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Stereodivergent Catalytic Doubly Diastereoselective Nitroaldol Reactions Using Heterobimetallic Complexes

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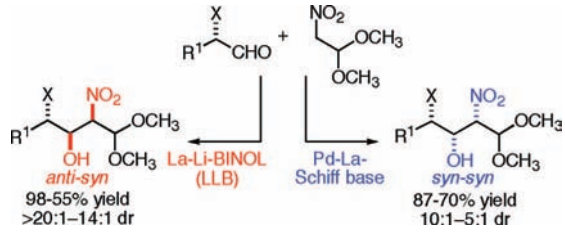
ABSTRACT



Stereodivergent construction of three contiguous stereocenters in catalytic doubly diastereoselective nitroaldol reactions of α-chiral aldehydes with nitroacetaldehyde dimethyl acetal using two types of heterobimetallic catalysts is described. A La−Li−BINOL (LLB) catalyst afforded *anti,syn*-nitroaldol products in >20:1−14:1 selectivity, and a Pd/La/Schiff base catalyst afforded complimentary *syn,syn*-nitroaldol products in 10:1−5:1 selectivity.

The construction of multiple stereocenters in one-pot via carbon−carbon bond-formation reaction enables rapid access to densely functionalized molecules from readily available substrates. Among several of the efficient strategies reported,[1] chiral catalyst-based methodologies are attractive in terms of the diversity in stereocontrol.[2] Depending on the chiral catalysts used, the stereochemical outcome of the reaction can, in principle, be flexibly modified. Here, we describe our studies on this issue with catalytic doubly diastereoselective nitroaldol (Henry) reactions.

Catalytic asymmetric nitroaldol reactions provide nitrogen-containing chiral building blocks useful for the synthesis of natural products and pharmaceuticals.[3] Since our report in 1992,[4,5] various chiral catalysts for enantio- and diastereoselective nitroaldol reactions have been reported.[6] Nitroaldol reactions of α-chiral aldehydes with nitromethane as a donor under catalyst-control conditions have been intensively studied to give nitroaldols with two contiguous stereocenters;[3,6] however, doubly diastereoselective nitroaldol reactions of α-chiral aldehydes with nitroalkanes other than nitromethane, wherein products with three contiguous stereocenters can be obtained, are quite limited.[7] Substrate-controlled reactions using a stoichiometric[7a,b] and/or substoichiometric[7c] amount of an achiral base have been developed, affording thermodynamically stable *anti,anti*-

(1) Recent reviews: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (e) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953.

(2) A review: Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(3) Reviews: (a) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561. (b) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442. (d) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(4) Selected early works on catalytic asymmetric nitroaldol reactions: (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahderon Lett.* **1994**, *35*, 6123. (c) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388. For other works see a review: (d) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1236.

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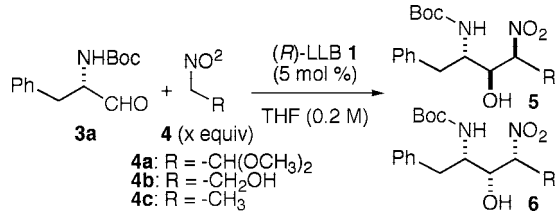
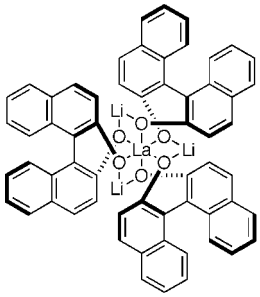
Table 1. Optimizations on Nitroaldol Reaction with (*R*)-LLB **1**



entry	nitroalkane (*x* equiv)	*T* (°C)	time (h)	product	yield[a] (%)	dr[b] (**5**:**6**:others)
1	**4a**(3.0)	−20	24	**5aa**	92	1.8:1:−
2	**4b**(3.0)	−20	24	**5ab**	82	0.8:1:0.8
3	**4c**(3.0)	−20	24	**5ac**	32	1:1:0.6
4	**4a**(3.0)	−40	48	**5aa**	97	11:1:−
5	**4a**(3.0)	−50	48	**5aa**	96	>20:1:−
6	**4a**(1.1)	−50	48	**5aa**	97	>20:1:−

[a] Isolated yield of **5**+**6**+others. [b] Determined by ^{1}H NMR.

