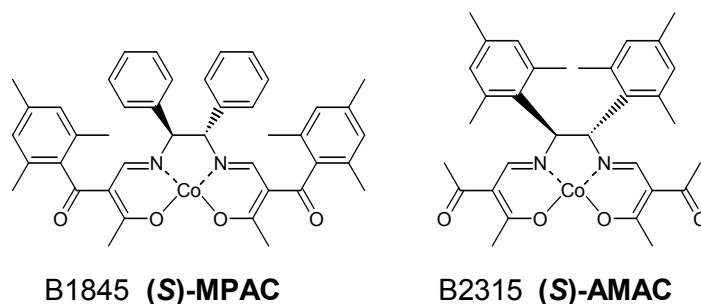
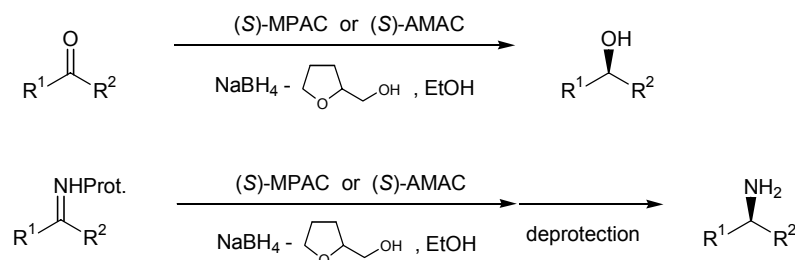


## Optically Active Ketoiminato Co(II) Complexes for Enantioselective Borohydride Reduction

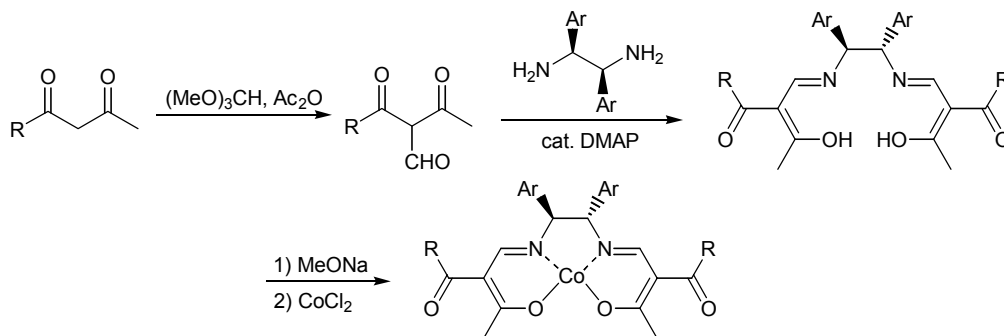


In the research and development of pharmaceuticals, agricultural chemicals or functional materials starting with ferroelectric liquid crystals, the demand for optically active compounds has increased more than ever. In order to obtain the desired optically active compounds through organic synthesis, diastereodifferentiating and enantiodifferentiating reactions have employed chiral auxiliaries or asymmetric catalysts. To achieve even higher optical purity and yield, new chiral auxiliaries and asymmetric catalysts are being developed and a considerable number of successful results have been reported.

The ketoiminato cobalt(II) complexes developed by Mukaiyama, Yamada and co-workers are one of the asymmetric catalysts, and are utilized for asymmetric reductions in the presence of NaBH<sub>4</sub> as reductant.



These ketoiminato cobalt(II) complexes can be synthesized following the reaction scheme below. The active methylene of 1,3-dicarbonyl compounds is formylated. The optically active ketoiminato ligands are obtained by reaction of formylated 1,3-dicarbonyl compounds with optically active 1,2-diarylethylenediamines. These ligands are treated with base and subsequently treated with cobalt(II) chloride to produce the optically active ketoiminato cobalt(II) complexes.



