学位論文

（要約）

Chiral Metal Nanoparticles as Heterogeneous Catalysts that Surpass Homogeneous Catalysts for Asymmetric C–C Bond Forming Reactions

（不斉炭素－炭素結合生成反応において、均一系触媒を凌駕する不均一系触媒としてのキラル金属ナノ粒子）

平成２６年１２月博士（理学）申請

東京大学大学院理学系研究科

化学専攻

安川　知宏

~Contents~

Abstract

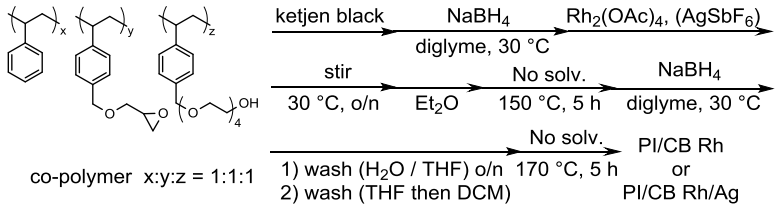
1. Introduction

Despite rapid progress in catalytic asymmetric C–C bond-forming reactions and, the importance of obtaining enantiopure compounds, applications of such reactions to large-scale industrial processes are still limited. Industry prefers heterogeneous catalysts due to their reusability and ease of separation from products; however, catalytic performance of conventional heterogeneous catalysts, such as immobilized chiral metal complexes on supports, are generally inferior to the corresponding homogeneous metal complexes. To develop truly sustainable and active chiral catalysts, I decided to investigate heterogeneous metal nanoparticle (NP) catalysts because of their high reusability, robustness, activity and unique selectivity.[1] In spite of recent studies on NP catalysis, including C–C bond forming reactions, successful examples of asymmetric catalysis using NPs with a chiral molecule as a modifier, so-called chiral NPs, which showed wide substrate scope and high selectivity, were limited. In my Ph.D studies, I developed heterogeneous chiral Rh NPs catalysts, for asymmetric 1,4-addition of arylboronic acids to electron deficient olefins. Notably, the heterogeneous NP catalysts showed superior performance when compared to the corresponding homogeneous metal complexes.

2. Chiral diene modified metal NPs catalyzed asymmetric 1,4-additions of arylboronic acids to enones

Rhodium catalyzed asymmetric 1,4-addition of arylboronic acids to electron deficient olefins is one of the most useful asymmetric C-C bond formation reactions.[2] Although widely investigated in academic research and for industrial processes, the development of recyclable and robust chiral heterogeneous Rh catalysts is desired since Rh is an expensive metal, and its contamination into products should be avoided. Therefore, I chose this reaction as a target reaction and began to investigate chiral Rh NP catalysts.

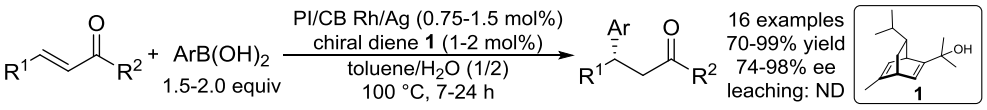
Scheme 1. Preparation of PI/CB Rh/Ag



In our laboratory, nanocomposites of polystyrene-based copolymers with cross-linking moieties and carbon black, that incarcerated various metal NP catalysts (PI/CB M), were developed.[3] Using this technique, Rh NPs were immobilized (PI/CB Rh, Scheme 1) and the catalytic activity was initially tested in the asymmetric 1,4-addition of arylboronic acids to cyclic enones in the presence of

2,2’bis(diphenylphosphino)-1,1’binaphthyl (BINAP) as a chiral modifier. The desired product was obtained in high yield and high enantiomeric excess (ee); however, a significant amount of metal leaching was observed by inductively coupled plasma (ICP) analysis. To suppress the leaching, various chiral modifiers were screened and it was found that use of chiral diene **1** could prevent the metal leaching without loss of activity and selectivity. The catalytic activity was enhanced by introducing Ag as a dopant to Rh NPs to form bimetallic NPs (PI/CB Rh/Ag), and with chiral diene **1** modified Rh/Ag bimetallic NP catalyst, wide substrate generality, including acyclic enones, was achieved in high yields with excellent ee without metal leaching (Scheme 2). Scanning transmission electron microscopy and energy-dispersive X-ray spectroscopy analysis of the catalysts revealed that in PI/CB Rh/Ag, alloy nanoparticles formed with random ratios of Rh and Ag in the particles and dispersed widely over the supports, while in PI/CB Rh, small NPs (~3 nm) were assembled in one area and not dispersed well. It was found that PI/CB Rh/Ag could be easily recovered by filtration and reused for several times while keeping high yields with excellent ee. This reaction system clearly demonstrates the high potential of heterogeneous chiral metal NP catalysts.

Scheme 2. Chiral Rh/Ag NPs catalyzed asymmetric 1,4-addition reactions with enones



(５年以内に雑誌等で刊行予定のため、該当箇所にあたる内容を一部略)

3. Conclusion

During my Ph.D studies, I have discovered that chiral diene modified heterogeneous Rh/Ag bimetallic NPs are efficient and robust chiral catalyst, and proved the great potential of chiral NPs as a practically useful asymmetric catalyst. This heterogeneous chiral NP system was evolved, by the introduction of a bifunctional modifier. These bifunctional heterogeneous chiral NP catalysts were found to surpass homogenous metal complex catalysts in terms of the catalytic performance and robustness.

4. References

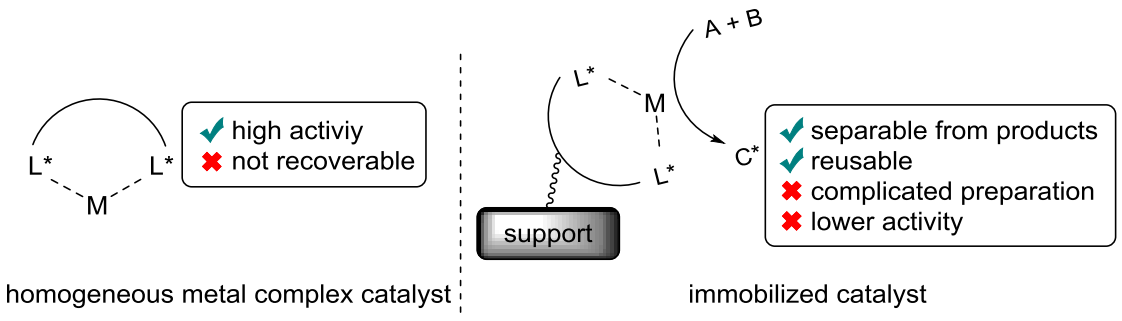
[1] Cong, H.; Porco, J. A. *ACS Catal*. **2012**, *2*, 65.
[2] Hayashi, T.; Yamasaki, K. *Chem. Rev*. **2003**, *103*, 2829.
[3] Miyamura, H.; Kobayashi, S. *Aldrichimica Acta*, **2013**, *46*, 3.

General Introduction

Heterogeneous asymmetric catalyst

Asymmetric C–C bond forming reactions are among the most important and fundamental transformation to construct basic skeletons of target molecules. Thanks to rapid progress in the field of homogeneous catalysis using chiral metal complexes, various types of difficult transformations including asymmetric C–C bond forming reactions were achieved with high selectivity.[1] However, the applications of such reactions to large-scale industrial processes are still limited compared with those of catalytic asymmetric hydrogenation reactions.[2] It is probably because the catalysts for asymmetric C–C bond forming reactions are metal based homogeneous catalysts with relatively high catalyst loadings (generally >1 mol%) and these metals and/or chiral ligands are difficult to recover and reuse. Therefore, industry prefers heterogeneous catalysts due to several advantages: 1) easy separation from products, 2) reusability, 3) avoidance of metal contaminations, 4) applications to reaction integrations such as continuous flow systems and tandem reactions.[3] One of the most common strategies to construct heterogeneous metal catalyst systems is immobilization of chiral ligands on organic or inorganic supports followed by introduction of metal salts to generate "immobilized chiral metal complexes" (Scheme 0-1).[4] Although this strategy was applicable for wide range of reaction systems, complicated preparation of monomeric ligands and individual fabrication of heterogeneous polymers are ineluctable problems and the catalytic activity of these catalysts were less than the corresponding homogeneous metal complex catalysts. In addition, stability issue of the original metal complex could not be overcome generally and it is difficult to revive their activity once the catalysts are deactivated. In this sense, the development of heterogeneous asymmetric catalysts has lagged far behind advances in homogeneous asymmetric catalysts and alternative strategy that produces more active and robust heterogeneous asymmetric catalysts should be required.

Scheme 0-1. Homogeneous catalysts vs. immobilized catalysts



Metal nanoparticle catalyst

Metal nanoparticles have been of great interest in many research fields because of their unique physical properties that are different from bulk metals and metal complexes. Such uniqueness can be realized from a view point of electronic states (Figure 0-1).[5] While metal complexes have energetically well-defined bonding and antibonding orbitals, bulk metals have typical consecutive bond structures. Metal nanoparticles possess a lot of discrete energy levels and forms a small band gap, in other words, the electronic states of metal nanoparticles have a middle of those two natures.

In the field of catalysis, chemistry of metal nanoparticles is an attractive subject in both academia and industry because of not only their very large surface areas that produce high catalytic performance, but also unique activity and selectivity.[6] One of the representative examples of unique nanoparticle catalysis is aerobic oxidations catalyzed by gold nanoparticles. In 1987, Haruta and co-workers discovered the catalytic ability of small gold nanoparticles in an oxidation of carbon monooxide to carbon dioxide at low temperature although bulk gold is inert for this reaction.[7] This example clearly demonstrated the characteristic nature of gold nanoparticle as a catalyst that is different from the nature of bulk gold and such remarkable catalytic activities for aerobic oxidation reactions have been widely studied since their discovery.[8]

