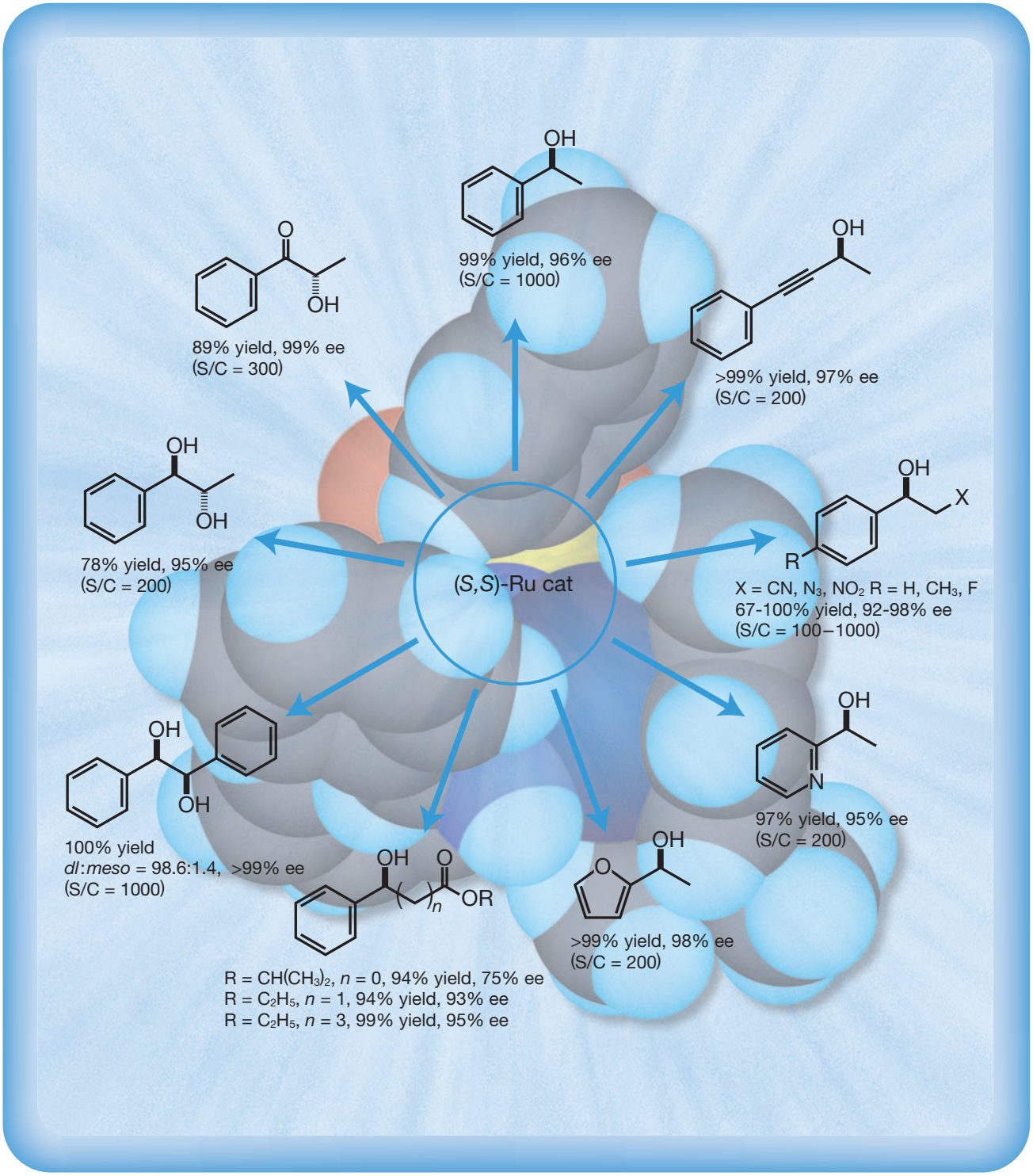
Asymmetric Transfer Hydrogenation Catalysts

