



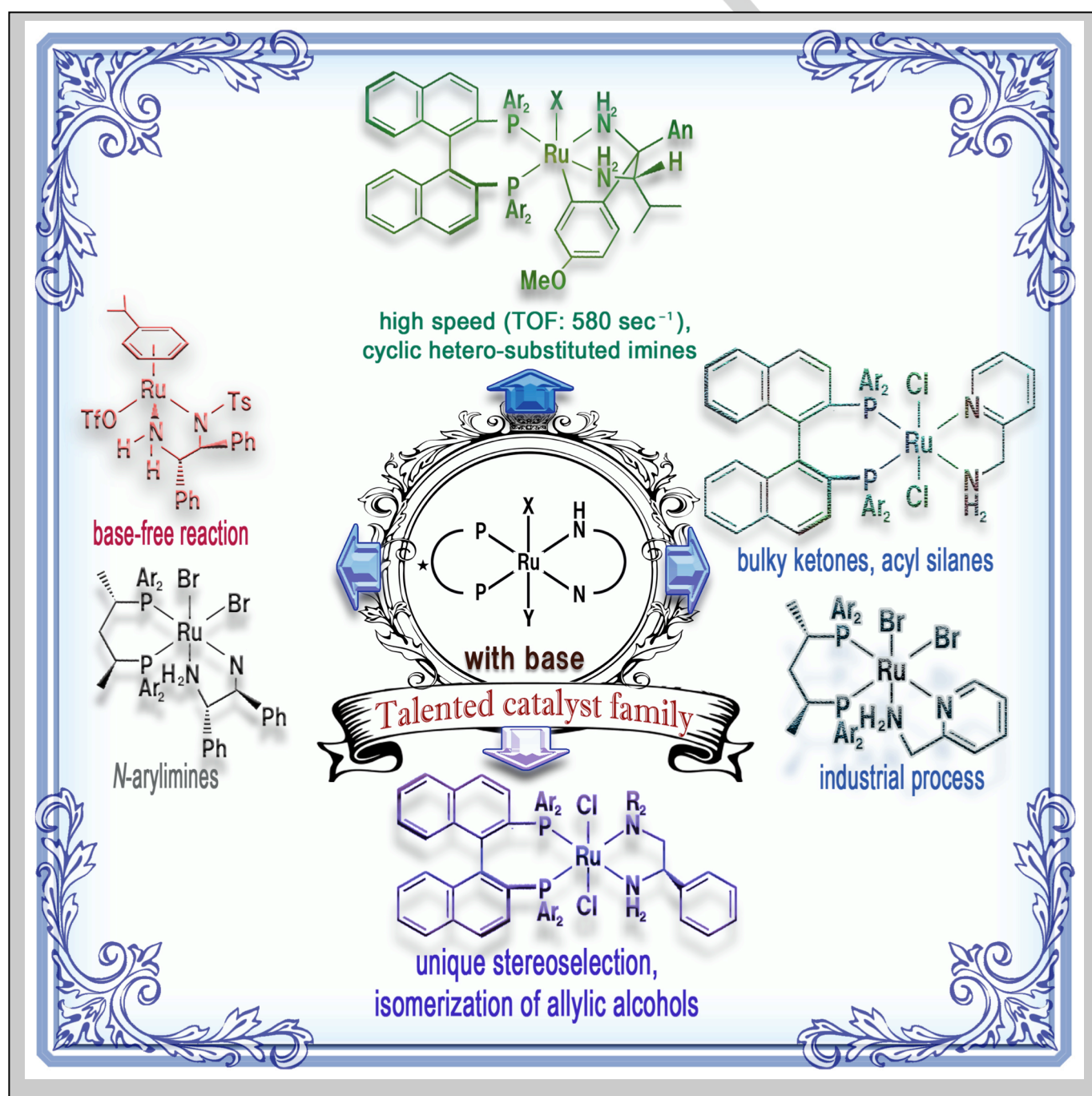
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# Advancement in Catalytic Asymmetric Hydrogenation of Ketones and Imines, and Development of Asymmetric Isomerization of Allylic Alcohols

Takeshi Ohkuma,<sup>\*,[a,b]</sup> Noriyoshi Arai<sup>[a]</sup>

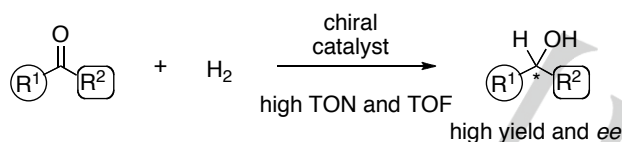
This paper is dedicated to Professor Ryoji Noyori on the occasion of the 15th anniversary of receiving the Nobel Prize in Chemistry in 2001.



**Abstract:** Catalytic asymmetric hydrogenation of ketones through the “metal–ligand cooperative mechanism” has been improved in terms of the efficiency, stereoselectivity, and scope of substrates by varying the arrangement of the catalyst structure and reaction conditions. Imino compounds are also smoothly converted to the optically active amines with appropriate catalysts. This type of catalyst exhibits excellent performance on the asymmetric isomerization of primary allylic alcohols into the optically active aldehydes. This personal account describes recent progress on these topics.

## 1. Introduction

Asymmetric hydrogenation of ketones is one of the most efficient and simplest transformations producing optically active secondary alcohols, which are utilized in the synthesis of a wide variety of chiral medicines, agrochemicals, perfumes, and other functional materials (Scheme 1).<sup>[1]</sup> Well-designed chiral catalysts repeatedly activate molecular hydrogen (H<sub>2</sub>) and ketonic substrates to afford the left-handed or right-handed alcohols with high selectivity. The reaction with an atom-efficiency of 100% provides desired products in a clean and environmentally benign manner. These benefits indicate that this reaction is suitable for large-scale (industrial-scale) synthesis of optically active compounds.



- one of the simplest chemical reactions
- 100% atom efficiency
- an environmentally benign reaction
- suitable for large-scale synthesis

**Scheme 1.** Properties of asymmetric hydrogenation of ketones.

The efficiency of this hydrogenation is primarily evaluated by the catalytic activity, enantioselectivity, and the substrate scope.<sup>[2]</sup> Highly active catalysts achieve a high turnover number (TON) leading to low catalyst loadings, and/or high turnover frequency (TOF = TON·min<sup>-1</sup> or TON·sec<sup>-1</sup>), giving rise to a short reaction period. The enantioselective ability of catalysts is estimated by the enantiomeric excess (ee) of the alcoholic

products, and achieving the perfect selectivity (100% ee) is the final goal. A wide scope of substrates is an essential factor for the usefulness of this reaction, because of the structural diversity of the chiral alcohols. Applicability to a specific useful ketone is also important from a practical viewpoint.

This article reviews our recent attempts to develop efficient catalysts for asymmetric hydrogenation of ketones and imino compounds. Asymmetric isomerization (1,3-hydrogen shift) of  $\gamma,\gamma$ -disubstituted primary allylic alcohols to the chiral aldehydes using catalysts related to the hydrogenation is also described.

Takeshi Ohkuma received his PhD in 1991 from Nagoya University under the supervision of Professor Ryoji Noyori. After working with Professor Paul A. Wender at Stanford University, he joined the ERATO Noyori Molecular Catalysis Project in 1992. In 1996, he became an Associate Professor in the Department of Chemistry at Nagoya University, and then he was promoted to Professor in the Division of Chemical Process Engineering at Hokkaido University in 2004. He was installed as director of the Frontier Chemistry Center in 2013, and Dean of the Graduate School of Chemical Sciences and Engineering at Hokkaido University in 2016 (he served in this capacity until 2018). His research focuses on the development of novel catalytic reactions that achieve a high level of reactivity and selectivity. Professor Ohkuma received the Progress Award in Synthetic Organic Chemistry, Japan in 1997 and the JSPS Prize in 2007.



Noriyoshi Arai received his PhD in 1996 from The University of Tokyo under the supervision of Professor Koichi Narasaka. After working on the development of fine polyimides for electronic devices in Hitachi Chemical Co. Ltd., he joined the research group of Professor Isao Kuwajima in the Japan Science and Technology Agency in 2000, to study the total synthesis of antitumor compounds from actinomycetes. In 2005, he moved to Hokkaido University to join Professor Okuma's research group, where he is currently Associate Professor of the Graduate School of Engineering. His research interests are focused on the creation of novel synthetic reactions based on the catalytic activation of inert molecules by using organometallic and/or photochemical methods.



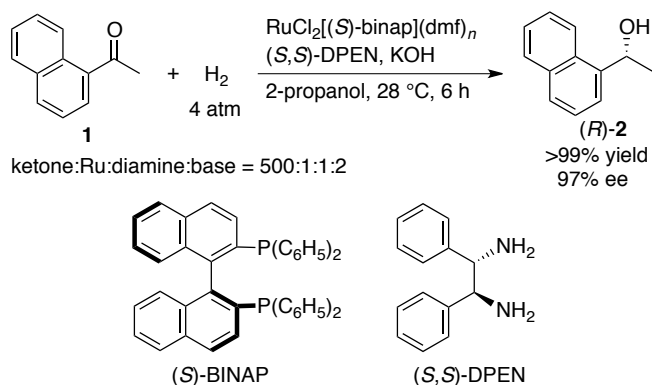
## 2. Early Attempts Using BINAP/Chiral 1,2-Diamine–Ru(II) Catalysts

In 1995, we first reported asymmetric hydrogenation of simple ketones by using a ternary catalyst system consisting of RuCl<sub>2</sub>[(S)-binap](dmf)<sub>n</sub> (oligomeric form; BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), (S,S)-1,2-diphenylethylenediamine (DPEN), and KOH in 2-propanol with

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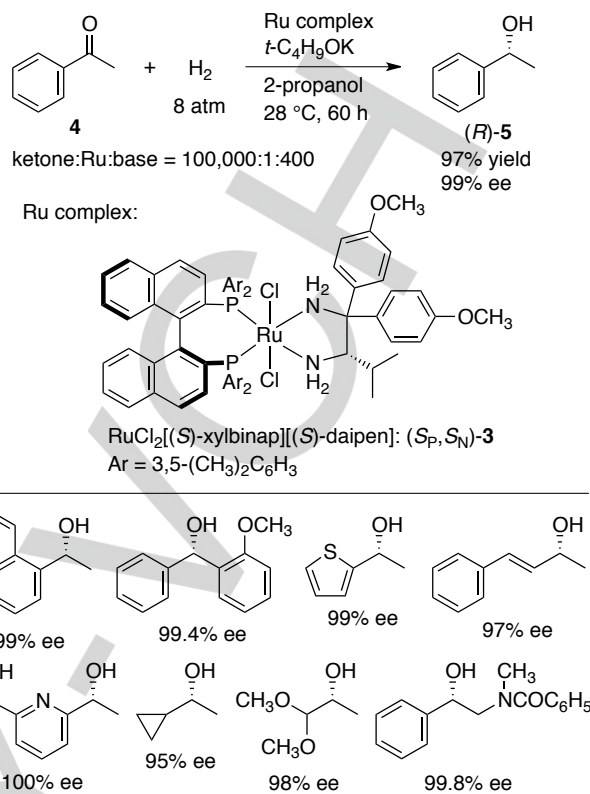
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Professor Ryoji Noyori at his national research project (Scheme 2).<sup>[3]</sup> For example, the reaction of 2'-acetonaphthone (**1**) with a substrate-to-catalyst molar ratio (S/C) of 500 under 4 atm of H<sub>2</sub> quantitatively afforded the chiral alcohol (*R*)-**2** in high ee.



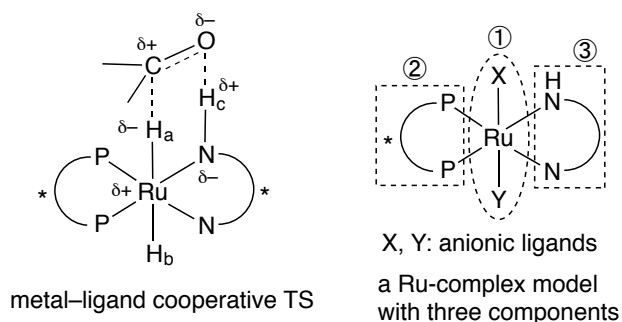
**Scheme 2.** Asymmetric hydrogenation of ketones with a ternary catalyst system.

The catalytic activity and enantioselectivity were remarkably increased by using a pre-formed complex RuCl<sub>2</sub>[(*S*)-xylbinap][(S)-daipen] ((*S<sub>p</sub>*,S<sub>N</sub>)-**3**; XylBINAP = 2,2'-bis(di-3,5-xyllylphosphino)-1,1'-binaphthyl, DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine) and the enantiomer in a *t*-C<sub>4</sub>H<sub>9</sub>OK-containing 2-propanol (Scheme 3).<sup>[4]</sup> Acetophenone (**4**), a typical simple ketone, was smoothly hydrogenated with an S/C of 100,000 under 8 atm of H<sub>2</sub> to give (*R*)-1-phenylethanol ((*R*)-**5**) in 99% ee. A series of chiral secondary alcohols was obtained with high enantioselectivity by using the catalyst system: Alkyl aryl ketones, unsymmetrical benzophenones, heteroaromatic ketones, alkenyl alkyl ketones, and some aliphatic and hetero-substituted ketones are typical examples.<sup>[5]</sup>



**Scheme 3.** Hydrogenation of ketones catalyzed by XylBINAP/DAIPEN–Ru(II) complex with a base.

The hydrogenation of ketones seems to proceed through a concerted six-membered cyclic transition state (TS) called the “metal–ligand cooperative TS” as schematically shown on the left of Fig. 1.<sup>[5,6]</sup> The RuH<sub>2</sub> complex with diphosphine and diamine ligands is a proposed active species. The H<sub>a</sub><sup>δ-</sup>–Ru<sup>δ+</sup>–N<sup>δ-</sup>–H<sub>c</sub><sup>δ+</sup> quadrupole on the catalytic species fits well with the C<sup>δ+</sup>=O<sup>δ-</sup> dipole of the ketonic substrate, resulting in a reduction in the activation energy of the TS. Thus, the hydrogenation of the ketone occurs in the outer coordination sphere of the Ru catalyst. The high chemoselectivity of the carbonyl group over the olefinic moiety, which requires coordination on the center metal, is explained by this model.<sup>[4,7]</sup> Since our initial proposal of this TS model, many theoretical studies on the model have been reported.<sup>[8]</sup> However, in this report we refer to our original model to clearly describe our catalyst design.