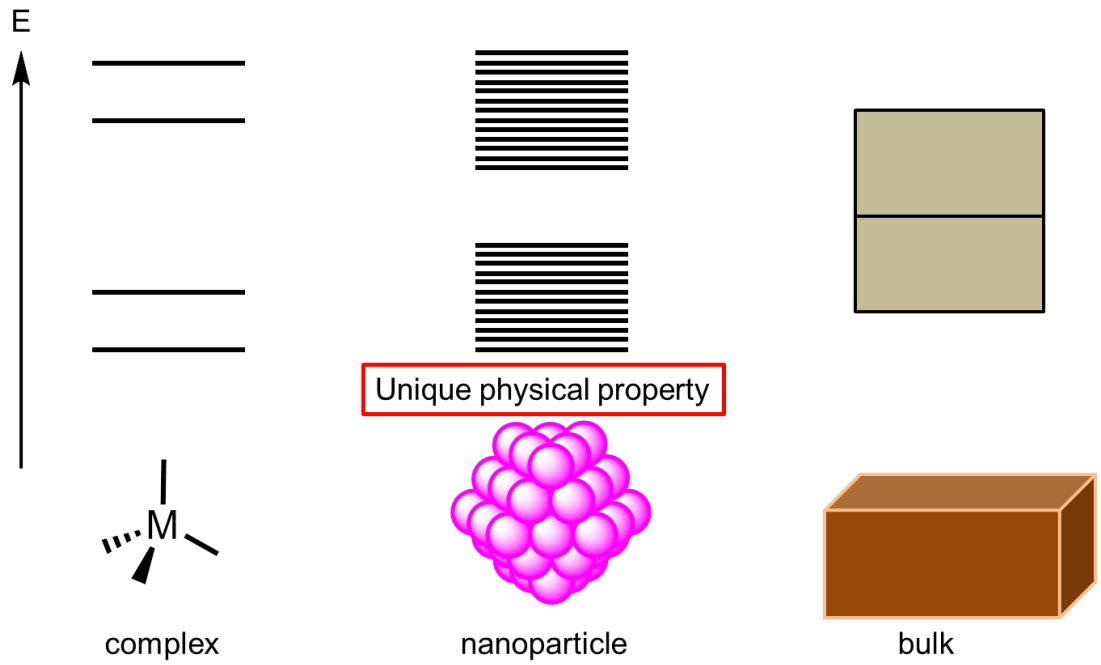
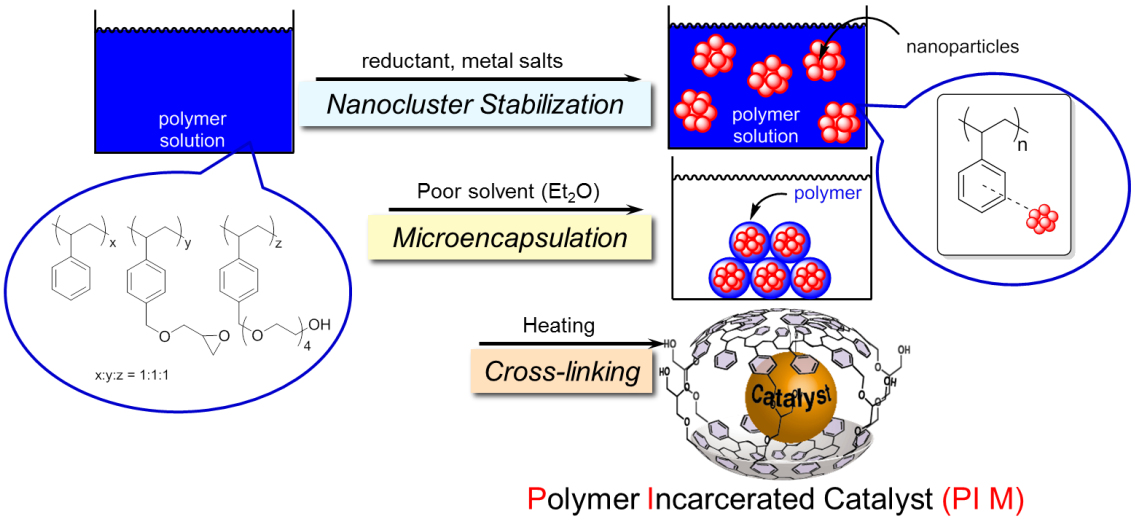


Figure 0-1. Illustration of the electronic states in complex, nanoparticle and bulk metals

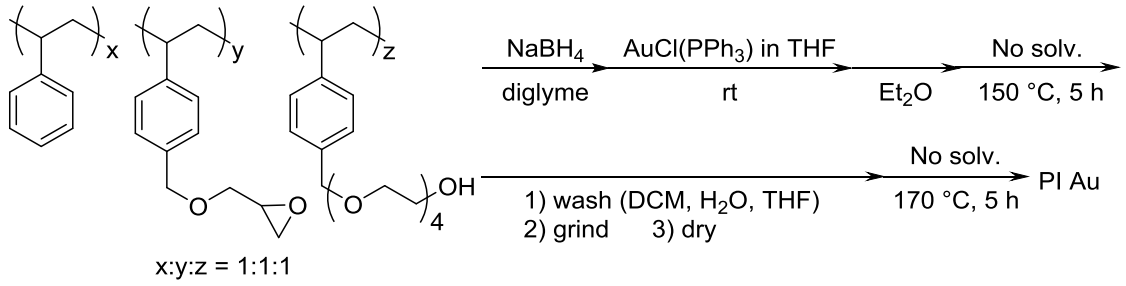
As metal nanoparticles themselves are unstable and easy to aggregate, stabilizers such as small ligand molecules, inorganic materials or polymers are required. When insoluble

solid stabilizers are used, robust heterogeneous nanoparticle catalysts can be constructed. Our group has developed polystyrene based co-polymers with cross-linking moieties incarcerated metal nanoparticle catalysts (PI M) by the following method (Scheme 0-2): 1) metal nanoparticles were generated from the reduction metal salts in a diglyme solution of the polymer and were stabilized by multiple interaction of π-electrons on benzene rings of the polymer, 2) the addition of a poor solvent for the polymer, usually ether, generated precipitations that contained metal nanoparticles as a "microencapsulation step", 3) the solid was heated under neat conditions to promote the cross-linking reaction that involved the attack of hydroxyl groups to epoxy rings to afford completely insoluble solid catalysts.[9] We successfully immobilized gold nanoparticles (representative detailed procedure was shown in Scheme 0-3) and platinum nanoparticles and performed various aerobic oxidation reactions (Scheme 0-4).[10] These PI catalysts could be recovered easily by simple filtration and reused without significant loss of activity. Moreover, bimetallic gold/platinum nanoparticles were also prepared by the simultaneous reduction of the mixture of two metal salts and the higher activity of PI Au/Pt than that of PI Au was observed in aerobic oxidation of alcohols.[11] Such higher catalytic activities of bimetallic nanoparticles often appeared in nanoparticle catalyses[12] and were explained by mainly two effects, ligand effect and ensemble effect (Figure 0-2).[13] The former effect is that electron transfer between two different metals changes the electronic state of the catalytically active center. The latter effect is that each metal activates different substrates individually to accelerate the reaction at interfaces of two metals.

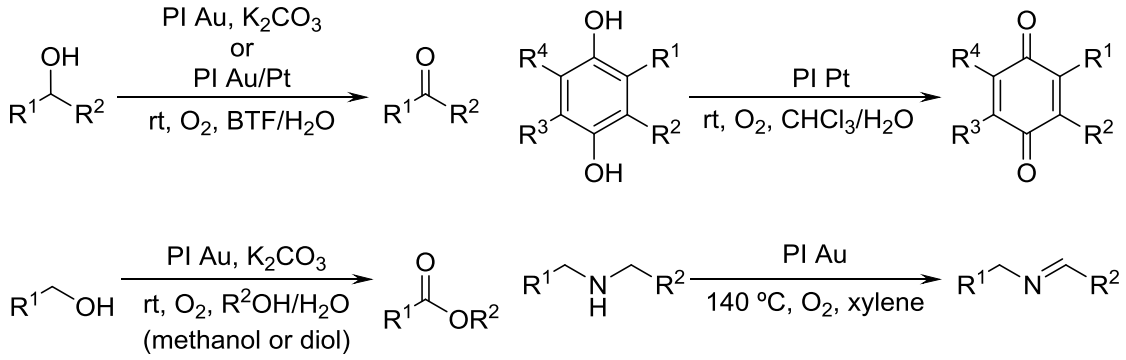
Scheme 0-2. The concept of PI catalyst



Scheme 0-3. Preparation of PI Au



Scheme 0-4. Aerobic oxidation reactions by PI catalysts



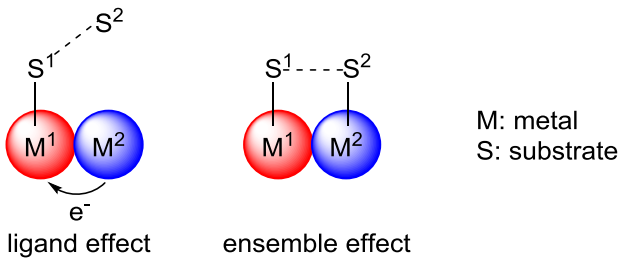


Figure 0-2. Effect of bimetallic nanoparticles

The capacity of the polymer in PI Au to stabilize small gold nanoparticles (~2 nm) was actually limited (~0.07 mmol/g) because when the high loading of gold nanoparticles (~0.28 mmol/g) were immobilized, aggregation of nanoparticles occurred and the catalytic activity of the aerobic oxidation of alcohols decreased[10g] as shown in Figure 0-3.[14] To overcome this problem, the technique was improved by introduction of spherical carbon black with high specific surface area as a second support to expand the surface area of the catalyst (PI/CB M).[15] Gold nanoparticles were highly dispersed over the polymer matrix that was stabilized on the surface of the carbon black, and could be immobilized at high loadings (~0.28 mmol/g) without loss of their catalytic activity. Using this improved method, we successfully demonstrated various aerobic oxidation reactions catalyzed by metal nanoparticles (Scheme 0-5).[16] None of the catalysts caused any significant metal leaching and the catalysts were easily recovered and reused.

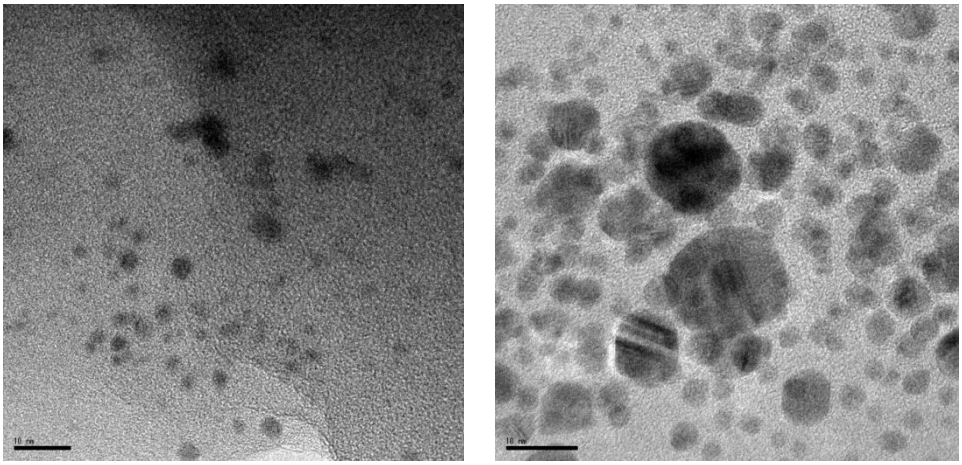
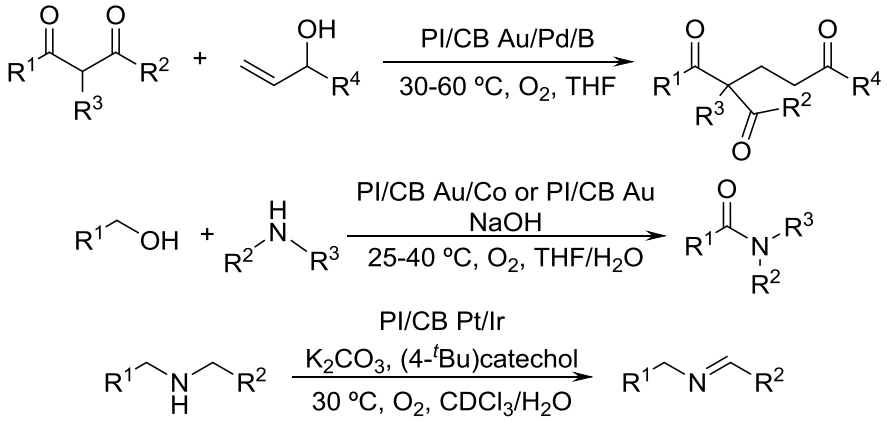