Kanto Reagents



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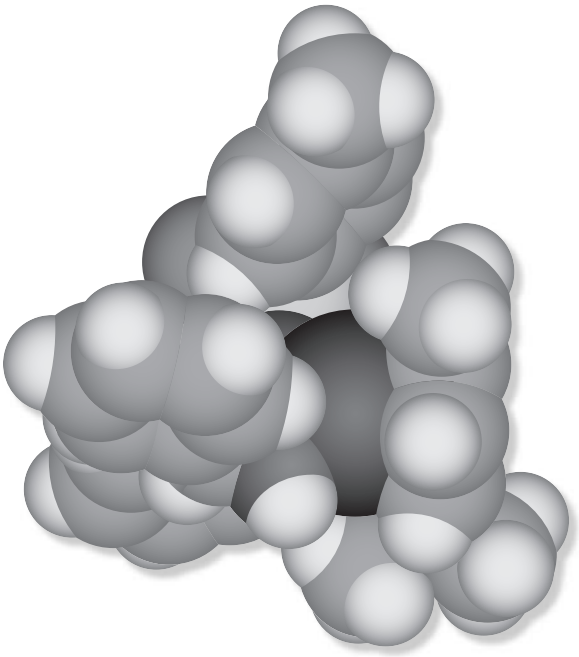


Contents

Introduction

Optically active alcohols and amines are useful intermediates of pharmaceuticals or pesticides. Chiral ruthenium complexes with chiral diamine ligands, which were discovered by NOYORI Molecular Catalysis Project of Exploratory Research for Advanced Technology (ERATO) by Japan Science and Technology Corporation (JST), are extremely effective catalysts for the asymmetric transfer hydrogenation of ketones [1)-11)] and imines [9), 12), 13)] leading to optically active alcohols and amines with high optical purities in high yields.

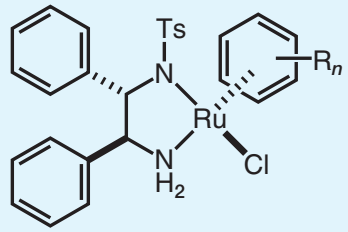
As organic compounds such as 2-propanol and formic acid are used as hydrogen donors in this asymmetric reaction, this reaction can be easily implemented using laboratory equipments such as flasks and is therefore highly versatile.

KANTO CHEMICAL CO.,INC. launches of pre-formed chiral ruthenium complexes, which are easily handled and can be used for this asymmetric transfer hydrogenation.

Asymmetric Transfer Hydrogenation Catalysts

Chloro complexes

RuCl[(S,S)-Tsdpen](η^6-arene)



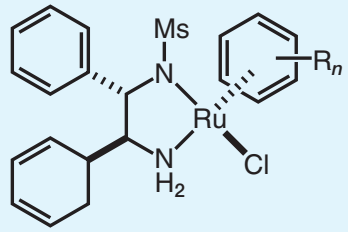
Ts = $SO_2C_6H_4$-*p*-CH_3

1a ; R_n = 1-CH_3-4-$CH(CH_3)_2$

1b ; R_n = 1,3,5-$(CH_3)_3$

1c ; R_n = 1,2,3,4,5,6-$(CH_3)_6$

RuCl[(S,S)-Msdpen](η^6-arene)

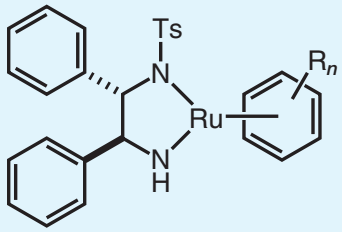


Ms = SO_2CH_3

2a ; R_n = 1-CH_3-4-$CH(CH_3)_2$

Amide complexes

Ru[(S,S)-Tsdpen](η^6-arene)



Ts = $SO_2C_6H_4$-*p*-CH_3

3a ; R_n = 1-CH_3-4-$CH(CH_3)_2$

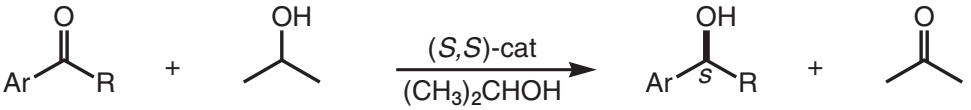
3b ; R_n = 1,3,5-$(CH_3)_3$

1. Asymmetric transfer hydrogenation of ketones [1)-10)] (Synthesis of optically active secondary alcohols)

《Selection of hydrogen donors》

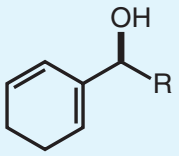
Organic compounds such as 2-propanol and formic acid can be used as the hydrogen donors for this reaction. As the reaction in 2-propanol is reversible, the reaction is proceeded after adjusting the substrate concentration and S/C (the substrate/catalyst molar ratio). Conversely, the reaction which uses formic acid as a hydrogen donor is not reversible, and therefore even if the reaction is implemented with a high substrate concentration or high S/C, a high yield of optically active alcohols with high optical purities can be obtained.

