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The First Tandem Inter-Intramolecular Catalytic Asymmetric Nitroaldol Reaction Utilizing a $\mathbf{LnLi_3tris((\mathit{R})\text{-}binaphthoxide)}$ Complex ((*R*)-LnLB) (Ln: Lanthanoid)[1]

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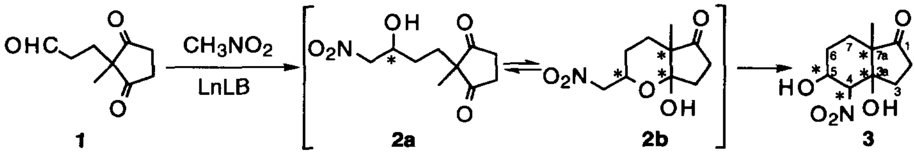
Abstract: *We have succeeded in synthesizing optically active (3aR,4R,5S,7aS)-3a,5-dihydroxy-7a-methyl-4-nitro-3a,4,5,6,7,7a-hexahydro-1-indanone (**3b**) with 65% ee in one-pot from aldehyde **1** and nitromethane using a tandem inter-intramolecular catalytic asymmetric nitroaldol reaction promoted by $LnLi_3tris((R)$-binaphthoxide) (LnLB; Ln = lanthanoid) and after crystallization **3b** with 79% ee was isolated in 41% yield. In addition, after recrystallization, the optical purity of **3b** was increased to 96% ee.* © 1997 Elsevier Science Ltd.

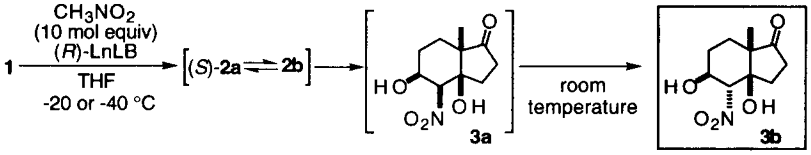
Recently, tandem reactions have been of interest in organic synthesis due to their efficient structural construction.[2a-h] Tandem catalytic asymmetric syntheses are especially useful because optically active compounds with several chiral centers can be constructed from simple achiral compounds in one-pot using a small amount of an asymmetric catalyst. The development of such methods has been recognized as one of the most challenging themes in organic synthesis.[2i-m] In previous publications,[3] we have demonstrated several catalytic asymmetric nitroaldol reactions promoted by the $LnLi_3$tris(binaphthoxide) complex (LnLB) (Ln: lanthanoid). Nevertheless, neither intramolecular catalytic asymmetric nitroaldol reactions nor tandem catalytic asymmetric inter-intramolecular catalytic asymmetric nitroaldol reactions have been achieved. We expected that a tandem inter-intramolecular catalytic asymmetric nitroaldol reaction could be achieved using **1**[4] and nitromethane in the presence of a catalytic amount of LnLB (Scheme 1). That is, first **1** would react with nitromethane in the manner of an intermolecular catalytic asymmetric nitroaldol reaction to give optically active **2**, and then **2** would react with an internal ketone in the manner of an intramolecular catalytic asymmetric nitroaldol reaction to give optically active 3a,5-dihydroxy-7a-methyl-4-nitro-3a,4,5,6,7,7a-hexahydro-1-indanone (**3**). Herein, we wish to report the first tandem inter-intramolecular catalytic asymmetric nitroaldol reaction promoted by LnLB.



