Doctoral Dissertation (Censored)

博士論文 (要約)

Development of Heterogeneous Rh Catalysts

for Asymmetric Arylation Reactions

(不均一系 Rh 触媒の開発と不斉アリール化反応)

A Dissertation Submitted for the Degree of Doctor of Philosophy

December 2020

令和２年１２月博士（理学）申請

Department of Chemistry, Graduate School of Science,

The University of Tokyo

東京大学大学院理学系研究科

化学専攻

Tatsuya Kuremoto

呉本　達哉

Abstract

1. Introduction

Catalysts play a crucial role in the synthesis of fine chemicals and immobilization of homogeneous catalysts for fine chemical synthesis has attracted much attention from both academia and industry. This technology facilitates catalyst separation from reaction mixtures and recovery/reuse of catalysts. In addition, the application of immobilized catalysts to continuous-flow reactions has been shown to be a powerful synthetic method due to its environmental compatibility, efficiency, and safety.[1]

2. Development of Ligand-Immobilized Heterogeneous Catalysts for Asymmetric Arylation Reactions

Asymmetric arylation catalyzed by Rh is highly useful in synthetic organic chemistry because it can create new C−C bonds with high enantioselectivities. This reaction can transform readily available materials into chiral molecules, and applications to the synthesis of active pharmaceutical ingredients or natural products are reported. I developed ligand-immobilized heterogeneous Rh catalysts for asymmetric arylation reactions.

A chiral diene with a styryl moiety was co-polymerized with styrene and divinylbenzene to afford a chiral diene ligand supported on cross-linked polystyrene (PS), and a heterogeneous chiral Rh complex (**PS-diene Rh**) was successfully isolated by complexation of the ligand on the polymer with a Rh(I) salt. The asymmetric 1,4-addition reactions of aryl boronic acids with α,β-unsaturated ketones were investigated in a batch system using this catalyst (Scheme 1 (a)). As a result, the target products were obtained with excellent enantioselectivities. The substrate scope was investigated, and broad substrates, including ketones, esters, nitroolefins, amides, and imines, could be arylated in high yields with excellent enantioselectivities. **PS-diene Rh** could be recovered and reused for several times.

To apply the catalyst to flow reactions, activation methods of the catalyst were investigated. It was found that the treatment of **PS-diene Rh** with a base could enhance the catalytic activity significantly. The continuous-flow reaction was then conducted with the base-treated **PS-diene Rh** (Scheme 1 (b)). A toluene solution of a substrate and an aqueous solution of phenylboronic acid were mixed in a T-shape joint and the biphasic flow was passed through a column packed with the catalyst. The product was continuously obtained in high yield with excellent enantioselectivity.

Scheme 1. (a) Asymmetric Arylation Reaction with PS-Diene Rh Catalyst, (b) Asymmetric Arylation Reaction in Continuous-Flow
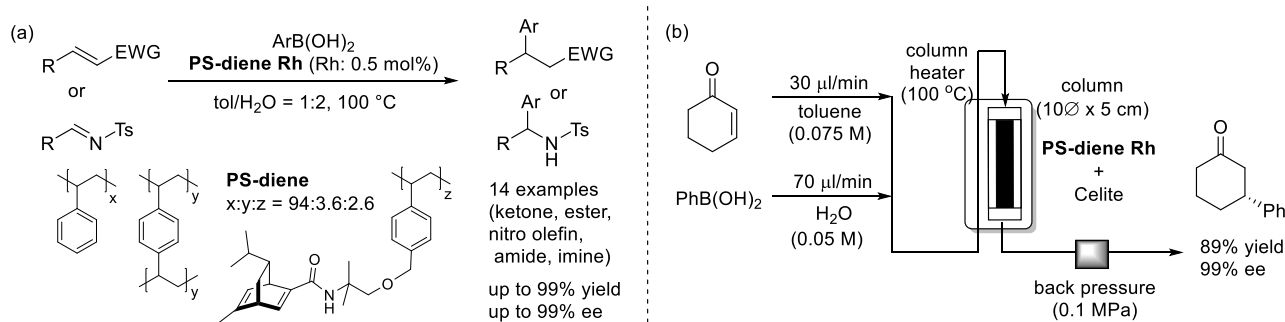

1

3. Development of Core/Shell-Type Supports for Catalyst Immobilization without Loss in Kinetics

A major common problem in current immobilized catalysts is the lower catalytic activities compared with the corresponding homogeneous catalysts. Thus, catalyst immobilization methods that do not adversely affect the kinetics are highly desired, and it is even listed as one of the Key Green Chemistry Research Areas.[2]

Cross-linked polystyrene, which is inert and commercially available, has been widely used for immobilization of homogeneous catalysts. It is acknowledged that active sites of immobilized catalysts have limited accessibility, which leads to diminished performance. While a high degree of cross-linking leads to decreased mass transport efficiency, there is a lower limit of a cross-linking degree below which the material becomes more soluble and less mechanically stable (Figure 1 (a)).

**Figure 1.** (a) Trade-off of stability and accessibility in cross-linked polystyrene and (b) general concept of this work.
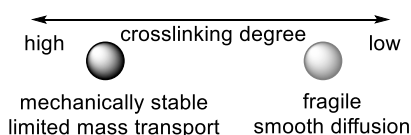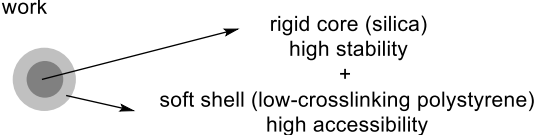
This trade-off has long been known since the first report of solid-phase synthesis. To address the issue, I have designed a core/shell-type support in which low-cross-linking degree PS is attached on a rigid core material to keep high mass transport efficiency and make the whole support insoluble, stable, and easy to handle (Figure 1 (b)). Herein, I have successfully immobilized a chiral catalyst while maintaining catalytic activity and enantioselectivity at levels comparable to those of the corresponding homogeneous catalyst in rhodium–diene complex-catalyzed asymmetric 1,4-addition reactions.

To synthesize a core/shell-type support, I selected a spherical silica particle as a core material because rigid and highly monodisperse particles can be obtained by application of the well-established Stöber method. The surface of the silica particles was functionalized with 3-(trimethoxysilyl)propyl methacrylate to attach low cross-linking degree PS shell covalently. Copolymerization of styrene, *meta*-divinylbenzene, and azidomethylstyrene in the presence of the core silica particles was conducted based on a reported procedure to afford spherical concentric core/shell particles (Scheme 2).

Scheme 2. Synthesis of SiO$_2$/PS core/shell particles
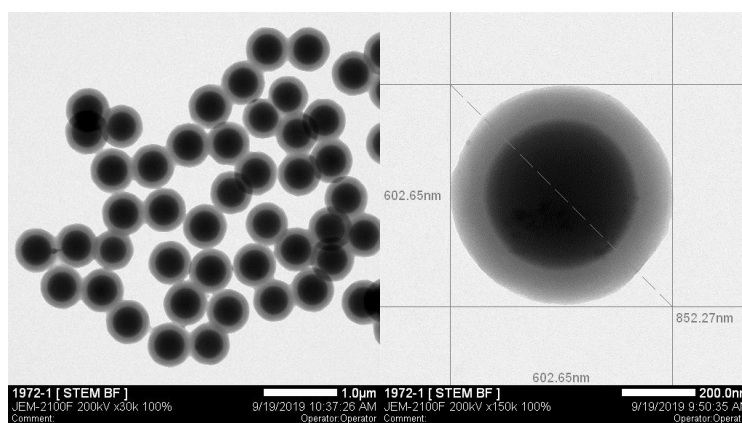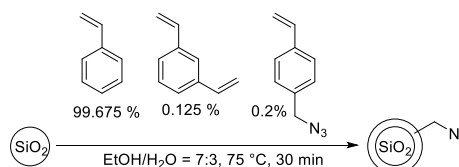
Formation of uniform thin shell confirmed using scanning transfer electron microscopy analysis. The chiral ligand **L1**, bearing bicyclo[6.1.0]nonyne (BCN) for immobilization, was synthesized as shown in Scheme 3. Readily available BCN **I** was converted into bromide **II**, which was treated with diene **A** in the presence of a phase-transfer

catalyst. The immobilization by strain-promoted alkyne–azide cycloaddition was conducted in the presence of an excess amount of **L1** to convert the azide moiety fully into the ligand. The excess amount of **L1** could be recovered without any noticeable degradation. The immobilized ligand was mixed with [Rh(C$_2$H$_4$)$_2$Cl]$_2$ to give the target immobilized chiral catalyst (**SiO$_2$/PS–diene Rh**) as a fine powder.

Scheme 3. Synthesis of SiO$_2$/PS core/shell particles
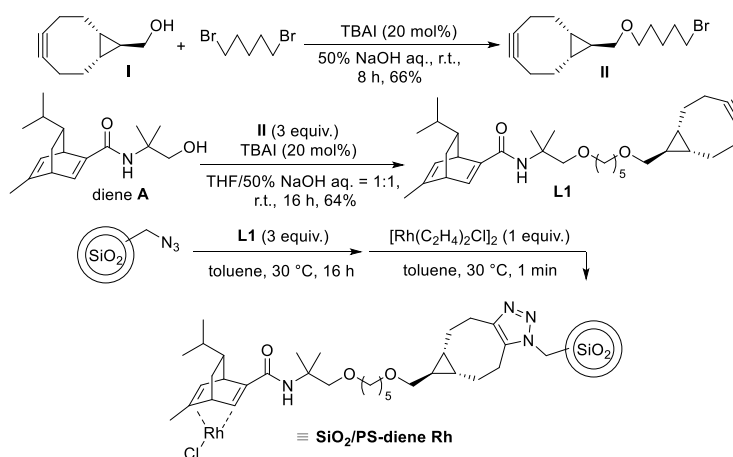
This **SiO$_2$/PS–diene Rh** and other control catalysts, those are corresponding homogeneous catalyst, the catalyst on Merrifield resin, and **PS–diene Rh** without core shown above, were evaluated in the asymmetric 1,4-addition of phenylboronic acid **2a** to α,β-unsaturated ester **1a**. Notably, plots of reaction progress clearly show that the core/shell-type catalyst has much better performance than conventional catalysts and confirmed that even better reaction rate than the homogeneous catalyst was achieved. Substrate generality including ketone, ester, amide, nitroolefin, imine, and arylboronic acids was confirmed with high yields and excellent enantioselectivities. Continuous-flow reactions using the core/shell-type catalyst were also conducted, where high efficiency (TOF >150 h^{-1}) was maintained until 260 min, where TON reached over 500.

4. Conclusion

In my Ph.D studies, I have developed heterogeneous **PS-diene Rh** catalyst to achieve high yields and excellent enantioselectivities for broad substrates. Furthermore, I designed a core/shell-type support with extremely low cross-linking degree PS shell, which enables the immobilization without adversely affecting the kinetics while maintaining its heterogeneity and ease of handling. As a proof of concept, I have developed **SiO$_2$/PS–diene Rh**, which showed significantly higher catalytic activity than those on conventional supports, and even better than the corresponding homogeneous catalyst. This strategy would be applicable to other immobilized catalysts and the catalytic activity could be improved.

Figure 2. Comparison of the reaction rates.

5. References

(1) Kobayashi, S. *Chem.—Asian J.* **2016**, *11*, 425–436. (2) Bryan, M. C. *et al*. *Green Chem.* **2018**, 5082–5103.

Table of Contents

Chapter 1:   General Introduction
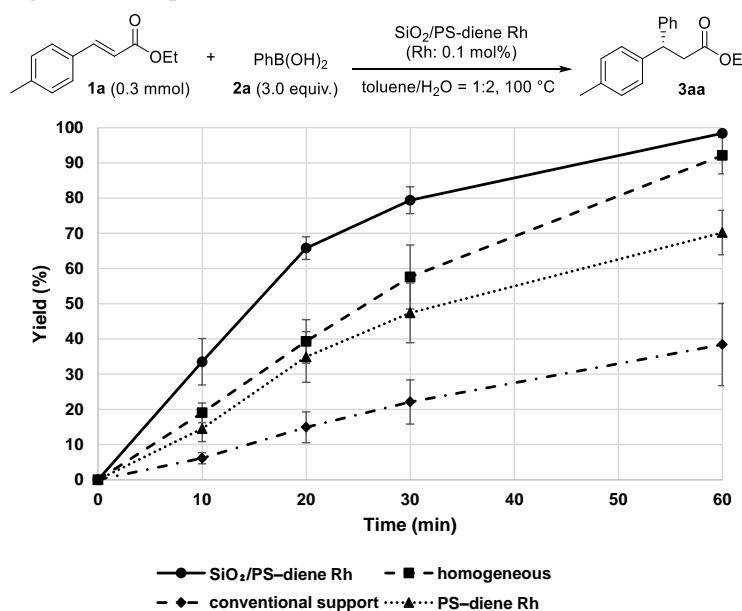
Catalysts have been played a crucial role in synthetic organic chemistry. They can be categorized into two parts. One is a homogeneous catalyst, and the other is a heterogeneous catalyst. Homogeneous catalysts were used in a solution phase typically after dissolved in solvents. The catalysts for fine chemical synthesis are mostly this type and many highly active and (enantio)selective catalysts have been developed over hundred years. In most cases, recovery of the catalyst after the reaction is not conducted because of its difficulty in separation. Although catalysts are used much less amount than starting materials or solvent, the actual waste derived from the catalyst is much larger than the apparent amount of the catalyst used in the reaction, because modern sophisticated catalysts require many synthetic steps accompanied with environmental and economic costs. On the other hand, heterogeneous catalysts can be easily separated by filtration and potentially reused many times. Toward a sustainable society, paradigm shift from homogeneous catalysis to heterogeneous catalysis is highly demanded in the viewpoint of green chemistry. However, there are not so many kinds of heterogeneous catalysts that show high catalytic activity and (enantio)selectivity for fine chemical synthesis. The realization of highly active and durable heterogeneous catalysts is still an unsolved problem and a long-standing challenge for chemists.

The fine organic synthesis has mainly been carried out in a system called "batch reaction" in which all reactants and solvents are mixed in a container such as a flask and reacted at once. On the other hand, a reaction system called "flow reaction" in which a solution flows continuously through a column or a tube has gathered much attention from both academia and industry because of its environmental compatibility, efficiency, and safety. Flow "fine" synthesis, where complex molecules are obtained in high yields with high selectivities using flow reactions, is a concept of an ideal synthetic method of the next generation.[1] If the starting materials are flowed into the column packed with heterogeneous catalysts, the desired product can be obtained continuously. Although it would be the most ideal synthetic method, there are few highly active and durable heterogeneous catalysts that can be used for this purpose, especially chiral C−C bond forming reactions.

Conventional heterogeneous catalysts, e.g. noble metal, metal oxide, zeolite, and so on, have been highly sophisticated for bulk chemical industry. However, reactions catalyzed by these catalysts were limited and were rarely utilized for the synthesis of fine chemicals such as agrochemicals or pharmaceuticals, especially including chiral center. It may take further time and research to develop these types of heterogeneous catalysts that meet the demand from modern chemical synthesis. On the other hand, homogeneous catalysts have been widely developed and used for the synthesis of elaborated compounds.

