Newly Designed Catalysts for the Enantioselective Borohydride Reduction: Prediction from the Theoretical Analysis

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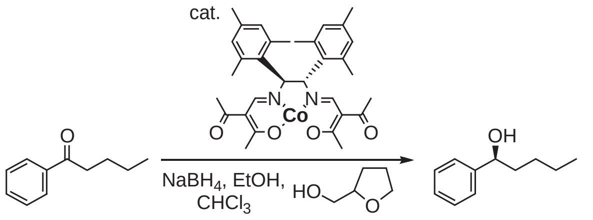
For the catalytic enantioselective borohydride reduction, the theoretical simulation of various axial groups in Co complex catalysts predicted that the Co–carbene complexes could be employed as efficient catalysts. The newly designed complexes generated from the Co complex and methyl diazoacetate made it possible to catalyze the enantioselective borohydride reduction in a halogen-free solvent.

In the presence of the chiral 3-oxobutylideneaminato Co^{II} complex, the enantioselective borohydride reduction of ketones,[1] imines,[2] and α,β-unsaturated carbonyl compounds[3] proceeded to afford the corresponding alcohols, amines, and the reduced carbonyl compounds with high enantiomeric excesses (ee) (eq 1).[4] Although the reduction can be applied to a broad range of substrates, the high enantioselectivity was achieved only in halogenated solvents, such as chloroform, while the borohydride reduction in a halogen-free solvent was desired. The recent studies on the mechanism of the borohydride reduction both in experimental and theoretical situations[5] proposed that a dichloromethyl–Co–hydride with a sodium cation (Na^+) should work as an active intermediate and the Na^+ activates and fixes the carbonyl group in the transition state that leads to the high reactivity and high enantioselectivity (Figure 1). The dichloromethyl–Co complex could be generated by the reaction of the Co complex and chloroform under the reductive conditions.[6] Accordingly, chloroform was considered to be an activator of the Co complex. On the basis of this assumption, the amount of chloroform was successfully reduced from solvent usage to a catalytic amount versus the substrates.[7] We reported that an equimolar amount of chloroform vs the Co complex catalyst efficiently promoted the enantioselective borohydride reduction to afford the products with a high enantioselectivity.



(1)

Based on these results, the rational design of the alkyl–Co complex will make it possible to completely exclude chloroform while maintaining the high enantioselectivity in halogen-free solvents. Toward this goal, the theoretical analysis of the reaction pathway with various axial ligands was performed.[8–10] Since the direct analysis of the real Co complex was too difficult, a simplified complex structure was adopted while maintaining the essential electronic nature, and formaldehyde was selected as the model substrate. The obtained energies for the various complex catalyzed systems are summarized in Table 1 and the energy profiles are shown in the Supporting Information.[11]

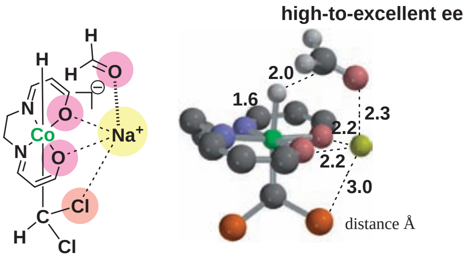
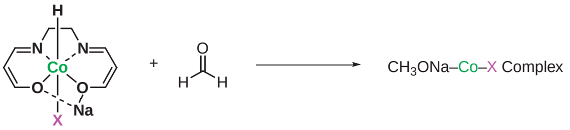


Figure 1. Proposed TS of cobalt-catalyzed borohydride reduction.

For the reactions catalyzed by the Co complex without any axial ligand and that attached by a methyl group, no transition state was obtained (Entries 1 and 2). As previously reported,[5] stabilization by the coordination of the axial group to the Na^+ was crucial for the reaction to proceed. When the chlorine atom was employed as the axial ligand, TS was obtained though the activation energy was high and the product was less stable than the reactant (Entry 3). Whereas, for the Co complexes with attached chloro-substituted methyl groups as the axial ligands, the TSs were successfully obtained and the products were more stable than the reactant (Entries 4–6). The activation energy increased as the number of chlorine atoms in the methyl group increased, probably due to the distance between the chlorine

Table 1. Calculated Gibbs energies with various axial ligands[a]



Entry	Axial ligand X	Reactant /kcal mol^{-1}	Intermediate /kcal mol^{-1}	TS /kcal mol^{-1}	Product /kcal mol^{-1}	Activation energy /kcal mol^{-1}
1	None			Not obtained		
2	CH_3			Not obtained		
3	Cl	0.00	−3.59	15.47	12.42	19.05
4	CH_2Cl	0.00	−3.70	0.28	−11.45	3.97
5	$CHCl_2$	0.00	−3.20	1.63	−6.42	4.83
6	CCl_3	0.00	−3.91	2.23	−2.30	6.14
7	CH_2COOMe	0.00	−4.18	4.05	−7.63	8.23
8	2-Pyridyl	0.00	−3.81	2.73	−10.30	6.54
9	CHCOOMe	0.00	−2.53	1.36	−7.44	3.89

