Tetrahedron Letters, Vol. 34, No. 5, pp. 855-858, 1993
Printed in Great Britain

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

Catalytic Asymmetric Nitroaldol Reaction: An Efficient Synthesis of (*S*) Propranolol Using the Lanthanum Binaphthol Complex

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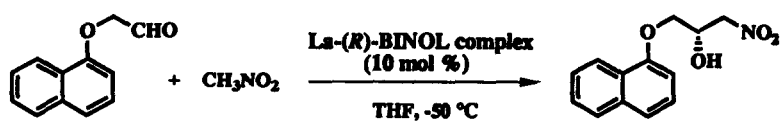
Abstract: (*S*) Propranolol, a more potent optical isomer of the widely used β-blocker, was conveniently synthesized in a highly enantioselective manner by the lanthanum-(*R*)-(+)-binaphthol complex catalyzed asymmetric nitroaldol reaction.

Nitroaldol reaction (*Henry* reaction)[2] is one of the powerful synthetic methods in organic synthesis, because nitroaldols are easily transformed into various useful derivatives such as β-amino alcohols and α-hydroxy carbonyl compounds. β-Amino alcohols are found as important partial structures of many bioactive compounds such as α/β-adrenergic agonists or antagonists,[3] HIV protease inhibitors[4] and antifungal or antibacterial peptides.[5] In spite of this advantage, nitroaldol reactions have not been so well investigated until recently especially in asymmetric control. We have already reported that the optically active lanthanum alkoxide is a versatile catalyst for C-C bond-forming reactions which involve an asymmetric nitroaldol reaction.[6] In this paper, as an effective utilization of our lanthanum binaphthol complex, a convenient preparation of optically active (*S*) propranolol, which is a representative of bioactive β-amino alcohol compounds, is presented.

As other β-blockers, the optically active (*S*) propranolol shows stronger β-blocking efficacy in cardiovascular diseases than both its (*R*) form and racemate. Therefore, many methods of (*S*) propranolol preparation have been published.[7] However, there has been no report in which a nitroaldol reaction is used as a key step. We planned to apply a catalytic asymmetric nitroaldol reaction using the lanthanum-(*R*)-(+)-binaphthol complex to a new synthetic approach to (*S*) propranolol.

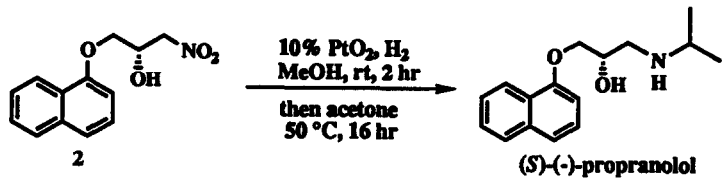
The requisite aldehyde **1** was first prepared from α-naphthol in two steps.[8] After several attempts, we were pleased to find that treatment of **1** with nitromethane at -50 °C in the presence of the asymmetric catalyst (10 mol %), which was prepared from $LaCl_3 \cdot 7H_2O$, dilithium (*R*)-(+)-binaphthoxide(1 mol equiv), NaO-*t*-Bu(1 mol equiv) and H_2O(4 mol equiv) in THF[9] gave the nitroaldol **2** of 92% ee[10] in 80% yield (Scheme 1). Even at -25 °C, using this lanthanum-(*R*)-(+)-binaphthol complex, the nitroaldol **2** was obtained maintaining the high enantiomeric selectivity (87% ee).



1 **2**
80% (92% ee)

Scheme 1

With the nitroaldol 2 of 92% ee available, the stage was set for reduction of the nitro group to the corresponding primary amino functionality followed by alkylation with retention of the absolute configuration. The desired conversion was best carried out by catalytic hydrogenation over PtO_2 followed by addition of acetone as shown in Scheme 2, producing (*S*)-(-)-propranolol of 92% ee in 90% yield. Thus, a catalytic asymmetric synthesis of (*S*)-(-)-propranolol (92% ee) has been achieved in a two-step sequence of reactions starting with 1 (72% overall yield). Furthermore, recrystallization of the HCl salt of propranolol (92% ee) from AcOEt-MeOH was found to give the optically pure drug.



