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Enantioselective Borohydride Reduction of Aliphatic Ketones Catalyzed by Ketoiminatocobalt(III) Complex with 1-Chlorovinyl Axial Ligand

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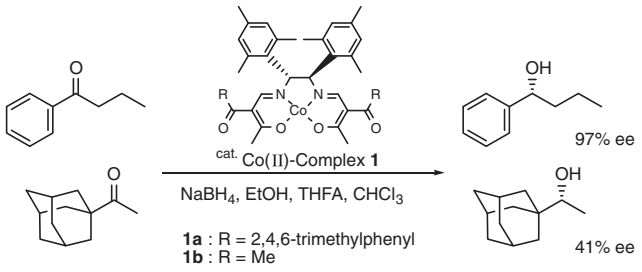
For the enantioselective borohydride reduction of aliphatic ketones, the optically active ketoiminatocobalt(II) catalysts was successfully designed based on their axial ligand. Instead of chloroform for the aryl ketone reduction, various axial ligand precursors were examined for the aliphatic ketone. Consequently, 1,1,1-trichloroethane was found to be the most effective activator of the cobalt(II) complexes to generate the corresponding 1-chlorovinyl cobalt(III) derivatives as the reactive intermediate. Several aliphatic ketones were successfully reduced to afford the corresponding secondary alcohols with high enantioselectivities.

The enantioselective reduction of carbonyl or imine derivatives is one of the most reliable methods to provide various optically active compounds.[1] Enzymatic processes[2] have been employed to prepare small molecules, such as optically active synthetic building blocks, though specificity on the substrates seems to be problematic as well as the efficiency related to the reaction time and/or reactor volume. Enantioselective reductions catalyzed by optically active metal-complexes are promising alternative processes for a wide variety of substrates and rather large molecules with a high efficiency. Various combinations of metal-complex catalysts with hydride reductants have been reported;[3] e.g., oxazaborolidine/borane,[4] ferrocenylphosphine–Rh/hydrosilane,[5] BINAP–Ru/hydrogen or a secondary alcohol,[6] and other metals.[7,8] From our research group, optically active cobalt(II) complexes with a conventional reductant, sodium borohydride, have been proposed as an effective system for the catalytic enantioselective reduction of ketone and imine derivatives to afford the corresponding secondary alcohols and amines in high-to-excellent yields with high enantioselectivities.[9] Although the aryl carbonyl derivatives are suitable substrates to achieve a high enantioselectivity, aliphatic ketones, such as 1-adamantyl methyl ketone, was converted into the reduced product in 89% yield, but with only 41% ee (Scheme 1). The highly enantioselective reduction of aliphatic ketones was limited to only a few methods, including the metal-complex-catalyzed system, though non-metal catalysts, chiral Lewis bases[10] and chiral Brønsted acids,[11] for the asymmetric reduction have also been recently reported. The enantioselective reduction of aliphatic ketones still needs to be developed for asymmetric synthesis. In this communication, we address one of the solutions for this problem based on the rational design of a reactive intermediate derived from cobalt(II) complex catalysts.

Under the original conditions of the enantioselective borohydride reduction for aromatic ketones catalyzed by optically active ketoiminatocobalt(II) complexes, $CHCl_3$ was employed as a unique solvent to achieve a high enantioselectivity as well as reactivity.[12] At least a catalytic amount of chloroform was required to realize a high enantioselectivity. This observation means that the effect of $CHCl_3$ is not only due to being a suitable solvent, but $CHCl_3$ itself reacted as an activator with the cobalt complex to generate an essential reactive intermediate that catalyzed the present reduction with the borohydride.[13] The FAB-MS analysis of the cobalt complex/borohydride solution suggested that cobalt–hydride (M + 1) and dichloromethyl–cobalt–hydride (M + 1 + 83) were generated in the reaction mixture. Based on the experimental or analytical examinations, the DFT calculations of the model system also afforded a reasonable transition-state (TS) with the dichloromethyl group on the cobalt complex (Figure 1). As a result, the mechanism of the present reaction was proposed as follows: the original cobalt(II) complex reacts with $CHCl_3$ in the presence of the hydride to generate the dichloromethyl–cobalt–hydride intermediate with the sodium cation (Na^+). Carbonyl substrates would be captured by the sodium cation, which leads to activation and stereochemical alignment of the carbonyl. The cobalt hydride intermediate would eventually attack the carbonyl via a quasi-six-membered TS to afford the reduced product with a high selectivity. Therefore, it is reasonable to consider that the (di)chloroalkyl group on the axial site would have a significant effect on both the reactivity and selectivity.

