Enantioselective Borohydride Reduction of *N*-Diphenylphosphinyl Imines Using Optically Active Cobalt(II) Complex Catalysts

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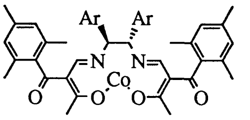
The enantioselective borohydride reduction using optically active cobalt(II) complex catalysts was successfully applied to various aryl *N*-diphenylphosphinyl imines, and the corresponding reduced products were obtained in good yields with high enantiomeric excesses (up to 99% ee). The optically active primary amines were obtained by the successive hydrolysis under mild conditions.

In order to prepare optically active alcohols in high efficiency, various methods for catalytic enantioselective reduction of prochiral ketones[1] had been extensively investigated. Likewise, analogous catalytic enantioselective reductions of imines were reported in the literatures,[2] however, a few examples were known for the syntheses of optically active amines with satisfactory enantiomeric excesses; for examples, the recent achievements of metal catalyzed enantioselective hydrogenations,[3] transfer hydrogenation,[4] hydrosilylations,[5] and oxazaborolidine catalyzed enantioselective borane reduction[6] of imines are worth noting. Therefore, a development of highly efficient enantioselective reduction of imines is still remained as challenging topics in synthetic organic chemistry.

Recently, optically active aldiminato cobalt(II) complexes (**A**,[7] **B**, and **C**, Figure 1) were demonstrated to be efficient catalysts in the enantioselective reduction of aryl ketones using pre-modified borohydride prepared by treating $NaBH_4$ with tetrahydrofurfuryl alcohol (THFA) and ethanol. In the presence of 0.1 - 1 mol% of properly selected cobalt(II) complexes, the corresponding optically active alcohols were obtained quantitatively with up to 98% ee in less than 45 min at 0 °C.[8]

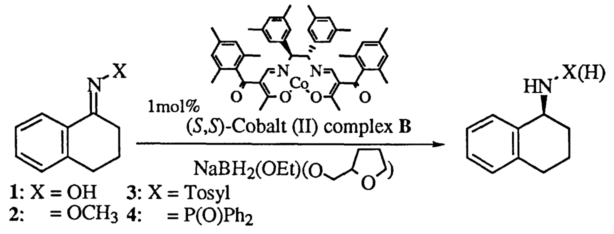


A: Ar = phenyl[7]
B: 3,5-dimethylphenyl
C: 2,4,6-trimethylphenyl

Figure 1. Cobalt(II) complexes.

The above enantioselective borohydride reduction was applied to compounds having C=N functionality,[9] and the reduction of *N*-substituted ketimines were effectively catalyzed by the cobalt(II) complexes to form the corresponding optically active amines with high enantiomeric purity. In this communication, we would like to describe the successful applications of the optically active cobalt(II) complex catalysts to the enantioselective reduction of the imines.

Preliminary experiments on synthesis of optically active primary amines from each aryl ketoximes and *N*-substituted ketimines[10] by the enantioselective borohydride reductions using 1 mol% of the cobalt(II) complex were tried at 0 °C for 4 h (Scheme 1).

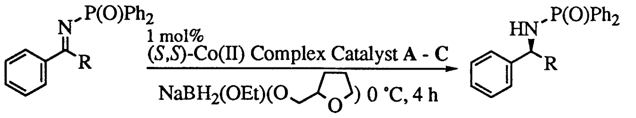


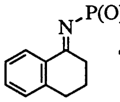
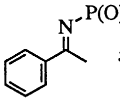
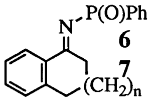
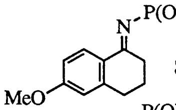
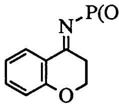
Scheme 1.

Treatments of oxime **1** or oxime methyl ether **2** by the borohydride reductions using the cobalt(II) complex **B** did not afford the optically active primary amines under the above conditions, and the starting substrates were recovered completely. On the contrary, when the reduction of protected imines such as *N*-toluenesulfonyl imine **3** (*N*-tosyl imine) or *N*-diphenylphosphinyl imine **4** was tried, the reactions took place smoothly and the corresponding optically active amines were obtained in 95 and 85% yields with 71 and 98% ee, respectively. The observed differences in optical purity of the resulted amines could be attributed to competitive direct reduction of imines with borohydrides[11] via non-catalytic reduction pathway. When *N*-tosyl imine **3** was subjected to the reduction in the absence of the catalyst, the corresponding racemic amine was obtained in 30% yield. On the other hand, *N*-phosphinyl imine **4** was inert toward pre-modified borohydride alone, and it suggested that *N*-phosphinyl imines are suitable substrates for the present reductions. Then, the enantioselective borohydride reduction using optically active cobalt(II) complex catalyst (**A**, **B**, or **C**) was examined using various *N*-diphenylphosphinyl imines,[12] and the results are summarized in Table 1.

