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Catalytic Asymmetric Nitroaldol Reactions. A New Practical Method for the Preparation of the Optically Active Lanthanum Complex

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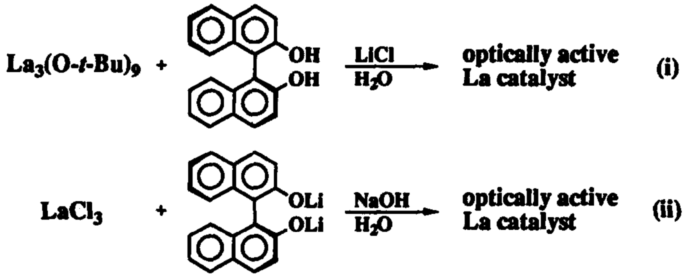
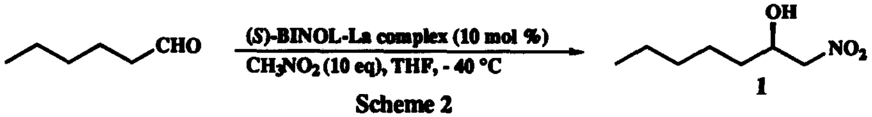
Abstract: The optically active La complex, which catalyzes asymmetric nitroaldol reactions, was found to be readily prepared from $LaCl_3 \cdot 7H_2O$*. The presence of water, LiCl or LiBr and an alkali metal hydroxide was essential for the formation of the effective lanthanum binaphthoxide complex.*

The nitroaldol reaction (*Henry* reaction) is one of the powerful C-C bond-forming reactions in organic synthesis. Recently, we have reported that rare earth metal alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$ exhibit basic character, which can be utilized in aldol reactions, cyanosilylations and nitroaldol reactions. Furthermore, we have succeeded in demonstrating the first catalytic asymmetric nitroaldol reaction using the optically active La complex.[2] The optically active lanthanum complex was originally prepared by the following two methods: (i) the reaction of $La_3(O\text{-}t\text{-}Bu)_9$ with (*S*)-(-)-binaphthol followed by the addition of H_2O and LiCl, (ii) the reaction of $LaCl_3$ with dilithium (*S*)-binaphthoxide in the presence of NaOH and H_2O (Scheme 1). In order to develop a more effective method for the preparation of the catalyst as well as obtain more structural information about the catalyst, we have further studied on the preparation of the optically active La complex. In this communication, we report a much more practical method for the preparation of the La complex using inexpensive $LaCl_3 \cdot 7H_2O$ directly, and more information about the structure of the La complex as well.



Scheme 1

Since $La_3(O\text{-}t\text{-}Bu)_9$ was found to be air and moisture sensitive, the direct preparation of the catalyst starting from $LaCl_3$ was further investigated in great detail. In general, synthesis of lanthanum alkoxides or aryloxides from lanthanum halides and alkali metal alkoxides or aryloxides is carried out in anhydrous conditions.[3,4] However, we found that the reaction of anhydrous $LaCl_3$ with dilithium binaphthoxide in THF did not proceed even at reflux temperature (4 hr). On the other hand, the reaction was found to proceed even at room temperature in the presence of a small amount of H_2O.[2] Therefore, we began examination of the effect of H_2O on the enantioselectivity in the catalytic asymmetric nitroaldol reaction. The various catalysts were first prepared from anhydrous $LaCl_3$, dilithium (*S*)-binaphthoxide (1 mol equiv), NaO-*t*-Bu (1 mol equiv)[5] and H_2O (0 - 30 mol equiv) (THF, room temperature),[6] and the catalytic asymmetric nitroaldol reactions of hexanal[7] were carried out using these catalysts. The results are summarized in Figure 1,[8] showing that the best result is obtained using the catalyst prepared from 10 molar equivalents of H_2O.



Scheme 2

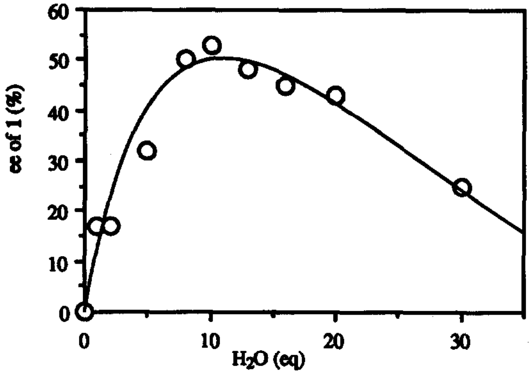
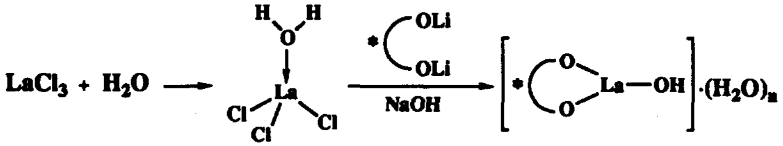


Figure 1. Effect of H_2O on the Catalytic Asymmetric Nitroaldol Reaction of Hexanal.