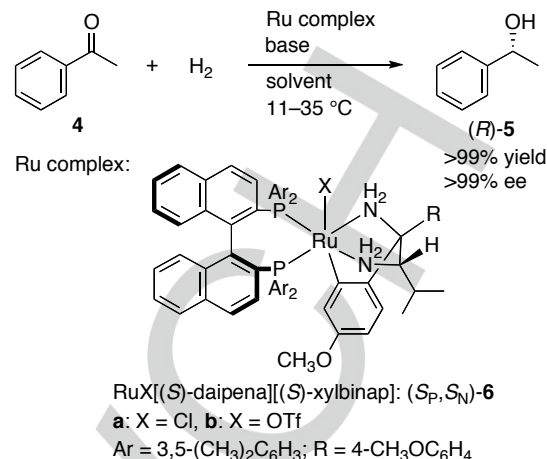


**Figure 1.** Proposed TS for hydrogenation of ketones and a Ru-complex (pre-catalyst) model.

Based on the proposed TS-model structure, we considered that the Ru complex (pre-catalyst) could be broadly modified while maintaining the essential functions, as shown on the right side of Fig. 1. The structure of the Ru complex is divided into three components: the first is the Ru center with two anionic ligands, X and Y, which strongly influences the catalytic activity. The second is the chiral diposphine, providing a chiral environment which primarily controls the enantioselectivity. The third is the nitrogen-based ligand with at least one NH moiety. It determines the direction of the ketonic substrate and the reaction area in the TS as shown on the left side of Fig. 1.

### 3. Highly Active Ruthenabicyclic Catalysts

We recently found that the novel chiral complex  $\text{RuCl}[(S)\text{-daipena}][[(S)\text{-xylbinap}]$  ( $(S_P, S_N)\text{-6a}$ ; DAIPENA = anion of DAIPEN at the 2-position of an anisyl group) with a unique ruthenabicyclic structure including a Ru–carbon covalent bond, which is called “RUCY” and is shown in Scheme 4, was readily synthesized from a known cationic complex  $[\text{RuCl}(\text{p-cymene})\{(S)\text{-xylbinap}\}]\text{Cl}^{[9]}$  and (S)-DAIPEN with  $(\text{C}_2\text{H}_5)_2\text{NH}$  in refluxed methanol.<sup>[10]</sup> The related  $\text{RuCl}_2$  complex **3** was not an actual intermediate to the ruthenabicyclic complex **6a**, so that only a trace amount of **6a** was obtained from **3** under the reaction conditions. The triflate complex **6b** was quantitatively obtained by the reaction of the chloride complex **6a** and NaOTf.



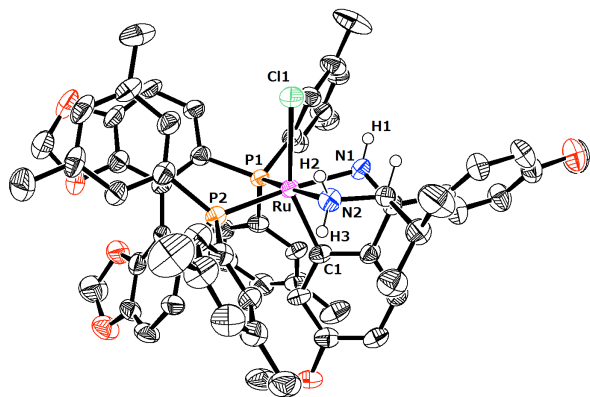
<b>6</b>	S/C	base	$\text{H}_2$ [atm]	solvent	time [h]
<b>6a</b>	100,000	<i>t</i> -C <sub>4</sub> H <sub>9</sub> OK	50	ethanol/ 2-propanol (1:1)	0.10
<b>6a</b>	10,000	<i>t</i> -C <sub>4</sub> H <sub>9</sub> OK	1	ethanol/ 2-propanol (1:1)	24
<b>6a</b>	2,000	<i>t</i> -C <sub>4</sub> H <sub>9</sub> OK	10	toluene	2.5
<b>6a</b>	10,000	DBU	10	ethanol/ 2-propanol (1:1)	0.13
<b>6b</b>	4,000	DBU	10	toluene	2.0

**Scheme 4.** Rapid hydrogenation of ketones with chiral ruthenabicyclic catalysts.

The ruthenabicyclic complex ( $S_P, S_N$ )-**6a** with *t*-C<sub>4</sub>H<sub>9</sub>OK exhibited remarkably high catalytic activity and enantioselectivity in the hydrogenation of ketones (Scheme 4).<sup>[10]</sup> The reaction of ketone **4** with an S/C of 100,000 under 50 atm of  $\text{H}_2$  in a 1:1 mixture of ethanol and 2-propanol was completed in only 6 min to afford the alcohol (*R*)-**5** in >99% ee quantitatively. The TOF between min 2 and 3 of this reaction reached about  $35,000 \text{ min}^{-1}$  or  $580 \text{ sec}^{-1}$ . This rate was about 10 times faster than the engine cycle of a standard automobile and was even faster than that of a Formula 1 racing car! The reaction under 1 atm of  $\text{H}_2$  with an S/C of 10,000 was completed in 24 h without loss of enantioselectivity. The excellent catalyst efficiency was achieved in alcoholic solvents, especially in a 1:1 mixture of ethanol and 2-propanol, but aprotic toluene and  $\text{CH}_2\text{Cl}_2$  were also usable. Addition of a base was required to activate the pre-catalyst **6a**. DBU, an organic base, could be used instead of an alkaline base in an alcoholic solvent. However, it was not basic enough in an aprotic medium. Fortunately, the hydrogenation proceeded smoothly in DBU-containing toluene or  $\text{CH}_2\text{Cl}_2$  when the triflate complex **6b** was used instead of the chloride complex **6a**.

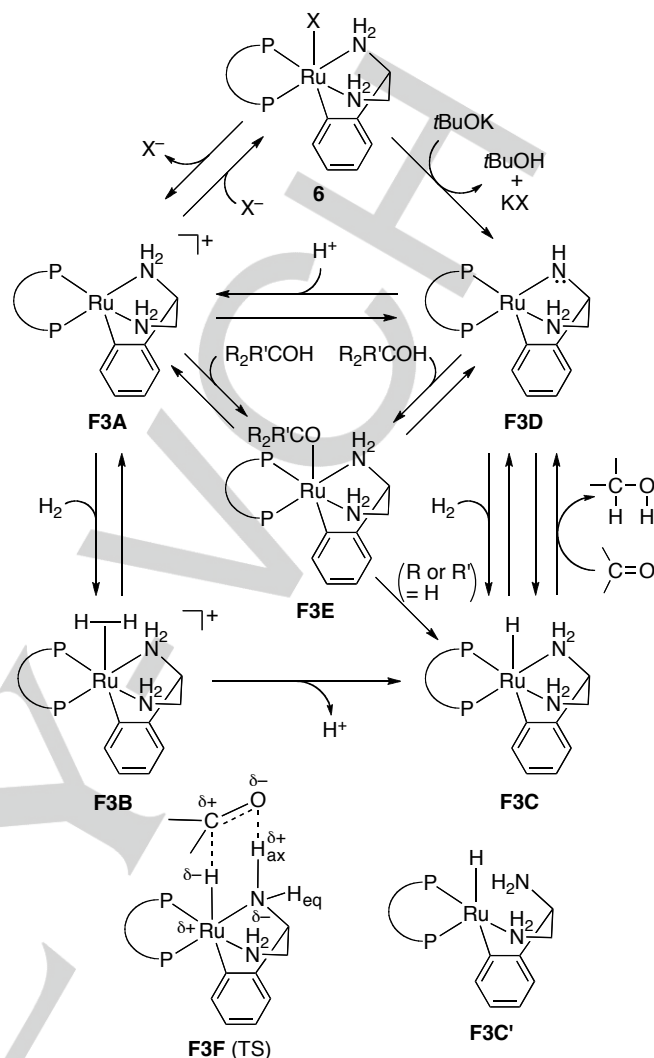
$\text{RuCl}[(S)\text{-daipena}][[(S)\text{-dm-segphos}]]$  ( $(S_P, S_N)\text{-7}$ ; DM-SEGPHOS = (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis(di-(3,5-xylyl)phosphine) was prepared using the same procedure as for **6a**.<sup>[10]</sup> The single-crystal X-ray structure of this complex is shown in Fig. 2. The unique ruthenabicyclic[2.2.1] skeleton results in a significantly distorted octahedral geometry (C(1)–Ru–Cl(1) angle =  $153^\circ$ ). The Cl(1)–Ru bond length of 2.64 Å is

fairly longer than that of the ordinary  $\text{RuCl}_2$ -type complexes (about 2.4 Å). The notably small  $\text{Cl}(1)\text{-Ru-N}(1)\text{-H}(1)$  torsion angle of about  $1.5^\circ$  indicates that the  $\text{Cl}(1)\text{-Ru}$  and  $\text{N}(1)\text{-H}(1)$  bonds are directed almost in parallel. The  $\text{Cl}(1)\text{-H}(1)$  distance of 2.65 Å is much shorter than the typical van der Waals separation length of 3.0 Å, suggesting the existence of hydrogen bonding.



**Figure 2.** ORTEP structure of  $(S_P, S_N)$ -7. All hydrogen atoms except those on the diamine backbone are omitted for clarity.

We proposed a catalytic cycle for the hydrogenation of ketones with ruthenabicyclic complexes **6** as shown in Fig. 3 based on the mechanistic experiments. In an alcoholic solvent the  $\text{X}^-$  (**6a**:  $\text{X} = \text{Cl}$ ; **6b**:  $\text{X} = \text{OTf}$ ) readily liberates from the pre-catalyst **6** to afford the cationic species **F3A**. Hydrogen reversibly interacts with **F3A** to give the molecular hydrogen complex **F3B**. The base ( $t\text{-C}_4\text{H}_9\text{OK}$  or DBU)-promoted heterolysis of hydrogen gives the active RuH species **F3C**, which is the rate-determining step. The feebly active monoamino RuH complex **F3C'** is formed as a minor species. The ketonic substrate is quickly reduced by **F3C** to form the alcohol and the Ru-amide species **F3D**. **F3D** is in rapid equilibrium with **F3A** and the alkoxide complexes **F3E**. The cationic **F3A** is the most preferable species in the presence of excess amounts of alcohol. The minor **F3D** reacts with hydrogen and partly with a primary or secondary alcohol to give **F3C**.



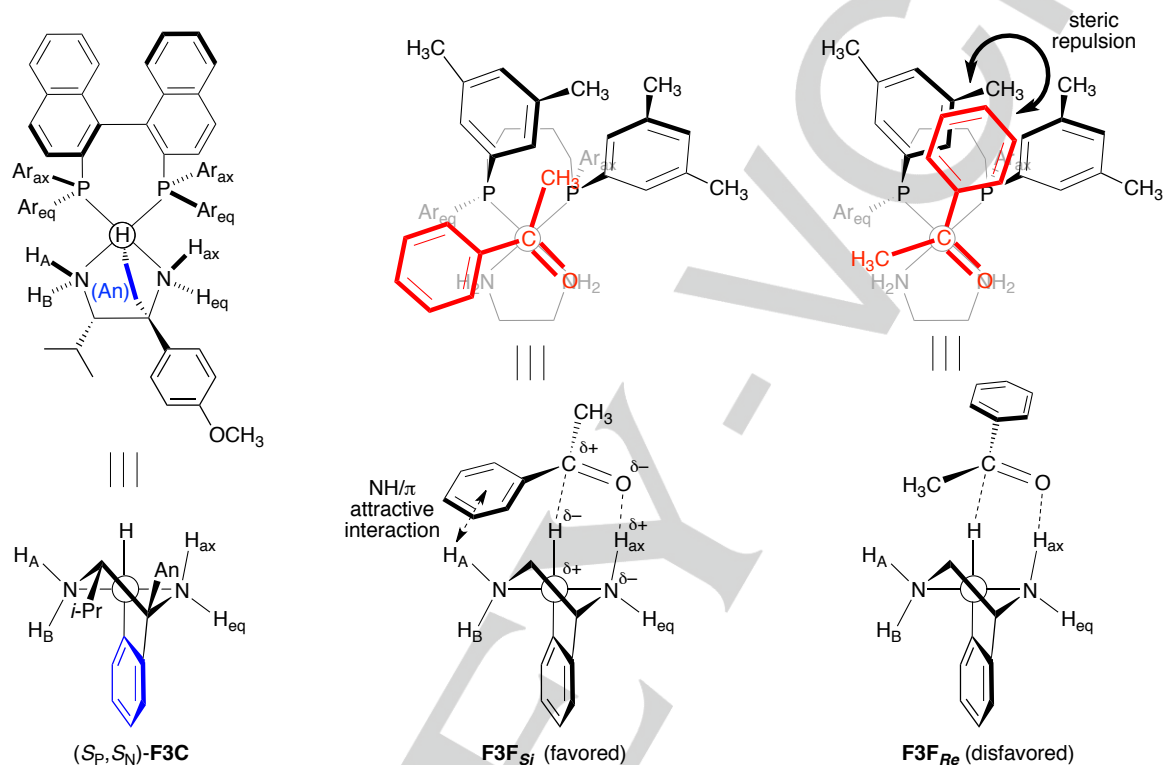
**Figure 3.** Proposed catalytic cycle for hydrogenation of ketones with the ruthenabicyclic complexes **6**.  $\text{X} = \text{Cl}$  or  $\text{OTf}$ .  $\text{R} = \text{alkyl, aryl}$ ,  $\text{H}$ .  $\text{R}' = \text{CH}_3$ ,  $\text{H}$ .  $\text{P-P} = \text{XylBINAP}$ .  $\text{NH}_2\text{-NH}_2 = \text{DAIPENA}$ .

