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Chiral Tartrate-Derived Dioxaborolidine: A Simple and Practical Catalyst for Enantioselective Diels-Alder Reaction

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Abstract: The (L)-tartrate derived catalyst **1**, has been used to effect enantioselective Diels-Alder reactions of bromoacrolein and cyclopentadiene. The reaction gives the product in good yield *(96%)*, high diastereofacial selectivity *(exo/endo 96:4)* and moderate enantioselectivty *(70%ee)*.
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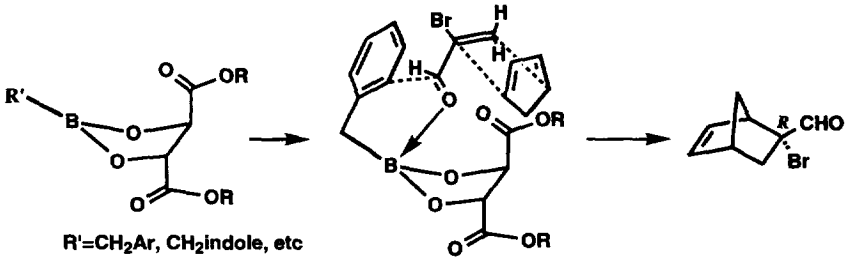
The Diels-Alder reaction is one of the most useful and powerful of known structural transformations in organic syntheses. Accordingly, much attention has been focused on the development of enantioselective versions, including most recently the use of chiral catalysts.[1] Nonetheless, rational design of practical and efficient catalysts for this reaction continue to pose an important challenge to organic chemists. In this paper, we report our effort in the design of a new class of catalyst for enantioselective Diels-Alder reaction that achieve selectivity through attractive interaction, electrostatic interaction, lone pair-lone pair repulsion as well as the usual steric repulsion.[2]

Conceptually, we envisaged that the dioxaborolidine **1** that can be readily prepared from commercially available (L)- or (D)-tartrate might channel the Diels-Alder pathway through the transition-state assembly **2**. It is reasonable on the basis of previous work with allyl boronate ester carried out by Roush and co-workers[3] that the 2-bromoacrolein and the two tartrate ester units prefer to occupy the axial position with respect to the dioxaborolidine unit. Furthermore, the tartrate esters are *syn* coplanar to the adjacent dioxaborolidine C-O bonds. The transition state is further stabilized by a favorable dipole-dipole interaction between the carbonyl carbon (δ+ bromoacrolein) and the proximate ester carbonyl oxygen (δ–). This stabilizing effect together with the attractive interaction of π-basic benzyl ring and the π-acidic dienophile will lock the dienophile in a fixed orientation. Thus, the aryl ring would provide steric



1 **2** **3**

shielding allowing the diene to attack only from the less sterically hindered side and affording the cycloadduct in high enantioselectivity. The preference of the *s-cis* conformation[4] of the dienophile catalyst complex will afford the (*2R*)-2-bromobicyclo[2.2.1] hept-5-ene-2-carboxaldehyde (**3**).

Reaction of (L)-tartrate with $PhCH_2B(OH)_2$[5] in toluene at reflux with removal of water gave a solution of catalyst **1** after 16 h, R'=$PhCH_2$, which showed a single ^{11}B NMR peak at 36 ppm (downfield from ext. $BF_3{\cdot}Et_2O$). The reactivities and enantioselectivities of the Diels-Alder reaction of 2-bromoacrolein with cyclopentadiene were screened using catalyst **1** in order to test the scope and limitations of the catalyst (Table 1). These reactions were performed by adding the diene to a premixed solution of the dienophile and 0.2 equiv of the catalyst **1**. The results are detailed in Table 1.

Table 1: Enantioselective Diels-Alder Reaction Catalyzed by Tartrate Derived 1,3,2-Dioxaborolidine (**1**)[a]

Entry	Chiral Ligands	R'B(OH)2	Solvent	%Yield[b]	Exo/Endo[c]	%ee[d]
1	(-)-Dimethyl Tarttrate	$PhCH_2B(OH)_2$	CH_2Cl_2	90	94:6	0
2	(+)-Diisopropyl Tartrate	$PhCH_2B(OH)_2$	CH_2Cl_2	94	92:8	40
3	(+)-Diisopropyl Tartrate	$PhCH_2B(OH)_2$	Toluene	96	96:4	70[e]
4	(+)-Diisopropyl Tartrate	$PhB(OH)_2$	Toluene	90	90:10	0
5	(+)-Diisopropyl Tartrate	*n*-$BuB(OH)_2$	Toluene	88	85:15	0
6	Dibenzyl-L-Tartramide	$PhCH_2B(OH)_2$	Toluene	91	67:33	0
7	(-)-Tetramethyl-D-Tartaric acid diamide	$PhCH_2B(OH)_2$	Toluene	90	75:25	0

a) All reactions were carried out on 1-2 mmol scale of dienophile in the presence of 20 mol % boron catalyst. b) Isolated yield. c) Determined by ^1H NMR analyses. d) Determined by ^1H NMR analyses with shift reagent $Eu(tfc)_3$. The absolute configuration was confirmed to be *R* by comparison of the sign of the optical rotation with the authentic compound. e) The enantioselectivity of the reaction is very sensitive to the purity of benzyl boronic acid and the complex.

Different tartrate esters were used to make the boron catalysts (Entries 1, 2, 6, 7). The nitrogen containing tartrates give no selectivity (Entries 6, 7). The best result was obtained when diisopropyl tartrate was used as ligand. For the tartrate derived boron catalyst, toluene is the better solvent than CH_2Cl_2 (Entries 2, 3). Especially noteworthy is that in the presence of 20 mole % of **1**, R'=$PhCH_2$, 2-bromoacrolein and cyclopentadiene (*ca.* 5 equiv) underwent smooth Diels-Alder addition (-78 °C, 6 h) to give the (*2R*)-bromo aldehyde **3** in 96% yield, 85:15 (*R:S*) enantioselectivity and 96:4 (*exo:endo* CHO) diastereoselectivity.

Diastereoselectivity was determined by 300 MHz ^1H NMR analysis. Enantioselectivity was determined both by 300 MHz ^1H NMR with chiral shift reagent $Eu(tfc)_3$ in $CDCl_3$ and by reduction with $NaBH_4$, conversion to the Mosher MTPA ester and ^1H NMR measurement. The figure given for

enantioselectivity refers to the major (*exo* CHO) diastereomer. The absolute configuration of the adduct from catalyst **1** was shown to be *2R* after conversion to the known alcohol ($[\alpha]_D^{23}$=+53.7° in $CHCl_3$; lit. $[\alpha]_D^{23}$=+78° purity >99%ee in $CHCl_3$).[6]

Of great mechanistic significance is the fact that the Diels-Alder reaction of cyclopentadiene and 2-bromoacrolein under catalyses of the dioxaborolidine (R'=Ph or *n*-Bu) gives no enantioselectivity. The low enantioselectivity obtained by using these dioxaborolidines provide strong evidence for the proposed transition-state assembly **2**.

In conclusion, a new concept for the design of enantioselective catalysts has been supported by experiments which demonstrated a very practical and promising method for future catalysts' design. This catalyst is very simple and practical for enantioselective synthesis. Further work is now focused on improving the catalyst to obtain higher enantioselectivity by using more π–basic groups than benzyl to strengthen the π–stacking with the dienophile, as well as to keep the enal (bromoacrolein) complex in the *s-cis* conformation. Application of this catalyst for other C-C bond formation reactions is also in progress.[7]

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