nitroaldols in good to excellent diastereoselectivity. Stereoselective synthesis of other diastereomers, however, remains a formidable task.[8] There are no efficient methods using chiral catalysts for kinetically controlling stereochemistry adjacent to a nitro group in the doubly diastereoselective nitroaldol reactions. Therefore, there is much room for improvement. Herein, we discuss the usefulness of heterobimetallic Lewis acid/Brønsted base bifunctional catalysts[9] to address this issue. In reactions of α-chiral aldehydes with a functionalized nitroalkane, $LaLi_3$tris(binaphthoxide) complex (LLB **1**, Figure 1) gave *anti*-*syn*-nitroaldols in up to



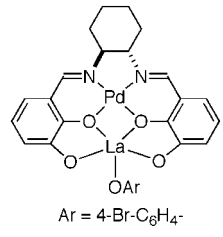
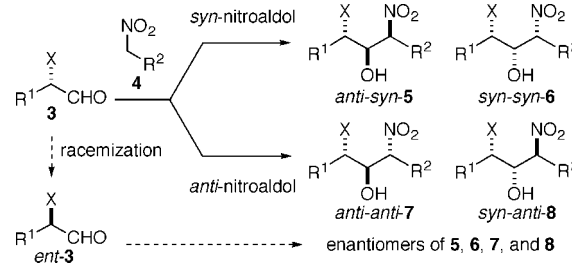


Figure 1. Structure of (*R*)-$LaLi_3$tris(binaphthoxide) (**1**: LLB) and proposed structure of a Pd:La:(*S*,*S*)-Schiff base:OAr = 1:1:1:1 complex **2**.

>20:1 (desired *anti*,*syn*-isomer:other isomers) diastereoselectivity, while a Pd−La−Schiff base complex[10] (**2**, Figure 1) gave *syn*,*syn*-nitroaldols in up to 10:1 diastereoselectivity.

A possible reaction profile of the doubly diastereoselective nitroaldol reaction is illustrated in Scheme 1. The difficulties in selectively synthesizing one of eight possible stereoisomers arises from two intrinsic factors: (1) α-chiral aldehydes are easily racemized under basic conditions, and (2) competitive retro-nitroaldol reaction and epimerization of the nitroaldol

Scheme 1. Doubly Diastereoselective Nitroaldol Reaction of α-Chiral Aldehyde **3** with Nitroalkane **4**



adducts often decrease the chiral-catalyst-induced kinetic stereoselectivity. We hypothesized that the heterobimetallic bifunctional catalysts developed in our group would overcome these problems.

From the viewpoint of synthetic accessibility, *N*-Boc-protected aldehyde (*S*)-**3a** derived from L-phenylalanine was selected as a model substrate. Because aldehyde **3a** is

(5) For related recent works in our group, see: (a) Tosaki, S.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776. (b) Mihara, H.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2008**, *3*, 359. (c) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272.

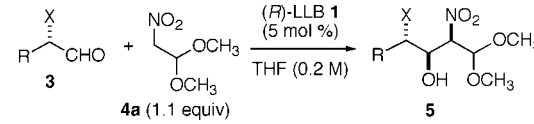
(6) For selected works by other groups, see: (a) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931. (b) Christensen, C.; Juhl, K; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875. and references therein. (c) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (d) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (e) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. (f) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881. (g) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150. and references therein. (h) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. (i) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (j) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595. and references therein. (k) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (l) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829. (m) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151. (n) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079. For other examples, see reviews in ref 3.

