Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6123-6126, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01240-7

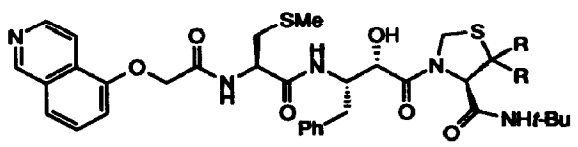
Diastereoselective Catalytic Asymmetric Nitroaldol Reaction Utilizing Rare Earth-Li-(*R*)-BINOL Complex. A Highly Efficient Synthesis of Norstatine

Hiroaki Sasai, Won-Sup Kim, Takeyuki Suzuki, and Masakatsu Shibasaki*
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Masaru Mitsuda, Junzo Hasegawa, and Takehisa Ohashi
Biochemical Research Laboratories, Kaneka Corporation
Miyamae-machi, Takasago-cho, Takasago-shi, Hyogo 676, Japan

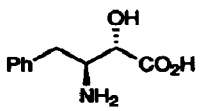
Abstract: Rare earth-Li-BINOL complexes were used to catalyze nitroaldol reactions of optically active α-amino-aldehydes with nitromethane in a highly diastereoselective manner. A typical adduct, (2*S*, 3*S*)-3-phthaloylamino-2-hydroxy-1-nitro-4-phenylbutane was conveniently converted to (2*S*, 3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (*erythro*-AHPA ; phenylnorstatine), a component of the HIV protease inhibitor KNI-227 and KNI-272.

Recently we succeeded in developing a catalytic asymmetric nitroaldol reaction for the first time utilizing rare earth-Li-BINOL complexes.[1-3] In addition we have also reported some applications of the catalytic asymmetric nitroaldol reaction to the syntheses of therapeutically important amino-alcohol derivatives[3,5] and have elucidated the structure of the catalyst.[4] However, no attempts have ever been made at a diastereoselective nitroaldol reaction using an optically active aldehyde as a starting material. It might be expected that reaction of optically active α-substituted aldehydes with nitromethane using an appropriate optically active rare earth-Li-BINOL catalyst would lead to enhanced diastereoselection to give 3-substituted-2-hydroxy-1-nitro derivatives. We have applied this methodology and report herein a practical method for the preparation of optically active *erythro*-3-amino-2-hydroxy-1-nitro derivatives by highly diastereoselective nitroaldol reaction of α-aminoaldehydes with nitromethane. The adducts, 3-amino-2-hydroxy-1-nitro derivatives would be versatile synthetic intermediates for the synthesis of unnatural *erythro*-3-amino-2-hydroxy acids, which are important components of several biologically active compounds. For example, the promising HIV-protease inhibitors KNI-227[6] (**1a**) and KNI-272[6] (**1b**) bear (2*S*, 3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (*erythro*-AHPA; phenylnorstatine) as a subunit. Although several reports have appeared on the synthesis of *threo*-AHPA,[7] little is known about the highly stereoselective synthesis of *erythro*-AHPA **2**.[8]



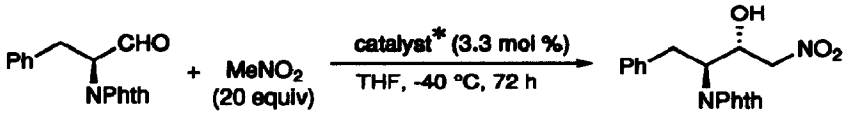
1a : KNI-227 (R = Me)
1b : KNI-272 (R = H)

Figure 1



2

We thus at first examined the nitroaldol reaction of *N*-phthaloyl-L-phenylalanal **3a** with nitromethane. The starting aldehyde **3a** was prepared from corresponding L-phenylalanine in three steps according to Gacek's procedure.[9] Although the aldehyde **3a** could be obtained as an almost pure enantiomer (>96% ee), the optical purity gradually reduced to 62% ee when it was stored at -30 °C for 3 months.[10] Therefore the aldehyde **3a** had to be prepared fresh prior to use. After several attempts, we were pleased to find that treatment of **3a** with nitromethane (20 mol equiv) at -40 °C, in the presence of the La-Li-(*R*)-BINOL catalyst[1-4] (3.3 mol %), gave (2*S*, 3*S*)-2-hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane (**4a**) in 92% yield with >99:1 *erythro*-selectivity (Table 1).[11] The *S*-configuration of the C-2 hydroxyl group of **4a** agreed with results previously observed in enantioselective nitroaldol reactions using La-Li-(*R*)-BINOL catalyst.[1-5] However it was shown that the methods of preparation[1,2,4] of the La-Li-(*R*)-BINOL catalyst somewhat affected the diastereoselectivity in the nitroaldol reaction (entries 1-3). Their optical purity was also found to

