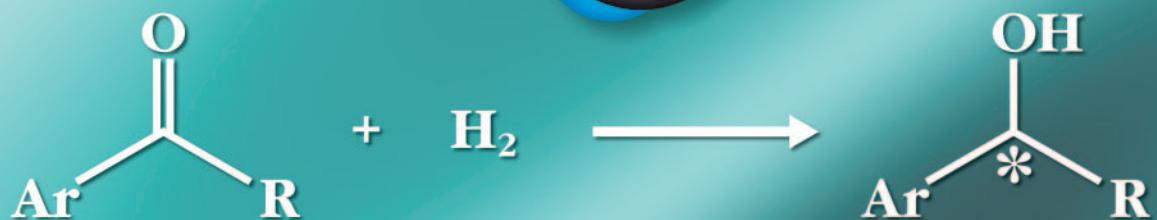
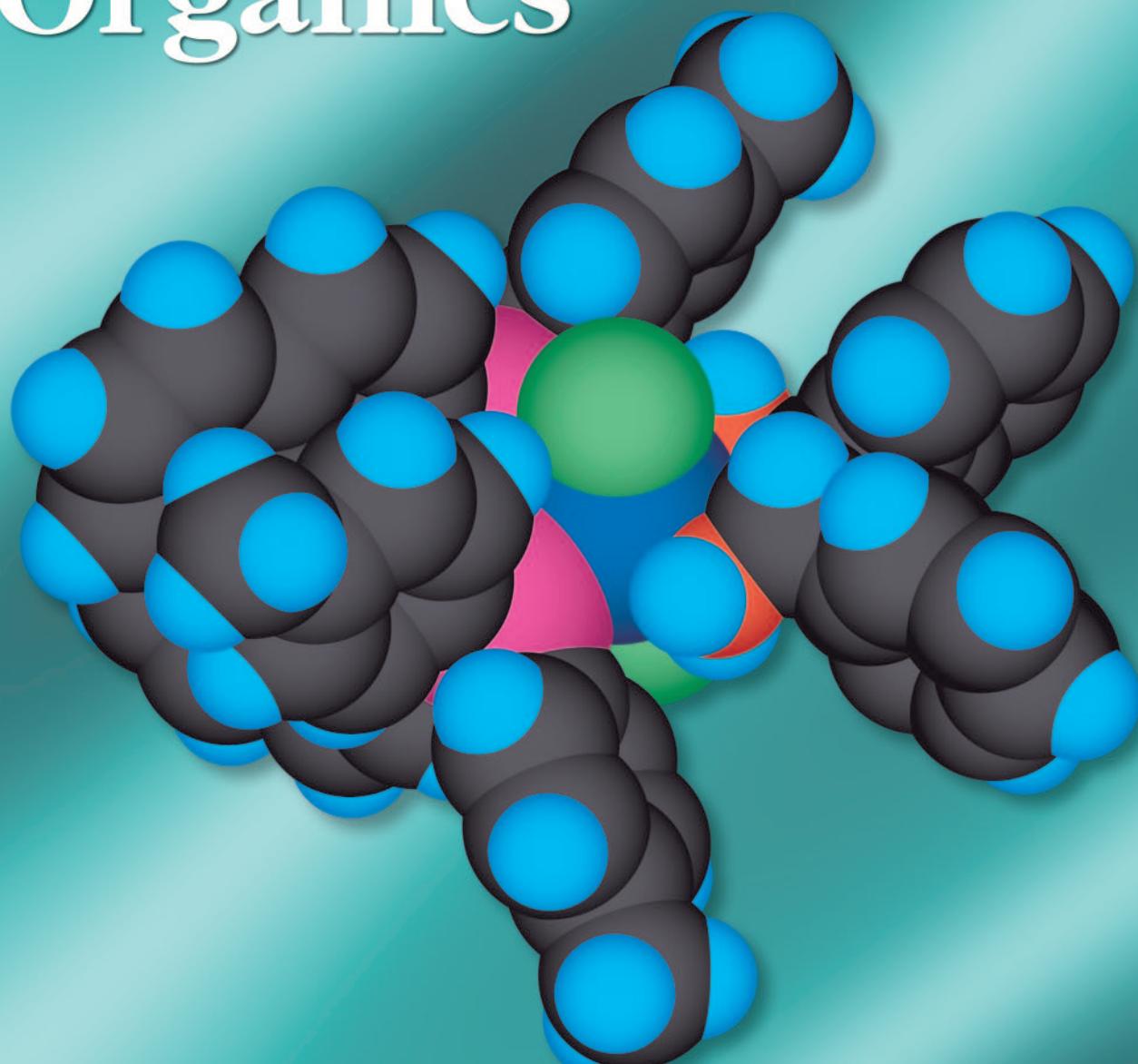


