CATALYTIC ASYMMETRIC SYNTHESIS OF ARBUTAMINE†

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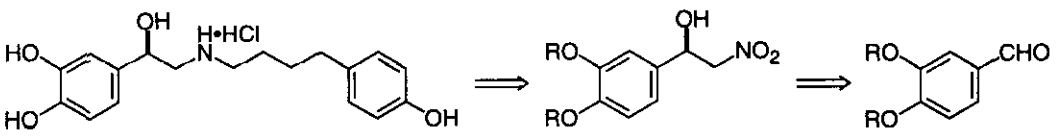
Abstract — An efficient catalytic asymmetric synthesis of (*R*)-arbutamine has been achieved using a catalytic asymmetric nitroaldol reaction promoted by a heterobimetallic multifunctional asymmetric catalyst as a key step.

(*R*)-Arbutamine (**1**) is a new catecholamine which is being developed as a pharmacological stress agent for the diagnosis of coronary artery disease and myocardial ischemia. The pharmacology of **1** suggests that it is a mixed β_{1+2}-adrenoceptor agonist with a significant affinity towards α_1-adrenoceptors.[1] (*R*)-Arbutamine (**1**) has been synthesized starting from (*R*)-norepinephrine and 4-(*p*-benzyloxyphenyl)butanal, by way of an imine-forming reaction followed by reduction.[1] In this communication we wish to report an efficient catalytic asymmetric synthesis of (*R*)-arbutamine (**1**) using a catalytic asymmetric nitroaldol reaction as a key step.

We selected the nitroaldol of type (**2**) as a key synthetic intermediate for **1**, which we hoped to synthesize from the corresponding aldehyde (**3**) using a catalytic asymmetric nitroaldol reaction (Scheme 1). Recently we have succeeded in developing the first catalytic asymmetric nitroaldol reaction, using $LnLi_3$tris(binaphthoxide) (LnLB) or related heterobimetallic asymmetric complexes as catalysts.[2] These heterobimetallic complexes function as both a Brønsted base and as a Lewis acid, just like an enzyme, making possible a variety of efficient catalytic asymmetric reactions.[3]



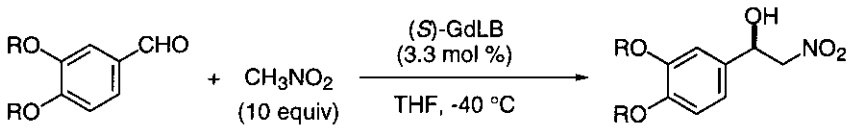
1: arbutamine **2** **3**

Scheme 1

†Dedicated to the memory of the late Professor Shun-ichi Yamada.

First, *O*-protecting group effects on the catalytic asymmetric nitroaldol reaction were carefully examined. Thus, the aldehydes (**3a-3d**) were prepared from commercially available 3,4-dihydroxy-benzaldehyde in 100,[4] 61, 76 and 69% yields respectively, and then subjected to catalytic asymmetric nitroaldol reactions using nitromethane and a heterobimetallic asymmetric catalyst. Among a variety of heterobimetallic asymmetric catalysts, we chose $GdLi_3$tris(binaphthoxide) (GdLB) because $LnLi_3$tris(binaphthoxide) complexes containing lanthanoids such as Gd, Eu and Sm had previously been found to give the best results when aromatic aldehydes were used as substrates.[5] GdLB was prepared by treatment of Gd(O-*i*-Pr)$_3$[6] and (*S*)-BINOL (3 mol equiv) in THF with 3 mol equiv of butyllithium followed by the addition of 1 mol equiv of H_2O, and the reactions were carried out in THF using 3.3 mol % of GdLB and 10 equiv of nitromethane. The results are summarized in Table 1, and show that the *tert*-butyldimethylsilyl group is the most efficient protecting group for the present purpose. Although the cause of the above-mentioned protecting group effects is not completely clear, it seems likely that as the aldehyde (**3a**) (of slightly lower reactivity than the other aldehydes) gives the best result, coordination of an aldehyde functionality to Gd may be essential for obtaining high stereoselectivity.[3] The enantiomeric excess of **2a** was determined by HPLC analysis using DAICEL CHIRALPAK AS (*i*-PrOH : hexane = 2 : 98), and the absolute configuration of **2a**, as expected from the precedent,[2d] was confirmed by converting **2a** to (*R*)-arbutamine (**1**).