One of the methods to make heterogeneous catalysts based on homogeneous catalysts is immobilization of homogeneous catalysts on insoluble material. Fortunately, there are many highly

active homogeneous catalysts and some of them have been already used in industrial manufacturing processes.[2] If these catalysts are physically or chemically adsorbed, encapsulated, or covalently attached to heterogeneous supports, e.g. polymer, carbon black, or metal oxide, it may become the catalyst with similar activity except its solubility.

Immobilization of catalysts has been reported from many groups and some of them have been applied to asymmetric C−C bond formation reactions in the flow system.[3] Among them, immobilized metal oxides or metal nanoparticle catalysts were out of the scope of the following review of previous researches. I will summarize the successful examples of continuous-flow reactions for asymmetric C−C bond formation by mainly focusing on immobilized metal complexes that have homogeneous counterparts with similar reactivities.

Salvadori et al. synthesized a bis(oxazoline) (box) type ligand which has a styrene moiety, and it was co-polymerized with styrene and divinylbenzene as a cross-linker to give the insoluble polystyrene-immobilized box ligand (PS-box). Cu(OTf)$_2$ was complexed with PS-box after the polymerization and the catalyst was used in the continuous-flow enantioselective glyoxylate-ene reaction.[4]

Scheme 1. Enantioselective glyoxylate-ene reaction with PS-box-Cu catalyst
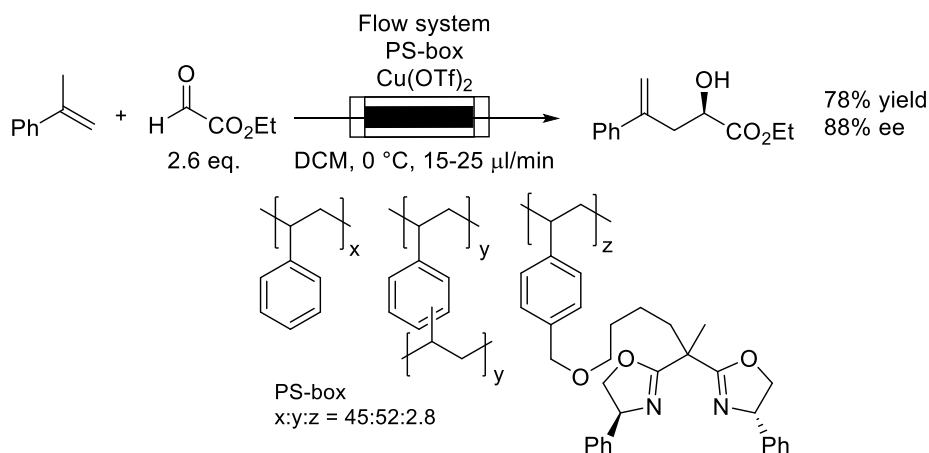
The series of research about asymmetric cyclopropanation were reported by Martínez-Merino, Mayoral and co-workers. They have successfully synthesized Pybox type ligands which have a vinyl group for polymerization and immobilized them onto polystyrene support.[5,6] They prepared a macroporous monolithic column for continuous flow reaction and have shown that the product was obtained in moderate yields and selectivities under conventional or solventless conditions or in supercritical carbon dioxide (Scheme 2).[7] Also, they have synthesized related oxazoline-containing ligands and corresponding heterogeneous Cu catalysts and succeeded in asymmetric cyclopropanation in the flow system.[8,9] The other groups reported similar heterogeneous catalysts supported on silica which can be applied to flow synthesis.[10,11]

**Scheme 2. Asymmetric cyclopropanation with PS-Pybox-Ru catalyst**
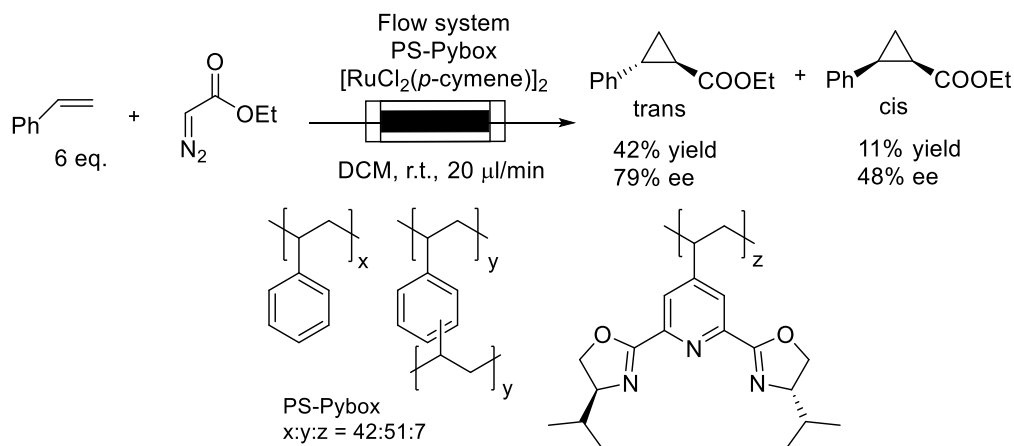
Moberg et al. achieved enantioselective cyanation of benzaldehyde in a microreactor charged with asymmetric polymeric catalysts (Scheme 3).[12] They selected macroporous divinylbenzene beads as solid support. The surface of the beads was modified with a hydrophilic coating and the terminal hydroxy group was connected to a salen type ligand. Asymmetric cyanation of benzaldehyde using TMSCN was conducted in a microreactor with flowing the reaction solution.

Scheme 3. Enantioselective cyanation with PS-salen-Ti catalyst
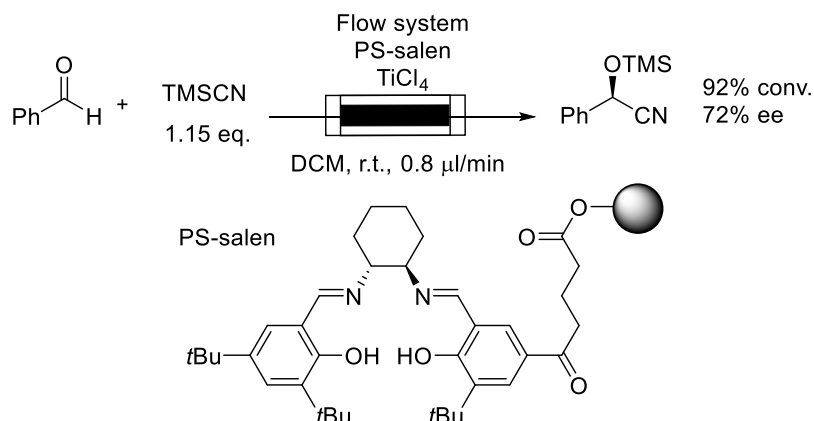
Seayad, Ramalingam and coworkers reported that partially hydrolyzed titanium alkoxide and chiral ligand worked as a homogeneous catalyst of enantioselective cyanation of imines.[13,14] Considering titanium alkoxides are readily hydrolyzable, they rationalized that hydrolyzing their catalyst can give self-supported heterogeneous catalysts. They have successfully prepared self-supported chiral titanium cluster (SCTC) catalysts and have shown the applicability of them to flow reactions (Scheme 4).[15] Continuous-flow three-component reaction, where an imine formation from aldehyde and amine was conducted in flow and was directly connected to the cyanation column, was also carried out.

Scheme 4. Asymmetric cyanation with self-supported chiral titanium cluster catalyst
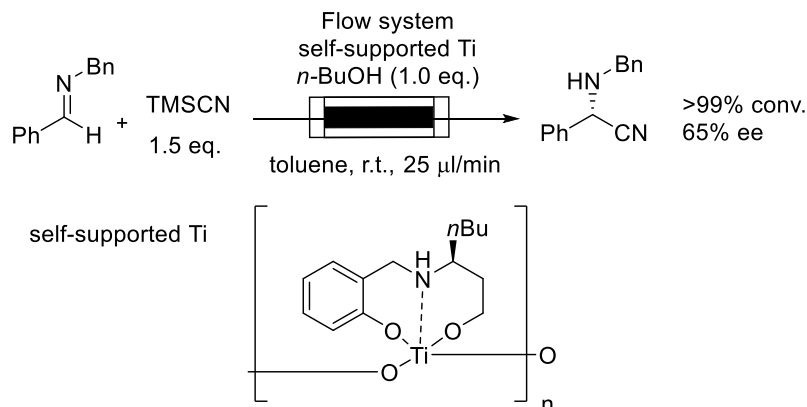
Hashimoto et al. reported the immobilization of a chiral chlorinated dirhodium(II) complex and its use for enantioselective ylide cycloaddition (Scheme 5).[16] They prepared a dirhodium complex-containing monomer and co-polymerized it with a fluorinated styrene derivative and a crosslinker. The polymer-supported complex was applied to continuous-flow reactions and the catalyst gave the desired products in high yields and excellent enantioselectivities.

Scheme 5. Enantioselective carbonyl ylide cycloaddition with polymer-supported dirhodium(II) catalyst
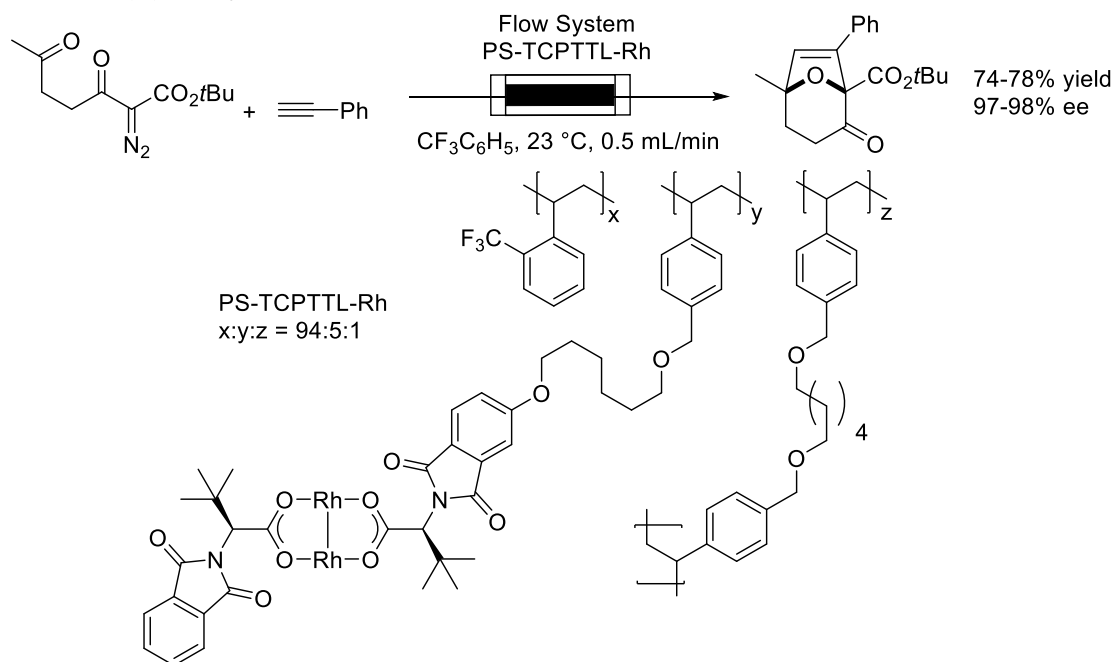
Shibasaki's group reported that a Nd/Na/amide-based ligand heterobimetallic catalyst can promote the asymmetric nitroaldol reaction (Henry reaction) in an *anti*-selective manner.[17–20] This catalytic system forms precipitation in THF and catalytically active species were found to be heterogeneous. They further refined this catalyst into an easily recoverable form, where the catalyst is confined in a multiwalled carbon nanotube (MWNT) network, and apply it to continuous-flow asymmetric nitroaldol reactions (Scheme 6).[21] They also utilized MWNT confinement technique to the other type

of catalytic system, Er catalyzed asymmetric Mannich-type reaction, and have shown that flow reaction is feasible.[22]

Scheme 6. Asymmetric nitroaldol reaction with MWNT-confined Nd/Na catalyst
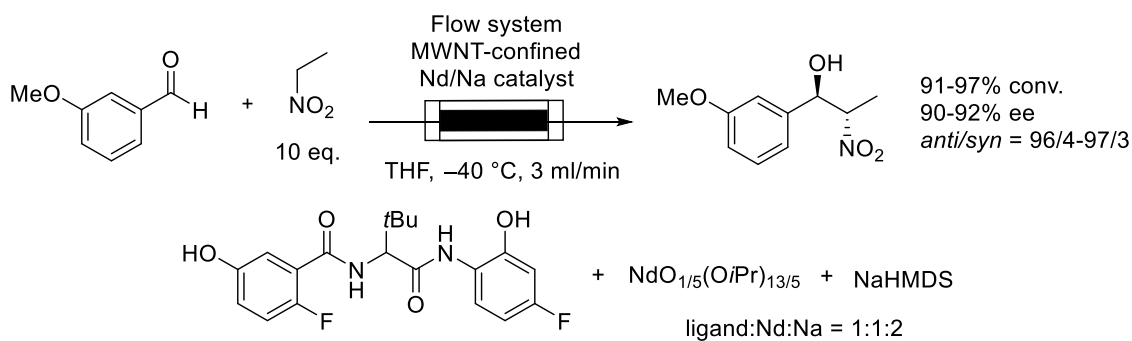
Hodge and co-workers selected thiol-containing polystyrene beads as a support and immobilized cinchonidine onto them. A ketoester and methyl vi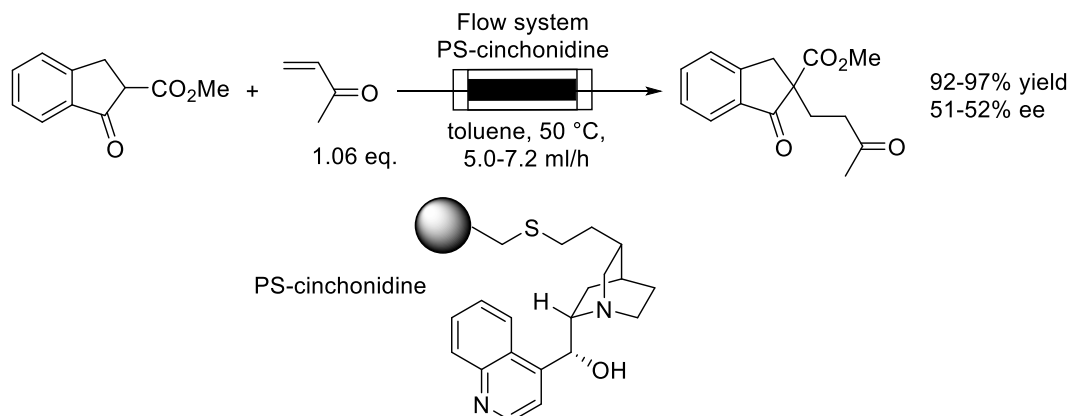nyl ketone were selected as substrates for their study. The desired product was obtained in high yields but not with satisfactory enantioselectivities (Scheme 7).[23]

Scheme 7. Asymmetric 1,4-addition of ketoesters to methyl vinyl ketone with PS-cinchonidine catalyst

Asymmetric 1,4-addition of aldehyde was reported by Fülöp et al. using polystyrene-supported proline catalysts (Scheme 8).[24] The catalysts were prepared by a well-known solid-phase synthesis of peptides. Without detaching the peptide from the solid support, the peptide containing beads can be utilized as heterogeneous catalysts. They achieved high yields and high enantioselectivities for several substrates. Subsequently, Wennemers's group also reported a similar reaction in the continuous-flow system using their original polymer-bound peptide catalyst.[25]

Scheme 8. Asymmetric 1,4-addition of aldehydes to a nitroolefin with PS-peptide catalyst
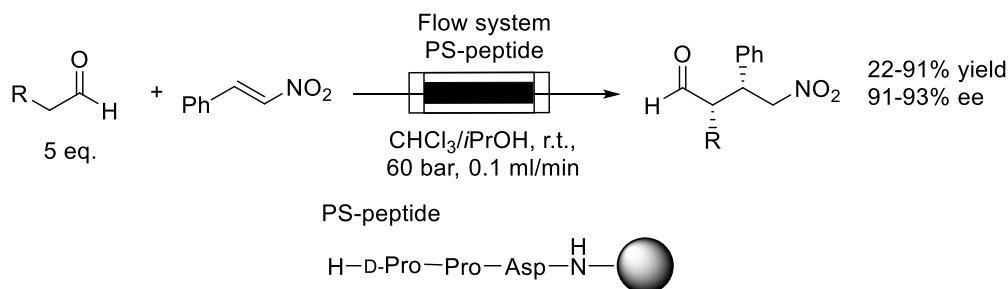
Our group reported that asymmetric 1,4-addition of 1,3-dicarbonyl compounds to α,β-unsaturated nitroolefins with a polystyrene-immobilized Pybox ligand and calcium chloride (Scheme 9).[26] We have also shown complex molecules can be synthesized by the multistep flow reaction. Rolipram, an anti-inflammatory drug, was successfully synthesized in high yield with high selectivity by flowing a solution of commercially available raw materials to multiple columns packed with heterogeneous catalysts continuously (Scheme 10).[27] The key step for constructing the chiral center of the final product is the asymmetric 1,4-addition reaction.