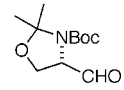
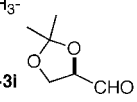
notoriously prone to racemize under basic conditions, suitable selection of the chiral catalyst and reaction conditions was important. Optimization studies with (*R*)-LLB **1** for the reaction of (*S*)-**3a**[11] and nitroalkanes **4** are summarized in Table 1. Among the nitroalkanes investigated (entries 1−3), nitroacetaldehyde dimethyl acetal (**4a**)[12] gave promising results. With nitroalkane **4a** at −20 °C, (*R*)-LLB **1** gave *anti*,*syn*-**5aa** as the major reaction product together with *syn*,*syn*-adduct **6aa** in 92% yield.[13,14] Although the ratio of **5**:**6** was unsatisfactory (entry 1, **5**:**6** = 1.8:1), the result was promising as an initial trial because *anti*-nitroaldol products **7** and **8** were not observed in entry 1. In contrast, complex mixtures of diastereomers were produced when using nitroethanol (**4b**) (entry 2: **5**:**6**:**7**+**8** = 0.8:1:0.8) and nitroethane (**4c**) (entry 3, **5**:**6**:**7**+**8** = 1:1:0.6). Because the acetal moiety in nitroalkane **4a** is potentially useful for further functionalization of the products, we selected **4a** for further optimizations. The reaction temperature was key to improving diastereoselectivity (entries 4 and 5), and *anti*,*syn*-**5aa** was obtained in 96% yield with >20:1 diastereoselectivity at −50 °C. The optical purity of **5aa** was confirmed to be >99% ee by chiral stationary phase HPLC analysis. These results suggested that racemization of the aldehyde, retro-reaction, and epimerization of the product were effectively suppressed under the optimized reaction conditions. It is also noteworthy that the reaction proceeded smoothly with as little as 1.1 equiv of **4a**, affording *anti*,*syn*-**5aa** in 97% yield with >20:1 diastereoselectivity (entry 6).

The optimized reaction conditions were applied to several α-chiral aldehydes (Table 2). (*R*)-LLB **1** promoted the reaction of (*S*)-α-amino aldehydes with 1.1 equiv of nitroalkane **4a**, giving *anti*,*syn*-nitroaldols **5** with >20:1 (**5**:other isomers) diastereoselectivity. Ester and acetal functional groups in aldehydes were compatible under the present reaction conditions, affording products in 98−86% yield and >20:1 diastereoselectivity (entries 4−6). The present system was also applicable to α-oxy aldehydes (entries 8 and 9). *O*-Benzyl-protected-aldehyde **3h** was less reactive than α-amino aldehydes, and the reaction was performed at −20 °C to give **5ha** in 80% yield with 14:1 diastereoselectivity (entry 8). With aldehyde (*R*)-**3i**, (*S*)-LLB **1** was suitable, and *ent*-**5ia** was obtained in >20:1 (*ent*-**5**:other isomers) diastereoselectivity (entry 9).

Preliminary trials to synthesize *syn*,*syn*-product **6aa** from (*S*)-**3a** using (*S*)-LLB failed, in which the stereochemical course of the reaction should be controlled by (*S*)-LLB to override the mismatched steric bias of α-chiral (*S*)-**3a** (Scheme 2). Nitroaldol adducts were obtained in 24% yield with poor diastereoselectivity (**5aa**:**6aa**:others = 2.8:1:2.6). Thus, we screened other chiral catalysts for switching the diastereoselectivity, and a Pd:La:(*S*,*S*)-Schiff base:OAr = 1:1:

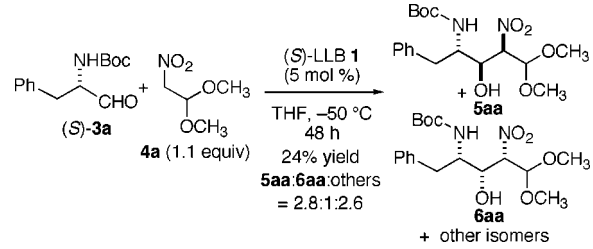
Table 2. Nitroaldol Reaction of Various α-Chiral Aldehydes **3a**-**3i** with Nitroalkane **4a** Using (*R*)-LLB **1** for *anti*,*syn*-**5**



entry	aldehyde R	X	temp (°C)	time (h)	5	yield (%)[a]	dr (5:others)[b]
1	**3a**: $PhCH_2$-	BocNH-	−40	48	**5aa**	97	>20:1
2	**3b**: CH_3-	BocNH-	−40	48	**5ba**	88	>20:1
3	**3c**: $PhCH_2$-	CbzNH-	−40	36	**5ca**	55	>20:1
4	**3d**: $EtO_2C(CH_2)_2$-	BocNH-	−40	48	**5da**	94	>20:1
5	**3e**: $EtO_2C(CH_2)_2$-	CbzNH-	−40	48	**5ea**	91	>20:1
6	**3f**: $(CH_3O)_2CH(CH_2)_2$-	BocNH-	−40	48	**5fa**	86	>20:1
7	**3g** 		−40	24	**5ga**	98	>20:1
8	**3h**: CH_3-	BnO-	−20	24	**5ha**	80	14:1
9[c]	*ent*-**3i** 		−40	48	*ent*-**5ia**	90	>20:1

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] (*S*)-LLB (**1**) was used.

