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Reductive Desymmetrization of 2-Alkyl-1,3-diketones Catalyzed by Optically Active β-Ketoiminato Cobalt Complexes

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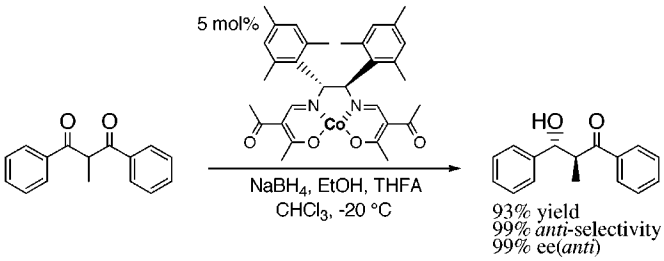
ABSTRACT



The reductive desymmetrization of acyclic 1,3-diketones was achieved for the first time by catalytic borohydride reduction in the presence of optically active β-ketoiminato cobalt(II) complex catalysts. In this reaction, various 2-substituted-1,3-diaryl-1,3-propanediones were converted into the corresponding optically active 2-substituted-1,3-diaryl-3-hydroxypropanone in good-to-high yields with excellent diastereo- and enantioselectivities and high catalytic efficiencies.

The strategy of enantioselective desymmetrization is often used for the preparation of optically active compounds because two or more stereocenters can be generated in one reaction step.[1] For example, the optically active 2-substituted-3-hydroxyketones can be obtained by the enantioselective reduction of the corresponding symmetrical 2-substituted-1,3-diketones, which are readily prepared by Claisen condensation,[2] etc. Whereas various reductive desymmetrizations of symmetrical diketones have already been reported in enzymatic reactions,[3] the applications of the asymmetric reduction catalyzed by metal complexes were limited to a few cyclic symmetrical imides,[4] diamides,[5] and diketones.[6] For the synthesis of the optically active 2-substituted-3-hydroxyketone units that often appear in various natural products,[7] many studies have been conducted to develop the most efficient methods. An aldol reaction is one of the most reliable methods for this purpose, and its enantioselective and catalytic versions have been examined using various optically active transition metal complexes.[8] In almost all

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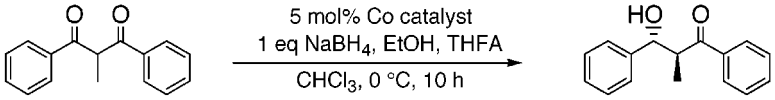
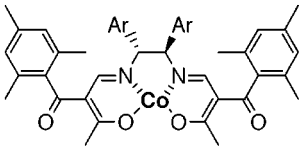
Table 1. Various Catalysts[a] for Enantioselective Desymmetrization

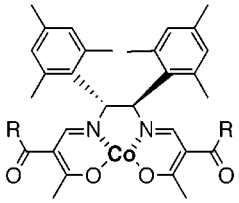


entry	catalyst	yield (%)[b]	*anti*-selectivity (%)[c]	ee (*anti*, %)[d]	recovery (%)[b]	diols yield (%)[b]
1	**1**	65	93	33	3	27
2	**2**	58	99	45		39
3	**3a**	65	94	89	24	11
4	**3b**	55	98	81	1	41
5	**3c**	71	96	87	1	28
6	**3d**	75	95	92	10	15
7[e]	**3d**	93	99	99		7

[a] Procedure A: to a solution of the modified borohydride was added a solution of the cobalt catalyst and the substrate; 0.5 mmol of substrate, 0.025 mmol (5 mol %) of cobalt catalyst, 0.5 mmol of $NaBH_4$, 1.5 mmol of EtOH, 7 mmol of tetrahydrofurfuryl alcohol (THFA) in $CHCl_3$ (total 28 mL) at 0 °C, 10 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] Procedure B: to a solution of the cobalt catalyst and the substrate was added a solution of the modified borohydride; 0.25 mmol of substrate, 0.0125 mmol (5 mol %) of cobalt catalyst **3d**, 0.25 mmol of $NaBH_4$, 0.25 mmol of EtOH, 3.5 mmol of THFA in $CHCl_3$ (total 14 mL) at −20 °C, 10 h.