Scheme 9. Asymmetric 1,4-addition with PS-Pybox-Ca
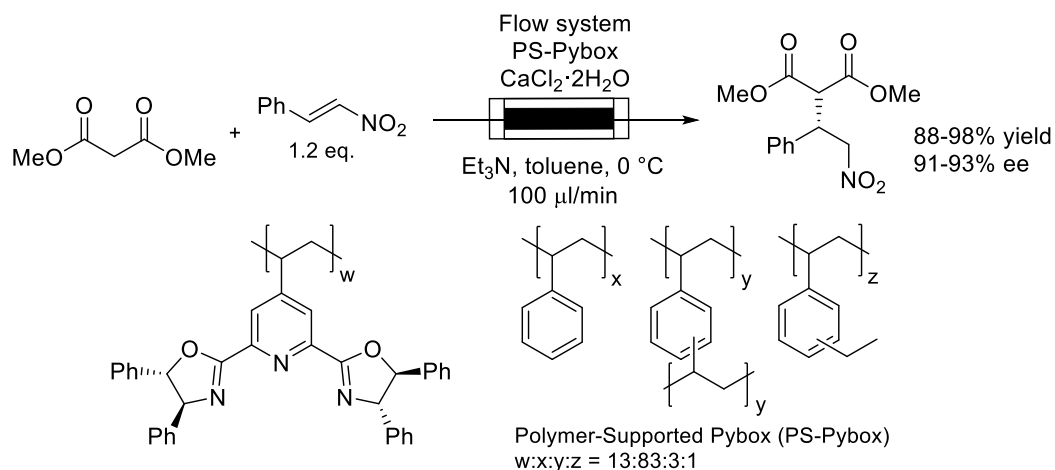
Scheme 10. Multistep continuous-flow synthesis of rolipram (from Kobayashi, S., et al. *Nature* 2015, *520*, 329.)
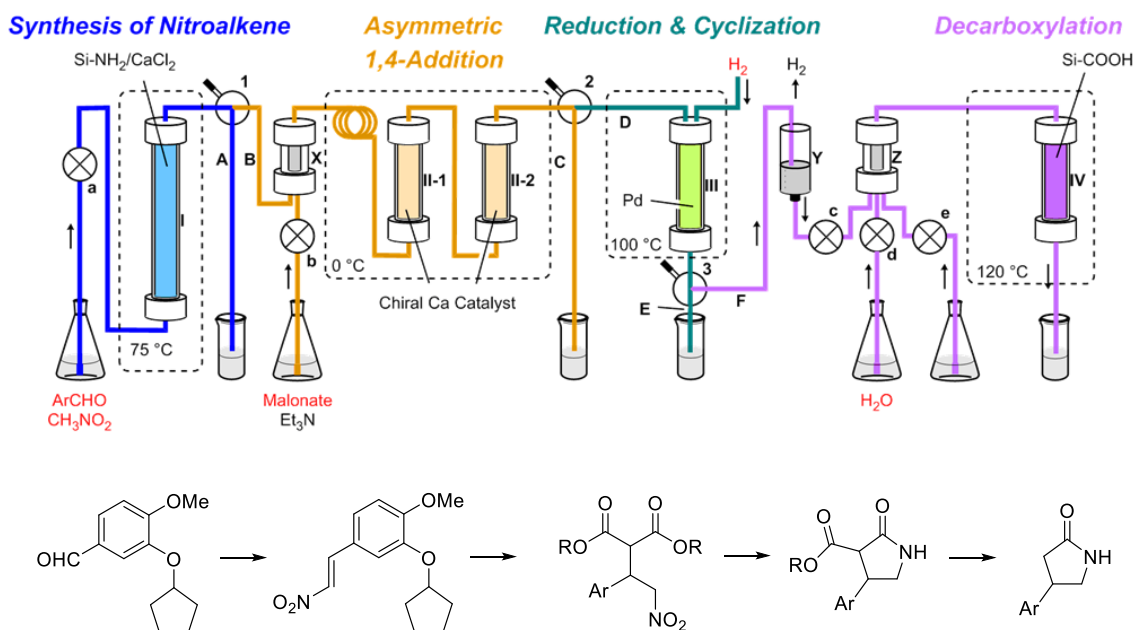
As shown in above, there are many researches that led to the successful immobilization of catalysts. However, almost all of them are far from practical probably due to lower activity and sometimes criticized in the literature.[28] Majority of such catalysts were negatively affected by its immobilization, resulting in inferior activities and selectivities. Until now, there is no truly successful example of immobilized catalysts that can compete with the chemical process based on corresponding homogeneous catalysts.[2] Although many supports were utilized in the immobilization of various kinds of catalyst, a deeper understanding of the factors which determine activity, selectivity, and durability are still demanded. Recently the conference of pharmaceutical manufacturers selected "Catalyst Immobilization without Significant Loss in Kinetics" as one of the "Key Green Chemistry Research Areas".[29] Therefore, in my Ph.D. course, I decided to overcome the current situation of immobilized catalysts by developing a general and reliable immobilization method without affecting activities and selectivities.

Chapter 2: Development of Ligand-Immobilized Heterogeneous Catalysts for Asymmetric Arylation Reactions

Section 1: Introduction

Asymmetric 1,4-addition reaction to α,β-unsaturated carbonyl compounds has been known for a long time using various organometallic reagents such as Grignard reagents, but due to their extremely high reactivity application to asymmetric reactions, requiring precise control of reaction conditions, was difficult. In 1999, however, Hayashi's group reported the asymmetric 1,4-addition of arylboronic acids, which has lower reactivity compared with other organometallic reagents, to α,β-unsaturated ketones with Rh catalyst and BINAP ligand (Scheme 11).[30] Later, an example using a chiral diene ligand was also discovered (Scheme 12).[31] Since this chiral diene ligand can effectively construct a chiral environment, it stimulated further development of arylation reactions with Rh catalysts. As a result, it has become possible to apply to various kinds of substrates and the synthesis of intermediates of useful compounds such as medicines has been shown.[32] Therefore, I selected this as a model reaction for the development of the novel method of immobilization.

Scheme 11. Rhodium catalyzed asymmetric 1,4-addition
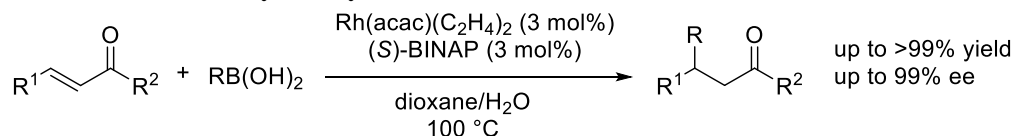
Scheme 12. Rhodium catalyzed asymmetric 1,4-addition using chiral diene ligand
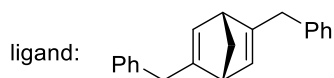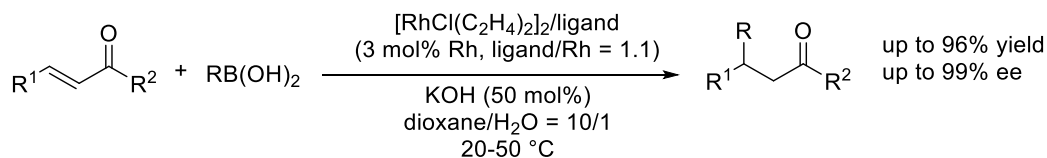
The use of immobilized Rh complex for asymmetric 1,4-addition was also reported from Hayashi's group (Scheme 13).[33] They selected a polystyrene-poly(ethylene glycol) copolymer (PS-PEG) resin as an immobilization partner and attached the BINAP ligand onto it. They showed asymmetric 1,4-addition of phenylboronic acids to several α,β-unsaturated ketones in high yields with excellent enantioselectivities. The catalyst could be recovered and reused four times during which the yields and enantioselectivities were kept high.
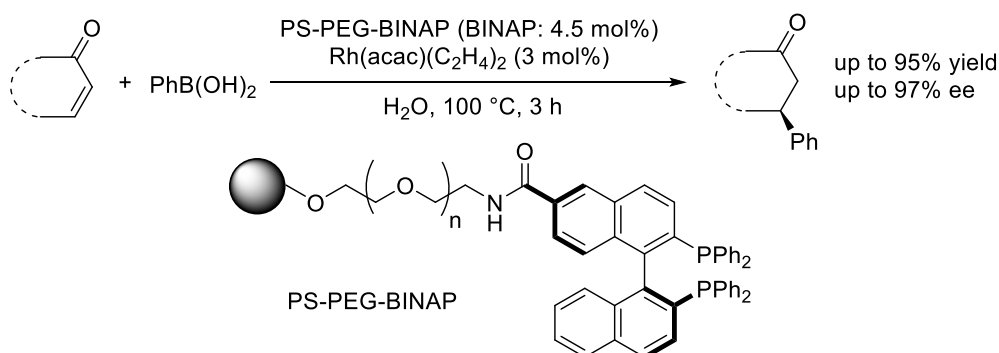
Scheme 13. Asymmetric 1,4-addition to α,β-unsaturated ketones with PS-PEG BINAP Rh catalyst

Supports for immobilization of the Rh complex are not limited to insoluble materials. Tunge *et al.* have synthesized a polystyrene-based polymer having the low molecular weight and narrow molecular weight distribution. The polymer is soluble in toluene but is insoluble in methanol. Therefore, the polymer can be precipitated by the addition of methanol and it can be recovered by the filtration. They incorporated biphephos ligand in the polymer and showed 1,4-addition of boronic acids to α,β-unsaturated ketones with this polymer catalyst complexed with Rh (Scheme 14).[34,35] In addition to this reaction, they also applied their catalyst to various kinds of Rh catalyzed reactions.

Lipshutz's group also adopted a soluble support. They attached BINAP to amphiphilic polyethylene glycol ubiquinol sebacate (PQS), which undergoes spontaneous self-aggregation in water to give nanomicelles. The hydrocarbon part of this polymer forms a lipophilic core, and the reaction is designed to occur there. Asymmetric 1,4-addition of boronic acids to α,β-unsaturated ketones in water were conducted and the products were collected by extraction while the catalyst remained in the aqueous phase (Scheme 15).[36]

Scheme 14. 1,4-Addition to α,β-unsaturated ketones with JanaPhos Rh catalyst

R-B(OH)$_2$

R = aryl, alkenyl

JanaPhos (3 mol%)
Rh(acac)(CO)$_2$ (2 mol%)

toluene, 50 °C, 15-17 h,
MeOH/H$_2$O = 1:1

up to 92% yield

JanaPhos
x:y = 10:1

*t*Bu

*t*Bu
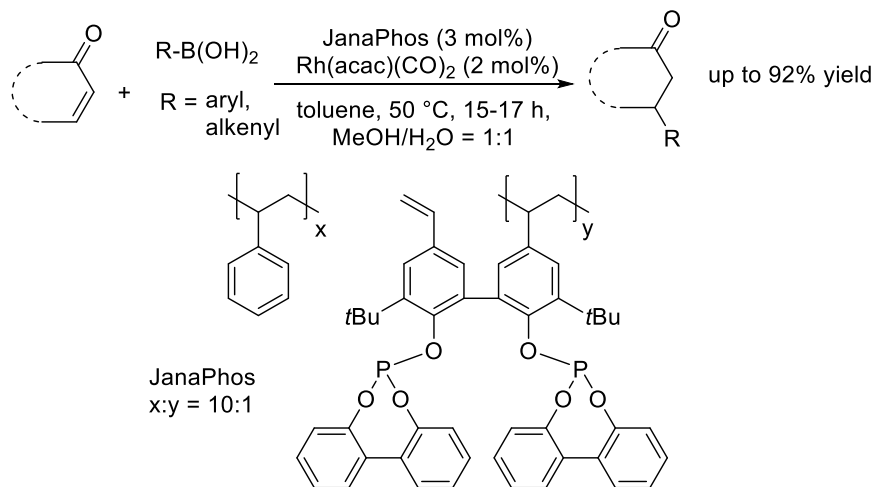
Scheme 15. Asymmetric 1,4-addition to α,β-unsaturated ketones with PQS-BINAP Rh catalyst

ArB(OH)$_2$

1.2 eq.

PQS-BINAP-Rh
(Rh: 3 mol%)
TEA (1.2 eq.)