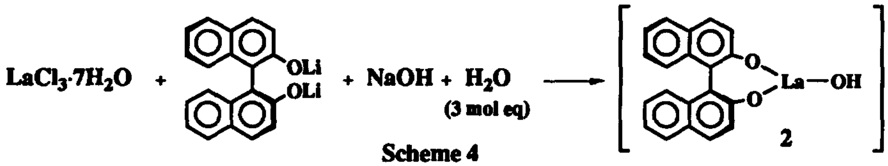
The effect of H_2O is considered to be as follows at present. First, it seems reasonable to suppose that the reaction of $LaCl_3$ with dilithium binaphthoxide or NaOH is accelerated by the coordination of H_2O to $LaCl_3$.[9] Second, some H_2O molecules are anticipated to coordinate to the optically active La complex, thereby modifying the asymmetric environment of the La complex.



Scheme 3. Possible Reaction Mechanism of $LaCl_3$ with Dilithium Binaphthoxide in the Presence of H_2O.

Next, the effect of an alkali metal hydroxide on the preparation of the La catalyst was investigated. The catalyst, prepared from $LaCl_3$, dilithium binaphthoxide (1 mol equiv) and KO-*t*-Bu (1 mol equiv)[10] in THF containing H_2O (11 mol equiv), was found to give the nitroaldol **1** of 43% ee in 85% yield. Likewise, the catalyst, prepared from LiOH,[11] afforded **1** of 37% ee in 85% yield. Furthermore, the catalyst, prepared from $LaCl_3$, dilithium binaphthoxide (1 mol equiv) and H_2O (10 mol equiv) in the absence of an alkali metal hydroxide, gave **1** of 56% ee albeit in modest yield (50%), revealing that an alkali metal hydroxide had not the great effect on the catalyst formation. In marked contrast to these results, an alkali metal binaphthoxide was found to have the great effect on the catalyst formation. That is, surprisingly, the reaction barely proceeded to give nearly racemic **1** in very low yield by the use of the catalyst, which was prepared from $LaCl_3$, disodium binaphthoxide, NaO-*t*-Bu[5] and H_2O in THF.[12] The asymmetric induction (37% ee), however, was observed by adding LiCl (2 mol equiv) to that catalyst albeit in low yield. Furthermore, the catalyst, prepared from $LaCl_3$ in the presence of LiCl (1 - 3 mol equiv), afforded optically active 1 in modest yield (1 mol equiv of LiCl : 55% yield, 44% ee ; 2 mol equiv of LiCl : 49% yield, 50% ee ; 3 mol equiv of LiCl : 67% yield, 48% ee), suggesting that LiCl affected the structure of the asymmetric catalyst as well as the reaction rate of the catalyst formation. Since lanthanum ate complexes containing LiCl have been often reported,[3] it seems reasonable to suppose that LiCl is incorporated into the asymmetric catalyst. Addition of other inorganic salts (2 mol equiv to La) such as LiF, LiI, NaCl, KCl, $CaCl_2$, $MgCl_2$ and $ZnCl_2$ gave the far less unsatisfactory results. However, the use of LiBr was found to give 1 of 42% ee in 87% yield (-40 °C, 41 hr).[13]

These results clearly show that the presence of 10 equiv of H_2O, 2-3 equiv of LiCl or LiBr and 1 equiv of alkali metal hydroxides such as NaOH, KOH and LiOH is essential for the formation of the effective lanthanum binaphthoxide catalyst. In order to simplify the procedure for the preparation of the catalyst, we undertook to make use of inexpensive hydrated $LaCl_3$ directly. After several attempts, we succeeded in developing the following procedure. To a stirred suspension of $LaCl_3 \cdot 7H_2O$ (1.85 g, 5.0 mmol) in THF (62 ml) was successively added a solution of dilithium (*S*)-binaphthoxide[14] in THF (31 ml), a solution of NaO-*t*-Bu (496 mg, 5.0 mmol) in THF (6 ml) and a solution of H_2O (20 mmol) in THF (1 ml). After being stirred vigorously for 30 hr at room temperature, the reaction mixture was allowed to stand overnight, and the supernatant was used as an asymmetric catalyst.[15] Reaction of hexanal with nitromethane (10 equiv) at -40 °C using the catalyst (10 mol %) thus prepared gave the (*R*) adduct 1 with 52% ee in 80% yield. Furthermore, reaction of cyclohexanecarboxaldehyde with nitromethane (10 equiv) at -40 °C afforded the (*R*) adduct of 87% ee. We believe that this procedure is practically useful, because $LaCl_3 \cdot 7H_2O$ is inexpensive[16] and binaphthol is perfectly recovered without racemization after the nitroaldol reaction. In addition, this catalyst is stable at room temperature and does not lose its activity over several months.