# Highly Selective Hydrogenation Catalysts



# Organics



Three-component catalyst effective for hydrogenation of simple ketones, composed of Ruthenium(II) complexes with phosphine ligands (or diphosphine), 1,2-diamine and strong base, was discovered by NOYORI Molecular Catalysis Project of Exploratory Research for Advanced Technology (ERATO) organized by Japan Science and Technology Corporation (JST).

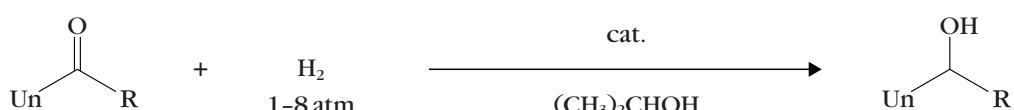
This catalyst catalyzes highly efficient hydrogenation of simple ketones. In addition to high activity, carbonyl-selective hydrogenation of aldehydes and ketones with conjugated or unconjugated carbon-carbon multiple bonds <sup>1)</sup>, and diastereoselective hydrogenation of various ketones <sup>2), 3)</sup> are performed smoothly under mild conditions, such as at room temperature and/or under low hydrogen-pressure(1-10atm), to give the corresponding alcohols in a nearly quantitative yields. The use of chiral Ruthenium(II)-diphosphine complex, in combination with appropriate chiral diamine, catalyzes enantioselective hydrogenation of prochiral ketones to give chiral alcohols with a very high enantiomeric purity <sup>1), 3), 4)</sup>. Furthermore this catalyst is environmentally conscientious because of extremely high acitivity minimizing metal disposal after the reaction, compared with the stoichiometric reduction with metal hydride reagents, and the use of 2-propanol as a solvent <sup>5)</sup>.

Exploitation and Application Study(participants : Nagoya University, Aich Institute of Technology, Tokyo Institute of Technology, Sumitomo Chemical Co., Ltd., Takasago International Corporation, Nissan Chemical Ind., Ltd., Nippon Soda Co., Ltd., and Kanto Chemical Co., Inc.) supported by JST has improved this catalyst into two-component catalyst : one of them is the shelf-stable and easy to handle Ruthenium(II) complexes, which have both of phosphine(or diphosphine) and 1,2-diamine ligands, and the other is strong base. We are now able to offer the ready-to-use Ruthenium(II) complexes for easy-handling and simpler preparation of catalyst in a laboratory. Two-component catalyst, which is composed of this improved Ruthenium(II) complexes and strong base, <sup>6)</sup> has realized an exceedingly efficient hydrogenation of simple ketones, which rates and productivities from one to two orders of magnitude higher than those obtained with three-component catalyst <sup>1)-4)</sup>, keeping the high selectivity. We recommend this catalyst for the laboratory-use, as well as the improvement and development in your production process.

## EXAMPLE OF HYDROGENATION

### 1. HYDROGENATION OF UNSATURATED ALDEHYDES AND KETONES <sup>1)</sup>

Carbonyl compounds with conjugated or unconjugated carbon-carbon multiple bonds can be converted rapidly and quantitatively to the corresponding unsaturated alcohols.

