

# TCIMAIL

number **172**



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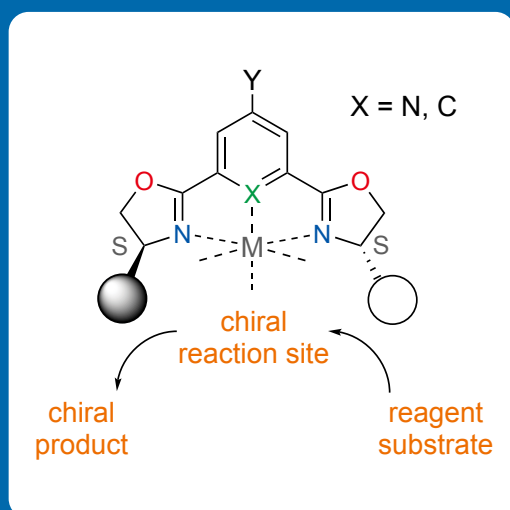
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## Asymmetric Catalysis with Chiral Bis(oxazolanyl)phenyl Transition-metal Complexes

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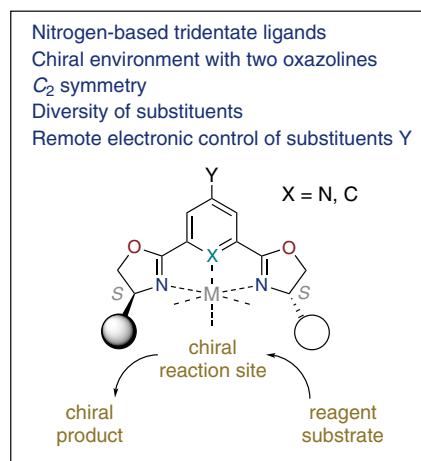
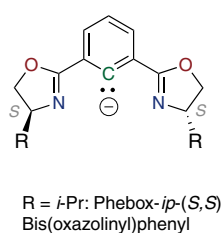
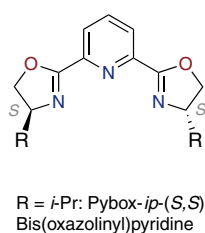
**Abstract:** The chiral ligands, *N,N,N* and *N,C,N*-tridentate ligands {bis(oxazolanyl)pyridine [Pybox] and bis(oxazolanyl)phenyl [Phebox]}, have been reviewed to show their high potential for asymmetric catalysis. The methods for preparation of their ligands and the corresponding complexes have been described. In addition, asymmetric catalytic reactions by use of Phebox complexes are introduced concisely to show high enantioselectivities with relatively lower catalyst loading (1 mol% or lower). These tridentate and nitrogen-based ligands and their complexes are useful in modern catalytic organic synthesis.

**Keywords:** Bis(oxazolanyl)pyridine, Pybox, Bis(oxazolanyl)phenyl, Phebox, Transition-metal complex, Asymmetric catalytic reaction

### 1. Introduction

Asymmetric catalysis is very important subject to provide optically active compounds, which are often applied to production of pharmaceutical and physically functional materials. Therefore, practical and environmentally benign methods have been desired for efficiently obtaining optically active compounds, especially by using transition-metal catalysts with chiral ligands. We have so far developed the optically active ligands, *N,N,N* and *N,C,N*-tridentate ligands [bis(oxazolanyl)pyridine, abbreviated as Pybox and bis(oxazolanyl)phenyl by Phebox], which consist of two lateral chiral oxazolines and one

central nitrogen atom or carbon atom, respectively (Figure 1).<sup>1,2)</sup> The oxazoline rings of the Pybox and Phebox ligands make the chiral reaction-site  $C_2$ -symmetric to form metal intermediates stereoselectively giving high enantioselectivity. The ligands are modulated by substituents on the oxazoline skeletons and at the remote para-position (Y) in order to control the catalysis sterically and electronically. In this article, preparation of the Phebox and Pybox ligands, preparation of the metal rhodium or ruthenium complexes, and development of asymmetric catalytic reactions are concisely described to show their potential for general use in organic synthesis.



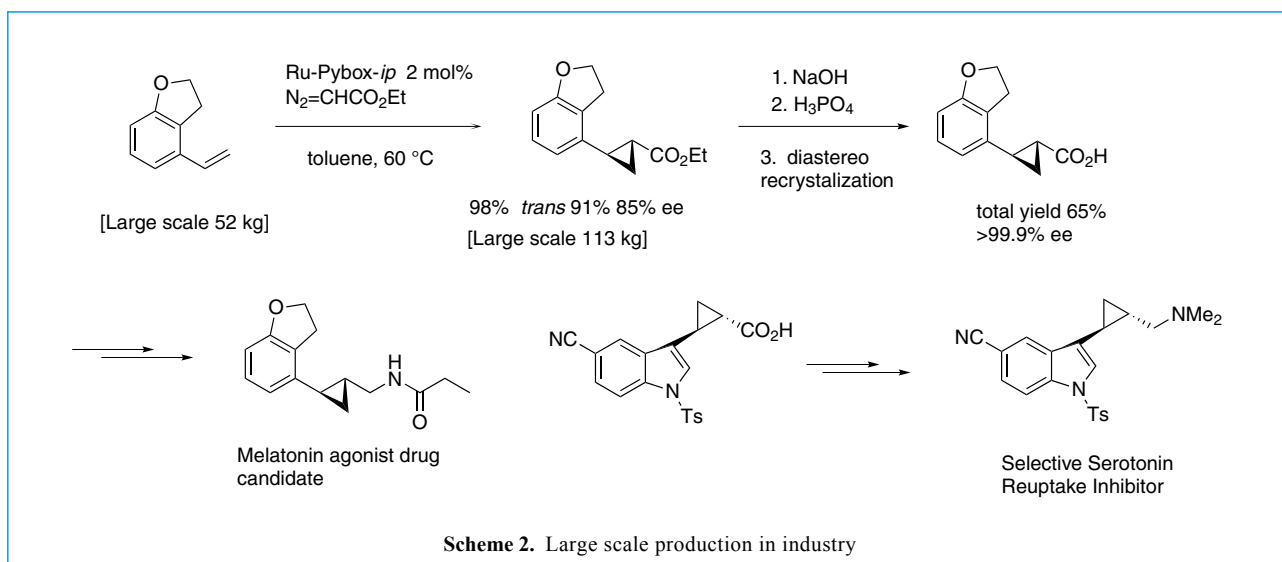
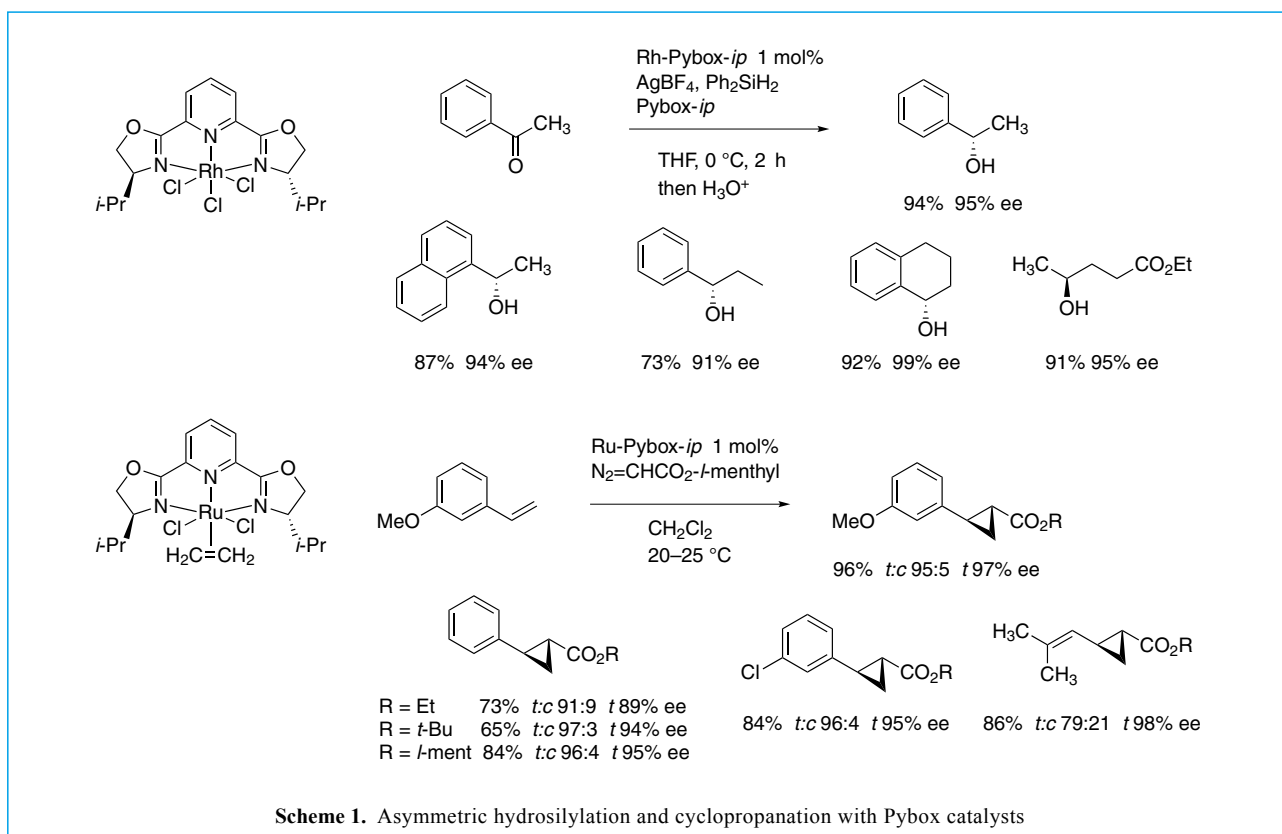
**Figure 1.** Chiral bis(oxazolanyl)pyridine and bis(oxazolanyl)phenyl ligands: features of the nitrogen-based tridentate coordination and the chiral reaction site

Rh-Pybox complexes catalyzed the hydrosilylation of ketones with diphenylsilane to give optically active secondary alcohols in high enantioselectivity up to 99% (Scheme 1).<sup>3</sup> Although Rh-Pybox trichloride itself did not show the catalytic activity for the hydrosilylation, the complex was treated with silver ion to work efficiently giving the hydrosilylation products. Next, Pybox reacts with a Ru-cymene complex under an ethylene atmosphere (1 atm) to form the corresponding ethylene complex, which exhibits high catalytic activity for asymmetric cyclopropanation of terminal alkenes with diazoacetates.<sup>4</sup> Fortunately, the *trans*-isomer of the cyclopropane product was obtained in a high *trans*-*cis* ratio up to 97% with high enantioselectivity. The mechanism was clarified by isolation of the intermediate Ru-carbene complex.<sup>4c)</sup>

The cyclopropanation with Ru-Pybox catalyst was later applied to the large scale production of pharmaceutical intermediates in industry (Scheme 2).<sup>5</sup>

Ru-Pybox catalysts have been applied to other synthetic reactions, for example, asymmetric transfer hydrogenation of ketones or asymmetric C–H amination.<sup>6,7)</sup>

Pybox ligands have been used for a number of asymmetric catalysts with a variety of metals to show high catalytic performance in enantioselective reactions. Pybox-*ip* and *ph* are now commercially available.