H$_2$O, r.t., 12 h

up to 99% yield
up to >99% ee

PQS-BINAP

O-MPEG

MeO

MeO

Ph$_2$P

Ph$_2$P

14
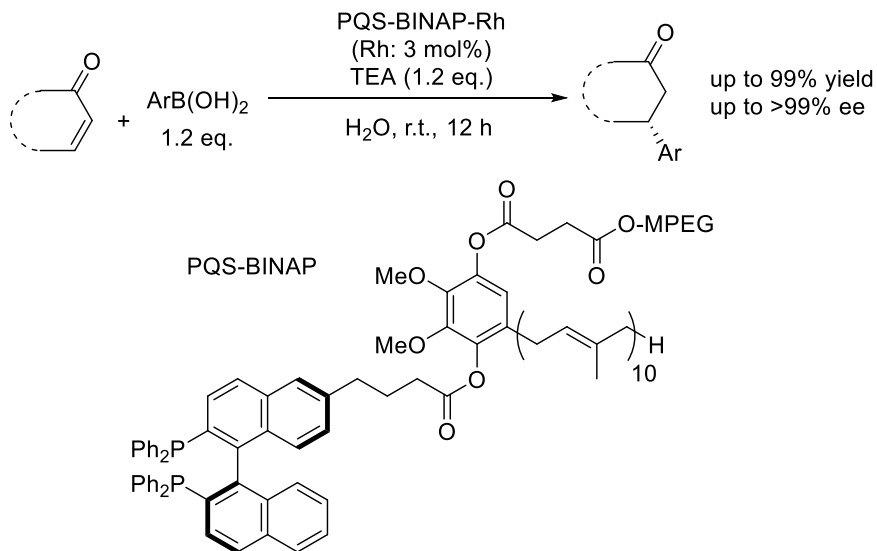
In the above examples, phosphine ligands were immobilized on supports. However, phosphine ligands are prone to be easily oxidized under air, which prevents facile recovery and reuse. Furthermore, phosphine ligated Rh complexes are less reactive in the 1,4-addition reactions catalyzed by Rh compared with chiral diene ligated ones.

The immobilization of a chiral diene-Rh complex was reported from Lin's group (Scheme 16).[37] They targeted the synthesis of the metal-organic framework (MOF) in which chiral diene ligands were incorporated. They found that the catalyst was highly effective for asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones with only 0.01-0.25 mol% catalyst loading. In the case of the reaction of 2-cyclohexenone, the catalyst showed a very high turnover number (TON) of 13400, which is comparable with that of a homogeneous control catalyst.

Scheme 16. Asymmetric 1,4-addition to α,β-unsaturated ketones with MOF-Rh catalyst
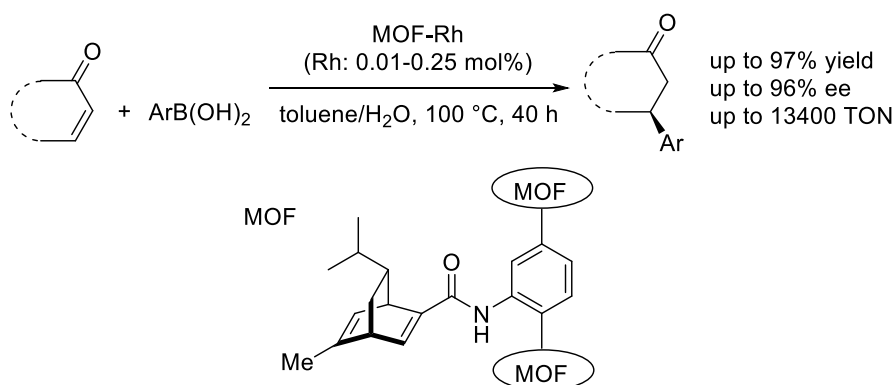
Uozumi et al. succeeded in the immobilization of a chiral diene-Rh complex on amphiphilic PS-PEG resin (Scheme 17).[38] Their catalyst exhibited efficient reaction to cyclic or linear enones in water under batch conditions. It was also applied in continuous flow reactions.

Scheme 17. Asymmetric 1,4-addition to α,β-unsaturated ketones with PS-PEG-diene-Rh catalyst
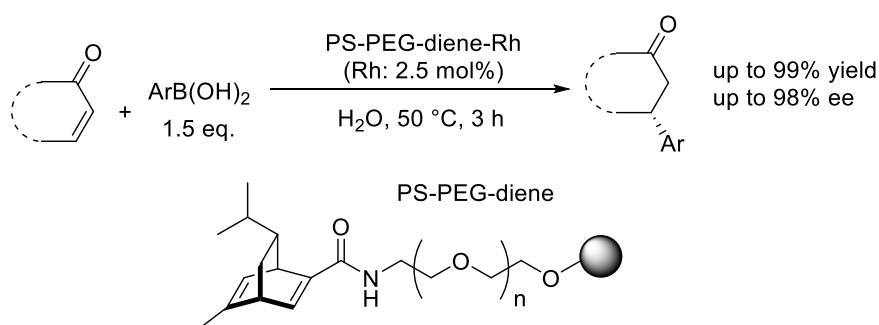
These examples showed that a diene Rh complex could be successfully immobilized on insoluble supports and they have good durability. However, no catalysts have sufficient catalytic activity, which is measured by turnover frequency (TOF), and broad substrate scope. Therefore, the development of highly active heterogeneous catalysts that show wide substrate generality for asymmetric arylation reactions is desired. In our laboratory, we have developed tertiary alkyl amine derived secondary amide substituted diene **L1** for both chiral Rh complexes and chiral Rh nanoparticle systems, which show outstanding reactivities and enantioselectivities for a wide variety of substrates.[39] Considering our previous investigations, the tertiary alkyl amine moiety in diene **L1** is essential to achieve excellent activity and enantioselectivity, probably because structurally rigid nature of the amide group that restricts the rotation of the ^{t}BuNH group to fix the favored conformation. Therefore, I embarked on the immobilization of diene **L1** and the application to continuous-flow synthesis.

Scheme 18. Asymmetric 1,4-addition to unsaturated esters with PI/CB Rh/Ag catalyst
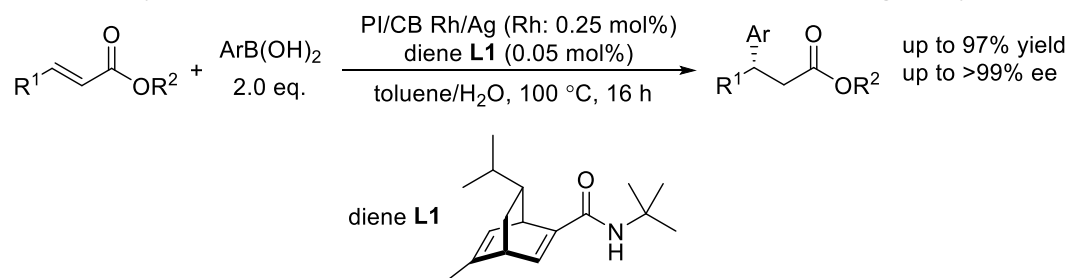
Section 2:   Results and Discussion

I selected polystyrene as a catalyst support because it is easily preparable and was successfully applied to continuous-flow reactions. In my master course study, chiral diene Rh complex on polystyrene was investigated and brief summary was shown in here.[40,41] First, I synthesized the diene with a styryl moiety according to the literature procedure. This diene **L2** was co-polymerized with styrene and divinylbenzene (DVB) to afford a chiral diene ligand supported on cross-linked polystyrene (PS-diene). PS-diene was then mixed with $[Rh(C_2H_4)_2Cl]_2$ in toluene to afford yellow powder, which is named PS-diene Rh (Scheme 19). Successful immobilization of Rh was assured by ICP measurement.

Scheme 19. Representative procedure for the synthesis of PS-diene Rh
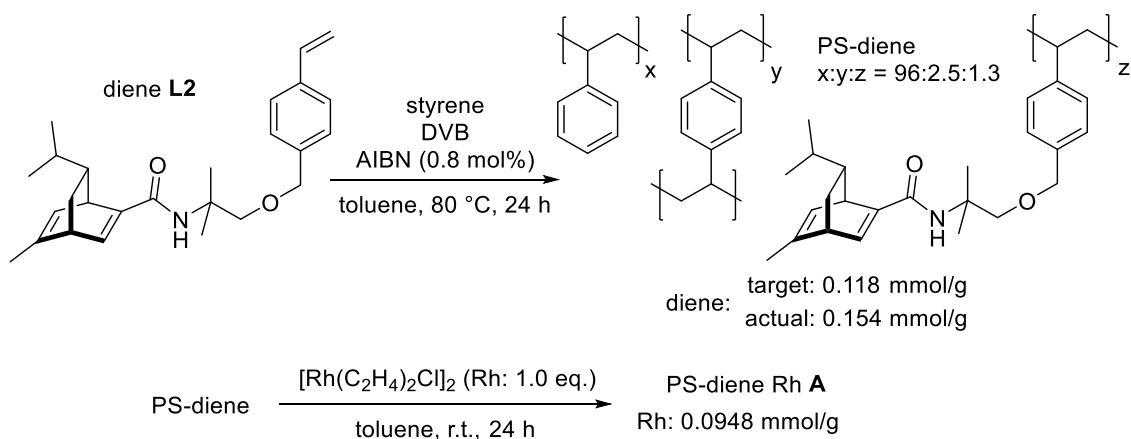
To check the catalytic activity of PS-diene Rh, I selected asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexenone as a model reaction (Table 1). When the reaction was conducted in toluene and water biphasic system, the desired product was obtained in high yield and excellent enantioselectivity and the leaching of Rh was low (entry 1). As decreasing the ratio of water led to a decrease in yield, optimal toluene and water ratio was determined to 1:2 (entries 2-3). Decreasing the catalyst loading gave the desired product in lower yields keeping the enantioselectivities high (entry 4-5), hence 1.0 mol% of PS-diene Rh was needed to achieve a full consumption of 2-cyclohexnenone.

Table 1. Reaction optimization (1)
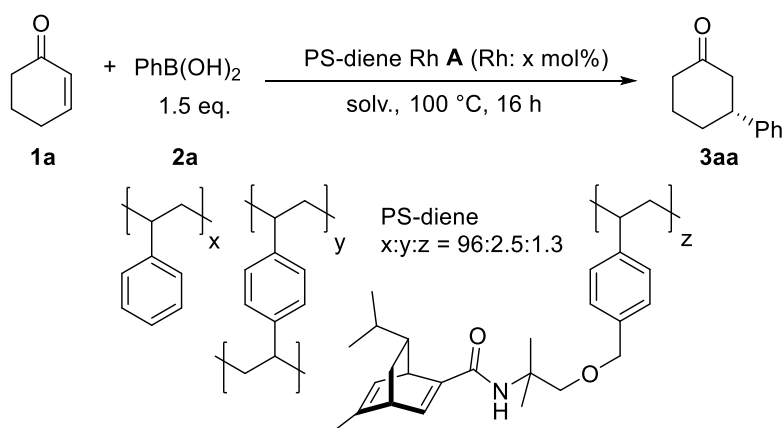
entry	cat. (mol%)	solv.	yield (%)[a]	ee (%)[b]	leaching (%)[c]
1	1.0	toluene/H_2O = 1:2	96	99	1.3
2	1.0	toluene /H_2O = 1:1	78	99	1.0
3	1.0	toluene /H_2O = 2:1	67	99	2.2
4	0.50	toluene /H_2O = 1:2	75	99	<2
5	0.25	toluene /H_2O = 1:2	64	99	<4

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis. [c] Determined by ICP analysis.

I embarked on the optimization of the composition of monomers in PS-diene Rh to improve the catalytic activity (Table 2). Increasing the amount of DVB led to an increase in yield though further increase of DVB led to the almost same yield (entries 1-3). Next, I changed the ratio of diene in the copolymer, which revealed that both increase and decrease of diene loading gave improved results and the catalyst with a higher amount of diene is the best in the viewpoint of yield (entries 4-5). Unfortunately, decreasing the catalyst loading of newly optimized PS-diene to 0.25 mol% led decrease both in yield and enantioselectivity (entry 6), hence I selected the composition shown in entry 5 as the optimal condition, and all the subsequent experiments were conducted with this catalyst if not otherwise noted.

Table 2. Reaction optimization (2)
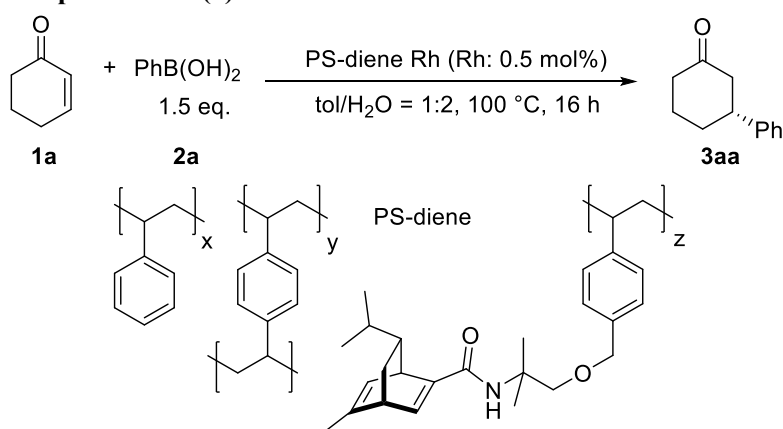
entry	cat.	x:y:z	yield (%)[a]	ee (%)[b]	leaching (%)[c]
1	PS-diene Rh **A**	96:2.5:1.3	75	99	<2
2	PS-diene Rh **B**	95:3.6:1.3	86	99	0.18
3	PS-diene Rh **C**	93:6.0:1.3	74	99	<0.2
4	PS-diene Rh **D**	96:3.6:0.7	91	99	0.6
5	PS-diene Rh **E**	94:3.6:2.6	98	99	0.5
6[d]	PS-diene Rh **E**	94:3.6:2.6	88	98	0.8

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis. [c] Determined by ICP analysis. [d] PS-diene Rh (Rh: 0.25 mol%) was used.

With PS-diene Rh **E** (0.5 mol%), several reactions of boronic acids with α,β-unsaturated carbonyl compounds were examined (Table 3). Neither electron-withdrawing nor electron-donating groups at the *para*-position of arylboronic acids (**2b** and **2c**) affected the catalytic activity, and high yields and outstanding enantioselectivities of the desired products were obtained (entries 2 and 3). *meta*-Methoxyphenylboronic acid (**2d**) was also a suitable substrate (entry 4). Arylboronic acid **2e**, with a substituent at the *ortho*-position, gave the desired product in lower yield (69%), presumably because of a steric effect, but outstanding enantioselectivity was observed (entry 5). The yield was improved to 92% by using 3 equiv. of **2e** while keeping the same enantioselectivity. As previously reported,[12] lower reactivity was observed for acyclic α,β-unsaturated ketones than for cyclic α,β-unsaturated ketone. For example, acyclic α,β-unsaturated ketone **1b** reacted with **2a** to afford the product in only 5% yield, although the enantioselectivity was very high (entry 6). Other acyclic α,β-unsaturated ketones **1c** and **1d** showed moderate to good yields, albeit with very high enantioselectivities (entries 7 and 8). These low-yield issues were solved by addition of cinnamyl alcohol or use of the catalyst preactivated by base (PS-diene Rh-OH). The effects of these additives are discussed later (see below). When acyclic α,β-unsaturated ester **1e** was treated with **2a**, the desired product was obtained in 76% yield with 98% ee. Given that decomposition of the boronic acid was observed, 3.0 equiv. of **2a** were used and the yield was improved to 99% with the same enantioselectivity (entry 9). Other α,β-unsaturated esters, including heteroaromatics and even cyclic α,β-unsaturated esters, also worked well to afford the desired products in satisfactory yields with very high enantioselectivities (entries 10–15). Finally, α,β-unsaturated amides were tested, and it was found that this type of compound was acceptable to this catalytic system (entries 16 and 17).