1 : Ar = Phenyl
2 : 3,5-Dimethylphenyl
3a : 2,4,6-Trimethylphenyl



3b : R = O^{t}Bu
3c : OEt
3d : Me

catalytic enantioselective aldol reactions, however, preparations of silyl or metal enolates[8,9] are required in advance along with a relatively large amount of loading of the catalyst for high enantio- and/or diastereoselectivity. These disadvantages have made the enantioselective and catalytic aldol reactions difficult to use on a multigram scale in laboratory and manufacturing processes. The diastereo- and enantioselective reductions of the corresponding 2-substituted-1,3-diketones conventionally prepared by the Claisen condensation should be an alternative solution for synthesis of aldol-type compounds.

Recently, we developed optically active β-ketoiminato cobalt complex catalysts[10] for the highly enantioselective borohydride reduction of ketones[11] and imines[12] to afford the corresponding secondary alcohol and amines with high catalytic efficiencies[13] and reported that the 1,3-diaryl-1,3-diketones were converted by the catalytic system into the corresponding 1,3-diols with high enantioselectivity.[14] In this communication, we would like to describe the first successful reaction for the reductive desymmetrization of acyclic symmetrical diketones with high stereoselectivities and high catalytic efficiencies and to propose a new method for the preparation of optically active aldol-type compounds with high enantioselectivity.

The desymmetrization of 1,3-diphenyl-2-methyl-1,3-propanedione into optically active 1,3-diphenyl-3-hydroxy-2-methylpropanone was adopted as a model reaction for screening the various optically active β-ketoiminato cobalt complexes for the catalytic borohydride reduction (Table 1). Each ligand of the cobalt catalyst was prepared from the corresponding optically active 1,2-disubstituted-1,2-ethylenediamine and 1,3-dicarbonyl compound.[13] Although the *anti*-selectivity of the resulting β-hydroxyketones was excellent in each case, the enantiomeric excesses of the *anti* products varied widely, being sensitive to the structure of the cobalt complex catalysts (entries 1−6). The catalyst **1** or **2** afforded a low or moderate ee of the *anti* product (entries 1 and 2), whereas the enantioselectivity was remarkably improved when employing the series **3** catalysts derived from the optically active 1,3-bis(2,4,6-trimethylphenyl)ethylenediamine (entries 3−6). Among the series **3** catalysts, it was found that catalyst **3d**, having acetyl groups on both side chains, was the most efficient catalyst for the reductive desymmetrization of the 1,3-diphenyl-2-methyl-1,3-propanedione (entry 6). After optimization of the reaction conditions, 99% ee of the *anti* product was isolated in 93% yield with 99% diastereoselection (entry 7).

The catalytic and enantioselective desymmetrization was successfully applied to the preparation of various optically active 2-substituted-1,3-diaryl-3-hydroxypropanones from the corresponding 1,3-diketones (Table 2). Various 2-methyl-

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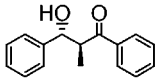
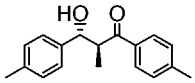
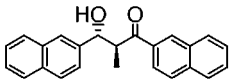
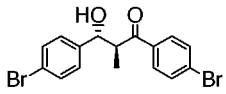
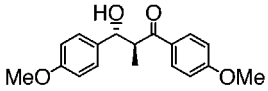
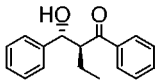
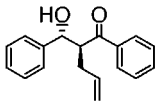
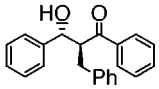
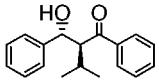
Table 2. Catalytic Desymmetrization of Various 2-Alkyl-1,3-diaryl-1,3-propanediones[a]

entry	β-hydroxyketones	yield/%[b]	*anti*-selectivity/%[c]	ee/%[d]
1		93	99	99
2		97	99	99
3		73	99	99
4		68	99	99
5		96	99	97
6		88	99	99
7		88	98	97
8		96	99	98
9		45	99	91

[a] Procedure B (see Table 1). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Values for ee's of *anti* products were determined by HPLC analysis.

1,3-diaryl-1,3-diketones, having *p*-methylphenyl-, 2-naphthyl-, *p*-bromophenyl-, or *p*-methoxyphenyl- as the aryl group, were converted into the corresponding *anti*-2-methyl-3-hydroxyketones in good-to-high yields with excellent *anti*-selectivity and excellent enantioselectivity (entries 2−5). For the catalytic and enantioselective desymmetrization of various 2-substituted-1,3-diketones, such as 2-ethyl-, 2-allyl-, 2-benzyl-, and 2-isopropyl-, the corresponding *anti*-2-alkyl-3-hydroxyketones were obtained with excellent *anti*-selectivity and excellent enantioselectivity (entries 6−9).

