



Catalytic Asymmetric Nitroaldol Reaction of α,α -Difluoro Aldehydes Mediated by Rare Earth-Lithium-BINOL Complexes

Katsuhiko Iseki,^{a,*} Satoshi Oishi,^a Hiroaki Sasai^b and Masakatsu Shibasaki^b

^aMEC Laboratory, Daikin Industries, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305, Japan

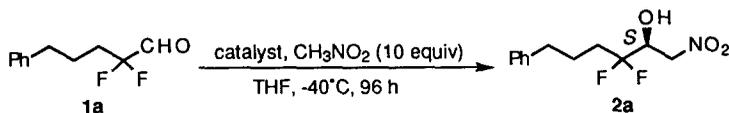
^bFaculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: Rare earth-Li-BINOL complexes were used to catalyze nitroaldol reactions of α,α -difluoro aldehydes with nitromethane in a good enantioselective manner. The optical yields of nitroaldol **2a** depend on the size of rare earth metals, and an Sm-Li-BINOL complex gave the highest enantioselectivity. The enantiotopic face selection of α,α -difluoro aldehyde **1a** was found to be different from that of nonfluorinated aldehydes employed in the usual catalytic asymmetric nitroaldol reactions. Copyright © 1996 Elsevier Science Ltd

The synthesis of chiral fluoroorganic compounds is important in biological and medicinal chemistry in consideration of the influence of fluorine's unique properties on biological activity.¹ Fluorine, due to its high electronegativity, has an important effect on its neighboring groups in a molecule. The introduction of a difluoromethylene residue into a peptide sequence has led to the discovery of potent, competitive and reversible protease inhibitors mimicking the transition state for amide bond cleavage.² Renin inhibitors with difluorostatine and difluorostatone and related analogs have been reported to possess the potentiality to control high blood pressure.³

In the case of fluorine-containing molecules with generally unusual reactivity, methodologies for synthesizing nonfluorinated chiral compounds are frequently impractical, giving rise to the term "flustrate" by Seebach.⁴ Thus, chiral geminal difluoro-substituted compounds have so far been prepared mainly by enzymatic resolution and a "chiron approach",⁵ and very few catalytic asymmetric reactions have been reported for such chiral molecules.⁶ In this paper, we describe for the first time the catalytic asymmetric nitroaldol reaction of α,α -difluoro aldehydes using rare earth-Li-BINOL complexes.

In a series of highly selective heterobimetallic catalysts developed for several catalytic asymmetric reactions,⁷⁻¹⁰ lanthanoid-lithium-BINOL (LnLB) complexes are the most efficient catalysts for asymmetric nitroaldol reactions. We began by employing various rare earth metals to optimize chemical and optical yields. Several Ln-Li-(*R*)-BINOL complexes were prepared from Ln(O-*i*-Pr)₃,¹¹ BuLi (3 molar equiv), H₂O (1 molar equiv) and (*R*)-BINOL (3 molar equiv) according to a literature procedure for the La complex formation.^{7h} Their utility as asymmetric catalysts was then assessed in nitroaldol reaction of nitromethane with 2,2-difluoro-5-phenylpentanal (**1a**).



In a typical reaction, a THF solution of an Ln-Li-(*R*)-BINOL complex (30 mM, 6.7 ml, 0.2 mmol) was diluted with anhydrous THF (7 ml). After the solution was cooled to -40°C, nitromethane (10 mmol) and **1a** (1 mmol) were added at intervals of 30 min. The reaction mixture was stirred at -40°C for 96 h prior to

quenching with 1*N* HCl. After the usual workup, nitroaldol product **2a** was isolated by flash chromatography and the optical yield was determined by HPLC using a chiral column. As shown in Table 1 (entries 1-5), all complexes gave good chemical yields. It was found that the Sm (87% ee), the Eu (86% ee) and the Gd (83% ee) complexes showed higher enantioselectivity compared to the La complex catalyst (55% ee) which generally gives the highest optical yield in the usual nitroaldol reactions of nonfluorinated aldehydes.⁷ The relationship between the ionic radii of rare earth metals and the optical yields in the reactions of α,α -difluoro aldehyde **1a** is similar to that of benzaldehyde, in the case of which the Eu-Li-BINOL complex exceptionally provides the best enantioselectivity.^{7d}