Table 3. Substrate scope (α,β-unsaturated carbonyl compounds)
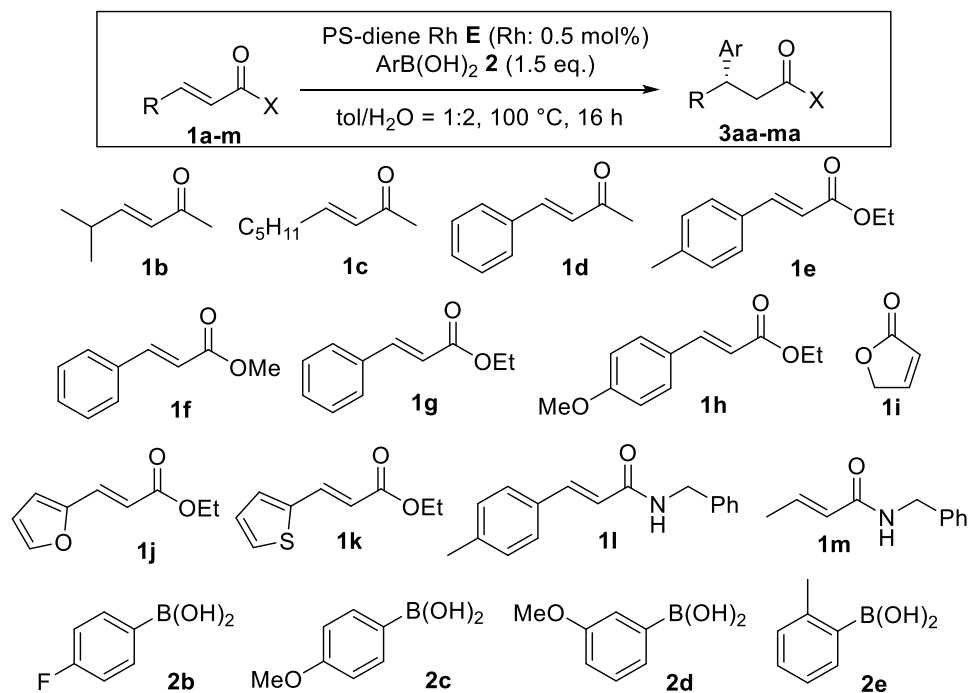
entry	1	2	yield (%)[a]	ee (%)[b]
1	1a	2a	98	99
2	1a	2b	88	99
3	1a	2c	90	99
4	1a	2d	94	99
5	1a	2e	69 (92)[c]	99
6	1b	2a	5 (87)[c,d]	99
7	1c	2a	25 (89)[c,d]	99
8	1d	2d	64 (90)[e]	96
9[c]	1e	2a	99	98
10[c]	1f	2d	89	98
11[c]	1g	2d	80	98
12[c]	1h	2a	93	98
13[c]	1i	2a	76	98
14[c]	1j	2a	60	96
15[c]	1k	2a	95	95
16	1l	2a	89	98
17	1m	2a	96	98

[a] Isolated yield. [b] Determined by HPLC analysis. [c] ArB(OH)$_2$ (3.0 equiv) was used. [d] Cinnamyl alcohol (1.0 mol%) was used as an additive. [e] PS-diene Rh−OH was used.

Recovery and reuse experiments of heterogeneous PS-diene Rh **E** were conducted (Table 4). Although PS-diene Rh **E** can be recovered by simple filtration, centrifugation was adopted for recovery to minimize the loss of the catalyst during the recovery operation. All the operation was conducted under Ar carefully. The recovered catalyst was washed roughly and quickly. Even after the 10th cycle, no loss of either yield or enantioselectivity was observed.

Table 4. Recovery and reuse
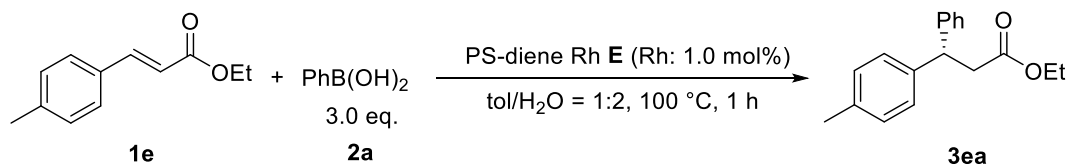
cycle	yield (%)[a]	ee (%)[b]
1	99	99
2	98	99
3	99	99
4	98	99
5	97	99
6	97	99
7	98	99
8	99	99
9	98	99
10	98	99

[a] Isolated yield. [b] Determined by HPLC analysis.

We then investigated asymmetric 1,4-addition reactions of aryl boronic acids with nitroalkenes, which are valuable because the resulting chiral nitro compounds can be converted into a range of useful compounds such as chiral amines. However, because of the strong coordination ability of the nitro group, stoichiometric to substoichiometric amounts of additives, such as KOH or KHF_2, were required to achieve an efficient catalytic turnover.[42,43] Moreover, reported examples of heterogeneous catalysts for this asymmetric reaction have been very limited. We conducted several reactions of boronic acids with nitroalkenes using PS-diene Rh **E** (Table 5). Nitrostyrene derivatives bearing either electron-donating or electron-withdrawing substituents on the benzene ring worked well (entries 1–5). Heteroarene-substituted nitroalkenes could react with **2a** to afford the corresponding adducts in high yields with high enantioselectivities (entries 6 and 7). Even aliphatic substrates could be utilized and a high level of enantioselectivity was kept (entries 8 and 9). Notably, PS-diene Rh **E** gave the same level or slightly higher enantioselectivities compared with the corresponding homogeneous Rh-diene **L1** complex system.

Table 5. Substrate scope (nitroalkenes)

R—CH=CH—NO$_2$ (**4a-i**) $\xrightarrow[\text{tol/H}_2\text{O} = 1:2,\ 100\ ^\circ\text{C},\ 16\ \text{h}]{\substack{\text{PS-diene Rh }\textbf{E}\ (\text{Rh: 0.5 mol\%})\\ \text{ArB(OH)}_2\ \textbf{2}\ (1.5\ \text{eq.})}}$ Ar—CH(R)—CH$_2$—NO$_2$ (**5ad-ia**)

4a **4b** (Me) **4c** (MeO)

4d (F) **4e** (Br) **4f**

4g **4h** **4i**
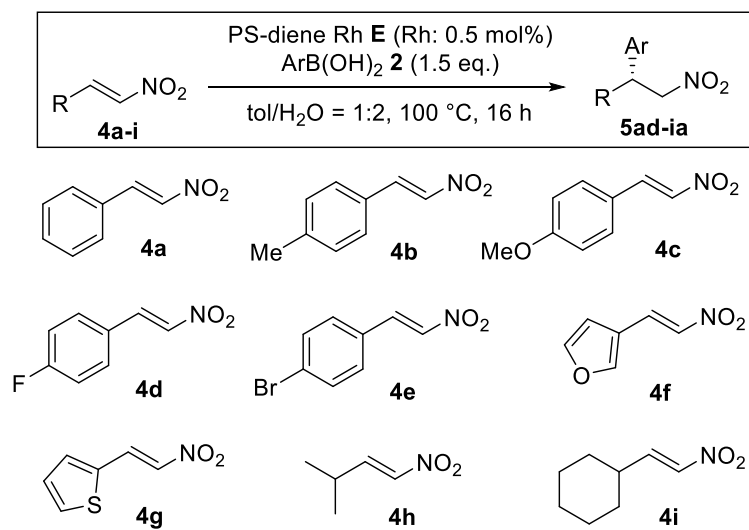
entry	**4**	**2**	yield (%)[a]	ee (%)[b]
1	**4a**	**2d**	88	94
2	**4b**	**2a**	91	93
3	**4c**	**2a**	95	95
4	**4d**	**2a**	92	93
5	**4e**	**2a**	94	93
6	**4f**	**2a**	93	96
7	**4g**	**2a**	93	93
8	**4h**	**2a**	90	90
9	**4i**	**2a**	94	89

[a] Isolated yield. [b] Determined by HPLC analysis.

We also examined asymmetric addition reactions of arylboronic acids with imines using PS-diene Rh **E**. Since the first report of asymmetric addition of arylboronic acids to aryl tosylimines catalyzed by chiral Rh complexes in 2004,[44] many efforts have been made to develop this type of reaction to provide chiral amines, which are found in many pharmaceutical skeletons.[45] By using PS-diene Rh **E** (0.5 mol%), several imines were treated with **2a** under the optimal conditions (Table 6). Regardless of the substituents, all aromatic (entries 1–5) and heteroaromatic imines (entries 6 and 7) worked well to afford the corresponding amines in high yields with outstanding enantioselectivities. Although aliphatic imines are usually unstable in aqueous media, imine 6 h could be smoothly converted to the corresponding amine **7ha** even in a water-rich co-solvent system (entry 8). These results indicated that the immobilized catalyst maintained enough fast reaction rate to avoid hydrolysis of substrates.

Table 6. Substrate scope (imines)
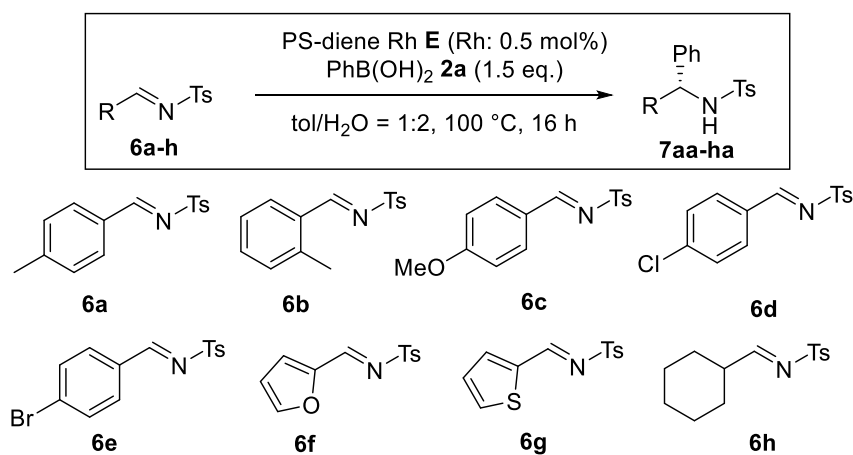
entry	6	yield (%)[a]	ee (%)[b]
1	**6a**	95	99
2	**6b**	93	98
3	**6c**	98	99
4[c]	**6d**	98	98
5[c]	**6e**	89	97
6	**6f**	85	99
7	**6g**	90	99
8[c]	**6h**	78	99

[a] Isolated yield. [b] Determined by HPLC analysis.

It is known that active spices in Rh catalyzed 1,4-addition reactions are Rh−OH complexes and treatment of Rh−Cl complex with a base generates more active Rh−OH complex.[46] Treatment of PS-diene Rh **E** with KOH was found to activate the catalyst significantly; PS-diene Rh treated with the base for 24 h (PS-diene Rh−OH) gave the desired product almost quantitatively within 10 minutes, which corresponds to TOF of over 1000 h^{-1} (Table 7).

Table 7. Activation of PS-diene Rh with base

PS-diene Rh **E** $\xrightarrow{\text{THF/5 M KOH aq. = 10:1, r.t., activation time}}$ PS-diene Rh–OH

$$\underset{\textbf{1a}}{\text{1a}} + \underset{\textbf{2a}}{\underset{\text{1.5 eq.}}{\text{PhB(OH)}_2}} \xrightarrow[\substack{\text{tol/H}_2\text{O} = 1:2,\ 100\ °\text{C},\\ \text{reaction time}}]{\text{PS-diene Rh–OH (Rh: 0.5 mol\%)}} \underset{\textbf{3aa}}{\text{3aa}}$$
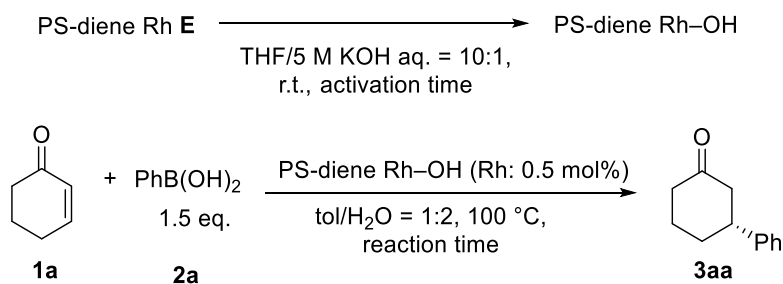
| entry	activation time	yield at each time (%)[a]		
		10 min	30 min	60 min
1	no activation	<1	6	12
2	30 min	66	86	91
3	24 h	91	95	96 (99% ee)

[a] Determined by ^{1}H NMR analysis.