Table 1. Catalytic Asymmetric Nitroaldol Reactions Using $GdLi_3$tris(binaphthoxide) (GdLB)



3a: R = TBDMS
3b: R = Ac
3c: R = CH_3
3d: R = Bn

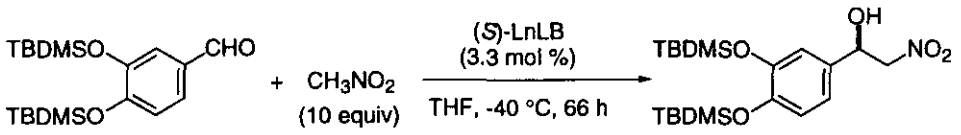
2a: R = TBDMS
2b: R = Ac
2c: R = CH_3
2d: R = Bn

entry	aldehyde	nitroaldol	time (h)	yield (%)	ee (%)
1	**3a**	**2a**	61	86	87
2	**3b**	**2b**	68	87	59
3	**3c**	**2c**	97	61	32
4	**3d**	**2d**	75	90	59

With this encouraging result in hand we proceeded to examine lanthanoid effects. As mentioned above lanthanoids such as Gd, Eu and Sm were expected to give the best results. However, for this particular reaction it was not clear which of these lanthanoids could be expected to give the best result, and so a variety of heterobimetallic asymmetric complexes were prepared using similar conditions to those described above,[6] and then utilized in catalytic asymmetric nitroaldol reactions. The results are summarized in Table 2 and show Sm and/or Gd complexes to give the best results,[7] and small changes in the structure of the catalyst (*ca.* 0.1 Å in the ionic radius of the lanthanoid cation) to cause an interesting change in the optical

purity of **2a** produced.

Table 2. Catalytic Asymmetric Nitroaldol Reactions Using $LnLi_3$tris(binaphthoxide) (LnLB)

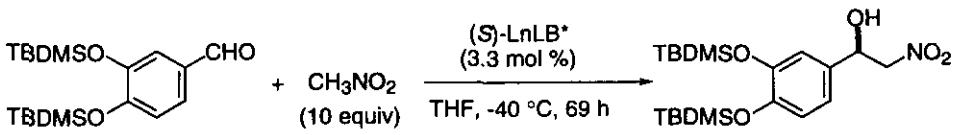


3a **2a**

entry	Ln	yield (%)	ee (%)
1	La	89	79
2	Pr	86	84
3	Sm	85	87
4	Gd	88	87
5	Dy	72	68
6	Er	69	15

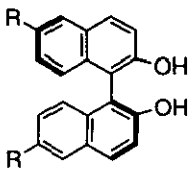
As already reported,[2] we have discovered that the introduction of a trialkylsilylethynyl group at the 6,6'-position of BINOL results in the formation of nitroaldols with higher enantiomeric excesses, probably owing to the higher stability of the resulting heterobimetallic asymmetric catalysts to undesired ligand exchange between a BINOL moiety and the acidic nitroalkane. Thus, in an attempt to obtain a better catalytic asymmetric nitroaldol reaction we examined the use of LnLB* (Ln = Gd and/or Sm) prepared from the BINOL derivatives (**4**), once again using the conditions described for LnLB. The results are summarized in Table 3, showing that **2a** could be obtained in 82% yield and with slightly higher enantiomeric excess (90%) using SmLB*.

Table 3. Catalytic Asymmetric Nitroaldol Reactions Using LnLB* (Ln = Gd, Sm)



3a **2a**

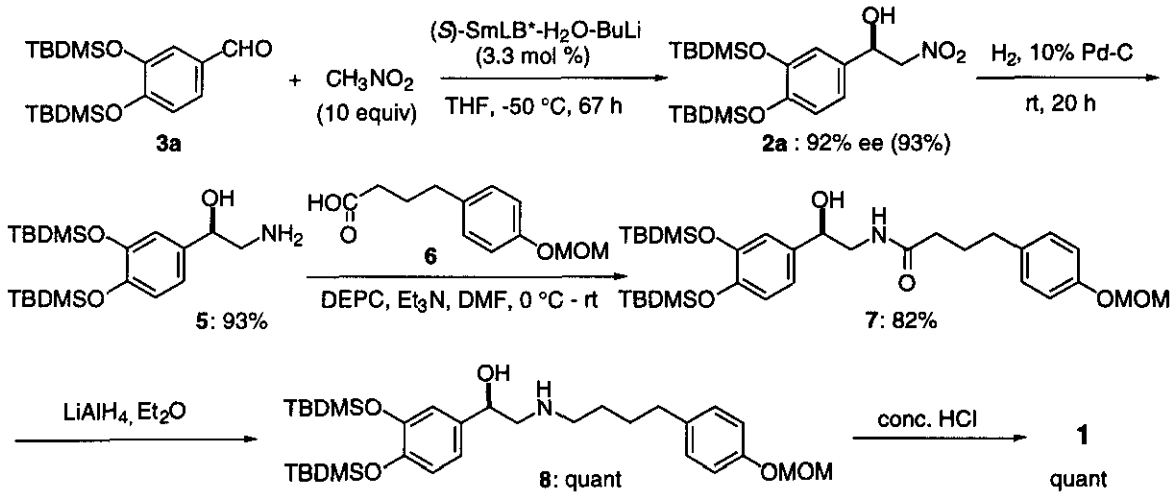
entry	Ln	BINOL derivative	yield (%)	ee (%)
1	Sm	**4a**	82	90
2	Gd	**4a**	53	86
3	Sm	**4b**	86	75
4	Gd	**4b**	71	49