Hydrogenation of nitroaldol **2a** in the presence of 5% Pd-C gave the corresponding amino alcohol which was determined to have the *S* configuration by X-ray analysis,¹² showing that nitronate reacts preferentially on the *Si* face of **1a** in the presence of Ln-Li-(*R*)-BINOL complexes. As previously reported,^{7a,b,d} Ln-Li-(*R*)-BINOL complexes generally cause the attack of nitrate with *Re* face preference to aldehydes. It is thus noteworthy that the enantiotopic face selection of the α,α -difluoro aldehyde is the reverse to that of nonfluorinated aldehydes employed in the usual catalytic asymmetric nitroaldol reactions. This stereoselection of **1a** is identical with that of β -oxa-aldehydes,¹³ suggesting that the fluorine atoms at the α -position exert pronounced influence on the enantiotopic face selection (Figure 1).¹⁴

The decrease in amount of the Sm-Li-(*R*)-BINOL complex caused the decrease in chemical and optical yields (Table 1, entries 2 and 6). Thus, we next examined Sm-Li-(*R*)-6,6'-disubstituted BINOL complexes to optimize the nitroaldol reaction.^{7h} Sm-Li-(*R*)-6,6'-dibromo-BINOL (20 mol%) and Sm-Li-(*R*)-6,6'-bis((triethylsilyl)ethynyl)-BINOL (20 mol%) complexes gave (*S*)-**2a** in 89% ee (69% yield) and 94% ee (58% yield), respectively (entries 7 and 8). Use of 5 mol% of the Sm-Li-(*R*)-6,6'-bis((triethylsilyl)ethynyl)-BINOL complex showed similar enantioselectivity and chemical yield compared to 20 mol% of the same catalyst, though a prolonged reaction time (168 h) was necessary (entry 9).

Table 1. Catalytic Asymmetric Nitroaldol Reaction of α,α -Difluoro Aldehyde **1a** in the Presence of Rare Earth-Li-(*R*)-BINOL and Rare Earth-Li-6,6'-Disubstituted (*R*)-BINOL Complexes

Entry	Catalyst ^a (mol%)	Yield ^b %	ee ^c %
1	La-Li-(<i>R</i>)-BINOL (20)	74	55
2	Sm-Li-(<i>R</i>)-BINOL (20)	77	87
3	Eu-Li-(<i>R</i>)-BINOL (20)	75	86
4	Gd-Li-(<i>R</i>)-BINOL (20)	69	83
5	Yb-Li-(<i>R</i>)-BINOL (20)	82	69
6	Sm-Li-(<i>R</i>)-BINOL (5)	67	74
7	Sm-Li-(<i>R</i>)-6,6'-dibromo-BINOL (20)	69	89
8	Sm-Li-(<i>R</i>)-6,6'-bis((triethylsilyl)ethynyl)-BINOL (20)	58	94
9 ^d	Sm-Li-(<i>R</i>)-6,6'-bis((triethylsilyl)ethynyl)-BINOL (5)	55	92

a) Prepared from rare earth metal isopropoxides. See reference 7h; b) Isolated yields based on **1a**; c) Determined by HPLC using a Daicel Chiralcel OD-H column; d) The reaction was carried out for 168 h.

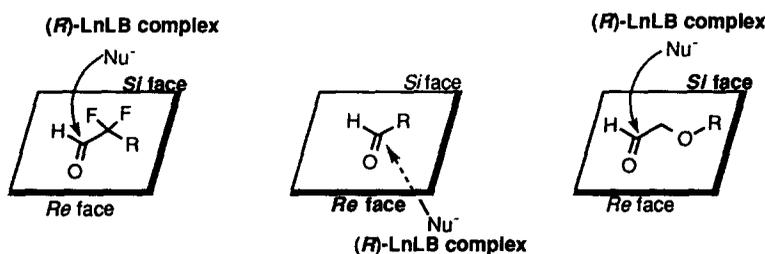
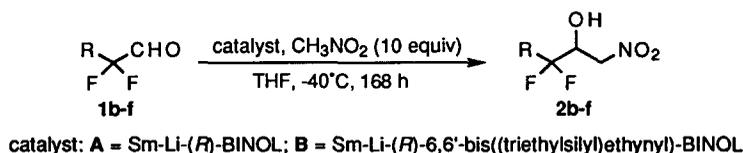