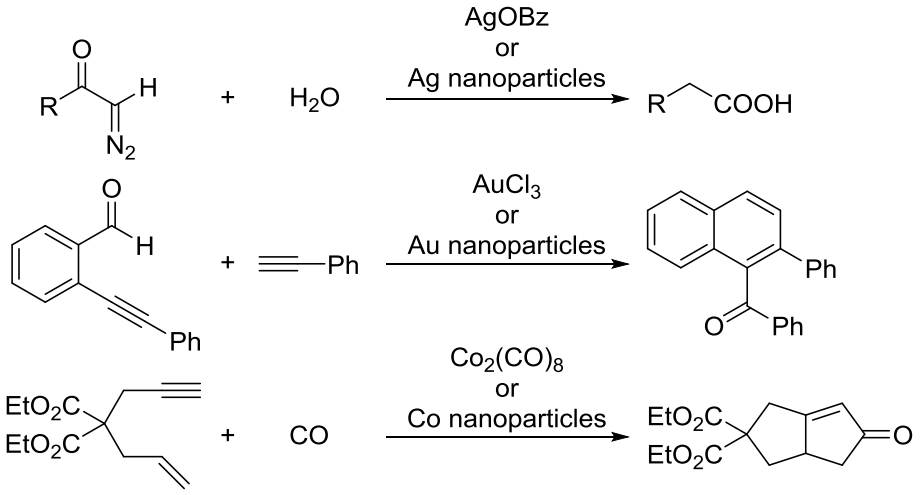
Figure 0-3. STEM images of PI Au with different target loading (left: 0.07 mmol/g, right: 0.28 mmol/g)

Scheme 0-5. Aerobic oxidation reactions catalyzed by PI/CB catalysts



Metal nanoparticle catalysis is not limited to only oxidation reactions. Recently, several groups have shown that reactions including C–C bond forming reactions, which usually required metal complex catalysts, could be performed by using the corresponding metal nanoparticle catalytic systems, with the advantages of the heterogeneous catalysts mentioned above (Scheme 0-6).[17] It might indicate that metal nanoparticles possess the potential for application in asymmetric synthesis, namely, the use of chiral ligand (chiral modifier) modified metal nanoparticles (chiral nanoparticles) as asymmetric catalysts (Figure 0-4).

Scheme 0-6. Examples of nanoparticle catalysis



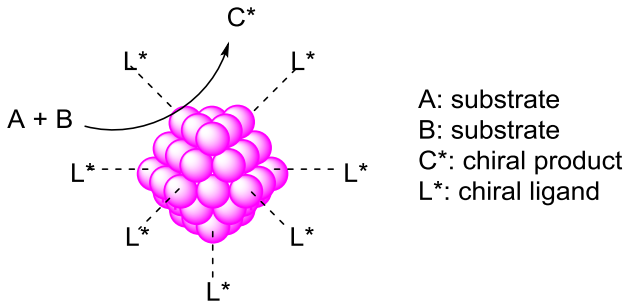


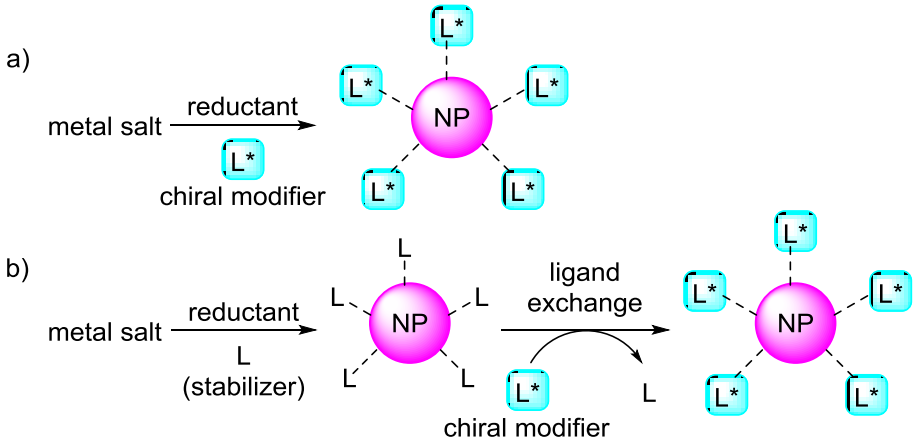
Figure 0-4. Schematic image of chiral nanoparticle catalysis

Chiral nanoparticle catalyst system

Chiral nanoparticles themselves have attracted the attention in various research fields as they show characteristic physical properties such as circular dichroism and metal-based electronic transitions[18] and are applicable for chiral nematic liquid crystal,[19] and chiral recognition etc.[20]

The preparation methods of chiral nanoparticles are roughly divided into two types of procedures: 1) direct synthesis of chiral nanoparticles in the presence of a chiral modifier as a stabilizer (Scheme 0-7, a) 2) ligand exchange from stabilized nanoparticles (Scheme 0-7, b).[18d] Chiral nanoparticles can form in situ with the latter method simply by combining chiral modifiers and metal nanoparticles in the reaction medium and then they can be used directly as chiral catalysts.

Scheme 0-7. Preparation methods of chiral nanoparticles

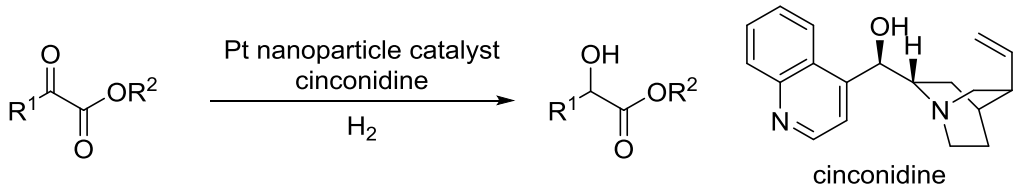


The concept using heterogeneous metal catalysts modified by chiral molecules was attempted more than 50 years ago. The first report of such concept was reported in 1956 by Akabori and co-worker that developed Pd catalyst immobilized on silk fibroin fibre used for asymmetric hydrogenation of imines.[21] Although a chiral source was not a small molecular and enantioselectivities were low levels in this system, this example postulated that chiral ligand modified metals can be applied for asymmetric catalysis and chiral nanoparticles as heterogeneous catalysts would be a promising strategy to develop truly sustainable and active chiral catalyst systems because of their high reusability, robustness, activity and unique selectivity.

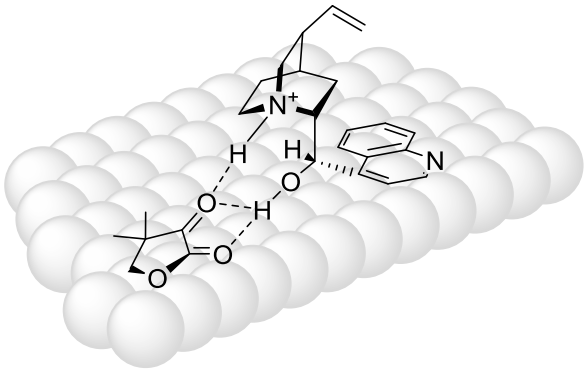
The first example of asymmetric catalysis using chiral ligand modified supported metal was reported by Orito and co-workers in 1979, demonstrating asymmetric hydrogenation of methyl pyruvate or methyl benzoylformate catalyzed by cinchonidine modified Pt on carbon.[22] This type of reaction (Scheme 0-8) was then still extensively studied[23] to improve the catalyst system[24] and to clarify the detail of mechanism.[25] These studies revealed that the chemisorption layer, through the formation of individual 1:1 diastereomeric complexes from substrates and chiral modifiers, is crucial for enantioselectivity.[25a] Recently, Maeda, Baiker and co-workers proposed a feasible intermediate in this reaction and interactions between a substrate and a modifier formed by multiple hydrogen bonds (Scheme 0-9).[25b] After pioneering works by Orito, various types of chiral nanoparticle catalysts for asymmetric hydrogenation reactions, for example nickel-boride nanoparticles,[26] Pd nanoparticles,[27] Ru nanoparticles,[28] Rh nanoparticles,[28c,29] Ir nanoparticles,[28c,30] and Fe nanoparticles,[31] have been investigated (Scheme 0-10). Although the concept of chiral nanoparticle catalysis was described more than 30 years ago, their applications were only limited to asymmetric hydrogenation reactions for a long time. It is probably because of the more complicated mechanism of chiral induction that requires multicoordination of both chiral modifier and substrates to nanoparticles in transition states. Moreover, such multicoordination may easily cause the metal leaching from supports or the nanoparticles themselves to

generate homogeneous molecular complexes. As it is possible that such a homogeneous molecular complex is an active species, the nature of the active species should be carefully studied.[32] The combination of conventional control experiments such as quantification of metal leaching, hot filtration test, mercury poisoning test and three phase test and the comparisons with the corresponding homogeneous metal complex system may aid to clarify these points.[32a]