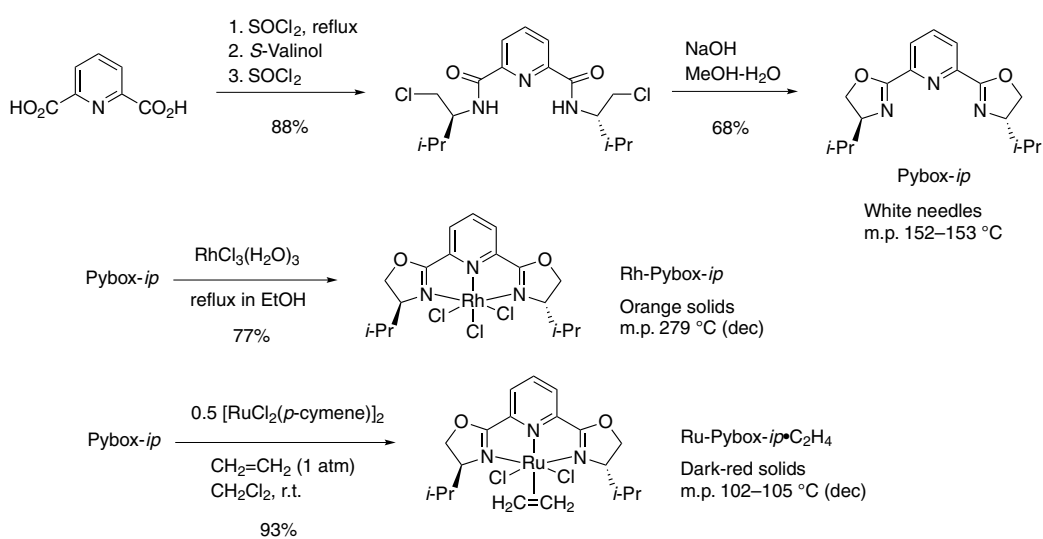


## 2. Preparation of Pybox and Phebox, and their Rh and Ru complexes

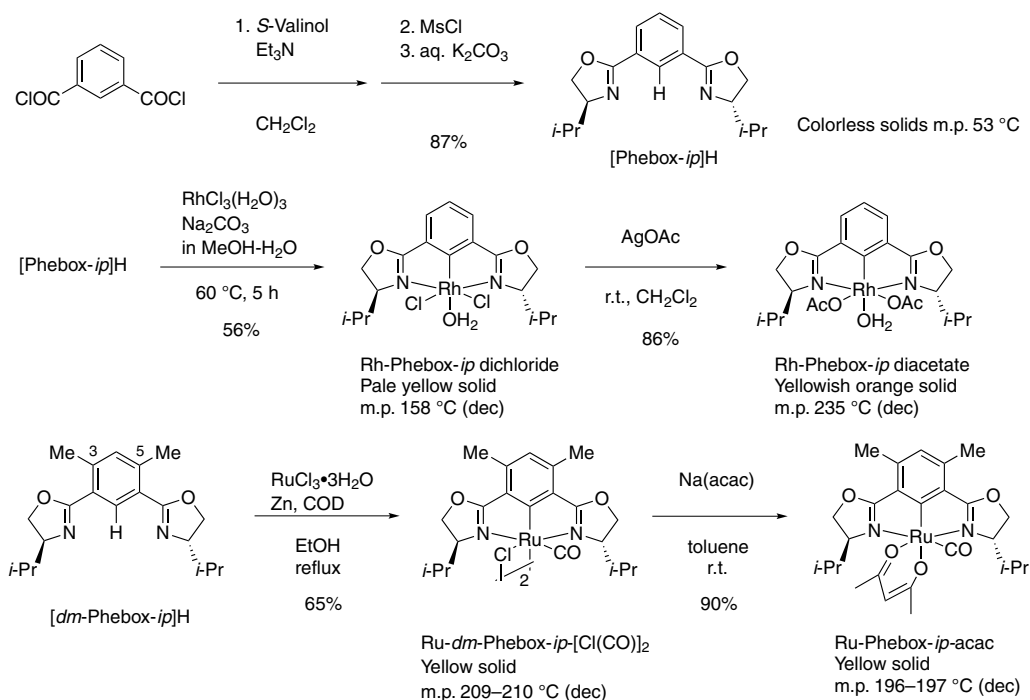
Preparation of Pybox starts from pyridine-2,6-dicarboxylic acid, which is treated with thionyl chloride giving the acid chloride followed by amide formation with valinol (Scheme 3).<sup>3</sup> Then, treatment of the amide-alcohol with thionyl chloride affords the corresponding amide-chloride, which is subsequently cyclized to form oxazoline rings by treatment with alkaline solution. Final product Pybox is purified by recrystallization to give white needles. The corresponding Rh and Ru complexes were prepared by the reaction with rhodium chloride and ruthenium-cymene complex, respectively.<sup>3,4</sup>

Preparation of the Phebox ligand precursor, [Phebox]H, starts from isophtharoyl dichloride, which is treated with valinol

followed by the reaction with MsCl forming the sulfonate and subsequently oxazoline formation with base (Scheme 4).<sup>8c</sup> In order to prepare Rh-Phebox-*ip*, a mixture of [Phebox]H and rhodium trichloride at 60 °C gives the corresponding Rh-Phebox dichloro complex, which is readily converted to the Rh-Phebox•H<sub>2</sub>O diacetate.<sup>8a</sup> Although the Ru-Phebox complex could not be prepared with [Phebox]H, the 3,5-dimethyl substituted ligand [*dm*-Phebox]H was found to be a good precursor for C–H bond formation.<sup>9,10,11</sup> The mixture of [*dm*-Phebox]H and ruthenium chloride in the presence of Zn and cyclooctadiene was heated at reflux temperature to give the corresponding Ru-Phebox complex, which was proved to be a dimeric complex. Then, the complex was converted to a monomeric form by treatment with acetylacetonate, Ru-*dm*-Phebox-*ip*-acac in good yield.<sup>9,10,11</sup>



Scheme 3. Preparation of Pybox and their Rh and Ru complexes



Scheme 4. Preparation of Phebox and their Rh and Ru complexes

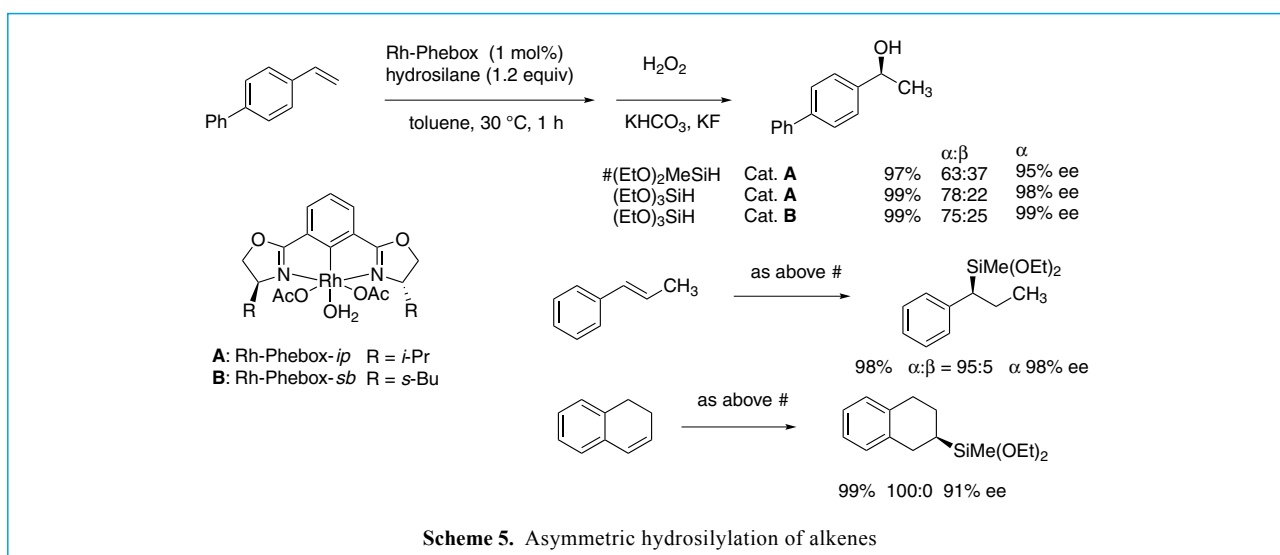
### 3. Asymmetric Hydrosilylation

#### 3-1. Asymmetric Hydrosilylation of Alkenes

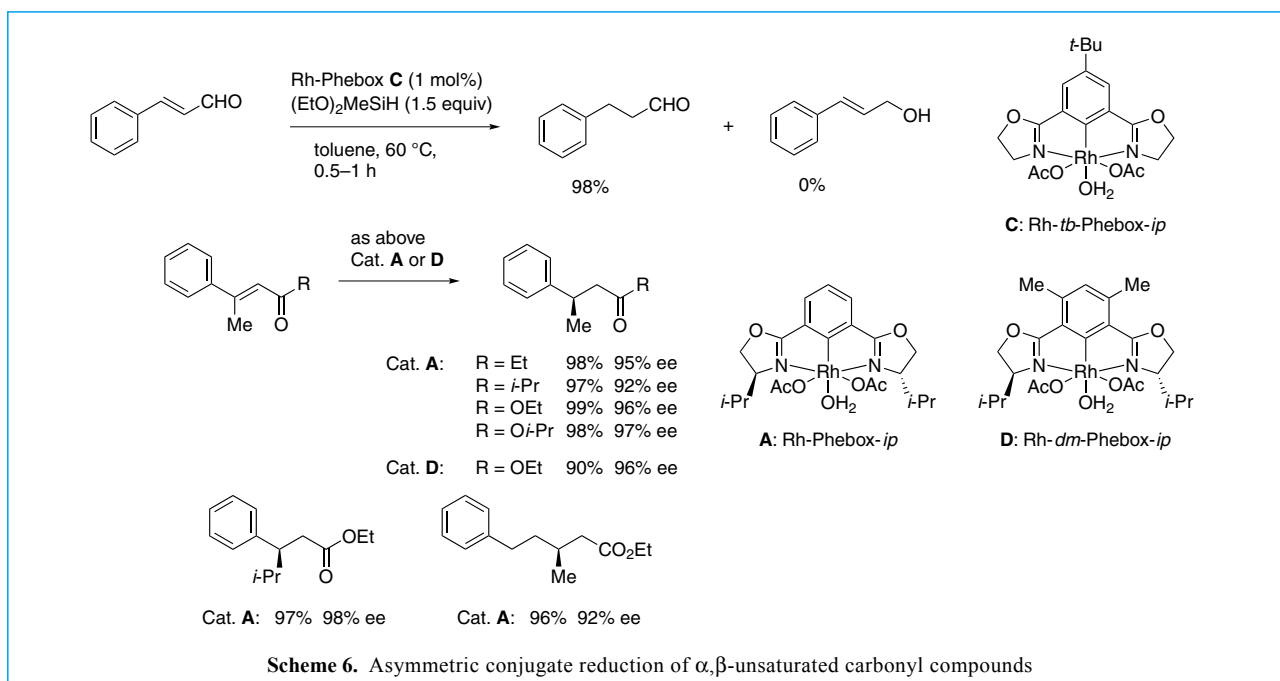
Asymmetric hydrosilylation of alkenes is a preparative method for optically active secondary alcohols via formation of silane-adducts with subsequent oxidation. Rh-Phebox-*R* diacetate complex (**A** and **B**, 1 mol%) works as a catalyst at 30 °C in 1 h efficiently to give the corresponding silane-adducts in high yields and high enantioselectivity up to 99% (Scheme 5).  $\beta$ -Methylstyrene was selectively converted to the  $\alpha$ -hydroxy compound.<sup>12)</sup>

#### 3-2. Asymmetric Conjugate Reduction

Rh-*tb*-Phebox-*ip* diacetate **C** was examined as an efficient catalyst for conjugate reduction of  $\alpha,\beta$ -unsaturated aldehydes such as cinnamaldehyde to exclusively produce the corresponding conjugate reduction products in high yields (Scheme 6).<sup>13)</sup> When chiral catalyst Rh-Phebox-*ip* **A** was used, the 1,2-reduction product was obtained in ca. 10–30% yield.  $\beta,\beta$ -Disubstituted  $\alpha,\beta$ -unsaturated ketones and esters were reduced with (EtO)<sub>2</sub>MeSiH and the acetate catalysts **A** and Rh-*dm*-Phebox-*ip* diacetate **D** to give the corresponding dihydro compounds in high yields and high enantioselectivities.<sup>8a,14,15)</sup>