The  $\text{RuCl}_2$  complex **6a** does not ionize and requires a strong alkaline base to remove  $\text{Cl}^-$  in a Dcb manner in a less polar aprotic solvent, such as toluene or  $\text{CH}_2\text{Cl}_2$ , affording the amide complex **F3D**. **F3D** is converted with hydrogen to **F3C**, and then **F3C** reduces the ketone to regenerate **F3D**. The  $\text{RuOTf}_2$  complex **6b** reversibly loses  $\text{TfO}^-$  to give **F3A** even in an aprotic medium, and it is converted to **F3D** through **F3B** and **F3C**. DBU is sufficiently basic for this process. Then **F3D** returns to **F3C** by reaction with hydrogen.

The hydrogenation seems to proceed through the six-membered cyclic TS **F3F**, which is stabilized by the charge-alternating character. The trans effect of the arene-carbon in the TS **F3F** could be crucial for yielding highly active RuH species, in contrast to the TS with the *trans*- $\text{RuH}_2$  structure in the hydrogenation using the  $\text{RuCl}_2$  pre-catalyst shown in Fig. 1. The very small  $\text{H-Ru-N-H}_{\text{ax}}$  torsion angle also seems to be preferable to form such a pericyclic-type TS.

Figure 4 schematically illustrates molecular models of the reactive  $\text{RuH}[(S)\text{-daipena}][(S)\text{-xylybinap}]$  ( $(S_P, S_N)\text{-F3C}$ ) and diastereomeric TSs,  $\text{F3F}_{Si}$  and  $\text{F3F}_{Re}$ , in the hydrogenation of ketone **4**. The labels of the complexes and TSs are related to Fig. 3. The rigid chiral structure of  $(S_P, S_N)\text{-F3C}$  is formed due to the ruthanabicyclo[2.2.1] skeleton. The hydrogenation of **4** occurs through the six-membered pericyclic-type TS,  $\text{F3F}_{Si}$  or

$\text{F3F}_{Re}$ .  $\text{F3F}_{Re}$  suffers significant repulsive interaction between the phenyl group of **4** and the expanding xylyl moieties of the catalyst. In contrast,  $\text{F3F}_{Si}$  does not have notable steric repulsion, and it could even be stabilized by the attractive  $\text{NH}/\pi$  interaction between the phenyl ring of **4** and  $\text{HN}_A$  of the complex. Therefore,  $(R)\text{-5}$  is produced via the TS  $\text{F3F}_{Si}$  with almost perfect enantioselectivity.

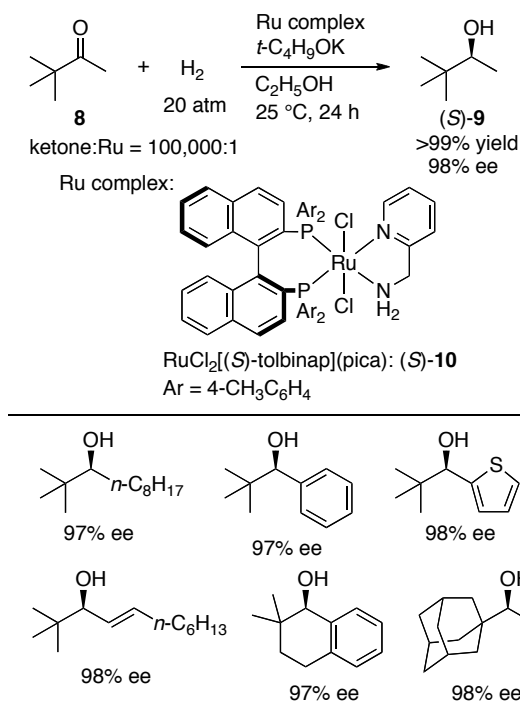


**Figure 4.** Structure of  $\text{RuH}$  species  $(S_P, S_N)\text{-F3C}$  and diastereomeric TS-models in the hydrogenation of acetophenone. Some aromatic groups and substituents are omitted for clarity. An = 4- $\text{CH}_3\text{OC}_6\text{H}_4$ . Ar = 3,5- $(\text{CH}_3)_2\text{C}_6\text{H}_3$ .

#### 4. Chiral Diphosphine/PICA/Ru(II) Catalysts for Expansion of Substrate Scope

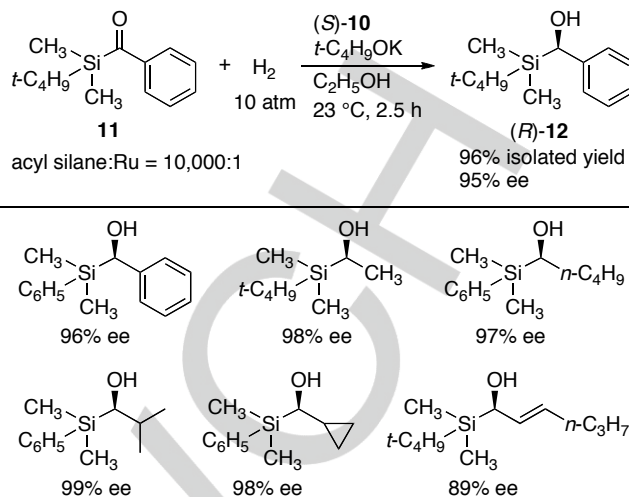
The difficulty in hydrogenating *tert*-alkyl ketones is clearly due to the significant steric hindrance around the carbonyl moiety. For example, the hydrogenation of pinacolone (**8**), an aliphatic *tert*-alkyl ketone, catalyzed by  $\text{RuCl}_2[(S)\text{-tolbinap}][(S, S)\text{-dpen}]$  and  $t\text{-C}_4\text{H}_9\text{OK}$  with an S/C of 2000 under 9 atm of  $\text{H}_2$  at 25 °C for 24 h gave the alcohol (*S*)-**9** in only 20% yield and in 14% ee (see the structures in Scheme 5).<sup>[11]</sup> This problem was solved by using  $\text{RuCl}_2[(S)\text{-tolbinap}](\text{pica})$  ( $(S)\text{-10}$ : PICA =  $\alpha$ -picolyamine) in a base-containing ethanol. PICA seems to behave as an unsymmetrical  $\text{NH}_2/\text{pyridine}$  hybrid bidentate ligand, providing a large vacancy over the flat pyridine ring. The *tert*-alkyl ketone **8** was hydrogenated with  $(S)\text{-10}$  and  $t\text{-C}_4\text{H}_9\text{OK}$  at an S/C of 100,000 under 20 atm of  $\text{H}_2$  to afford (*S*)-**9** in 98% ee quantitatively (Scheme 5).<sup>[11,12]</sup> Interestingly, the reaction in 2-propanol, which is an appropriate solvent for our ordinary

catalyst systems, decreased the enantioselectivity. A range of *tert*-butyl ketones with alkyl, aryl, hetero-aryl, and vinyl groups as well as *tert*-alkyl cyclic ketones and 1-adamantyl ketone were hydrogenated with equally excellent enantioselectivity.



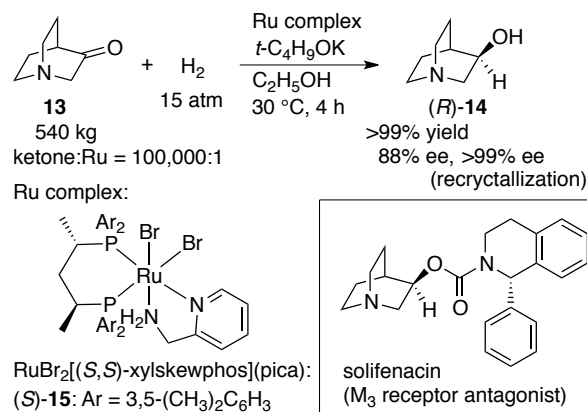
**Scheme 5.** Asymmetric hydrogenation of *tert*-alkyl ketones with TolBINAP/PICA–Ru(II) catalyst.

The (*S*)-**10**/*t*-C<sub>4</sub>H<sub>9</sub>OK-catalyst system also showed excellent performance in asymmetric hydrogenation of acyl silanes to the chiral secondary  $\alpha$ -hydroxysilanes, which are regarded as a kind of chiral functionalized organometallic compounds (Scheme 6).<sup>[13]</sup> Benzoyl-*tert*-butyldimethylsilane (**11**) was hydrogenated with an S/C of 10,000 under 10 atm of H<sub>2</sub> to give the (*R*)- $\alpha$ -hydroxysilane (*R*)-**12** in 96% isolated yield and in 95% ee. Low base-concentration (10 mM) was required to avoid the Si–C(OH) bond cleavage of the product through a base-promoted Brook-type rearrangement. The catalyst system was applied to a series of acyl silanes with alkyl, aryl, and vinyl groups to yield the desired products in high ees. The chiral  $\alpha$ -hydroxysilane was converted to the chiral vinylsilane compound without loss of optical purity by using the Ireland–Claisen rearrangement.



**Scheme 6.** Asymmetric hydrogenation of acyl silanes with chiral Ru(II) catalyst.

The chiral structure of the Ru complexes is diversely arranged by changing the combination of diphosphine and nitrogen-based ligands. Indeed, the Ru complex (*S*)-**15** bearing (*S,S*)-2,4-bis(di-3,5-xylylphosphino)pentane ((*S,S*)-XylSkewphos), a diphosphine with a chiral aliphatic backbone, and PICA efficiently catalyzed asymmetric hydrogenation of 3-quinuclidinone (**13**) in a base-containing ethanol (Scheme 7).<sup>[14]</sup> The desired (*R*)-3-quinuclidinol ((*R*)-**14**) in 88% ee was produced in the reaction with an S/C of 100,000 under 15 atm of H<sub>2</sub> in 4 h. The optical purity of (*R*)-**14** was readily increased to >99% by recrystallization. When the reaction was carried out with the (*S*)-TolBINAP complex (*S*)-**10** (S/C = 1000, 19 h, 92% yield), the product (*S*)-**14** was obtained in only 47% ee. The reaction of 540-kg scale with the complex (*S*)-**15** was performed in Kanto Chemical Co. Inc., and 11 tons of the alcohol (*R*)-**14** has been produced since 2009. The chiral alcohol (*R*)-**14** is utilized in the industrial synthesis of solifenacin (M<sub>3</sub> receptor antagonist), a medicine for urinary frequency and urinary incontinence.<sup>[15]</sup> We later found that two other related Ru catalysts show even higher enantioselectivity for this hydrogenation.<sup>[10,16]</sup>

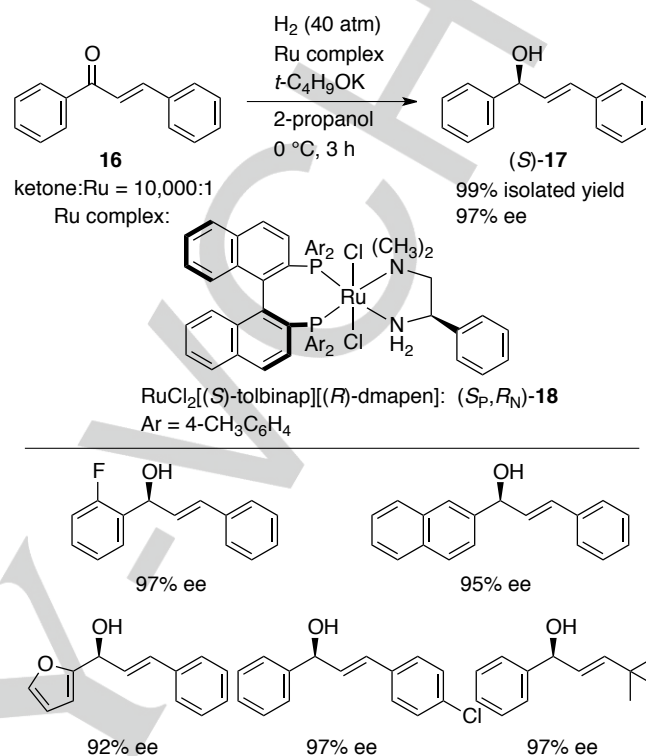


**Scheme 7.** Asymmetric hydrogenation of 3-quinuclidinone (**13**) catalyzed by XylSkewphos/PICA/Ru(II) complex.

### 5. ToIBINAP/DMAPEN/Ru(II) Catalyst and the Search for a New Type of Stereoselectivity

For achievement of high enantioselectivity in the hydrogenation of ketones ( $R^1COR^2$ ,  $R^1 \neq R^2$ ), the catalyst should precisely differentiate between carbonyl substituents,  $R^1$  and  $R^2$ , binding to the carbonyl group. Differentiation of  $sp^2$ -carbon groups ( $sp^2$ -CGs), such as aryl, hetero-aryl, and vinyl groups, from  $sp^3$ -carbon groups ( $sp^3$ -CGs), including primary-, secondary-, and tertiary-alkyl groups, has been achieved by using chiral Ru complexes as described in the previous sections. The Ru complex **3** also differentiates *ortho*-substituted benzene rings ( $sp^2$ -CGs) from phenyl group ( $sp^2$ -CG).<sup>[17]</sup> However, accurate differentiation between vinyl ( $sp^2$ -CG) and aryl ( $sp^2$ -CG) groups had not been realized in the catalytic hydrogenation of ketones. For instance, the reaction of (*E*)-chalcone (**16**) with the Ru complex **3**/*t*-C<sub>4</sub>H<sub>9</sub>OK catalyst gave the allylic alcohol **17** in only 45% ee, possibly due to the small size-difference between the phenyl and phenylethenyl moieties. This problem was overcome by the use of RuCl<sub>2</sub>[(*S*)-tolbinap][(*R*)-dmapen] ((*S*<sub>P</sub>,*R*<sub>N</sub>)-**18**: DMAPEN = 2-dimethylamino-1-phenylethylamine) with *t*-C<sub>4</sub>H<sub>9</sub>OK in 2-propanol (Scheme 8).<sup>[18]</sup> The enone **16** was smoothly hydrogenated with an S/C of 10,000 under 40 atm of H<sub>2</sub> at 0 °C in 3 h to afford the allylic alcohol (*S*)-**17** in 99% yield and in 97% ee. The saturated ketone 1,3-diphenyl-1-propanone (1% yield) was obtained as a byproduct. A range of aryl vinyl ketones was hydrogenated (S/C = 1000, 0 °C, 8 atm H<sub>2</sub>) with high enantioselectivity. The 2'-naphthyl and 2'-furyl enones as well as the substituted chalcones were appropriate examples.

