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Highly Chemo-, Diastereo-, and Enantioselective Reduction of 1,2-Dialkyl-3-aryl-1,3-diketones for Preparation of Aldol-Type Compounds

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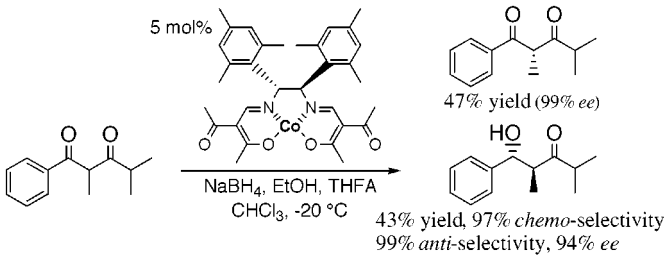
ABSTRACT



Highly chemo-, diastereo-, and enantioselective borohydride reduction of 2-substituted-1,3-diketones was achieved in the presence of the optically active *β*-ketoiminato cobalt complex catalysts to afford the optically active 2-substituted-3-hydroxyketones. The present catalytic and enantioselective reduction could provide an alternative potential for preparation of optically active *anti*-aldol-type compounds.

The aldol reaction is one of the most useful and reliable methods in organic synthesis for preparation of 2-substituted-3-hydroxycarbonyl units accompanied with new carbon−carbon bond formation.[1] Optically active 2-substituted-3-hydroxycarbonyl units are often observed in natural products, and their hydroxy or carbonyl groups could be stereoselectively[2] or stereospecifically[3] converted into various functionalities. Therefore, highly diastereoselective and/or enantioselective versions of the aldol reaction are indispensable for the total synthesis of complicated natural products. A wide variety of enantioselective aldol reactions, especially catalytic versions by optically active transition-metal complexes, have been dynamically studied for a decade.[4] For multigram preparation in laboratories, however, some difficulties can be found in almost all of catalytic aldol reactions; the preparation of silyl or metal enolates is required beforehand or a relatively large loading of optically active catalysts is needed in order to achieve high diastereo- and enantioselectivities, etc. Alternatively, optically active 2-substituted-3-hydroxyketones could be also prepared from the corresponding 2-substituted-1,3-diketones with catalytic and enantioselective reductions. Very recently, we reported that symmetrical 2-substituted-1,3-diaryl-1,3-diketones could be

(1) (a) Heathcock, C. H. *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 133. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(2) For recent examples of the total synthesis of natural products, see: (a) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372. (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033. (c) Ma, D.; Sun, H. *Tetrahedron Lett.* **2000**, *41*, 1947.

(3) For recent examples of the total synthesis of natural products, see: (a) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603. (b) Shing, T. K. M.; Jiang, Q. *J. Org. Chem.* **2000**, *65*, 7059. (c) Davenport, R. J.; Regan, A. C. *Tetrahedron Lett.* **2000**, *41*, 7622.

(4) (a) Carreira, E. M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds: Springer, Heidelberg, 1999; Vol. 3, p 998. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

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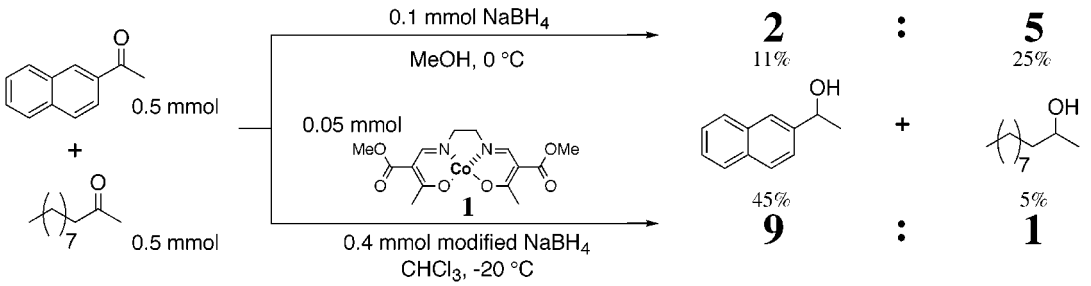
Scheme 1. Chemoselective Borohydride Reduction of Aromatic vs. Aliphatic Ketones