4a: R = TMS—≡
4b: R = TMS

Finally the catalytic asymmetric nitroaldol reaction was carried out at -50 ℃ using 3.3 mol % of SmLB* for 67 h in order to improve the enantiomeric excess of **2a**. Gratifyingly, **2a** was formed with 92% ee, although the chemical yield did decrease slightly to 74%. We had already succeeded in enhancing the reactivity of the heterobimetallic asymmetric catalysts while retaining their stereoselectivity by an addition of alkali metal reagents to heterobimetallic catalysts.[3c] That is, sequential addition of H_2O (1 equiv) and then butyllithium (0.5 - 1 equiv) to heterobimetallic asymmetric catalysts is known to give "second-generation" catalysts whose structures have not been unequivocally determined, although it seems likely that they are tightly-bound complex of the heterobimetallic asymmetric catalysts and LiOH. The use of second-generation SmLB* prepared from SmLB*, H_2O (1 equiv) and butyllithium (0.6 equiv) in the present catalytic asymmetric nitroaldol reaction pleasingly gave **2a** in 92% ee and in 93% yield.[8]

With the nitroaldol (**2a**) in 92% ee in hand, we then directed our efforts towards a catalytic asymmetric synthesis of (*R*)-arbutamine (**1**). Hydrogenation of **2a** (92% ee) in ethanol using 10% Pd-C under H_2 atmosphere (room temperature, 20 h) gave **5**, $[\alpha]_D^{25}$ -21.9°(*c* 1.21, $CHCl_3$), in 93% yield. Conversion of **5** to **1** through the corresponding imine was first attempted using the previously reported synthetic route.[1] However, several attempts using a variety of conditions resulted in the formation of **1** in unsatisfactory yield. Thus, the synthesis of **1** by way of the amide (**7**) was investigated. Treatment of **5** with the carboxylic acid (**6**),[9] DEPC[10] and Et_3N in DMF at 0 ℃ - room temperature afforded the amide (**7**) in 82% yield, which was subjected to reduction ($LiAlH_4$ in refluxing ether), giving the amine (**8**) in quantitative yield. Exposure of **8** to conc. HCl in methanol and THF at room temperature for 0.5 h afforded (*R*)-arbutamine (**1**) in nearly quantitative yield as a pale yellow solid, mp 53-58 ℃, $[\alpha]_D^{23}$ -17°(*c* 1.15, ethanol); lit.,[1a] mp 55-58 ℃, $[\alpha]_D^{23}$ -18.5°(*c* 1.0, ethanol).



Scheme 2

In conclusion, we have succeeded in developing an efficient catalytic asymmetric synthesis of arbutamine (**1**) using a catalytic asymmetric nitroaldol reaction as a key step. The synthetic method described in this communication should be also useful for the catalytic asymmetric synthesis of bioactive compounds such as

albuterol, terbutaline, metaproterenol, MEN1792-BR and isoproterenol. Further studies are in progress.

