/5	40	98/2	80	R(-)
		2	20	96/4	46	98/2	74	R(-)
1d	$PhCH_2$	1	20	95/5	6	95/5	28	R(-)[8]
		1	60	95/5	6	95/5	30	R(-)
		2	5	94/6	6			R(-)
1e	$PhCH_2CH_2$	1	20	98/2	62	98/2	70	R(-)
		2	20	98/2	58	97/3	72	R(-)
1f	$PhCH_2OCH_2$	1	20	96/4	44	97/3	32	S(+)
		1	60			96/4	33	S(+)
		2	20	94/6	48	97/3	33	S(+)
		2	5	94/6	56			S(+)
1g	*cyclo*-hexyl-CH_2OCH_2	2	20	98/2	18	98/2	22	S(+)

[a] All reactions were carried out overnight (ca. 16 h) on 4 mmol of methacrolein at -78 °C; the product 4 was obtained in a quantative yield (*ca.* 99%);[b] The chiral ligands were efficiently recovered; [c] Determined by 100 MHz ^{1}H-NMR analysis; [d] Determined by ^{1}H-NMR analysis with the chiral shift reagent Eu(hfc)$_3$; [e] For assignment of absolute configuration the product was purified by silicagel "flash"chromatography (CH_2Cl_2 : cyclohexane = 3:2) and optical rotation was measured and compared with literature data[9].

The results from Table 1 show that the two different methods for catalyst preparation did not have a significant effect on enantioselectivity of this almost quantitative and exo-selective Diels-Alder reaction. However, a strong solvent effect is apparent on this reaction. Donor solvent THF gives rise to a significant increase in enantioselectivity[10] (*exo-R(-)*-enantiomer is formed in excess) compared to acceptor solvent CH_2Cl_2, where association of the catalyst is supposed to decrease the enantioselectivity by shielding of the C_α-*Si* enal face[3]. The catalyst concentration did not have a pronounced effect on enantioselectivity[11]. The enantioselectivity of entry 1a, 1b and 1c can be explained satisfactory with transition state model 2. In this model substituent R operates only as a group that causes steric repulsion and leads to preferential formation of the *exo-R(-)*-enantiomer.

For reversal of enantioselectivity the *position* of atoms with electron donating ability is very important and should be located at position 2 and 4 of substituent R, as appears from results in entries 1c to 1f. This can be illustrated in transition state model 5 for R = $PhCH_2OCH_2$ (entry 1f). A strong donor-acceptor interaction is possible between the oxygen atom in position 2 of the substituent R and the carbonyl carbon of the complexed dienophile (interaction a). Molecular models show that a second donor-acceptor interaction is possible between the *ipso*-carbon atom of the phenylsubstituent (entry 1f) in position 4 and the β-carbon atom of the dienophile (interaction b) which fits the dienophile in the *s-cis* conformation[12]. The lower enantioselectivity found for

entry 1g is due to the lack of the second donor-acceptor interaction in position 4. No reversal of enantioselectivity was observed for entry 1e although the position of the phenyl ring is very similar to the position of the phenyl part in the indolylmethyl substituent (see 3). This indicates that a phenylring at position 3 is not sufficient for effective donor-acceptor interactions with the dienophile. The low enantioselectivity found in entry 1d can be ascribed to the weak donor-acceptor interaction of the aromatic sp^2 carbon atom in position 2 of the substituent R with the dienophile.



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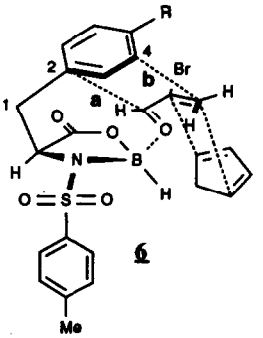

6

Stronger donor-acceptor interactions can be expected in the catalyzed cycloaddition with the more electron-poor 2-bromoacrolein[4]. Therefore we also investigated the cycloaddition of cyclopentadiene with 2-bromoacrolein at -78 °C in CH_2Cl_2 with 5 mol% catalyst 1 for R = Me, $PhCH_2$ and $PhCH_2OCH_2$. The reactions were complete within 3 hours (for reaction parameters and analyses of the products see Table 1).