Figure 1. Stereochemical Course of Asymmetric Nitroaldol Reaction

Results of the catalytic asymmetric nitroaldol reaction of a variety of α,α -difluoro aldehydes with nitromethane using Sm-Li-(*R*)-BINOL and Sm-Li-(*R*)-6,6'-bis((triethylsilyl)ethynyl)-BINOL complexes are summarized in Table 2. With aldehyde **1b** (R = *n*-heptyl), the (*R*)-6,6'-bis((triethylsilyl)ethynyl)-BINOL complex (catalyst **B**) gave a lower chemical yield but a slightly higher enantiomeric excess compared to the (*R*)-BINOL complex (entries 1 and 2). In all cases, five or eight molar percent of catalyst **B** afforded nitroaldols **2b-f** in good optical yields and the highest enantioselectivity was obtained with aldehyde **1f** (R = cyclohexyl, entry 6).

Table 2. Catalytic Asymmetric Nitroaldol Reaction of α,α -Difluoro Aldehydes **1b-f** Promoted by Sm-Li-(*R*)-BINOL and Sm-Li-(*R*)-6,6'-bis((triethylsilyl)ethynyl)-BINOL Complexes



Entry	Aldehyde		Catalyst ^a (mol%)	Product		
	1	R		2	Yield ^b %	ee ^c %
1	b	<i>n</i> -heptyl	A (5)	b	73	70
2	b	<i>n</i> -heptyl	B (5)	b	55	74
3	c	PhCH ₂ O(CH ₂) ₂	B (5)	c	52	80
4	d	<i>i</i> -PrSCH ₂	B (5)	d	55	85
5	e	4-(CH ₃ OC ₂ H ₄)C ₆ H ₄ O	B (8)	e	52	77
6	f	cyclohexyl	B (8)	f	58	95

a) Prepared from Sm(O-*i*-Pr)₃. See reference 7h; b) Isolated yields based on the starting aldehydes; c) Determined by HPLC using a Daicel Chiralcel OD-H or AD column.

In conclusion, the nitroaldol reaction of α,α -difluoro aldehydes with nitromethane mediated by Ln-Li-BINOL complexes proceeded with good enantiomeric excess. Further study to improve chemical and optical yields and application of the present synthesis to that of useful difluorinated bioactive compounds are now being carried out.

References and Notes

- For reviews see: a) *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y. Eds.; Kodansha Ltd. and Elsevier Biomedical Press: Tokyo and Amsterdam, 1982. b) Welch, J.T. *Tetrahedron* 1987, 43, 3123-3197. c) Bravo, P.; Resnati, G. *Tetrahedron: Asymm.* 1990, 1, 661-692. d) Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons, Inc.: New York, 1991. e) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J.T. Ed.; American Chemical Society: Washington, 1991. f) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L.M. Eds.; Elsevier: Amsterdam, 1993. g) Resnati, G. *Tetrahedron* 1993, 49, 9385-9445. h) Iseki, K.; Kobayashi, Y. *J. Synth. Org. Chem. Jpn.* 1994, 52, 40-48. i) Iseki, K.; Kobayashi, Y. *Rev. Heteroatom Chem.* 1995, 12, 211-237.
- a) Gelb, M.H.; Svaren, J.P.; Abeles, R.H. *Biochemistry* 1985, 24, 1813-1817. b) Gelb, M.H. *J. Am. Chem. Soc.* 1986, 108, 3146-3147. c) For a review see: Kirk, K.L. Synthesis and Biochemical Applications of Fluorine-containing Peptides and Proteins. In *Fluorine-containing Amino Acids*; Kukhar', V.P.; Soloshonok, V.A. Eds.; John Wiley and Sons, Inc.: New York, 1995; pp. 343-401.