converted into the corresponding optically active 2-substituted-3-hydroxyketones with excellent diastereoselectivity and enantiomeric excess with high catalytic efficiency catalyzed by the optically active β-ketoiminato cobalt complexes.[5] In this Letter, we would like to describe that a highly chemo-, diastereo-, and enantioselective borohydride reduction of unsymmetrical 2-substituted-1,3-diketones was achieved in the presence of the optically active β-ketoiminato cobalt complexes to afford optically active *anti*-2-substituted-3-hydroxyketones.

A preliminary examination of the borohydride reduction using a catalytic amount of the cobalt complexes revealed that aromatic ketones were preferentially reduced in the presence of aliphatic ketones. As shown in Scheme 1, to the methanol solution of 0.5 mmol of 2-undecanone and 0.5 mmol of 2-acetonaphthone was added 0.1 mmol of sodium borohydride. After 8 h, 2-undecanone, an alkyl ketone, was reduced to the corresponding alcohol in 25% yield and 2-acetonaphthone, an aromatic ketone, in 11% yield, respectively. The chemoselectivity for the reduction of the aliphatic ketone was about 70%. In contrast, in the presence of 0.05 mmol of β-ketoiminato cobalt complex **1**, the chemoselectivity was completely reversed. By treatment of the premodified borohydride,[6] an aromatic ketone, 2-acetonaphthone, was selectively reduced to 1-(2-naphthyl)-1-ethanol in 45% yield while the aliphatic ketone was reduced in only 5% yield. The chemoselectivity of the aromatic ketone was 90%. These observations encouraged us to apply the cobalt-catalyzed reduction to 1-alkyl-3-aryl-1,3-diketones to prepare the corresponding 1-alkyl-3-aryl-3-hydroxyketones.

As the unsymmetrical 2-substituted-1,3-diketone model for chemo-, diastereo-, and enantioselective reduction, 2,4-dimethyl-1-phenyl-1,3-pentanedione was adopted. Since kinetic resolution must be considered for the model substrate, 0.5 equiv of the premodified borohydride was employed in the presence of 5 mol % of the optically active β-ketoiminato cobalt complex catalyst **2**. After 24 h, the reaction was quenched to afford the corresponding hydroxyketones in 44% yield with 88% aromatic vs 12% aliphatic alcohol. Though the diastereoselectivity in the aromatic alcohol was determined to be 93% *anti*, the enantioselectivity of the *anti*-aromatic alcohol was 67% ee. When only 0.25 equiv of the premodified borohydride was used, high enantioselectivity was realized with high chemo- and diastereoselectivity.

These observations suggested that the excess hydride in the catalytic system caused noncatalytic reduction, resulting in low selectivities. To maintain the initial reaction conditions, therefore, five portions of the 0.1 equiv of the premodified borohydride were successively added at 1 h intervals to the reaction to obtain the 3-aryl-3-hydroxyketones in 43% yield with 97% chemoselectivity, 99% *anti*-selectivity, and 94% enantiomeric excess (Scheme 2). The enantiomeric excesses of the 2-methyl-1,3-diketone remaining after the kinetic resolution were determined by HPLC. Since racemization of 2-substituted-1,3-diketones gradually proceeded at room temperature, the reaction mixture was directly injected into an HPLC chiral column (Daicel chiralpak AD, 5% 2-propanol in *n*-hexane) to determine the ee of 2,4-dimethyl-1-phenyl-1,3-pentanedione to be 99% ee. These observations indicated that the cobalt complex catalyzed reduction selectively afforded one isomer among the possible eight isomers and that the kinetic resolution was excellent.

