Efficient Diastereoselective and Enantioselective Nitroaldol Reactions from Prochiral Starting Materials: Utilization of La–Li–6,6′-Disubstituted BINOL Complexes as Asymmetric Catalysts

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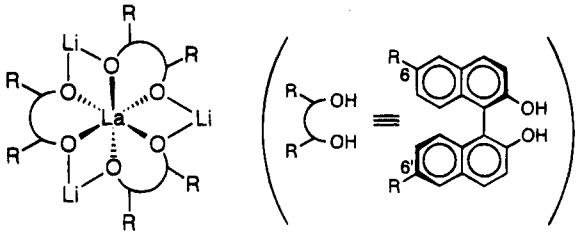
The nitroaldol (Henry) reaction is a powerful synthetic tool and has been applied in the construction of numerous natural products and other useful compounds.[1] Until our recent publications in which rare earth–lithium–BINOL complexes (LnLB) were successfully utilized as asymmetric catalysts,[2] no reports had appeared on asymmetric nitroaldol reactions promoted by optically active catalysts. Moreover, in spite of the potential of diastereoselective asymmetric nitroaldol reactions using prochiral aldehydes and nitroalkanes, even our preliminary attempts gave unsatisfactory results in terms of both diastereoselectivity (*syn–anti* ratio 63:37 to 77:23) and enantioselectivity (<78% ee).[2d] In order to obtain both high enantio- and diastereoselectivity, we focused our attention on the preparation of a novel asymmetric catalyst. On the centennial of the 1895 discovery of the nitroaldol reaction,[3] we report herein the first example of a highly enantio- and diastereoselective catalytic asymmetric nitroaldol reaction.

We began by preparing of a number of complexes from La(O-*i*-Pr)$_3$,[4] BuLi (3 mol equiv), H_2O (1 mol equiv), and (*R*)-BINOL derivatives (3 mol equiv) in which certain positions were substituted by alkyl, alkenyl, alkynyl, aryl, and/or cyano groups. Their utility as asymmetric catalysts was then assessed in a nitroaldol reaction of nitromethane with hydrocinnamaldehyde (**1**). Although 3,3′-dimethyl-BINOL- and 3,3′-bis(trimethylsilyl)-BINOL-derived complexes gave racemic 2-hydroxy-1-nitro-4-phenylbutane (**2**) and BIPOL[5] -derived catalyst gave **2** in only 39% ee,[6] substitution at the 6,6′-positions of BINOL produced superior asymmetric catalysts.[7,8] The structures of these rare earth–lithium–6,6′-disubstituted



3, R = H (LLB)
4, R = Br
5, R = Me
6, R = C≡N
7, R = C≡C–H
8, R = C≡CPh
9, R = C≡CSiMe$_3$
10, R = C≡CSiEt$_3$
11, R = C≡CTBS
12, R = C≡CSiMe$_2$Ph

Figure 1. Structure of the hetero-bimetallic complexes.

BINOL complexes (elucidated by ^{1}H- and ^{13}C-NMR) are similar to that of lanthanum–lithium–(*R*)-BINOL complex (**3**: LLB)[2c] as depicted in Figure 1. Representative results of the nitroaldol reaction at −40 °C for 91 h in THF using 3.3 mol % of the various catalysts and 10 equiv of nitromethane are as follows: catalyst **4**, 67% ee (80% yield); catalyst **5**, 63% ee (84% yield); catalyst **6**,[9] 55% ee (67% yield); catalyst **7**, 71% ee (69% yield).[10,11] Under these conditions, the control reaction using LLB (**3**) gave **2** in 62% ee (72% yield). Further study using the 6,6′-bisethynyl derivatives of BINOL as a chiral source revealed that 6,6′-bis((trialkylsilyl)ethynyl)BINOLs gave the best results (99 h): catalyst **8**, 79% ee (74% yield); catalyst **9**, 88% ee (85% yield); catalyst **10**, 85% ee (84% yield); catalyst **11**, 85% ee (59% yield); catalyst **12**, 86% ee (54% yield).[10,11] Using catalysts **8**-**12**, nitroaldol adducts were routinely obtained with optical purity superior to that of adducts obtained with LLB (**3**).[12]

With effective asymmetric catalysts in hand, we next applied catalyst **9** and/or **10** to diastereoselective nitroaldol reactions. We were pleased to find that, in all cases, higher *syn*-selectivity and enantioselectivity were obtained using the new catalysts (3.3 mol %).[13,14] Representative results are shown in Table 1. It is noteworthy that structurally simple aldehydes such as hexanal, which has no neighboring group to assist asymmetric induction, gave nitroaldols in high optical purity. In addition, 6,6′-bis((trialkylsilyl)ethynyl)-substituted BINOL-derived catalysts were found to make the nitroaldol

(1) For representative papers see: (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–18. (b) Rosini, G. *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 321 and references therein.