Based on the proposed mechanism for the aliphatic ketone reduction, various haloalkanes were examined as an activator precursor of an effective intermediate (Figure 1). Various di- or



Scheme 1. Enantioselective reductions of aromatic and/or aliphatic ketones (the original system).[9h]

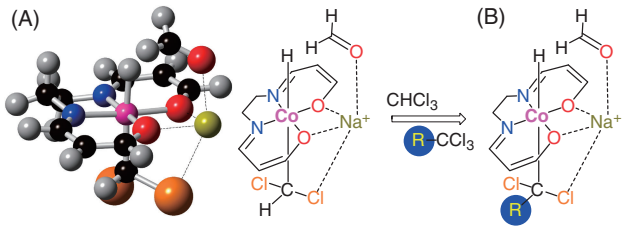
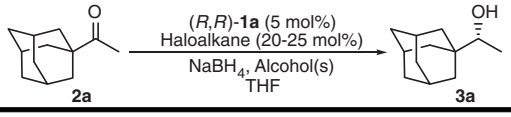


Figure 1. (A) TS proposed by DFT calculation. (B) A new design for cobalt complex catalysts.

Table 1. Examination of various trihaloalkanes as an activator[a]



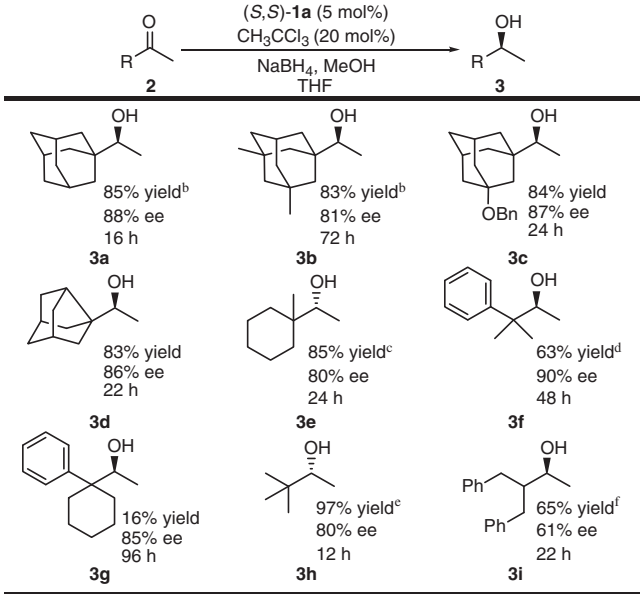
Entry	Haloalkane	Yield/%	ee/%
1	—	quant.	13
2	$CHCl_3$	85	40
3	$CHBr_3$	97	28
4[b]	CHI_3	94	29
5[b]	CCl_4	51	29
6	CH_2Cl_2	98	45
7	CH_3CCl_3	75	64
8[c]	CH_3CCl_3	91	85