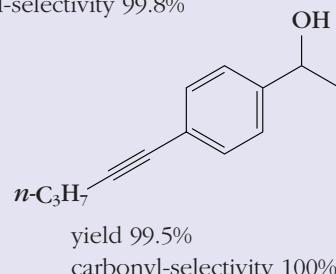
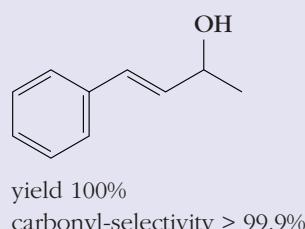
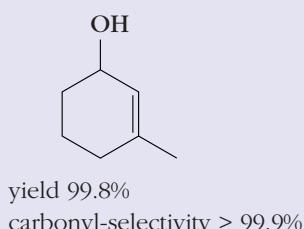
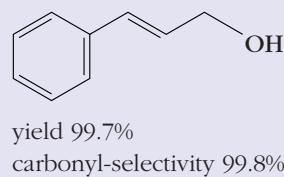
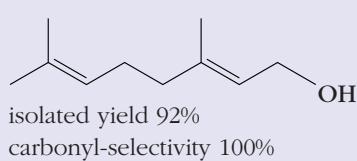


R = H, alkyl, aryl

Un = olefin-, or acetylene-containing group

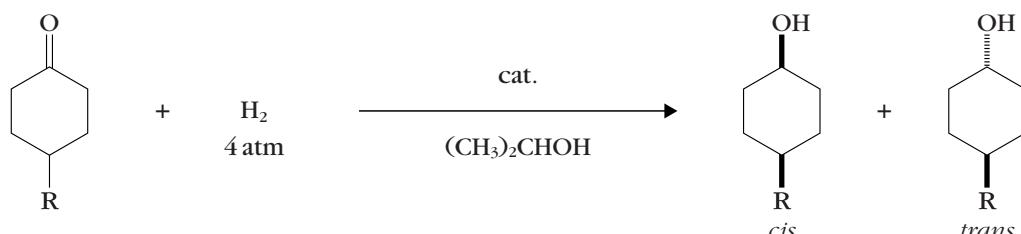
cat. = RuCl<sub>2</sub>[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>3</sub>–NH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>–KOH (1 : 1 : 2 molar ratio)

#### Example



## 2. DIASTEREOSELECTIVE HYDROGENATION OF KETONES<sup>2)</sup>

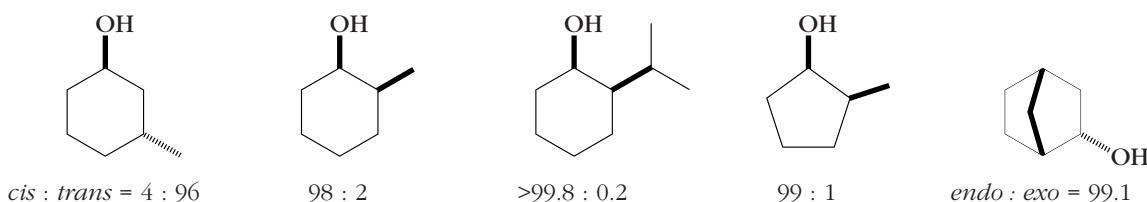
### Example 1.



cat. =  $\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_5)_3]_3-\text{NH}_2(\text{CH}_2)_2\text{NH}_2-\text{KOH}$  (1 : 1 : 2 molar ratio)

R	% yield	<i>cis</i> : <i>trans</i>
<i>t</i> -C <sub>4</sub> H <sub>9</sub>	>99	98 : 2
C <sub>6</sub> H <sub>5</sub>	>99	96 : 4
CH <sub>3</sub>	97	92 : 8