According to the analysis with scanning transmission electron microscopy (STEM), no aggregation of Rh was observed and Rh existed on the whole polymer (Scheme 20 and Scheme 21). Therefore, Rh worked as complex immobilized on the polymer, not nanoparticle. Almost the same observation holded for PS-diene Rh−OH, and immobilization of Rh complex after the treatment with base was verified (Scheme 22 and Scheme 23). According to the elemental analysis of PS-diene Rh **E**, the almost same amount of Cl as Rh was detected and the amount of Cl was significantly decreased after the treatment with base. Therefore, improvement of the catalytic activity of PS-diene Rh can be ascribed to the formation of Rh−OH spices, excluding the possibility of the activation of boronic acids by the residual base.
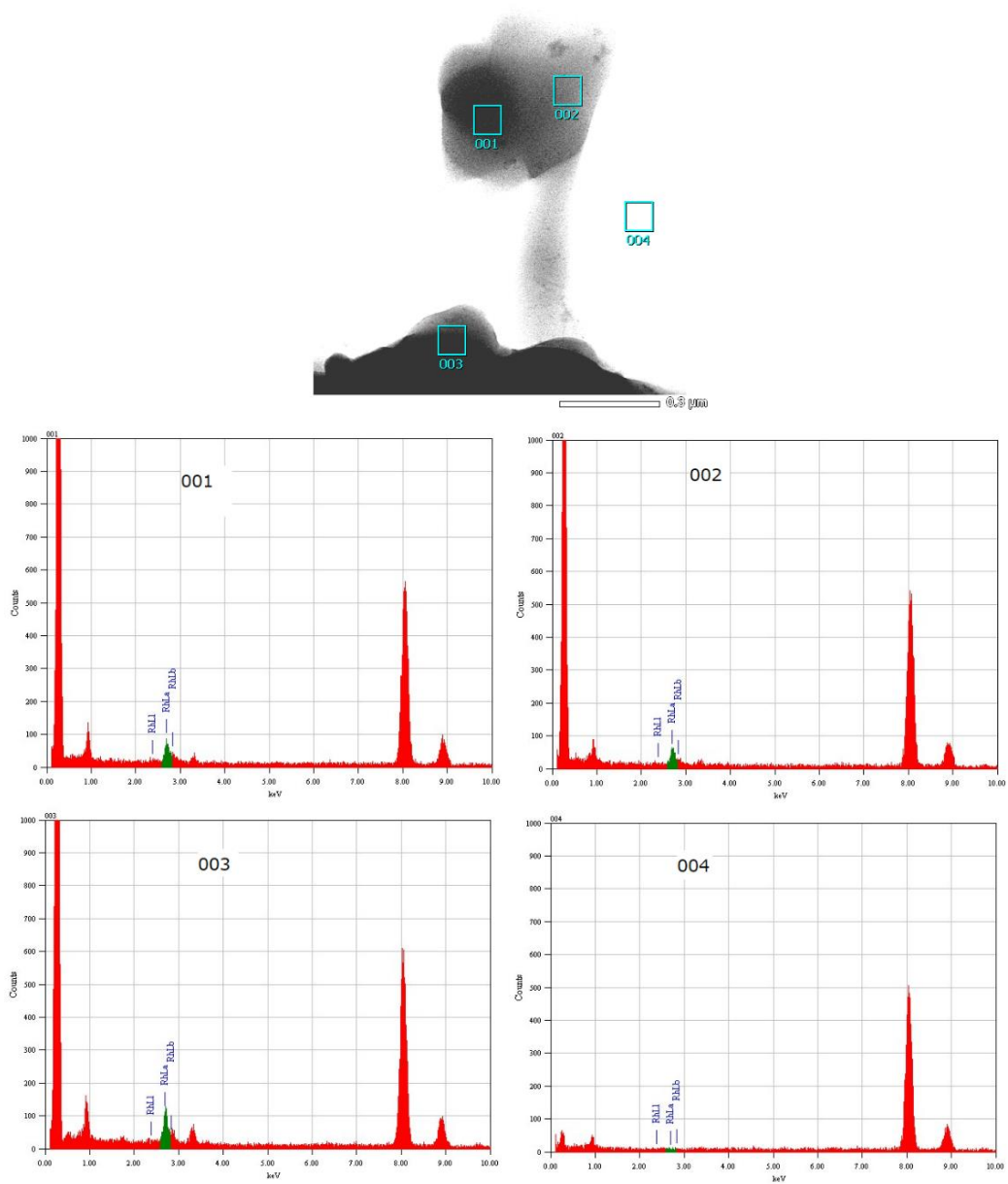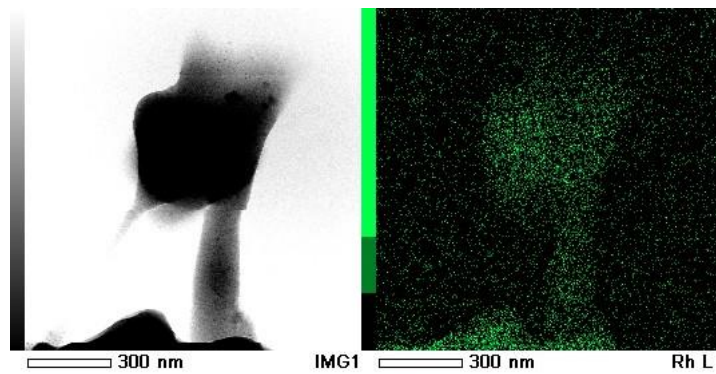
Scheme 20. STEM image and EDS analysis of PS-diene Rh
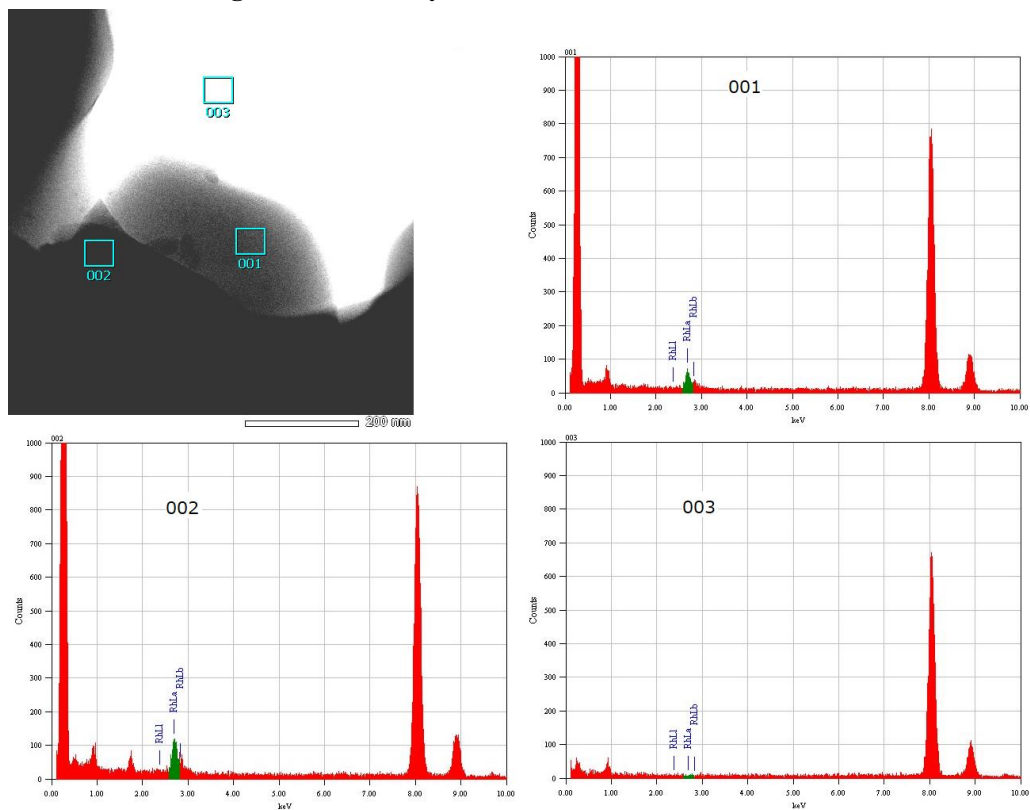

Scheme 21. EDS mapping of PS-diene Rh
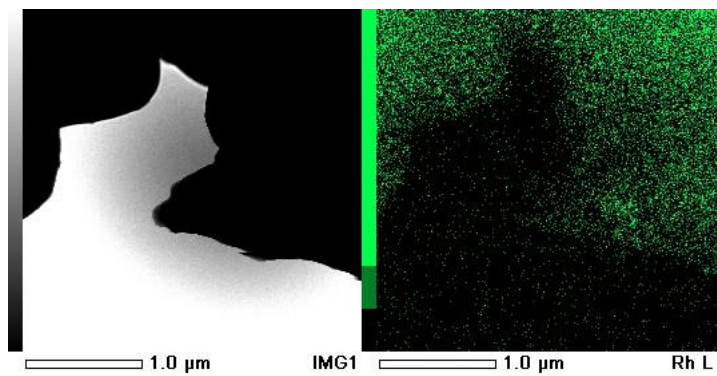
Scheme 22. STEM image and EDS analysis of PS-diene Rh−OH

**Scheme 23. EDS mapping of PS-diene Rh−OH**

On the other hand, the rate acceleration by the base-treatment of the catalyst was not large in the case of the reaction with ester **1e** (Table 8). Therefore, I hypothesized that ester **1e** was involved in the transformation of Rh−Cl spices to Rh−OH spices. To check this hypothesis, the competitive reaction experiments were conducted, where ketone **1a** and ester **1e** were reacted in the same pot (Table 9). In the presence of ester **1e**, ketone **1a** reacted quickly even when PS-diene Rh **E** without activation was used. Similar acceleration effect was also observed in the presence of amide **1l** (Table 10). In the presence of amide **1l**, the reaction rate of ketone **1a** was slower than that in the presence of ester **1e** probably because amide **1l** coordinated to active spices stronger than ester **1e** to form a stable intermediate. Therefore, it can be said that unsaturated carbonyl compounds are involved in the generation of catalytically active spices and the rate of this process is slower in the reaction of 2-cyclohexenone than that in the reaction of esters or amides. The observations can also be explained that unsaturated carbonyl compounds accelerate the first transmetalation of phenylboronic acid to Rh−Cl spices.

Table 8. Reaction rate with ester

PS-diene Rh **E** $\xrightarrow{\text{THF/5M KOH aq. = 10:1,}\atop\text{r.t., 24 h}}$ PS-diene Rh–OH
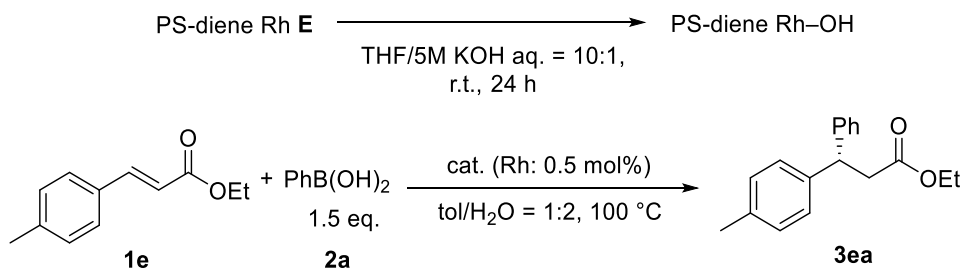
entry	cat.	yield at each time (%)[a]			
		10 min	30 min	60 min	16 h
1	PS-diene Rh **E**	18	48	79	76
2	PS-diene Rh−OH	24	55	70	73

[a] Determined by ^{1}H NMR analysis.

Table 9. Competitive reaction with ketone and ester
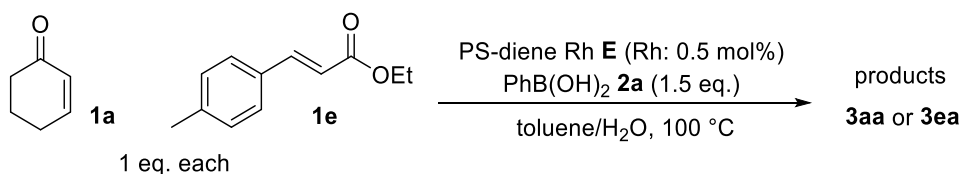
product	yield at each time (%)[a]					
	10 min	30 min	60 min	2.5 h	5.5 h	16 h
3aa	11	34	47	57	62	59
3ea	2.7	11	17	23	25	27

[a] Determined by ^{1}H NMR analysis.

Table 10. Competitive reaction with ketone and amide
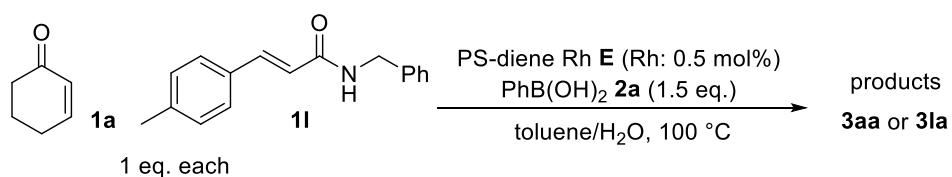
product	yield at each time (%)[a]					
	10 min	30 min	60 min	2.5 h	5.5 h	16 h
3aa	4.1	16	27	50	53	63
3la	1.5	5.7	11	23	27	35

[a] Determined by ^{1}H NMR analysis.

Unsaturated ketones and esters are known to be more electrophilic than amides, which can be explained by a higher LUMO energy of unsaturated amides. Therefore, in the above substrate scope investigation, it is unexpected that amides gave the better yield than acyclic ketones and esters. Then,

I investigated and compared the reaction rates of esters and amides.

In the comparison between aliphatic ester **1n** and amide **1m**, amide **1m** reacted significantly faster and almost quantitative yield was obtained within half an hour while the reaction of ester **1n** resulted in low yield (Table 11). The reaction using a homogeneous Rh-diene complex also ceased within half an hour, and amide **1m** reacted faster than ester **1n** (Table 12). Therefore, the difference in yields of aliphatic ester **1n** and amide **1m** is a common feature in both homogeneous and heterogeneous Rh-diene catalytic systems.

Table 11. Comparison of reaction rate: aliphatic ester vs. amide

entry	substrate	yield at each time (%)[a]			
		10 min	30 min	60 min	16 h
1	**1n**	4.6	9.2	14	24
2	**1m**	39	73	93	96

[a] Determined by ^{1}H NMR analysis.

Table 12. Comparison of reaction rate in homogeneous system: aliphatic ester vs. amide

entry	substrate	cat. (mol%)	yield at each time (%)[a]		
			10 min	20 min	30 min
1	**1n**	0.5	57	59	62
2	**1m**	0.5	99	98	98
3	**1n**	0.1	9.1	12	13
4	**1m**	0.1	42	-	54

[a] Determined by ^{1}H NMR analysis.

In the comparison between aromatic ester **1e** and amide **1l**, ester **1e** reacted slightly faster than amide **1l** (Table 13). Also, using the homogeneous Rh(I) complex under the same condition, the initial rate in the reaction of ester **1e** was faster than that of amide **1l** (Table 14). Therefore, the tendency of catalytic activity is not different between PS-diene Rh and homogeneous Rh (I) complex at the initial stage. On the other hand, the final yield of the product from ester **1e** was higher than that from amide **1l**, which is the opposite tendency compared with the homogeneous catalysis. The lower final yield in the case of ester **1e** reflected a quicker decomposition rate of phenylboronic acid because using the double amount of phenylboronic acid can proceed the reaction to full conversion (*vide supra*). In the case of amide **1l**, the coordination ability of amide **1l** is stronger, and it may prevent the decomposition of phenylboronic acid, which led slower reaction rate but higher final yield. Rh-diene complex was known to mainly exist as a dimer in the solution phase, but in PS-diene Rh, stabilization through the dimer formation was restricted. This difference between PS-diene Rh and homogeneous Rh-diene complex probably led to the difference in the decomposition rate of phenylboronic acid and appeared as the difference of final yields.

The competition reaction experiment between ester **1e** and amide **1l** was conducted (Table 15). In this case, amide **1l** reacted faster than ester **1e**, which is the opposite trend when ester **1e** and amide **1l** were reacted independently (Table 13). It can be explained that amide **1l** formed more a stable intermediate and the catalytically active site was occupied.

Table 13. Comparison of reaction rate: aromatic ester vs. amide
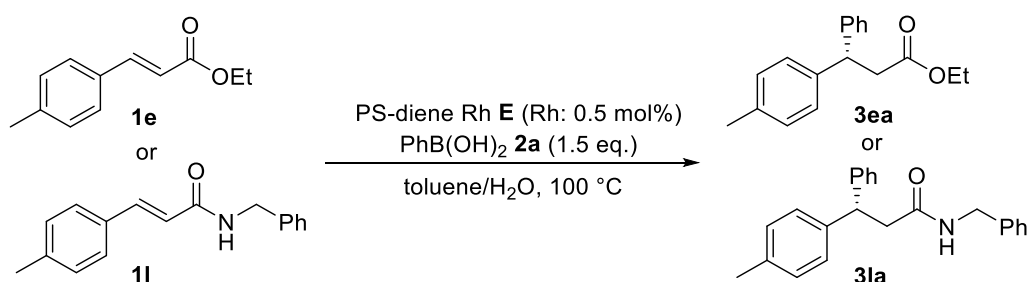
entry	substrate	yield at each time (%)[a]				
		10 min	20 min	30 min	70 min	16 h
1	**1e**	18	36	48	76	76
2	**1l**	15	29	39	60	89

[a] Determined by ^{1}H NMR analysis.

