Enantioselective Borohydride 1,4-Reduction of α,β-Unsaturated Carboxamides Using Optically Active Cobalt(II) Complex Catalysts

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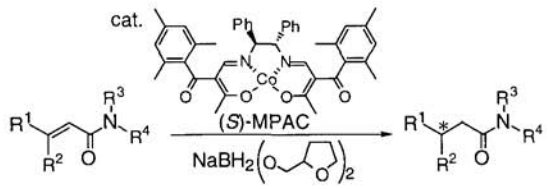
(Received August 12, 1998; CL-980616)

The enantioselective borohydride reduction catalyzed by cobalt(II) complex was successfully applied to 1,4-reduction of β,β-disubstituted α,β-unsaturated carboxamides. In the presence of less than 1 mol% of optically active aldiminato cobalt(II) complex catalyst, the corresponding carboxamides were obtained in high yields with high enantiomeric excesses.

The optically active aldiminato cobalt(II) complexes (MPAC) were recently demonstrated to be efficient catalysts in the enantioselective reduction of aryl ketones[1] and *N*-phosphinyl imines[2] using pre-modified borohydride prepared by treating $NaBH_4$ with tetrahydrofurfuryl alcohol (THFA) and ethanol (or methanol), and the corresponding optically active secondary alcohols and amines were obtained respectively in quantitative yields with high enantioselectivities. In addition of the enantioselective 1,2-reduction of C=O and C=N double bonds, the conjugate reduction of β,β-disubstituted α,β-unsaturated carbonyl compounds is one of the most significant reaction to construct an asymmetric center on their β-position. It was reported that optically active cobalt(II) complexes generated *in situ* from semicorrin ligand and $CoCl_2$ effectively employed as catalyst in the enantioselective reduction of prochiral β,β-disubstituted α,β-unsaturated ester[3] and amide[4] with $NaBH_4$. Although high enantioselection and high efficiency were achieved in that reaction, preparation of semicorrin ligand required many synthetic steps[5] and it took much long time to complete the enantioselective reduction catalyzed by semicorrin-cobalt complexes. Here, we would like to disclose that optically active aldiminato cobalt(II) complexes efficiently catalyzed enantioselective 1,4-reduction of β,β-disubstituted α,β-unsaturated carboxamides with pre-modified borohydride to afford the corresponding optically active carboxamide with high enantioselectivities.



The catalytic activity of aldiminato cobalt(II) complex was at first examined in 1,4-reduction of *N*-methyl-*N*-phenyl-3-phenylacrylamide using borohydride modified with THFA in presence or absence of (*S*)-MPAC[6] (Figure 1). In the absence of cobalt(II) complex catalyst, no reaction with pre-modified borohydride proceeded in 120 min at all and the starting material was recovered without any conversion. On the contrary, a catalytic amount of cobalt(II) complex, (*S*)-MPAC, remarkably accelerated 1,4-reduction of α,β-unsaturated amide to afford the corresponding propionamide in 89% yield in 60 min.

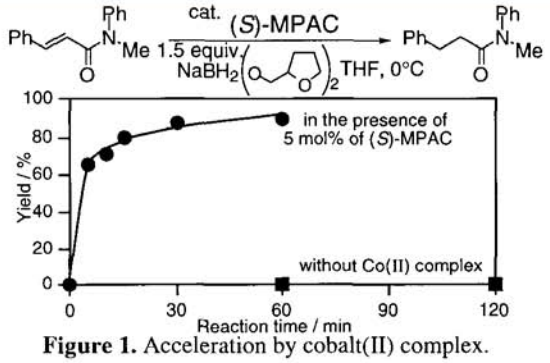
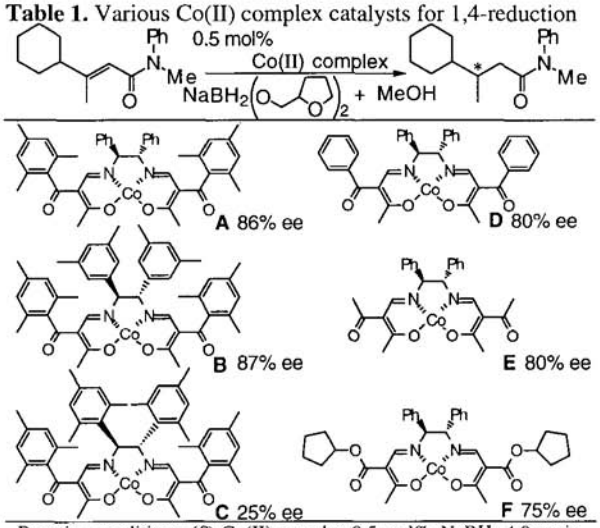


Figure 1. Acceleration by cobalt(II) complex.