### Example 2.



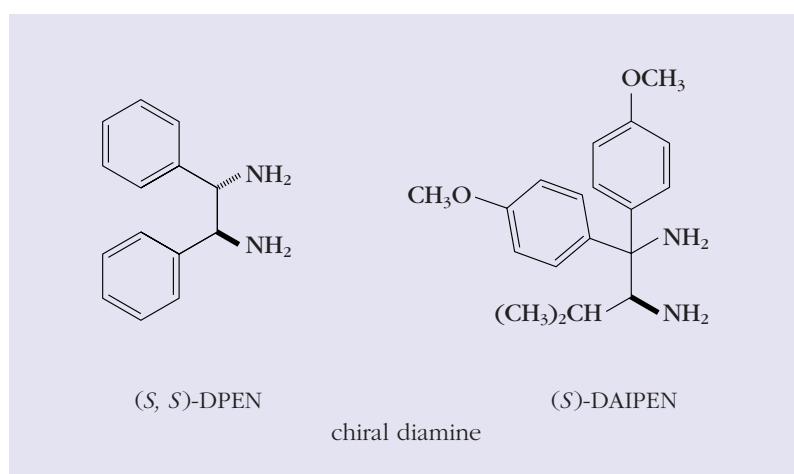
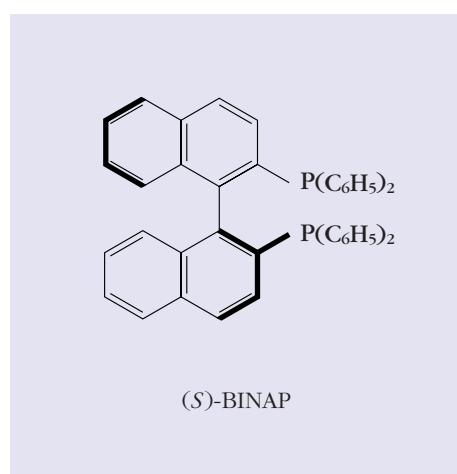
## 3. ENANTIOSELECTIVE HYDROGENATION OF KETONES<sup>1), 3), 4)</sup>



R = alkyl

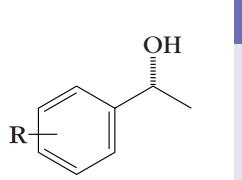
Un = aromatic, olefin-, or acetylene-containing group

cat. =  $\text{RuCl}_2(\text{binap})(\text{dmf})_n$ -chiral diamine-KOH (1 : 1 : 2 molar ratio)

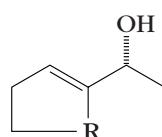


# Organics

## Examples of chiral cat : $\text{RuCl}_2[(S)\text{-binap}](\text{dmf})_n-(S,S)\text{-DPEN(or }S\text{)-DAIPEN)-KOH}$

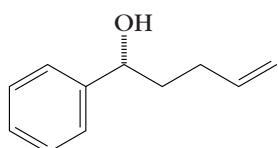


R	% ee
<i>o</i> -, <i>m</i> -, <i>p</i> -CH <sub>3</sub>	86 - 94
<i>p</i> -(CH <sub>3</sub> ) <sub>3</sub> C	96
<i>o</i> -, <i>m</i> -, <i>p</i> -Cl	90 - 94
<i>m</i> -, <i>p</i> -CH <sub>3</sub> O	88, 92

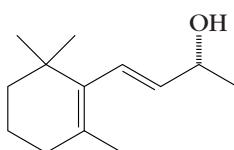


carbonyl-selectivity > 98%

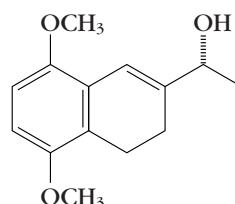
R	% ee
CH <sub>2</sub>	91
(CH <sub>2</sub> ) <sub>2</sub>	98
(CH <sub>2</sub> ) <sub>3</sub>	81