Table 14. Comparison of reaction rate in homogeneous system: aromatic ester vs. amide
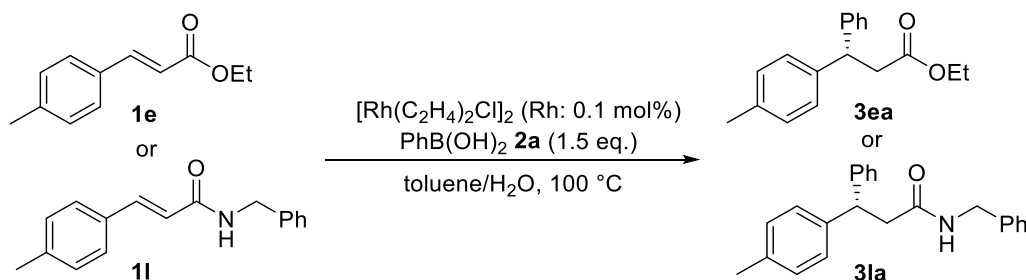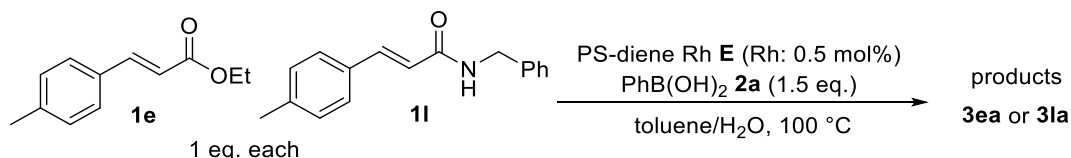

entry	substrate	yield at each time (%)[a]			
		10 min	30 min	60 min	16 h
1	**1e**	5.1	21	40	75
2	**1l**	4.6	11	21	70

[a] Determined by ^{1}H NMR analysis.

Table 15. Competitive reaction with ester and amide

| product	yield at each time (%)[a]					
	10 min	30 min	60 min	2.5 h	5.5 h	16 h
3ea	3.6	11	18	30	34	39
3la	3.4	19	28	45	52	57

[a] Determined by ^{1}H NMR analysis.

In summary of mechanistic studies, I propose some modifications to the catalytic cycle originally introduced by Hayashi's group (Scheme 24).[46] I found that the generation of catalytically active spices from Rh-Cl complex to Rh-OH complex, or the first transmetalation of phenylboronic acid to Rh-Cl complex, is affected by the substrate and the rate of the decomposition of phenylboronic acid also depends on the substrate. Based on these observations, I propose that a vacant site of Rh monomer intermediates should be occupied with substrates in addition to solvent and the coordination of substrates possibly changes the nature of Rh complexes. Based on these observations, I screened the additives and found the use of 1 mol% of cinnamyl alcohol gave the improved yields in some cases (see above). I assume that cinnamyl alcohol coordinates to Rh of PS-diene Rh−Cl to accelerate the formation of PS-diene Rh−OH.

Scheme 24. Modified catalytic cycle
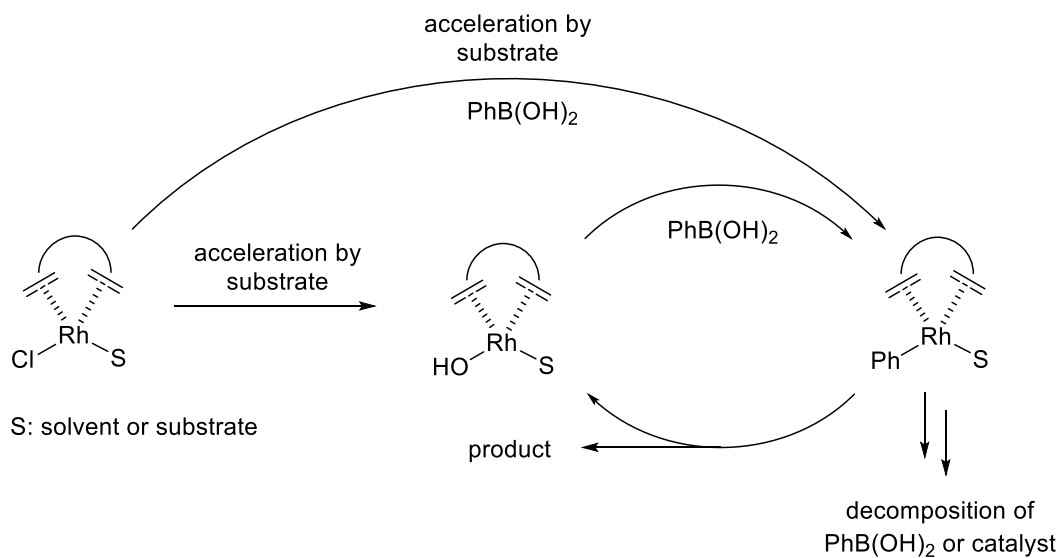
To apply PS-diene Rh catalyst to flow reaction, several problems must be solved. One is the miscibility of toluene and water inside a flow reactor. The other is the solubility of phenylboronic acid **2a** in toluene/water solvent system. Phenylboronic acid **2a** can be dissolved in toluene/water at 100 °C but it is difficult to heat whole the flow system, not only the column packed with the catalyst but also a tube or a pump. Therefore, some modifications may be needed for the flow reaction (Table 16). To solve both miscibility and solubility issues, dioxane, which is miscible with water and common solvent for Rh catalyzed 1,4-addition reaction, was used instead of toluene. However, only a small amount of the desired product was obtained (entry 2). Next, I used phenylboronic acid ester **2f**, which can be dissolved in toluene, instead of phenylboronic acid **2a**. In this case, a moderate amount of the desired product was obtained (entry 3). High yield and excellent enantioselectivity were obtained using the base for activation of phenylboronic acid ester **2f** (entry 4). Using the base also improved the yield in dioxane/water monophasic system and I adopted this condition for the further optimization of the PS-diene Rh (entry 5).

Table 16. Optimization for flow reaction (1)
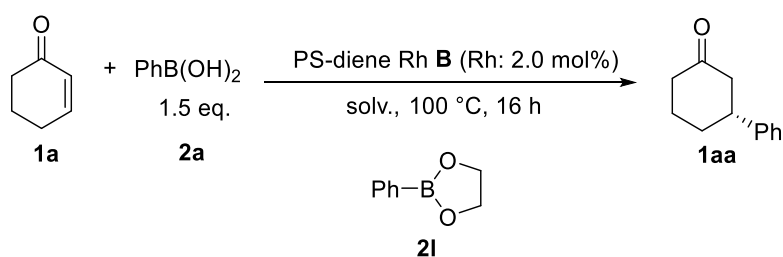
entry	solv.	yield (%)[a]	ee (%)[b]
1	toluene/H$_2$O = 1:2	78	99
2	dioxane/ H$_2$O = 1:2	8	99
3[c]	toluene/H$_2$O = 1:2	44	99
4[c,d]	toluene/H$_2$O = 1:2	89	99
5[d]	dioxane/ H$_2$O = 1:2	41	99

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis. [c] Phenylboronic acid ester **2f** (1.5 eq.) was used instead of phenylboronic acid **2a**. [d] K$_2$CO$_3$ (1.0 eq.) was added.

Decreasing the amount of DVB resulted in the improved yield (Table 17, entry 1). On the other hand, increasing the amount of DVB caused a slight decrease in enantioselectivity (entry 3). Varying the loading of diene did not improve the yield (entries 4-5). Therefore, the catalyst used in entry 1 was selected for the application to flow reaction.

**Table 17. Optimization for flow reaction (2)**
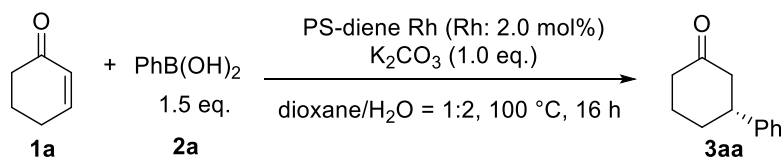
entry	cat.	x:y:z	yield (%)[a]	ee (%)[b]
1	PS-diene Rh **A**	96:2.5:1.3	53	99
2	PS-diene Rh **B**	95:3.6:1.3	41	99
3	PS-diene Rh **C**	93:6.0:1.3	47	96
4	PS-diene Rh **F**	96:2.5:2.6	53	99
5	PS-diene Rh **G**	96:2.5:3.9	43	99

[a]Determined by ^{1}H NMR analysis. [b]Determined by HPLC analysis.

The initial trial of flow reaction was conducted without pressure at the end of the column. In this case, severe boiling of solvent was observed, and no product was flowed out. Applying the back pressure could suppress the boiling of the solvent and the solution smoothly flowed. However, an only small amount of the desired product was obtained though enantioselectivity was high (Scheme 25).

Scheme 25. Flow reaction (1)
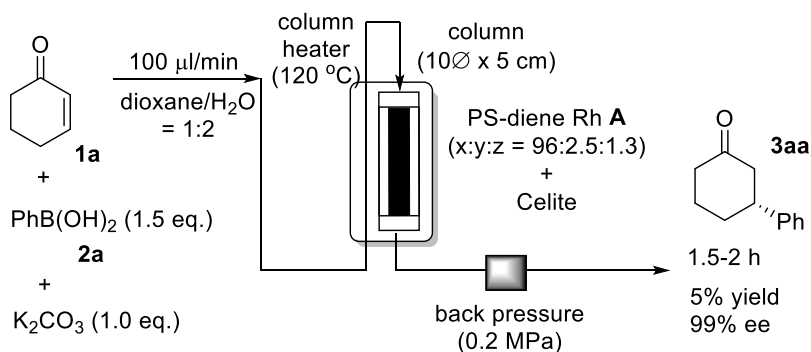
I noticed that phenylboronic acid can be dissolved in a large amount of water at room temperature. Therefore, the flow reaction with the more diluted condition was investigated. In addition, the activation of PS-diene Rh in the column might not be efficient as batch condition. Therefore, I changed the catalyst to activated PS-diene Rh-OH. A toluene solution of the substrate and an aqueous solution of phenylboronic acid were mixed in a T-shape joint and the biphasic flow was passed through the column with backpressure. The desired product was continuously obtained in high yield with excellent enantioselectivity (Scheme 26). However, the catalyst was stacked at the end of the column after 3 h and the improvement in the preparation of a column is needed.

Scheme 26. Flow reaction (2)
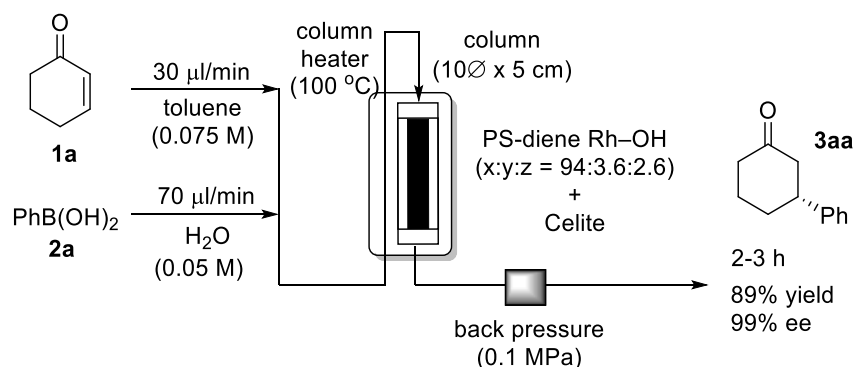
In conclusion, ligand immobilized heterogeneous catalysts for asymmetric arylation reactions have been demonstrated. A wide variety of substrates, including ketones, esters, nitroolefins, amides and imines, were suitable for the PS-diene Rh catalytic system. PS-diene Rh could be recovered and reused several times without any decline in catalytic activity. Several new insights into the reaction mechanism were also shown and the treatment with the base could enhance the catalytic activity significantly. Finally, I successfully applied PS-diene Rh−OH catalytic system to the continuous-flow reaction and the desired product was obtained in high yield with excellent enantioselectivity.

Chapter 3: Development of Core/Shell-Type Supports for Catalyst Immobilization without Loss in Kinetics

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

Chapter 4:　　Conclusion

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

Chapter 5:　　　Experimental

本章については、5 年以内に雑誌等で刊行予定のため、非公開。

Chapter 6:   References

(1)   Kobayashi, S. *Chem. - An Asian J.* **2016**, *11*, 425.

(2)   Pugin, B.; Blaser, H. U. *Top. Catal.* **2010**, *53*, 953.

(3)   Masuda, K.; Ichitsuka, T.; Koumura, N.; Sato, K.; Kobayashi, S. *Tetrahedron* **2018**, *74* (15), 1705–1730.

(4)   Mandoli, A.; Orlandi, S.; Pini, D.; Salvadori, P. *Tetrahedron Asymmetry* **2004**, *15* (20), 3233–3244.

(5)   Cornejo, A.; Fraile, J. M.; García, J. I.; García-Verdugo, E.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *Org. Lett.* **2002**, *4* (22), 3927–3930.

(6)   Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **2005**, *70* (14), 5536–5544.

(7)   Burguete, M. I.; Cornejo, A.; García-Verdugo, E.; Gil, M. J.; Luis, S. V.; Mayoral, J. A.; Martínez-Merino, V.; Sokolova, M. *J. Org. Chem.* **2007**, *72* (12), 4344–4350.

(8)   Burguete, M. I.; Cornejo, A.; García-Verdugo, E.; García, J.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A.; Sokolova, M. *Green Chem.* **2007**, *9* (10), 1091.

(9)   Aranda, C.; Cornejo, A.; Fraile, J. M.; García-Verdugo, E.; Gil, M. J.; Luis, S. V.; Mayoral, J. A.; Martínez-Merino, V.; Ochoa, Z. *Green Chem.* **2011**, *13* (4), 983.

(10)   Lim, J.; Riduan, S. N.; Su, S. L.; Ying, J. Y. *Adv. Synth. Catal.* **2008**, *350* (9), 1295–1308.

(11)   Castano, B.; Gallo, E.; Cole-Hamilton, D. J.; Dal Santo, V.; Psaro, R.; Caselli, A. *Green Chem.* **2014**, *16* (6), 3202–3209.

(12)   Lundgren, S.; Ihre, H.; Moberg, C. *Arkivoc* **2008**, *2008* (6), 73–80.

(13)   Seayad, A. M.; Ramalingam, B.; Yoshinaga, K.; Nagata, T.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 264.

(14)   Ramalingam, B.; Seayad, A. M.; Chuanzhao, L.; Garland, M.; Yoshinaga, K.; Wadamoto, M.; Nagata, T.; Chai, C. L. L. *Adv. Synth. Catal.* **2010**, *352*, 2153.

(15)   Seayad, A. M.; Ramalingam, B.; Chai, C. L. L.; Li, C.; Garland, M. V.; Yoshinaga, K. *Chem. - A Eur. J.* **2012**, *18* (18), 5693–5700.

