The mechanism of asymmetric reduction catalyzed by a $C_2$ symmetric bis-amino alcohol catalyst

— *In situ* NMR study of the structure of new type of dual-centered catalyst

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**Abstract**  By means of $^1$H, $^{13}$C, $^{11}$B NMR, polar transfer DEPT135, DEPT90 and 2D NMR experiments, IR, etc, the structure of the dianinodihydroxyl ligand and its derivatives used in the asymmetric reduction of prochiral ketones were detected. The catalysts derived from the ligand and borane formed *in situ* were also studied and the structure transformations in solution were monitored. The structure of the catalyst was proved to be a new type of dual-centered catalyst—bis-oxazaborolidine.

**Keywords:** 2D gradient experiment, *in situ* NMR, dianinodihydroxylborane, bis-oxazaborolidine.

The preparation of highly optically pure compounds is important in organic chemistry. Optical alcohols, as the key intermediates of many medicines and pesticides, have aroused much attention. Asymmetric borane reduction reactions catalyzed by chiral oxazaborolidines (the CBS method)$^{[1-3]}$, which was found by Itsuno et al., are effective approaches to highly enantioselective reduction of carbonyl groups to obtain optical alcohols. A great number of amino alcohol ligands$^{[4]}$ and $C_2$ symmetric o-bis-amino ligands$^{[5]}$ were then developed which are very likely to be another kind of promising Corey chemzyme to serve as effective ligands for asymmetric hydroboration. Recently, dual-centered catalysis, which imitates the function of enzyme catalysis in nature, becomes a hot topic of catalysis$^{[6, 7]}$. However, chiral bis-$\beta$-amino alcohol or bis-oxazaborolidine with high activity was seldom obtained$^{[8]}$. Designing and synthesizing ligands with two catalytic centers and making them match each other may give rise to good enantioselectivity and reduce the amount of catalyst in the reaction, thus making the catalysts easily recovered and the whole process simplified.

The Shanghai Institute of Organic Chemistry and the Du Pont Company have cooperated to develop a kind of bis-amino chiral ligand applicable in the enantioselective borane reduction of prochiral aromatic ketones such as acetophenone (fig.1, L3). The results show that the ligand itself...
cannot give ideal catalytic activity, but its hydrolyzed derivative L1 shows good asymmetric induction effect. As the ligand can be synthesized from cheap tartaric acid and has the characteristics of both amino alcohol and bis-amino ligands, it has potentiality for further development. The structure of the ligand may affect its coordinated structure with borane, the attacking route and enantioselectivity in the course of the reaction. It is important to make clear the structure of the ligand and furthermore, to study the structure of the chiral catalyst formed *in situ* and the mechanism. In order to know in detail the structure of the catalyst formed *in situ*, effective enantioselective catalyst L1 and its two derivatives with two amino groups (L2, OH was protected) or vicinal hydroxyl group (L4, NH$_2$ was alkylated) were prepared by controlling the condition of hydrolysis. Using $^1$H, $^{13}$C NMR, polar transfer experiments of DEPT135, DEPT90 and 2D NMR, and IR techniques, the structure of the ligand and its derivatives were characterized and their $^1$H and $^{13}$C NMR spectral lines were assigned. Utilizing $^{11}$B NMR spectra with or without decoupling and the *in situ* NMR technique, the reactions of these compounds are studied and the variations of the structure of the catalysts formed *in situ* were observed. The structure of the catalyst together with its catalytic performance have proved it is a new type of dual-centered bis-oxazaborolidine.

**1 Experimental**

1.1 Synthesis of the ligand and its derivatives

The compound L3 was synthesized from L-tartaric acid through esterification, hydrazine reduction, benzyl lithium condensation, etc\(^1\). The effective catalyst L1 was obtained by complete hydrolysis of L3. L4 was synthesized from alkylation of L1 by formaldehyde. L2 was prepared through hydrolysis in aqueous sodium hydrate, then extracted with ether.

1.2 NMR and IR experiments

The ligand sample was dissolved in DMSO-d$_6$ with TMS as an internal standard. An *in situ* NMR method was applied to determine the structure of the coordinated catalysts. The sample was transferred from the reaction system to the NMR sample tube under argon atmosphere, then the tube was sealed. The NMR sample tube was vacuumed, then filled with argon gas before the sample was introduced and a small tube with D$_2$O added to lock the magnetic field. The internal standard for $^{11}$B spectra was BF$_3$ · Et$_2$O. NMR tests of the complex were accomplished at room temperature, 303 and 308K, respectively.

$^1$H, $^{13}$C, $^{11}$B NMR and 2D NMR experiments with gradient were carried out on a BRUKER DRX-400 NMR spectrometer with BBI 5mm probehead (with Z-gradient) at room temperature. $^1$H, $^{13}$C and $^{11}$B NMR spectra were recorded at 400.13, 100.6 and 128.4 MHz and the 90°C pulses were 10 (7.5 db), 10.1 (0 db), 10 μs (0 db), respectively. Their spectral widths were 4807.692, 25062.66, 25641.025 Hz, and the acquisition times were 1.75, 0.33 and 0.16s with a data point 16, 16 and 8K, respectively. DEPT90 and DEPT135 were completed with a relaxation delay of 1s.