ORGANIC LETTERS

2003
Vol. 5, No. 20
3555−3558

Enantioselective Borodeuteride Reduction of Aldimines Catalyzed by Cobalt Complexes: Preparation of Optically Active Deuterated Primary Amines

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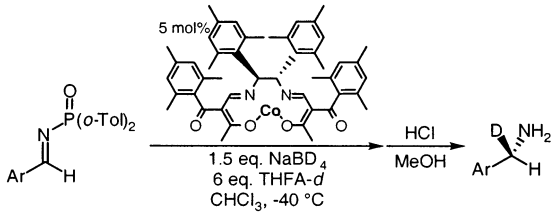
Received June 4, 2003 *(Revised Manuscript Received August 12, 2003)*

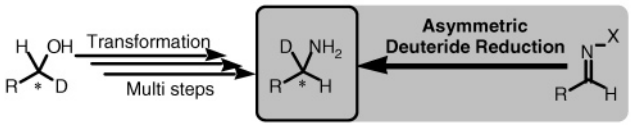
ABSTRACT



The enantioselective borodeuteride reduction catalyzed by optically active β-ketoiminato cobalt complexes was applied to *N*-(di(*o*-tolyl)phosphinyl)-aldimines to afford the corresponding optically active deuterated primary amines in high yields with high enantiomeric excesses after simple deprotection. The present deuteride reduction of aldimines is in the opposite sense of the enantioselective for the previously reported borohydride reduction of ketones or diphenylphosphinyl aldimines. The stereochemical course in these enantioselective reductions is discussed.

Deuteride is one of the most available labeling atoms for the mechanistic investigations of both chemical and biological reactions,[1] and reliable isotope labeling techniques have been desired for these purposes. Optically active primary amines with deuteride of the chiral center are employed as versatile precursors for various labeled compounds containing a nitrogen atom adjacent to the deuterated chiral center.[2] Two strategies should be synthetically considered for the preparation of the deuterated primary amines; one is the derivation from the corresponding primary alcohols by functional group interconversion,[3] and the other is the application of the enantioselective deuteride reduction to the corresponding aldimines or their equivalents (Scheme 1). In the former method, the corresponding primary alcohol deuterated on a chiral center must be prepared in advance and routine synthetic steps are required for the transformation to the

Scheme 1. Two Strategies for Preparation of Optically Active Deuterated Amine



(1) (a) Stille, J. K.; Lau, K. S. Y. *J. Am. Chem. Soc.* **1976**, *98*, 5832−5840. (b) Parry, R. J.; Trinor, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 5243−5244. (c) Shibuya, M.; Chou, H.-M.; Fountoulakis, M.; Hassam, S.; Kim, S.-U.; Kobayashi, K.; Otsuka, H.; Rogalska, E.; Casssady, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1990**, *112*, 297−304. (d) Mu, Y.-Q.; Omer, C. A.; Gibbs, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 1818−1823.

(2) (a) Lown, J. W.; Akhtar, M. H. *J. Chem. Soc., Chem. Commun.* **1973**, 511−513. (b) Battersby, A. R.; Staunton, J.; Summers, M. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1052−1056. (c) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263−1265.

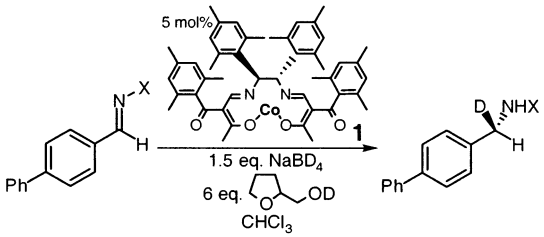
10.1021/ol0349920 CCC: $25.00
Published on Web 09/03/2003

deuterated amine. In the latter method, the optically active primary amine with deuteride on the chiral center could be directly obtained by the enantioselective deuteride reduction of the C=N bond followed by conventional deprotection of the amino group; however, there has been no report on the catalytic enantioselective deuteride reduction of aldimine or its equivalent.