(2) (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.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372–10373. (d) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855–858. (e) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657–2660. (f) Sasai, H.; Yamada, Y. M. A.; Suzuki, T.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 12313–12318. (g) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett.* **1994**, *35*, 6123–6126.

(3) Henry, L. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.

(4) Purchased from Kojundo Chemical Laboratory Co., Ltd., Saitama, Japan, and Soekawa Rikagaku Co. Ltd., Tokyo, Japan.

(5) Yamamoto, K.; Noda, K.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 1065–1066.

(6) Formation of the LLB like complex[2c] would be prevented by the steric hindrance of 3,3′-substituent.

(7) Prepared readily from commercially available 6,6′-dibromo-BINOL. See the supporting information.

(8) For the use of 6,6′-dibromo-BINOL Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693–6696.

(9) 6,6′-Dicyano-BINOL of 93% ee was used.

(10) Enantiomeric excesses were determined by HPLC using a DAICEL CHIRALPAK AD as a column. See the supporting information.

(11) All complexes prepared from (*R*)-BINOL derivatives gave nitroaldols of (*S*)-configuration.

(12) The reason why the substitutions at the 6,6′-position of BINOL are effective in obtaining nitroaldols in higher optical purities and diastereoselectivities is not completely clear at present. We prepared various La–Li–6,6′-disubstituted BINOL complexes from the following point of view. First, substituents at 6,6′-position of BINOL would make the asymmetric space of hetero-bimetallic catalysts smaller. Second, the cyano and/or ethynyl substituents at the 6,6′-position of BINOL would affect the Lewis acidity of La. It is likely that higher enantiomeric excesses and diastereoselectivities can be explained by the above-mentioned matters.

(13) For **13** + **14** and **15** + **16**, diastereoselectivities were directly determined by ^{1}H-NMR of the crude reaction mixture and enantiomeric excesses were determined by HPLC analyses using a DAICEL CHIRALPAK AD column. On the other hand, for **17** + **18** and **20** + **21**, diastereoselectivities were determined by ^{1}H-NMR after rough purification using a Lobar LiChroprep RP-8 prepacked column (CH_3CN–H_2O, 1:1), and enantiomeric excesses were determined by HPLC analyses using a DAICEL CHIRALPAK AD column. Rough purification by other chromatography techniques resulted in the epimerization of the *syn*-adducts to the *anti*-adducts.

(14) In all cases we examined, the catalyst prepared from (*R*)-BINOL derivatives gave adducts of (*S*,*S*)-configuration.

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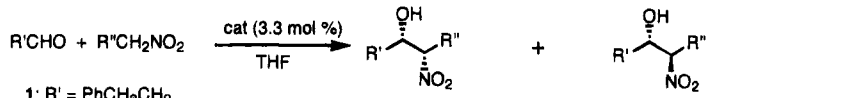
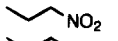
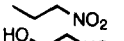
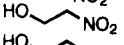
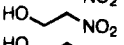
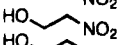
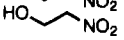
Table 1. Diastereoselective and Enantioselective Nitroaldol Reactions



1: R' = $PhCH_2CH_2$
19: R' = $CH_3(CH_2)_4$

13: R' = $PhCH_2CH_2$, R" = Me
15: R' = $PhCH_2CH_2$, R" = Et
17: R' = $PhCH_2CH_2$, R" = CH_2OH
20: R' = $CH_3(CH_2)_4$, R" = CH_2OH

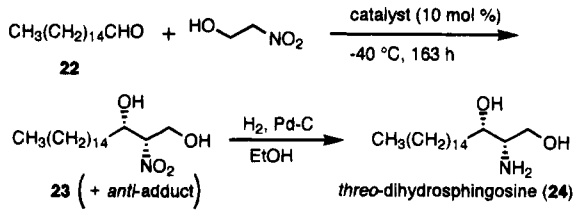
14: R' = $PhCH_2CH_2$, R" = Me
16: R' = $PhCH_2CH_2$, R" = Et
18: R' = $PhCH_2CH_2$, R" = CH_2OH
21: R' = $CH_3(CH_2)_4$, R" = CH_2OH