carbonyl-selectivity 99%  
99% ee



carbonyl-selectivity 99%  
92% ee



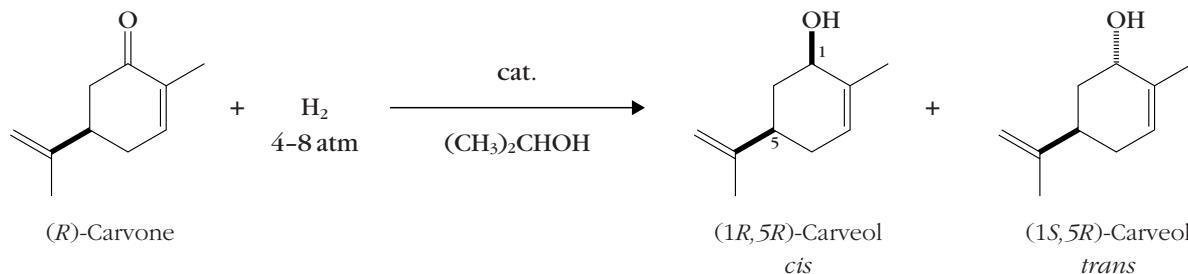
carbonyl-selectivity 99%  
94% ee

## ■ SELECTION OF THE CATALYST

Enantioselectivity is influenced by the structure and the combination (matched or mismatched) of chiral diphosphine and diamine ligands<sup>5)</sup>. Appropriate diphosphine and diamine ligands should be selected, depending on the structure of ketones, to obtain chiral alcohols in high optical yields.

Examples above mentioned show the results using the combination of *S*-configured diphosphine and *S*-configured diamine ligand. However, some cases prefer to employ the other combination of diphosphine and diamine ligands as follows. Regarding the selection of the best combination, please refer to the references or contact with our Technical Department of Reagent Division.

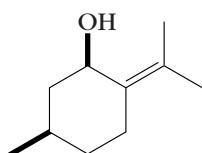
**Example 1.** The preferable combination of (*S*)-BINAP and (*R,R*)-DPEN<sup>3)</sup>



cat. =  $\text{RuCl}_2(\text{binap})(\text{dmf})_n\text{-DPEN-KOH}$

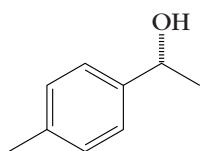
diphosphine	1,2-diamine	S/C	H <sub>2</sub> , atm	time, h	% yield of alcohol	<i>cis</i> : <i>trans</i>
( <i>S</i> )-BINAP	( <i>R,R</i> )-DPEN	500	4	3.5	100	100 : 0
( <i>S</i> )-BINAP	( <i>S,S</i> )-DPEN	500	4	16	94	87 : 13
( <i>R</i> )-BINAP	( <i>R,R</i> )-DPEN	500	8	17	99	88 : 12
( <i>R</i> )-BINAP	( <i>S,S</i> )-DPEN	500	8	17	99	34 : 66

**Example 2.** The preferable combination of (*S*)-BINAP and (*S,S*)-DPEN<sup>3)</sup>



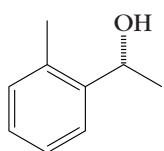
substrate : (*R*)-Pulegone  
diphosphine : (*S*)-BINAP  
diamine : (*S,S*)-DPEN  
*cis* : *trans* = 98 : 2

**Example 3.** DAIPEN complex is preferable than DPEN complex



- 1) diphosphine : (*S*)-BINAP  
1,2-diamine : (*S*)-DAIPEN  
94% ee\*
- 2) diphosphine : (*S*)-BINAP  
1,2-diamine : (*S,S*)-DPEN  
82% ee\*

**Example 4.** DPEN complex is preferable than DAIPEN complex



- 1) diphosphine : (*S*)-BINAP  
1,2-diamine : (*S*)-DAIPEN  
89% ee\*
- 2) diphosphine : (*S*)-BINAP  
1,2-diamine : (*S,S*)-DPEN  
94% ee\*