Sodium borodeuteride is commercially available and is an easily handled reducing agent like the borohydride. The highly enantioselective reductions of ketones[4] and ketimines[5] with sodium borohydride were realized in the presence of the optically active β-ketoiminato cobalt complexes to afford the corresponding secondary alcohols or amines in high yields with high enantiomeric excesses. The enantioselective reduction system with sodium borodeuteride was recently applied to aldehydes to obtain the corresponding optically active deuterated primary alcohols in high yields with good optical yields.[6] In this letter, we report that the cobalt-catalyzed reduction system with sodium borodeuteride was successfully applied to aldimines or their equivalents to provide a convenient and preparative method for chiral deuterated primary amines with high enantioselectivity.

The enantioselective deuteride reduction of various aldimines or their equivalents derived from *p*-phenylbenzaldehyde was initially examined using sodium borodeuteride modified by tetrahydrofurfuryl alcohol-*d* (THFA-*d*)[7] in the presence of 5 mol % cobalt catalyst **1** (Table 1). Under these conditions, the *N*-*p*-methoxybenzylimine **2** and the *N*-*p*-methoxyphenylimine **3** were not reduced at all even at room temperature (entries 1 and 2). The oxime ether **4** and the hydrazone **5** were also inert under the same conditions (entries 3 and 4). The reduction of the *N*-mesylimine **6** and the *N*-tosylimine **7** rapidly proceeded even at −60 °C and afforded the corresponding sulfonamides in high yields, while their enantiomeric excesses were determined to be less than 10% ee[8] (entries 5 and 6). In the absence of the catalyst **1**, the reduction of the *N*-sulfonylimines **6** and **7** with only the modified borodeuteride was completed in 0.25 h. Eventually,

Table 1. Enantioselective Deuteride Reduction of Various Aldimines or Their Equivalents Derived from *p*-Phenylbenzaldehyde[a]

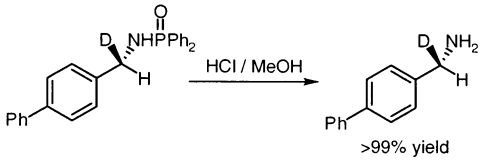


entry	X		temp/°C	yield/%[b]	ee/%[c]
1	*p*-$CH_3OC_6H_4CH_2$−	**2**	rt	no reaction	
2	*p*-$CH_3OC_6H_4$−	**3**	rt	no reaction	
3	CH_3O−	**4**	rt	no reaction	
4	Me_2N−	**5**	rt	no reaction	
5[d]	Ms	**6**	−60	>99	<10
6[d]	Ts	**7**	−60	>99	<10
7[e]	$Ph_2P(O)$−	**8**	−40	>99	83
8[e]	$(o\text{-Tol})_2P(O)$−	**9a**	−40	>99	93

[a] Reaction conditions: to a solution of the cobalt catalyst and the aldimine or its analogue was added a solution of the modified borodeuteride; 0.25 mmol of the aldimine or its analogue, 0.0125 mmol (5 mol %) of cobalt catalyst, 0.375 mmol of $NaBD_4$, and 1.5 mmol of THFA-*d* in $CHCl_3$. [b] Isolated yield. [c] After deprotection, the enantiomeric excesses were determined by the ^1H NMR analysis of the corresponding (*R*)-2-methoxy-2-(1-naphthyl)propionic amide. [d] Reaction was completed in 15 min. [e] Reaction was completed in 4 h.

it was found that the *N*-(diphenylphosphinyl)imine[9] **8** was appropriately reactive and smoothly reduced to the corresponding phosphinamide in high yield (entry 7). The obtained phosphinamide was treated with HCl/MeOH to afford the desired chiral deuterated primary amine in quantitative yield (Scheme 2).[10] The enantiomeric excess was determined to

Scheme 2. Deprotection of *N*-Diphenylphosphinamide



be 83% on the basis of ^1H NMR analysis of the corresponding (*R*)-2-methoxy-2-(1-naphthyl)propionic amide ((*R*)-MαNP amide).[11]

Various types of optically active β-ketoiminato cobalt complexes[12] were then examined by adopting the imine **8**

(3) (a) Streitwieser, A.; Wolfe. J. R. *J. Org. Chem.* **1963**, *28*, 3263−3264. (b) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65*, 6121−6131.