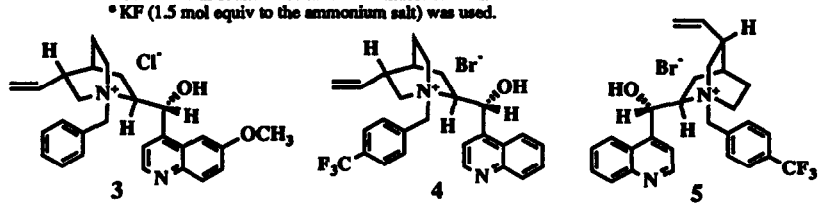
Scheme 2

In order to improve the synthesis of (*S*) propranolol described above as well as develop another asymmetric catalyst, we further investigated a catalytic asymmetric nitroaldol reaction of 1. Optically active nitronate species, which would work as reactants in the nitroaldol reaction, were expected to be generated by use of the combination of an asymmetric phase transfer catalyst and an inorganic base. Among many phase transfer catalysts, quaternary cinchona alkaloid derivatives such as *N*-benzylquininium chloride 3, *N*-[4-(trifluoromethyl)benzyl]cinchonidinium bromide 4 and *N*-[4-(trifluoromethyl)benzyl]cinchonium bromide 5, which had been already utilized in asymmetric Michael reactions,[11] appeared to be promising asymmetric catalysts. After several attempts, reaction of 1 with nitromethane (10 mol equiv), 3 (10 mol%) and KF (15 mol%) in toluene at -20 °C was found to give the nitroaldol 2 of 23% ee in 41% yield, while the use of 4 or 5 afforded the less satisfactory result. The results are summarized in Table 1, showing that the asymmetric lanthanum catalyst is much more effective than the quaternary cinchona alkaloid derivatives.

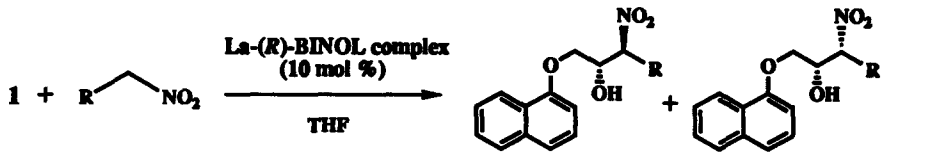
Table 1. Reaction of the Aldehyde 1 with Nitromethane

entry	catalyst[a]	solvent	temp(°C)	time(hr)	yield(%)	ee(%)
1[b]	La-(*R*)-BINOL	THF	-25	17	62	87 (*S*)
2[c]	La-(*R*)-BINOL	THF	-50	60	80	92 (*S*)
3[b,e]	3	toluene[d]	-20	19	41	23 (*S*)
4[b,e]	4	toluene[d]	-20	72	60	16 (*S*)
5[b,e]	5	toluene[d]	-20	72	36	3 (*R*)

[a] The catalyst (10 mol %) was used in all cases.
[b] CH_3NO_2 (10 mol equiv) was used.
[c] CH_3NO_2 (50 mol equiv) was used.
[d] Toluene was found to be the most suitable solvent.
[e] KF (1.5 mol equiv to the ammonium salt) was used.



The capability of the lanthanum-(*R*)-(+)-binaphthol complex as an asymmetric catalyst was further studied in other reaction systems. Reaction of 1 with nitropropane (30 mol equiv) and the lanthanum catalyst (10 mol%) in THF at -30 °C for 40 hr gave the nitroaldol 7 as a mixture of the two diastereomers (70% yield, syn/anti = 1.7:1). The enantiomeric excesses were found to be 78% (syn) and 75% (anti), respectively. Furthermore, use of nitroethane (-30 °C) afforded 8 [73%, syn (54% ee)/anti (66% ee) = 1.8:1][12], and use of 2-(*t*-butyldimethylsilyloxy)nitroethane (-40 °C) gave 9 [61%, syn (68% ee)/anti (64% ee) = 3.3:1].[13] Although the enantiomeric excesses are modest to good, these results will pave the way for further progress.



