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Highly enantioselective borohydride reductions of 2-phenacylpyridine catalyzed by optically active β-ketoiminato cobalt(II) complexes

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Abstract

The highly enantioselective reduction of 2-phenacylpyridine catalyzed by optically active β-ketoiminato cobalt(II) complexes with pre-modified sodium borohydride was achieved affording in high enantiomeric excess 1-phenyl-2-(2-pyridyl)ethanol, a precursor of sedamine derivatives. The enantioselective sense in the present reduction is discussed and compared to the asymmetric reduction catalyzed by other complex catalysts.

Catalytic enantioselective reactions with optically active transition-metal complexes are one of the most attractive methods for the preparation of beneficial chiral building blocks and the total synthesis of various natural products. Many studies have continued to develop versatile catalysts for promising enantioselective reactions,[1] for example, optically active metal–salen catalysts for enantioselective epoxidations,[2] chiral bisoxazoline catalysts,[3] BINAP catalysts for enantioselective hydrogenation,[4] etc. Recently, we developed optically active β-ketoiminato cobalt(II) complex catalysts for the highly enantioselective borohydride reduction of ketones and imines to afford the corresponding secondary alcohols and amines in high enantiomeric excess with high efficiencies.[5] It has been recently reported that the enantioselective borohydride reduction of 2-phenacylpyridine was catalyzed by Jacobsen's manganese(III) complexes to give in high enantiomeric excess 1-phenyl-2-(2-pyridyl)ethanol, the useful precursor for the asymmetric synthesis of sedamine.[6] In this communication, we would like to describe that the optically active β-ketoiminato cobalt(II) complexes efficiently catalyzed the enantioselective borohydride reduction of 2-phenacylpyridine to obtain in high enantiomeric excess 1-phenyl-2-(2-pyridyl)ethanol and discuss the enantioselective sense of the cobalt complex-catalyzed reduction compared to the manganese complex-catalyzed reduction with the β-ketoiminato ligand or Jacobsen's ligand.

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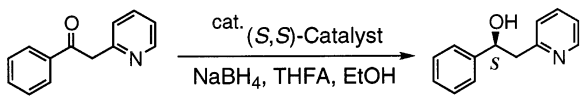
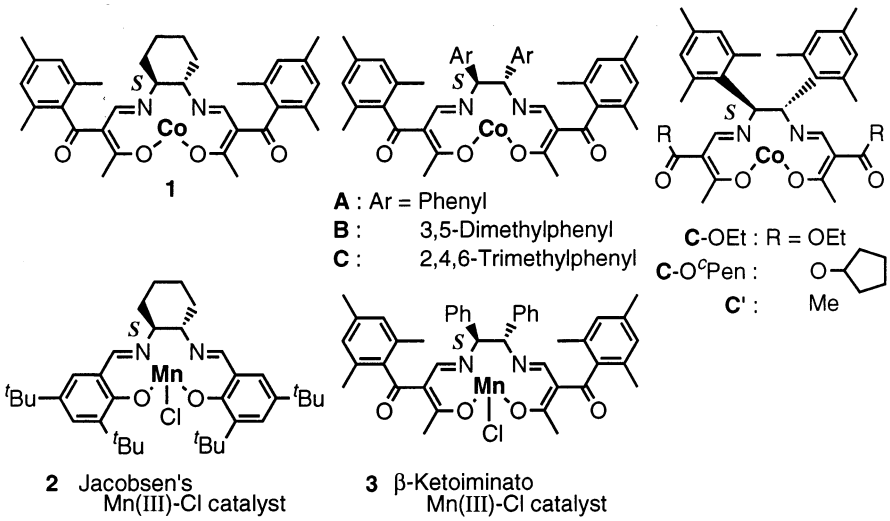
A variety of β-ketoiminato cobalt(II) complexes were subjected to the catalytic borohydride reduction of 2-phenacylpyridine (Table 1). Each ligand of the cobalt(II) catalyst was easily prepared from the corresponding optically active 1,2-disubstituted-1,2-ethylenediamine and 1,3-dicarbonyl compound.[7] The enantiomeric excesses of the resulting 1-phenyl-2-(2-pyridyl)ethanol were low or moderate in the reactions catalyzed by complex **A** or **B** (entries 1 and 2), whereas the enantioselectivity was improved with complexes from series **C** and its

Table 1
Enantioselective reduction of 2-phenacylpyridine[a]



Entry	Catalyst	Yield/%[b]	Ee/%ee[c]	Absolute config.[d]
1	**A**	89	22	*S*
2	**B**	93	39	*S*
3	**C**	93	64	*S*
4	**C**–OEt	90	71	*S*
5	**C**–O^{c}Pen	96	78	*S*
6	**C′**	92	86	*S*
7[e]	**C′**	94	92	*S*
8[f]	**2**	82	85	*R*
9	**3**	90	5	*R*
10	**1**	92	24	*S*