(4) (a) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145−2147. (b) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1996**, 737−738. (c) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1996**, 1081−1082. (d) Nagata, T.; Sugi, K. D.; Yamada, T.; Mukaiyama, T. *Synlett* **1996**, 1076−1078.

(5) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, 493−494.

(6) Miyazaki, D.; Nomura, K.; Ichihara, H.; Ohtsuka, Y.; Ikeno, T.; Yamada, T. *New J. Chem.* **2003**, *27*, 1164−1166.

(7) For the borodeuteride reduction of the aldehyde, employing THFA resulted in decreasing the isotopic purity of the corresponding alcohol because the deuteride of sodium borodeuteride could be exchanged with a proton from the alcohol: (a) Cornforth, R. H. *Tetrahedron* **1970**, *26*, 4635−4640. (b) Davis, R. E.; Bromels, E.; Kibby, C. L. *J. Am. Chem. Soc.* **1962**, *84*, 885−892. Therefore, THFA-*d* was prepared and employed for the borodeuteride modification instead of THFA, and the product was obtained with a >95% deuteration degree.

(8) Enantiomeric excesses were determined by ^1H NMR analysis of the corresponding (*R*)-MαNP amide after deprotection of the sulfonamides. The mesyl group was removed by reduction with $LiAlH_2(OCH_2CH_2OCH_3)_2$ in toluene, while the tosyl group was removed by treatment with SmI_2 in THF (Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056). It was, however, found that the degree of deuteration of the products decreased through both deprotection processes.

(9) (a) Hutchins, R. O.; Abdel-Magid, A.; Stercho, Y. P.; Wambsgans, A. *J. Org. Chem.* **1987**, *52*, 704−706. (b) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097−1098.

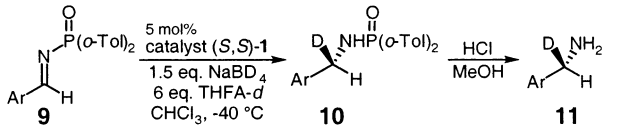
(10) Greene, T. W.; Wuts, P. G. *Protective Group in Organic Synthesis*; John Wiley & Sons: New York, 1999; p 598.

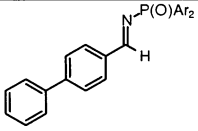
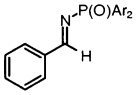
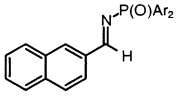
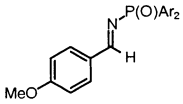
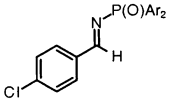
(11) (a) Ichikawa, A.; Hiradate, S.; Sugio, A.; Kuwahara, S.; Watanabe, M.; Harada, N. *Tetarahedron*: *Asymmetry* **1999**, *10*, 4075−4078. (b) Harada, N.; Watanabe, M.; Kuwahara, S.; Sugio, A.; Kasai, Y.; Ichikawa, A. *Tetarahedron*: *Asymmetry* **2000**, *11*, 1249−1253.

as the model substrate. These complexes exhibited excellent catalytic activity for the reduction of the imine **8** to afford the phosphinic amides in high yields, though none of them improved the enantioselectivity. It was expected that the more sterically demanding aryl of the phosphinyl group could enhance the discrimination of the (*Re*)- and (*Si*)-faces of the prochiral imine using the cobalt-deuteride intermediate.[4d,13] Actually, the phosphinylimine **9a**, possessing *o*-tolyl groups[14] in place of the phenyl in the phosphinylimine **8**, was subjected to the reduction system to afford the corresponding phosphinic amide **10a** with 93% ee (Table 1, entry 8).