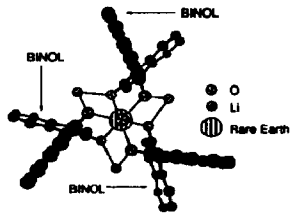


3a **4a**

Table 1

entry	catalyst	Ln source	yield (%)	erythro (% ee) : threo
1	La-Li-(*R*)-Binol complex	$La(O\text{-}i\text{-}Pr)_3$	92	> 99 (96) : 1
2	La-Li-(*R*)-Binol complex	$LaCl_3$	80	93 (95) : 7
3	La-Li-(*R*)-Binol complex	$LaCl_3 \cdot 7H_2O$	97	90 (95) : 10
4	La-Li-(*S*)-Binol complex	$LaCl_3$	96	74 (90) : 26
5	$La(O\text{-}i\text{-}Pr)_3$		52	89 (95) : 11
6	Pr-Li-(*R*)-Binol complex	$Pr(O\text{-}i\text{-}Pr)_3$	88	96 (96) : 4
7	Nd-Li-(*R*)-Binol complex	$NdCl_3$	78	94 (90) : 6
8	Sm-Li-(*R*)-Binol complex	$SmCl_3$	79	97 (94) : 3
9	Eu-Li-(*R*)-Binol complex	$EuCl_3$	73	98 (94) : 2
10	Gd-Li-(*R*)-Binol complex	$GdCl_3$	79	95 (92) : 5
11	Dy-Li-(*R*)-Binol complex	$DyCl_3$	91	83 (91) : 17
12	Er-Li-(*R*)-Binol complex	$ErCl_3$	81	80 (95) : 20
13	Yb-Li-(*R*)-Binol complex	$YbCl_3$	89	78 (92) : 22
14	Y-Li-(*R*)-Binol complex	YCl_3	95	79 (95) : 21
15	NaO-*t*-Bu	—	95	62 (65) : 38
16	LDA (1 equiv)	—	80	74 (49) : 26

* The structure of this catalyst has been shown to be :

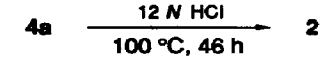


Rare earth-Li-(*S*)-BINOL complex

be ~96% ee,[12] indicating no racemization had occurred in the nitroaldol reaction. Reaction of the (*S*)-aldehyde **3a** with nitromethane, using the La-Li-(*S*)-BINOL complex as catalyst, in which the two asymmetric compounds were acting in opposition, led to reduced diastereoselection (entry 4). We have also investigated the rare earth metal effect in the nitroaldol reaction (entries 6-14). As shown in Table 1, no significant differences were observed in the yield and diastereoselectivity of products. Contrary to these results, commonly used bases such as LDA and NaO-*t*-Bu gave the nitroaldol **4a** with lower diastereo- and enantioselectivity (entries 15, 16),[13] whereas the achiral mild base La(O-*i*-Pr)$_3$, afforded **4a** with 89:11 diastereoselectivity without any racemization (entry 5).

Conversion of the nitroaldol adduct **4a** into desired *erythro*-AHPA **2** was carried out as shown in Scheme 1.[14] Under the conditions indicated, deprotection of the phthaloyl group and hydrolysis of the nitro group were achieved at the same time, yielding desired **2** in 80% yield. The nitroaldol reaction towards the synthesis of **2** was able to be carried out even under air and in the presence of a small amount of water. Furthermore, BINOL can be recovered easily without any racemization. Thus this sequence of reactions provides a practical method for the synthesis of phenylnorstatine **2**.

Scheme 1



In order to investigate the generality of the abovementioned diastereoselective nitroaldol reaction, we have also examined the reaction of *N*-protected L-alanal and L-valinal. The results, summarized in Table 2, showed that the La-Li-(*R*)-BINOL catalyst was also effective in the nitroaldol reaction of either *N*-phthaloyl alanal (**3b**) or *N*-phthaloyl valinal (**3c**) with nitromethane. However in the case of *N*-benzyloxycarbonyl (Z) and *N*-*t*-butoxycarbonyl (*t*-Boc) protected aldehydes[15,16] the nitroaldol adducts were obtained with lower diastereoselectivity and moderate optical purity. These results are probably due to the fact that Z or *t*-Boc protected α-aminoaldehydes are relatively unstable configurationally, particularly in solution.[10]

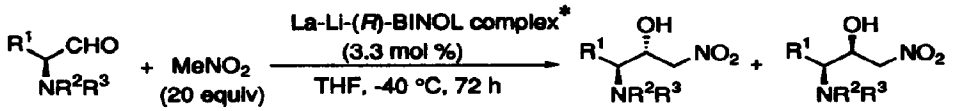


Table 2 **3b-g** **4b-g**

entry	aldehyde	yield (%)	*erythro* (% ee) : *threo*
1	**3b** : R^1 = Me, R^2, R^3 = Phth	**4b** : 99	99 (96) : 1
2	**3c** : R^1 = Me_2CH, R^2, R^3 = Phth	**4c** : 99	99 (96) : 1
3	**3d** : R^1 = Me, R^2 = H, R^3 = *t*-Boc	**4d** : 85	88 (84) : 12
4	**3e** : R^1 = Me_2CH, R^2 = H, R^3 = *t*-Boc	**4e** : 77	95 (91) : 5
5	**3f** : R^1 = $PhCH_2$, R^2 = H, R^3 = *t*-Boc	**4f** : 81	96 (90) : 4
6	**3g** : R^1 = $PhCH_2$, R^2 = H, R^3 = *Z*	**4g** : 95	83 (66) : 17