\* obtained by the two-component catalyst composed of the ready-to-use Ruthenium(II) complex and strong base

## HYDROGENATION UNDER THE ATMOSPHERIC PRESSURE OF HYDROGEN

Hydrogenation of simple ketones by two-component catalyst, composed of the ready-to-use Ruthenium(II) complex and strong base, takes place even under the atmospheric pressure of hydrogen, so that hydrogenation can be achieved without a pressure vessel such as an autoclave. In these cases, the enantioselectivities are almost the same as those under higher pressures of hydrogen. When the rate of the reaction is insufficient, increasing the molar ratio of the catalyst to the substrate provides the product in the higher yield in shorter reaction time. (cat. = Ru complex-(CH<sub>3</sub>)<sub>3</sub>COK (molar ratio 1 : 10)).

substrate	Ru-complex	S/C	time, h	% yield of alcohol	% ee*
$\beta$ -Ionone	RuCl <sub>2</sub> [P( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ] <sub>2</sub> [NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> ]	500	24	100	—
1'-Acetonaphthone	RuCl <sub>2</sub> [( <i>R</i> )-binap][( <i>R</i> , <i>R</i> )-dpen]	500	12	100	97
1'-Acetonaphthone	RuCl <sub>2</sub> [( <i>R</i> )-binap][( <i>R</i> , <i>R</i> )-dpen]	2000	24	100	97
1'-Acetonaphthone	RuCl <sub>2</sub> [( <i>R</i> )-binap][( <i>R</i> , <i>R</i> )-dpen]	10000	24	52	97
1'-Acetonaphthone	RuCl <sub>2</sub> [( <i>R</i> )-binap][( <i>R</i> , <i>R</i> )-dpen]	10000	48	84	97

\* enantiomeric excess, % of (*S*)-1-(1'-Naphthyl)ethanol

## PROCEDURE FOR HYDROGENATION OF KETONES (with a pressure vessel)

cat. = RuCl<sub>2</sub>(binap)(dpen), S/C = 2000 (molar ratio)

Reaction vessel (internal volume : 100 ml)<sup>\*1</sup>

the ready-to-use Ruthenium(II) complex<sup>\*2</sup> : ca. 10 mg (0.01 mmol)  
(a solid substrate of ketone should be added with the ready-to-use Ruthenium(II) complex at this point.  
Ketone substrate<sup>\*3</sup> : 20 mmol)

Purging away the inside gas of the vessel and displacing with argon or nitrogen gas (1 time)

Ketone substrate<sup>\*3</sup> : 20 mmol  
0.01 M solution of potassium alkoxide in 2-propanol<sup>\*4,\*5</sup> : 10ml (0.1mmol)

Purging away the inside gas of the vessel and displacing with argon gas<sup>\*6</sup>

Purging away the inside gas of the vessel and displacing with hydrogen gas (3–5 times)<sup>\*7</sup>

Pressurizing with hydrogen gas (9 atm)

Hydrogenation<sup>\*8</sup>

Isolating the alcohol product

\*1 : In case of hydrogenation at the lower hydrogen pressure than 9 atm, a pressure resistant glass vessel with guard jacket can be used, as well as a stainless steel autoclave.

\*2 : Ruthenium(II) complex can be handled in the air, however, it should be kept in inert gas for a long term preservation.

\*3 : Because this hydrogenation is sensitive even to a small amount of acid, acidic impurities should be carefully removed. By the following step, washing the substrate dissolved in appropriate solvent with an aqueous KOH solution, then drying the solution with Na<sub>2</sub>SO<sub>4</sub> anhydride, the substrate can be purified with an appropriate purity.

\*4 : The strong base more than 2 times of Ruthenium(II) complex in molar ratio is required for hydrogenation of a ketone substrate. Unstable enones against the base may polymerize this conditions. In that case, the concentration of the strong base should be optimized, or K<sub>2</sub>CO<sub>3</sub>, a weak base cocatalyst in place of the strong base, is effective.

