Dynamic Kinetic Resolution with Enantioselective Borohydride Reduction Catalyzed by Optically Active β-Ketoiminato Cobalt(II) Complexes: Highly Diastereo- and Enantioselective Preparation of Optically Active *anti*-Aldol Compounds

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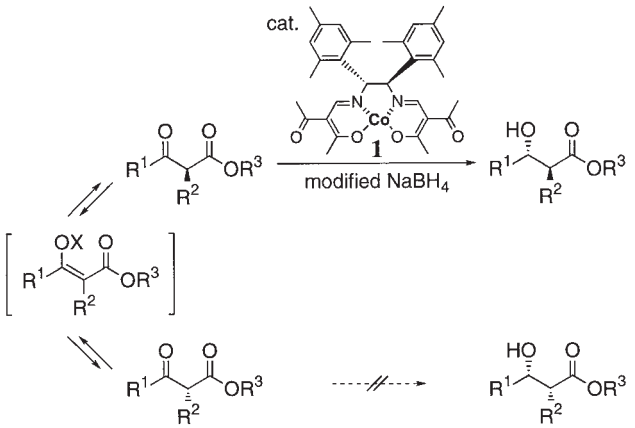
Optically active *anti*-2-alkyl-3-hydroxy esters were stereoselectively obtained from the corresponding 2-alkyl-3-keto esters using enantioselective borohydride reduction along with dynamic kinetic resolution in the presence of optically active β-ketoiminato cobalt complex catalysts. The reduction system provided an alternative preparation for *anti*-aldol compounds with high diastereo- and enantioselectivities.

Kinetic resolution is one of the most useful and reliable methods to obtain optically active compounds,[1] however, the chemical yields of the desired optically active products are limited to only 50% even under the best reaction conditions. If racemization equilibrium would proceed during the kinetic resolution of the enantioselective reaction, it should be a much more efficient and promising method for the generation of two or more stereocenters in one reaction step ideally in 100% chemical yield.[2] Therefore, the dynamic kinetic resolution with enantioselective reaction has been recently focused on as an attractive strategy to prepare beneficial chiral synthons.[3]

The highly enantioselective borohydride reduction catalyzed by optically active β-ketoiminato cobalt complexes was recently developed[4] and successfully applied to 2-substituted-1,3-diketones to afford the corresponding optically active *anti*-2-substituted-3-hydroxyketones with high diastereo- and enantioselectivities.[5] These reactions were applicable to a limited number of substrates, for example, symmetrical 1,3-diaryl-1,3-diketones[5a] or asymmetrical 1-alkyl-3-aryl-1,3-diketones along with kinetic resolution.[5b]

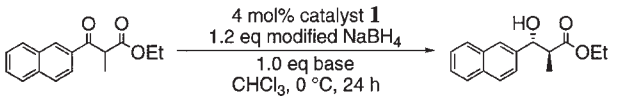
As mentioned above, the combination of the dynamic kinetic resolution with the enantioselective reaction should provide an attractive preparation for the optically active 2-substituted-3-hydroxy esters, *anti*-aldol-compounds in high yield and with high stereoselectivities (Scheme 1). Several trials of dynamic kinetic resolution during the enantioselective reduction of 2-substituted-3-keto esters have already been reported; for example, the ruthenium-complex catalyzed hydrogenation was successfully applied to 2-substituted-3-keto esters to obtain *syn*-aldol products with high stereoselectivities.[6] Otherwise, the aldol derivatives could be prepared by the enantioselective aldol reaction catalyzed by optically active transition-metal complexes, though the *syn*-aldol is predominantly obtained.[7,8] In this communication, we would like to describe the highly enantioselective synthesis of optically active *anti*-2-substituted-3-hydroxy esters from the corresponding 2-substituted-1,3-diketones by enantioselective borohydride reduction in the presence of a catalytic amount of β-ketoiminato cobalt complexes.



Scheme 1. Dynamic kinetic resolution.

For the screening of the reaction conditions for the dynamic kinetic resolution, 2-methyl-3-(2-naphthyl)-3-oxopropionic acid ethyl ester was adopted as the model substrate and various bases were examined for racemization equilibrium (Table 1). In the presence of 4 mol% of the cobalt catalyst **1**, the enantioselective borohydride reduction afforded 3-hydroxy-2-methyl-3-(2-naphthyl)propionic acid ethyl ester with moderate *anti*-selectivity and enantioselectivity (entry 1). These observations indicated that the racemization equilibrium was not sufficient without any base. In order to accelerate the racemization equilibrium *via* its enolates, several bases were added to the reaction mixture. In the presence of alkalimetal carbonates, the reduction smoothly proceeded though the *anti*-selectivity and enantioselectivity were not improved at all (entries 2 and 3). The addition of amine bases slightly improved the stereoselectivity, but their selectivities did not reach a satisfactory level (entries 4 and 5). The high diastereo- and enantioselectivities were achieved with the addition of an

Table 1. Various bases for dynamic kinetic resolution[a]



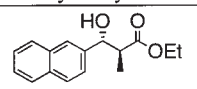
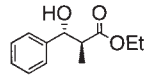
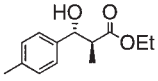
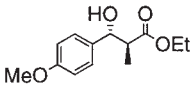
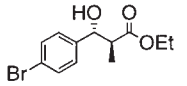
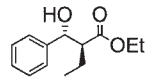
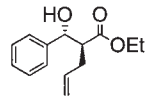
Entry	Base	Yield/%[b]	*anti*-Selectivity/%[c]	Ee(*anti*)/% ee[d]
1	-	99	69	83
2	Na_2CO_3	99	69	81
3	Cs_2CO_3	96	66	82
4	Et_3N	95	79	87
5	HN^iPr_2	94	82	87
6	NaOEt	86	88	91
7	NaOMe	66	88	90
8[e]	NaOMe	91	92	95