Scheme 1

We first carried out a tandem inter-intramolecular catalytic asymmetric nitroaldol reaction using **1**, nitromethane (10 mol equiv) in the presence of $LaLi_3$tris((*R*)-binaphthoxide) complex (LLB) (10 mol %) in THF at -20 °C, resulting in the formation of **2a**, **2b** and one diastereoisomer of **3**.[5] After the complete disappearance of **1**, as detected by TLC (115 h), the reaction mixture was warmed to room temperature and stirred for an additional 24 h at the same temperature, which gave rise to complete conversion of **3a** into another diastereoisomer **3b**. The structure of the new compound **3b** was determined by X-ray structural analysis as shown in Table 1.[6] The optical purity of **3b** was found to be 39% ee. Although the purification of **3b** by silica gel column chromatography was quite difficult, direct crystallization of the crude mixture from CH_2Cl_2 gave a white powder of **3b** with 41% ee in 59% yield.[7]

Table 1. Tandem Inter-intramolecular Catalytic Asymmetric Nitroaldol Reaction



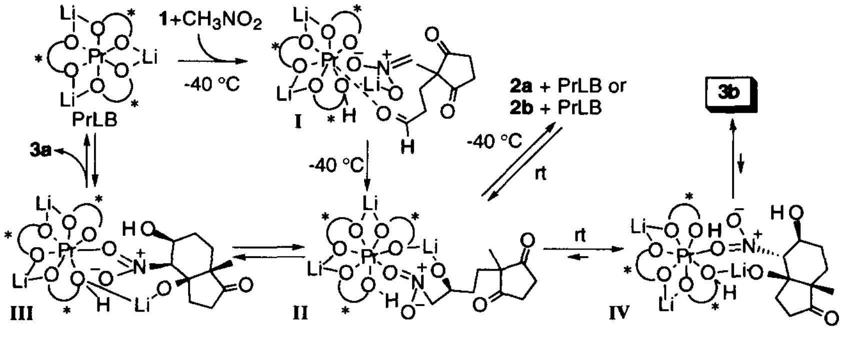
entry	catalyst (mol %)	temp (°C) (time (h))	ee of crude **3b**	yield of **3b** (%) (1st crop)	ee of **3b** (%) (1st crop)
1	LLB (10)	-20 (115) to rt (24)	39	59	41
2	LLB (10)	-20 (115) to 50 (25)	~5	56	7
3	PrLB (10)	-20 (119) to rt (24)	48	47	60
4	SmLB (10)	-20 (119) to rt (24)	28	43	51
5	GdLB (10)	-20 (119) to rt (24)	36	47	41
6	DyLB (10)	-20 (119) to rt (24)	34	34	43
7	YbLB (10)	-20 (119) to rt (24)	7	37	12
8	PrLB (10)	-40 (115) to rt (24)	58	42	71
9	PrLB (5)	-40 (145) to rt (71)	53	45	66
10[a]	PrLB (5)	-40 (112) to rt (24)	65	41	79

a: 30 mol equiv of nitromethane were used.

With the first rather interesting result in hand, the use of other many heterobimetallic asymmetric catalysts such as LnLB, LnSB, LnPB, ALB and GaLB was examined under a variety of reaction conditions, showing that, as expected,[3] LnLB was the most useful asymmetric catalyst for the present purpose.[8] Table 1 shows only the modest to good results using LnLB in THF. An increase in reaction temperature to 50 °C caused a decline in ee of **3b** (entry 2).[9] Selection of lanthanoid metals was found to be effective for the improvement of ee of **3b** (entries 3-7).[3d] When using $PrLi_3$tris((*R*)-binaphthoxide) (PrLB) as a catalyst, the optical purity of the crude **3b** was improved to 48% ee. The initial temperature also appeared to affect the ee. That is, when the initial temperature was -40 °C, the optical purity of **3b** was increased to 58% ee (entry 8). Moreover, it was possible to reduce the amount of (*R*)-PrLB; when 5 mol % of PrLB was used, **3b** with 53% ee was formed (entry 9). An increase in the amount of nitromethane was surprisingly found to improve the ee of **3b**.[10] That is, **3b** with 65% ee was produced by the reaction of **1** and 30 mol equiv of nitromethane catalyzed by 5 mol % of (*R*)-PrLB (-40 °C for 112 h and then at room temperature for 24 h) and, after crystallization, **3b** with 79% ee was isolated in 41% yield (entry 10).[11] The optical purity of **3b** (69% ee) was increased to 96% ee[12] (57% recovery) after recrystallization from AcOEt-hexane (3/1) in the presence of a small amount of CH_3OH.