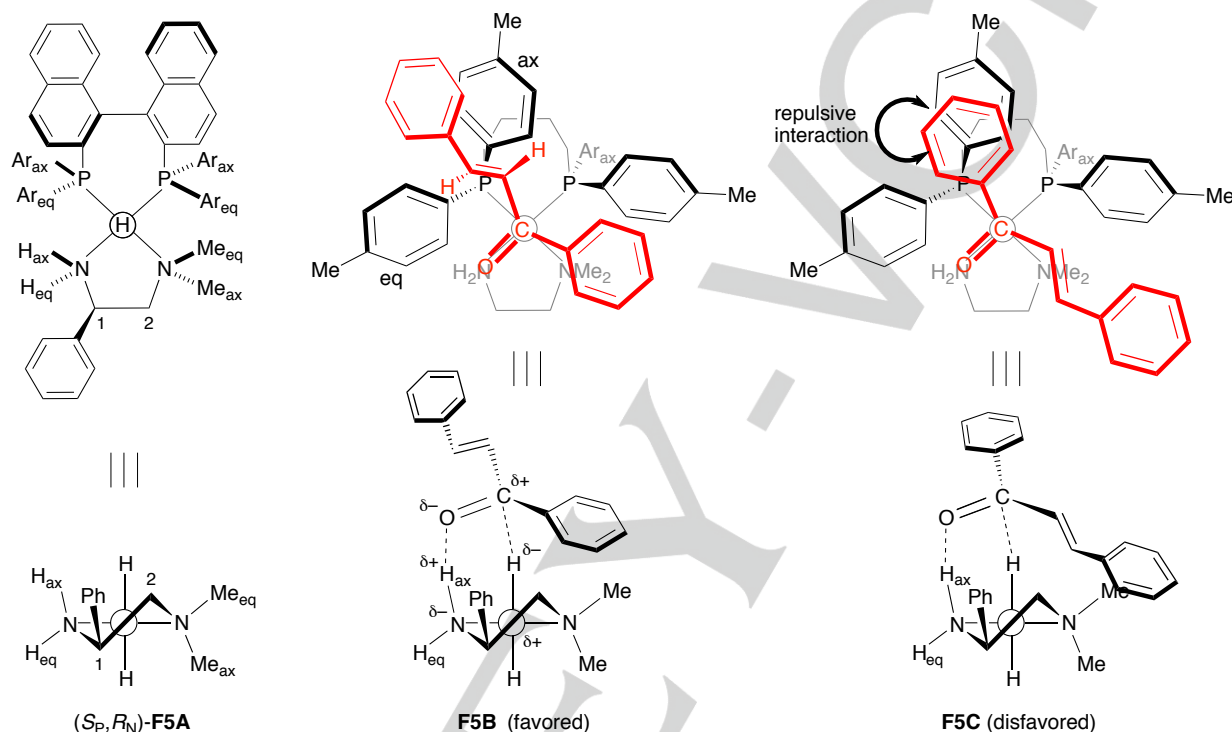
Addition of 1 equiv of P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub> to the Ru complex decreased formation of the saturated ketones in some cases.



**Scheme 8.** Asymmetric hydrogenation of aryl vinyl ketones with ToIBINAP/DMAPEN/Ru(II) catalyst.

The hydrogenation seems to proceed through a mechanism similar to that shown in Fig. 3, except the active species is *tans*-RuH<sub>2</sub>[(*S*)-tolbinap][(*R*)-dmapien], which is schematically illustrated in Fig. 5 as (*S<sub>P</sub>*,*R<sub>N</sub>*)-**F5A**.<sup>[18]</sup> The aryl vinyl ketone **16** is reduced via the six-membered cyclic TS, **F5B** or **F5C**, by utilizing a chiral section of the BINAP-ligand different from that of the TS shown in Fig. 4. **F5B** is much more favored than **F5C**, because the “sickle-shape” phenylethenyl group fits in the “V-

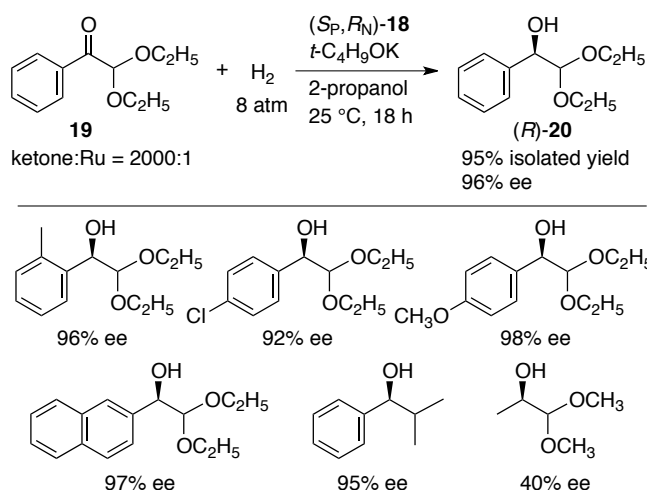
shape” channel formed with the Ar<sub>ax</sub>-P-Ar<sub>eq</sub> moiety of the TolBINAP ligand. On the other hand, a “plate-shape” phenyl ring can not enter in this channel, which results in the high activation energy in the TS **F5C**. Thus, the chiral environment formed in the TolBINAP/DMAPEN/Ru(II) catalyst primarily differentiates two carbonyl substituents, R<sup>1</sup> and R<sup>2</sup>, of prochiral ketone R<sup>1</sup>COR<sup>2</sup> by their shape but not their size.



**Figure 5.** Structure of RuH<sub>2</sub> species (*S<sub>P</sub>*,*R<sub>N</sub>*)-**F5A** and diastereomeric TS-models in the hydrogenation of **16**. Some aromatic groups and substituents in the TSs are omitted for clarity. Ar = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>.

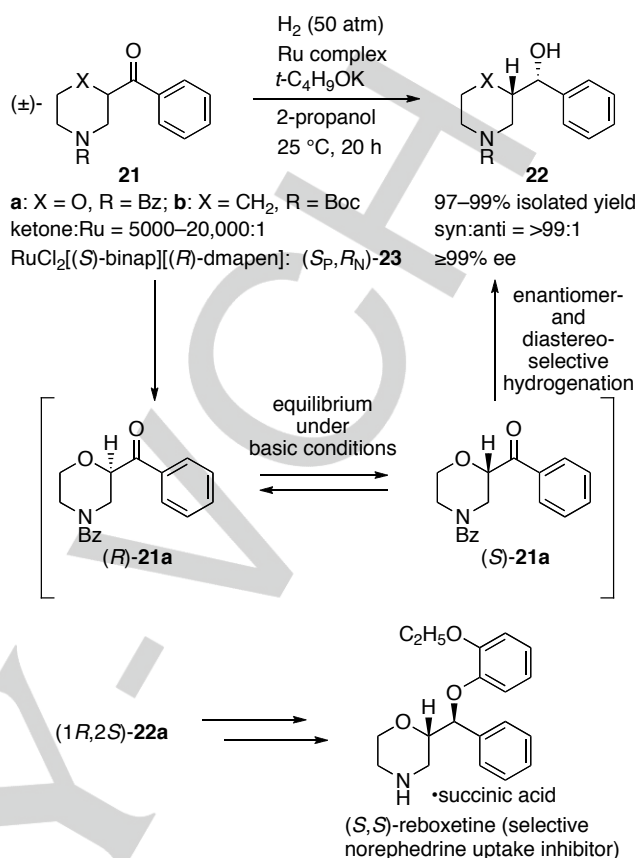
The shape-differentiated (*S<sub>P</sub>*,*R<sub>N</sub>*)-**18**/*t*-C<sub>4</sub>H<sub>9</sub>OK catalyst was applied to asymmetric hydrogenation of arylglyoxal dialkylacetals, a kind of  $\alpha$ -functionalized aromatic ketones (Scheme 9).<sup>[19]</sup> The obtained optically active  $\alpha$ -hydroxy acetals are facile synthetic intermediates convertible to the corresponding  $\alpha$ -hydroxy carbonyl compounds, 1,2-diols,  $\beta$ -amino alcohols, etc.<sup>[20]</sup> When phenylglyoxal diethylacetal (**19**) was hydrogenated in the presence of (*S<sub>P</sub>*,*R<sub>N</sub>*)-**18** and *t*-C<sub>4</sub>H<sub>9</sub>OK in 2-propanol with an S/C of 2000 under 8 atm of H<sub>2</sub> in 18 h, it yielded (*R*)-hydroxy acetal (*R*)-**20** in 95% isolated yield and in 96% ee. The reaction proceeded smoothly under 1.5 atm of H<sub>2</sub> (initial pressure) at an S/C of 500 without loss of enantioselectivity. A series of arylglyoxal dialkylacetals was equally reduced with high enantioselectivity as exemplified in Scheme 9. Notably, the (*S<sub>P</sub>*,*R<sub>N</sub>*)-**18**/*t*-C<sub>4</sub>H<sub>9</sub>OK system hydrogenated isobutyrophenone, a simple aromatic ketone, with comparably high enantioselectivity to that in the reaction of keto acetal **19**, while pyruvic aldehyde dimethylacetal was converted to the alcohol in only 40% ee. These results suggested that the (*S<sub>P</sub>*,*R<sub>N</sub>*)-**18**/*t*-C<sub>4</sub>H<sub>9</sub>OK catalyst recognizes the keto acetal **19** as a

simple  $\alpha$ -branched aromatic ketone. The sense of enantio-face selection based on the phenyl ring was the same as that observed in the hydrogenation of (*E*)-chalcone **16**, as shown in Scheme 8.<sup>[18]</sup> Therefore, the hydrogenation of **19** seems to proceed through the TS resembling **F5B** in Fig. 5 with an acetal moiety instead of the vinyl group.



**Scheme 9.** Asymmetric hydrogenation of  $\alpha$ -branched ketones.

The successful results in the asymmetric hydrogenation of  $\alpha$ -branched aromatic ketones prompted us to investigate the reaction of racemic  $\alpha$ -substituted aromatic ketones through dynamic kinetic resolution, affording the  $\beta$ -substituted secondary alcohols with two contiguous stereogenic centers with high diastereo- and enantioselectivities.<sup>[21]</sup> Representative examples are shown in Scheme 10. A racemic  $\alpha$ -substituted ketone **21a** ( $X = O$ ,  $R = Bz$ ) was hydrogenated with  $RuCl_2[(S)\text{-binap}][(R)\text{-dmapen}]$  ( $(S_P, R_N)\text{-23}$ ) with an S/C of 5000 in a  $t\text{-C}_4\text{H}_9\text{OK}$ -containing 2-propanol (30 mM) under 50 atm of  $H_2$  in 20 h to afford (1*R*,2*S*)-**22a** (syn:anti = >99:1) in 99% isolated yield and 99% ee.<sup>[22]</sup> The product was transformed to (*S,S*)-reboxetine (>99% ee),<sup>[23]</sup> a selective norepinephrine uptake inhibitor, through four-step reaction (61% yield). The reaction of **21b** ( $X = CH_2$ ,  $R = Boc$ ) catalyzed by the same complex (S/C = 20,000) gave (1*S*,2*S*)-**22b** with almost perfect diastereo- and enantioselectivities. Three requirements should be satisfied to achieve high stereoselectivity in this reaction: 1) the racemization rate of chiral ketone **21** (between (*R*)-**21a** and (*S*)-**21a** for example) should be sufficiently faster than the rate of hydrogenation; 2) discrimination between the two enantiomers of **21** should be extremely high; 3) diastereoselectivity in the hydrogenation of (*R*)- or (*S*)-**21** ((*S*)-**21a** in Scheme 10) should be excellent. The first requirement was easily satisfied because the stereomutation of the ketone- $\alpha$ -position was accelerated under the basic condition. The second and third ones were achieved by the precisely regulated chiral structure of the BINAP/DMAPEN/Ru(II) catalyst.

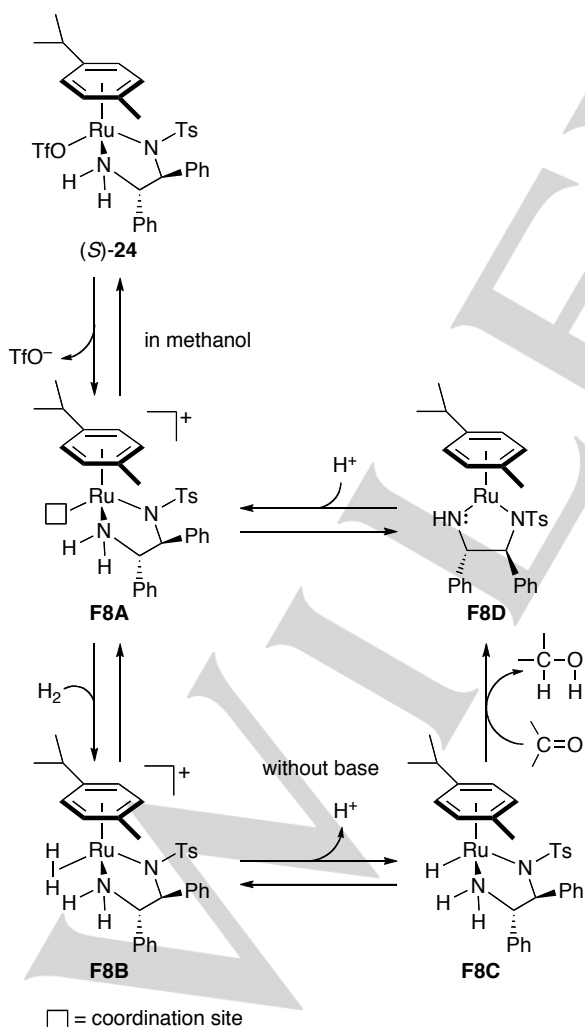


**Scheme 10.** Catalyst-controlled diastereo- and enantioselective hydrogenation of racemic ketones via dynamic kinetic resolution.

