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Catalytic Asymmetric Nitroaldol Reaction Using Optically Active Rare Earth BINOL Complexes: Investigation of the Catalyst Structure

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In recent years, numerous attempts have been made to develop catalytic asymmetric C–C bond-forming reactions. Nevertheless, elucidation of catalyst structure and mode of enantioselection have remained at a primitive level, limiting both their application and further development. Recently[2-5] we developed the first catalytic asymmetric nitroaldol reaction using rare earth BINOL complexes of La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Er, Yb, and Y, prepared from rare earth metal trichlorides, dilithium (*R*)-binaphthoxide, NaOH, and H_2O, and showed[4,5] some of its applications in the efficient catalytic asymmetric syntheses of important therapeutic agents. The rare earth metals are generally regarded as a group of 17 elements with similar properties, especially with respect to their chemical reactivity. However, in the case of the above-mentioned nitroaldol reaction, we have observed pronounced differences both in the reactivity and in the enantioselectivity among the various rare earth metals used.[5] In addition, the presence of LiCl and H_2O appears to be essential for obtaining nitroaldols of high optical purity.[2,3] Nevertheless, structures of the catalysts have still remained unclear. Thus the question arises not only about the catalyst structure and the role of additives but also about the mode of enantioselection. In this communication we report on the structures of optically active rare earth catalysts, which should be quite helpful in further studies of their reactions.

The relatively simple ^{13}C and ^{1}H NMR peak patterns of the La catalyst suggest[6] either a simple structure for the catalyst or the magnetic equivalence of the BINOL moiety if the catalyst has an oligomeric structure. An NMR study of all the rare earth complexes, with the exception of the La catalyst complex, provided little information on catalyst structure due to the paramagnetism of the rare earth elements.

By conventional EI- and FAB-MS methods, we could obtain only obscure spectra with complex fragment peaks. In contrast, the laser desorption/ionization time-of-flight mass spectrometry (LDI-TOF MS)[7,8] proved to be quite a powerful tool in the analysis of the structure of rare earth BINOL complexes. By the LDI-TOF MS method, anionic and cationic species could be detected independently according to the measurement mode. As shown in Figure 1, in both anionic and cationic modes, a tris(binaphthoxy) mixed-metal complex of La and Li came up as a candidate for the framework of the catalyst. Surprisingly, no Cl atom-containing fragment was detected. The other BINOL–rare earth complexes (Pr, Nd, and Eu) also showed a peak pattern similar to that of the La–BINOL complex, suggesting that these rare earth complexes have fundamentally similar structures.[9] Although the LDI-TOF MS has a mass accuracy of about ±0.1%,[7] the proposed framework was strongly supported by the similarity of the mass spectra of the various rare earth complexes, since rare earth elements have their own atomic weight and isotope abundance distribution.

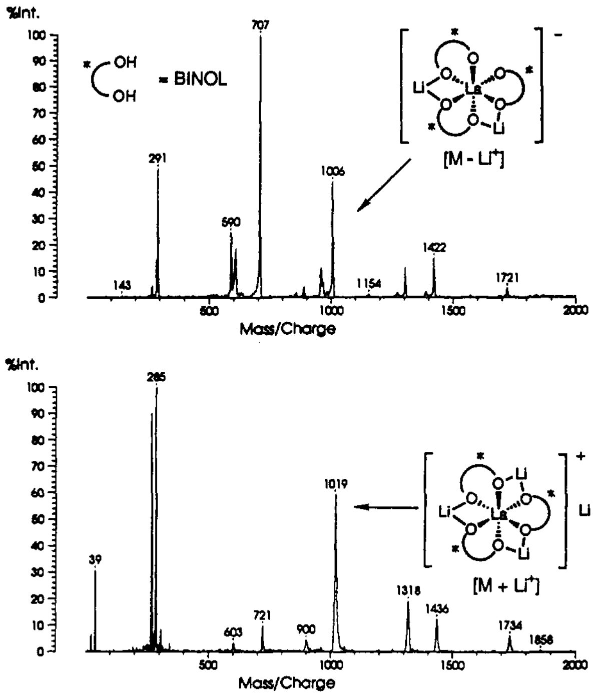

Figure 1. Laser desorption/ionization time-of-flight mass spectra of La–(*S*)-BINOL complex in anionic (top) and cationic (bottom) modes.