The proposed mechanism by which **3b** was produced is shown in Scheme 2. PrLB is a multifunctional heterobimetallic asymmetric catalyst displaying both Lewis acidity and Brϕnsted basicity; the Pr atom works as a Lewis acid and the Li-naphthoxide portion functions as a Brϕnsted base.[13] Thus, **1** is activated by the Pr atom and nitromethane is deprotonated by the Li-naphthoxide portion, resulting in the formation of **I**.[3h,13b] Then **1** and nitromethane react intermolecularly to give **II**. In addition, a lithium nitronate, again formed from **II**, reacts kinetically with an internal ketone (-40 or -20 °C) to give **III**, followed by the generation of **3a** and a regeneration of PrLB. At room temperature, however, an equilibrium appears to exist between **III**, **II** and **IV**, and the reaction appears to proceed towards the generation of the thermodymamically more stable **3b**.[14]

In fact, the reaction of **3b** with 42% ee and 30 mol equiv of nitromethane in the presence of 10 mol % of PrLB at room temperature for 7 days generated a trace amount of **2a** and **2b** and recovered **3b** with 42% ee, confirming that **3a** is a kinetic product, and an equilibrium exists between **III-II-IV** at room temperature.[15] The reaction of a mixture of **2a** and **2b**, isolated after the reaction of **1** and nitromethane in the presence of PrLB at -40 °C, with nitromethane in the presence of PrLB at -40 °C for 59 h and at room temperature for 28 h gave **3b** with 65% ee. Whereas, the reaction of a mixture of **2a** and **2b** obtained under similar conditions, in the presence of NaO-*t*-Bu instead of PrLB, generated **3b** with 66% ee. These results suggest that the optical purity of **3b** depends only on the enantioselection of the intermolecular nitroaldol reaction and that, in an intramolecular reaction, there is no kinetic resolution of **2**, with the cyclization to **3b** from **2** being controlled by the absolute configuration of the hydroxy group of **2a**.[16]



Scheme 2

In conclusion, we have succeeded in developing a tandem inter-intramolecular catalytic asymmetric nitroaldol reaction promoted by PrLB. Optically active **3b** with many functionalities has been synthesized in only 2 steps from 2-methyl-1,3-cyclopentanedione. This optically active compound would be a key intermediate for the synthesis of natural products and/or bioactive compounds such as digitoxigenin,[17a] vitamin D_3[17b] and wortmannin.[17c] In addition, the amine-diol, produced by the reduction of **3b**, would be a lead compound of optically active chiral ligands for the catalytic asymmetric syntheses. Moreover, we have succeeded in demonstrating that a heterobimetallic multifunctional asymmetric catalyst, $LnLi_3$tris(binaphthoxide) is useful not only for catalytic asymmetric nitroaldol reactions but also for tandem inter-intramolecular catalytic asymmetric nitroaldol reactions. Further studies are under investigation.

Acknowledgment

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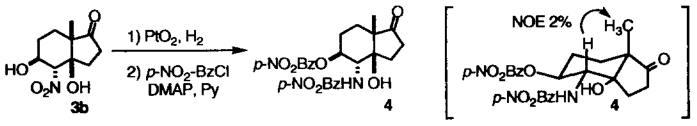
4. **1** was easily synthesized from 2-methyl-1,3-cyclopentanedione and acrolein in one step (89%). See: Schick, H.; Roatsch, B.; Schwarz, H.; Hauser, A.; Schwarz, S. *Liebigs Ann. Chem.* **1992**, 419.
5. A relative configuration of **3a** was tentatively assigned as shown in Table 1.
6. The relative configuration of **3b** was determined by the X-ray structure analysis, and the absolute configuration was determined by a CD analysis of **4** derived from **3b**.