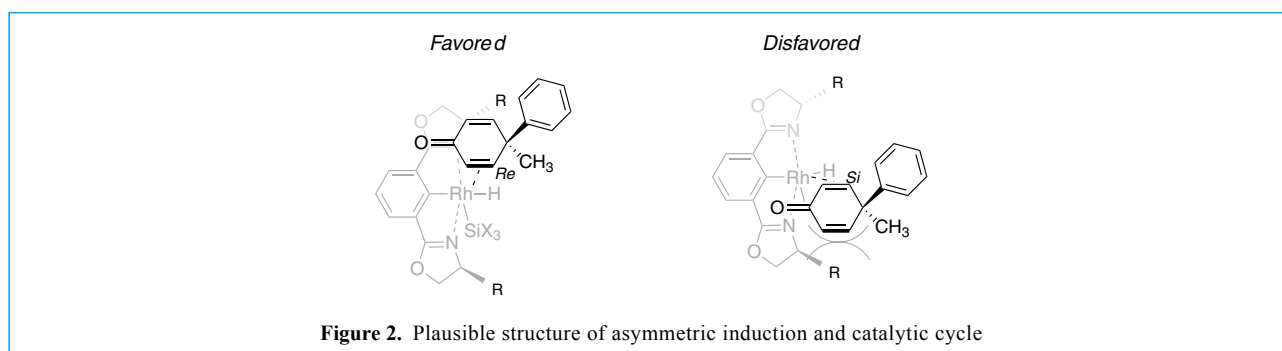
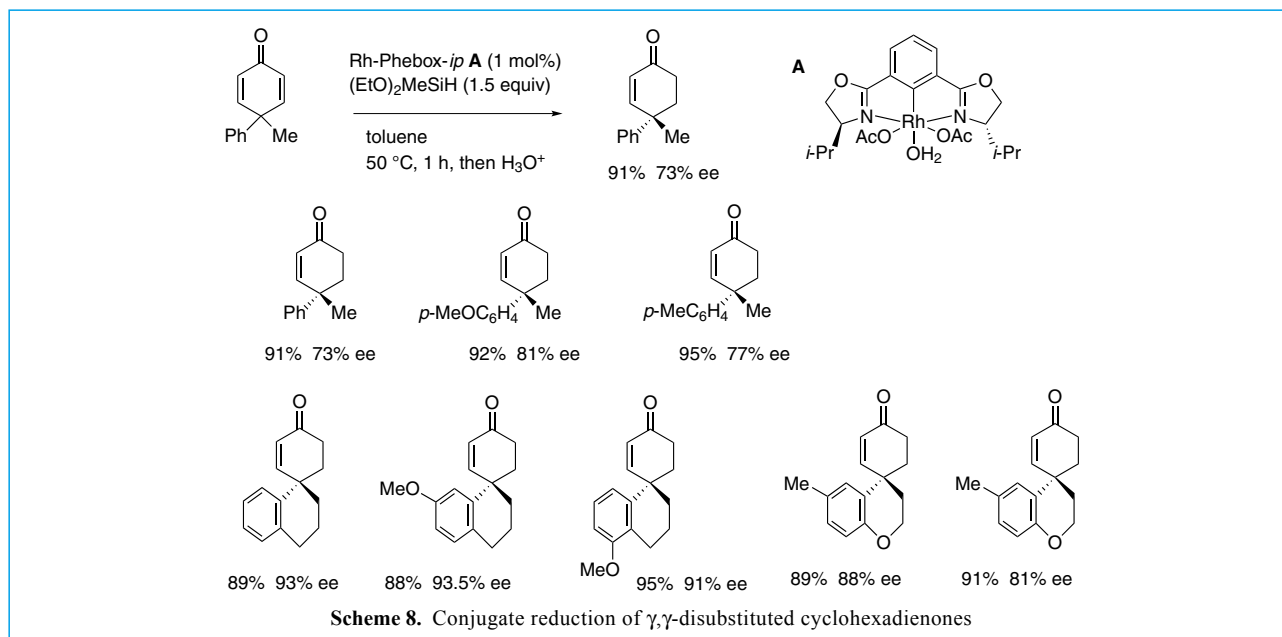
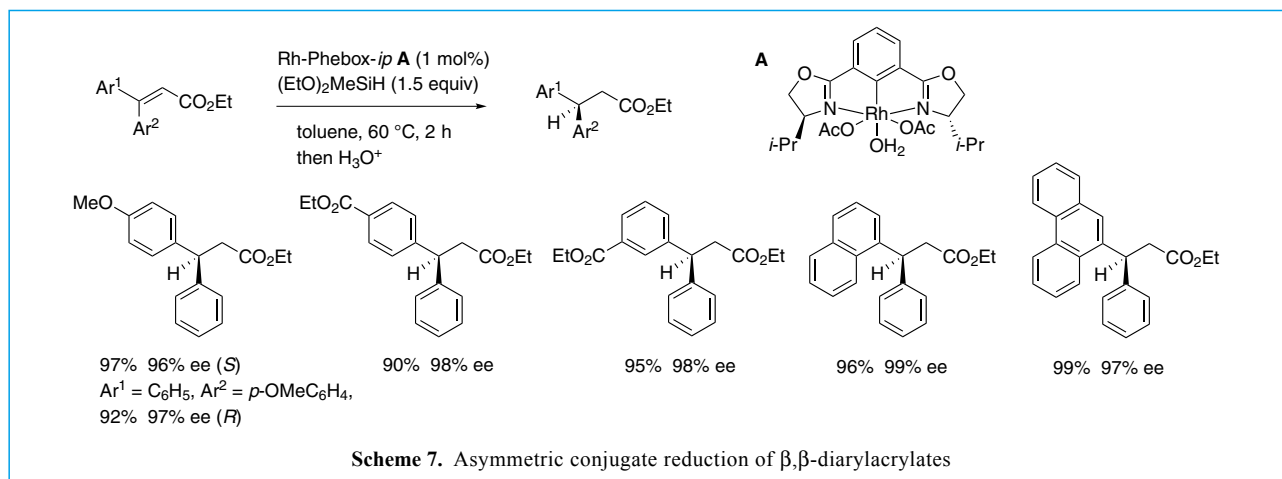
Scheme 5. Asymmetric hydrosilylation of alkenes



Scheme 6. Asymmetric conjugate reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds

$\beta,\beta$ -Diarylacrylates ( $Ar^1 \neq Ar^2$ ) were reduced under the same conditions of the conjugate hydrosilylation to give optically active 3,3-diarylpropanoates, which are useful precursors for various pharmaceutical compounds (Scheme 7).<sup>16</sup> Although it is congested around the  $\beta$ -carbon, the reaction took place smoothly. The reaction on a gram scale was demonstrated. The starting  $\beta,\beta$ -diarylacrylates can be prepared by a stereospecific copper catalyzed coupling reaction with arylboronic acids and substituted phenylpropiolates according to Yamamoto's procedure.<sup>17</sup>

The conjugate reduction with hydrosilane and the Rh-Phebox catalyst can be applied to reductive desymmetrization of  $\gamma,\gamma$ -disubstituted cyclohexadienones (Scheme 8).<sup>18</sup> 4-Alkyl-4-aryl-cyclohexadienones were reduced to give the corresponding  $\gamma,\gamma$ -disubstituted cyclohexenone derivatives in high yields and up to 77% ee. Spiro-carbocyclic skeletons were subjected to the reduction giving higher ees up to 93%. The reaction with  $Ph_2SiD_2$  clarified the direction of hydride attack on the  $\beta$ -carbon atom (Figure 2). A plausible model of the reduction and an optimized structure, which have the hydride in the equatorial position and attacks the *Re* face of the double bond, was described.

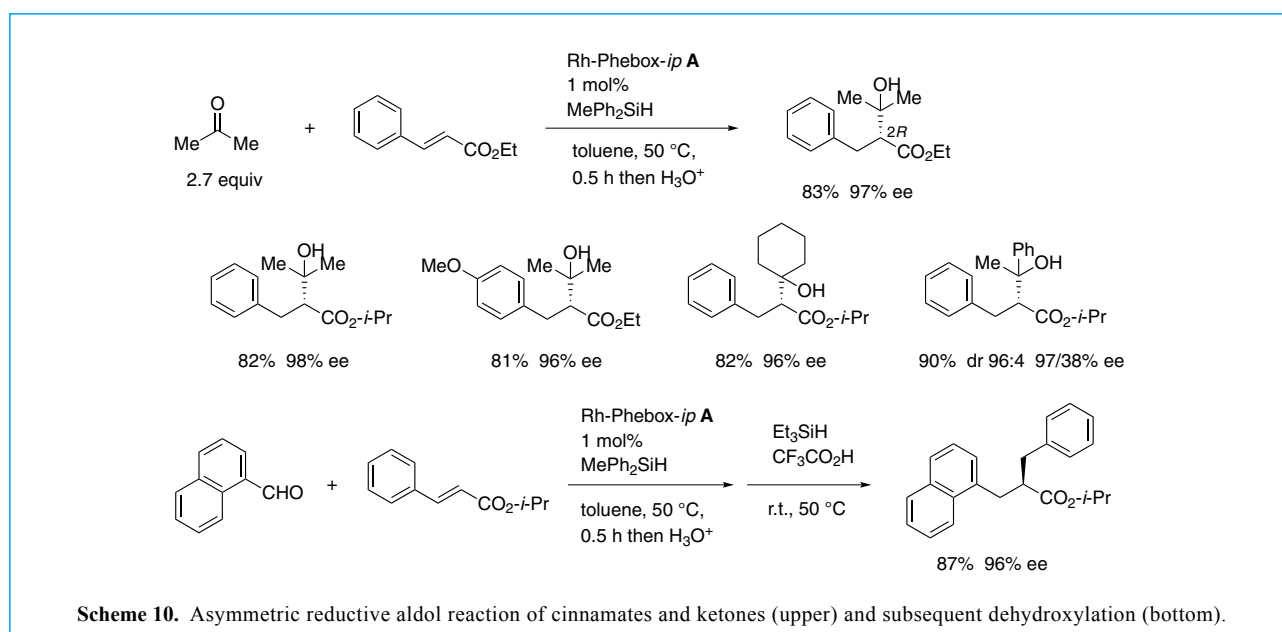
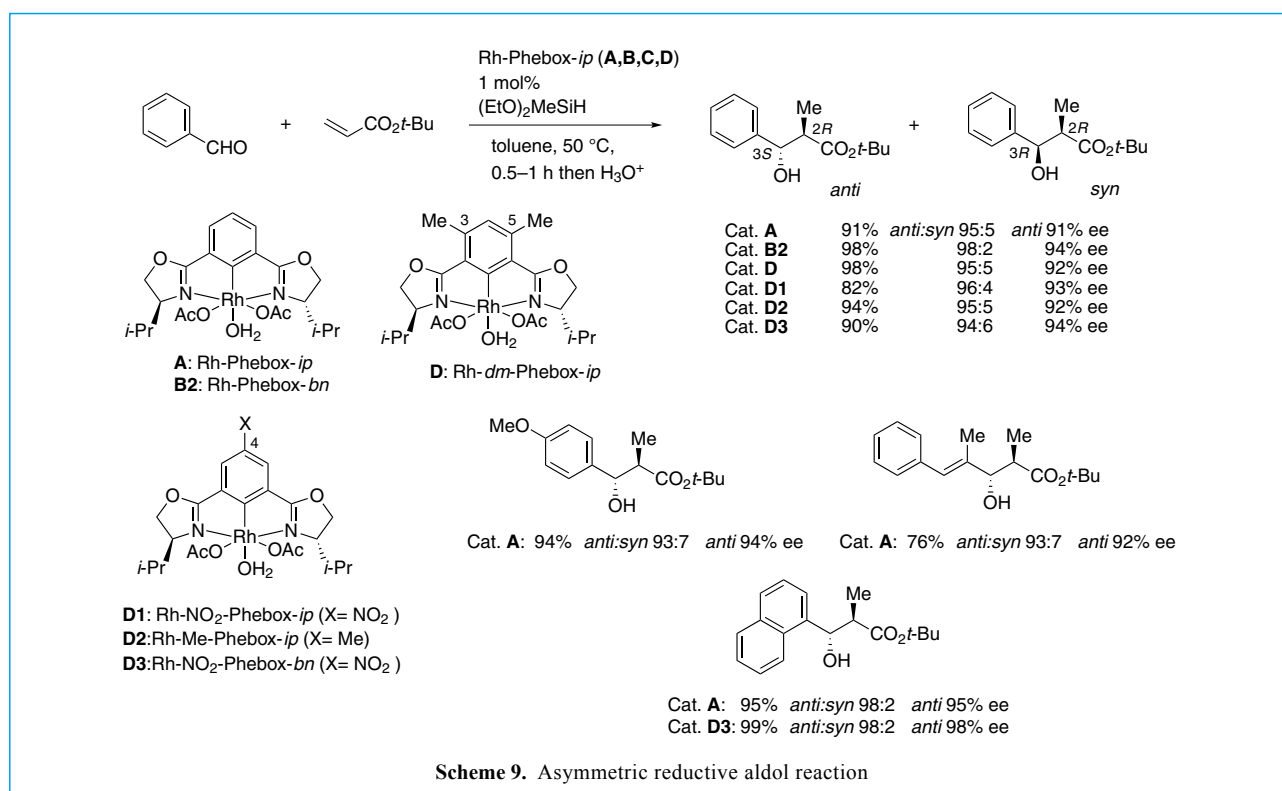