In the presence of 1 mol% of the above catalyst **A**, **B**, or **C**, various aryl *N*-phosphinyl imines were smoothly converted to the corresponding optically active amines in good yields (up to 97%) at 0 °C within 4 h. As shown in the previously reported enantioselective borohydride reduction of aryl ketones,[8] a suitable combination of the cobalt(II) catalyst and aryl imine was one of the important factors in achieving high enantioselection. When the cyclic aryl imine **4** was subjected to the reductions, the cobalt(II) complex **B** was the best choice, and the corresponding amine was obtained in 98% ee whereas complex **A** gave 92% ee (Entries 1 and 2). It should be noted that when complex **C** was used, no reaction had taken (Entry 3). It may be attributed to high degree of steric congestion for *N*-diphenylphosphinyl imines with cobalt(II) complexes. The complex **C** gave the corresponding amine with the best optical purity (90% ee, Entry 6) in case of acyclic aryl imine **5**. The complexes **A** and **B** gave lower outcomes as 77 and 80% ee, respectively (Entries 4 and 5). The observed combinations of the catalyst and imine are paralleled with the suitable pairs found for the aryl ketone reductions,[8] and thus the cyclic aryl substrates with complex **B**

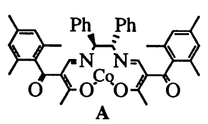
Table 1. Enantioselective borohydride reduction of *N*-diphenylphosphinyl imines by cobalt(II) complex catalyst



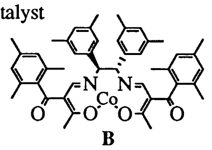
Entry[a]	Imines	Co(II) complex	Ee /%ee[b] (Yiled /%[c])	Abs. config.[e]
1	 **4**	A	92 (88)	
2		B	98 (85)	(*S*)
3		C	NR[d]	
4	 **5**	A	77 (96)	
5		B	80 (95)	(*S*)
6		C	90 (97)	
7	 **6** n = 0	B	91 (86)	(*S*)
8	**7** n = 2	B	94 (81)	ND[f]
9	 **8**	B	99 (97)	ND[f]
10	 **9**	B	92 (81)	ND[f]

[a] Reaction conditions; see Ref. 15. [b] Determined by HPLC analysis using Daicel Chiralpak AD. [c] Isolated yield. [d] No reaction. [e] Determined by sign of optical rotaion; see Ref. 14. [f] Not determined.

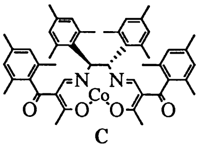
(*S*,*S*)-Co(II) Complex Catalyst



A



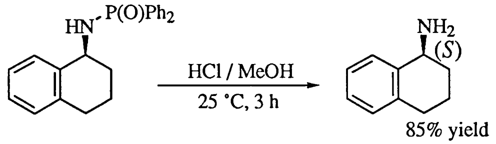
B



C

and acyclic aryl substrates with complex **C** are preferable. Accordingly, various cyclic *N*-phosphinyl imines **6** - **9** were applied to the reductions using 1 mol% of complex **B**, and the corresponding optically active amines were obtained in 91 - 99% ee (Entries 7 - 10).

The resulting *N*-phosphinyl amine represents an additional advantage over *N*-sulfonyl amine since preparation of optically active primary amine by subsequent removal of diphenylphosphoryl group can be carried out under mild conditions;[13] for example, using HCl/MeOH at 25 °C for 3 h, the optically active primary amine having (*S*) configuration[14] was obtained in good yield without the loss of optical purity (Scheme 2).



Scheme 2.

Thus, a new and efficient method for the synthesis of various optically active amines was presented, and the preparation of the optically active primary amine by subsequent hydrolysis was carried out smoothly. The further study on mechanism of present reduction system is under investigation.

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Catalytic borohydride reduction; While maintaining solution of pre-modified borohydride at 0 °C, its solution was slowly added to the solution of 3.7 mg of cobalt(II) catalyst **B** (0.005 mmol, 1 mol%) and 172.6 mg of *N*-phosphinyl imine **4** (0.50 mmol) in 5.0 ml of $CHCl_3$, and the mixture was continued to stir for 4 h at 0 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and the excess solvents were removed under reduced pressure. The purification by column chromatography on silica gel (hexane / ethyl acetate / dichloromethane) gave 148.0 mg of the corresponding amine; 85% yield. The optical purity was determined by using Daicel Chiralpak AD (hexane / 2-propanol).