6a R = Et
6b R = Me
6c R = CH_2OTBS

7a
8a
9a

7b R = Et
8b R = Me
9b R = CH_2OTBS

Scheme 3

The detailed procedure for the preparation of (*S*) propranolol is as follows.

(*S*) 3-(α-Naphthoxy)nitropropan-2-ol

α-Naphthoxyacetaldehyde (56 mg, 0.3 mmol) and nitromethane (0.8 ml, 15 mmol) were added to 1.5 ml of THF at room temperature. After the solution was cooled to -50 °C, 0.6 ml (0.03 mmol) of the lanthanum-(*R*)-binaphthol THF solution (ca. 0.05 *M*) was gradually added. The reaction mixture was stirred at -50 °C for 60 hr, and then the reaction was quenched by the addition of 1 ml of 1 *N* HCl. After the usual work up, purification by silica gel column chromatography eluted by CH_2Cl_2 yielded a mixture of the desired aldol adduct 2 and (*R*)-binaphthol (72 mg). The chemical yield of the desired product was determined to be 80% based on the integral line of the ^{1}H-NMR of the mixture. The enantiomeric excess was revealed to be 92% by HPLC analysis.

(*S*)-(-)-Propranolol

To a solution of the mixture obtained above [72 mg, containing 0.24 mmol of (*S*) 3-(α-naphthoxy) nitropropan-2-ol] in 5 ml methanol was added platinum(IV) oxide (10 mg) and the reaction mixture was vigorously stirred at room temperature under hydrogen atmosphere for 2 hr. And then acetone (17 μl, 0.29 mmol) was added and the reaction mixture was additionally stirred for 16 hr at 50 °C. After conversion to the HCl salt by adding ethereal HCl to a ether solution of the crude product, silica gel column chromatography (CH_2Cl_2/MeOH = 20/1 → 10/1) gave 65 mg of (*S*)-(-)-propranolol HCl salt (90 %). $[\alpha]^{25}_D$ -27.9 ° (*c* 0.91, EtOH); Lit.[7c] $[\alpha]^{25}_D$ -25.5 ° (*c* 1.05, EtOH).

In conclusion, a novel approach to (*S*)-(-)-propranolol, a representative of bioactive β-amino alcohol compounds, has been achieved with the excellent enantiomeric selectivity by the catalytic asymmetric nitroaldol reaction using the lanthanum-(*R*)-binaphthol complex catalyst. Furthermore, catalytic asymmetric nitroaldol reactions using quaternary chincona alkaloid derivatives as well as nitroalkanes other than nitromethane have been also developed.

Acknowledgments: This study was financially supported by a Grant-in Aid for Scientific Research on Priority Areas (Multiplex Organic Systems) from the Ministry of Education, Science and Culture, Japan.

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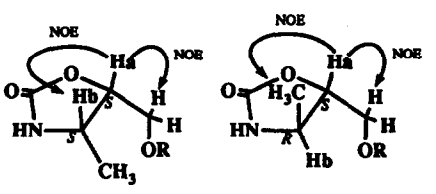
12. In the case of nitroethane, both the diastereomeric and enantiomeric excesses were improved at -40 °C: syn (82% ee)/anti (52% ee) = 2.7:1
13. The absolute configuration of the carbon adjacent to the hydroxyl group was determined to be *S* (HPLC) by comparison with opticaliy active **8a** derived from **2** in three steps (silylation, methylation and deprotection). The absolute configuration of the asymmetric center adjacent to the nitro group and the relative configurations of **8a** and **8b** were elucidated by the coupling constants of the vicinal protons and the NOE experiments as shown below.



J_{Hab} = 7.9 Hz J_{Hab} = 5.6 Hz

R = α-Naphthyl

(Received in Japan 25 September 1992)