### 3-3. Asymmetric Reductive Aldol Reaction

Rh-Phebox diacetate complexes can work as catalysts for the conjugate reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds with hydrosilanes. On the basis of this fact, it was thought that the intermediate rhodium enolate species might be directly trapped with aldehyde to give the aldol coupling product. Into a mixture of benzaldehyde and acrylate, the catalyst Rh-Phebox **B** and hydrosilane were added to start the reaction, which gave the aldol coupling product, propionate derivative, in high yields with high ees for the *anti* isomer and high *anti*-selectivity (Scheme 9).<sup>19</sup> 4-Substituted catalysts and 3,5-dimethyl catalyst **D** work as catalysts giving almost the same yields and up to 98% ee.<sup>15,20</sup>

The conjugate reduction of cinnamates and successive aldol reaction with acetone gives the intermolecular aldol coupling products in high ee up to 98% (Scheme 10).<sup>21</sup>  $\text{PhMe}_2\text{SiH}$  is the best choice of hydrosilane. After the aldol reaction, subsequent dehydroxylation of the  $\beta$ -hydroxy group resulted in formation of  $\alpha$ -chiral dihydrocinnamates in high yields and kept the enantioselectivity with 90% ee.<sup>22a)</sup> As an extension of the reductive aldol reactions, there is the Felkin-Anh selectivity in the reaction of 2-phenylpropionaldehyde and unsaturated esters.<sup>22b)</sup>

Rh-Phebox diacetate complex catalyzed the reductive Mannich-type coupling of acrylates and aldimines to form selectively the *anti*-product, but asymmetric induction could not be observed.<sup>23)</sup>



## 4. Asymmetric Boration

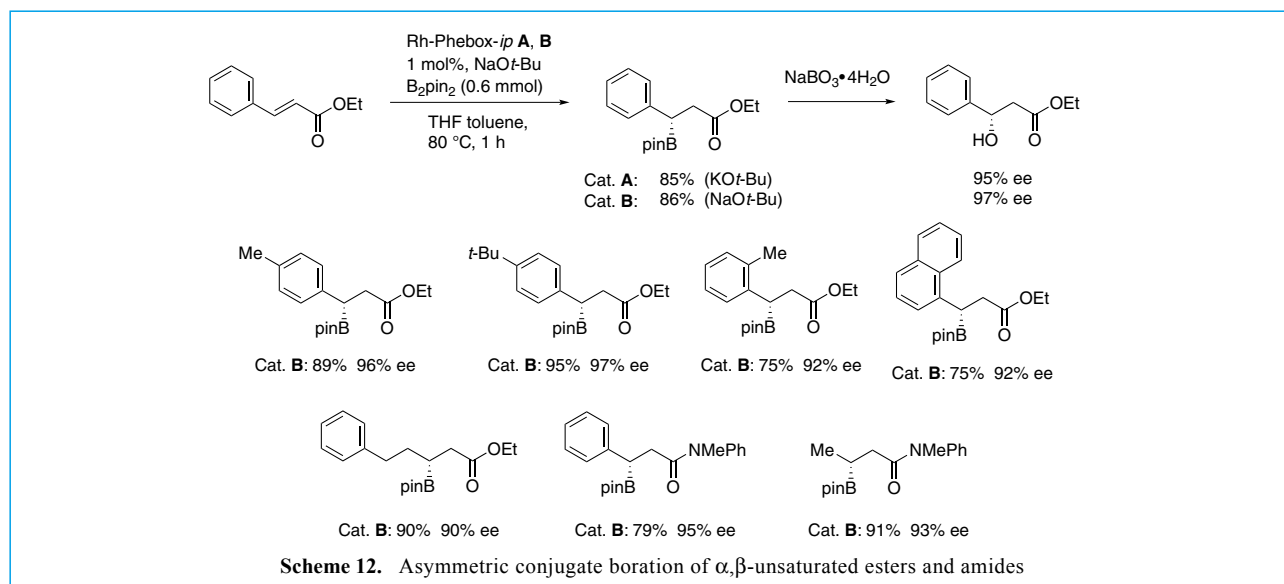
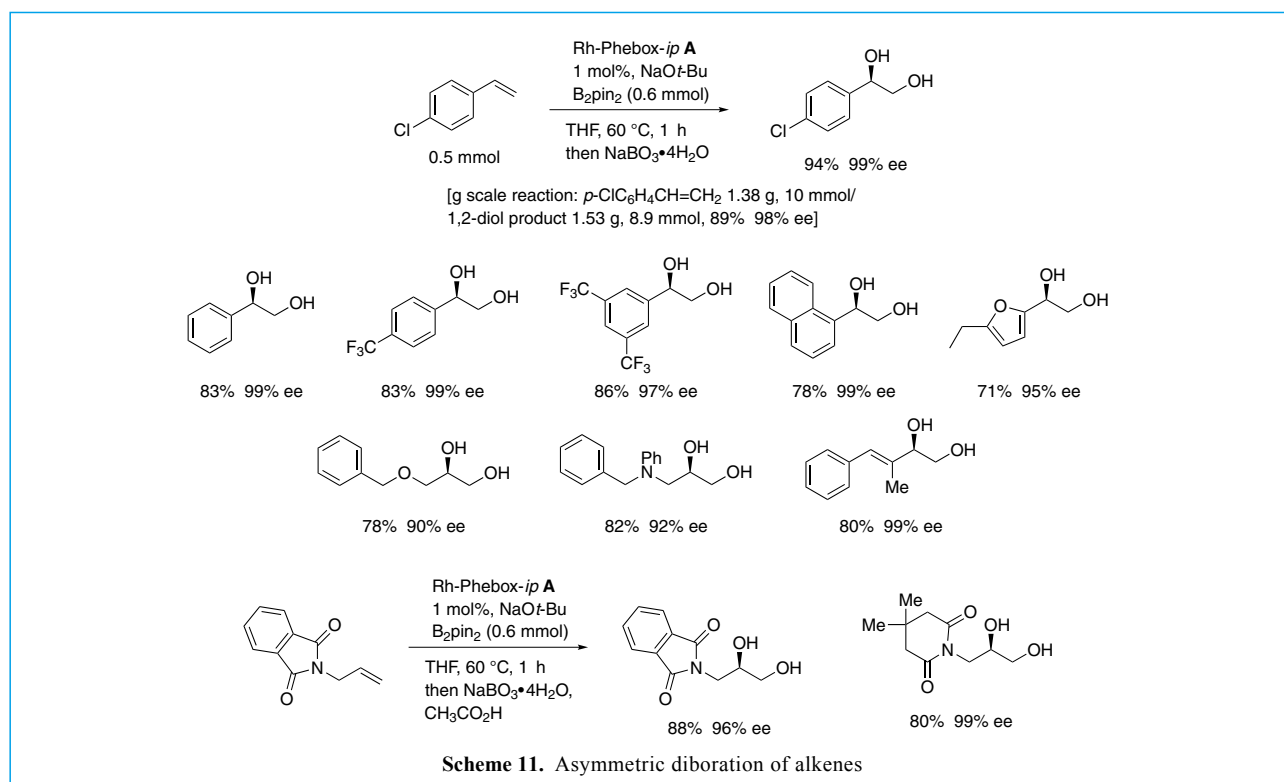
### 4-1. Asymmetric Diboration of Alkenes

Rh-Phebox diacetate complex **A** is capable of catalyzing the asymmetric diboration of terminal alkenes followed by oxidation to form the corresponding optically active 1,2-diols in high ee (Scheme 11).<sup>24</sup> The diboration reaction was accelerated by addition of a small amount of bases such as NaOt-Bu or KOt-Bu. The mixture of alkene and bis(pinacolato)-diboron ( $B_2pin_2$ ) was treated with 1 mol% of the catalyst to give the 1,2-diborated product, which was converted to 1,2-diol by oxidation with aqueous sodium perborate. A variety of terminal alkenes such as ethers, *tert*-amines, dienes can be subjected to the reaction. *N*-Acyl protected

allylamines also can be used as substrates to give the diols via the diboration reaction (Scheme 11, bottom).<sup>25</sup> The products are optically active 3-amino-1,2-diols, the skeletons of which are often included in many pharmaceutical compounds or synthetic intermediates.

### 4-2. Asymmetric Conjugate Boration of $\alpha,\beta$ -Unsaturated Carbonyl Compounds

Rh-Phebox-*ip* diacetate **A** can catalyze the conjugate boration of  $\alpha,\beta$ -unsaturated carbonyl compounds to produce the  $\beta$ -boryl propanoates in high yields (Scheme 12).<sup>26</sup> Subsequent oxidation of the boryl products resulted in formation of  $\beta$ -hydroxy propanoates and related amides with high ee.