\*5 : When a ketone substrate is hard to dissolve in 2-propanol, toluene or tetrahydrofuran can be used as a co-solvent (for example, 2-propanol : toluene = 1 : 1 or 2-propanol : tetrahydrofuran = 1 : 1).

\*6 : Depending on a substrate, even a small amount of air should be more strictly eliminated. Freeze-pump-thaw and purifying technique can be recommended (refer to the procedure in the literature : *Purification of Laboratory Chemicals*, 3rd Edition, p 19, Pergamon Press (1998)).

\*7 : For keeping safety, purifying with hydrogen in a pressure vessel and hydrogenation procedure should be operated in a draft-chamber (refer to the procedure in the literature : M. Kitamura, M. Tokunaga, T. Ohkuma, and R. Noyori, *Org. Synth.*, 71, 1-13, (1993))

\*8 : After the completion of hydrogenation, the hydrogen pressure will be decreased up to the range of 4-5 atm.

Hydrogenation with more than 2000 substrate/catalyst molar ratio can be operated by the same procedure as mentioned above. 100% yield was achieved with 2,400,000 substrate/catalyst molar ratio by the optimization of the conditions, such as concentration of the strong base and hydrogen pressure (strong base/Ruthenium(II) complex = 24000/1, hydrogen pressure = 45 atm)<sup>6)</sup>. Regarding details of the operating condition, please refer to the references or contact us.

## Reference

1. T. Ohkuma, H. Ooka, T. Ikariya, and R. Noyori, Preferential Hydrogenation of Aldehydes and Ketone, *J. Am. Chem. Soc.*, 117, 10417-10418 (1995).
2. T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, and R. Noyori, Stereoselective Hydrogenation of Simple Ketones Catalyzed by Ruthenium(II) Complexes, *J. Org. Chem.*, 61, 4872-4873 (1996).
3. T. Ohkuma, H. Ikehira, T. Ikariya, and R. Noyori, Asymmetric Hydrogenation of Cyclic  $\alpha,\beta$ -Unsaturated Ketones to Chiral Allylic Alcohols, *Synlett*, 467-468 (1997).
4. T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, and R. Noyori, Practical Enantioselective Hydrogenation of Aromatic Ketones, *J. Am. Chem. Soc.*, 117, 2675-2676 (1995).
5. T. Ohkuma, R. Noyori, Enantioselective Hydrogenation of Simple Ketones, *J. Syn. Org. Chem., Japan*, 57, 553-563 (1996).
6. H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, and R. Noyori, *trans*-[RuCl<sub>2</sub>(phosphane)<sub>2</sub>(1,2-diamine)] and Chiral *trans*-[RuCl<sub>2</sub>(diphosphane)(1,2-diamine)] : Shelf-Stable Precatalysts for Rapid, Productive, and Stereoselective Hydrogenation of Ketones, *Angew. Chem., Int. Ed. Engl.*, 37, 1703-1707 (1998).
7. T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, and R. Noyori, Asymmetric Hydrogenation of Alkenyl, Cyclopropyl, and Aryl Ketones. RuCl<sub>2</sub> (xylbinap)(1,2-diamine) as a Precatalyst Exhibiting a Wide Scope, *J. Am. Chem. Soc.*, 120, 13529-13530 (1998).