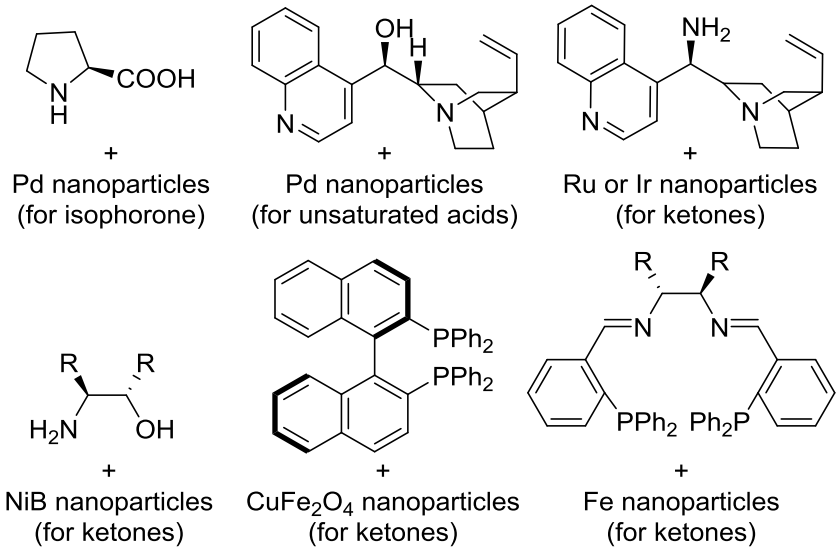
Scheme 0-8. Orito reactions



Scheme 0-9. Reaction mechanism of Orito reaction



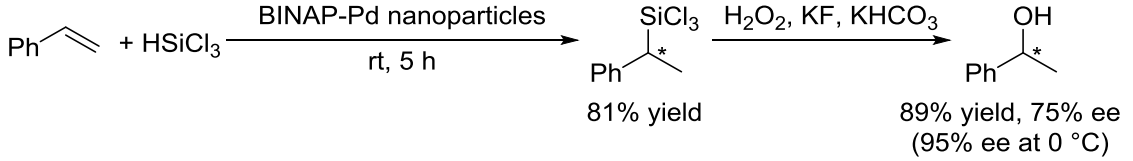
Scheme 0-10. Examples of chiral nanoparticle catalysts for asymmetric hydrogenations



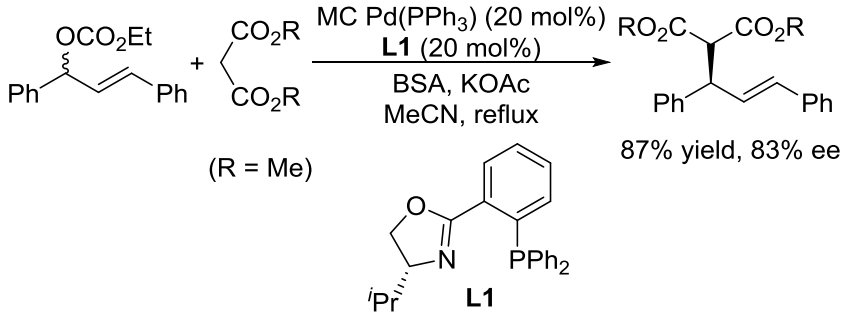
Early examples of chiral nanoparticle catalysis for other type of reactions were often

found in chiral Pd nanoparticle catalysis. In 2003, Fujihara reported that BINAP modified chiral Pd nanoparticle catalyzed asymmetric hydrosilylation of styrene and excellent enantioselectivity of the final product was obtained while the corresponding BINAP-Pd complex could not catalyze this reaction under the same conditions (Scheme 0-11).[33] As for asymmetric C-C bond forming reactions, chiral Pd nanoparticles catalyzed asymmetric allylic alkylations were reported by several groups. In 2001, our group demonstrated heterogeneous microencapsulated (MC) Pd(0) catalyzed this reaction in the presence of chiral ligand **L1** to afford the product in good enantioselectivity (Scheme 0-12).[34] In 2004, Gómez, Philippot, Chaudret and co-workers reported asymmetric allylic alkylations catalyzed by chiral diphosphite **L2** with xylose-backbone modified colloidal Pd nanoparticles.[35] Interestingly, the reaction in the nanoparticles system mainly proceeded with only one enantiomer of the starting material and, consequently, a very high degree of kinetic resolution was performed, while no kinetic resolution was observed in the corresponding Pd complex system (Scheme 0-13). A choice of the ligand was crucial to determine the nature of the active species for these reactions. Diéguez, Gómez, Leeuwen and co-workers reported chiral oxazolinyl-phosphite ligands **L3a-3e** modified Pd nanoparticles systems for the same reaction and the nature of the active species was determined as the leached molecular nature by several control studies.[36]

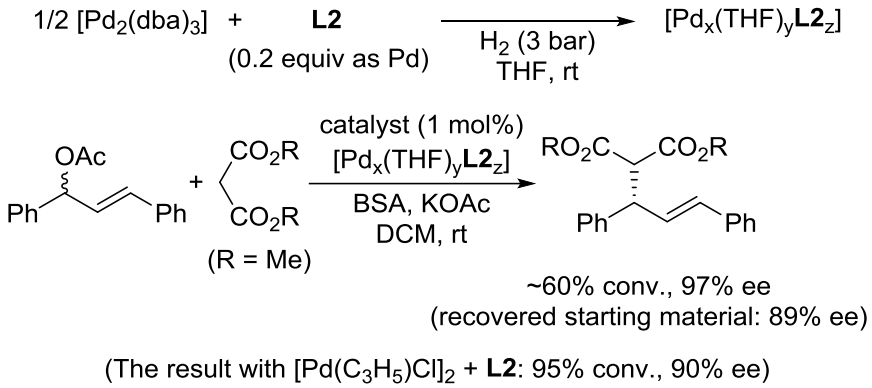
Scheme 0-11. BINAP-Pd nanoparticles catalyzed asymmetric hydrosilylation of styrene



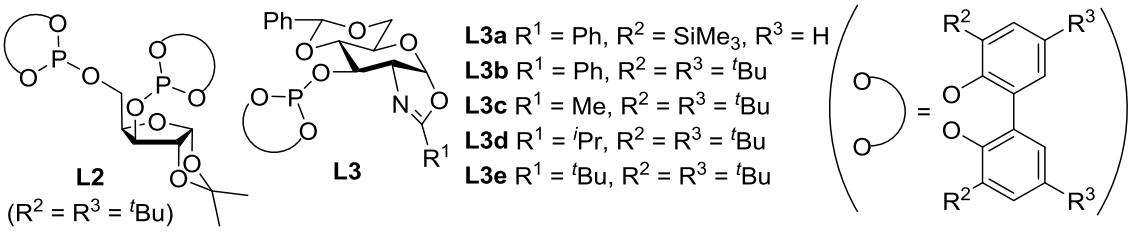
Scheme 0-12. Microencapsulated $Pd(PPh_3)$ catalyzed asymmetric allylic alkylation with chiral ligand



Scheme 0-13. Asymmetric allylic alkylation by chiral Pd catalyst and observations of kinetic resolution



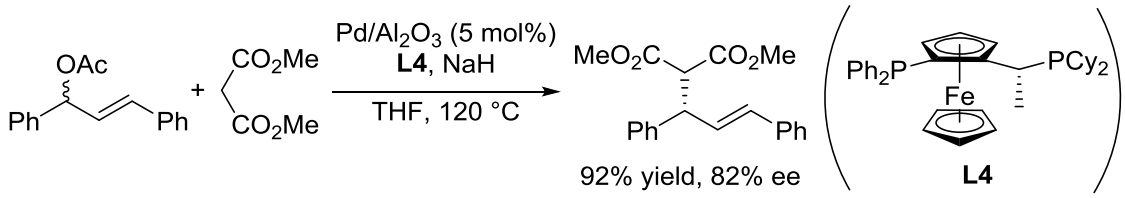
Scheme 0-14. Chiral ligand **L2** and **L3**



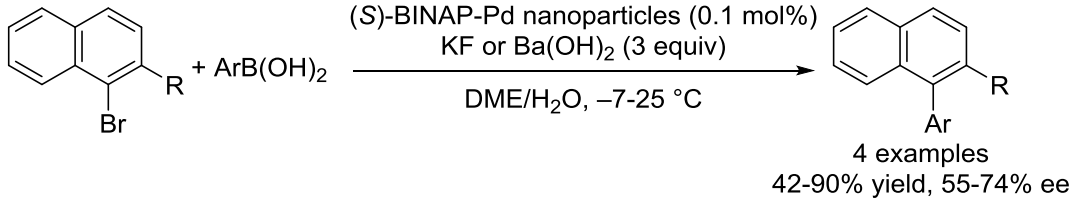
The heterogeneous nanoparticle systems for this reaction were also demonstrated.[37] Among them, Baiker and co-workers reported chiral ferrocenyl phosphine **L4** modified Pd/Al_2O_3 system for asymmetric allylic alkylation.[37b] No dependence of enantioselectivity on temperature was observed in this system, while the enantioselectivity was decreased by increasing the reaction temperature from 85% ee at 60 ˚C to 55% ee at 120 ˚C in the corresponding homogeneous complex system.

Chiral Pd nanoparticles were employed to other type of asymmetric reactions such as asymmetric Suzuki-Miyaura couplings by BINAP modified chiral Pd nanoparticles (Scheme 0-16)[38] and asymmetric α-arylations by chiral NHC modified Pd nanoparticles on Fe_3O_4 that could be recovered using a magnet (Scheme 0-17).[39] Substrate generality was examined and the products were obtained in moderate to good enantioselectivities and the characteristic activities of nanoparticle systems were confirmed in both cases. In the latter reaction system, the choice of chiral ligand was also important for both stability and activity of the Pd nanoparticles as catalysts because a combination of Fe_3O_4/Pd and quinine generated the active species with homogeneous nature in the same reaction[40] while the heterogeneity was confirmed in chiral NHC **L5** system. In fact, the catalyst was reusable for five times without significant loss of the yield and selectivity in chiral NHC **L5** system.

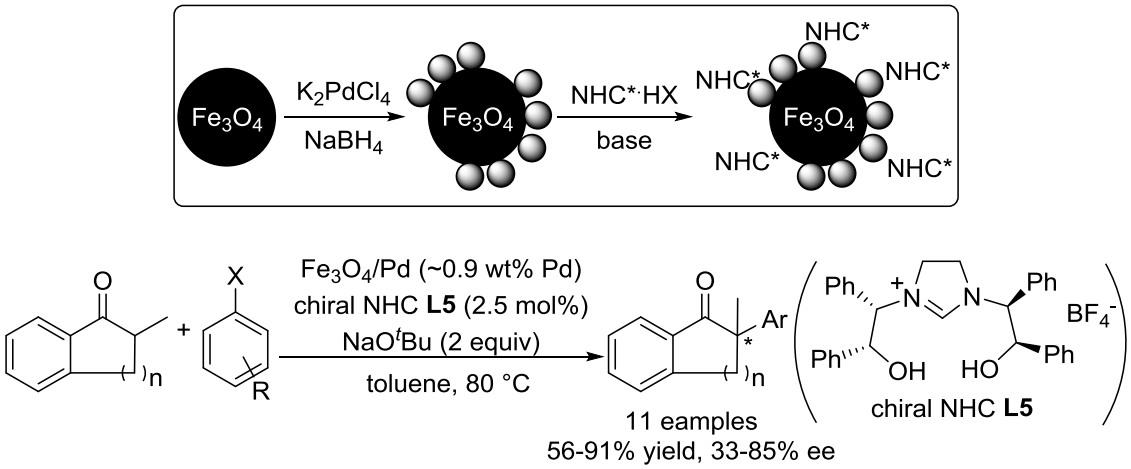
Scheme 0-15. Asymmetric allylic alkylation by heterogeneous chiral Pd nanoparticles