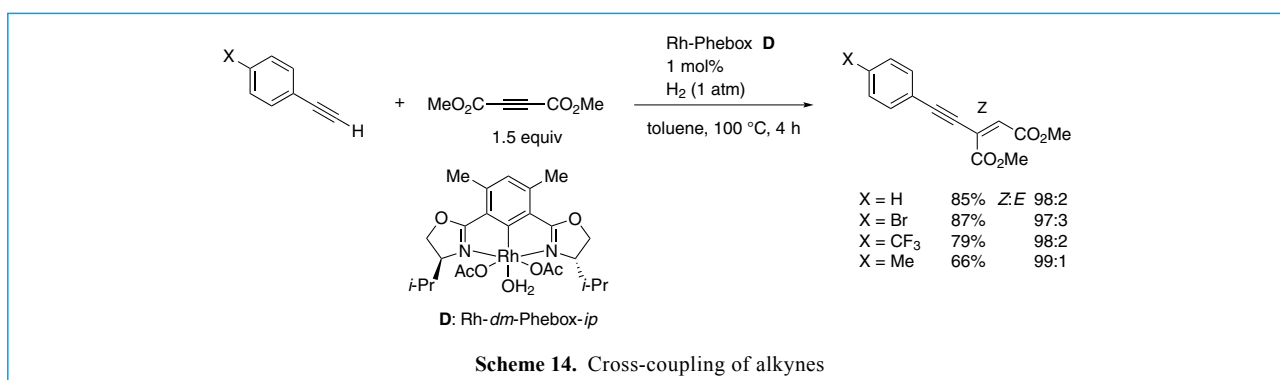
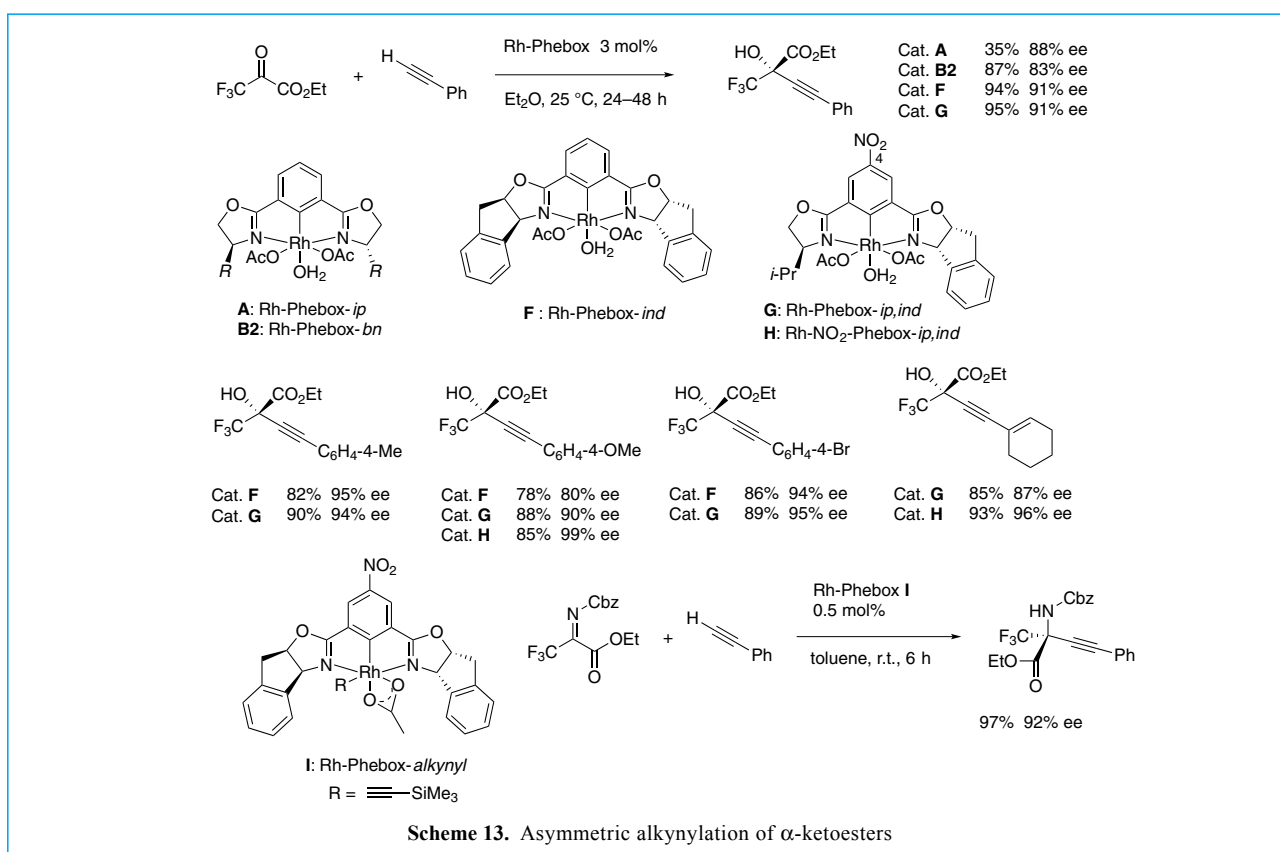
## 5. Asymmetric Alkynylation

### 5-1. Asymmetric Alkynylation of $\alpha$ -Ketoesters

Ohshima and Mashima *et al.* reported that various Rh-Phebox diacetate complexes can be synthesized and catalyze asymmetric alkynylation of  $\alpha$ -ketoesters and aryl-substituted or alkyl-substituted terminal alkynes to give functionalized propargylic alcohols in good yields with high ee up to 99% (Scheme 13).<sup>27a</sup> Morimoto and Ohshima extended the reaction using alkynyl complex **I** and found the highly reactive catalyst which was applied to alkynylation of ketiminoesters.<sup>27b</sup>

### 5-2. Cross-coupling of Alkynes

The cross coupling reaction of terminal alkynes and dimethyl acetylenedicarboxylate proceeded with Rh-Phebox catalyst **D** under hydrogen atmosphere (1 atm) at 100 °C for 4 h to give the corresponding coupling product, the enyne derivatives, in high yield and high Z ratio (Scheme 14).<sup>28</sup> The acetylide complex was isolated and analyzed. C–H Bond activation by deprotonation from the terminal alkyne with acetate ligand as a base forms the corresponding acetylide complex followed by insertion of the alkyne and then elimination of the enyne product.



## 6. Other C–C Bond Formation Reactions with Rh-Phebox Catalysts

Rh-Phebox complexes also catalyzed several C–C bond formation reactions as follows: asymmetric direct aldol reaction of benzaldehyde with cyclohexanone and cyclohexenone, respectively,<sup>29,30)</sup> asymmetric allylation reaction of benzaldehyde with allyl- or methallyl-tributyltin,<sup>31)</sup> asymmetric Michael addition of  $\alpha$ -cyanopropionates to acrolein,<sup>32)</sup> asymmetric aldol-type condensation of isocyanide group on Rh-Phebox,<sup>33)</sup> asymmetric hetero Diels–Alder reaction of Danishefsky's dienes and glyoxylates.<sup>34)</sup> The vacant site of Rh-Phebox intermediate acts as a Lewis acid catalyst for those C–C bond formation reactions.

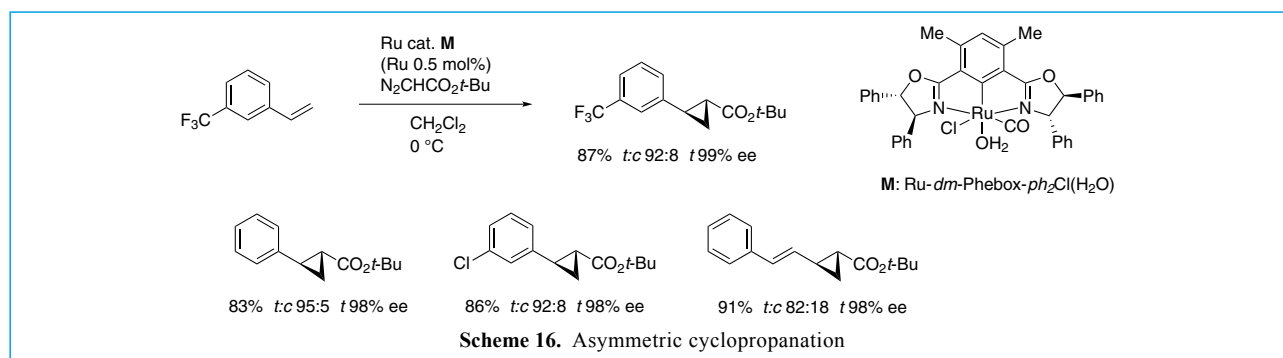
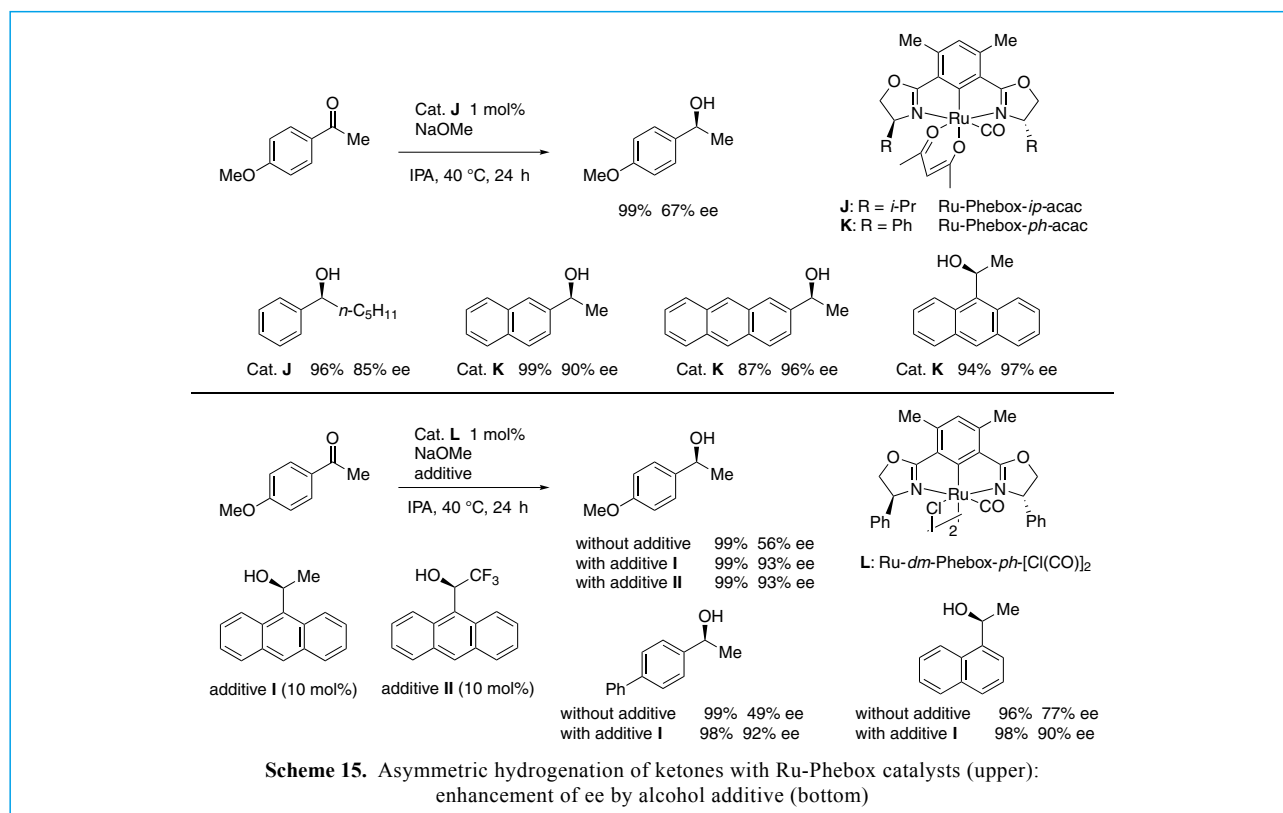
## 7. Asymmetric Catalysis with Ru-Phebox Complexes

### 7-1. Asymmetric Hydrogenation of Ketones

Ru-Phebox complexes **J** and **K** act as catalysts for asymmetric hydrogenation of ketones to give optically active secondary alcohols (Scheme 15).<sup>35)</sup> Relatively bulky ketones were reduced with high enantioselectivities of up to 97% ee. Aryl-substituted acetophenones were reduced in the middle range of ee.<sup>36)</sup> It was interesting in that using the catalyst **O**, addition of optically active alcohols, such as additives **I** or **II** (10 mol%), enhanced ee over 90%. The bulky anthracenyl alcohol improves the selectivity due to coordination to the Ru atom.

### 7-2. Asymmetric Cyclopropanation

Mono nuclear Ru-Phebox complex **M** was prepared by C–H bond activation with magnesium as a reducing agent in ethanol (Scheme 16).<sup>10)</sup> The complex **M** catalyzed the cyclopropanation of styrene derivatives to form the corresponding *trans*-cyclopropanes in high yields.