3. a) Thaisrivongs, S.; Pals, D.T.; Kati, W.M.; Turner, S.R.; Thomasco, L.M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080-2087. b) For a review see: Sham, H.L. Renin Inhibitors with Fluorine-containing Amino Acid Derivatives. In *Fluorine-containing Amino Acids*; Kukhar⁷, V.P.; Soloshonok, V.A. Eds.; John Wiley and Sons, Inc.: New York, 1995; pp. 333-342.
4. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320-1367.
5. Hanessian, S. *Total Synthesis of Natural Products: the Chiron Approach*; Pergamon Press: Oxford, **1983**.
6. a) Braun, M.; Vonderhagen, A.; Waldmüller, D. *Liebigs Ann.* **1995**, 1447-1450. b) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimar, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85-98.
7. Lanthanoid-lithium-BINOL complex-catalyzed asymmetric nitroaldol reactions: a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418-4420. b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851-854. c) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855-858. d) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657-2660. e) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett.* **1994**, *35*, 6123-6126. f) Sasai, H.; Yamada, Y.M.A.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 12313-12318. g) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372-10373. h) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388-7389.
8. Lanthanoid-sodium-BINOL complex-catalyzed asymmetric Michael reactions: a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K.N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194-6198. b) Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561-5564.
9. Lanthanoid-potassium-BINOL complex-catalyzed asymmetric hydrophosphonylations of imines: Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656-6657.
10. Aluminum-lithium-BINOL complex-catalyzed asymmetric Michael-aldol reactions and hydrophosphonylation of aldehydes: a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104-106. b) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926-2927.
11. Purchased from Kojundo Chemical Laboratory Co., Ltd., Saitama, Japan.
12. Recrystallization of **2a** from ether-hexane and hydrogenation with 5% Pd-C in methanol gave the corresponding amino alcohol. Treatment of the amino alcohol with hydrochloric acid and recrystallization from methanol afforded colorless plates of optically pure 1-amino-3,3-difluoro-6-phenylhexan-2-ol. The X-ray structure analysis was made at Toray Research Center Inc., Tokyo. Crystal data: C₁₂H₁₈NOF₂Cl, 265.73, colorless plate, 0.60 x 0.30 x 0.08 mm, monoclinic, space group C2 (#5); *a* = 10.005 (3) Å, *b* = 5.010 (3) Å, *c* = 27.544 (2) Å, β = 94.82 (1)°; *V* = 1375.8 (6) Å³; *Z* = 4; *D*_{calc} = 1.283 g/cm³; *F* (000) = 560.00. The diffraction data were collected on a Rigaku AFC7R diffractometer at 26°C in the ω -2 θ mode using Cu-K α radiation (μ = 25.60 cm⁻¹, λ = 1.54178 Å) to a maximum 2 θ value of 120.1°. The structure was solved by direct methods (SHELXS86). The final cycle of full-matrix least squares refinement was based on 1601 unique reflections (*I* > 1.50 σ (*I*)) and 153 variable parameters and converged with unweighted and weighted agreement factor of *R* = 0.104 (*R*_w = 0.109).
13. Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Appl. Organomet. Chem.* **1995**, *9*, 421-426.
14. The α -fluorines would coordinate to either the hydroxyl group of BINOL through a hydrogen bond or the lithium cation to markedly affect the asymmetric induction. For interaction of fluorine with a proton or metals, see: a) Murray-Rust, P.; Stallings, W.C.; Monti, C.T.; Preston, R.K.; Gluster, J.P. *J. Am. Chem. Soc.* **1983**, *105*, 3206-3214. b) Dutta, A.; Jaman, A.I.; Nandi, R.N. *J. Mol. Spectrosc.* **1985**, *114*, 274-279. c) Yamazaki, T.; Haga, J.; Kitazume, T.; Nakamura, S. *Chem. Lett.* **1991**, 2171-2174. d) Yamazaki, T.; Kitazume, T. *J. Synth. Org. Chem. Jpn.* **1994**, *54*, 665-674.

(Received in Japan 7 October 1996; revised 24 October 1996; accepted 28 October 1996)