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Catalytic enantioselective protonation of cobalt–enolate equivalents generated by 1,4-reduction with borohydride

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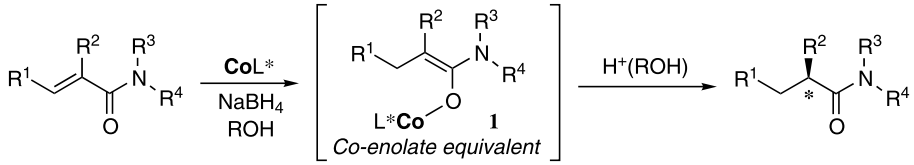
Abstract—In the presence of a catalytic amount of the optically active β-ketoiminato cobalt(II) complex and borohydride modified with appropriate alcohols, the 1,4-reduction of α-substituted-α,β-unsaturated carboxamides followed by in situ enantioselective protonation proceeded smoothly to afford optically active α-substituted carboxamides with good enantiomeric excess.

The enantio- and/or diastereoselective protonation of enolates or their equivalents is one of the most reliable methods for creating an asymmetric center at the α-position of carbonyl compounds.[1] Many effective chiral auxiliaries,[2] chiral ligands,[3] and chiral proton sources[4] have been developed for these reactions in recent years to achieve high stereoselectivities. However, the method suffers from a number of disadvantages: In principle, metal enolates including silyl enol ethers have to be prepared in advance by treatment of the corresponding carbonyl compounds with strong bases such as butyllithium and the enantioselective protonation generally requires relatively low temperature conditions. Additionally, a stoichiometric amount of the chiral ligand or chiral proton source is usually required. These drawbacks have made such reactions difficult to complete as practical reactions on multi-gram scale. Recently, the highly enantioselective 1,4-reduction of β,β-disubstituted-α,β-unsaturated carboxylates was reported using borohydride derivatives and a catalytic amount of optically active β-ketoiminato cobalt(II) complexes,[5] which were originally developed as effective catalysts for the enantioselective borohydride reduction of prochiral ketones and *N*-diphenylphosphinyl imines to afford the optically active alcohols and amines with high enantioselectivities and high efficiencies.[6] Even in the presence of only 0.5 mol% of the cobalt complex catalyst, the 1,4-reduction proceeded smoothly to afford the corresponding optically active carboxamides with high enantioselectivities. Thus, it is reasonable to assume that the cobalt–enolate equivalent **1** with an optically active ligand was generated as a reactive intermediate. It could also be anticipated that the cobalt–enolate equivalent **1** derived from the α-substituted-α,β-unsaturated carboxamides would be protonated in an enantioselective manner in the presence of optically active β-ketoiminato cobalt(II) complexes (Scheme 1). The sodium borohydride employed in the present reaction system is relatively mild, safe to handle, and reasonably priced both for laboratory and industrial use. In particular, because it can be employed in protic solvents such as methanol or ethanol, the conjugate reduction followed by enantioselective protonation can proceed in situ. In this communication, we would like to report the first example of the catalytic enantioselective protonation reaction of enolate equivalents generated by



Scheme 1. Catalytic enantioselective protonation.

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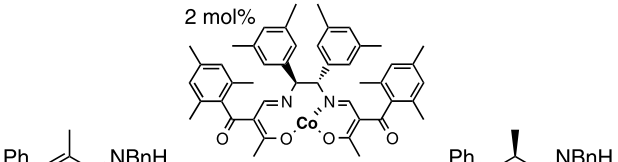
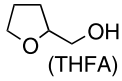
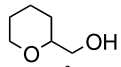
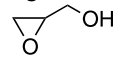
the 1,4-reduction of α-substituted-α,β-unsaturated carboxamides.