### 7-3. Asymmetric Alkynylation of Aldehydes

Ru-Phebox complexes catalyzed asymmetric alkynylation of aldehydes with terminal alkynes to produce optically active propargylic alcohols with high ee up to 93% (Scheme 17).<sup>11)</sup> The acetate complex did not require base additives such as NaOAc to give the alcohols in a similar yield and ee. As an acceptor,  $\alpha,\beta$ -unsaturated carbonyl compounds were used to give Michael addition derivatives in high yields.<sup>37)</sup>

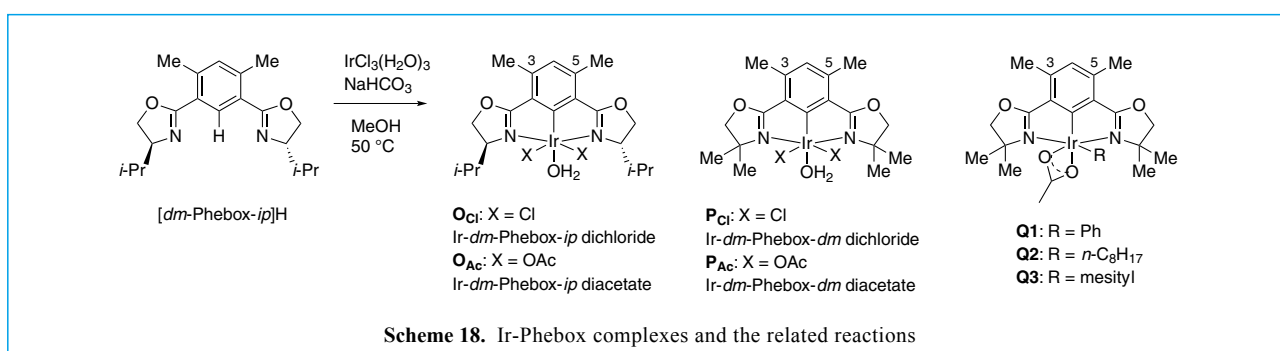
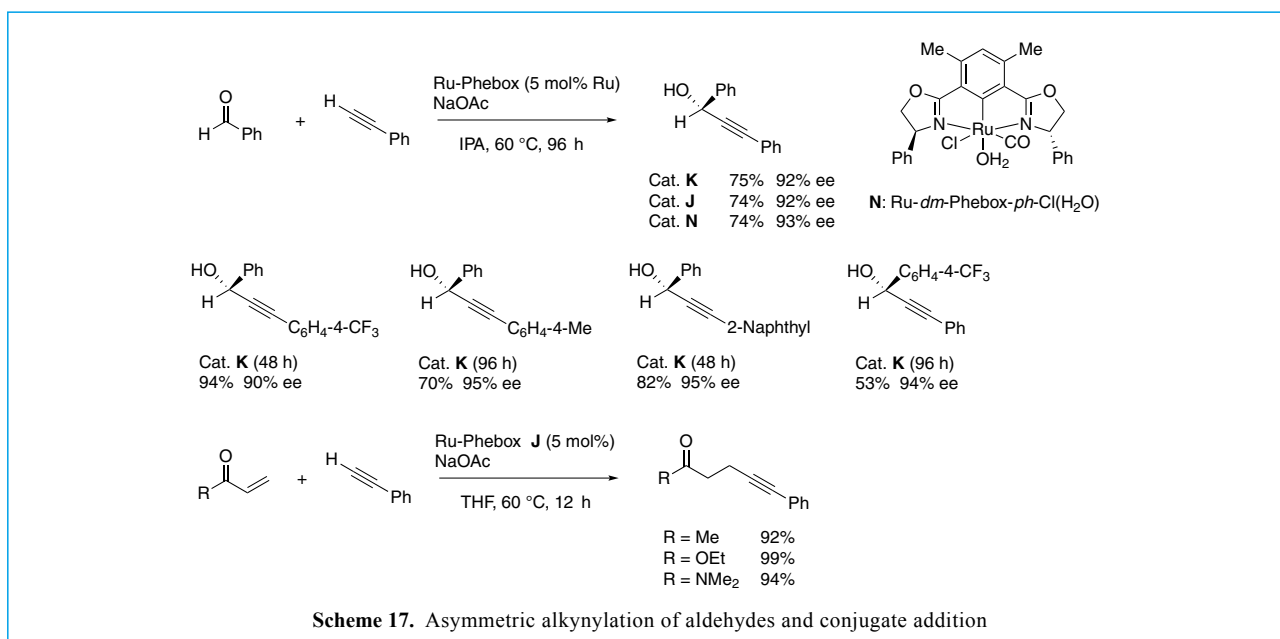
## 8. Asymmetric Catalysis with Ir-Phebox Complexes

### 8-1. C–H Activation on Ir-Phebox Complexes

A series of Ir-Phebox dichloro complexes was prepared by the C–H bond activation reaction with [*dm*-Phebox]H or [*4-tb*-Phebox]H and iridium salts, followed by treatment with AgOAc to give the corresponding acetates (Scheme 18).<sup>15,37,38,39,40)</sup> The chiral Ir-Phebox **O** catalyzed asymmetric conjugate reduction and asymmetric reductive aldol reaction to attain high enantioselectivity.<sup>15)</sup> Our group, the Goldberg group, and the Goldman group reported that the acetate complex **P<sub>Ac</sub>** reacts with benzene, *n*-octane, or mesitylene to form phenyl, octyl or mesityl complexes (**R**) by C–H activation on the iridium atom, respectively.<sup>37,38,39)</sup> Boration of arenes was realized with B<sub>2</sub>pin<sub>2</sub> and Ir-Phebox **O**.<sup>15)</sup>

### 8-2. Asymmetric C–H Insertion Reaction

Musaev, Davies, and Blakey group reported Ir-Phebox complexes **R** and **S** catalyzed the asymmetric C–H insertion reaction with cyclohexadienes and phenyldiazoacetate in high ee up to 99% (Scheme 19).<sup>40)</sup> The products can be converted to optically active  $\alpha,\alpha$ -diarylacetates. They also proposed the reaction pathway and calculated the stereoisomer of the reactive carbene complexes.



## 9. Phebox Complexes of Other Metals

Phebox complexes of other metals, for examples, iron,<sup>41)</sup> cobalt,<sup>42)</sup> palladium,<sup>43)</sup> and platinum,<sup>44)</sup> were prepared by oxidative addition reactions of Phebox-X (X = halogen) (Figure 3). However, asymmetric catalysis with the complexes has not yet been explored extensively. Further applications are strongly expected.

For other metal complexes, for examples, van Koten *et al.* reported synthesis of Phebox-Li and Phebox-Au complexes, which were successively used to prepare the corresponding Ti, V, Cr, Zr, Hf, Nb complexes.<sup>45)</sup> Xu and Lu *et al.* reported Phebox-Lu complex, which was applied to the regioselective polymerization of isoprene.<sup>46)</sup>

## 10. Summary

Asymmetric catalysis with bis(oxazoliny)phenyl ligands and their transition metal complexes, mainly rhodium and ruthenium complexes, has been developed to attain high enantioselectivities with relatively lower catalyst loading (1 mol% or lower). Phebox ligands and their complexes are readily prepared and have high potential for organic reactions including asymmetric reactions and polymerizations. These tridentate and nitrogen-based ligands and the complexes are useful in modern catalytic organic synthesis.

### Procedures of Asymmetric Conjugate Reduction and Asymmetric 1,2-Diol Synthesis

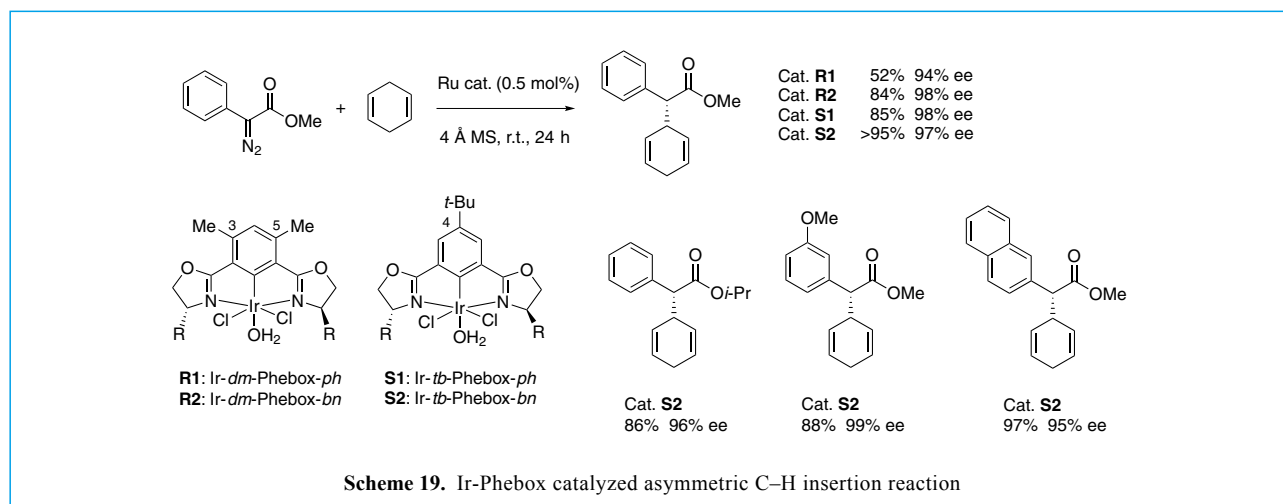
#### Scheme 7. The preparation of (*S*)-ethyl 3-(naphthalen-1-yl)-3-phenylpropanoate<sup>16)</sup>

Diethoxymethylsilane (202 mg, 1.5 mmol) was added at 60 °C to a solution of (*E*)-ethyl 3-(naphthalen-1-yl)-3-phenylacrylate

(302 mg, 1.0 mmol) and Rh-Phebox-*ip* diacetate **A** (5.4 mg, 0.010 mmol) in toluene (2.0 mL). The mixture was stirred for 2 h. At 0 °C, THF (1 mL), MeOH (1 mL), and hydrochloric acid (1 mL, 1 *N*) were added, and the mixture was stirred for 1 h. The mixture was then extracted with ethyl acetate, and was washed with aq. sodium bicarbonate and saturated brine. The organic layer was dried over magnesium sulfate, and then concentrated to give a residual oil, which was purified by silica gel column chromatography with ethyl acetate/hexane to give the propanoate (293 mg, 0.961 mmol, 96% yield) as a colorless oil:  $[\alpha]_D^{24} = +16.8$  (c 1.01, CHCl<sub>3</sub>); Chromatography: DAICEL CHIRALCEL OD-H, hexane/2-propanol (97:3, 1 mL/min), 27 °C, retention time = 9.7 min for *R* (minor) and 17.5 min (major) for *S*, 99% ee; HRMS-FAB (*m/z*, *M* = C<sub>21</sub>H<sub>20</sub>O<sub>2</sub>): found: 327.1365 [M+Na]<sup>+</sup>, calcd: 327.1361.

#### Scheme 11. The preparation of (*R*)-1-(4-chlorophenyl)-ethane-1,2-diol from 4-chlorostyrene<sup>24)</sup>

Rh-Phebox-*ip* diacetate **A** (2.7 mg, 0.0050 mmol), bis(pinacolato)diboron (152 mg, 0.60 mmol), and NaOt-Bu (2.5 mg, 0.026 mmol) were placed in a flask. 4-Chlorostyrene (69.3 mg, 0.50 mmol) and THF (1.0 mL) were added under an argon atmosphere. The mixture was stirred at 60 °C for 1 h. At room temperature, NaBO<sub>3</sub>·4H<sub>2</sub>O (385 mg, 2.5 mmol), THF (5 mL), and water (2.5 mL) were added to the reaction mixture, which was stirred for 1 h. The mixture was extracted with ethyl acetate (2 mLx5) and concentrated to give a crude product, which was purified by silica gel column chromatography with ethyl acetate/hexane as eluent. The diol was obtained in 94% yield (80.9 mg, 0.469 mmol) as a white solid, m.p. 84–86 °C:  $[\alpha]_D^{22} = -57.4$  (c 1.0, CHCl<sub>3</sub>); Chromatography: DAICEL CHIRALCEL OD-H, hexane/2-propanol (98:2, 1.5 mL/min): retention time = 46.0 min (major), 52.8 min (minor), 99.5% ee; Elemental Anal: calcd. (%) for C<sub>8</sub>H<sub>9</sub>ClO<sub>2</sub>: C 55.67; H 5.26. Found: C 55.94; H 5.34.