Although several attempts were made to obtain an X-ray grade crystal of a rare earth complex, these were largely unsuccessful. One reason for the low crystalline character of these rare earth complexes might be contamination due to soluble LiCl in the catalyst solution. Therefore, we turned our attention to preparing the crystals under Li-free conditions. Starting from rare earth (La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Er, Yb, and Y) trichlorides, disodium (*S*)-binaphthoxide, NaO-*t*-Bu, and H_2O,[10] we were pleased to find that several of the rare earth complexes, with the exception of La, could be crystallized from THF. Thermal analysis of the crystals showed that none of the crystals had a clear melting point and that all of the crystals lost almost 30% of their weight when heated to 300 °C.[9] These results suggested the presence of six THF molecules coordinated to the metal and a few H_2O molecules in the crystal. The composition was attributable to $LnNa_3$tris(binaphthoxide)·6THF·2H_2O (Ln = rare earth metal) from the elemental analysis.[9] X-ray crystallographic analyses of Eu, Nd, and Pr complexes prove this hypothesis. Figure 2 displays the structure of the Eu complex. X-ray crystallographic analyses shows that Eu-, Pr-, and Nd-containing crystals have almost the same structure except for the distance of the atoms around the center rare earth metal.[9,11] For example, the bond

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(2) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.

(3) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851–854.

(4) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* 1993, *34*, 855–858.

(5) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657–2660.

(6) See supplementary material of ref 2.

(7) Performed by use of the Shimadzu/Kratos KOMPACT MALDI III apparatus.

(8) Hillenkamp, F.; Karas, M. *Methods in Enzymology, Vol. 193. Mass Spectrometry;* McCloskey, J. A., Eds.; Academic Press, Inc.: San Diego, CA, 1990; pp 280–295.

(9) See supplementary material.

(10) The molar ratio was 1:2:1:11, respectively. See ref 5.

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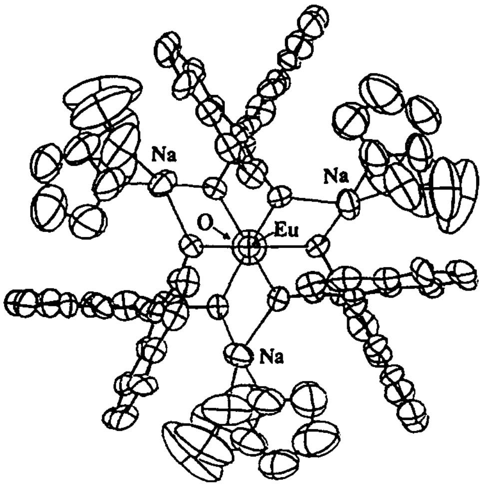
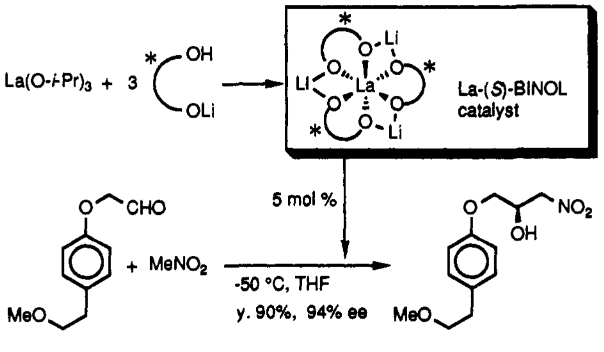


Figure 2. ORTEP drawing for EuNa$_3$tris((*S*)-binaphthoxy)·6THF·H$_2$O with 50% thermal ellipsoids (hydrogens omitted).

Scheme I



length between the rare earth metals and oxygens of BINOL were Eu–O, 2.286 and 2.312; Nd–O, 2.338 and 2.363; and Pr–O, 2.365 and 2.386 Å. These results suggest that small changes in the structure of the catalyst (*ca.* 0.1 Å in bond length) cause a drastic change in the optical purity of nitroaldols produced.[5,9] Each rare earth (*S*)-BINOL complex has an asymmetric center at the rare earth metal so that the (*S*)-BINOL complex can exist as a diastereomixture. Nevertheless, it is interesting to note that Pr, Nd, and Eu complexes starting from (*S*)-BINOL exist only in the Λ-configuration, perhaps due to the greater thermodynamic stability of this configuration than the Δ-form.