In the presence of 2 mol% of the optically active cobalt(II) complex **A** and borohydride modified by tetrahydrofurfuryl alcohol, the (*E*)-*N*-methyl-*N*-phenyl-α-methylcinnamic amide (**2a**) was subjected to the 1,4-reduction system to obtain the reduced product, which was analyzed by chiral HPLC and found to have ee of 19%. Racemizaton of the 1,4-reduction product is not observed in this case. This preliminary result showed that the novel protonation was occurring stereoselectively and this encouraged us to examine various reaction conditions. The modification of sodium borohydride is essential for the enantioselective borohydride reduction catalyzed by the cobalt(II) complex because borohydride can be chelated and solvated by alcohols such as tetrahydrofurfuryl alcohol (THFA) which makes the reaction system homogeneous and serves to activate the borohydride.[6a,b] In addition to these effects, the second alcohol present in the reaction should act not only as an accelerator for the borohydride reduction[7] but also as a proton source in the protonation of the cobalt–enolate equivalent. The choice of the alcohols to be used as a modifier and a proton source was first examined (Table 1). When the combination of THFA (modifier) and MeOH (proton source) was employed the catalytic enantioselective protonation proceeded smoothly to produce the reduced product in 95% yield with 60% ee (entry 1). The reaction system using EtOH as the second alcohol afforded the chiral carboxamide with 45% ee (entry 2) while 1-propanol and 2-propanol were not effective at all (entries 3 and 4). Tetrahydropyran-2-methanol[5] and glycidol can be employed as the first alcohol in combination with methanol to afford the reduced carboxamide with 48–50% ee (entries 5 and 6).

Table 1. Combination of modifier alcohols for borohydride[a]

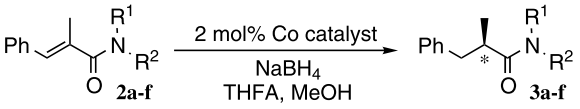


Entry	R^1OH	R^2OH	Yield / %[b]	Ee / %[c]
1	 (THFA)	MeOH	95	60
2		EtOH	92	45
3		1-Propanol	No reaction	
4		2-Propanol	No reaction	
5		MeOH	94	50
6		MeOH	96	48

[a] Reaction conditions: Ref. 9.
[b] Isolated yield.
[c] Determined by HPLC.

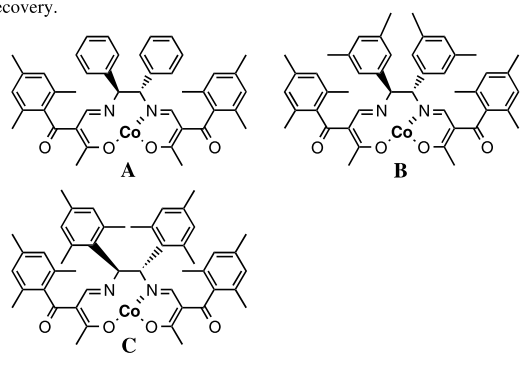
Various substituents on the amide functionality were next examined and it was found that the combination with the optically active cobalt(II) complex catalysts were significant for the enantioselection (Table 2). In the presence of the cobalt(II) complex catalyst **A** derived from 1,2-diphenylethylenediamine, *N*,*N*-disubstituted (*E*)-α-methylcinnamic amides **2a** and **2b** were converted to the corresponding carboxamides in yields of 41–47% and their enantiomeric excesses were 19–27% (entries 1 and 2). In the reactions of the *N*-monosubstituted (**2c**) or non-substituted (**2d**) amides, the chemical yields of the reduced products were improved to 76–98% and also the enantiomeric excess increases to 40–45% ee (entries 3 and 4). The combination of the amide **2d** with the cobalt complex **B** improved the product ee to 50%, while low enantioselectivity was observed using the catalyst **C**, which was one of the best catalysts for various enantioselective reactions.[8]

Table 2. Effects of amide substituents and cobalt catalyst[a]



Entry	R^1, R^2 on amide	Catalyst	Yield / %[b]	Ee / %[c]
1	Ph, Me **2a**	**A**	41 (48)[d]	19
2	Me, Me **2b**	**A**	47 (51)[d]	27
3	Ph, H **2c**	**A**	76 (19)[d]	40
4	H, H **2d**	**A**	98	45
5		**B**	95	50
6		**C**	96	22
7	Me, H **2e**	**A**	96	45
8		**B**	96	59
9		**C**	94	47
10	Bn, H **2f**	**A**	92	44
11		**B**	95	60
12		**C**	97	44

[a] Reaction conditions: Ref. 9.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Recovery.