**Keywords :** chiral Co(II) complex, enantioselective borohydride reduction

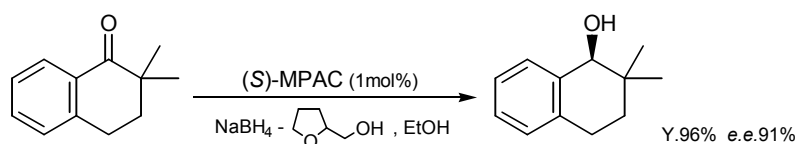
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The asymmetric recognition ability of these optically active ketoiminato cobalt(II) complexes can be changed by varying the aryl group (Ar), substituting asymmetric carbon atoms, and varying the substituent (R) located on the sidechain. The resulting complexes can be applied to various asymmetric reductions.

We now offer MPAC which has the bulky mesityl group on R and the phenyl group on Ar, and also AMAC which has the bulky mesityl on Ar and methyl groups on R. By using each appropriately, it is possible to conduct various asymmetric reductions in high yields.

### 1. Reduction of Ketones <sup>1)</sup>

Many methods have been reported for obtaining optically active alcohols from prochiral ketones. Ones using chiral catalysts are being studied as economically favorable methods for obtaining optically active alcohols, since a large amount of optically active alcohol can be obtained from a small amount of chiral catalyst. Methods using a Ru-BINAP complex, oxazaborolidine derivatives, and others are given as examples in which alcohols of high optical purity can be successfully obtained. However, there are drawbacks to using these common methods. For instance, utilizing the Ru-BINAP complex requires running the reaction in an autoclave. When using oxazaborolidine derivatives, a relatively expensive borane sulfide is utilized as a reductant. On the other hand, the asymmetric reduction using optically active ketoiminato cobalt(II) complexes developed by Yamada and co-workers, can use sodium borohydride, a widely used reducing agent. Therefore, this method using ketoiminato cobalt(II) complexes, is receiving much attention as it is likely to become a popular, convenient and economical method for obtaining optically active alcohols.

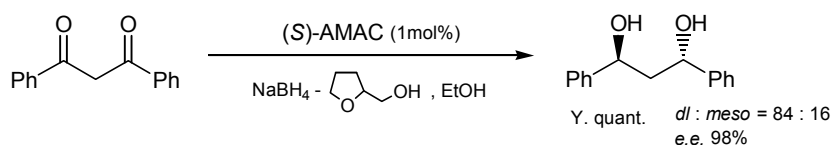


This asymmetric reduction method is quite simple. In the presence of 1 mol% of (*S*)-MPAC in chloroform, reduction of 2,2-dimethyl-1-tetralone using pre-modified borohydride prepared by treating NaBH<sub>4</sub> with tetrahydrofurfuryl alcohol and ethanol, produces (*S*)-2,2-dimethyl-1-tetralol in 96% yields and 91% *e.e.*. Furthermore, when 2-methyl-1-tetralone is reduced in the presence of (*S*)-MPAC, (*S*)-2-methyl-1-tetralone is preferentially reduced to yield (1*S*,2*S*)-2-methyl-1-tetralol, and unreacted (*R*)-2-methyl-1-tetralone can be recovered. Accordingly, kinetic resolution of  $\alpha$ -substituted carbonyl compounds can be carried out.

### 2. Synthesis of optically active 1,3-diols <sup>2)</sup>

The usefulness of optically active 1,3-diaryl-1,3-propanediols and their derivatives as chiral auxiliaries or as a chiral source of chiral ligands is already known. Asymmetric hydrogenation of 1,3-diketones using a rhodium complex catalyst has been employed to generate them. Since this reaction requires pressure conditions, it is desired to have a simpler method.