Various optically active aldimine ligands for cobalt(II) complexes were examined in the enantioselective 1,4-reduction of (*E*)-3-cyclohexyl-2-butenamide (Table 1). When 0.5 mol% of cobalt(II) complex **A** ((*S*)-MPAC) or **B** was employed as a catalyst, α,β-unsaturated carboxaminde was smoothly converted to the corresponding amide in quantitative yield with 86% and 87% ee, respectively. On the contrary, complex **C** derived from optically active 1,2-dimesityl-1,2-ethylenediamine was not efficient catalyst for the 1,4-reduction to afford the reduced carboxamide with 25% ee. When complex **D** having benzoyl groups, complex **E** having acetyl groups, or complex **F** having cyclopentyloxycarbonyl groups as its side chains respectively was subjected to the 1,4-reduction with the THFA-modified borohydride, enantioselectivity of the reduced product was slightly lower than that in the reaction catalyzed by complex **A** or **B**. For the present 1,4-reduction of β,β-disubstituted α,β-unsaturated carboxamide, it was approved that complex **A** or **B** was suitable to achieve high yield and high enantioselectivity.

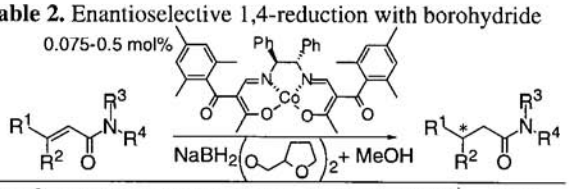
Table 1. Various Co(II) complex catalysts for 1,4-reduction

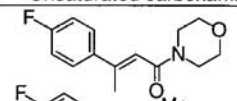
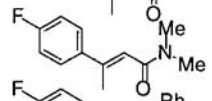
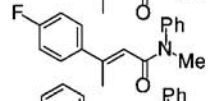
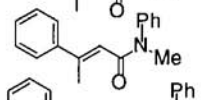
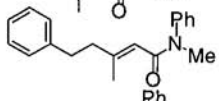
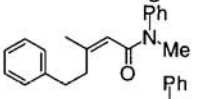
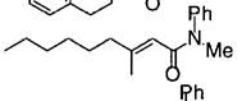
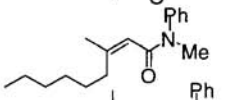
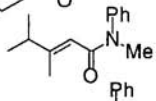
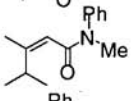
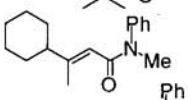
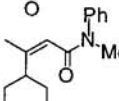


Reaction conditions: (*S*)-Co(II) complex 0.5 mol%, $NaBH_4$ 4.0 equiv., THFA 8.0 equiv., in CH_2Cl_2, RT, 2-12 h. MeOH was employed as an accelerator (ref. 7).

Several susbstitutents on nitrogen atom of amide in substrates were examined (Table 2). Reduction of morpholine derivatives (Entry 1) and *N,N*-dimethylamide (Entry 2) proceeded to afford the corresponding carboxamides in 69% and 79% yield with 49% and 56% ee, respectively. *N*-Methylanilide was smoothly converted to the corresponding carboxaminde in 93% yield and the enantioselectivity was improved to be 74% ee (Entry 3).

Table 2. Enantioselective 1,4-reduction with borohydride



Entry[a]	Unsaturated carboxamide	Yield / %	Ee / %[b]	Note
1		69	49	
2		79	56	
3		93	74	
4[c]		92	70	(*S*)[d]
5		98	83	
6		86	83	
7		97	85	
8		99	84	
9		97	86	
10		98	86	
11		99	86	(*S*)[d]
12[e]		99	91	(*S*)[d]
13[e]		99	88	0.075 mol% (*S*)-MPAC
14		98	83	(*R*)[d]
15		99	90	(*R*)[d]

[a] Reaction conditions: (*S*)-MPAC 0.5 mol%, $NaBH_4$ 4.0 equiv., THFA 8.0 equiv., in CH_2Cl_2, RT, 2 h. [b] Determined by HPLC analysis. [c] Reaction time 4 h. [d] Compared with the authentic sample. [e] Tetrahydropyran-2-methanolwas employed in place of THFA.