The amides **2e** and **2f** were subjected to the catalytic enantioselective protonation in the presence of the cobalt complexes **A**, **B**, and **C**. It was found that complex **B** is the best catalyst for the *N*-methyl- and *N*-benzyl-(*E*)-α-methylcinnamic amides to afford the corresponding carboxamides in high yields and with 59–60% ee.[9]

Because α-substituted-α,β-unsaturated carboxamides were not reduced at all without the β-ketoiminato cobalt catalysts, the active species for the 1,4-reduction was examined by FAB mass analysis. A peak at 697 Da of FAB mass spectra was observed under negative mode for the original cobalt complex **1a** (Fig. 1A). After the treatment of cobalt complex **1a** with modified borohydride, the peak at 697 Da vanished and a new peak was observed at 698 Da, which can be assigned as a cobalt–hydride complex (Fig. 1B). Borodeuteride was employed instead of borohydride, the original peak of the cobalt catalyst **1a** at 697 Da disappeared and a new peak at 699 Da, assigned as the cobalt–deuteride complex, was seen (Fig. 1C). These results clearly indicate that the cobalt–hydride intermediate would mainly exist in the reaction media and could react with α,β-unsaturated carboxamides as an active species. Therefore, it was naturally predicted that the optically active cobalt–enolate equivalent was formed as an enantiodiscriminating intermediate after the 1,4-reduction.

The absolute configurations of the amide products were determined. By comparing the specific rotation with the previously reported results,[10] it was revealed that (*R*)-amides were obtained corresponding to the (*S*,*S*)-catalyst **B**, for 2-methyl-3-phenyl-propanamide (**3d**, $[\alpha]_D^{22}$ −27.0 (*c* 1.20, EtOH), entry 5). As an analogue of *N*-benzyl-2-methyl-3-phenylpropanamide (**3f**, entry 11), the corresponding 2-ethyl-derivative was subjected to the present system and the (*R*)-amide[11] was obtained corresponding to the (*S*,*S*)-catalyst **B**. On the basis of these observations, the present enantiofacial selection, the (*R*)-amide corresponding to (*S*,*S*)-cobalt complexes (*Si* facial selection), can be explained as illustrated in Figure 2. The cobalt–enolate equivalent with the optically active cobalt complex could probably be formed and oriented between two coordinating oxygen atoms on the planar 3-oxobutylideneaminato ligand.[12] The *Re* face of the enolate equivalent is shielded by two aryl groups of the side chain and the chiral diamine, whereas the *Si* face would be relatively unhindered for reaction. The alcohol proton source could approach and protonate the enolate equivalent to afford the (*R*)-carboxamide.

In summary we have shown that the 1,4-reduction of α-substituted-α,β-unsaturated carboxamides followed by in situ enantioselective protonation catalyzed by optically active β-ketoiminato cobalt complexes with modified borohydride occurs with good levels of selectivity. Reduced carboxamides with chirality α to the carbonyl group are obtained. The present reaction system is assumed to be a novel strategy for the synthesis of chiral carboxylates. Further studies aimed at improving the enantioselectivity of the process are currently underway.