The catalytic and enantioselective borodeuteride reduction was successfully applied for the preparation of various optically active deuterated primary amines from the corresponding *N*-(di(o-tolyl)phosphinyl)imines **9** (Table 2). Various aromatic imines **9b**−**e** derived from the corresponding aldehyde such as benzaldehyde, 2-naphthaldehyde, *p*-methoxybenzaldehyde, and *p*-chlorobenzaldehyde were converted into the corresponding deuterated phosphinic amides **10b**−**e** in quantitative yields. Each product was treated with HCl/MeOH to afford the corresponding deuterated amine **11b**−**e** in high yields. Benzyl-α-*d* amine **11b** and 2-naphthalenemethyl-*d* amine **11c** were obtained with 90 and 89% ees, respectively (entries 2 and 3). Both electron-donating and electron-withdrawing groups were found to be tolerated in the present enantioselective reduction system, i.e., the enantiomeric excesses of *p*-methoxybenzyl-α-*d* amine **11d** and *p*-chlorobenzyl-α-*d* amine **11e** were 88 and 94%, respectively (entries 4 and 5).

Table 2. Enantioselective Deuteride Reduction of Various *N*-(Di(*o*-tolyl)phosphinyl)imines[a]



entry	aldimine (Ar = *o*-Tol)		10 yield/%[b]	11 yield/%[b]	11 ee/%[c]
1		**9 a**	>99	>99	93
2		**9 b**	>99	89	90
3		**9 c**	>99	85	89
4		**9 d**	>99	90	88
5		**9 e**	>99	87	94

[a] Reaction conditions: to a solution of the cobalt catalyst and the *N*-di(o-tolyl)phosphinyl aldimine was added a solution of the modified borodeuteride; 0.25 mmol of *N*-di(o-tolyl)phosphinyl aldimine, 0.0125 mmol (5 mol %) of cobalt catalyst, 0.375 mmol of $NaBD_4$, 1.5 mmol of THFA-*d* in $CHCl_3$. [b] Isolated yield. [c] After deprotection, the enantiomeric excesses were determined by the ^1H NMR analysis of the corresponding (*R*)-2-methoxy-2-(1-naphthyl)propionic amide.

The stereochemical course of the cobalt complex-catalyzed reduction could be explained as follows.[4d,15] When the modified borohydride was added to the cobalt(II) complex solution, the reaction mixture instantly turned from yellowish orange, the color of the original catalyst solution, to reddish violet. The FAB mass analysis of this solution indicated the mass number corresponding to cobalt-hydride.[6,13] These observations suggested that the cobalt(II) complex was converted to the corresponding cobalt-hydride intermediate by the modified borohydride. The cobalt-hydride of (*S*,*S*)-configuration formed in this manner reduced the aryl ketones via *Re*-face attack to afford the corresponding (*S*)-alcohols. During the reaction, the aryl groups of the optically active diamine and the side chain effectively blocked the undesired approach (TS2 in Figure 1),[16] and the aromatic ring of the substrate was placed parallel to the delocalized π-system plane of the cobalt complex by π-interaction[17] as depicted in TS1. Since in the enantioselective reduction of imines, the diphenylphophinyl group is comparatively sterically demanding, its competitive repulsion[18] should be considered (TS1 vs TS2). A preliminary investigation of the structure of the diphenylphosphinyl aldimine by DFT method[19] suggested that its steric repulsion could be enhanced in the reaction of aldimines. Comparing the calculated structures,

(12) Catalysts employed all appeared in the following report: Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 2543−2546.

(13) Cobalt-hydride was assumed to be the reactive intermediate in the borohydride reduction catalyzed by the optically active β-ketoiminato cobalt complexes and was recently detected by FAB mass analysis: Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron*: *Asymmetry* **2003**, *14*, 967−970.

(14) (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 317−348. (b) White, D.; Coville, N. J. *Adv. Organomet. Chem.* **1994**, *36*, 95−158.

(15) Yamada, T.; Nagata, T.; Sugi, K. D.; Yorozu, K.; Ikeno, T.; Ohtsuka, Y.; Miyazaki, D.; Mukaiyama, T. *Chem. Eur. J.* **2003**, *9*, in print.

