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The Asymmetric Diels-Alder Reaction of α,β-Unsaturated Aldehydes with Dienes Using a Chiral Boron Reagent as a Catalyst

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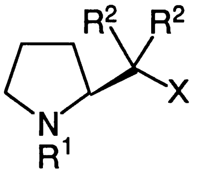
The asymmetric Diels-Alder reaction of α,β-unsaturated aldehydes with cyclopentadiene is catalyzed by a novel chiral boron reagent generated in situ from boron tribromide and a chiral prolinol derivative, to afford the corresponding adducts in good yields with fairly good to excellent ees.

The asymmetric Diels-Alder reaction, especially the catalytic asymmetric Diels-Alder reaction using a chiral Lewis acid, is now of great interest because of its utility to introduce some asymmetric centers simultaniously during carbon-carbon bond formation.1) Through our investigation on catalytic chiral induction, an efficient catalytic asymmetric aldol reaction using a chiral tin(II) Lewis acid2) or a chiral titanium oxide,3) and the catalytic asymmetric Michael reaction using chiral tin(II) enolates4) have been reported. In this communication, we would like to describe the asymmetric Diels-Alder reaction of α,β-unsaturated aldehydes with dienes using a novel chiral boron reagent simply prepared in situ from boron tribromide and a chiral prolinol derivative.5)

In a series of our investigations on asymmetric synthesis, we have demonstrated that bicyclo[3,3,0]octane structure utilizing proline derivatives provides excellent asymmetric environment for chiral induction.6) Based on this acquaintance, novel chiral catalysts prepared by suitable combinations of Lewis acids and proline derivatives as ligands were examined in the model Diels-Alder reaction of methacrolein with cyclopentadiene. The reaction smoothly proceeded at -78 °C in the presence of a catalyst generated in situ from boron tribromide and proline derivative **1** to afford the corresponding adduct in 56% yield, however, exo/endo ratio was low (exo/endo=69/31) and no chiral induction was observed. It was suggested from the molecular modeling study that R^2 group in the proline derivatives would strongly effect on the stereoselectivity. Recently, Soai et al. developed chiral amino alcohol **2** and successfully employed in the catalytic asymmetric alkyltion reaction of aldehydes with dialkylzinc.[7)] Corey et al. also utilized this ligand in the catalytic asymmetric reduction of ketones using borane as a reducing agent.[8)]



1 R^1=Me, R^2=H, X=NHTf

2 R^1=Me, R^2=Ph, X=OH

3 R^1=CH_2Ph, R^2=Ph, X=OH

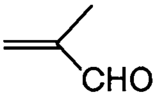
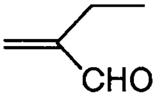
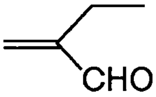
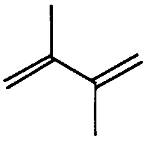
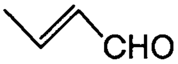
Remarkable improvement on the diastereo- and enantioselectivities was observed by combination of boron tribromide and **2** (20 mol% each) as expected, and the Diels-Alder adduct was obtained in 84% yield with almost perfect exo selectivity and the optical yield of the exo form was improved up to 97% ee, which was determined by HPLC analysis after reduction of the adduct followed by derivation to the corresponding MTPA ester.[9)]

Several examples of this asymmetric Diels-Alder reaction are shown in Table 1. 2-Ethylacrolein smoothly reacts with cyclopentadiene to give the corresponding exo adduct in 73% ee by using **2** as a ligand. In the reaction of crotonaldehyde, the best ligand is **3** and the corresponding endo adduct was obtained in 59%ee.

A typical experimental procedure is as follows; the chiral catalyst was generated in situ by stirring BBr_3 (0.08 mmol) and **2** or **3** (0.08 mmol, 20 mol%) in dichloromethane for 1 h at rt. The solvent was removed under reduced pressure (0.5 mmHg, 1 h) and the catalyst in dichloromethane (1 ml) was added to a dichloromethane solution of a diene (1.2 mmol) and a dienophile (0.4 mmol) at -78 °C. The mixture was stirred overnight at -78 °C, and then quenched with aqueous sodium hydrogencarbonate. After usual work-up, the crude product was chromatographed on silica gel to yield the desired Diels-Alder adduct.

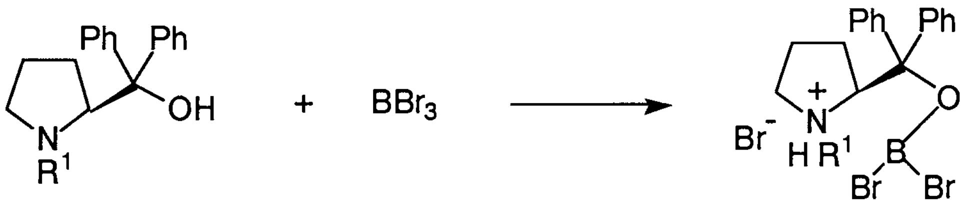
At present, it is assumed that the active catalyst in this reaction is the HBr salt **4** shown in Scheme 1. When the catalyst was prepared by successive treatment of **2** with NaH and BBr_3 (HBr free condition), the adduct of the model reaction between methacrolein and cyclopentadiene gave rather low selectivitiy (70% yield, exo/endo=>99/ 1, exo form=69%ee). On the other hands, the adduct was produced in high selectivities (72% yield, exo/endo=>99/ 1, exo form 96%ee) when the catalyst was prepared by treatment of **2** with NaH, BBr_3, and further HBr gas. It should be noted that the other salts prepared from HCl and trifluoromethanesulfonic acid were not effective in this reaction.

Table 1. The Diels-Alder Reaction of α, β-Unsaturated Aldehyeds with Dienes

Dienophile	Diene	Ligand	Yield/%	exo/endo[a]	ee/%[b]
		2	84	>99/1	97
		2	87	>99/1	73
		3	70	—	48
		3	77	31/69	59
		3	80	42/58	70

a) Determined by ^{1}H NMR.

b) Enantiomeric excesses of major isomers determined by HPLC analysis.



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Further investigations on scope and limitation of this catalytic asymmetric Diels-Alder reaction as well as application of these catalysts to other asymmetric reactions are now in progress.

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