Table 2. Enantioselective Diels-Alder reaction of 2-bromoacrolein and cyclopentadiene catalyzed by chiral boron catalysts 1

entry	1 : R =	prep.meth.	mol% cat.	exo/endo	e.e. (%)	exo-conf.
2a	Me	2	5	98/2	33	S
2b	$PhCH_2$	2	5	95/5	55	R
2c	4-MeO-$PhCH_2$	2	10	96/4	72	R
2d	4-$PhCH_2O$-$PhCH_2$	2	10	96/4	81	R
2e	$PhCH_2OCH_2$	2	5	96/4	54	R

The results in Table 2 show that now for R = $PhCH_2$ (entry 2b) reversal of enantioselectivity occurs which can be explained with a predominance of a transition state of type 6. Enhanced electron density on the aromatic ring in position 2 and 4 induced by electron donating *para*-substituents should increase the electron donor-acceptor interactions in the transition state. For this purpose commercially available O-protected *L*-tyrosine derivatives were screened as suitable chiral precursors. Higher enantioselectivity was indeed observed with a *para*-MeO substituent (72% ee, entry 2c) and with a *para*-$PhCH_2O$ substituent (81% ee, entry 2d). With N-tosyl-L-serine(OBzl)-OH as chiral ligand enantioselectivity can be explained by transition state model 5.

However, the reaction with methacrolein and cyclopentadiene catalyzed by these *L*-tyrosine-derived oxazaborolidines proceeded in a quantitative yield but with very low enantioselectivity (ca. 5% ee). Probably the donating *para*-substituents are too weak to cause sufficiently strong donor-acceptor interactions with

methacrolein. For this reason we are currently studying phenylalanine- and serine-derived oxazaborolidines having more electron rich aromatic rings.

Acknowledgements

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References and Notes

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4. a) Corey, E.J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**,*113*, 8966; b) Corey, E.J.; Loh, T.-P.; Roper, T.D.; Azimioara, M.D.; Noe, M.C. *J. Am. Chem. Soc.* **1992**, *114*, 8290; c) Marshall, J.A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987.
5. According to Corey *et al.* (ref. 4b) the indole nitrogen in transition state model **3** is in proximity to the carbonyl carbon. Other donor atoms of the indole ring could give a charge transfer interaction with the α,β-enal as well.
6. For influence of a remote phenyl group in chiral dienes on stereoselectivity of Diels-Alder reactions see de Bie, J.F.M.; van Strijdonck, G.P.F; Seerden, J.P.G.; Beurskens,G.; Scheeren, J.W. *Tetrahedron Lett.* **1990**, *31*, 7233; Siegel, C.; Thornton, E.R. *Tetrahedron: Asymmetry* **1991**, *2*, 1413.
7. The sulphonamides were prepared from commercially available amino acids and derivatives according to Houben-Weyl, *'Methoden der Organischen Chemie'*, Band 15/1, *Synthese von Peptiden* I, 4^{e}Auflage, Georg Thieme Verlag, Stuttgart, **1974**, pp. 223-233. Under these conditions no racemisation of the sulphonamides has been reported. Physical data of chiral sulphonamides : **1e** : m.p. = 95 °C; $[\alpha]_D^{20}$= +30.8 (c = 1.5, acetone); **1f** : m.p. = 110-112°C $[\alpha]_D^{20}$= +22.2 (c = 2.5, 96% EtOH); **1g** was prepared from commercially available *L*-serine-O-benzyl ether after hydrogenation with H_2 and 5% Rh/Al_2O_3 as catalyst in a 5:2:5 MeOH/AcOH/H_2O solution and subsequent reaction with *p*-toluenesulphonyl chloride; m.p. = 88 °C; $[\alpha]_D^{25}$= +27.7 (c = 1, $CHCl_3$); 68% overall yield.
8. Complementary results (formation of *S(+)*-**4**) were obtained when instead of *L(+)*-phenylalanine (entry **1d**) the unnatural *D(-)*-phenylalanine was used as starting material for the chiral catalyst.
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10. ref.2c ; Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.
11. The catalyst preparation starts with BH_3.THF and introduces ca. 12 eq. THF into the reaction mixture. Higher catalyst concentration can in principle cause association of the catalyst, but this effect will be counterbalanced by concomitant increased THF concentration.
12. Unless the chiral Lewis acid is structured to favor the *s-cis* α,β-enal complex, in solution the *s-trans* complex will predominate: Corey, E.J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945.

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