After the detailed optimization,[7] the present kinetic resolution system was successfully applied to enantioselective reduction of various 2-substituted-1-alkyl-3-aryl-1,3-diketones to optically active 2-substituted-3-hydroxyketones (Table 1). The 1,3-diketones having 2-methyl, 2-ethyl, and 2-allyl groups were converted into the corresponding 3-aryl-3-hydroxyketones with high chemo-, diastereo-, and enantioselectivities (entries 1−3). Kinetic resolution in the enantioselective reduction of the substrate containing a *tert*-butyl ketone (entry 4) showed that the corresponding reduced product was obtained in 48% yield and indicated 99% chemoselectivity, 99% *anti*-selectivity, and 97% ee. The present highly selective kinetic resolution could also be applied to substrates having primary alkyl ketones, such as *n*-nonyl ketone, isobutyl ketone, and benzyl ketone, to obtain the corresponding *anti*-hydroxyketones with high selectivities (entries 5−7).

The excellent stereoselectivity in the present catalytic reduction system can be explained as follows: In the presence of (*R*,*R*)-cobalt catalyst, the enantioselective reduc-

(5) Ohtsuka, Y.; Koyasu, K.; Ikeno,; T. Yamada, T. *Org. Lett.* **2001**, *3*, 2543.

(6) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1996**, 1081.

(7) To reduce the excess hydride in the catalytic system and avoid noncatalytic reduction further, four portions of the 0.1 equiv of the premodified borohydride were successively added at 2 h intervals to the reaction mixture.

Scheme 2. Highly Chemo-, Diastereo-, and Enantioselective Borohydride Reduction of 2-Methyl-1,3-diketone

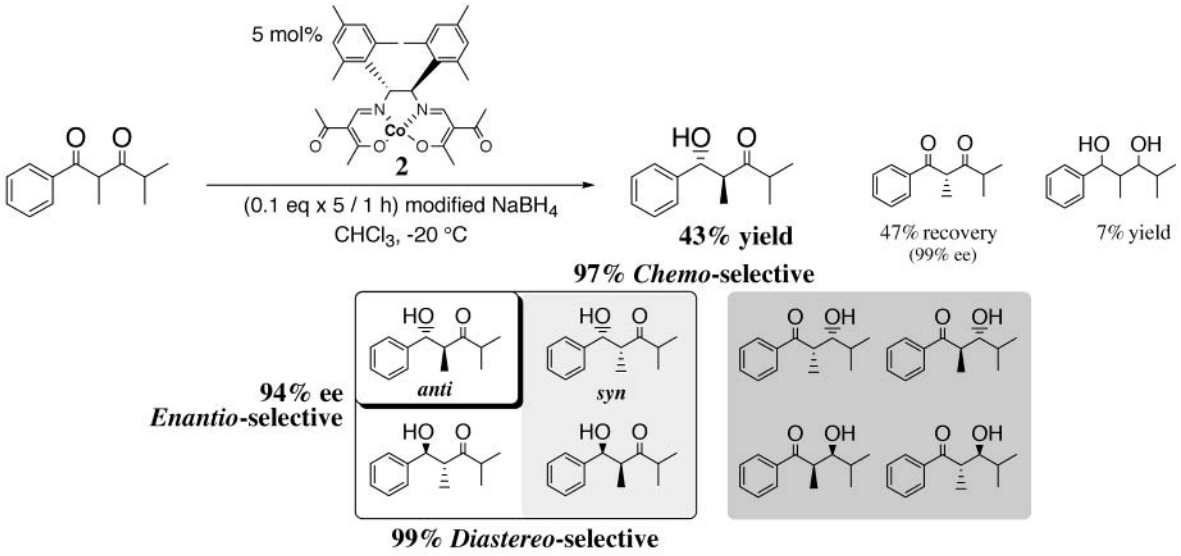
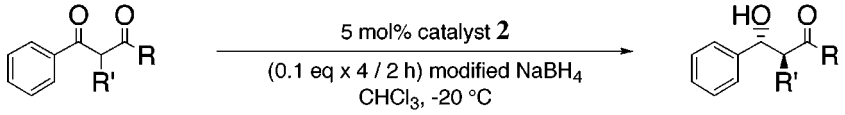
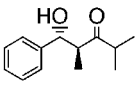
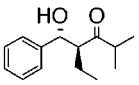
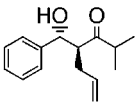
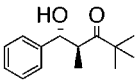
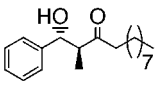
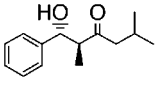
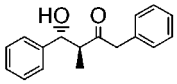