entry	aldehyde	nitroalkane	catalyst	time (h)	temp (°C)	nitroaldols	yield (%)	*syn* / *anti*	ee of *syn* (%)
1	**1**	$EtNO_2$	**3**	75	-20	**13** + **14**	79	74:26	66
2	**1**	$EtNO_2$	**5**	75	-20	**13** + **14**	80	74:26	65
3	**1**	$EtNO_2$	**7**	75	-20	**13** + **14**	77	84:16	90
4	**1**	$EtNO_2$	**9**	75	-20	**13** + **14**	72	85:15	92
5	**1**	$EtNO_2$	**10**	75	-20	**13** + **14**	**70**	**89:11**	**93**
6	**1**	$EtNO_2$	**10**	115	-40	**13** + **14**	21	94:6	97
7	**1**		**3**	138	-40	**15** + **16**	89	85:15	87
8	**1**		**10**	138	-40	**15** + **16**	**85**	**93:7**	**95**
9	**1**		**3**	111	-40	**17** + **18**	62	84:16	66
10	**1**		**10**	111	-40	**17** + **18**	**97**	**92:8**	**97**
11	**19**		**3**	93	-40	**20** + **21**	79	87:13	78
12	**19**		**10**	93	-40	**20** + **21**	**96**	**92:8**	**95**

reaction of nitroethanol faster than the same reaction catalyzed by **3**. If the rate-determining step in the catalytic cycle is a dissociation of the nitroaldol product from the catalyst, then this rate acceleration may be attributable to the steric bulk of the intermediary complex of the catalyst and the nitroaldol product, which promotes faster regeneration of the catalyst or the nitronate complex of the catalyst.[15] Interestingly, optical purities of minor *anti*-adducts were lower than those of *syn*-adducts.[16] These results demonstrate that *anti*-adducts were not generated by epimerization of the nitro group.[17,18]

Preliminary success in an application of the *syn*-selective asymmetric nitroaldol reaction was achieved with the synthesis of *threo*-dihydrosphingosine (**24**) (Scheme 1).[19] Nitroaldol reaction of **22** with 3 equiv of nitroethanol gave the corresponding nitroaldol adducts with high *syn*-selectivity (91:9) in 78% yield.[20] The optical purity of the *syn*-adduct **23** was up to 97% ee. In this case, the LLB catalyzed reaction proceeded slowly to give a 86:14 ratio of *syn*- and *anti*-adducts in 31% yield (83% ee). Hydrogenation of **23** in the presence of 10% Pd/C afforded the desired **24** in 71% yield.

Scheme 1



catalyst **10**:
78% (*syn* / *anti* = 91:9), *syn*: 97% ee
catalyst **3**:
31% (*syn* / *anti* = 86:14), *syn*: 83% ee

In conclusion, highly enantio- and *syn*-selective nitroaldol reactions have been achieved for the first time using rare earth–lithium–6,6'-bis((trialkylsilyl)ethynyl)-BINOL complexes as catalysts. This powerful new reaction has been applied to the efficient synthesis of **24**. Full mechanistic studies are in progress.

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Supporting Information Available: Further details of experimental procedures for the reactions described and of product characterization of compounds described (64 pages).

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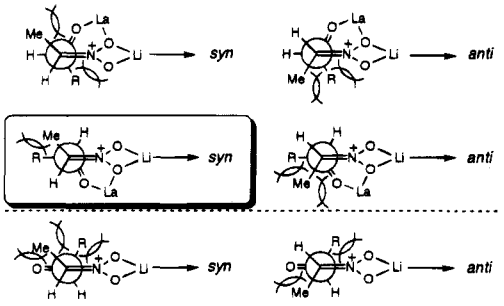
(15) Although the reason is not clear at present, the reaction of nitroethane and/or nitropropane appears to be slower.

(16) The optical purity of **14** (3*S*, 4*R*) and **16** (3*S*, 4*R*) was 20–49% ee, and the optical purity of **18** (2*S*, 3*R*) was 33% ee using catalyst **3** and 82% ee using catalyst **10**.

(17) Treatment of a mixture of nitroaldol adducts **13** and **14** with LLB (3.3 mol %) in the presence of nitromethane (10 equiv) resulted in no changes in *syn*/*anti* ratio and optical purity of **13**. Moreover, nitroaldol **2** was not observed, suggesting the enantio- and diastereoselectivities were controlled kinetically.

(18) It appears that the *syn*-selectivity in the nitroaldol reaction is best explained by steric hindrance in the bicyclic transition state as can be seen in Newman projections, which suggest that the transition state leading to the *syn* adduct is most favorable. In the favored transition state, the catalyst is believed to act as a Lewis acid and base at the same time. In contrast, the non-chelation-controlled transition state appears to afford *anti*-adducts in lower optical purity. In order to confirm the above mechanism, calculation is under investigation. Examples of the other hetero-bimetallic multifunctional catalysts: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194–6198. (b) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.*, in press.



(19) (a) Schwartz, G. K.; Jiang, J.; Kelsen, D.; Albino, A. P. *J. Nat. Cancer Inst.* **1993**, *85*, 402–407. (b) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500–507. (c) Hannun, Y. A.; Loomis, C. R.; Merrill, A. H., Jr.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 12604–12609.

(20) Diastereoselectivity was determined by ^{1}H-NMR after rough purification using silica gel column chromatography and enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AD as a column.