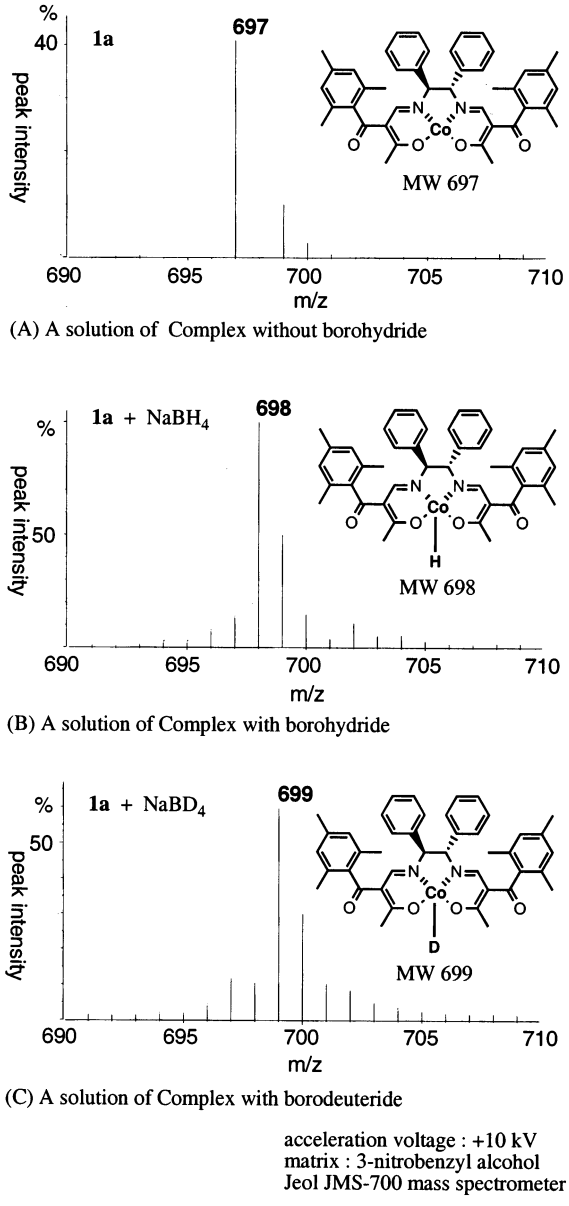


Figure 1. FAB mass spectra of the cobalt complex treated with borohydride.

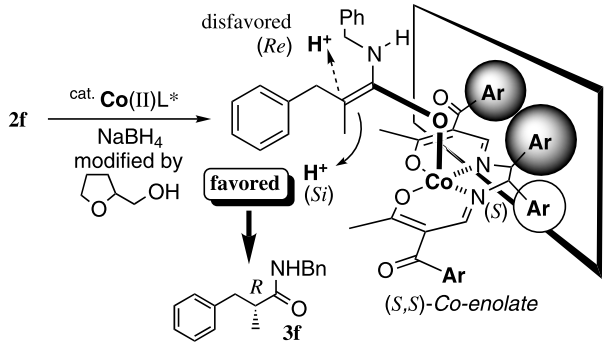


Figure 2. Reasonable explanation of the favored absolute configuration during the catalytic enantioselective protonation reaction.

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7. It was pointed out that the second alcohol would essentially enhance the transfer of the hydride. See: Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000–4005.
8. (a) For cyclopropanation, see: Ikeno, T.; Sato, M.; Sekino, H.; Nishizuka, A.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2139–2150; (b) For borohydride reduction, see: Sato, H.; Watanabe, H.; Ohtsuka, Y.; Ikeno, T.; Fukuzawa, S.-I.; Yamada, T. *Org. Lett.* **2002**, *4*, 3313–3316.
9. **Typical procedure for reduction/enantioselective protonation**: Under a dry nitrogen atmosphere at room temperature were placed $NaBH_4$ (1.5 mmol, 56.7 mg) and CH_2Cl_2 (12 mL). To the suspension was added THFA (3.0 mmol, 0.29 mL) and the mixture was allowed to stir at room temperature for 15 min. To the resulting mixture was added a solution of the cobalt(II) complex catalyst (0.005 mmol, 2 mol%) in CH_2Cl_2 (1 mL) and subsequently a solution of the α-substituted-α,β-unsaturated carboxamide (0.25 mmol) in CH_2Cl_2 (2 mL) was added. Successively, three portions of MeOH (3.0 mmol, 0.12 mL each) were added at 10 min intervals and the mixture was stirred for 24 h at room temperature. The reaction was quenched by the addition of pH 7 buffer solution, and extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4, and then the solvents were removed under reduced pressure. The purification by SiO_2 column chromatography (hexane/EtOAc) gave the corresponding carboxamide. Its ee was determined by HPLC using a chiral column.
10. (*S*)-Amide (>98% ee): $[\alpha]_D^{24}$ +55.4 (*c* 0.675, EtOH). See: Davies, S. G.; Dixon, D. J. *Synlett* **1998**, 963–964.
11. (*E*)-*N*-Benzyl-α-ethylcinnamic amide was reduced using the same protocol (Ref. 9) to afford *N*-benzyl-2-ethyl-3-phenylpropanamide in 98% yield with 31% ee $[\alpha]_D^{22}$ −15.8 (*c* 0.763, CH_2Cl_2). (*R*)-Amide (>99% ee): $[\alpha]_D^{23}$ −51.0 (*c* 1.00, CH_2Cl_2). See: Backes, B. J.; Dragoli, D. R.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 5472–5478.
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