Diastereoselective reduction of  $\alpha$ -substituted ketones has been intensively studied, primarily by using stoichiometric metal hydrides.<sup>[24]</sup> The stereoselective outcome is explained with TS-models represented by the Felkin–Anh and chelation-controlled models, in which the reducing agent is recognized as a naked hydride (Fig. 6, a) and b). Therefore, the selectivity is principally determined by the substrate structure, and a high level of diastereoselectivity is achieved only when the  $\alpha$ -substituents, L, M, S, and X, have notable differences in size and/or electronic character. Diastereoselective reduction of ketones **21** with such metal-hydride reagents is difficult due to the small difference in size and electronic properties between the  $-\text{X}(\beta)\text{CH}_2(\gamma)-$  (**21a**:  $X = O$ , **21b**:  $X = CH_2$ ) and  $-\text{CH}_2(\beta)\text{NR}(\gamma)-$  (**21a**:  $R = Bz$ , **21b**:  $R = Boc$ ) moieties. In fact, the syn/anti-selectivities in the metal-hydride reduction of **21** were very low: for **22a**,  $\text{NaBH}_4$  (60:40),  $\text{Zn}(\text{BH}_4)_2$  (80:20),  $\text{KB}(\text{sec-C}_4\text{H}_9)_3\text{H}$  (70:30); for **22b**,  $\text{NaBH}_4$  (53:47),  $\text{Zn}(\text{BH}_4)_2$  (59:41),  $\text{KB}(\text{sec-C}_4\text{H}_9)_3\text{H}$  (49:51).

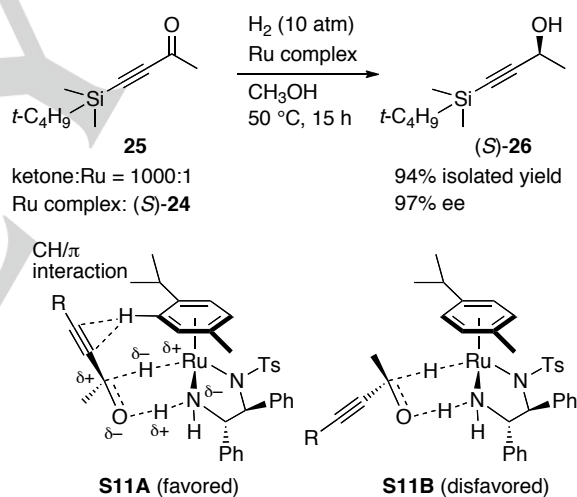


species **F3B** with removal of  $\text{TfO}^-$  followed by a base-induced deprotonation, yielding the active RuH complex **F3C** (see Fig. 3). This mechanistic consideration suggests that the hydrogenation under base-free conditions is possible when the  $[\text{Ru}(\text{H}_2)]^+$  species is transformed to the RuH complex without the assistance of a base. We found that  $\text{Ru}(\text{OTf})[(\text{S,S})\text{-TsDPEN}](\eta^6\text{-}p\text{-cymene})$  (**(S)-24**; TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) exhibits the desired catalytic performance in methanol. Figure 8 shows the proposed mechanism for this hydrogenation according to the structural and kinetic studies.<sup>[25,26]</sup> The Ru complex **24** has a neutral  $\text{Ru}(\text{OTf})$  structure in less polar toluene, but the cationic **F8A** is formed with release of  $\text{TfO}^-$  in polar methanol. Hydrogen coordinates at the vacant site to give  $[\text{Ru}(\text{H}_2)]^+$  species **F8B**. The electronic property allows deprotonation without an additional base to afford RuH complex **F8C**. Methanol may assist in this process. The reduction of ketone by **F8C** gives amide complex **F8D**, and then protonation re-generates **F8A**. No reaction was observed in less polar 2-propanol, which is known as the best solvent for the transfer hydrogenation of ketones with  $\text{RuCl}(\text{TsDPEN})(\eta^6\text{-}p\text{-cymene})$  in the presence of an alkaline base.<sup>[27]</sup>



**Figure 8.** Proposed catalytic cycle for hydrogenation of ketones with the  $\eta^6$ -arene/TsDPEN/Ru(II) complex **24** in the absence of base.

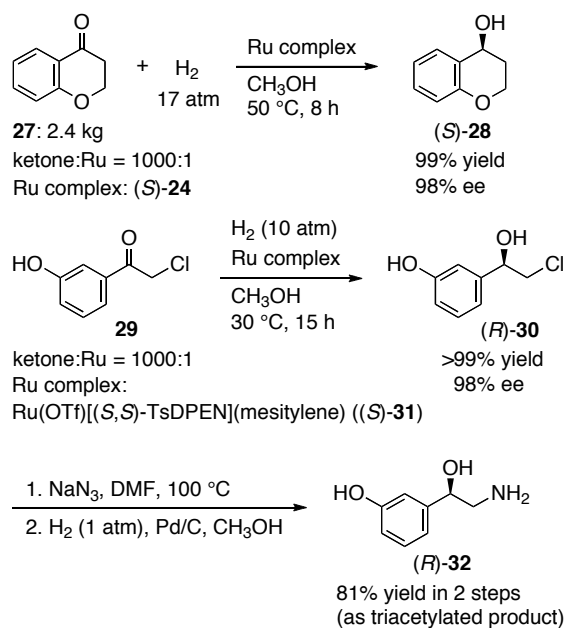
The base-free catalyst system was successfully applied to the asymmetric hydrogenation of base-labile ketones. For example, alkynyl ketone **25** was smoothly hydrogenated in the presence of (**S**)-**24** with an S/C of 1000 under 10 atm of  $\text{H}_2$  at 50 °C to afford the propargylic alcohol (**S**)-**26** in 97% ee (Scheme 11).<sup>[28]</sup> A range of alkyl alkynyl ketones was converted to the 1,2-reduction products in high enantioselectivity. Small amounts of the 1,4-reduction product (<4%) were obtained in some cases. The reduction of ketones with the RuH species of **F8C** seems to occur via the six-membered cyclic TS, **S11A** or **S11B**, which resembles the process for diphosphine/*N*-based ligand/Ru(II)-catalyzed hydrogenation. The high 1,2-reduction-selectivity supports the TS-model. The excellent enantioselectivity means that the chiral catalyst precisely discriminates between the alkynyl and alkyl groups with small-size differences. The favorite TS **S11A** is thought to be stabilized by the  $\text{CH}/\pi$  attractive interaction between the alkynyl  $\pi$ -bond and the *p*-cymene CH moiety.<sup>[28]</sup> The diastereomeric TS **S11B** with no stabilization effect is disfavored.



**Scheme 11.** Asymmetric hydrogenation of alkynyl ketones with  $\eta^6$ -arene/TsDPEN/Ru(II) catalyst and the diastereomeric TS-models.

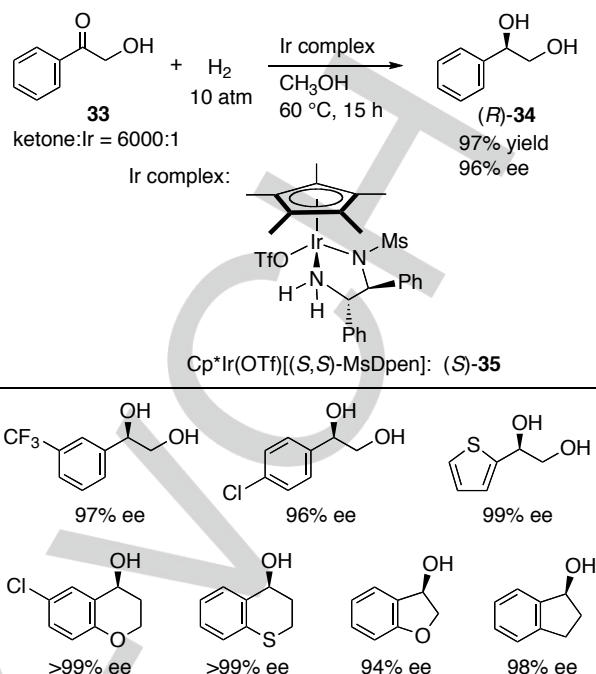
The  $\eta^6$ -arene/Ru catalyst was also applied to the hydrogenation of other base-sensitive ketones, 4-chromanones and  $\alpha$ -chloro aromatic ketones.<sup>[25,29]</sup> Typical examples are shown in Scheme 12. A 2.4-kg scale reaction of 4-chromanone (**27**) was performed by using (**S**)-**24** with an S/C of 1000 under 17 atm of  $\text{H}_2$  to yield (**S**)-4-chromanol ((**S**)-**28**) in 98% ee quantitatively.<sup>[25]</sup> The mesitylene/Ru complex **31** sometimes gave even higher enantioselectivity in the hydrogenation of  $\alpha$ -chloro ketones. Notably, phenacyl chloride with a phenolic hydroxy group **29** was quantitatively hydrogenated to the phenolic chlorohydrin **30** in 98% ee, which was converted to

norphenylephrine **32** in two-step reactions without a protection-deprotection procedure.<sup>[29]</sup>



**Scheme 12.** Asymmetric hydrogenation of 4-chromanones and  $\alpha$ -chloro aromatic ketones with  $\eta^6$ -arene/TsDPEN/Ru(II) catalysts.

$\alpha$ -Hydroxyacetophenone (**33**) has electronic resemblance to the corresponding  $\alpha$ -chloro ketone. The  $\eta^6$ -arene/TsDPEN/Ru(II) complexes efficiently catalyzed asymmetric hydrogenation of the  $\alpha$ -chloro ketones as described above; however, these catalysts were virtually inert for the reaction of **33**. This problem was solved by using an isoelectronic complex Cp\*Ir(OTf)[(S,S)-MsDPEN] ((S)-**35**: Cp\* = pentamethylcyclopentadienyl, MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine). The reaction of **33** with (S)-**35** at an S/C of 6000 under 10 atm of H<sub>2</sub> at 60 °C in 15 h afforded the (R)-1,2-diol (S)-**34** in 97% yield and in 96% ee (Scheme 13).<sup>[30]</sup> Selection of the sulfonyl group on the DPEN ligand was crucial to achieve high catalytic activity and enantioselectivity. The use of the TsDPEN/Ir complex resulted in only 12% yield and 85% ee under the same conditions. Methanol was also the most appropriate solvent. The reaction proceeded smoothly under atmospheric pressure of H<sub>2</sub> with an S/C of 200 in 15 h. Synthetically useful chiral 1,2-diols with aromatic and heteroaromatic substituents in high enantiomeric purity were obtained by this method.



**Scheme 13.** Asymmetric hydrogenation of  $\alpha$ -hydroxy ketones and aromatic heterocyclic ketones with MsDPEN/Cp\*Ir(III) catalyst.

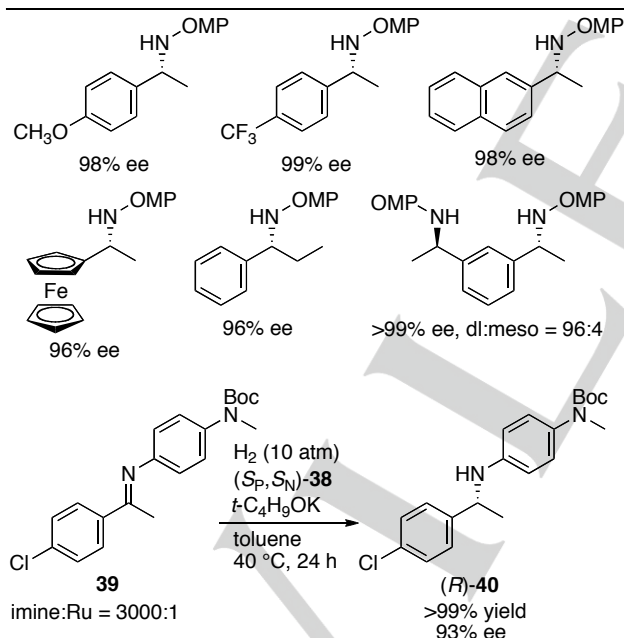
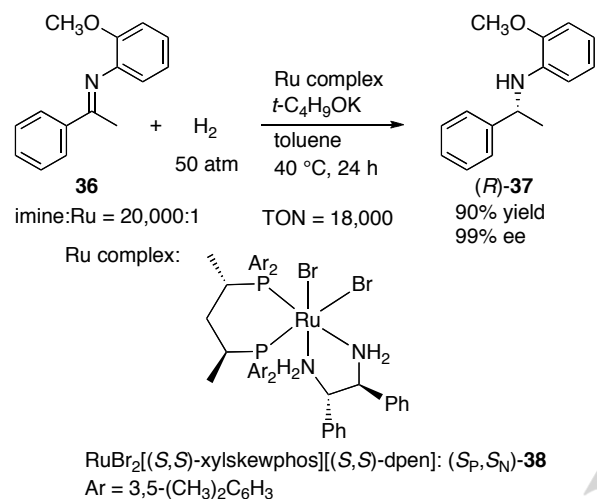
The Ir complex **35** was also useful in the hydrogenation of aromatic heterocyclic ketones.<sup>[31]</sup> As exemplified in Scheme 13, a series of five- and six-membered heterocyclic ketones such as 3(2*H*)-benzofuranone, 4-chromanone, and 4-thiochromanone, as well as indanone, a base-labile cyclic aromatic ketone, were hydrogenated with an S/C of 200–5000 under 15 atm of H<sub>2</sub> in 24 h to afford the cyclic alcohols in up to >99% ee.

## 7. Asymmetric Hydrogenation of Imino Compounds with Chiral Ru(II) Catalysts

The chiral *trans*-RuCl<sub>2</sub>(diphosphine)(diamine) complexes with base effectively catalyze asymmetric hydrogenation of ketones as described in the former sections. However, this type of catalyst system was not very suitable for the reaction of imino compounds. For example, the RuCl<sub>2</sub>(et-duphos)(dach)/*t*-C<sub>4</sub>H<sub>9</sub>OK was reported to catalyze hydrogenation of *N*-phenyl acetophenone-derived imine with an S/C of 100 under 15 atm of H<sub>2</sub> at 65 °C in 69 h, yielding the chiral amine in 94% ee (97% conversion).<sup>[32]</sup> Both C=O and C=NAr (Ar = aryl group) are polar double bonds, but the difference of polarizability and the bulkiness by the *N*-aryl group could cause a slow reaction. The *E/Z* isomerism of the C=NAr moiety makes the enantio-face selection difficult.