Scheme 0-16. Asymmetric Suzuki-Miyaura couplings by chiral Pd nanoparticles

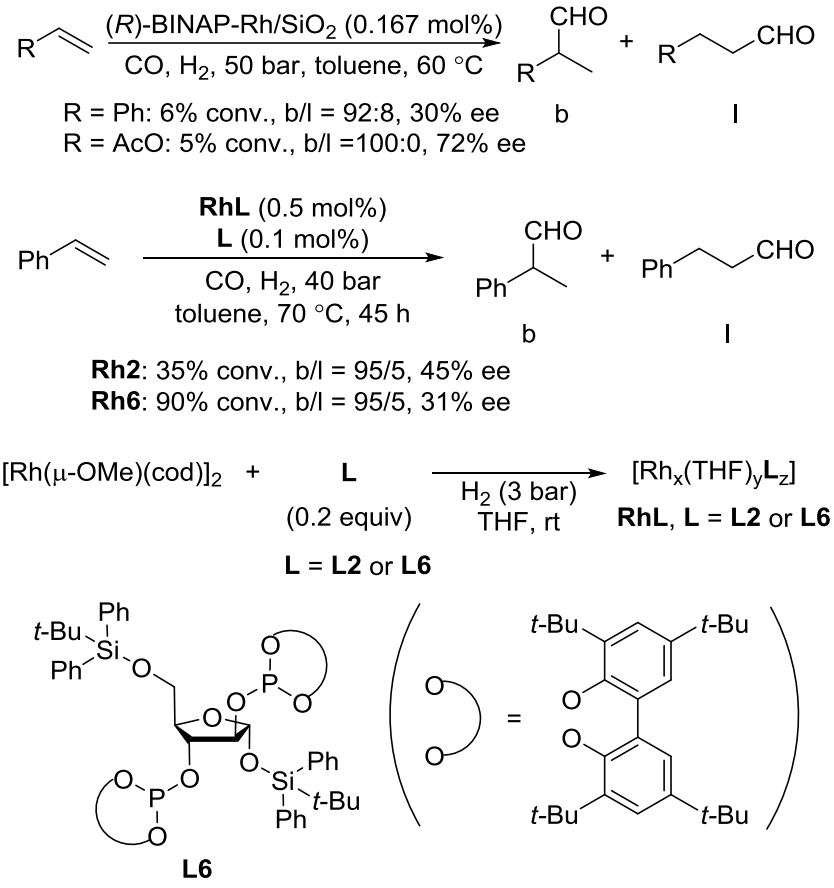


Scheme 0-17. Asymmetric α-arylations by chiral NHC modified Pd nanoparticles

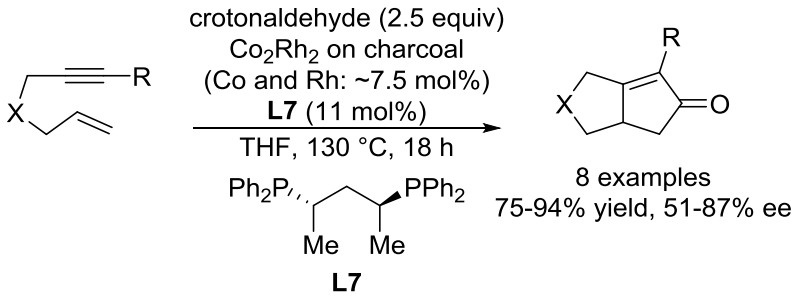


Asymmetric catalysis by chiral metal nanoparticles using other transition metals was not widely investigated. Asymmetric hydroformylation reactions using chiral Rh nanoparticles were reported by several groups; however, conversion or enantioselectivities were still in a low level (Scheme 0-18).[41] Park, Chung and co-workers reported charcoal-immobilized Co/Rh heterobimetallic nanoparticles catalyzed asymmetric Pauson–Khand type reactions with a chiral modifier **L7** (Scheme 0-19).[42] In this report, substrate scope was demonstrated and the products were obtained in moderate to good enantioselectivities. The catalyst could be reused five times with the addition of a new portion of the chiral modifier without significant loss of yield and enantioselectivity.

Scheme 0-18. Asymmetric hydroformylation reactions by chiral Rh nanoparticles



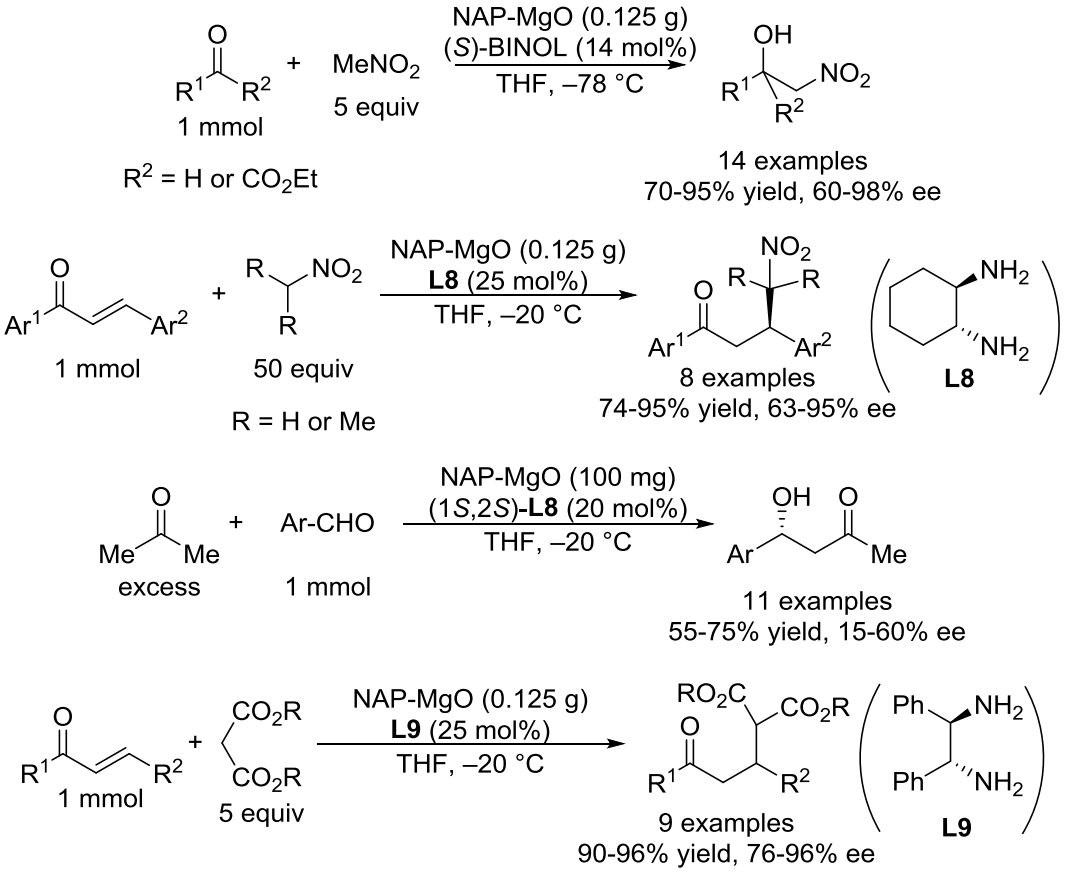
Scheme 0-19. Asymmetric Pauson-Khand reactions by chiral Rh nanoparticles



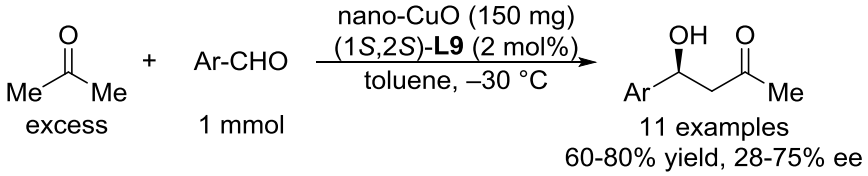
Choudary, Kantam and co-workers discovered that nanocrystalline magnesium oxide (NAP-MgO), which possesses a large surface area (590 m^2/g) and a three-dimensional polyhedral structure could be applied to various asymmetric C-C bond forming reactions, such as Henry reactions, Michael reactions with nitro compounds or malonates and aldol reactions in the presence of a suitable chiral modifier (Scheme 0-20).[43] Similar nanocrystalline copper oxide (nano-CuO) was also employed to asymmetric aldol reactions (Scheme 0-21).[44] Wide reaction scopes were demonstrated

in these nanocrystalline metal oxide systems and the reusability of the catalyst was confirmed; however, these systems required relatively high loading of chiral modifier and/or metal.

Scheme 0-20. Asymmetric reactions by NAP-MgO with chiral modifiers



Scheme 0-21. Asymmetric aldol reactions by nano-CuO with chiral modifiers



Since the field of chiral nanoparticle catalysis is a growing field, the structure of truly active species was unclear in most cases. In this context, it is sometimes difficult to define chiral nanoparticle catalysis. For example, in asymmetric hydrogenations of carbonyl compounds catalyzed by Raney Ni modified with small chiral molecules, such as amino acids or tartaric acids, it is difficult to identify whether the active species are bulk metals or small particles.[45]

As introduced here, chiral nanoparticle catalytic systems have a potential to construct

truly efficient and practical catalyst systems from the following aspects. First, metal nanoparticles can be immobilized on several supports to form heterogeneous catalyst systems and the addition of chiral modifiers can create chiral environments on nanoparticle catalysts. Second, high reusability demonstrated the robustness of chiral nanoparticle systems. Third, the enantioselectivities in chiral nanoparticle systems were comparable to those in the corresponding homogeneous metal complex systems and chiral nanoparticle systems sometimes showed superior activities and/or selectivities compared with the corresponding homogeneous metal complex systems. In light of these points, chiral nanoparticle catalysts are not just "immobilized homogeneous catalysts" and they should be considered as distinct catalysts. However, as described here, the examples of chiral nanoparticle catalysis for asymmetric C–C bond forming reactions that achieved an unprecedented level of enantioselectivity with wide substrate scope were very limited. Therefore, the development of robust chiral nanoparticle systems as heterogeneous catalysts that show high activity and selectivity is still challenging probably because a lack of mechanistic insights, in particular information about active species, makes it difficult to configure new chiral nanoparticle catalyst systems and choose a suitable chiral modifier that does not lead to the decomposition of a nanoparticle catalyst to a corresponding homogeneous metal complex catalyst.