●Reaction with the 2-propanol as a hydrogen donor [1), 4)-6), 8)]

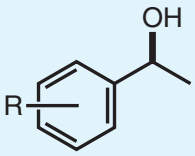


93～98% yield

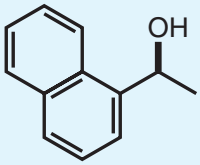
(*S,S*)-cat = $[RuCl_2(mesitylene)]_2$—(*S,S*)-TsDPEN—KOH(mole ratio 1:2:5)



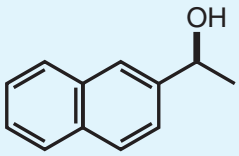
R = CH_3 97% ee
R = C_2H_5 97% ee



R = *m*-Cl 98% ee
R = *p* -Cl 93% ee
R = *m*-OCH_3 96% ee

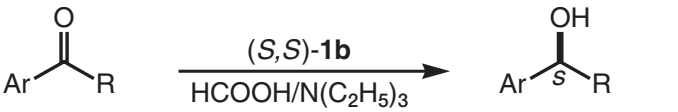


93% ee

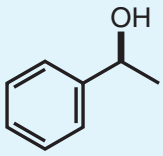


98% ee

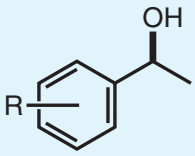
●Reaction with the formic acid as a hydrogen donor [2), 4)]



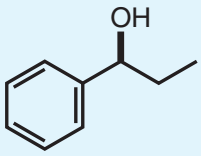
93～99% yield



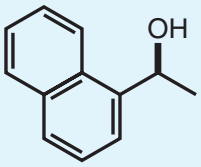
S/C = 1000
96% ee



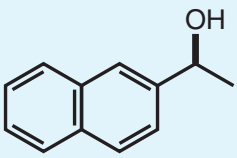
S/C = 200
R = *m*-Cl 97% ee
R = *p* -Cl 95% ee
R = *m*-OCH_3 98% ee
R = *p* -OCH_3 97% ee



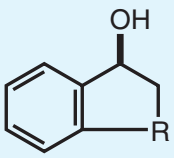
S/C = 200
97% ee



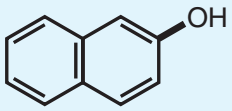
S/C = 200
83% ee



S/C = 200
96% ee



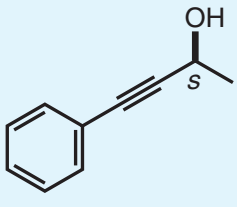
S/C = 200
R = CH_2 99% ee
R = $(CH_2)_2$ 99% ee



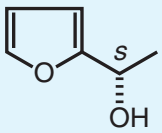
S/C = 200
70% yield, 83% ee

《Selection of substrates》

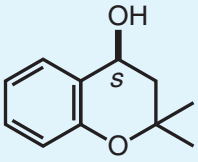
In addition to the simple ketones referred to above, the reaction can also proceed efficiently and without loss of the functional group in the case of ketones that have a functional group such as a carbon-carbon multiple bond or a heteroatom, producing optically active alcohols with high optical purities. For example, acetylenic alcohol with 97% ee can be obtained in a high yield by an reaction of acetylene-ketone. The reaction of ketones that have a furan ring or thiophene ring also proceed properly, resulting in alcohols with high optical purities. Moreover ketone having a pyridyl group also react well, resulting in optically active pyridyl alcohol with 95% ee. This reaction can also be applied to the reaction of ketones that have a multiple number of functional groups such as a pyridyl group, carbon-carbon multiple bond or an ester group, allowing the successful synthesis of the key intermediate of a carbonic anhydrase inhibitor, MK-0417. Furthermore, the reaction of unsymmetrically substituted 1, 2- diketones leads to optically active α-hydroxyketones or optically active 1, 2- diols separately depending on the reaction conditions. Further, the reaction of acetophenone derivatives with a cyano group, azido group or nitro group in the second position also proceeds efficiently, producing optically active alcohols. These compounds can be easily reduced by usual reducing agents, leading to optically active amino alcohols, which are useful synthetic intermediates for pharmaceutical products.