Scheme 2. Unsuccessful Nitroaldol Reaction of (*S*)-**3a** with Nitroalkane **4a** by Using Mismatched (*S*)-LLB **1**



(7) (a) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261. (b) Hanessian, S.; Devasthale, P. V. *Tetrahedron Lett.* **1996**, *37*, 987. (c) Wehner, V.; Jäger, V. *Angew. Chem., Int. Ed.* **1990**, *29*, 1169. (d) Fernández, R.; Gasch, C.; Gómez-Sánchez, A.; Vílchez, J. E.; Castro, A. L.; Diánez, M. J.; Estrada, M. D.; Pérez-Garrido, S. *Carbohydr. Res.* **1993**, *247*, 239. (e) Soengas, R. G.; Estévez, J. C.; Estévez, R. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3955. (f) Bernardi, L.; Bonini, B. F.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Gavioli, S.; Ricci, A.; Varchi, G. *J. Org. Chem.* **2003**, *68*, 1418.

(8) Hanessian et al. reported an exceptional example using (*R*)-LLB **1** as a chiral catalyst. Although there remained a room for improvement in diastereoselectivity (*anti*-*syn*-**5**:*syn*-*syn*-**6**:others = 20:5.5:2.5), *anti*-*syn*-**5** was obtained as a major product. See Hanessian, S.; Brassard, M. *Tetrahedron* **2004**, *60*, 7621.

(9) (a) Reviews on Lewis acid-Brønsted base bifunctional catalysis Matsunaga, S.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60. (b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.

(10) (a) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230. For related bimetallic Schiff base catalysts, see: (b) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (c) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.

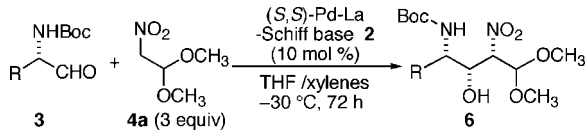
(11) For the synthesis of aldehyde **3** without racemization: Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121, and references therein.

(12) Synthesis of nitroalkane **4a**: Jäger, V.; Poggendorf, P. *Org. Synth.* **1997**, *74*, 130. For the use of nitroacetaldehyde diethyl acetal for *anti*-*anti*-selective nitroaldol reaction, see ref 7c.

(13) The stereochemistry of **5aa** was determined by *O*-methyl mandelate method: (a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. See the Supporting Information.

(14) The stereochemistry of **6aa** was unequivocally determined by X-ray crystallographic analysis. See the Supporting Information.

Table 3. Nitroaldol Reaction of α-Chiral Aldehydes **3** with Nitroalkane **4a** Using (*S*,*S*)-Pd−La complex **2** for *syn*,*syn*-**6**



entry	aldehyde (R)	product	yield[a] (%)	dr[b] (**6**:**5**:others)
1	**3a**: $PhCH_2-$	**6aa**	87	10:1:trace
2	**3b**: CH_3-	**6ba**	70	5:1:trace
3	**3d**: $EtO_2C(CH_2)_2-$	**6da**	78	8:1:trace

[a] Isolated yield. [b] Determined by ^1H NMR.

1:1 complex **2** (Ar = 4-Br-C_6H_4-, Figure 1)[10a] gave promising results (Table 3). With the heterobimetallic (*S*,*S*)-Pd−La complex **2**, nitroaldol reactions of **3a**, **3b**, and **3d** proceeded at −30 °C, giving *syn*,*syn*-nitroaldol **6** with 10:1−5:1 (**6**:**5**) diastereoselectivity.[15] No racemization of α-chiral aldehyde occurred during the nitroaldol reaction, as confirmed by chiral stationary-phase HPLC analysis.

In the present reactions, (*R*)-LLB **1** gave *anti*,*syn*-product **5** (Table 2) and the Pd:La:(*S*,*S*)-Schiff base:OAr = 1:1:1:1 complex **2** gave *syn*,*syn*-product **6** (Table 3). Stereochemisty adjacent to a nitro group is speculated to be kinetically controlled by chiral catalysts.[16] Interestingly, facial selectivity of aldehydes changed depending on the chiral catalysts used. Because the results in both Tables 2 and 3 were obtained with matched pairs of chiral catalysts and aldehydes, the results implied that the conformation of aldehydes **3** in the transition state in Table 2 is different from that in Table 3. The stereochemical course of the reaction with (*R*)-LLB **1** can be explained by Felkin−Anh model from the opened conformation of (*S*)-**3** (Figure 2a), while that with (*S*,*S*)-Pd−La complex **2** is speculated to be obtained from the chelated conformation of (*S*)-**3** through intramolecular hydrogen bonding (Figure 2a).[17,18] We believe that the favorable conformation of aldehyde **3** in the transition-state changes depending on the property of chiral catalysts. Mechanistic studies to clarify the origin of selectivity are ongoing.