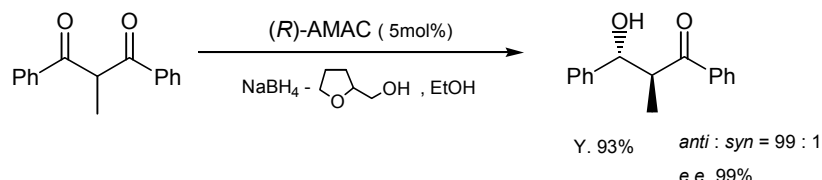
Yamada and co-workers have demonstrated asymmetric reduction of 1,3-diaryl-1,3-propanedione using optically active ketoiminato cobalt(II) complexes as catalysts and sodium borohydride as the hydrogen source, and have achieved high *dl*-selectivity and enantioselectivity. When AMAC, which has bulky mesityl groups on the asymmetric carbon atoms, was used, the optically active 1,3-diols were obtained with the highest *dl*-selectivity and enantioselectivity.



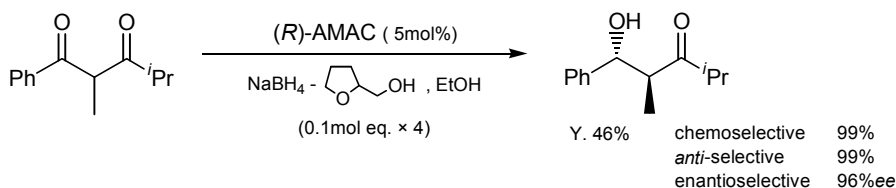
This asymmetric reduction method is very simple, and purification is also readily performed. For example, when 1,3-diphenyl-1,3-propanedione was used as the substrate, the reduced products were recrystallized from ethyl acetate. Optically pure 1,3-diphenyl-1,3-propanediol in approx. 60% isolation yield was obtained.

### 3. Synthesis of optically active anti-aldol compounds <sup>3)</sup>

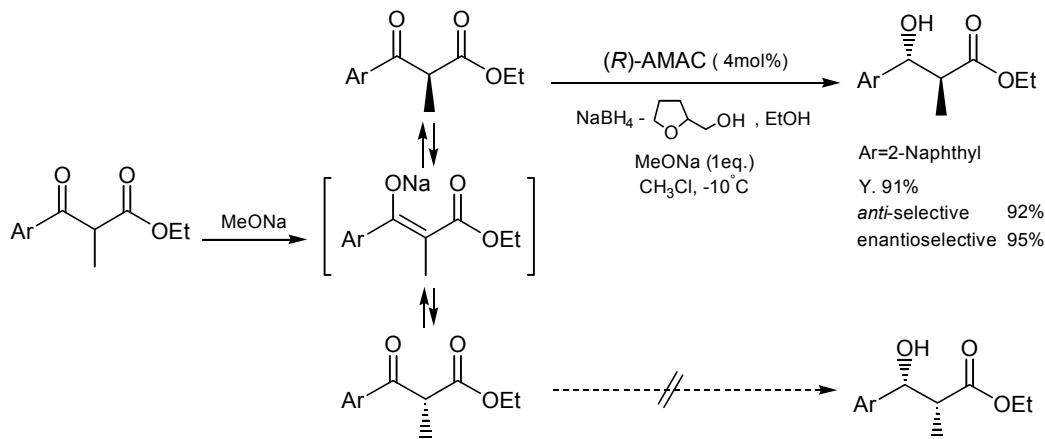
As the synthetic method of optically active *anti*-aldol compounds, some effective methods including the method of Abiko, Masamune and co-workers using chiral auxiliaries have been reported. Yamada and co-workers have demonstrated asymmetric reduction of 2-substituted 1,3-dicarbonyl compounds which are obtained by Claisen condensation to give *anti*-aldol compounds. For example, 2-methyl-1,3-diphenyl-1,3-propanedione, in the presence of 5 mol% AMAC, was reduced by pre-modified sodium borohydride, to obtain 3-hydroxyketone (99% *e.e.* of the *anti*-product was isolated in 93% yield with 99% diastereoselectivity).