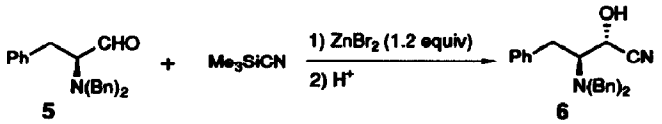
* Prepared from La(O-*i*-Pr)$_3$. See reference 4.

In conclusion, the use of rare earth-Li-(*R*)-BINOL catalysts have made possible the diastereoselective nitroaldol reactions of optically active α-aminoaldehydes with nitromethane. The mild basicity of the catalysts causes no racemization of the starting aldehydes **3a-3c**. As a result *erythro*-AHPA **2**, an important synthetic intermediate for the HIV protease inhibitors KNI-227 and KNI-272, was readily obtained in two steps.

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

REFERENCES AND NOTES

1. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.*, **1992**, *114*, 4418-4420.
2. Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.*, **1993**, *34*, 851-854.
3. Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.*, **1993**, *34*, 2657-2660.
4. Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.*, **1993**, *115*, 10372-10373.
5. Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.*, **1993**, *34*, 855-858.
6. (a) Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.*, **1992**, *40*, 2251-2253. (b) Kageyama, S.; Mimoto, T.; Murakawa, Y.; Nomizu, M.; Ford, H., Jr.; Shirasaka, T.; Gulnik, S.; Erickson, J.; Takada, K.; Hayashi, H.; Broder, S.; Kiso, Y.; Mitsuya, H. *Antimicrob. Agents Chemother.* **1993**, *37*, 810-817.
7. (a) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M.T. *J. Chem. Soc., Chem. Soc.*, **1989**, 938-939. (b) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M.T. *Synthsis*, **1989**, 703-706. (c) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron*, **1992**, *48*, 1853-1868. (d) Pearson, W. H.; Hines, J. V. *J. Org. Chem.*, **1989**, *54*, 4235-4237. (e) Norman, B. H.; Morris, M. L. *Tetrahedron Lett.*, **1992**, *33*, 6803-6806. (f) Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Fuji, K. *Tetrahedron Lett.*, **1993**, *34*, 5127-5130.
8. Reetz *et al.* obtained *erythro*-**6** utilizing a $ZnBr_2$ mediated cyanohydrin-forming reaction of *N,N*-dibenzyl-α-aminoaldehyde **5** with TMSCN (79% yield, 90% de); see, Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.*, **1988**, *27*, 3295-3298.



5 **6**

9. Gacek, M.; Undheim, K. *Tetrahedron*, **1974**, 30, 4233-4237.
10. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, 89, 149-164.
11. The detailed procedure for the preparation of (2S, 3S)-2-hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane (**4a**) is as follows. (S)-N-Phthaloyl phenylalanal (56.6 mg, 0.2 mmol) and nitromethane (0.21 ml, 4.0 mmol) were dissolved in THF (0.8 mL) at room temperature. After the solution was cooled to -40 °C, a THF solution (0.25 mL) of the La-Li-(R)-BINOL complex (3.3 mol %) was gradually added. The reaction mixture was stirred at the same temperature for 72 hr, and then quenched by an addition of 1N HCl (0.2 mL). After the usual work up, purification by silica gel column chromatography (hexane: ethyl acetate = 4:1) yielded the desired aldol adduct **4a** (63.4 mg, 92%). The diastereomeric ratio was determined by HPLC analysis using JASCO Fine-Pack C 18-5 (H_2O/MeCN = 55/45 as an eluent) and the erythro configuration of **4a** was determined by conversion into known AHPA **2**; see reference 7.
12. The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OJ (for **4a**,**4b**,**4c**) or CHIRALPAK AD (for **4d**, **4e**, **4f**, **4g**).
13. The results using other common bases were as follows: Et_3N; 86% yield (erythro : threo = 74 : 26), KF; 73% yield (e : t = 56 : 44), KO-t-Bu; 86% yield (e : t = 61 : 39), KOH; 72% yield (e : t = 66 : 34).
14. Sakai, K.; Takahashi, K.; Terashima, S.; Tsunemoto, D.; Kamijo, T.; Harada, H. *Jpn. Kokai Tokkyo Koho* JP02 59545 [90 59545] (CA 113: 98035q).
15. Fehrentz, J-A.; Castro, B. *Synthesis*, **1983**, 676-678.
16. Ito, A.; Takahashi, R.; Baba, Y.; *Chem. Pharm. Bull.* **1975**, 23, 3081-3087.

(*Received in Japan* 29 *December* 1993; *accepted* 6 *June* 1994)