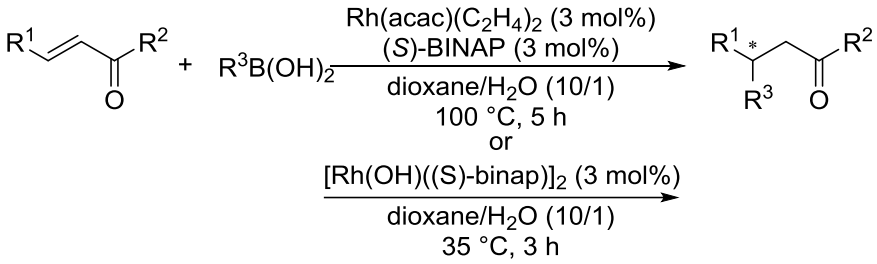
In my Ph.D studies, I focused on the development of heterogeneous chiral nanoparticle systems as robust and active catalysts for asymmetric C–C bond forming reactions. In chapter 1, I will report the discovery of chiral diene modified chiral Rh nanoparticle catalytic systems for asymmetric 1,4-addition of arylboronic acids to enones. In chapter 2, I will report a further improvement of chiral Rh nanoparticle systems by introduction of bifunctional chiral modifier and mechanistic investigations of these systems. In chapter 3, I will report biomass supported Rh nanoparticle catalyst systems as sustainable catalyst systems.

Chapter 1: Discovery of chiral diene modified Rh nanoparticle catalysis

Section 1: Background

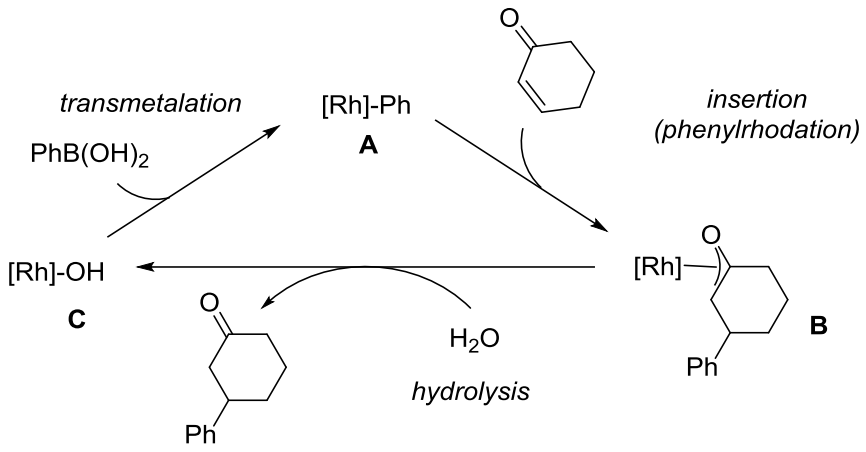
Rh complex catalyzed asymmetric 1,4-addition of arylboronic acids to electron deficient olefins is one of the most useful asymmetric C-C bond formation reactions.[46] The first non-asymmetric version of such 1,4-addition reactions was reported by Miyaura and co-workers in 1997 using phosphine Rh complex.[47] Miyaura, Hayashi and co-workers then reported first asymmetric 1,4-addition of arylboronic acids to enones in 1998 using chiral Rh complex from BINAP and $Rh(acac)(C_2H_4)_2$ (Scheme 1-1-1).[48] High enantioselectivity was achieved and several advantages were realized: 1) use of stable organoboron reagents, 2) neutral conditions in aqueous media, 3) no uncatalyzed pathway to afford racemic products and/or corresponding 1,2-adducts.

Scheme 1-1-1. First report of asymmetric 1,4-addition of boronic acids to unsaturated ketones

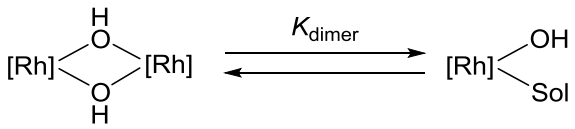


The detailed reaction mechanism of this reaction was studied by Hayashi and co-workers.[49] They observed phenylrhodium species (**A**), oxa-π-allylrhodium (**B**) and hydroxorhodium complexes (**C**) by NMR analysis and proposed the mechanism as follows: 1) transmetallation with arylboronic acid gives intermediate **A**, 2) phenylrhodation to enone occurs to give intermediate **B**, 3) hydrolysis affords the desired product and the Rh complex **C** was regenerated (Scheme 1-1-2). During this study, they discovered $[Rh(OH)(binap)]_2$ as a more active catalyst and performed the reaction at milder conditions (Scheme 1-1-1). Further detailed kinetic studies and nonlinear effect analysis by the same group revealed that the reaction mechanism involves equilibrium between the catalytically active monomeric species and the inactive dimeric species as the resting state (Scheme 1-1-3).[27n,50] They also concluded that transmetallation step is rate-determining step in the reaction with cyclic enone under their reaction conditions. To accelerate transmetallation, base additive was sometimes employed.[51]

Scheme 1-1-2. Proposed catalytic cycle



Scheme 1-1-3. Equilibrium between dimer and monomer species



The important factor of this reaction is a chiral ligand because chiral ligands provide not only chiral environments but also strong rate acceleration. Especially, several ligands with strong π-accepting ability increase electrophilicity of Rh and accelerate transmetallation step.[52] Thus, to enhance the catalytic activity, a wide variety of chiral ligands were explored[46f] such as diphosphine ligands and disulfoxide ligands and the breakthroughs may be development of chiral diene ligands.[53]

Use of olefin as a ligand for transition metal complexes has a very long history and Zeise's salt ($K[Pt(C_2H_4)Cl_3]\cdot H_2O$) is the first example of olefin metal complex reported in 1827.[54] Since this discovery, various olefin metal complexes were synthesized and theoretical and experimental approaches were investigated to elucidate the nature of olefin ligands.[55] According to Dewar-Chatt-Duncanson model,[56] there are two types of interactions, σ donation and π back-donation, between metal and olefin and these interactions are synergistic (Scheme 1-1-4). Several theoretical calculation methods were performed to estimate the interaction between metal and ligand. Charge decomposition analysis (CDA) for HAu-L complexes provided information about strength of donation and back-donation ability (Table 1-1-1).[57] According to this model, olefins have enough strong electron donating abilities and similar accepting abilities with those of N-heterocyclic carbenes, while phosphines possess stronger donation ability and amines possess weak acceptors. Bond dissociation energies (D_e) between Pt and several olefins or phosphanes were calculated by extended transition state (ETS) method (Table 1-1-2).[58] Interestingly, substitution of electron withdrawing group increases D_e of olefin (entry 2) and substitution of electron donating group significantly

weaken the bond (entries 4 and 5). On the other hand, electron donating groups can strengthen the bond between Pt and phosphane ligands (entries 9 and 10).

Scheme 1-1-4. Dewar-Chatt-Duncanson model

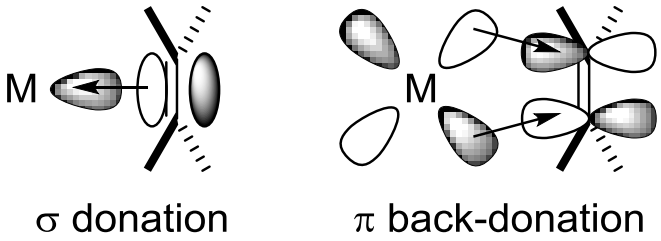
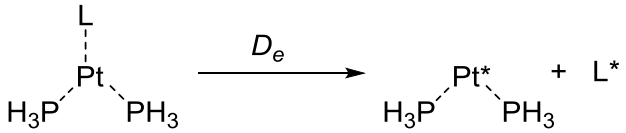
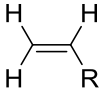


Table 1-1-1. CDA analyses for HAu-L complexes

entry	ligand	*d* (electron donation)	*b* (back donation)	*d*/*b*
1	C_2H_4	0.36	0.13	2.9
2	C_2H_2	0.16	0.12	1.3
3	CO	0.27	0.22	1.2
4	PMe_3	0.53	0.16	3.3
5	imidazol-2-ylidene	0.36	0.12	3.0
6	NMe_3	0.20	0.01	32.7

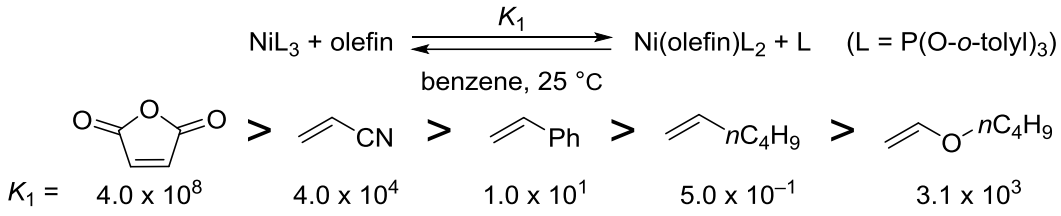
Table 1-1-2. ETS analyses for Pt complexes



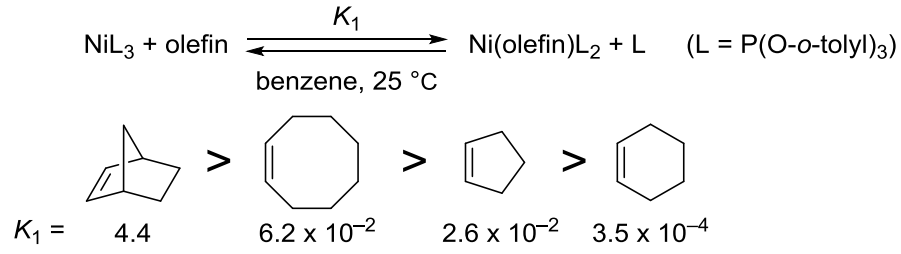
entry	ligand (L)		D_e (kcal/mol)
1		R = H	15.4
2		R = CN	17.6
3		R = F	11.9
4		R = NH_2	6.6
5		R = OH	9.9
6		R = H	9.7
7		R = CN	11.4
8		R = F	19.6
9		R = NH_2	14.2
10		R = OH	16.3

Effect of electron withdrawing groups for relative stability of olefin complexes was also studied experimentally.[59] The equilibrium constant of the reaction with Ni complex and olefin was determined spectrophotometrically and these measurements revealed that electron poor olefins gave more stable complexes (Scheme 1-1-5). These studies clearly illustrated the importance of back donation ability for the stability of olefin-metal complexes. The same experiments for cyclic olefins showed that olefins with high strain formed strong bonding due to relief of strain after coordination (Scheme 1-1-6) and a chelation with diene ligand assisted olefin coordination (Scheme 1-1-7). In addition to such strong interaction between olefins and metals, rigid and pre-organized framework for dienes may stabilize the corresponding metal complexes.