In order to generalize this reaction, this reaction is applied to 2-substituted-1-alkyl-3-aryl-1,3-diketones. 3-Hydroxyketone was obtained from 2,4-dimethyl-1-phenyl-1,3-pentanedione in 46% yields, with 99% of chemoselectivity, 99% *anti*-selectivity and 99% *e.e.* Two conventionally known partial asymmetric reduction methods of 2-substituted-1-alkyl-3-aryl-1,3-diketones are the hydrogenation reaction using Ru-BINAP complexes as catalyst, and the hydrogen transfer reaction using optically active Ru-complexes. In these cases, the sterically less hindered alkyl-side carbonyl group is reduced. On the other hand, the method using ketoiminato cobalt(II) complexes developed by Yamada and co-workers, reduces the aryl-side carbonyl group, which is much more effective.

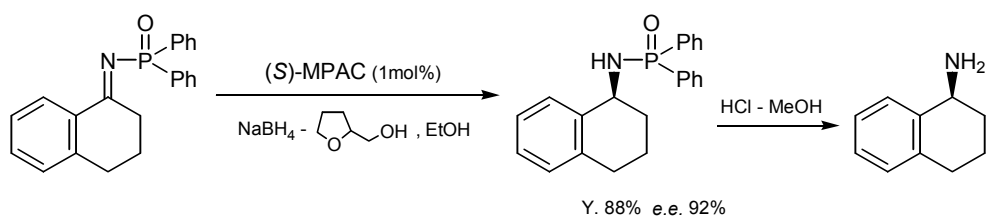


Furthermore, Yamada and co-workers have applied this reduction method to 2-substituted-3-ketoesters, and reported the dynamic kinetic resolution. According to which, the ethyl 2-methyl-3-(2-naphthyl)-3-oxopropionate produced the optically active ethyl 3-hydroxy-2-methyl-3-(2-naphthyl)propionate with yields of 91%, *anti*-selectivity of 92%, and 95% *e.e.*



### 4. Reduction of Imines <sup>4)</sup>

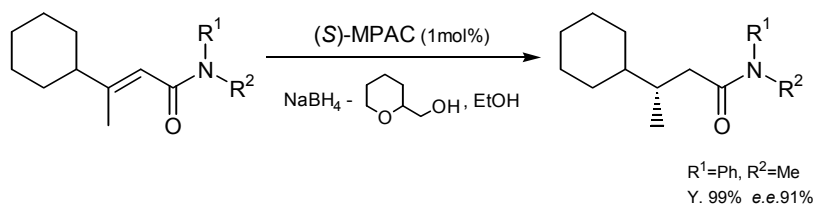
In the presence of 1 mol% of (*S*)-MPAC, *N*-phosphorylimines are reduced by sodium borohydride pretreated with tetrahydrofurfuryl alcohol and ethanol, and produced (*S*)-*N*-phosphorylamines in high yields with high optical purity. For Example, *N*-diphenylphosphoryl-1,2,3,4-tetrahydro-1-naphthylimine was reduced to obtain corresponding (*S*)-*N*-phosphorylamine in yields of 88% and 92% *e.e.*



The phosphoryl group of this *N*-phosphorylamine can be removed under mild conditions, and gives the optically active amine without loss of optical purity.

#### 5. 1,4-Reduction of $\alpha,\beta$ -unsaturated amides <sup>5)</sup>

In the presence of 0.5 mol% of (*S*)-MPAC, reduction of (*Z*)-3-cyclohexyl-2-butenamide with NaBH<sub>4</sub> pre-treated with tetrahydropyran-2-methanol produces (*S*)-butanamide in 99% yields and 91% *e.e.*. Using (*E*)-butenamide yields (*R*)-butanamide.



Asymmetric reductions using the optically active ketoiminato cobalt(II) complex catalysts can be carried out under mild conditions by using sodium borohydride, a widely available reducing agent to produce products of high optical purity in high yields. Accordingly, it is receiving positive attention as a synthetically useful method for obtaining optically active alcohols, amines, 1,3-diols, 3-hydroxycarbonyl compounds,  $\beta$ -substituted amides, etc..

B1845	( <i>S</i> )-MPAC	100mg
B1844	( <i>R</i> )-MPAC	100mg
B2315	( <i>S</i> )-AMAC	100mg
B2314	( <i>R</i> )-AMAC	100mg

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