Scheme 4

Finally, we investigated the asymmetric amplification[17] using the reaction of nitromethane with α-naphthoxyacetaldehyde.[18] The asymmetric La complex was first prepared from (*S*)-binaphthol (optical purity 56%), and it was found that this catalyst gave (*R*) adduct of 68% ee in 65% yield at -40 °C. This result suggests that the asymmetric catalyst should exist as an oligomer. At present, the structure of the monomer is speculated to be 2 on the basis of the results described in this paper (Scheme 4).

In conclusion, we have found that lithium halides such as LiCl and LiBr, alkali metal hydroxides such as NaOH, KOH and LiOH, and H_2O play a key role in the preparation of the effective La catalyst. Furthermore, we have succeeded in developing a practical method for the preparation of the asymmetric catalyst from $LaCl_3 \cdot 7H_2O$.[19] The structural elucidation of the catalyst is under investigation.

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References and Notes

1. On leave from Upjohn Pharmaceuticals Limited, Tsukuba, Japan.
2. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M., *J. Am. Chem. Soc.*, **1992**, *114*, 4418.
3. a) Mehrotra, R. C.; Singh, A.; Tripathi, U. M., *Chem. Rev.*, **1991**, *91*, 1287.
   b) Evans, W. J.; Sollberger, M. S.; Hanusa, T. P., *J. Am. Chem. Soc.*, **1988**, *110*, 1841.
4. Lappert, M. F.; Singth, A., *J. Chem. Soc., Chem. Commun.*, **1981**, 1191.
5. NaO-*t*-Bu is used instead of NaOH just for convenience, because NaO-*t*-Bu is soluble in THF and powdered NaOH is readily prepared from NaO-*t*-Bu and H_2O in situ.
6. To a suspension of anhydrous $LaCl_3$ in THF was successively added dilithium (*S*)-binaphthoxide (1 mol equiv), NaO-*t*-Bu (1 mol equiv), and H_2O (0 - 30 mol equiv) at room temperature. After being stirred overnight, the reaction mixture was centrifuged, and the supernatant was used as an asymmetric catalyst.
7. The optical purity of the adduct is readily determined by HPLC analysis using DAICEL CHIRALPAK AS. The absolute configuration of **1** was determined by the CD exciton chirality method using the dibenzoate derived from the corresponding amino alcohol.
8. The nitroaldol reaction of hexanal with nitromethane (10 equiv) was carried out using 10 mol % of the catalyst at -40 °C, giving **1** in yields ranging from 70% to 90%.
9. The coordination of H_2O to $LaCl_3$ may lengthen a La-Cl bond, therby increasing the reactivity of $LaCl_3$. See: Greeves, N.; Lyford, L., *Tetrahedron Lett.*, **1992**, *33*, 4759.
10. Used instead of KOH just for convenience.
11. BuLi was used just for convenience.
12. The reason why the nitroaldol reaction hardly proceeded is not clear at present. These reaction conditions may produce inactive species mainly.
13. For the recent report of the effect of LiX on asymmetric alkylation, see:
    Murakata, M; Nakajima, M.; Koga, K., *J. Chem. Soc., Chem. Commun.*, **1990**, 1657.
14. The dilitium binaphthixide was prepared from dry binaphthol (1.43 g, 5.0 mmol) and BuLi (1.54*M* hexane solution: 6.5 ml, 10.0 mmol) at 0 °C. Binaphthol was dried under reduced pressure at about 50 °C for 2 hr before use.
15. Used as ca. 0.05 *M* catalyst solution.
16. $LaCl_3$ (Soekawa, 25 g, 8,600 yen) ; $LaCl_3 \cdot 7H_2O$ (Wako EP, 25 g, 1,000 yen).
17. For the recent reports of asymmetric amplification, see:
    a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B., *J. Am. Chem. Soc.*, **1986**, *108*, 2353.
    b) Oguni, N.; Matsuda, Y.; Kaneko, T., *J. Am. Chem. Soc.*, **1988**, *110*, 7877.
    c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R., *J. Am. Chem. Soc.*, **1989**, *111*, 4028.
    d) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K., *Chem. Lett.*, **1989**, 1581.
    e) Hayashi, M.; Matsuda, T.; Oguni, N., *J. Chem. Soc., Chem. Commun.*, **1990**, 1364.
    f) Terada, M.; Mikami, K.; Nakai, T., *J. Chem. Soc., Chem. Commun.*, **1990**, 1623.
18. The asymmetric La complex prepared from optically pure (*S*)-binaphthol produced the adduct in 91% ee at -40 °C. See the following paper in this issue.
19. The use of other binaphthol derivatives such as 3,3'-dimethyl-binaphthol has been also investigated. However, more satisfactory results have not been obtained so far.

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