Tetrahedron Letters, Vol. 34, No. 16, pp. 2657-2660, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Effects of Rare Earth Metals on the Catalytic Asymmetric Nitroaldol Reaction

Hiroaki Sasai, Takeyuki Suzuki, Noriie Itoh,[1]
Shigeru Arai, and Masakatsu Shibasaki*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: Various asymmetric rare earth complexes have been prepared from rare earth metal trichlorides such as YCl_3, $LaCl_3$, $PrCl_3$, $NdCl_3$, $SmCl_3$, $EuCl_3$, $GdCl_3$, $TbCl_3$ and $YbCl_3$, dilithium (*R*)-binaphthoxide, NaOH and H_2O. The optical purities of nitroaldols obtained using these rare earth complexes as an asymmetric catalyst have been highly dependent on the size of rare earth metals. The application to a catalytic asymmetric synthesis of (*S*)-metoprolol, a β_1-selective β-blocker, has been also achieved.

Rare earth complex catalyzed asymmetric syntheses have received much attention in recent years.[2] In the previous papers,[3-5] we have also reported the first success on the development of a catalytic asymmetric nitroaldol reaction utilizing the optically active La binaphthoxide complex as a base. Rare earth metals are a series of analogous elements in which the +3 oxidation state is most stable. The ionic radius of an octa coordinated trivalent rare earth element decreases as the increase of atomic number of a rare earth element from 1.18 Å in La to 0.97 Å in Lu, reflecting the so-called lanthanoid contraction.[6] On the other hand, the ionic radius increases with increase in coordination number. It was envisioned that the shorter metal-oxygen bonds in asymmetric rare earth metal complexes would result in the formation of a closer asymmetric environment without changing the fundamental structure of catalysts, thereby showing different reactivities in the asymmetric nitroaldol reaction. In this letter, we report effects of various rare earth elements on the catalytic asymmetric nitroaldol reaction. This is the first systematic study which reveals the correlation between a series of rare earth metals and a catalytic asymmetric reaction.

At the beginning of this study, all the rare earth metal complexes were attempted to be prepared according to the previous method for the La complex formation.[4] Namely, an anhydrous rare earth metal trichloride, dilithium (*R*)-binaphthoxide, NaOH, and H_2O were successively mixed in a molar ratio of 1:1:1:10 in THF (8 ml per 0.4 mmol of rare earth metal chloride). The capability of these complexes as an asymmetric catalyst was studied by the nitroaldol reaction utilizing nitromethane and hydrocinnamaldehyde (**1a**). As shown in Table 1 (run 1), we were pleased to find that either the Pr or the Nd complex showed similar or slightly higher reactivity compared to the La complex catalyst. In contrast, other rare earth metals

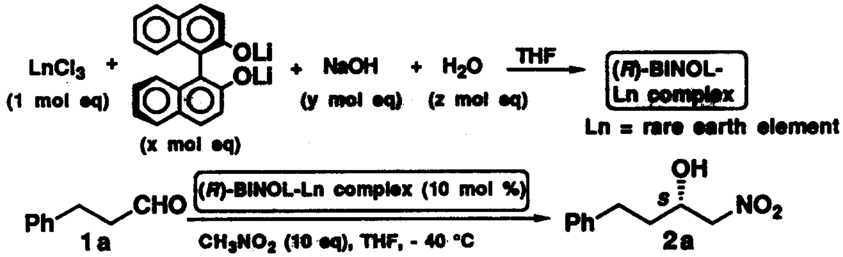


Table 1

run	ratio (1:x:y:z)	% yield (ee, %) of 2a La	Pr	Nd	Sm	Eu	Gd	Tb	Yb	Y
1	(1:1:1:10)	78(71)	68(72)	86(69)	25(15)	93(29)	78(33)	89(24)	11(4)	72(5)
2	(1:2:1:10)	79(53)	82(56)	87(54)	76(70)	65(69)	96(63)	100(44)	70(10)	76(39)
3	(1:1:2:10)		75(47)	89(59)	87(69)	55(59)	76(53)		89(5)	87(25)
4	(1:1:1:20)		92(67)	35(46)	68(42)	99(28)	94(13)	97(15)	30(0)	78(5)*