[a]Reaction conditions: ketone **2a** (0.25 mmol), (*R*,*R*)-**1a** (12.5 μmol, 5 mol %), $NaBH_4$ (0.38 mmol, 1.5 equiv), EtOH (0.38 mmol), THFA (5.25 mmol), haloalkane (50 mmol, 20 mol %), THF (6.5 mL) at 0 °C for 24 h. Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by HPLC analysis of 1-naphthoate derivative (Chiralpak IB). [b]Haloalkane (63 mmol, 25 mol %). [c]Reaction conditions: $NaBH_4$ (0.50 mmol, 2.0 equiv), MeOH (3.0 mmol, 12 equiv), CH_3CCl_3 (50 mmol, 20 mol %), THF (6.5 mL) at −20 °C for 24 h.

trihaloalkanes were screened as an activator for the cobalt(II) complex **1a** in the presence of a borohydride modified by EtOH and tetrahydrofurfuryl alcohol (THFA) in THF. Without any haloalkane, 1-adamantyl methyl ketone (**2a**) was reduced to 1-(1-adamantyl)ethanol (**3a**) with only 13% ee (Table 1, Entry 1). As a result of examining the effect by halogen atoms, chlorine was found to work the most effectively among the three haloforms, i.e., $CHCl_3$, $CHBr_3$, and CHI_3 (Entries 2–4). Several carbon chloride derivatives, such as CCl_4 and CH_2Cl_2 (Entries 5 and 6 and see Supporting Information[14]), were next examined. Most of them did not improve the enantioselectivity and were less effective or slightly better than $CHCl_3$. When 1,1,1-trichloroethane was employed as the activator, the enantioselective reduction effectively proceeded to provide the reduced product **3a** in 75% yield with 64% ee (Entry 7). After optimization of the reaction conditions, the enantioselectivity was enhanced with replacement of the borohydride modifier from EtOH/THFA to MeOH. The corresponding alcohol **3a** was obtained in 91% yield with 85% ee at −20 °C (Entry 8).

The optimized conditions were then successfully applied to the catalytic enantioselective borohydride reduction of various aliphatic ketones. The present scope is shown in Table 2. Tertiary alkyl ketones were reduced into the corresponding alcohols **3** with over 80% ee. The adamantyl ketones **2a**–**2c** and noradamantyl ketone **2d** were converted into the optically active alcohols with 81–88% ee. The methyl 1-methylcyclohexyl ketone (**2e**) was also an applicable substrate; the product **3e** was obtained in 85% yield with 80% ee. Though the reactivities for the reductions of the more bulky substrates **2f** and **2g** were low, high enantioselectivities were also observed; especially, 3-methyl-3-phenyl-2-butanol (**3f**) was obtained with 90% ee. The simple tertiary alkyl ketone **2h** was smoothly converted into **3h** with 80% ee. When the secondary alkyl ketone **2i** was employed in the same system, a moderate enantioselectivity was observed (61% ee).

Table 2. Enantioselective borohydride reduction of aliphatic ketones[a]



[a]Reaction conditions: ketone **2** (0.25 mmol), (*S*,*S*)-**1a** (12.5 μmol, 5 mol %), $NaBH_4$ (0.50 mmol, 2.0 equiv), MeOH (3.0 mmol, 12 equiv), CH_3CCl_3 (50 mmol, 20 mol %) at −20 °C. Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by HPLC analysis of 1-naphthoate derivative (Chiralpak IB). Absolute configuration of **3a** was determined by specific optical rotation. [b]CH_3CCl_3 (75 mmol, 30 mol %) was used. [c](*R*,*R*)-**1a** was used and the modified borohydride ($NaBH_4$ 0.75 mmol and MeOH 4.5 mmol in THF 6 mL) was added in three portions every 3 h. [d]The reaction was run at −30 °C. [e](*R*,*R*)-**1a**, $NaBH_4$ (0.38 mmol, 1.5 equiv), MeOH (2.3 mmol, 9 equiv) were used. The yield was based on GC conversion. [f](*S*,*S*)-**1b** was used.