Scheme 19. Ir-Phebox catalyzed asymmetric C–H insertion reaction

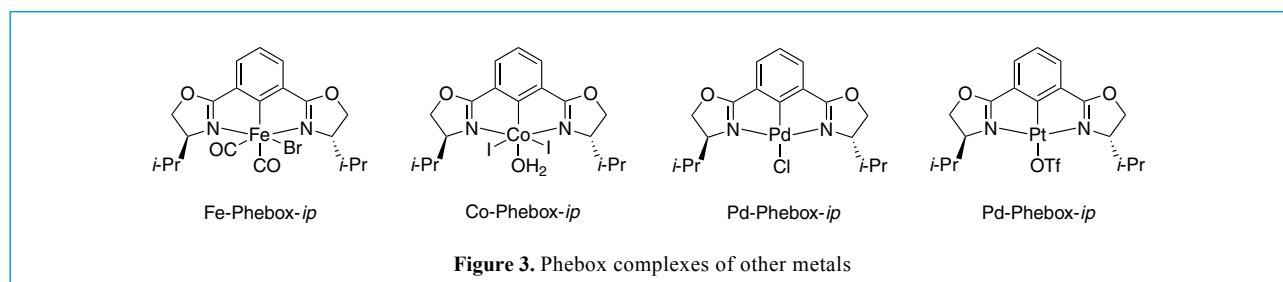


Figure 3. Phebox complexes of other metals

## Acknowledgments

I sincerely thank all my collaborators for their efforts to discover new chemistry. In addition, I am deeply grateful to The Ministry of Education, Culture, Science, Sports, and Technology and the Japan Society for the Promotion of Science for the financial support.

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### Introduction of the author:



#### Hisao Nishiyama

Emeritus Professor, Nagoya University

Hisao Nishiyama was born in 1951 in Mie, Japan. He received his BEng and MSci under the direction of Professor Yoshio Ishii from Nagoya University in 1973–1975, respectively. He received his Dr. Sci. from Tokyo Institute of Technology in 1980. He worked at Research Centers of Toray Industries Inc. in 1975–1980. Since 1980, he worked at Toyohashi University of Technology, where he was associate professor from 1985 to 1996 and full professor from 1996 to 2002. In September 2002, he moved to Nagoya University as a professor. His main research interests are homogeneous catalysis, asymmetric catalysis with nitrogen-based ligands and late transition metals, and organometallic chemistry. He received the Progressive Award of Young Chemists from the Chemical Society of Japan in 1984 and the Award of Organic Synthetic Chemistry of Japan in 1996 and 2015.  
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## TCI Related Products

### Ligands for Pybox and Phebox

B2217	( <i>R,R</i> )-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine	250mg	1g	5g
B2218	( <i>S,S</i> )-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine		500mg	5g
B4196	( <i>S,S</i> )-4,6-Bis(4-isopropyl-2-oxazolin-2-yl)- <i>m</i> -xylene			20mg

### Rh-Phebox Complex

B4195	Bis(acetato)aqua[( <i>S,S</i> )-4,6-bis(4-isopropyl-2-oxazolin-2-yl)- <i>m</i> -xylene]rhodium			10mg
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### Major Reagents for the Synthesis of Ligands and Complexes

P0554	2,6-Pyridinedicarboxylic Acid	25g	100g	500g
I0159	Isophthaloyl Chloride		25g	500g
D4377	4,6-Dimethylisophthalic Acid		200mg	1g
V0058	L-Valinol ( <i>S</i> -Valinol in the article)		5g	25g
D2751	Dichloro( <i>p</i> -cymene)ruthenium(II) Dimer		1g	5g

### Aldehydes

C0352	<i>trans</i> -Cinnamaldehyde		25mL	500mL
B2379	Benzaldehyde			500g

### Alkoxysilanes

D2403	Diethoxymethylsilane			25mL
T1040	Triethoxysilane	25mL	100mL	500mL

### Alkynes

A0090	Dimethyl Acetylenedicarboxylate	25mL	100mL	500mL
B3701	1-Bromo-4-ethynylbenzene		1g	5g
E0196	Ethynylbenzene	25mL	100mL	500mL
E0626	1-Ethynyl-4-(trifluoromethyl)benzene		1g	5g
E0655	4-Ethynyltoluene		5g	25g

### Boron Compounds

B1964	Bis(pinacolato)diboron (= B <sub>2</sub> pin <sub>2</sub> )	1g	5g	25g	100g
S0446	Silver Tetrafluoroborate			5g	25g

### Esters

A1389	<i>tert</i> -Butyl Acrylate (stabilized with MEHQ)		25mL	500mL
A0143	Ethyl Acrylate (stabilized with MEHQ)		25mL	500mL
C0359	Ethyl Cinnamate	25g	100g	500g
T0432	Ethyl Trifluoroacetate	25g	100g	500g

### Others

V0054	4-Vinylbiphenyl		1g	5g
C0290	4-Chlorostyrene (stabilized with TBC)		10mL	25mL
C0468	1,4-Cyclohexadiene (stabilized with BHT)		10mL	25mL
D1091	<i>N,N</i> -Dimethylacrylamide (stabilized with MEHQ)		25g	500g
M0105	4'-Methoxyacetophenone		25g	500g
M0460	Methyl Vinyl Ketone (stabilized with HQ + AcOH)	25mL	100mL	500mL
S0450	Sodium <i>tert</i> -Butoxide	25g	100g	500g
S0887	Sodium Perborate Tetrahydrate		25g	500g
T1520	( <i>R</i> )-(-)-2,2,2-Trifluoro-1-(9-anthryl)ethanol		100mg	1g
T3354	3-(Trifluoromethyl)styrene (stabilized with HQ)		1g	5g

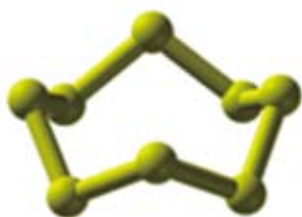
## New Allotropes of Main Group Elements (3)

Kentaro Sato

### Sulfur

#### (1) S<sub>8</sub>

When it comes to allotropes, sulfur is one of the most versatile of all elements. High school textbooks list a few of sulfur allotropes, such as orthorhombic sulfur, monoclinic sulfur, and amorphous sulfur. The first two allotropes both consist of eight-membered ring molecules of sulfur (S<sub>8</sub>) as a basic unit and differ in the crystal packing pattern. The yellow crystal we associate with “sulfur” is the orthorhombic sulfur (aka. α-sulfur), which is the only stable allotrope at room temperature.



The eight-membered ring sulfur (S<sub>8</sub>) (Wikipedia)

The molecule of S<sub>8</sub> takes a crown-like shape in which the sulfur atoms are connected in zigzag-fashion. The bond angle is roughly 108° and not so apart from that of carbon (109.5°), yet it is interesting that sulfur is most stable as an eight-membered ring unlike carbon.

#### (2) Amorphous Sulfur

When this orthorhombic sulfur is heated, it melts into a dark red liquid after passing through monoclinic sulfur state.

Fast cooling of the melt in cold water leads to the formation of amorphous sulfur (or “rubbery” sulfur). It is the product of ring-opening polymerization of S<sub>8</sub> and very elastic as its nickname suggests. Upon long storage, it spontaneously returns to orthorhombic form.

The color of rubbery sulfur had been considered either black or dark brown, but in 2009, a seventeen-year-old boy experimentally proved it inaccurate and textbooks had to be rewritten. In the experiment, when he converted a sample of orthorhombic sulfur with 99% purity into rubbery sulfur, he obtained a brown product as expected. However, when he used 99.5% pure orthorhombic sulfur, he obtained a surprisingly light yellow product.

It should be noted that the composition of amorphous sulfur changes depending on how it is prepared and so does its color. Therefore, the yellow color the boy observed was probably not the outcome of purity factor alone. Nevertheless, it was a remarkable finding made thanks to his careful analysis and critical thinking.

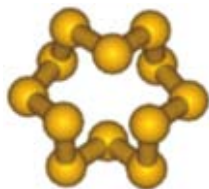
#### (3) Other cyclic sulfur allotropes

Sulfur can exist in shapes other than eight-membered ring and many of them have been created by chemical synthesis. For example, the six-membered sulfur (S<sub>6</sub>) was synthesized by reacting H<sub>2</sub>S<sub>4</sub> and S<sub>2</sub>C<sub>12</sub>. On molecular level, S<sub>6</sub> takes a chair conformation similar to cyclohexane, and on macroscopic level, it forms a red-orange rhombohedral crystal.

The twelve-membered ring sulfur is fairly stable and has been studied in detail. The molecule of S<sub>12</sub> has a three-fold rotational axis and looks like a compressed cuboctahedron.



Interestingly, this structure is unique and different from other molecules such as cyclododecane and crown ether.



The twelve-membered ring sulfur ( $S_{12}$ ) (Wikipedia)

In addition, various sulfur allotropes such as 7, 9, 10, 11, 13, 14, 15, 18, and 20-membered rings have been synthesized.

#### (4) Additional sulfur allotropes

The boiling point of sulfur is 445 degrees Celsius. The composition of the vapor is  $S_8$  near the boiling point, but  $S_2$  starts to form at around 750 degrees. The purple-colored gas of diatomic sulfur is, like oxygen, in the state of triplet radical.

Other sulfur allotropes include fibrous and sheet sulfurs. It is said that sulfur has more than 30 allotropes in total. Sulfur does not make nanotube- or graphene-equivalent structures unlike elements such as phosphorus, but instead its allotropes form an impressively diverse chemical space. It is very well possible that new allotropes of sulfur will be discovered in future.

## Selenium

Let us touch on selenium, which is positioned below sulfur in the periodic table. Selenium has many allotropes too, and the most stable one at room temperature and under normal pressure is called gray selenium or metallic selenium. In gray selenium, the atoms are bonded to form a long helical structure.

On the other hand, selenium also makes an eight-membered ring like sulfur, and the crystalline form of this is known as  $\alpha$ -selenium. Six- and seven-membered ring allotropes and amorphous selenium are also known.

Selenium is, however, highly toxic and the compounds often have a strongly bad smell. It was once used in rectifiers but is diminishing now after having been replaced by silicon. Perhaps for these reasons, the research on selenium is not as active as other elements. Selenium may

get more attention if a new unique allotrope is discovered, but the possibility is uncertain.

## Germanium

Germanium is below silicon in the periodic table and it takes a diamond-like structure like silicon at ambient temperature and pressure. Having semi-conducting property, this  $\alpha$ -germanium used to be found in transistors.

Germanium has another allotrope called  $\beta$ -germanium. When a high pressure (higher than 120 kilobar) is applied to  $\alpha$ -germanium, it undergoes phase transition to become  $\beta$ -germanium, which has metallic properties.

In previous columns, we have covered several examples of flat or almost flat two-dimensional honeycomb-structured allotropes of boron, silicon, phosphorus, and other elements. Like graphene, these substances exhibit unique physical properties and are attracting attentions.

It is then natural to wonder whether germanium can do the same. The carbon-based graphene and the silicon-based silicene were synthesized on copper and silver surfaces, respectively. If copper and silver has been used already, why not trying gold next? So, in 2014, when the vapor of germanium was deposited on a gold surface using a method called germanium molecular beam epitaxy, an impressive single-layered “germanene” was obtained. This is one of the new promising materials for which further progress can be expected.

## Tin

The element that sits below germanium is tin, which is one of the metallic elements we humans have been using for a long time. There is a famous episode about the allotropes of tin. In 1812, when the Napoleon-led French army went deep into Russia, the soldiers were wearing uniforms equipped with buttons made with tin. And the freezing temperature of the Russian winter caused the tin to undergo phase transition, from metallic  $\beta$ -tin to nonmetallic  $\alpha$ -tin. The later has lower density and is weaker, so the buttons crumbled and the soldiers couldn't protect themselves from the cold.

However, this story is generally considered to be doubtful by historians. The actual temperature needed for the phase transition of tin is  $-30$  degrees Celsius and it takes a long time too, so it was unlikely that even the Russian winter was that harsh. The story was probably made up to explain the nightmarish defeat of the heroic figure.

In the same way as germanium,  $\alpha$ -tin is a non-metal with diamond-like structure and  $\beta$ -tin is a metal with tetragonal crystalline structure. However, unlike germanium, the  $\beta$ -tin is the stable form at ambient temperature and pressure. Additionally, the allotropes of tin include  $\gamma$ -tin, which exists at higher than 161 degrees Celsius, and  $\sigma$ -tin, which can exist only under high pressure conditions.

The tin-equivalent of graphene, silicene, and germanene as yet another two-dimensional material had been predicted for some time. In 2015, it was actually synthesized in lab using molecular beam epitaxy, the same way germanene was produced.

The newly obtained “stanene” is expected to possess “perfect conductivity” at room temperature, meaning that it can transfer electricity without wasting any energy as heat. Also, stanene is predicted to react quickly with oxides of nitrogen and sulfur, which could be developed into a technology for the removal of air pollution substances.