   Crystal data and structure refinement for **3b**: $C_{10}H_{15}NO_5$, F.W. = 229.23, orthorhombic, $P2_12_12_1$, a = 10.81 (16), b = 16.76 (7), c = 6.05 (10), volume = 1096.8 (2) Å^3, Z=4, absorption coefficient = 0.949/mm, F(000) = 488, crystal size = 0.3 x 0.3 x 0.2 mm, θ range for data collection 4.87 to 65.00 deg., index range $0 \le h \le 12$, $0 \le k \le 19$, $0 \le l \le 7$, reflections collected 1112, independent correction 1112 [R (int) = 0.0000], Final R indices [I > 2Σ (I)] R1 = 0.0297 wR2 = 0.0776, R indices (all data) R1 = 0.0308 wR2 = 0.0785



7. Enantiomeric excess of **3b** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AD, flowing eluent hexane/2-propanol (12/1), detected at 230 nm).
8. For example, other asymmetric heterobimetallic catalysts which we have reported: LaNa$_3$tris(binaphthoxide): (LSB) (14% ee); LaK$_3$tris(binaphthoxide): (LPB) (4% ee); AlLibis(binaphthoxide): (ALB) (trace); GdLibis(binaphthoxide): (GaLB) (trace). Solvent effects (LLB): CH_3CN (11% ee); DMF (1% ee (*3aS,4S,5R,7aR*)); toluene (11% ee (*3aS,4S,5R,7aR*)); CH_2Cl_2 (28% ee (*3aS,4S,5R,7aR*)); Et_2O (22% ee). For LSB, see reference 13a; for ALB, see reference 2k; for LPB, see Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656.; for GaLB, see Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M.; *J. Am. Chem. Soc.* **1997**, *119*, 4783.
9. The reason for this appears to be that the equilibrium in the intermolecular reactions exists at 50 °C.
10. The reason for this is not clear at present.
11. Although we have reported that the second generation LnLB, which is prepared from LnLB, 1.0 mol equiv of H_2O and 0.6-1.0 equiv of strong bases such as BuLi, makes it possible to accelerate reactions more efficiently than LLB itself, the use of second generation PrLB has caused a decline in ee of **3b**. We have also reported LnLi3tris((*R*)-6,6'-disubstituted binaphthoxide) which improves the enantioselectivity of catalytic asymmetric nitroaldol reactions. However although PrLi3tris((*R*)-bis((trimethysilyl)ethynyl)binaphthoxide) slightly improved the ee of **3b**, the yield of **3b** was decreased and an unknown-byproduct was detected. See references 3h, 3i, 3k.
12. $[\alpha]_D^{25}$ -22.3 (*c* 0.36, CH_3OH) (96% ee).
13. a) Sasai, H.; Arai, T.; Satow, K.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. b) Yamada, Y. M. A.; Yoshikawa, N.; Sasai. H; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, in press.
14. PM3 calculation shows **3b** was 1.58 kcal/mol more stable than **3a**. For PM3, see Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
15. We have already found that there is no equilibrium in an intermolecular nitroaldol reaction catalyzed by LnLB. See reference 3h.
16. Treatment of LLB (3.3 mol %) with 30 mol equiv of nitromethane for 2 days at room temperature prior to use as a catalyst caused a decline in the optical purity of the nitroaldol adduct (19 h, -40 °C; 19% ee, 53% yield, Sasai; H., Tokunaga, T.; Shibasaki, M., unpublished result) generated from hydrocinnamaldehyde and nitromethane (cf. usual method: 60% ee, 88% yield). These results do not necessarily deny the possibility that at room temperature LLB partially decomposes by an interaction with nitromethane to form catalysts with less potential to produce optically active nitroaldol adducts in intramolecular reactions.
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