* (*R*)-configuration

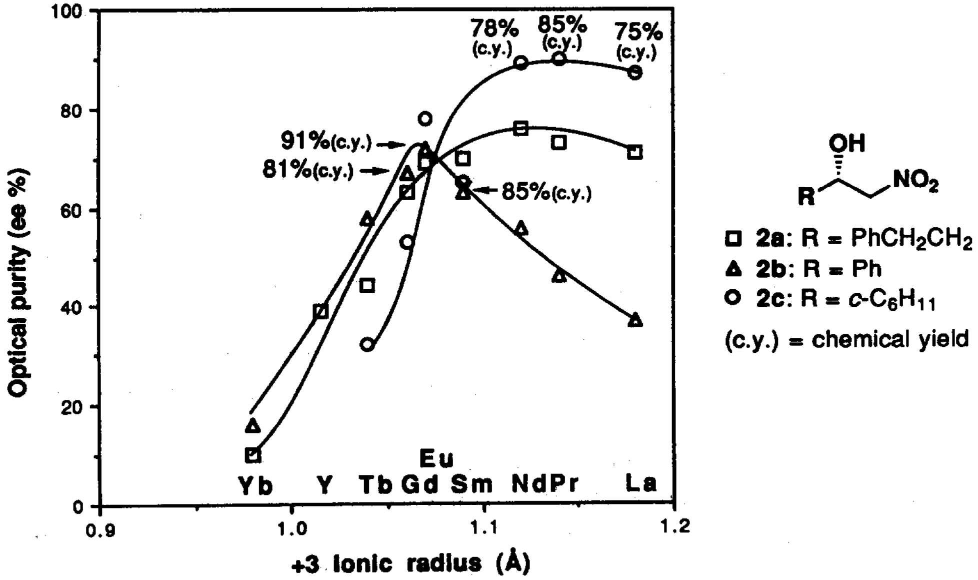


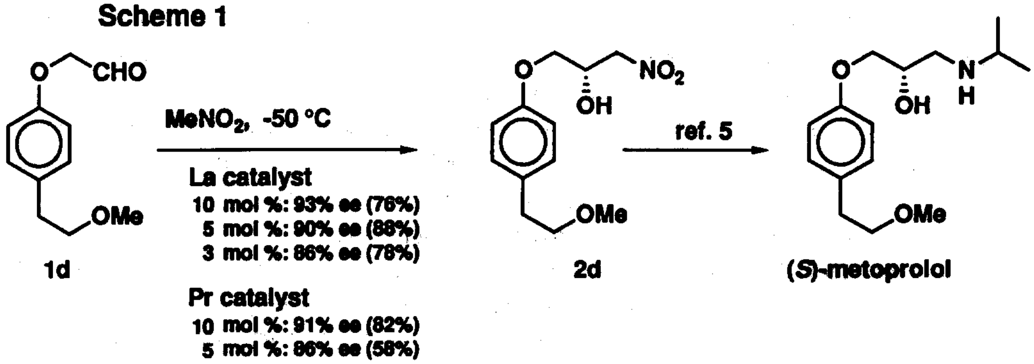
Figure 1. Effects of the ionic radii of rare earth elements on the optical purities of nitroaldol derivatives.

with shorter ionic radius gave unsatisfactory results in terms of both chemical and optical yields. In order to find much better conditions for the rare earth complex formation, next we examined the mixing ratio of a rare earth trihalide, dilithium (*R*)-binaphthoxide, NaOH and H_2O. The representative results are given in Table 1 (run 2, 3, 4), showing that all the rare earth (*R*)-binaphthoxide catalysts give the nitroaldols **2a** with (*S*)-configuration except for a certain Y catalyst (run 4).[7,8] Furthermore, in the case of Sm, Eu, Gd, Tb, Yb, and Y the ratio of 1:2:1:10 turned out to give the best chemical and optical yields.[9,10] However, for the Tb, the Yb and the Y catalysts, the optical yields of **2a** did not reach the level obtained by the use of the early rare earth catalysts. These differences between early rare earth metals (La, Pr, Nd) and late rare earth metals (Sm, Eu, Gd, Tb, Yb, Y) could be attributed to the following two facts. Firstly, compared to the La complex formation in which a part of $LaCl_3$ remained undissolved, $SmCl_3$, $EuCl_3$, $GdCl_3$, $TbCl_3$, $YbCl_3$ and YCl_3 showed fairly good reactivity toward dilithium (*R*)-binaphthoxide, thereby the mixing ratio of a rare earth metal and lithium (*R*)-binaphthoxide for the preparation of best catalysts had to be changed. In particular, $EuCl_3$ reacted smoothly with dilithium (*R*)-binaphthoxide to give a deep yellow clear solution. Nevertheless, addition of NaOH and H_2O was found to be necessary to obtain nitroaldols of high ee.[11] Secondly, rare earth complexes derived from late rare earth metals with shorter ionic radius possibly result in the formation of structurally different oligomers,[4] hereby giving **2a** of lower ee.