[a]The calculation was performed at the B3LYP/6-31G* level. The Gibbs energy was calculated at 298.15 K without scaling. Reactant energy is set for standard ($E_{\mathrm{ref}} = 0$) and the energies of the other species are shown as relative energies.

and Na atoms in the TS. The distances in the TS are 2.82 Å in CH_2Cl (Entry 4), 2.99 Å in $CHCl_2$ (Entry 5), and 3.12 Å in CCl_3 (Entry 6). The shortest Cl–Na bond was observed in CH_2Cl and the activation energy was the lowest. It was considered that the complex with the shorter hetero atom–Na bond should give the better results. Therefore, other alkyl groups containing the coordination site, such as methoxycarbonylmethyl, pyridyl methoxycarbonylmethyl carbene (oxygen atom), and 2-group (nitrogen atom) were examined. TSs were obtained, though the activation energies of the methoxycarbonylmethyl and 2-pyridyl groups were unexpectedly higher than that of the dichloromethyl group (Entries 7 and 8). On the contrary, the activation energy of the carbene complex was lower than those of the methoxycarbonylmethyl and 2-pyridyl groups and similar to that of the dichloromethyl group. (Entry 9 in Table 1 and Figure 2). The transition state's structure of the Co–carbene complex was similar to that of the dichloromethyl group; the Na^+ was efficiently coordinated by the oxygen atoms of the aminato-ligand and ester part in the carbene part.

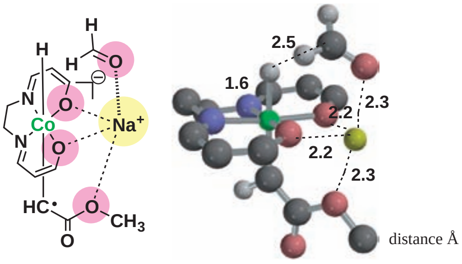
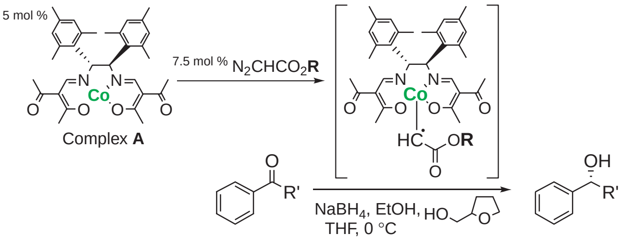
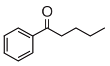
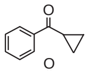
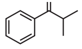


Figure 2. TS structure of the cobalt–carbene complex.

Table 2. Enantioselective borohydride reduction catalyzed by cobalt–carbene complexes



Entry	Substrate	Catalyst	Yield/%	ee/%
1		Complex **A**	74	41
2		Co–carbene R = Me	76	97
3		R = Et	74	69
4		R = *t*-Bu	quant.	75
5		R = Bn	93	48
6		Co–carbene R = Me	98	85
7			90	96

Based on the prediction from these theoretical calculations, the enantioselective borohydride reduction was examined using the Co–carbene complex prepared from the original Co complex and alkyl diazoacetate. Various alkyl diazoacetates were first screened using the reduction of valerophenone as the model reaction. When the original Co^{II} complex was employed as the catalyst in THF solvent, valerophenone was converted into the corresponding alcohol in good yield, but with a low enantioselectivity. Whereas, the Co–carbene complexes prepared by the treatment with diazoacetates catalyzed the enantioselective borohydride reduction to afford the corresponding alcohol with good-to-high enantioselectivity. As shown in Table 2, methyl diazoacetate was found to work as the best activator of the Co^{II} complex among the methyl, ethyl, *t*-butyl, and benzyl diazoacetates. Under the optimized conditions, the corresponding reduced product with a 97% ee was obtained in 76% yield. The Co–carbene complex derived from methyl diazoacetate was then successfully applied to the catalytic enantioselective reduction of aryl alkyl ketones. For examples, the cyclopropylphenyl ketone and isopropylphenylketone were reduced to the corresponding alcohols with 85 and 96% ee, respectively. These results suggested that the Co–carbene complexes derived from the diazoacetates would work as efficient catalysts for the enantioselective borohydride reduction in a halogen-free solvent.

It is noted that the rational reaction simulation based on the theoretical analysis could provide a promising method for the ligand design of catalytic enantioselective reactions. Further studies on the design of the axial ligands, the optimization of the reaction conditions, and the scope and limitation of the present catalytic system are ongoing.

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10 Theoretically, it was considered that the solvent effect might make an influence on the results, because the reaction was performed in the polar solvents. However, the previous study showed that the results were little effected by the solvent,[5] accordingly, the present calculations were performed without considering the solvent effect.

11 Supporting Information is available electronically on the CSJ-Journal web site, http://www.csj.jp/jounals/chem-lett/index.html.

Published on the web (Advance View) May 9, 2007; doi:10.1246/cl.2007.738