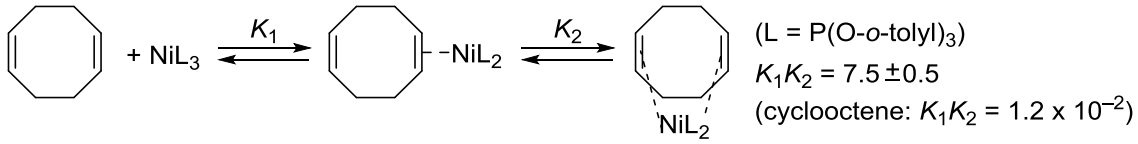
Scheme 1-1-5. Equilibrium constants for olefins and Ni complexes (1)



Scheme 1-1-6. Equilibrium constants for olefins and Ni complexes (2)



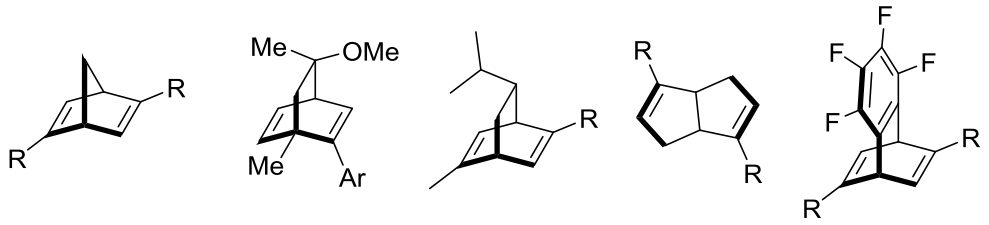
Scheme 1-1-7. Equilibrium constant for diene and Ni complex



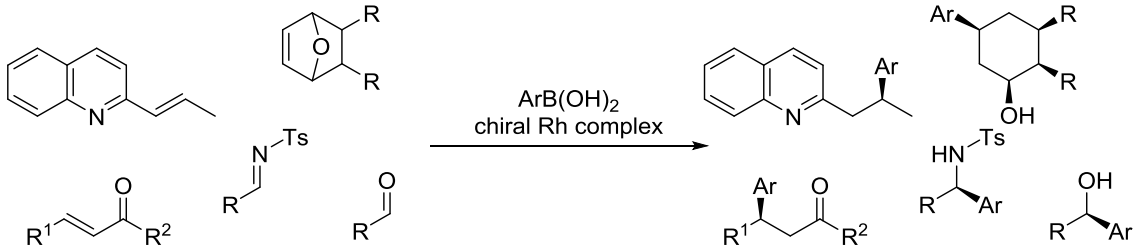
In 2003, Hayashi and co-workers reported the first development of chiral diene ligands with bicyclo[2,2,1]heptadiene frameworks for Rh catalyzed asymmetric reactions.[60] Concurrently, Carreira and co-workers reported another chiral diene ligand with bicyclo[2,2,2]octadiene framework and development of chiral Ir complex with this ligand for asymmetric catalysis.[61] Because of high activity of chiral diene-Rh complexes, intensive researches of chiral dienes were promoted and several new structures of chiral dienes and new ligands with hybrid structure including olefin were developed (Scheme 1-1-8).[62] Thanks to these active chiral Rh complex catalysts, Rh catalyzed asymmetric

arylation of various substrates including not only α,β-unsaturated carbonyl compound but also aldehydes, imines, strained alkenes and alkenyl arenes were achieved with excellent enantioselectivity (Scheme 1-1-9)[46f] and applications of these reactions to tandem reactions,[63] total synthesis of natural products and drug synthesis[64] were investigated. Not only academic research, but also a large scale (> 20 kg) process was demonstrated.[65] For example, Parker and co-workers successfully obtained the desired product as an intermediate of the compounds with general structure which were required as part of a drug development program in AstraZeneca (Scheme 1-1-10).[65b] However, residual Rh in the product was unacceptably high level (~200 ppm) in their process considering a permitted daily exposure (PDE) of Rh for oral exposure is 100 μg/day.[66] To remove the residual Rh, additional procedures involving the oxidation of Rh by Oxone and subsequent treatment with scavenger, Smopex-234 were required (Scheme 1-1-11). Therefore, in spite of broad range of researches in Rh catalyzed asymmetric arylation, development of active, reusable and robust heterogeneous catalysts without metal leaching are demanded because toxic Rh contamination in products should be avoided and Rh is one of the most expensive precious metals.

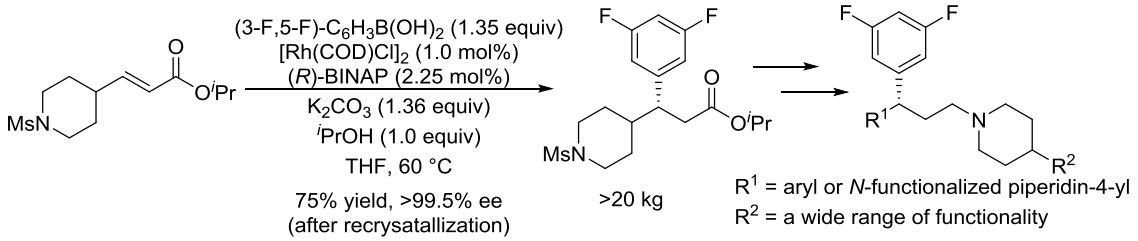
Scheme 1-1-8. Representative frameworks of chiral diene ligands



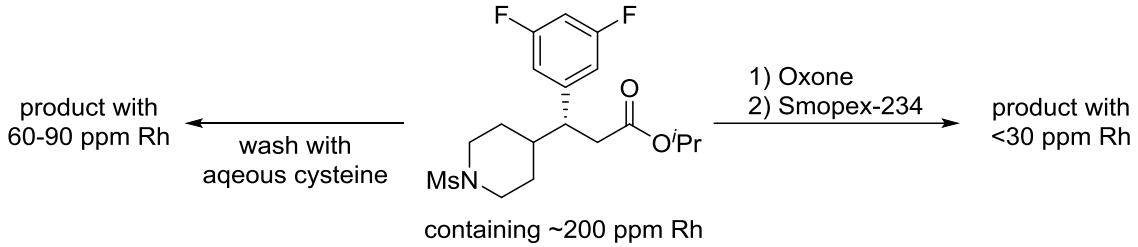
Scheme 1-1-9. Rh catalyzed asymmetric arylation of various substrates



Scheme 1-1-10. Asymmetric 1,4-addition reaction in large scale process

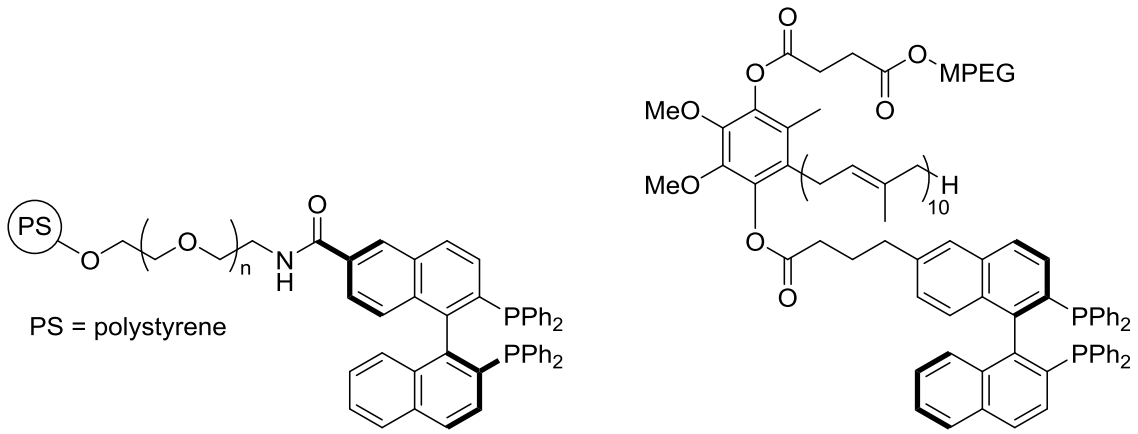


Scheme 1-1-11. Removal of Rh contamination into the product



There are roughly two reported strategies to construct heterogeneous Rh catalysts: 1) immobilization of ligands on supports, 2) immobilization of cationic Rh on supports. The former strategy has already been investigated for several C−C bond-forming reactions by using immobilized phosphine ligands[67] and supported BINAP ligands were employed for asymmetric 1,4-addition to enones with an addition of Rh salt (Scheme 1-1-12).[67b,67f] However, these systems require additional complicated preparation steps of monomeric ligands and individual fabrication to polymers and robustness of these catalysts basically depends on the stability of immobilized ligands. In facts, supported BINAP ligands could not be exposed to air to maintain high activity because of instability to oxidative conditions. Moreover, relatively high catalyst loading (3 mol%) was required.

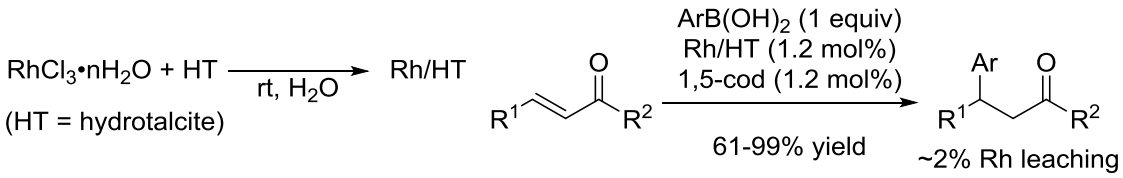
Scheme 1-1-12. Polymer supported BINAP ligand for Rh catalyzed asymmetric 1,4-addition



In contrast, the latter strategy no further modification of an original structure of chiral ligand was required and the screening of ligand was easily conducted by external addition of ligands to immobilized metal catalysts. Several group reported that Rh salt could be deposited on inorganic supports such as hydrotalcite, fluoroapatite and mesoporous materials by simple mixing of a metal solution and a support and the obtained deposited catalysts were used for non-asymmetric 1,4-addition of arylboronic

acids enones.[68] However, metal leaching is more difficult to prevent with this strategy because strong coordination of the ligands to cationic Rh may dissociate the metal from the support (Scheme 1-1-13).[68a,68g] To the best of my knowledge, there has been no report of an asymmetric version of the 1,4-addition of arylboronic acids to enones in heterogeneous systems using the latter strategy.

Scheme 1-1-13. Representative example of immobilized cationic Rh catalyst system



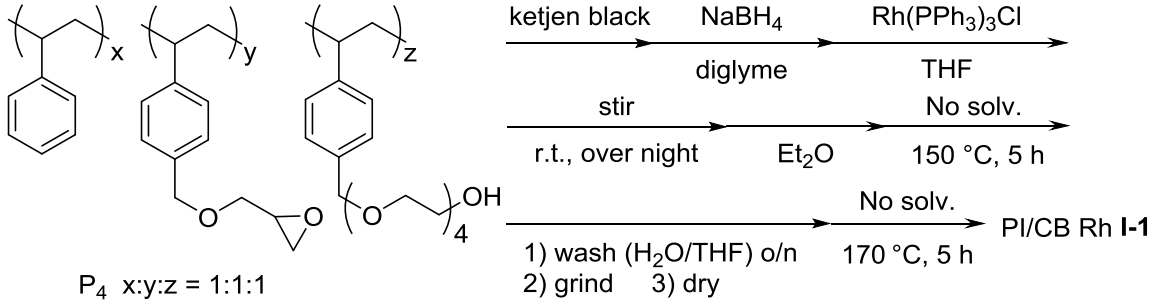
Obviously, another strategy to prepare efficient and robust heterogeneous Rh catalyst system was required and use of chiral nanoparticle catalysts might be a good candidate. Therefore, I chose this reaction as a target reaction and began to investigate chiral Rh NP catalysts.