RuBr<sub>2</sub>[(S,S)-xylskewphos][(S,S)-dpn] ((S<sub>P</sub>,S<sub>N</sub>)-**38**) was readily prepared from RuBr<sub>2</sub>[(S,S)-xylskewphos] and (S,S)-DPEN in DMF as a 60:40 mixture of the *cis*-RuBr<sub>2</sub> complex and the *trans* isomer.<sup>[33]</sup> The Ru complex (S<sub>P</sub>,S<sub>N</sub>)-**38** and *t*-C<sub>4</sub>H<sub>9</sub>OK catalyzed asymmetric hydrogenation of *N*-OMP imine derived

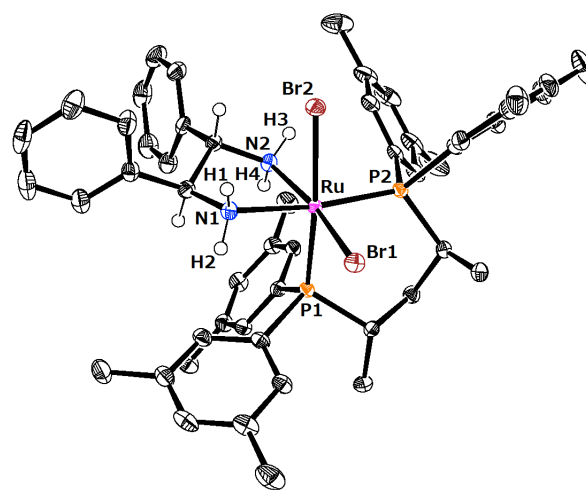
from acetophenone **36** (OMP = 2-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>). The reaction with an S/C of 20,000 under 50 atm of H<sub>2</sub> in toluene at 40 °C in 24 h afforded the *R* amine **37** in 90% yield and in 99% ee (Scheme 14). A very high TON of 18,000 was achieved. A comparable result was obtained in THF solution, but no reaction was observed in 2-propanol, which is one of the best solvents for the hydrogenation of ketones with diphosphine/diamine/Ru(II) complexes. Readily removable OMP with a reductive treatment was selected as the typical *N*-substituent, although several other aryl groups could also be used.



**Scheme 14.** Asymmetric hydrogenation of *N*-arylimines catalyzed by XylSkewphos/DPEN/Ru(II) complexes.

A variety of aromatic and unsaturated imines were converted to the desired amines with high enantioselectivity at an S/C of 500–3000 under 10 atm of H<sub>2</sub> in 15–24 h (Scheme 14).<sup>[33]</sup> The size and electronic properties of the aromatic moiety on the imino carbon did not substantially influence the catalyst performance. The ferrocenyl imine was hydrogenated with comparably high selectivity. Double hydrogenation of the *meta*-diimine gave the diamine in a diastereomeric ratio of 96:4 and in >99% ee for the major diastereomer. The widely applicable catalyst hydrogenated the substituted *N*-arylimine **39** to quantitatively give the amine **40** in 93% ee, which is the intermediate for the synthesis of a C5a receptor antagonist.<sup>[34]</sup>

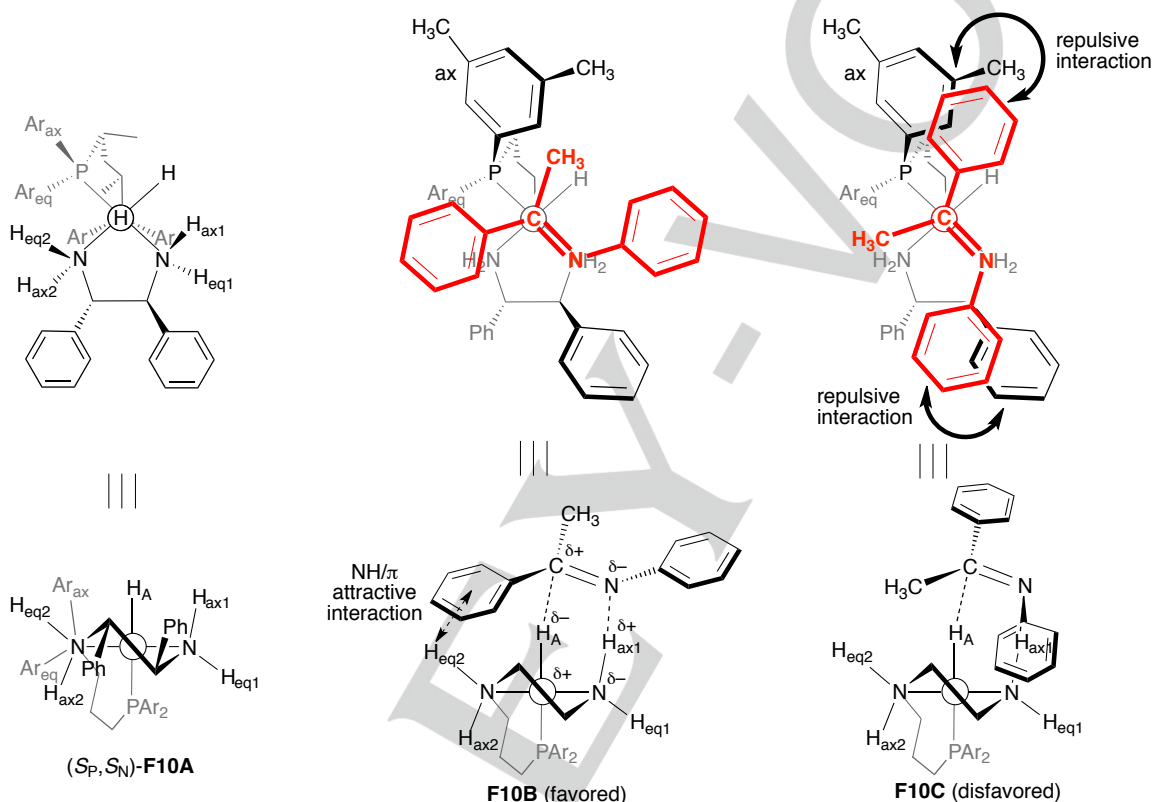
Figure 9 shows the ORTEP structure of the *cis* diastereomer of (*S<sub>P</sub>*,*S<sub>N</sub>*)-**38**. The catalytic efficiencies with *cis*-**38** and with the 60:40-*cis/trans* mixture were the same, including the enantioselective ability. Therefore, we considered that *cis*-RuH<sub>2</sub>[(*S,S*)-xylskewphos][(*S,S*)-dpn] is the active species exhibiting excellent catalyst performance in the hydrogenation of *N*-arylimines, and its structure is closely related to that of (*S<sub>P</sub>*,*S<sub>N</sub>*)-*cis*-**38**. This complex has a distorted octahedral structure with a Br(2)–Ru–P(1) angle of 174°. The stronger *trans*-effect of P(1) relative to N(2) causes the longer Ru–Br(2) bond length of 2.65 Å compared to 2.57 Å for Ru–Br(1). The Br(2)–Ru–N(1)–H(1) torsion angle of 26° is much smaller than the Br(2)–Ru–N(1)–H(2) angle of 143°, indicating that the amino protons H(1) and H(2) are differently placed to be axial (*H<sub>ax</sub>*) and equatorial (*H<sub>eq</sub>*), respectively. The distance between H(1) and Br(2) of 2.79 Å suggests the presence of hydrogen bonding.



**Figure 9.** ORTEP structure of (*S<sub>P</sub>*,*S<sub>N</sub>*)-**38**. All hydrogen atoms except those on the diamine backbone are omitted for clarity.

Based on the X-ray structure of  $(S_P, S_N)$ -**38** shown in Fig. 9, models of the expected active *cis*-RuH<sub>2</sub> complex  $(S_P, S_N)$ -**F10A** and the possible diastereomeric TSs, **F10B** and **F10C**, for the hydrogenation of *N*-phenylimine derived from acetophenone are illustrated in Fig. 10.<sup>[33]</sup> A <sup>1</sup>H NMR measurement indicated that the *N*-phenylimine exclusively adopts an *E* configuration in toluene. The imine reduction occurs through the six-membered cyclic TS similar to the reaction of ketones, as discussed in the former sections, except that the active RuH<sub>2</sub> has *cis* geometry. The H<sub>A</sub> placed trans to the strongly electron-donating PAR<sub>2</sub> group

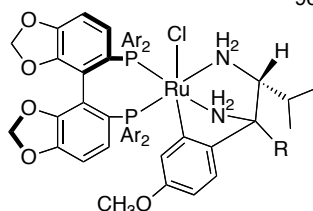
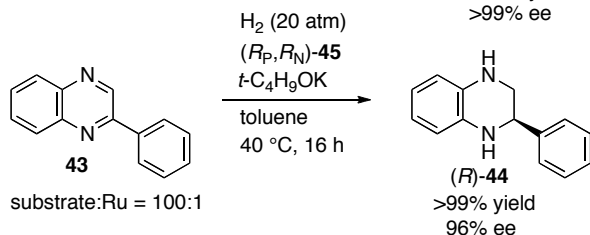
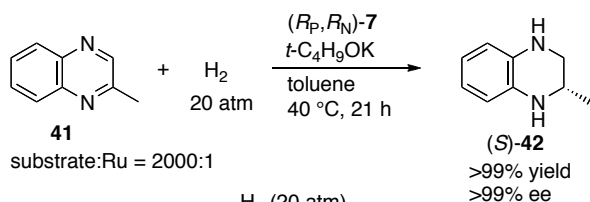
acts as a hydride nucleophile. The TS **F10C** suffers two serious steric repulsions between the axial *P*-xylyl moiety of XylSkewphos and the *C*-phenyl group of the imine, as well as between the *C*-phenyl ring of DPEN and the *N*-phenyl group of the imine. In contrast, the TS **F10B** has no significant repulsion and is even stabilized by the NH/ $\pi$  interaction between the amine proton of DPEN and the *C*-phenyl group of the imine. Therefore, the hydrogenation resulted in notably high enantioselectivity via the much favored TS **F10B**.



**Figure 10.** Structure of RuH<sub>2</sub> complex  $(S_P, R_N)$ -**F10A** derived from  $(S_P, R_N)$ -**38** and diastereomeric TS-models in the hydrogenation of *N*-phenylimine. The structures are simplified for clarity. Ar = 3,5-(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

Asymmetric hydrogenation of 2-substituted quinoxalines as well as 3-substituted 2*H*-1,4-benzoxadines and the benzothiazines was achieved by using chiral ruthenabicyclic complexes with bases as catalysts, producing the optically active bicyclic *N*-arylamines bearing a  $\beta$ -heteroatom which are observed as core structures in various bioactive compounds.<sup>[35]</sup> Some examples are shown in Scheme 15. Double hydrogenation of 2-methylquinoxaline (**41**) catalyzed by a RuCl[(*R*)-daipena][(*R*)-dm-segphos] ( $(R_P, R_N)$ -**7**)/*t*-C<sub>4</sub>H<sub>9</sub>OK system with an S/C of 2000 under 20 atm of H<sub>2</sub> at 40 °C was completed in 21 h to afford the *S* cyclic 1,2-diamine (*S*)-**42** in almost optically pure form. The hydrogenation proceeded under 1–1.5 atm of H<sub>2</sub> at an S/C of 100 without lowering of the enantioselectivity. The reaction in an alcoholic solvent somewhat slowed the rate. The XylBINAP-complex **6a** (see Scheme 4) showed lower enantioselectivity. No hydrogenation of 2-phenylquinoxaline (**43**) was observed with the Ru complex **7**,

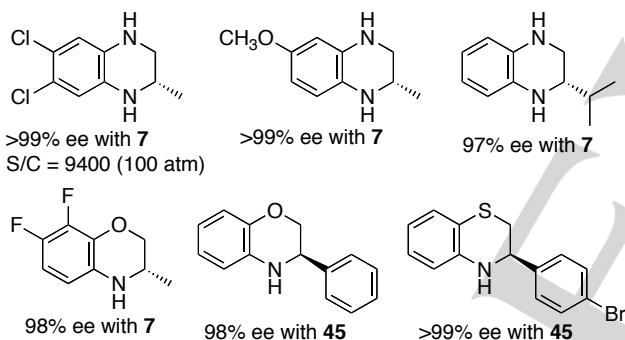
possibly due to steric hindrance of the 2-phenyl substituents on **43**. This problem was solved by using the less stereo-demanding RuCl[(*R*)-daipena][(*R*)-segphos] ( $(R_P, R_N)$ -**45**: SEGPHOS = (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis(diphenylphosphine))/*t*-C<sub>4</sub>H<sub>9</sub>OK system as a catalyst with an S/C of 100 under 20 atm of H<sub>2</sub> to yield the product (*R*)-**44** in 96% ee. The reverse sense of the enantioface-selection is notable.