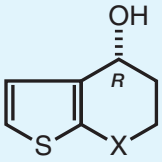
cat : (*S,S*)-**3b**
S/C = 200
>99%, 97% ee[4)]



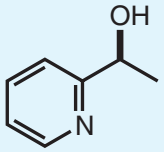
cat : (*S,S*)-**1b**
S/C = 200
>99%, 98% ee[2), 4)]



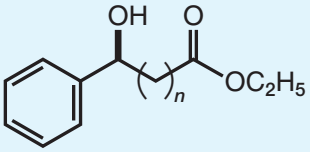
cat : (*S,S*)-**1b**
S/C = 200
47%, 98% ee[2), 4)]



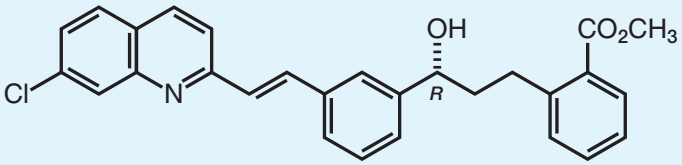
cat : (*R,R*)-**1b**
S/C = 200
X = S 95%, 99% ee
X = SO_2 95%, 98% ee[2), 4)]



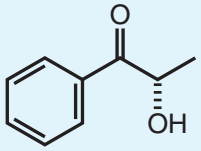
cat : (*S,S*)-**1a**
S/C = 200
>97%, 95% ee[5)]



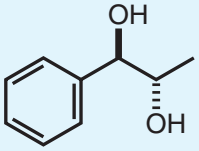
cat : (*S,S*)-**1a**
n = 1 94%, 93% ee[4)]
n = 3 99%, 95% ee[2)]



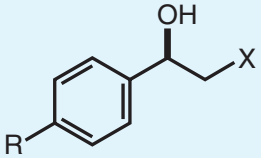
cat : (*R,R*)-**1b**
S/C = 200
68%, 92% ee[2),4)]



cat : (*S,S*)-**1a**
S/C = 300 (10 ℃)
89%, 99% ee[6)]



cat : (*S,S*)-**1a**
S/C = 200 (40 ℃)
78%, 95% ee[6)]

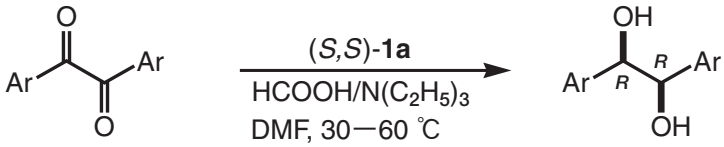


X : CN, N_3, NO_2[7)]
cat : (*S,S*)-**1a**
S/C = 100—1000 (30 ℃)

R = H; X = CN 100%, 98%ee
R = H; X = N_3 65%, 92%ee
R = H; X = NO_2 90%, 98%ee
R = F; X = NO_2 95%, 96%ee
R = CH_3; X = NO_2 67%, 95%ee

2. Asymmetric transfer hydrogenation of benzyls [11] (Synthesis of optically active hydrobenzoins)

Benzyls can be rapidly reduced at room temperature with a chiral ruthenium catalyst in a mixture of formic acid/triethylamine, producing optically active hydrobenzoins with high optical purities almost quantitatively.

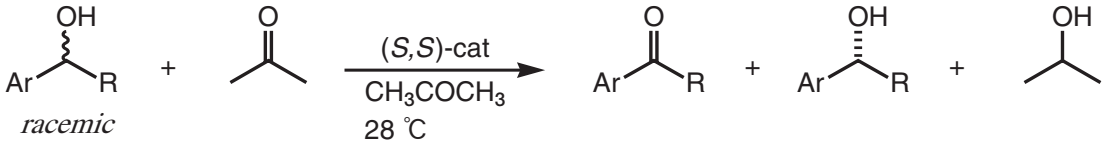


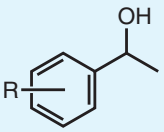
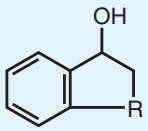
S/C = 1000—2000