ACKNOWLEDGMENTS

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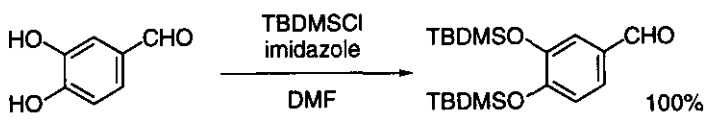
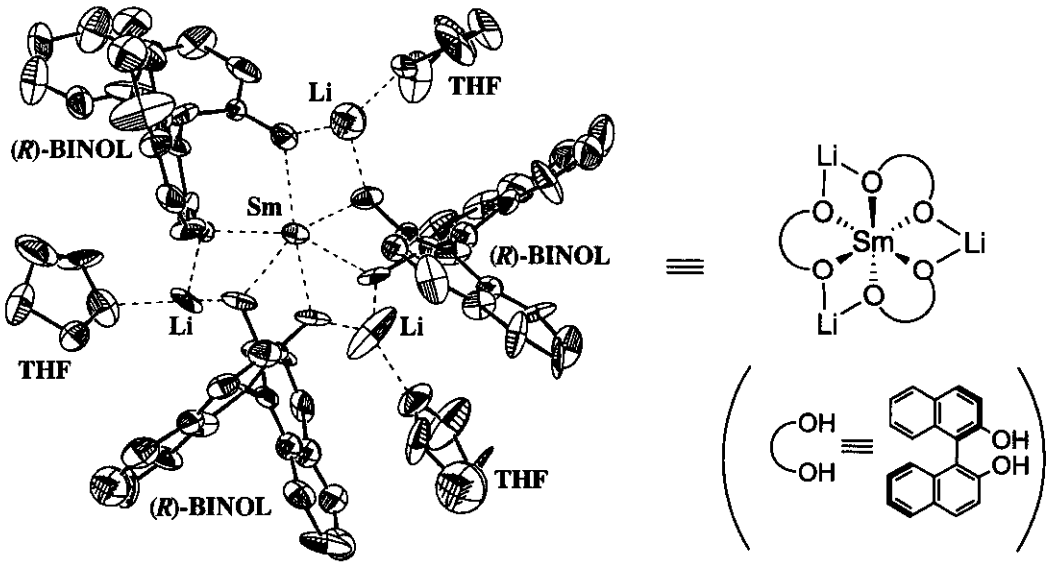
4. The compound (**2a**) was prepared as follows.



5. For lanthanoids effects, see reference 2d.

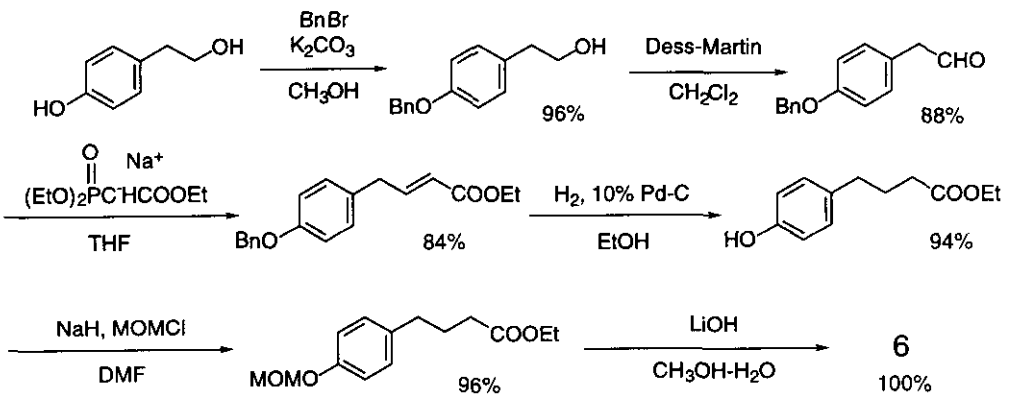
6. All lanthanoid reagents used were purchased from Kojundo Chemical Laboratory Co. Ltd., 5-1-28 Chiyoda, Sakado-shi, Saitama 350-02, Japan. Fax: +81-492-84-1351.

7. The structure of SmLB was tentatively determined by X-ray crystallographic analysis as shown below (ORTEP II (Johnson, 1976) diagram. Displacement ellipsoids are drawn at the 50% probability level). The rather large R value (*ca.* 13%) may be ascribed to high lability in the coordination of THF. Details will be reported at a later date.



8. The second generation (*S*)-SmLB* was prepared as follows: To a solution of (*S*)-SmLB* (0.0375 mmol) in THF (1.5 mL) were successively added a solution of H_2O (0.0375 mmol) in THF (0.0375 mL) at rt and a solution of BuLi (0.0225 mmol) in hexane (0.0144 mL) at 0 ℃. The resulting clear green solution was used as the second generation (*S*)-SmLB* (SmLB* II).
Typical experimental procedure for asymmetric nitroaldol reaction catalyzed by (*S*)-SmLB* II: To a solution of **3a** (74.0 mg, 0.202 mmol) in THF (0.74 mL) was added (*S*)-SmLB* II (6.73 μmol) in THF (0.269 mL) at rt and the mixture was stirred for 25 min at -50 ℃. Nitromethane (0.109 mL, 2.01 mmol) was then added to the above mixture at - 50 ℃. After being stirred for 67 h at -50 ℃, the reaction mixture was treated with 1*N* HCl (2.0 mL), extracted with AcOEt (3 x 10 mL), and the extract was washed with brine, dried over Na_2SO_4 and concentrated to give an residue. Purification by flash chromatography (SiO_2, acetone/hexane = 1/10) gave nitroaldol (**2a**) (80.2 mg, 92% ee) in 93% yield.

9. The carboxylic acid (**6**) was prepared as follows.



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