$(R_P, R_N)$ -**7**: Ar = 3,5-( $\text{CH}_3$ ) $_2\text{C}_6\text{H}_3$

$(R_P, R_N)$ -**45**: Ar =  $\text{C}_6\text{H}_5$

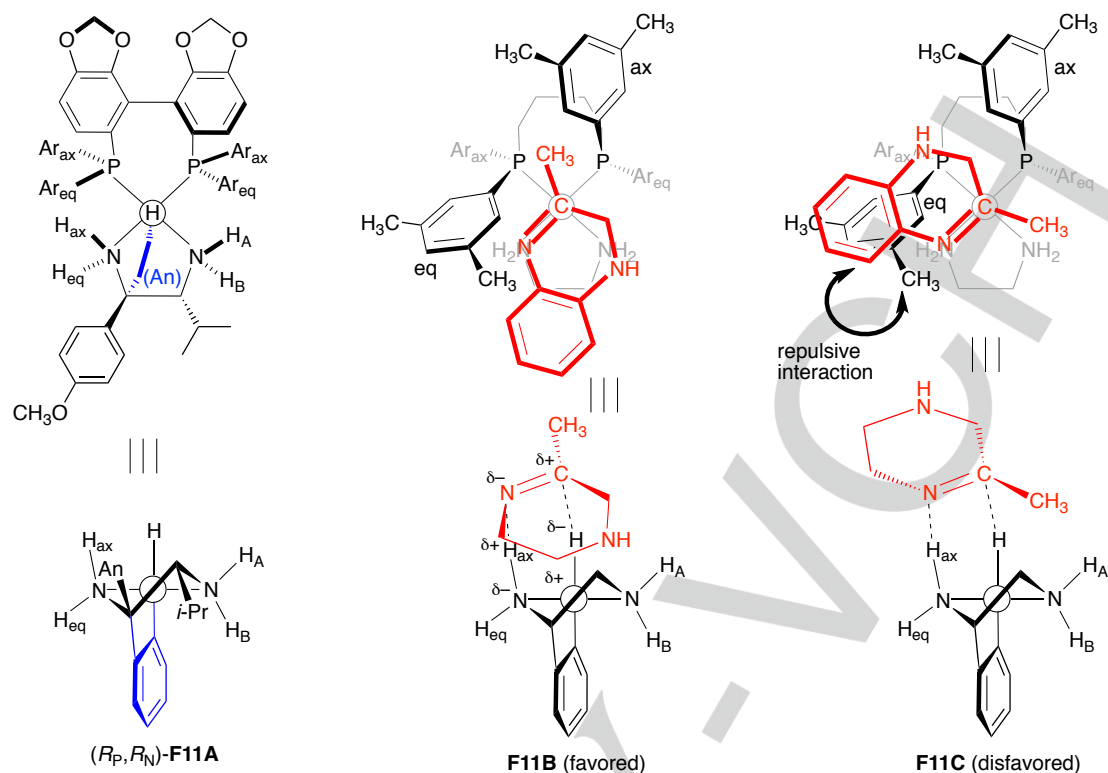
R = 4- $\text{CH}_3\text{OC}_6\text{H}_4$



**Scheme 15.** Asymmetric hydrogenation of quinoxalines, benzoxazines, and benzothiazines with chiral ruthenabicyclic catalysts.

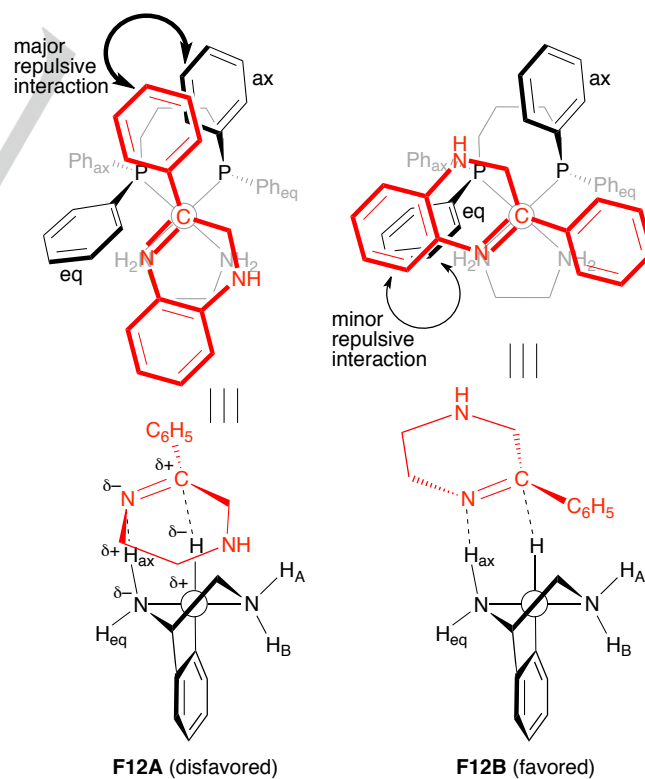
The asymmetric hydrogenation using the ruthenabicyclic complexes **7** and **45** was applicable to a wide range of this type of cyclic hetero-substituted imines. 2-Alkylquinoxalines were successfully hydrogenated with the DM-SEGPHOS-complex **7**. The reaction of 6,7-dichloro-2-methylquinoxaline with an S/C of 9400 under 100 atm of  $\text{H}_2$  was completed in 72 h. 7,8-Difluoro-3-methyl-2H-1,4-benzoxazine was also reduced with the **7**/ $t\text{-C}_4\text{H}_9\text{OK}$  catalyst to give the cyclic amine in 98% ee, which is a key compound for the asymmetric synthesis of antibacterial levofloxacin.<sup>[36]</sup> The 2H-1,4-benzoxazine and -benzothiazine with a 3-aryl substituent were hydrogenated with the SEGPHOS-complex **45** in excellent enantioselectivity.

The reaction of the cyclic imines catalyzed by the ruthenabicyclic complexes seems to proceed through a mechanism similar to that of the reaction with ketonic substrates, as shown in Fig. 3. The DM-SEGPHOS-complex  $(R_P, R_N)$ -**7**/ $t\text{-C}_4\text{H}_9\text{OK}$  system plausibly forms the active  $\text{RuH}[(R)\text{-daipena}][(R)\text{-dm-segphos}]$ , the structure of which is schematically drawn as  $(R_P, R_N)$ -**F11A** in Fig. 11. The quinoxaline substrate **41** is reduced in two steps to obtain the diamine product **42**. The second step of the hydrogenation with  $(R_P, R_N)$ -**F11A** occurs via the TS **F11B** or **F11C** containing the outer-sphere six-membered cyclic structure. **F11C** suffers a significant repulsive interaction between the fused phenyl ring of the imine and the equatorially oriented *P*-xylyl group of DM-SEGPHOS. The favored TS **F11B** can avoid such steric repulsion, and thereby produce the *S* product exclusively.



**Figure 11.** Structure of RuH species  $(R_P, R_N)$ -F11A and diastereomeric TS-models in the second step of hydrogenation of **41**. Some aromatic groups and substituents are omitted for clarity. An = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>. Ar = 3,5-(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

The preference of stereoselection in TSs is largely changed in the hydrogenation of the 2-phenyl substrate **43** catalyzed by the  $(R_P, R_N)$ -**45**/*t*-C<sub>4</sub>H<sub>9</sub>OK system, as shown in Fig. 12. The flat 2-phenyl ring of the imine causes remarkable steric repulsion with the axial *P*-phenyl group of SEGPHOS in the TS **F12A**. On the other hand, the repulsive interaction between the imine fused-phenyl ring and the equatorial *P*-phenyl moiety in the TS **F12B** is minor. Therefore, the *R*-configured diamine **44** is obtained as the major product.

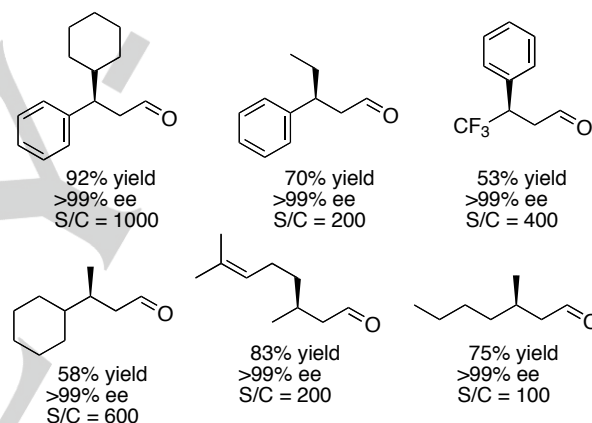
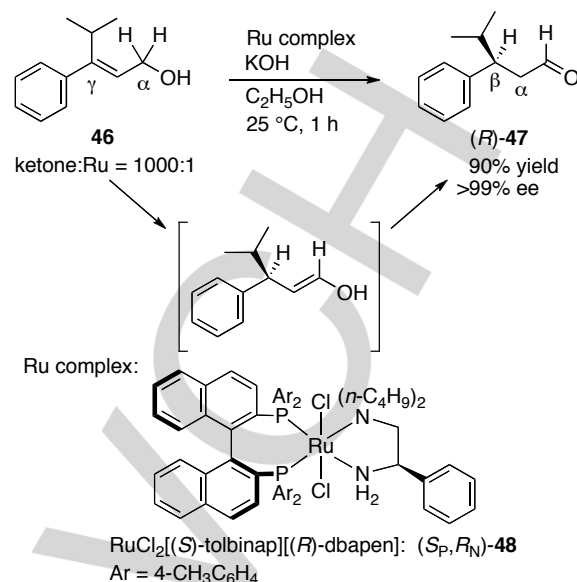


**Figure 12.** Structure of diastereomeric TS-models in the second step of hydrogenation of **43** with  $(R_P, R_N)$ -**45**. Some aromatic groups and substituents are omitted for clarity.

## 8. Asymmetric Isomerization of Primary Allylic Alcohols into the Optically Active Aldehydes with Ru(II) Catalysts

As we described in Section 5,  $\text{RuCl}_2[(S)\text{-tolbinap}][(R)\text{-dmapen}]$  ( $(S_P, R_N)$ -**18**) with a base efficiently catalyzed asymmetric hydrogenation of (*E*)-chalcone (**16**) at 0 °C to afford the *S* allylic alcohol **17** in 99% yield and in 97% ee (see Scheme 8). When this reaction was carried out at 30 °C, 1,3-diphenyl-1-propanone, a saturated ketone, and 1,3-diphenyl-1-propanol, a saturated alcohol, were obtained as byproducts in 8% and 9% yield, respectively.<sup>[18]</sup> The separate experiment treating allylic alcohol (*S*)-**17** under the hydrogenation conditions in 1 h gave the saturated ketone in 7% yield. These results suggested that the saturated ketone was formed by an isomerization (1,3-hydride migration) of the allylic alcohol (*S*)-**17**, but not by a conjugate hydrogenation of the enone **16**. Therefore, we next investigated the asymmetric isomerization of prochiral primary allylic alcohols into the optically active aldehydes by using our original Ru catalyst.

We selected (*E*)-4-methyl-3-phenyl-2-penten-1-ol (**46**), a  $\gamma, \gamma$ -disubstituted allylic alcohol, as a typical substrate to optimize the catalyst structure and reaction conditions (Scheme 16).<sup>[37]</sup> The reaction is started from site-selective C–H activation at the  $\alpha$ -position, an allylic carbon with a hydroxy group, over the simple allylic  $\delta$ -position. The hydride is enantioselectively transferred onto the  $\gamma$ -carbon with a shift of the  $\pi$ -bond to produce the enol intermediate. Then keto–enol tautomerization produces the optically active  $\beta$ -substituted aldehyde **47**. After careful investigations, we optimized the catalyst structure and the reaction conditions. The isomerization of **46** with  $\text{RuCl}_2[(S)\text{-tolbinap}][(R)\text{-dbapen}]$  ( $(S_P, R_N)$ -**48**: DBAPEN = 2-dibutylamino-1-phenylethylamine) at an S/C of 1000 in a KOH-containing ethanol at 25 °C in 1 h afforded the chiral aldehyde (*R*)-**47** in 90% yield in an almost optically pure form. The corresponding saturated alcohol (*R*)-4-methyl-3-phenylpentan-1-ol (>99% ee) in 7% yield was obtained as a byproduct under the reductive conditions. Ethanol was the solvent of choice. The yield of **47** was decreased in other alcoholic and aprotic solvents. Interestingly, use of the DBAPEN/Ru complex ( $S_P, R_N$ )-**18** under otherwise identical conditions gave the aldehyde **47** in only 7% yield.  $\text{RuCl}_2[(S)\text{-tolbinap}](\text{dmf})_n$ , without a diamine ligand catalyzed the reaction under the regular conditions to give (*R*)-**47** in a medium yield of 79% and with >99% optical purity. These results suggest that the enantioselection of this isomerization is solely controlled by TolBINAP, and DBAPEN has a role for enhancing the yield of **47**.



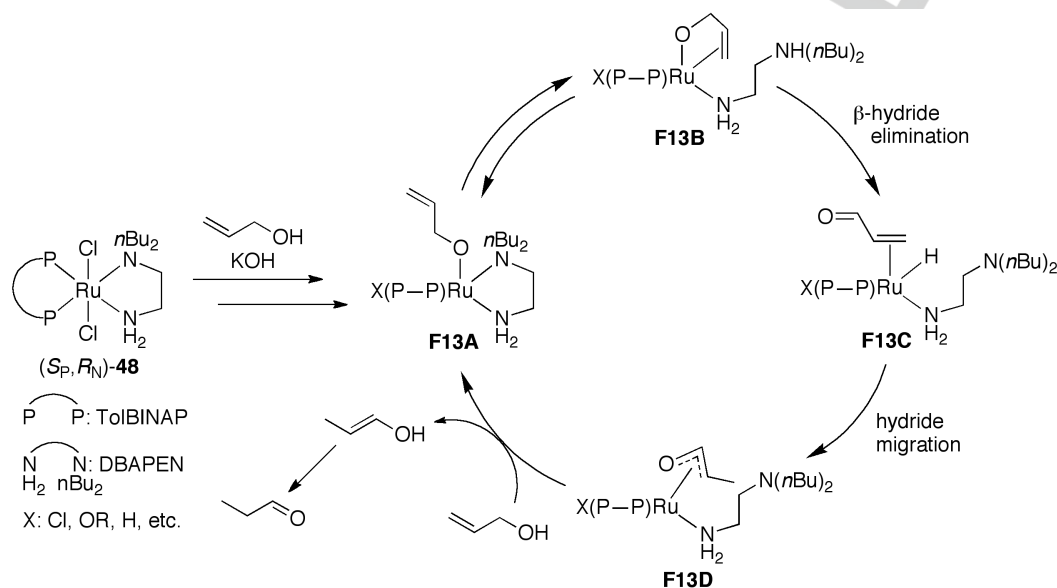
**Scheme 16.** Asymmetric isomerization of primary allylic alcohols with TolBINAP/DBAPEN/Ru(II) catalyst.

The catalytic reaction was applied to a variety of  $\gamma, \gamma$ -disubstituted primary allylic alcohols (Scheme 16). The aliphatic and aromatic  $\beta$ -substituted aldehydes were obtained in  $\geq 99\%$  ee in all cases. The reaction rate was dependent on the substrate structure. The allylic alcohols with a  $\gamma$ -secondary alkyl group tended to give a higher TON. No isomerization was observed at the simple (without hydroxy group) allylic moiety. Notably, the reaction of (*E*)-3-methyl-2-hepten-1-ol, an allylic alcohol with methyl and primary alkyl  $\gamma$ -substituents, also resulted in >99% selection of the enantioface.