Enantioselective 1,4-reduction of *N*-methylanilide with modified borohydride and a catalytic amount of optically active cobalt(II) complex was successfully applied to various β,β-disubstituted α,β-unsaturated carboxamides. *N*-Methylanilide of β-substituted cinnamic acid, for example, (*E*)-3-phenyl-2-butenamide was converted to (*S*)-3-phenylbutanamide in 92% yield with 70% ee. Its absolute configuration was determined to be (*S*) corresponding to (*S*)-MPAC by comparing with the authentic sample.[8] The present system was also applicable to various β-substituted α,β-alkenoic acid derivatives to afford the reduced *N*-methylanilide in good-to-high yields and with high enantioselectivities; 5-Phenyl-3-methyl-2-pentenamide, 3-methyl-2-nonenamide and 3,4-dimethyl-2-pentenamide were converted to the corresponding reduced carboxamides with 83-86% ee (Entries 5-10). It should be noted here that the absolute configuration of the resulting product from (*E*)-carboxamide and (*Z*)-carboxamide was revealed to be opposite each other by HPLC analysis. For the 1,4-reduction of (*E*)- and (*Z*)-3-cyclohexyl-2-butenamide, the absolute configuration was determined by comparing with the authentic sample[9] to be (*S*)-butanamide from (*E*)-butenamide[10] with 86% ee, (*R*)-butanamide from (*Z*)-butenamide with 83% ee, respectively corresponding to (*S*)-MPAC. When tetrahydropyran-2-methanol was employed in place of THFA for pre-modification of borohydride, enantioselectivities in 1,4-reduction of both (*E*)- and (*Z*)-butenamides were improved to be 91% cc and 90% ee, respectively (Entries 12 and 15). Also high efficiency of catalyst was noted. In the presence of 0.075 mol% (S/C=1,333) of (*S*)-MPAC, 1,4-reduction with modified borohydride completed in 2 h and the reduced product was obtained quantitatively with 88% ee (Entry 13).

It is noted that in the presence of less than 1 mol% of cobalt(II) complex catalyst ((*S*)-MPAC) various β,β-disubstituted α,β-unsaturated carboxamides were smoothly reduced in high yield with high enantioselectivities. Further application to various α,β-unsaturated carboxylates other than anilide derivatives and the detailed study on mechanism of the present reduction system is currently under way.

References and Notes

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2 K. D. Sugi, T. Nagata, T. Yamada, and T. Mukaiyama, *Chem. Lett.*, **1997**, 493.

3 H. Fritschi, U. Leutenegger, K. Siegmann, A. Pfaltz, W. Keller, and C. Kratky, *Helv. Chim. Acta*, **71**, 1541 (1988); H. Fritschi, U. Leutenegger, and A. Pfaltz, *Helv. Chim. Acta*, **71**, 1553 (1988); U. Leutenegger, A. Madin, and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, **28**, 60 (1989).

4 P. von Matt and A. Pfaltz, *Tetrahedron: Asym.*, **2**, 691 (1991).

5 Semicorrin ligands are available from Fluka (Cat. No. 28600 and 14556), however they are considerably costly.

6 The cobalt(II) complex, (*S*)-MPAC and (*R*)-MPAC, are available from Tokyo Kasei Kogyo Co. Ltd. (*S*)-MPAC: B1845, (*R*)-MPAC:B1844.

7 K. Soai and A. Ookawa, *J. Org. Chem.*, **51**, 4000 (1986).

8 (*S*)-3-Phenylbutylic acid, which is commercially available, was converted to the corresponding *N*-methylanilide in a conventional manner.

9 (*S*)-3-Cyclohexylbutylic acid was prepared by hydrogenation of (*S*)-3-phenylbutylic acid in the presence of PtO_2, and then was converted to the corresponding *N*-methylanilide.

10 The typical procedure; Under dry nitrogen atmosphere in a vessel at room temperature were placed $NaBH_4$ (2.0 mmol, 76.0 mg) and CH_2Cl_2 (15.0 ml). To the suspension was added THFA (4.0 mmol, 0.39 ml) at room temperature and the mixture was stirred for 15 min. To the solution was added a CH_2Cl_2 solution (1.0 ml) of cobalt(II) complex catalyst ((*S*)-MPAC, 0.0025 mmol, 1.7 mg) at room temperature and then (*E*)-*N*-methyl-*N*-phenyl-3-cyclohexyl-2-butenamide (0.5 mmol, 128.7 mg) in CH_2Cl_2 (5.0 ml) was added. Successively, three portions of MeOH (81 μL each) were added at 10 min intervals and the solution was stirred for 2 h at room temperature. The reaction was quenched by the addition of pH7 buffer solution, and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, and then solvents were removed under the reduced pressure. The purification by silica-gel column chromatography (hexane/EtOAc) gave the corresponding carboxamide ((*S*)-*N*-methyl-*N*-phenyl-3-cyclohexylbutanamide, 128.5 mg) in 99% yield. The optical purity was determined by HPLC analysis (Daicel Chiralpak AD, hexane/EtOH) to be 86% ee.