All the above-mentioned crystals were basic and acted as catalysts for the nitroaldol reaction. However, the nitroaldols thus obtained were mostly racemic mixtures. For example, in the case of reaction of hydrocinnamaldehyde with nitromethane at –40 °C, the results were as follows: Eu, 72% yield, 3% ee (*S*) configuration; Nd, 83%, 7% ee (*R*); Pr, 80%, 9% ee (*R*). On the other hand, only after they were stirred for 3 days with 3 equiv of LiCl in THF did the solutions prove to be efficient asymmetric catalysts (Eu, 84%, 70% ee (*R*); Nd, 71%, 68% ee (*R*); Pr, 84%, 73% ee (*R*)). Again by analysis with the LDI-TOF MS method, all Li-free crystals showed similar mass patterns (cf. Figure 1) except that they contained Na instead of Li.[9] Moreover, complete exchange of Na with Li, on addition of LiCl to the catalyst, was also observed with LDI-TOF MS.[9]

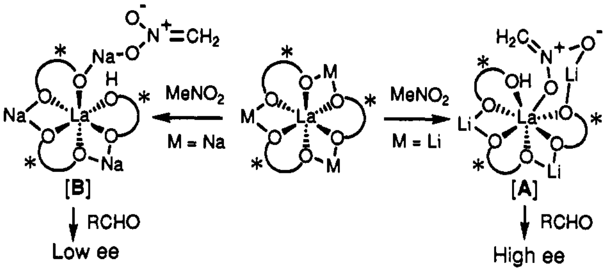


Figure 3. Proposed mechanisms for the rare earth BINOL complex catalyzed asymmetric nitroaldol reactions.

The disclosed structure of the rare earth complexes led us to prepare the La–BINOL complex in a rationally designed procedure.[12] Namely, to a stirred suspension of monolithium (*S*)-binaphthoxide was added a THF solution of La(O-*i*-Pr)$_3$[13] (0.33 mol equiv) at room temperature.[9] This catalyst solution also gave almost the same LDI-TOF mass spectra as depicted in Figure 1, and also showed excellent catalytic activity in the asymmetric nitroaldol reaction (Scheme I).

On the basis of the knowledge of the structure of the catalyst, we propose the following mechanism for the asymmetric nitroaldol reaction Figure 3. Reaction of the catalyst with nitromethane initially affords a rare earth nitronate [**A**], wherein the increased coordination around the La atom causes it to be more acidic. The carbonyl oxygen of an aldehyde can then coordinate to the La atom more easily to form the nitroaldol derivative. In contrast, with the Li-free catalyst (Na-containing catalyst), sodium nitronate [**B**], in which the asymmetric center is far from the arising carbon–carbon bond, is formed, resulting in poor enantioselectivity. This result appears to be ascribed to the difference of electronegativity between Li and Na. Further studies along this line are now in progress.

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Supplementary Material Available: Synthetic, spectroscopic, and analytical data, LDI-TOF mass spectra for the rare earth complexes, X-ray experimental details including tables of positional and anisotropic displacement parameters, tables of bond lengths and angles for the Eu, Pr, and Nd complexes, and perspective drawings for the Nd and Pr complexes (37 pages); listings of observed and calculated structure factor amplitudes for the Eu, Pr, and Nd complexes (29 pages). Ordering information is given on any current masthead page.

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(11) Crystal data for the rare earth BINOL complexes collected at 291 K: EuNa$_3$C$_{60}$H$_{36}$O$_6$·6THF·H$_2$O, space group $P6_3$, a = 15.279(2) Å, b = 15.279(2) Å, c = 18.454(8) Å; α = 90.00(0)°, β = 90.00(0)°, γ = 120.00(0)°, Z = 6. The structure was solved by direct methods and refined to $R(F)$ = 0.055, $R_w(F)$ = 0.045. NdNa$_3$C$_{60}$H$_{36}$O$_6$·6THF·H$_2$O, space group $P6_3$, a = 15.295(1) Å, b = 15.295(1) Å, c = 18.459(2) Å; α = 90.00(0)°, β = 90.00(0)°, γ = 120.00(0)°, Z = 6. The structure was solved by direct methods and refined to $R(F)$ = 0.050, $R_w(F)$ = 0.049. PrNa$_3$C$_{60}$H$_{36}$O$_6$·6THF·H$_2$O, space group $P6_3$, a = 15.309(2) Å, b = 15.309(2) Å, c = 18.452(8) Å; α = 90.00(0)°, β = 90.00(0)°, γ = 120.00(0)°, Z = 6. The structure was solved by direct methods and refined to $R(F)$ = 0.042, $R_w(F)$ = 0.048.

(12) It is essential to add NaOH and H$_2$O for the preparation of the effective catalyst from LaCl$_3$. It appears that NaOH neutralizes HCl generated by the reaction of LaCl$_3$ with H$_2$O. Furthermore, it seems likely that the presence of H$_2$O accelerates the catalyst formation.

(13) Purchased from Soekawa Chemical Co., Ltd., Tokyo, Japan.