A proposed mechanism for the isomerization of allylic alcohols catalyzed by the TolBINAP/DBAPEN/Ru(II) complex is shown in Fig. 13.<sup>[37]</sup> The catalyst precursor  $\text{RuCl}_2$  complex **48** is converted to the allylic alkoxide complex **F13A** in the presence of a catalytic amount of base and the allylic alcohol substrate, in which X is an anionic ligand, including Cl, OR, and H. **F13A** is reversibly converted to the olefin-coordinated complex **F13B** with elimination of the  $\text{N}(n\text{-Bu})_2$  group of DBAPEN. The

bulkiness of the  $N(n\text{-Bu})_2$  moiety causes the hemilabile character of DBAPEN. Strongly binding diamine ligands disturb the formation of **F13B**, so that the isomerization with the TolBINAP/DMAPEN/Ru(II) complex **18** gave a poor conversion.  $\beta$ -Hydride elimination in **F13B** gives the RuH species **F13C** with an  $\alpha,\beta$ -unsaturated aldehyde. Hydride transfer from the Ru

center to the enal  $\beta$ -carbon forms the  $\eta^3$ -oxaallyl species **F13D**. Then enol is replaced with the substrate allylic alcohol to reproduce the alkoxide complex **F13A**. Hemilabile DBAPEN could promote the release of the enol by reforming the chelate structure. The enol is quickly converted to the aldehyde product in the alcoholic medium.



**Figure 13.** Proposed mechanism of isomerization of allylic alcohols to the aldehydes with  $(S_P, R_N)$ -**48** and a base.

## 9. Summary and Outlook

The BINAP/chiral daimine/Ru(II) catalysis developed by our research group with Professor Ryoji Noyori has contributed greatly to the progress of chemistry on asymmetric hydrogenation. For example, the Ru catalysts enabled very high TON >1,000,000 and optical yield >99% in the reaction of simple ketones in the best cases. The “metal–ligand cooperative (bifunctional) transition state” model is now widely accepted and utilized in the catalyst design for novel reactions. We have extended this chemistry to a wide range of asymmetric hydrogenations of ketones and imines based on the structural diversity of this type of Ru catalysts. 1) The extremely fast hydrogenation of ketone (TOF = 580  $\text{sec}^{-1}$ ) was achieved by using a ruthenabicyclic complex RuCl(daipena)(xylbinap). 2) The development of chiral diphosphine/PICA/Ru(II) catalysts expanded the substrate scope to *tert*-alkyl ketones, acyl silanes, and fused bicyclic ketones. The XylSkewphos/PICA/Ru(II)-catalyzed hydrogenation of 3-quinuclidinone was used in the industrial synthetic process of a medicine solifenacin. 3) Hardly accessible asymmetric hydrogenation of aryl vinyl ketones requiring definite differentiation of two  $\text{sp}^2$ -carbon groups, aryl and vinyl, was achieved by using the TolBINAP/DMAPEN/Ru(II) catalyst with a unique shape-selected chiral environment. The catalyst-controlled diastereoselection as well as enantioselection of this type of catalyst resulted in quantitative transformation of racemic heterocyclic aromatic ketones into alcohols with two contiguous stereogenic centers in almost pure form through

dynamic kinetic resolution. 4) Base-labile ketones, such as  $\alpha$ -chloro and -hydroxy ketones, alkynyl ketones, and fused heterocyclic aromatic ketones, were quantitatively hydrogenated to the functionalized alcohols in high ee, when a catalytic amount of Ru(OTf)(TsDPEN)( $\eta^6$ -arene) or the isoelectronic Cp\*Ir(OTf)(MsDPEN) was used under base-free conditions. 5) The longstanding problem of asymmetric hydrogenation of *N*-aryl imines was solved by the use of a XylSkewPhos/DPEN/Ru(II) catalyst in toluene. Formation of the *cis*-RuH<sub>2</sub> species seems to be crucial. A wide range of  $\alpha$ -hetero-substituted cyclic aromatic imines, including 2-substituted quinoxalines as well as 3-substituted 2*H*-1,4-benzoxazines and -benzothiazines, were hydrogenated with ruthenabicyclic RuCl(daipena)(dm-segphos) and the SEGPHOS complex to afford the heterocyclic amines in excellent ee. The novel challenge of applying the chiral Ru catalysts to asymmetric isomerization of primary allylic alcohols into the optically active aldehydes has also realized. Almost optically pure  $\beta$ -substituted aldehydes were obtained by the reaction of  $\gamma,\gamma$ -disubstituted primary allylic alcohols with the TolBINAP/DBAPEN/Ru(II) catalyst. We will continue our pursuit of ideal catalyst systems for asymmetric hydrogenation and the related reactions with both scientific importance and practical usefulness.

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**Keywords:** asymmetric catalysis • hydrogenation • iridium • isomerization • ruthenium

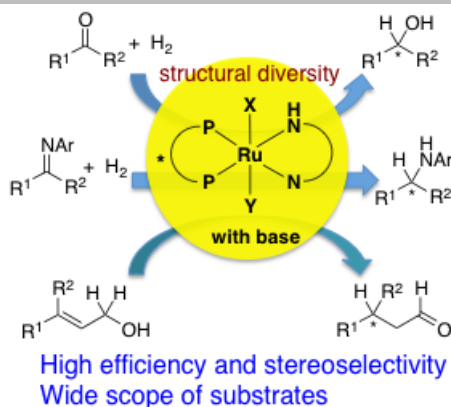
- [1] Recent reviews: a) T. Ohkuma, R. Noyori in *The Handbook of Homogeneous Hydrogenation*, Vol. 3 (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 1105–1163; b) N. Arai, T. Ohkuma in *Science of Synthesis: Stereoselective Synthesis 2; Stereoselective Reactions of Carbonyl and Imino Groups* (Ed.: G. A. Molander), Thieme, Stuttgart, **2010**, pp. 9–57; c) T. Ohkuma and N. Arai in *Comprehensive Chirality*, Vol. 5 (Eds.: E. M. Carreira, H. Yamamoto, K. Maruoka), Elsevier, Amsterdam, **2012**, pp. 270–300.
- [2] a) *Asymmetric Catalysis on Industrial Scale* (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2003**; b) N. Arai, T. Ohkuma, *Chem. Rec.* **2012**, *12*, 284–289.
- [3] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676.
- [4] T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.
- [5] Reviews: a) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73; b) T. Ohkuma, *Proc. Jpn. Acad., Ser. B* **2010**, *86*, 202–219.
- [6] a) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; b) R. Noyori, M. Kitamura, T. Ohkuma, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5356–5362; c) R. Noyori, C. A. Sandoval, K. Muñiz, T. Ohkuma, *Phil. Trans. R. Soc. A* **2005**, *363*, 901–912.
- [7] a) T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417–10418; b) T. Ohkuma, H. Ikehira, T. Ikariya, R. Noyori, *Synlett* **1997**, 467–468.
- [8] a) K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2002**, *124*, 15104–15118; b) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; c) R. J. Hamilton, S. H. Bergens, *J. Am. Chem. Soc.* **2006**, *128*, 13700–13701; d) S. A. French, D. Di Tommaso, A. Zanotti-Gerosa, F. Hancock, C. R. A. Catlow, *Chem. Commun.* **2007**, 2381–2388; e) S. Takebayashi, N. Dabral, M. Miskolzie, S. H. Bergens, *J. Am. Chem. Soc.* **2011**, *133*, 9666–9669; f) P. A. Dub, N. J. Henson, R. L. Martin, J. C. Gordon, *J. Am. Chem. Soc.* **2014**, *136*, 3505–3521.
- [9] K. Mashima, K. Kusano, T. Ohta, R. Noyori, H. Takaya, *J. Chem. Soc., Chem. Commun.* **1989**, 1208–1210.
- [10] K. Matsumura, N. Arai, K. Hori, T. Saito, N. Sayo, T. Ohkuma, *J. Am. Chem. Soc.* **2011**, *133*, 10696–10699.
- [11] T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289.
- [12] For transfer hydrogenation of ketones with RuCl<sub>2</sub>(diphosphine)(pica), see: W. Baratta, E. Herdtweck, K. Siega, M. Toniutti, P. Rigo, *Organometallics* **2005**, *24*, 1660–1669.
- [13] N. Arai, K. Suzuki, S. Sugizaki, H. Sorimachi, T. Ohkuma, *Angew. Chem.* **2008**, *120*, 1794–1797; *Angew. Chem. Int. Ed.* **2008**, *47*, 1770–1773.
- [14] K. Tsutsumi, T. Katayama, N. Utsumi, K. Murata, N. Arai, N. Kurono, T. Ohkuma, *Org. Process Res. Dev.* **2009**, *13*, 625–628.
- [15] R. Naito, Y. Yonetoku, Y. Okamoto, A. Toyoshima, K. Ikeda, M. Takeuchi, *J. Med. Chem.* **2005**, *48*, 6597–6606.
- [16] N. Arai, M. Akashi, S. Sugizaki, H. Ooka, T. Inoue, T. Ohkuma, *Org. Lett.* **2010**, *12*, 3380–3383.
- [17] T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659–662.
- [18] N. Arai, K. Azuma, N. Nii, T. Ohkuma, *Angew. Chem.* **2008**, *120*, 7567–7570; *Angew. Chem. Int. Ed.* **2008**, *47*, 7457–7460.
- [19] N. Arai, H. Ooka, K. Azuma, T. Yabuuchi, N. Kurono, T. Inoue, T. Ohkuma, *Org. Lett.* **2007**, *9*, 939–941; b) H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, *J. Org. Chem.* **2008**, *73*, 9084–9093.
- [20] a) M. Studer, S. Burkhardt, H.-U. Blaser, *Chem. Commun.* **1999**, 1727–1728; b) S. Sato, I. Matsuda, Y. Izumi, *J. Organomet. Chem.* **1988**, *352*, 223–238.
- [21] For stereoselective synthesis through dynamic kinetic resolution, see: R. Noyori, M. Tokumaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56.
- [22] M. Akashi, N. Arai, T. Inoue, T. Ohkuma, *Adv. Synth. Catal.* **2011**, *353*, 1955–1960.
- [23] For example, see: a) E. Brenner, R. M. Baldwin, G. Tamagnan, *Org. Lett.* **2005**, *7*, 937–939; b) K. E. Hanegar, M. Cebula, *Org. Process Res. Dev.* **2007**, *11*, 354–358; c) T.-X. Métro, G. Pardo, J. Cossy, *J. Org. Chem.* **2008**, *73*, 707–710.
- [24] Selected reviews: a) H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567–607; b) E. L. Eliel in *Asymmetric Synthesis*, Vol. 2 (Ed.: J. D. Morrison), Academic Press, New York, **1983**, pp. 125–155; c) N. Greeves in *Comprehensive Organic Synthesis*, Vol. 8 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, pp. 1–24; d) E. Juaristi, *Introduction to Stereochemistry and Conformational Analysis*, Wiley, New York, **1991**, pp. 178–198; e) A. P. Davis in *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed., Vol. E21d (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 3988–4048; f) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1223.
- [25] T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval, R. Noyori, *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725.
- [26] C. A. Sandoval, T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, R. Noyori, *Chem. Asian J.* **2006**, *1–2*, 102–110.
- [27] For example, see: a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406; c) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300–1308.
- [28] N. Arai, H. Satoh, N. Utsumi, K. Murata, K. Tsutsumi, T. Ohkuma, *Org. Lett.* **2013**, *15*, 3030–3033.
- [29] T. Ohkuma, K. Tsutsumi, N. Utsumi, N. Arai, R. Noyori, K. Murata, *Org. Lett.* **2007**, *9*, 255–257.
- [30] T. Ohkuma, N. Utsumi, M. Watanabe, K. Tsutsumi, N. Arai, K. Murata, *Org. Lett.* **2007**, *9*, 2565–2567.
- [31] N. Utsumi, K. Tsutsumi, M. Watanabe, K. Murata, N. Arai, N. Kurono, T. Ohkuma, *Heterocycles* **2010**, *80*, 141–147.
- [32] C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201.
- [33] N. Arai, N. Utsumi, Y. Matsumoto, K. Murata, K. Tsutsumi, T. Ohkuma, *Adv. Synth. Catal.* **2012**, *354*, 2089–2095.
- [34] K. Schnatbaum, D. Scharn, E. Locardi, T. Polakowski, U. Richter, U. Reineke, G. Hummel (Jerini AG.), PCT Int. WO2006/128670 A1, **2006**.
- [35] N. Arai, Y. Saruwatari, K. Isobe, T. Ohkuma, *Adv. Synth. Catal.* **2013**, *355*, 2769–2774.
- [36] a) S. Atarashi, S. Yokohama, K. Yamazaki, K. Sakano, M. Imamura, I. Hayakawa, *Chem. Pharm. Bull.* **1987**, *35*, 1896–1902; b) K. Satoh, M. Inenaga, K. Kanai, *Tetrahedron: Asymmetry* **1998**, *9*, 2657–2662.
- [37] N. Arai, K. Sato, K. Azuma, T. Ohkuma, *Angew. Chem.* **2013**, *125*, 7648–7652; *Angew. Chem. Int. Ed.* **2013**, *52*, 7500–7504.

## Entry for the Table of Contents (Please choose one layout)

Layout 1:

## PERSONAL ACCOUNT

Optically active diphosphine/diamine/Ru(II) and the related complexes successfully catalyze asymmetric hydrogenation of ketones and imines with a base co-catalyst. The structural diversity of this type of complex achieves extremely high catalyst efficiency (TOF = 580  $\text{sec}^{-1}$ ) and enantioselectivity of >99% in the best cases as well as a wide scope of substrates. Asymmetric isomerization (1,3-hydrogen shift) of  $\gamma,\gamma$ -disubstituted primary allylic alcohols is also catalyzed, affording the  $\beta$ -substituted aldehydes in almost enantiomerically pure form.

*Takeshi Ohkuma\**, *Noriyoshi Arai*

Page No. – Page No.

**Advancement in Catalytic  
Asymmetric Hydrogenation of  
Ketones and Imines, and  
Development of Asymmetric  
Isomerization of Allylic Alcohols**