Ar = C_6H_5 100%, *dl*:*meso* = 98.6:1.4, >99% ee
Ar = *p*-CH_3-C_6H_4 67%, *dl*:*meso* = 96.7:3.3, >99% ee
Ar = *p*-CH_3O-C_6H_4 75%, *dl*:*meso* = 94.4:5.6, >99% ee
Ar = *p*-F-C_6H_4 100%, *dl*:*meso* = 94.2:5.8, >99% ee

3. Kinetic resolution of secondary alcohols [4), 12)]

As asymmetric transfer hydrogenation in 2-propanol is a reversible reaction, it has previously been difficult to implement the high enantioselectivities in the reduction of high-reduction-potential ketones with an electron donating group on the aromatic ring. However, through the kinetic resolution of racemic alcohols using a chiral ruthenium catalyst, optically active alcohols with high optical purities are now obtainable. This method can also be applied to the synthesis of natural products such as (-)-chokol G[14] and (-) -pentenomycin[15] .

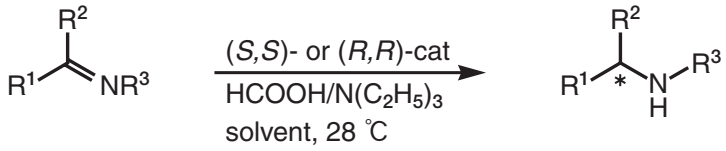


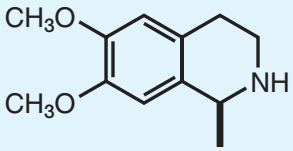
substrate	catalyst	time, h	unreacted alchol			k_f/k_s
			recovery, %	ee, %	config.	
						
R = H	**3a**	36	50	92	*R*	>80
R = *p*-OCH_3	**3a**	22	47	92	*R*	>30
R = *p*-$N(CH_3)_2$	**3b**	30	44	98	*R*	>30
						
R = CH_2	**3a**	6	47	97	*R*	>40
R = $(CH_2)_2$	**3a**	6	49	99	*R*	>50

S/C = 500

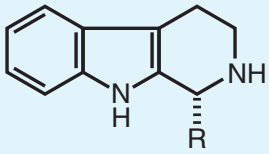
4. Asymmetric transfer hydrogenation of imines [4), 15)]

Up until now, it has been difficult to achieve the efficient synthesis of optically active amines through the catalytic asymmetric hydrogenation of imines. However, the reduction of imines using this catalyst is efficient, and optically active amines with a high optical purities can be obtained in high yields.

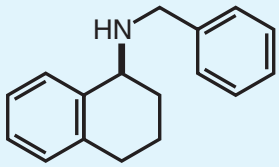




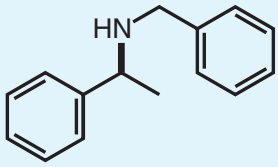
cat : (*S,S*)-**1a**
S/C = 1000
97%, 94% ee (*R*)



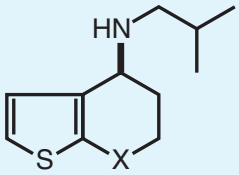
cat : (*S,S*)-**1a**
S/C = 200
R = CH_3 86%, 97% ee (*R*)
R = C_6H_5 83%, 96% ee (*R*)



cat : RuCl[(*S,S*)-ArSO_2dpen](η^6-benzene)
Ar = 1-naphthyl
S/C = 100
90%, 89% ee (*S*)



cat : RuCl[(*S,S*)-ArSO_2dpen](η^6-benzene)
Ar = 1-naphthyl
S/C = 200
72%, 77% ee (*S*)



cat : RuCl[(*S,S*)-ArSO_2dpen](η^6-benzene)
Ar = 1-naphthyl
S/C = 200
X = S 82%, 85% ee (*S*)
X = SO_2 84%, 88% ee (*S*)

Standard operating procedures for the asymmetric transfer hydrogenation of ketones

Example procedures are shown below for the **1)** production of optically active alcohols by the reduction of the ketonic substrates [2] and **2)** production of optically active hydrobenzoin from benzyl [11] , both using a chiral ruthenium catalyst in a mixture of formic acid and triethylamine.