The exciting thing about new materials is that they open up a new path that expands the possibility of science. The new allotropes we have just covered will likely trigger further discoveries and push the scientific research to higher levels.

#### Introduction of the author :

##### **Kentaro Sato**

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2008-Present Freelance science writer. 2009-2012 Project assistant professor of the graduate school of Science, the University of Tokyo. 2014-present Publicist for  $\pi$ -system figuration, scientific research on innovative areas.

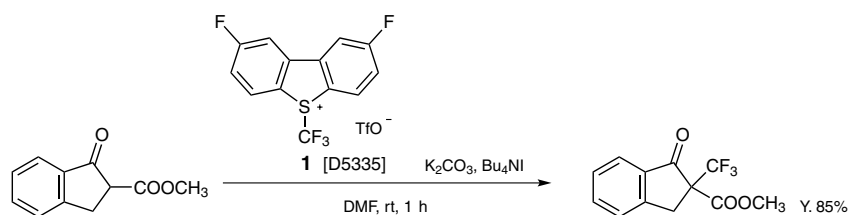
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[Website] The Museum of Organic Chemistry <<http://www.org-chem.org/yuuki/MOC.html>>

## New Umemoto's Reagent II for Trifluoromethylation

### D5335 2,8-Difluoro-5-(trifluoromethyl)-5H-dibenzo[b,d]thiophen-5-ium Trifluoromethanesulfonate (1) 5g 25g

The trifluoromethyl group has unique properties such as high electronegativity, metabolic stability and lipophilicity. The installment of a trifluoromethyl group is one of the significant functionalizations and is utilized for development in various fields, like pharmaceuticals, agricultural chemicals and material science. S-(Perfluoroalkyl)dibenzothiophenium salt **1**, which has been developed by Umemoto *et al.*, is useful as an electrophilic trifluoromethylating reagent. **1** is applicable for many reactions under basic conditions such as trifluoromethylation of  $\beta$ -ketoesters at the  $\alpha$ -position, direct trifluoromethylation of indoles at the 2-position, and hydroxytrifluoromethylation of styrene derivatives using photoredox catalysts.<sup>1)</sup>

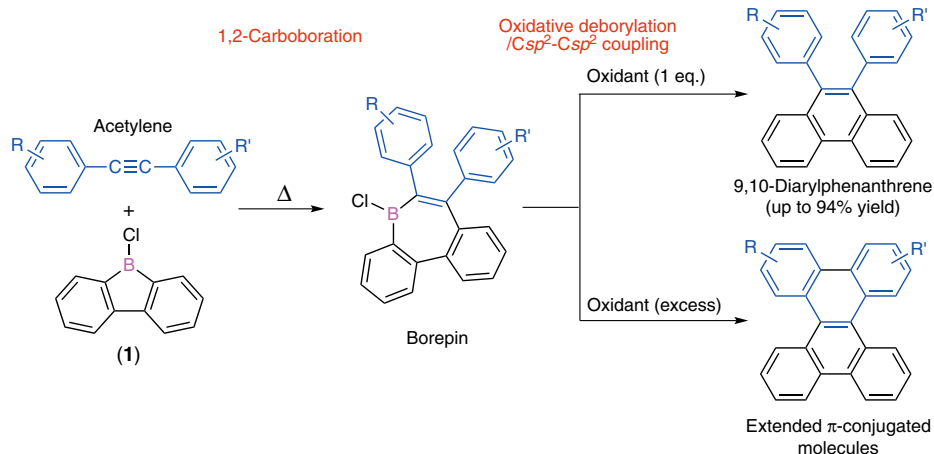


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## An Efficient Borafluorene for the Construction of Extended $\pi$ -Conjugated Systems

### C3421 9-Chloro-9-borafluorene (1) 1g



Fukushima, Shoji and coworkers reported that 9-chloro-9-borafluorene (**1**) mediates sequential alkyne insertion (1,2-carbaboration) and oxidative deborylation/ $Csp^2-Csp^2$  coupling reactions, affording extended  $\pi$ -conjugated molecules. The sequential reactions can be performed in a one-pot fashion and are very useful for the construction of a wide variety of  $\pi$ -conjugated systems, which are potentially applicable to organic electronics.

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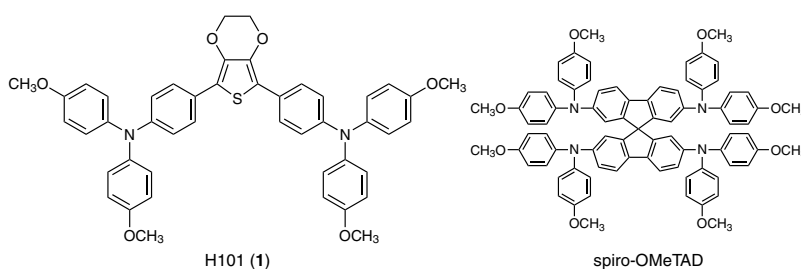
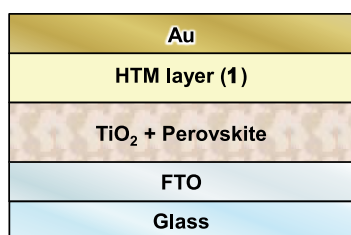
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## A Novel Hole Transport Material for Perovskite Solar Cells : H101

D5155 H101 [= 4,4'-(2,3-Dihydrothieno[3,4-b][1,4]dioxine-5,7-diyl)bis[N,N-bis(4-methoxyphenyl)aniline]] (1) 200mg

Recently, perovskite solar cells have been receiving much attention and novel hole transport materials (HTMs) for the solar cell devices have been developed. Grimsdale *et al.* have reported a novel HTM containing a 3,4-ethylenedioxythiophene core (H101, **1**).<sup>1)</sup> One advantage of using **1** is the simple synthetic pathway, compared with the spirobifluorene-based spiro-OMeTAD. Power conversion efficiency of the perovskite solar cell using **1** was 13.2% reported in 2014, which was comparable with that of the spiro-OMeTAD device (13.7%).<sup>1)</sup>



### Reference

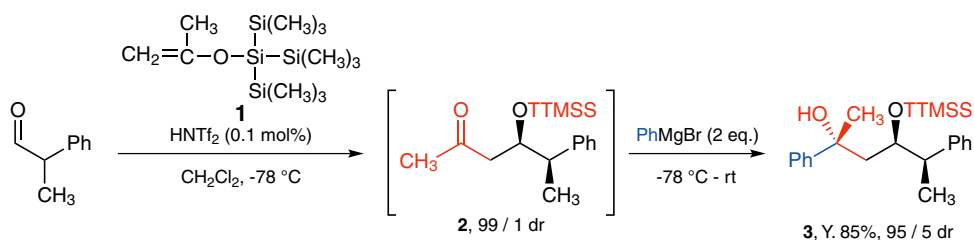
- 1) A simple 3,4-ethylenedioxythiophene based hole-transporting material for perovskite solar cells  
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## Silyl Enol Ether Usable for Highly Stereoselective Aldol Reactions

I0885 Isopropenyloxytris(trimethylsilyl)silane (1)

1g

Isopropenyloxytris(trimethylsilyl)silane (**1**) is a silyl enol ether substituted with three trimethylsilyl groups on a silicon atom. The tris(trimethylsilyl)silyl (TTMSS) group having a characteristic sterically hindered structure is called “super silyl group” and it contributes to highly diastereoselective synthetic reactions. For example, when **1** is treated with 2-phenylpropanal in the presence of an acid catalyst, the reaction proceeds to obtain the adduct **2** as a nearly single diastereomer. Following treatment with phenyl magnesium bromide affords the three-component adduct **3** with high *anti*-selectivity.<sup>1)</sup>



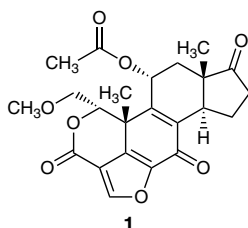
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## PI3K Inhibitor

W0007 Wortmannin (1)

20mg



Autophagy is a catabolic process that digests components of the cytoplasm via lysosomes and is mediated by an organelle called the autophagosome.<sup>1,2)</sup> Autophagy is regulated by various serine/threonine protein kinases, such as mTOR, AKT, MARK *etc.*<sup>3)</sup> Phosphoinositide 3-kinases (PI3Ks) are also a class of such enzymes regulating autophagy. Especially, the class III PI3K promotes the formation of the autophagosome vesicle<sup>4)</sup> and a complex of the PI3K and beclin controls autophagy.<sup>5)</sup>

Wortmannin (1) is a potent PI3K inhibitor. Phosphatidylinositol 3,4,5-trisphosphate formation of fMLP-stimulated neutrophils is inhibited with a dose-responsive manner of 1 (IC<sub>50</sub>: 5 nM).<sup>6)</sup> It was shown that the treatment of rat hepatocytes with 1 inhibits autophagy with an IC<sub>50</sub> of 30 nM.<sup>7)</sup>

It has been known that the properties of induced pluripotent stem cells (iPSCs), self-renewing and differentiation, make these cells tumorigenic.<sup>8)</sup> Zouboulis *et al.* reported that 1 can rapidly induce apoptosis in iPSCs.<sup>9)</sup> They discussed about apoptotic elimination of remaining undifferentiated iPSCs using 1 in their article.

mTOR: mammalian target of rapamycin

AKT: from the name of AKT8 retrovirus (*J. Exp. Med.* **1988**, 167, 1259.)

MARK: mitogen-activated protein kinase

fMLP: *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine

This product is for research purpose only.

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### Related Products

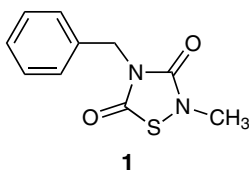
M2410 LY294002  
I0975 PluriSin 1

25mg  
20mg 100mg

## Glycogen Synthase Kinase (GSK) Inhibitor

B4436 TDZD-8 (1)

5mg 25mg



**Table** Inhibition of selected protein kinases by TDZD-8<sup>5,6)</sup>

	Protein kinase	IC <sub>50</sub> (μM)
Study I	GSK-3β	2
	Cdk-1/cyclin B	> 100
	Ck-II	> 100
	PKA	> 100
	PKC	> 100
Study II	PKCβ1	1.4
	PKCδ	1.1
	PKCι	5.5
	FLT3	673

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase and was first isolated from rabbit skeletal muscle.<sup>1)</sup> There are two isoforms of mammalian GSK-3, including GSK-3α and GSK-3β, which are encoding by separate genes (*GSK3A*, *GSK3B*).<sup>2)</sup> GSK-3 is associated with various signaling pathways including the wnt/β-catenin pathway.<sup>3)</sup>

A large number of GSK-3 inhibitors have been reported and classified into two types, ATP-competitive and non-ATP-competitive inhibitors.<sup>4)</sup> TDZD-8 (thiadiazolidine-8, **1**) is a non-ATP-competitive inhibitor of GSK-3β (Study I in the Table).<sup>5)</sup> Interestingly, in the study using PKC isoforms, it is shown that PKCβ1, PKCδ, and PKCι are also inhibited by **1** (Study II in the Table).<sup>6)</sup>

This product is for research purpose only.

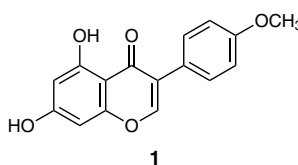
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## Tyrosine Kinase Inhibitor: Biochanin A

B4098 Biochanin A (1)

200mg 1g 5g



Biochanin A (**1**) is an estrogenic substance and is isolated from various plants.<sup>1,2)</sup> **1** inhibits tyrosine protein kinase.<sup>3)</sup>

Through much research, data supporting activation of PPARα and PPARγ by **1** have been reported.<sup>4)</sup> **1** also induces adipogenesis in 3T3-L1 cells.<sup>5)</sup> In adipose-derived stem cells (ADSCs), **1** inhibits the adipogenic differentiation and promotes the osteogenic differentiation.<sup>6)</sup>

PPAR: peroxisome proliferator-activated receptor

The product is for research purpose only.

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