[a]Reaction conditions: 0.25 mmol of substrate, 0.01 mmol of catalyst **1**, 0.25 mmol of base, 0.30 mmol of $NaBH_4$, 0.30 mmol of EtOH, 4.2 mmol of tetrahydrofurfuryl alcohol, and $CHCl_3$ (total 14.4 ml) at 0 °C for 24 h. [b]Isolated yield. [c]Determined by ^1H NMR analysis. [d]Determined by HPLC analysis. [e]At -10 °C for 15 h.

alkalimetal alkoxide, though the isolated yields were low due to the *retro*-aldol reaction from the resulting products. To avoid any side reaction, the reaction was tried at −10 °C to improve the isolated yield to 91% with maintaining high diastereo- and enantioselectivities.

Various 2-alkyl-3-aryl-3-keto esters were successfully subjected to the enantioselective reduction with dynamic kinetic resolution for the preparation of the *anti*-aldol-type compounds (Table 2).[9] The optically active 3-hydroxy-2-methyl esters containing 2-naphthyl, phenyl, *p*-bromophenyl, *p*-methylphenyl, or *p*-methoxyphenyl as a 3-aryl group could be prepared in the present dynamic kinetic resolution system with high diastereo- and enantioselectivities in high isolated yields (entries 1–5). The 3-phenyl-3-keto esters, having an ethyl or allyl group on the active methyne, were also converted into the corresponding 3-aryl-3-hydroxy ester with good diastereoselectivity and high enantiomeric excesses (entries 6 and 7).

Table 2. Dynamic kinetic resolution of enantioselective reduction for *anti*-aldol compounds[a]

Entry	3-Hydroxyester	Yield/%[b]	*anti*-Selectivity/%[c]	Ee/% ee[d]
1		91	92	95[e]
2		91	89	93[e,h]
3		88	88	94[f]
4		93	87	94[f]
5		91	90	90[e]
6		82	83	91[g]
7		84	87	95[e]

[a]Reaction conditions: Ref. 9. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis (2-propanol/hexane). [e]Using Daicel Chiralpak AD-H. [f]Using Daicel Chiralcel OB-H. [g]Using Daicel Chiralpak AD-H after acylation. [h](2*S*,3*R*)-Product was obtained corresponding to (*R*,*R*)-catalyst **1**, see text.

The absolute configuration of the obtained *anti*-3-hydroxy-2-methyl-3-phenylpropionic acid ethyl ester (entry 2 in Table 2) was confirmed as follows: The *anti*-3-hydroxy-2-methyl ester was treated with lithium aluminum hydride for conversion into the corresponding *anti*-1-phenyl-2-methyl-1,3-propanediols. The optical rotation of the resulting 1,3-diol was compared with the previously reported result.[8a] It was revealed to be (2*R*, 3*R*)-*anti*-1,3-diol, therefore, the (2*S*, 3*R*)-*anti*-3-hydroxy ester should be generated and correspond to the (*R*, *R*)-catalyst **1**. The enantioselective sense in the present reduction was in perfect accord with the various examples of the cobalt complex-catalyzed reductions of the previously reported carbonyl compounds.[10] The high stereoselectivity in the present catalytic reduction system can be explained as follows: Since the enolate from the 2-alkyl-3-keto esters could be rapidly formed in the presence of sodium methoxide, the chiral hydride equivalent nucleophile should attack the carbonyl group of the favorable enantiomer according to the Felkin-Anh model to afford the corresponding *anti*-product with the highly enantioselective sense,[5] therefore, the *anti*-2-alkyl-3-(*R*)-hydroxy ester was predominantly obtained using the (*R*, *R*)-cobalt catalyst **1**.

It was demonstrated that the optically active *anti*-2-substituted-3-hydoxyesters could be prepared from the corresponding 2-substituted-3-keto esters using enantioselective borohydride reduction. In contrast, the *syn*-aldol was generally produced by in the transition-metal catalyzed reactions; the present enantioselective reduction would provide an alternative approach of the preparation for *anti*-aldol-type compounds. Further applications to other types of compounds using the catalytic and enantioselective reduction are currently underway.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

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9 The preparation of the pre-modified borohydride solution: To the suspension of $NaBH_4$ (113.5 mg, 3.0 mmol) in $CHCl_3$ (20.0 mL), EtOH (176 μL, 3.0 mmol) and tetrahydrofurfuryl alcohol (4.07 mL, 42.0 mmol) were added at 0 °C under a dry nitrogen atmosphere. The mixture was stirred for 3 hours at 0 °C, and then cooled at −10 °C. The diastereo- and enantioselective reduction of the 2-alkyl-3-keto ester: Under a dry nitrogen atmosphere in a pre-cooled vessel at −10 °C were placed the (*R*, *R*)-cobalt catalyst **1** (5.7 mg, 0.01 mmol), sodium methoxide (13.5 mg, 0.25 mmol), the 2-alkyl-3-keto ester (0.25 mmol), and $CHCl_3$ (12.0 mL). The pre-modified $NaBH_4$ (2.4 mL, 0.30 mmol) was added to the reaction mixture, and stirred for 15 hours at −10 °C. The reaction was quenched by a pre-cooled aqueous THF solution at −10 °C and pH 7 buffer solution, then the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica-gel column chromatography (hexane/AcOEt) to give the corresponding 2-alkyl-3-hydroxy ester. The *anti*-selectivity was determined by ^{1}H NMR analysis. The optical purity was determined by HPLC analysis.

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