1) Synthesis of optically active alcohols

Under an inert gas atmosphere, add the ketononic substrate (5.0 mmol) and RuCl [(S,S)-Tsdpen] (mesitylene) (15.5mg, 0.025 mmol) into a Shrenk flask.

↓ ← Add 2.5 ml of a mixture of formic acid/triethylamine note 1. note 2

Mix for 48-hours at 28°C. note 3

↓

Dilute the reaction mixture with water, and extract with ethyl acetate or similar solvents. Wash the organic layer with a sodium hydrogen carbonate solution and then with a saturated sodium chloride solution.

↓

The optically active alcohols can be obtained through the prescribed refining operations. note 4

2) Synthesis of optically active hydrobenzoin

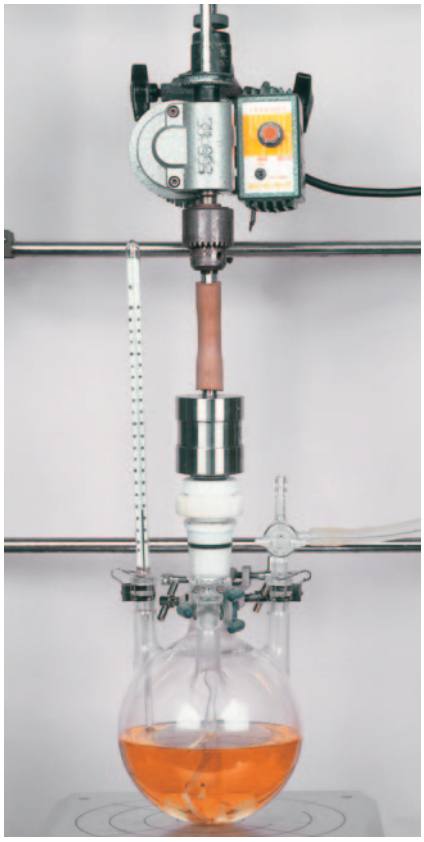
In an inert gas atmosphere, mix triethylamine (19.0 ml, 136 mmol) and formic acid (8.7 ml, 230 mmol) in a Shrenk flask while keeping the mixture cool. note 1

↓ ← Add benzyl (11.0g, 52.3 mol)note5 and RuCl [(S,S)-Tsdpen]-(*p*-cymene) (33.3 mg, 0.523 mmol)note2

Mix for 24-hours at 40°C. note 3

↓

Add water to the reaction mixture, and filter out the deposited crystals. (*R,R*)- Hydrobenzoin can be obtained from the recrystallization with ethanol. note 4



Note 1: The original research paper uses an azeotropic mixture but a mixture of formic acid and triethylamine in the optimum ratio can also be used without distillation. We recommends investigating the optimum mixture ratio of formic acid and triethylamine for the substrate, since the optimum ratio varies depending on the substrate.

Note 2: Do not induce the reaction in a closed system, since carbon dioxide will be released. For example, as shown in the photograph on the previous page, insert an inert gas line or attach a highly airtight gas balloon.

Note 3: Even if the reaction temperature is raised, the lowering of the optical yield is minimal. Therefore please optimize the reaction temperature and time according to the reactivity of the substrate.

Note 4: The residual catalyst can be removed by filtering the organic layer through a short column of silica gel.

Note 5: An optically active hydrobenzoin can also be obtained from the racemic benzoin as a high yield. See the references for details.