Table 1. Highly Chemo-, Diastereo-, and Enantioselective Reduction of Various 2-Alkyl-1,3-diketones[a]



entry	3-hydroxy ketones	yield/%[b] / conversion/%[b]	selectivity		
			chemo-/%[c]	*anti*-/%[c]	*enantio*-/% ee[d]
1		46/48	99	99	96
2		41/42	99	99	98
3		47/55	95	98	96
4		48/49	99	99	97
5		47/54	96	98	96
6		47/54	99	98	95
7		45/52	93	94	98

[a] Procedure: Four portions of the 0.1 equivalent of the pre-modified borohydride were successively added at 2 hours intervals to the solution of the cobalt catalyst and the substrate; 0.25 mmol of substrate, 0.0125 mmol (5 mol%) of cobalt catalyst **2**, 0.1 mmol of $NaBH_4$, 0.1 mmol of EtOH, 1.4 mmol of tetrahydrofurfuryl alcohol (THFA) in $CHCl_3$ (total 12.8 mL) at -20 °C. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis.

tion of aromatic ketone proceeds by *Si*-face selectivity.[8] In addition to the enantioselective sense, the reduction of the aromatic ketone in 2-alkyl-1,3-diketone should be dominant according to the Felkin−Anh model. Since racemization on the activated methyne of 2-alkyl-1,3-diketone was not observed during the present reaction conditions (−20 °C), the *Si*-face of carbonyl in the aromatic ketone should be attacked by a hydride equivalent on condition that the reduction proceeded according to the Felkin−Anh model.[5] Therefore, the *anti*-2-substituted-3-(*R*)-hydroxyketones should be afforded predominantly. The absolute configurations of the resulting 2-substituted-3-hydroxyketones were determined. The *anti*-1-hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (entry 4 in Table 1) was conventionally transformed into the corresponding *p*-bromobenzoate. As a result of the X-ray analysis, it was revealed that the (1*R*,2*S*)-form was obtained, corresponding to the (*R*,*R*)-cobalt complex catalyst **2** (Figure 1). The enantioselective sense in the present cobalt-catalyzed reduction of 1,2-dialkyl-3-aryl-l,3-diketone was in perfect accord with the previous results of enantioselective reduction of various carbonyl compounds[9] and also supported the proposed mechanism for the high diastereo- and enantioselectivity.[5]

It is noted that the highly chemo-, diastereo-, and enantioselective borohydride reduction catalyzed by the optically active β-ketoiminato cobalt complex was successfully applied to the preparation of optically active 2-substituted-3-aryl-3-hydroxyketones. It was expected that the present catalytic reaction could provide an alternative potential for preparation of optically active *anti*-aldol-type compounds. Further studies on the enantioselective catalytic reduction of other types of dicarbonyl compounds are currently underway.

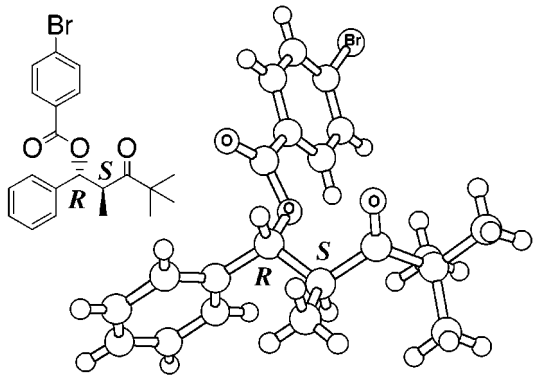


Figure 1. The absolute configuration of *p*-bromobenzoate of *anti*-1-hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone corresponding to the (*R*,*R*)-cobalt catalyst was determined by X-ray analysis.

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

OL016676W

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(9) Nagata, T.; Sugi, K. D.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Catal. Surv. Jpn.* **1998**, *2*, 47.