Transformations of **5ha** and **6aa** were successfully performed without epimerization, demonstrating its potent synthetic utility (Scheme 3). Reduction of the nitro group in

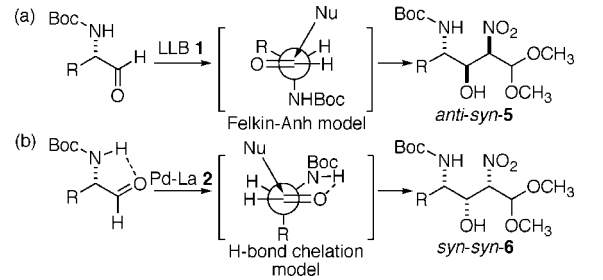
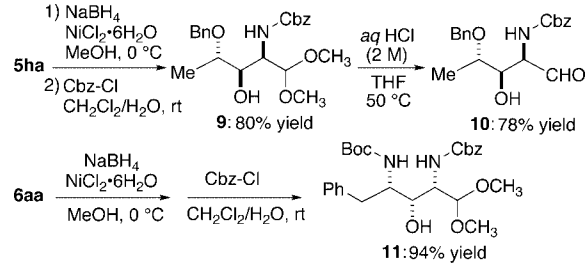


Figure 2. Two hypothetical transition-state models: (a) Felkin−Anh model for *anti*,*syn*-**5** using LLB **1** and (b) hydrogen-bond chelation model for *syn*,*syn*-**6** using Pd−La complex **2**.

Scheme 3. Transformations of Nitroaldol Adduct **5ha** and **6aa**



5ha and **6aa** followed by treatment with Cbz-Cl gave *N*-Cbz-protected amine **9** and **11** in 80% and 94% yield, respectively. Hydrolysis of the acetal moiety in **9** under acidic conditions afforded **10** in 78% yield.

In summary, we achieved stereodivergent doubly diastereoselective nitroaldol reactions of α-chiral aldehydes with a functionalized nitroalkane using two types of heterobimetallic catalysts, LLB **1** for *anti*,*syn*-products **5** and a Pd−La−Schiff base complex **2** for *syn*,*syn*-products **6**. The facial selectivity of α-chiral aldehydes in nitroaldol reactions changed depending on the chiral catalysts. Further investigations to develop a catalyst to selectively synthesize other isomers, especially *syn*,*anti*-**8** are ongoing.

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Supporting Information Available: Experimental procedures, spectral data of new compounds, and X-ray crystallography data of **6aa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Trials to synthesize *anti*,*syn*-**5** by mismatched (*R*,*R*)-Pd−La complex **2** failed. (*R*,*R*)-Pd−La complex **2** afforded products **6aa** as a major adduct in lower dr and yield (**6aa**:others = 8:1, 61% yield) than (S,S)-Pd−La complex **2.**

(16) LLB **1** is known as a suitable catalyst for *syn*-selective nitroaldol reaction of prochiral aldehydes with nitroehthane and nitroethanol (ref 4c). The Pd-La-Schiff base complex **2** gave *anti*-nitroaldol adducts in the reaction of prochiral aldehydes with nitroehthane (ref 10a). Although the precise reason why the Pd−La complex **2** gave *syn*,*syn*-**6** with nitroalkane **4a** has not been clarified yet, we speculate that coordinating dimethylacetal moiety in nitroalkane **4a** may be important for changing the geometry of nitronate generated from **4a**. Further mechanistic studies are required for more detailed discussion.

(17) For related reports utilizing intramolecular hydrogen bonding for *anti*-Felkin−Anh stereocontrol of *N*-Boc-protected α-amino aldehydes, see: (a) Jung, C.-K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. (c) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.

(18) Aldehyde **3g** lacking an N−H group gave much less satisfactory results with the Pd−La Schiff base complex **2.**