## Ruthenium Complexes

Cat.No.	Product Name	Package Size
11400-65	Dichlorobis(triphenylphosphine)(1,2-ethanediamine)ruthenium(II) RuCl <sub>2</sub> [P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> ] <sub>2</sub> [NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> ]	1g
11400-95		200mg
11401-65	Dichlorobis(tri- <i>p</i> -tolylphosphine)(1,2-ethanediamine)ruthenium(II) RuCl <sub>2</sub> [P( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ] <sub>2</sub> [NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> ]	1g
11401-95		200mg
11403-65	Dichloro[( <i>S</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][( <i>S,S</i> )-1,2-diphenylethanediamine]ruthenium(II) RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>S,S</i> )-dpen]	1g
11403-95		200mg
11409-65	Dichloro[( <i>S</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][( <i>S</i> )-1,1'-bis( <i>p</i> -methoxyphenyl)-2-isopropylethane-1,2-diamine]ruthenium(II) RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>S</i> )-daipen]	1g
11409-95		200mg
11402-65	Dichloro[( <i>S</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][( <i>R,R</i> )-1,2-diphenylethanediamine]ruthenium(II) RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>R,R</i> )-dpen]	1g
11402-95		200mg
11405-65	Dichloro[( <i>R</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][( <i>S,S</i> )-1,2-diphenylethanediamine]ruthenium(II) RuCl <sub>2</sub> [ <i>(R</i> )-binap][( <i>S,S</i> )-dpen]	1g
11405-95		200mg
11404-65	Dichloro[( <i>R</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][( <i>R,R</i> )-1,2-diphenylethanediamine]ruthenium(II) RuCl <sub>2</sub> [ <i>(R</i> )-binap][( <i>R,R</i> )-dpen]	1g
11404-95		200mg
11408-65	Dichloro[( <i>R</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][( <i>R</i> )-1,1'-bis( <i>p</i> -methoxyphenyl)-2-isopropylethane-1,2-diamine]ruthenium(II) RuCl <sub>2</sub> [ <i>(R</i> )-binap][( <i>R</i> )-daipen]	1g
11408-95		200mg

## Hydrogenation Catalysts Trial Kits

Cat.No.	Product Name	Content	
18707-96	Hydrogenation Catalysts Trial Kit 1	RuCl <sub>2</sub> [P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> ] <sub>2</sub> [NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> ] RuCl <sub>2</sub> [P( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ] <sub>2</sub> [NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> ]	20mg 20mg
18708-96	Hydrogenation Catalysts Trial Kit 2	RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>S,S</i> )-dpen] RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>S</i> )-daipen]	20mg 20mg
18709-96	Hydrogenation Catalysts Trial Kit 3	RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>S,S</i> )-dpen] RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>S</i> )-daipen] RuCl <sub>2</sub> [ <i>(S</i> )-binap][( <i>R,R</i> )-dpen] RuCl <sub>2</sub> [ <i>(R</i> )-binap][( <i>S,S</i> )-dpen]	20mg 20mg 20mg 20mg
34062-95	Potassium <i>tert</i> -butoxide, in 2-propanol	0.01mol/l <i>tert</i> -C <sub>4</sub> H <sub>9</sub> OK in 2-propanol	100ml

## Auxiliary Chiral Ligands

Cat.No.	Product Name	Package Size	
04970-55	( <i>S</i> )-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl	( <i>S</i> )-(-)-BINAP	5g
04970-65			1g
04969-55	( <i>R</i> )-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl	( <i>R</i> )-(+)-BINAP	5g
04969-65			1g
11406-65	( <i>S</i> )-1,1'-Bis( <i>p</i> -methoxyphenyl)-2-isopropylethane-1,2-diamine	( <i>S</i> )-DAIPEN	1g
11406-95			200mg
11407-65	( <i>R</i> )-1,1'-Bis( <i>p</i> -methoxyphenyl)-2-isopropylethane-1,2-diamine	( <i>R</i> )-DAIPEN	1g
11407-95			200mg



**KANTO CHEMICAL CO., INC.**

REAGENT DIVISION

MARUSAN Bldg-2F 11-5, Nihonbashi-Honcho 3-chome, Chuo-ku, Tokyo 103-0023

Telephone +813-3639-8301

Telefax +813-3639-9435

<http://www.kanto.co.jp> [reag-info@gms.kanto.co.jp](mailto:reag-info@gms.kanto.co.jp)