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Products

■Asymmetric Transfer Hydrogenation Catalysts

Product Name	Cat.No.	Package Size
Chloro [(1*S*, 2*S*)-*N*- (*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium (Ⅱ) **RuCl [(*S,S*)-Tsdpen] (*p*-cymene)** Chloro complex; (*S,S*)-**1a**	08153-65	1g
	08153-95	200mg
Chloro [(1*R*, 2*R*)-*N*- (*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium (Ⅱ) **RuCl [(*R,R*)-Tsdpen] (*p*-cymene)** Chloro complex; (*R,R*)-**1a**	08154-65	1g
	08154-95	200mg
Chloro [(1*S*, 2*S*)-*N*- (*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(mesitylene)ruthenium (Ⅱ) **RuCl [(*S,S*)-Tsdpen] (mesitylene)** Chloro complex; (*S,S*)-**1b**	08174-65	1g
	08174-95	200mg
Chloro [(1*S*, 2*S*)-*N*- (*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(mesitylene)ruthenium (Ⅱ) **RuCl [(*R,R*)-Tsdpen] (mesitylene)** Chloro complex; (*R,R*)-**1b**	08173-65	1g
	08173-95	200mg
Chloro [(1*S*, 2*S*)-*N*-methanesulfonyl-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium (Ⅱ) **RuCl [(*S,S*)-Msdpen] (*p*-cymene)** Chloro complex; (*S,S*)-**2a**	08176-65	1g
	08176-95	200mg
Chloro [(1*R*, 2*R*)-*N*-methanesulfonyl-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium (Ⅱ) **RuCl [(*R,R*)-Msdpen] (*p*-cymene)** Chloro complex; (*R,R*)-**2a**	08175-65	1g
	08175-95	200mg
[(1*S*, 2*S*)-*N*- (*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium (Ⅱ) **Ru [(*S,S*)-Tsdpen] (*p*-cymene)** Amide complex; (*S,S*)-**3a**	41067-65	1g
	41067-95	200mg
[(1*R*, 2*R*)-*N*- (*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium (Ⅱ) **Ru [(*R,R*)-Tsdpen] (*p*-cymene)** Amide complex; (*R,R*)-**3a**	41066-65	1g
	41066-95	200mg

＜Quality certification＞

Every lot of above products is certified the quality by the performance test.

Ex. RuCl[(*S*,*S*)-Tsdpen](*p*-cymene)

Lot No.＊＊＊＊＊＊＊＊

substrate	yield	hydrobenzoin	
		dl : meso	optical purity
benzil	100 %	97.8 : 2.2	100% ee (*R,R*)

Conditions: S/C = 1000, $HCO_2H/(C_2H_5)_3N$ = 4.4/2.6, 40 ℃, 24h

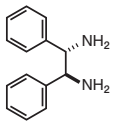
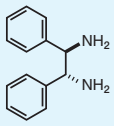
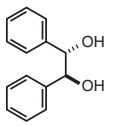
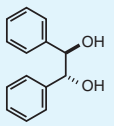
■Auxiliary Chliral Ligands

Product Name	Optical Purity	Cat.No.	Package Size
(1*S*, 2*S*)-*N*-(*p*-Toluenesulfonyl)-1,2-diphenylethanediamine (*S,S*)-TsDPEN	>99% ee (HPLC)	41051-55	5 g
		41051-65	1g
(1*R*, 2*R*)-*N*-(*p*-Toluenesulfonyl)-1,2-diphenylethanediamine (*R,R*)-TsDPEN	>99% ee (HPLC)	41052-55	5g
		41052-65	1g
(1*S*, 2*S*)-*N*-(Methanesulfonyl)-1,2-diphenylethanediamine (*S,S*)-MsDPEN	>99% ee (HPLC)	25954-55	5g
		25954-65	1g
(1*R*, 2*R*)-*N* (Methanesulfonyl)-1,2-diphenylethanediamine (*R,R*)-MsDPEN	>99% ee (HPLC)	25953-55	5g
		25956-65	1g

■Ruthenium Complex

Product Name	Purity	Cat.No.	Package Size
Dichloro(*p*-cymene)ruthenim(Ⅱ), dimer $[RuCl_2(p\text{-cymene})]_2$	>99 %	11443-35	25g
		11443-55	5g
		11443-65	1g

■Chiral Compounds

Product Name	Optical Purity	Cat.No.	Package Size
(1*S*, 2*S*)-(−)-1,2-Diphenyl-1,2-ethanediamine 	>99% ee (HPLC)	11445-35	25g
		11445-55	5g
		11445-65	1g
(1*R*, 2*R*)-(+)-1,2-Diphenyl-1,2-ethanediamine 	>99% ee (HPLC)	11444-35	25g
		11444-55	5g
		11444-65	1g
(*S,S*)-(−)-Hydrobenzoin 	>99% ee (HPLC)	18618-35	25g
		18618-55	5g
(*R,R*)-(+)-Hydrobenzoin 	>99% ee (HPLC)	18617-35	25g
		18617-55	5g

■Ruthenium Salt

Product Name	Assay	Cat.No.	Package Size
Ruthenium(Ⅲ) chloride *n*-hydrate $RuCl_3 \cdot nH_2O$	>37% (as Ru)	36502-35	25g
		36502-55	5g
		36502-65	1g

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