An ESI-MS analysis of the reaction mixture of the cobalt(II) complex/borohydride was performed in the presence of 1,1,1-trichloroethane to reveal the structure of the reactive intermediate (Figure 2). After the solution color of the cobalt catalyst changed from yellow (cobalt(II) complex) to red after treatment with the borohydride in the presence of 1,1,1-trichloroethane, a peak at m/z 877 was observed in the negative mode. It could be assigned as the cobalt(III) complex containing dichloroethyl group on the axial site based on the previous observation in the original $CHCl_3$ solvent system. Also, the isotopic pattern corresponding to the molecule containing two chlorine atoms was definitely observed, whereas in the positive mode, the peak at m/z 879 or neighborhood derived from dichloroethyl–cobalt was not detected. The peak observed at m/z 843 could be assigned as ($M^+ + CH_2CCl$; $782 + 35 + 24 + 2$), and these observations could be explained as follows: Initially, the dichloroethylcobalt(III) **4a** could be derived from the original cobalt(II) complex with 1,1,1-trichloroethane in the presence of the borohydride, similar to the original cobalt catalyst system with chloroform. The proton of the terminal methyl on dichloromethyl group should be acidic enough due to the two chlorine atoms on the α-position and cobalt(III) atom on the β-position to be removed in the reaction system (Scheme 2). The chloride was then released. The molecular weight of the resulting structure **5a**, 1-chlorovinyl group on cobalt(III) com-

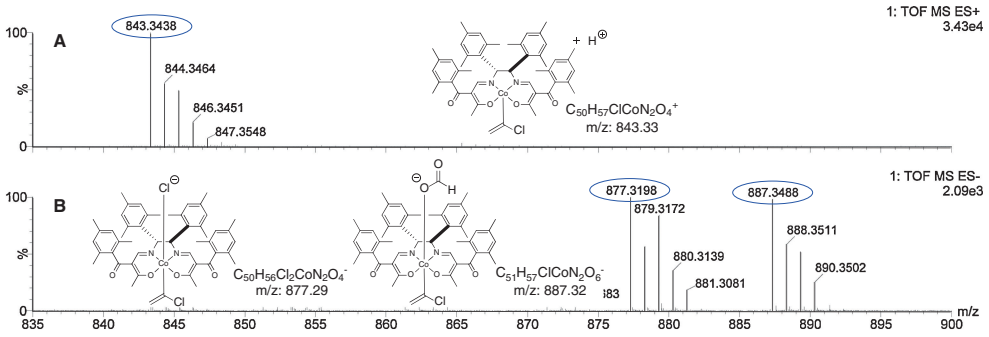
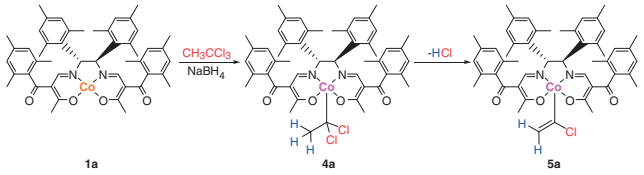


Figure 2. ESI-MS in positive (A) and negative (B) modes.



Scheme 2. Leaving process of hydrogen chloride from dichloromethyl–cobalt complex.

plex, is 843. This hypothesis can be supported by the negative mode ESI-MS analysis. A free chloride anion could coordinate to another axial site to generate the corresponding ate-complex containing two chlorine atoms. Consequently, the isotopic pattern was observed. Furthermore, the peak observed at m/z 887 could be assigned as the 1-chlorovinyl cobalt(III) complex **5a** with a formate anion in place of the chloride anion (formic acid was employed as the solvent for ESI-MS measurement). The obtained cobalt(III) complex could form a similar quasi-six-membered transition-state with the sodium cation, chlorine atom, and carbonyl substrate to achieve a high reactivity and high selectivity similar to the mechanism proposed in the previous report.[12]

In summary, the catalytic enantioselective borohydride reduction of dialkyl ketones was successfully developed using the newly designed cobalt(III) complex in the presence of 1,1,1-trichloroethane. Further studies regarding the details of the catalyst structure will be discussed in a continuing paper.

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