(16) (a) Ohba, S.; Nagata, T.; Yamada, T. *Acta Crystallogr. E* **2001**, m124−m126. (b) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1333−1342. (c) Kezuka, S.; Kogami, Y.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 49−58.

(17) Observation that the aryl ketones were reduced faster than the alkyl ketones could be explained similarly by $\pi-\pi$ interaction between the substrate and cobalt complex. Ohtsuka, Y.; Koyasu, K.; Miyazaki, D.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 3421−3424.

(18) Diphenylphosphinyl imine of tetralone could not be reduced in the enantioselective borohydride reduction catalyzed by the cobalt complex **1**. See ref 5.

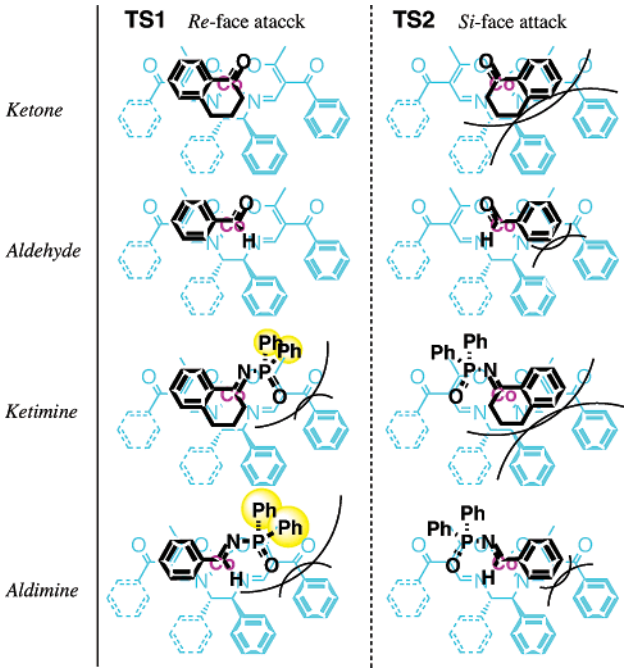


Figure 1. Possible transition states of enantioselective reduction catalyzed by the cobalt complex.

it is assumed that the space occupied by two aromatic rings on the phosphinyl group in aldimine could be larger than that of ketimine (Figure 2). Therefore, the steric repulsion of diphenylphosphinyl group would dominate the stereochemical course of reduction and *Si*-face attack (TS2) on aldimines would be preferred, affording the (*S*)-deuterated primary amines enantioselectively. This hypothesis is fully in accord with the observation that a di(*o*-tolyl)phosphinyl group improved the enantioselectivity in aldimine reduction.

It is noted that the enantioselective borodeuteride reduction catalyzed by the optically active β-ketoiminato cobalt complexes was used for the preparation of optically active deuterated primary amines and that high yields with high

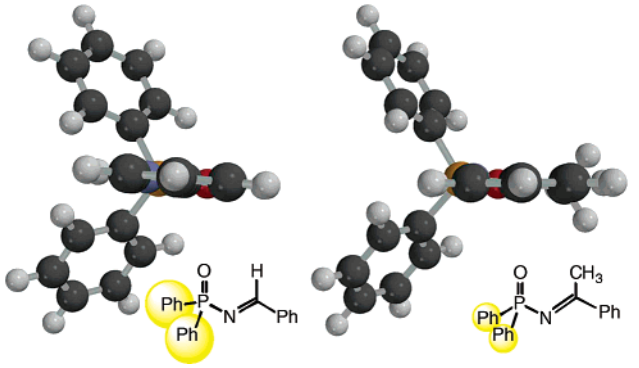


Figure 2. Side views of the diphenylphosphinyl aldimine and ketimine.

enantiomeric excesses were achieved. Further applications to other aldimines such as aliphatic aldimines are currently underway.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0349920

(19) Theoretical analysis of the structures of diphenylphosphinyl aldimine and ketimine was performed using the B3LYP method with 6-31G* as basis sets. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785−789. (c) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 2001.