The excellent stereoselectivity in the present catalytic reduction system can be explained as follows (Figure 1). The hydride equivalent nucleophile should attack one of the carbonyl groups in the 1,3-diaryl-1,3-propanedione according to the Felkin−Anh model to afford the corresponding *anti* product with high selectivity. Concerning the excellent enantioselectivity, the optically active *β*-ketoiminato cobalt complex could distinctly recognize the *re*/*si* face of the carbonyl group similar to the cobalt-catalyzed borohydride reduction of the aryl ketones.[11c] Since the reaction takes place with high enantioselectivity and the operation of path A appears as a consequence of the absolute configuration of

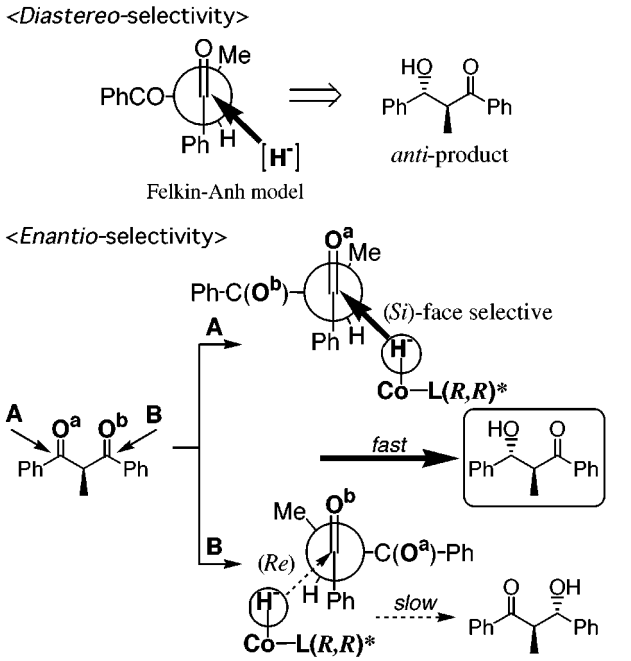


Figure 1. Diastereo- and enantioselectivity in the catalytic reduction system.

one of the products, the presentation in Figure 1 is fully supported by experimental results.

The absolute configuration of the resulting α-substituted-*β*-hydroxyketones was confirmed. The stereoselectively obtained product, the *anti*-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone, was conventionally converted into the corresponding (*R*)-α-methoxyphenylacetate. As a result of the X-ray analysis, it was revealed that (2*S*,3*R*)-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone was obtained, corresponding to the (*R*,*R*)-cobalt complex catalyst (Figure 2). The enantioselective sense in the present reduction of 1,3-diaryl-2-substituted-1,3-propanedione was in perfect accord with various examples of cobalt complex catalyzed

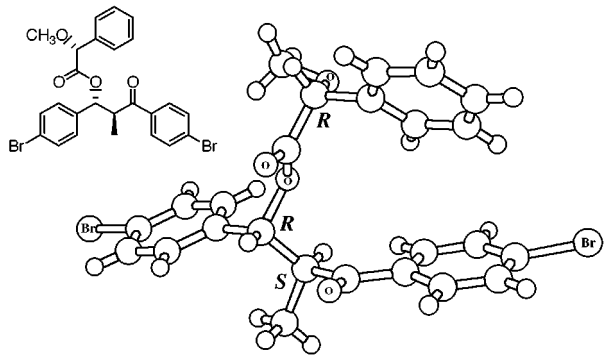


Figure 2. X-ray analysis of (*R*)-α-methoxyphenylacetate of *anti*-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone corresponding to the (*R*,*R*)-cobalt catalyst.

reductions of carbonyl compounds reported by our research group.[13] Also, this observation would support the above-mentioned mechanism for the highly diastereo- and enantioselection.

In summary, the successful reaction of the catalytic desymmetrization of acyclic symmetrical diketones was first achieved for the enantioselective reduction catalyzed by the optically active β-ketoiminato cobalt complexes. In the presence of a 5 mol % or less amount of the cobalt complex catalysts, various 2-substituted-1,3-diaryl-1,3-propanediones were transformed into the corresponding optically active 2-substituted-1,3-diaryl-3-hydroxypropanones with high diastereo- and enantioselectivities. These results indicated that enantioselective borohydride reduction catalyzed by cobalt complexes would provide a new method for preparing optically active aldol-type compounds. Further applications to other types of dicarbonyl compounds are currently underway.

Supporting Information Available: Experimental procedures, spectral data for new compounds, and X-ray analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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