[a] Each reaction was carried out using 0.5 mmol of 2-phenacylpyridine, 2 mol% of catalyst, 1.5 equiv. $NaBH_4$, 1.5 equiv. EtOH, 21 equiv. tetrahydrofurfuryl alcohol (THFA) and $CHCl_3$ (10 ml) at 0°C for 12 h.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralcel OD-H).
[d] Determined by optical rotation.
[e] Using MeOH instead of EtOH and 4 mol% of catalyst at −20°C for 72 h.
[f] Ref. 6.



derivatives (entries 3–5). It was found that complex **C′**, having acetyl groups as both side chains, was the most efficient catalyst for the enantioselective reduction of 2-phenacylpyridine (entry 6). The combined use of methanol with THFA (tetrahydrofurfuryl alcohol) was found to be more suitable for modification of the borohydride in the present reduction than that of ethanol.[8] According to the optimized reaction conditions, in the presence of a catalytic amount of the β-ketoiminato cobalt(II) complex catalyst **C′**, 2-phenacylpyridine was efficiently reduced to the optically active 1-phenyl-2-(2-pyridyl)ethanol in 94% yield with 92% ee (entry 7).[9] The catalytic enantioselective reduction with the cobalt(II) complex and sodium borohydride proved to be a reliable and widely applicable reduction system for various carbonyl compounds with a heteroatom.

Recently, it was reported that Jacobsen's manganese(III) complexes as well as β-ketoiminato cobalt(II) complexes could be used as catalysts for the enantioselective borohydride reduction of 2-phenacylpyridine. It should be pointed out here that (*S*)-1-phenyl-2-(2-pyridyl)ethanol was obtained using the (*S*,*S*)-cobalt(II) complexes (entries 1–7), whereas the (*R*)-product was obtained with the (*S*,*S*)-salen-type manganese complex **2** (entry 8) and β-ketoiminato manganese complex **3** (entry 9).[10] It was proposed that Jacobsen's manganese(III) catalysts could be employed as a chiral Lewis acid to form a stable chelate complex with 2-phenacylpyridine, which was then enantioselectively reduced by the THFA-modified borohydride.[11] On the other hand, the formation of a similar tight chelate with cobalt(II) complexes could not be expected since the Lewis acidity of the cobalt(II) complex is presumed to be generally weak. Concerning the enantioselective sense, the manganese(III) chloride complex with the β-ketoiminato ligand afforded the opposite enantiomer against the corresponding β-ketoiminato cobalt(II) complex although both structures of the manganese and cobalt complexes were very similar based on an X-ray analysis.[12] The enantioselective sense in the present reduction of 2-phenacylpyridine was in accord with the various examples of the cobalt complex-catalyzed reductions of carbonyl compounds reported by our research group.[13] These observations suggest that the enantioselective borohydride reductions with cobalt(II) and manganese(III) complex catalysts proceeded by different mechanisms. Therefore, it is reasonable to assume that the 'cobalt-hydride equivalent' generated from the optically active cobalt catalyst and pre-modified borohydride could react with carbonyl compounds in a highly enantioselective manner.

In summary, the highly enantioselective reduction of 2-phenacylpyridine catalyzed by the optically active β-ketoiminato cobalt(II) complexes was achieved as the key step in the asymmetric synthesis of sedamine. It was demonstrated that the β-ketoiminato cobalt(II) complex was a more enantioselective catalyst for the reduction of 2-phenacylpyridine than Jacobsen's manganese(III) complex. In addition, the mechanisms for the cobalt and manganese complex-catalyzed reactions were suggested to be different from each other based on the enantioselective sense. A further study on the detailed mechanism of the present reduction system is currently underway.

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9. **Typical procedure for the preparation of pre-modified $NaBH_4$ solution:** To the suspension of $NaBH_4$ (76 mg, 2.0 mmol) in $CHCl_3$ (10.6 ml), MeOH (81 μl, 2.0 mmol) and tetrahydrofurfuryl alcohol (2.7 ml, 28 mmol) were added at 0°C under a dry nitrogen atmosphere. The mixture was then stirred for 3 h at 0°C. **The enantioselective reduction of 2-phenacylpyridine:** Under a dry nitrogen atmosphere in a pre-cooled vessel at 0°C were placed the (*S*,*S*)-**C**′ catalyst (11.5 mg, 0.020 mmol), 2-phenacylpyridine (99 mg, 0.50 mmol) and $CHCl_3$ (5.0 ml). To this solution was added the solution of pre-modified $NaBH_4$ (5.0 ml), and stirred for 72 h at −20°C. The reaction was quenched by pH 7 buffer solution and the crude products were extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After evaporation, the residue was purified by silica-gel column chromatography (hexane/AcOEt) to give (*S*)-1-phenyl-2-(2-pyridyl)ethanol in 94% yield. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H) to be 92.5% ee.
10. Manganese(III) chloride catalyst with the β-ketoimine **C**′-ligand and Jacobsen's cobalt(II) catalyst afforded the product with very low ee, although β-ketoiminato **C**′ cobalt(II) catalyst and Jacobsen's manganese(III) chloride catalyst were very efficient on the reaction. Therefore, the combination of the center metal and the chiral ligand is essential for the highly enantioselective reduction of 2-phenacylpyridine.
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