With a number of rare earth metal complex solutions available, we further investigated rare earth metal effects on the catalytic asymmetric nitroaldol reaction using structurally different aldehydes. Interestingly the optical purities of nitroaldols were also found to be highly dependent on the structure of aldehydes. The unique relationship between ionic radius of rare earth metals and the optical purities of the nitroaldols is depicted in Figure 1. For example, when benzaldehyde and nitromethane were used as a starting material, the Eu complex gave (*S*)-**2b** in 72% ee (91%) in contrast to 37% ee (81%) in the case of the La complex (-40 °C, 40 h).[7,12,13] Many bioactive amino-alcohol derivatives have been developed which could be prepared by the catalytic asymmetric nitroaldol reaction of an aromatic aldehyde with a nitroalkane.[14] Thus, the Eu complex could serve as an effective reagent for *de novo* synthetic routes to useful compounds. In the case of the aldehyde **1d**,[15] the optical purity of the nitroaldol **2d** was 89% ee (86%, Nd), 91% ee (82%, Pr) and 93% ee (76%, La) at -50 °C.[7,8] Furthermore when using 5 mol % and 3 mol % of the La complex, we obtained the nitroaldol **2d** in 90% ee (88%) and 86% ee (78%), respectively. The slight decrease in the optical purity of the nitroaldol **2d** with the decrease in percent of the catalyst employed could be attributed to the dissociation of (*R*)-binaphthol from the catalyst by an exchange with nitromethane. The nitroaldol **2d** was easily converted into the β_1-selective β-blocker, metoprolol, in one pot reaction (Scheme 1).[5]

In conclusion, we have revealed the relationship between the ionic radii of rare earth metals and the optical purities of products in the catalytic asymmetric nitroaldol reaction. Rare earth metals are abundant elements but their isolation from one another requires expensive ore processing plants. Similar reactivity in early rare earth metal catalysts suggests the use of a mixture of early rare earth metals (misch metal) which is easily obtained from the ore. Isolation of each rare earth complex and the structural elucidation are now under progress.

Scheme 1



References and Notes

1. On leave from Upjohn Pharmaceuticals Limited, Tsukuba, Japan.
2. For the recent progress in asymmetric reactions using rare earth elements, see the following reviews and references. (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68. (c) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.*, **1992**, *114*, 2761-2762. (d) Gagne, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics*, **1992**, *11*, 2003-2005. (e) Takeuchi, S.; Miyoshi, N.; Hirata, K.; Hayashida, H.; Ohgo, Y. *Bull. Chem. Soc. Jpn.*, **1992**, *65*, 2001-2003. (f) Okawa, H.; Katsuki, T.; Nakamura, M.; Kumagai, N.; Shuin, Y.; Shinmyozu, T.; Kida, S. *J. Chem. Soc., Chem. Commun.*, **1989**, 139-140. (g) Gu, J.-H.; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.*, **1992**, *33*, 1465-1468. (h) Gu, J.-H.; Okamoto, M.; Terada, M.; Mikami, K.; Nakai, T. *Chem. Lett.*, **1992**, 1169-1172. (i) Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.*, **1990**, *112*, 8189-8190. (j) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **1990**, *112*, 6447-6449. (k) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.*, **1983**, *105*, 3717-3719. (l) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.*, **1986**, *108*, 7060-7067. (m) Quimpère, M.; Jankowski, K. *J. Chem. Soc., Chem. Commun.*, **1987**, 676-677. (n) Zehani, S.; Gelbard, G. *J. Chem. Soc., Chem. Commun.*, **1985**, 1162-1163. (o) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.*, **1991**, *113*, 8036-8045. (p) Starodubtseva, E. V.; Konenko, I. R.; Fedorovskaya, E. A.; Klabunovskii, E. I.; Mordovin, V. P. *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1988**, 2725-2728.
3. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.*, **1992**, *114*, 4418-4420.
4. Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.*, *in press*.
5. Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.*, *in press*.
6. Sinha, S. P. *Structure and Bonding*, **25**, Springer-Verlag: New York. 1976; pp. 69-149.
7. The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AD or CHIRALCEL OJ.
8. The absolute configuration was determined by the CD exciton chirality method using the dibenzoate derived from the corresponding amino-alcohol.
9. In the case of the Pr catalyst preparation, the ratio of 1:1.5:1:10 gave the slightly better result (73% ee, 76% yield).
10. In the case of the Nd catalyst preparation, the ratio of 1:1:1:5 gave the best result (76% ee, 76% yield). The use of hydrated $NdCl_3$ also afforded the nitroaldol **2a** in 85% yield (72% ee). See reference 4.
11. The Eu catalyst prepared without NaOH and H_2O afforded **2b** in 32% ee (90%) and without NaOH gave **2b** in 51% ee (93%).
12. The absolute configuration was determined by comparison of the specific rotation of the corresponding amino-alcohol.
13. Lowering the reaction temperature (-60 °C) increased the optical purity of **2b** to 75% ee (92% yield).
14. For pharmacologically important β-amino alcohols, see: Lednicer, D. A.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; J. Wiley and Sons: New York. 1975.
15. Prepared according to the method for the synthesis of the propranolol intermediate. See ref. 5.

(Received in Japan 18 January 1993)