(16)   Takeda, K.; Oohara, T.; Shimada, N.; Nambu, H.; Hashimoto, S. *Chem. - A Eur. J.* **2011**, *17* (50), 13992–13998.

(17)   Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49* (2), 272–276.

(18)   Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131* (38), 13860–13869.

(19)   Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chemie - Int. Ed.* **2013**, *52* (24), 6196–6201.

(20)   Sureshkumar, D.; Hashimoto, K.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2013**, *78* (22), 11494–11500.

(21)   Hashimoto, K.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2014**, *16* (13), 3496–3499.

(22)   Hashimoto, K.; Kumagai, N.; Shibasaki, M. *Chem. - A Eur. J.* **2015**, *21* (11), 4262–4266.

(23)   Bonfils, F.; Cazaux, I.; Hodge, P.; Caze, C. *Org. Biomol. Chem.* **2006**, *4* (3), 493–497.

(24)   Ötvös, S. B.; Mándity, I. M.; Fülöp, F. *ChemSusChem* **2012**, *5* (2), 266–269.

(25)   Arakawa, Y.; Wennemers, H. *ChemSusChem* **2013**, *6* (2), 242–245.

(26)   Tsubogo, T.; Yamashita, Y.; Kobayashi, S. *Chem. - A Eur. J.* **2012**, *18* (43), 13624–13628.

(27)   Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329–332.

(28)   Hübner, S.; De Vries, J. G.; Farina, V. *Adv. Synth. Catal.* **2016**, *358*, 3.

(29)   Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J. *Green Chem.* **2018**, *20*, 5082.

(30)   Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron Asymmetry* **1999**, *10*, 4047–4056.

(31)   Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125* (38), 11508–11509.

(32)   Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39* (6), 2093.

(33)   Otomaru, Y.; Senda, T.; Hayashi, T. *Org. Lett.* **2004**, *6* (19), 3357–3359.

(34)   Jana, R.; Tunge, J. A. *Org. Lett.* **2009**, *11* (4), 971–974.

(35)   Jana, R.; Tunge, J. A. *J. Org. Chem.* **2011**, *76* (20), 8376–8385.

(36)   Lipshutz, B. H.; Isley, N. A.; Moser, R.; Ghorai, S.; Leuser, H.; Taft, B. R. *Adv. Synth. Catal.* **2012**, *354* (17), 3175–3179.

(37)   Sawano, T.; Ji, P.; McIsaac, A. R.; Lin, Z.; Abney, C. W.; Lin, W. *Chem. Sci.* **2015**, *6*, 7163–7168.

(38)   Shen, G.; Osako, T.; Nagaosa, M.; Uozumi, Y. *J. Org. Chem.* **2018**, *83*, 7380.

(39)   Yasukawa, T.; Suzuki, A.; Miyamura, H.; Nishino, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 6616–6623.

(40)   Kuremoto, T. Master Course Thesis, 2018.

(41)   Kuremoto, T.; Yasukawa, T.; Kobayashi, S. *Adv. Synth. Catal.* **2019**, *361*, 3698.

(42)   Wang, Z. Q.; Feng, C. G.; Zhang, S. S.; Xu, M. H.; Lin, G. Q. *Angew. Chemie - Int. Ed.* **2010**, *49*, 5780.

(43)   Fang, J. H.; Jian, J. H.; Chang, H. C.; Kuo, T. S.; Lee, W. Z.; Wu, P. Y.; Wu, H. L. *Chem. - A Eur. J.* **2017**, *23*, 1830.

(44)   Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584.

(45)   Marques, C. S.; Burke, A. J. *ChemCatChem* **2011**, *3*, 635.

(46)   Kina, A.; Iwamura, H.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128* (12), 3904–3905.

(47)   Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

(48)   Grubbs, R. H.; Kroll, L. R. C. *J. Am. Chem. Soc.* **1971**, *93*, 3062.

(49)   Grubbs, R. H.; Kroll, L. C.; Sweet, E. M. *J. Macromol. Sci. Part A - Chem.* **1973**, *7*, 1047.

(50)   M.Čapka; P.Svoboda; M.Černý; J.Hetflejš. *Tetrahedron Lett.* **1971**, *12* (50).

(51)   Coliman, J. P.; Hegedus, L. S.; Cooke, M. P.; Norton, J. R.; Dolcetti, G.; Marquardt, D. N. *J. Am. Chem. Soc.* **1972**, *94*, 1789.

(52)   Sussman, S. *Ind. Eng. Chem.* **1946**, *38*, 1228.

(53)   Bayer, E.; Eckstein, H.; Hagele, K.; König, W. A.; Brüning, W.; Hagenmaier, H.; Parr, W. *J. Am. Chem. Soc.* **1970**, *92*, 1735.

(54)   Bayer, E.; Jung, G.; Halász, I.; Sebestian, I. *Tetrahedron Lett.* **1970**, *11*, 4503.

(55)   Mutter, M.; Hagenmaier, D. D. H.; Bayer, E. *Angew. Chemie - Int. Ed.* **1971**, *10*, 811.

(56)   Bayer, E.; M., M. *Nature* **1972**, *237*, 512.

(57)   Mutter, M.; Bayer, E. *Angew. Chemie Int. Ed. English* **1974**, *13*, 88.

(58)   Bayer, E.; Mutter, M.; Uhmann, R.; Polster, J.; Mauser, H. *J. Am. Chem. Soc.* **1974**, *96*, 7333.

(59)   H.Köster. *Tetrahedron Lett.* **1972**, *13* (16), 1527.

(60)   H.Köster; K.Heyns. *Tetrahedron Lett.* **1972**, *13* (16), 1531–1534.

(61)   H.Köster. *Tetrahedron Lett.* **1972**, *13* (16), 1534.

(62)   Chapman, T. M.; Kleid, D. G. *J. Chem. Soc. Chem. Commun.* **1973**, 193.

(63)   Atherton, E.; Clive, D. L. J.; Sheppard, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 6584.

(64)   Gait, M. J.; Sheppard, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 8514.

(65)   Arshady, R.; Atherton, E.; Gait, M. J.; Lee, K.; Sheppard, R. C. *J. Chem. Soc. Chem. Commun.* **1979**, 423.

(66)   Atherton, E.; Brown, E.; Sheppard, R. C.; Rosevear, A. *J. Chem. Soc. Chem. Commun.* **1981**, 1151.

(67)   Sparrow, J. T. *J. Org. Chem.* **1976**, *41*, 1350.

(68)   Becker, H.; Lucas, H.; Maul, J.; Pillai, V. N. R.; Anzinger, H.; Mutter, M. *Die Makromol. Chemie, Rapid Commun.* **1982**, *3*, 217.

(69)   Hellermann, H.; Lucas, H.; Maul, J.; Pillai, V. N. R.; Mutter, M. *Die Makromol. Chemie* **1983**, *184*, 2603.

(70)   Bayer, E. *Angew. Chemie - Int. Ed.* **1991**, *30* (2), 113–129.

(71)   Gooding, O. W.; Baudart, S.; Deegan, T. L.; Heisler, K.; Labadie, J. W.; Newcomb, W. S.; Porco, J. A.; Van Eikeren, P. *J. Comb. Chem.* **1999**, *1*, 113.

(72)   Howard Adams, J.; Cook, R. M.; Hudson, D.; Jammalamadaka, V.; Lyttle, M. H.; Songster, M. F. *J. Org. Chem.* **1998**, *63*, 3706.

(73)   Meldal, M. *Tetrahedron Lett.* **1992**, *33* (21), 3077–3080.

(74)   Auzanneau, F. -I; Meldal, M.; Bock, K. *J. Pept. Sci.* **1995**, *1* (1), 31–44.

(75)   Renil, M.; Meldal, M. *Tetrahedron Lett.* **1996**, *37* (34), 6185–6188.

(76) Rademann, J.; Grøtli, M.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1999**, *121* (23), 5459–5466.

(77) Kempe, M.; Barany, G. *J. Am. Chem. Soc.* **1996**, *118* (30), 7083–7093.

(78) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40* (35), 6329–6332.

(79) Liu, G.; Toy, P. H.; Malikayil, J. A.; Garibay, P.; Janda, K. D.; Garno, J. C.; Reger, T. S. *J. Comb. Chem.* **2001**, *3* (1), 117–124.

(80) Mijalis, A. J.; Thomas, D. A.; Simon, M. D.; Adamo, A.; Beaumont, R.; Jensen, K. F.; Pentelute, B. L. *Nat. Chem. Biol.* **2017**, *13*, 464.

(81) Hartrampf, N.; Saebi, A.; Poskus, M.; Gates, Z. P.; Callahan, A. J.; Cowfer, A. E.; Hanna, S.; Antilla, S.; Schissel, C. K.; Quartararo, A. J.; Ye, X.; Mijalis, A. J.; Simon, M. D.; Loas, A.; Liu, S.; Jessen, C.; Nielsen, T. E.; Pentelute, B. L. *Science (80-.).* **2020**, *987*, 980.

(82) Côté, S. AMPHIPHILE SOLID SUPPORT FOR PEPTIDE SYNTHESIS, BIOORGANIC AND ORGANIC CHEMISTRY, 2002, WO2002040559.

(83) Côté, S. NEW POLYETHER BASED MONOMERS AND HIGHLY CROSS-LINKED AMPHIPHILE RESINS, 2005, WO2005012277.

(84) García-Martín, F.; Quintanar-Audelo, M.; García-Ramos, Y.; Cruz, L. J.; Gravel, C.; Furic, R.; Côté, S.; Tulla-Puche, J.; Albericio, F. *J. Comb. Chem.* **2006**, *8* (2), 213–220.

(85) Cho, J. K.; Park, B. D.; Lee, Y. S. *Tetrahedron Lett.* **2000**, *41*, 7481.

(86) Cho, J. K.; Park, B. D.; Park, K. B.; Lee, Y. S. *Macromol. Chem. Phys.* **2002**, *203*, 2211.

(87) Kim, H.; Jin, K. C.; Chung, W. J.; Lee, Y. S. *Org. Lett.* **2004**, *6*, 3273.

(88) Lee, T. K.; Ryoo, S. J.; Byun, J. W.; Lee, S. M.; Lee, Y. S. *J. Comb. Chem.* **2005**, *7*, 170.

(89) Lee, T. K.; Lee, S. M.; Ryoo, S. J.; Byun, J. W.; Lee, Y. S. *Tetrahedron Lett.* **2005**, *46*, 7135.

(90) Lee, T.; Choi, J.; Ryoo, S.; Lee, Y. S. *J. Pept. Sci.* **2007**, *13*, 655.

(91) Choi, J. H.; Lee, T. K.; Byun, J. W.; Lee, Y. S. *Tetrahedron Lett.* **2009**, *50*, 4272.

(92) Liu, R.; Marik, J.; Lam, K. S. *J. Am. Chem. Soc.* **2002**, *124*, 7678.

(93) Cho, H. J.; Lee, T. K.; Kim, J. W.; Lee, S. M.; Lee, Y. S. *J. Org. Chem.* **2012**, *77*, 9156.

(94) Kim, J.; Kim, S.; Shin, D. S.; Lee, Y. S. *J. Pept. Sci.* **2018**, *24*, 1.

(95) Kim, J. H.; Jun, B. H.; Byun, J. W.; Lee, Y. S. *Tetrahedron Lett.* **2004**, *45*, 5827.

(96) Kim, J. H.; Kim, J. W.; Shokouhimehr, M.; Lee, Y. S. *J. Org. Chem.* **2005**, *70*, 6714.

(97) Shokouhimehr, M.; Kim, J. H.; Lee, Y. S. *Synlett* **2006**, 618.

(98) Kim, J. H.; Lee, D. H.; Jun, B. H.; Lee, Y. S. *Tetrahedron Lett.* **2007**, *48*, 7079.

(99) Choi, B. G.; Song, R.; Nam, W.; Jeong, B. *Chem. Commun.* **2005**, 2960.

(100) Bo, G. C.; Ko, S. Y.; Nam, W.; Jeong, B. *Bull. Korean Chem. Soc.* **2005**, *26*, 1819.

(101) Yamada, Y.; Qiao, K.; Bao, Q.; Tomida, D.; Nagao, D.; Konno, M.; Yokoyama, C. *Catal. Commun.* **2009**, *11*, 227.

(102) Sugimura, R.; Qiao, K.; Tomida, D.; Yokoyama, C. *Catal. Commun.* **2007**, *8*, 770.

(103) Qiao, K.; Hagiwara, H.; Yokoyama, C. *J. Mol. Catal. A Chem.* **2006**, *246*, 65.

(104)   Haraguchi, N.; Nishiyama, A.; Itsuno, S. *J. Polym. Sci. Part A Polym. Chem.* **2010**, *48* (15), 3340–3349.

(105)   Ullah, M. W.; Thao, N. T. P.; Sugimoto, T.; Haraguchi, N. *Mol. Catal.* **2019**, *473* (April), 110392.

(106)   Ullah, M. W.; Haraguchi, N. *Catalysts* **2019**, *9* (11), 960.

(107)   Li, X.; Chen, M.; Yang, B.; Zhang, S.; Jia, X.; Hu, Z. *RSC Adv.* **2014**, *4* (82), 43278.

(108)   Li, X.; Yang, B.; Jia, X.; Chen, M.; Hu, Z. *RSC Adv.* **2015**, *5*, 89149.

(109)   Li, X.; Yang, B.; Zhang, S.; Jia, X.; Hu, Z. *Colloid Polym. Sci.* **2017**, *295*, 573.

(110)   Vaino, A. R.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 579.

(111)   Bouillon, I.; Soural, M.; Miller, M. J.; Krchňák, V. *J. Comb. Chem.* **2009**, *11*, 213.

(112)   Li, Y.; Liu, B. *ACS Macro Lett.* **2017**, *6*, 1315.

(113)   Stöber, W.; Fink, A.; Bohn, E. *Jounal Colloid Interface Sci.* **1968**, *26*, 62.

(114)   Rostovtsev, V. V; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chemie - Int. Ed.* **2002**, *41*, 2596.

(115)   Shao, C.; Wang, X.; Zhang, Q.; Luo, S.; Zhao, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 6832.

(116)   Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.

(117)   Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046.

(118)   Dommerholt, J.; Schmidt, S.; Temming, R.; Hendriks, L. J. A.; Rutjes, F. P. J. T.; Van Hest, J. C. M.; Lefeber, D. J.; Friedl, P.; Van Delft, F. L. *Angew. Chemie - Int. Ed.* **2010**, *49*, 9422.

(119)   Gordon, C. G.; MacKey, J. L.; Jewett, J. C.; Sletten, E. M.; Houk, K. N.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2012**, *134*, 9199.

(120)   Yasukawa, T.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 16963–16966.

(121)   Yasukawa, T.; Saito, Y.; Miyamura, H.; Kobayashi, S. *Angew. Chemie - Int. Ed.* **2016**, *55* (28), 8058–8061.

(122)   Miyamura, H.; Nishino, K.; Yasukawa, T.; Kobayashi, S. *Chem. Sci.* **2017**, 8362–8372.

(123)   Yasukawa, T.; Kuremoto, T.; Miyamura, H.; Kobayashi, S. *Org. Lett.* **2016**, *18* (11), 2716–2718.