Section 2: Asymmetric 1,4-addition of arylboronic acids to enones catalyzed by Rh chiral nanoparticle catalysts

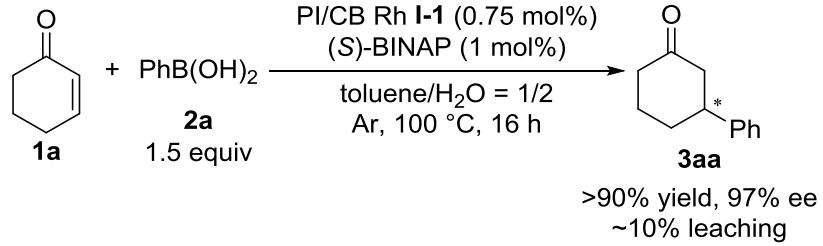
Development of the catalyst system using Rh nanoparticle

In my master course study,[69] I investigated PI/CB Rh as Rh nanoparticle catalytic system and found the effect of chiral modifiers and bimetallic nanoparticles on metal leaching and catalytic activity in the asymmetric 1,4-addition reactions. Initially, PI/CB Rh **1** was prepared from $Rh(PPh_3)_3Cl$ following the preparation method of PI/CB Au (Scheme 1-2-1).[15] Rh nanoparticles could be immobilized on nano composite of polymer and carbon black and this prepared heterogeneous catalysts could catalyze asymmetric 1,4-addition of phenylboronic acid to cyclic enone **1a** to afford the product **3aa** with externally added (*S*)-BINAP ligand in high yield and high enantioselectivity; however, the significant amount of Rh was leached out (Scheme 1-2-2).

Scheme 1-2-1. Preparation of PI/CB Rh **I-1**



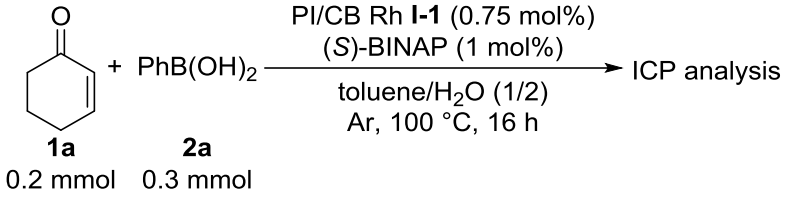
Scheme 1-2-2. Asymmetric 1,4-addition reaction with PI/CB Rh **I-1** and (*S*)-BINAP



To elucidate which components in the reaction mixture caused the leaching, control experiments using several reaction mixtures were performed (Table 1-2-1). As the leaching was not observed in the presence of only substrate or only ligand (entries 1-3), phosphine ligands themselves do not cause the leaching. On the other hand, the leaching was observed in the presence of both substrate and ligand (entries 4-6). It indicated that the leaching might occur during formation of catalytic intermediates, which are

coordinated by both substrates and ligands, such as intermediate **A** and **B** shown in Scheme 1-1-2 because there was a lack of coordination sites in polymer backbone to interact with Rh center strongly due to steric hindrance of coordinations to Rh by both substrates and ligands (Scheme 1-2-3, b). On the other hand, the leaching did not occur in the presence of only ligands or only substrates because polymer backbone can interact with Rh center (Scheme 1-2-3, a). It was hypothesized that polymer backbone may maintain interactions with Rh intermediates with smaller ligands or ligands which have weak coordination ability to Rh (Scheme 1-2-3, c). To examine the relationships between ligands and the leaching, I chose chiral diene ligands that were reported by Hayashi's group (Scheme 1-2-4).[70]

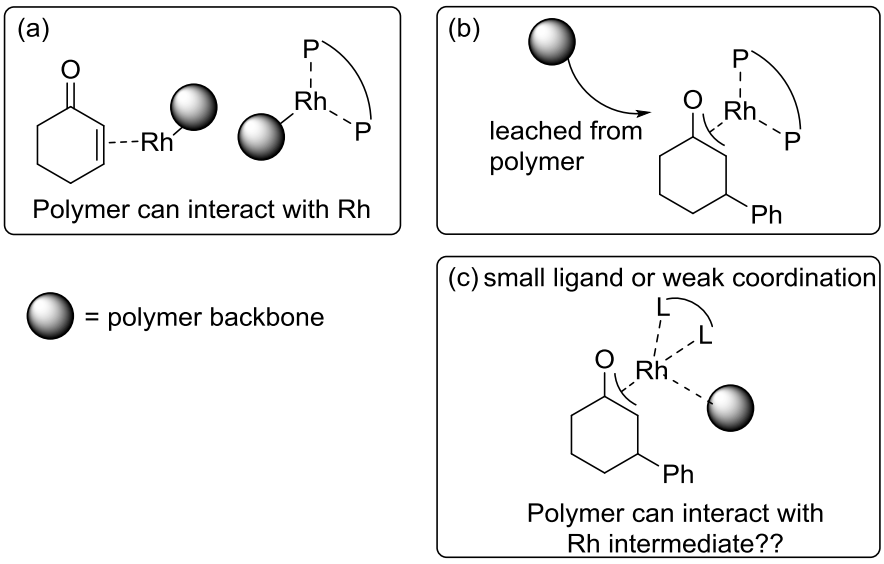
Table 1-2-1. Elucidation of the components that caused the leaching



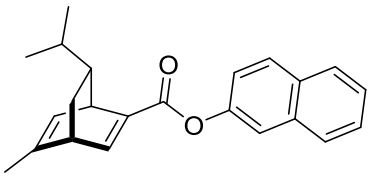
entry	**1a**	**2a**	BINAP	leaching (%)[a]
1	+	−	−	0
2	−	+	−	0
3	−	−	+	0
4	+	−	+	4
5	−	+	+	9
6	+	+	+	11

[a] Determined by ICP analysis.

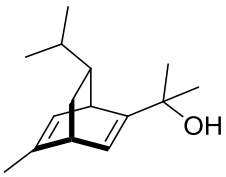
Scheme 1-2-3. Possible interactions between polymer and Rh intermediate



Scheme 1-2-4. Chiral diene **4a** and **4b**



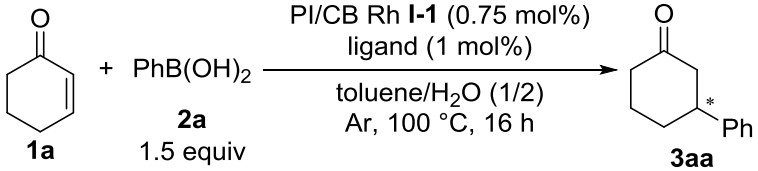
diene **4a**



diene **4b**

Asymmetric 1,4-addition reactions were conducted using these diene ligands (Table 1-2-2). Although both the yield and the ee were decreased, the leaching was dramatically decreased when diene **4a** was used (entries 1 vs. 2). On the other hand, when diene **4b** was used, excellent ee was obtained and increase of the amount of the catalyst and the ligand afforded excellent yield; however, around 5% of leaching was observed (entries 3 and 4).

Table 1-2-2. Ligand screening



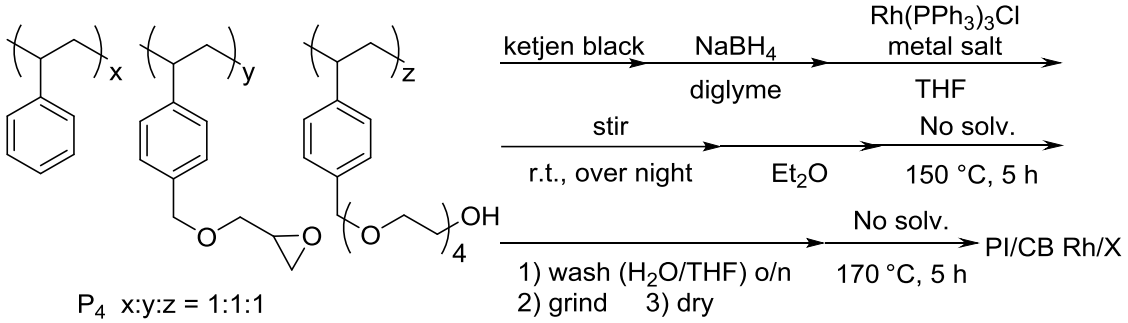
1a 3aa

entry	ligand	conv. (%)[a]	yield (%)[a]	Rh leaching (%)[b]	ee (%)[c]
1	(*S*)-BINAP	92	93	~10	97
2	diene **4a**	81	72	1.4	80
3	diene **4b**	86	79	5.7	-
4[d]	diene **4b**	97	99	5.0	98

0.2 mmol scale. [a] Determined by GC analysis. [b] Determined by ICP analysis. [c] Determined by HPLC analysis. [d] 1.5 mol% of Rh catalyst and 2 mol% of ligand were used.

To prevent the leaching completely, several bimetallic catalysts, which were prepared by the method shown in Table 1-2-3, were examined (Table 1-2-4). In this procedure, after second metal salt and $Rh(PPh_3)_3Cl$ were dissolved in THF and mixed, the solution of metals were added to reduce them simultaneously. In the case of PI/CB Rh/Ag, $Rh_2(OAc)_4$ was used instead of $Rh(PPh_3)_3Cl$ in order to prevent formation of AgCl as a precipitation. The leaching during asymmetric reaction was completely suppressed with PI/CB Rh/Co, Rh/Ru and Rh/Ag (entries 2-4) while Rh/Cu could not completely suppress the leaching (entry 5). On the other hand, Rh/Au and Rh/Pt gave the low yield due to generation of phenol and cyclohexanone from 2-cyclohexenone as side reactions (entries 6 and 7).

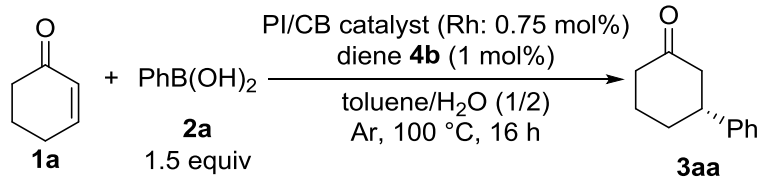
Table 1-2-3. Preparation of bimetallic catalysts



entry	cat.	metal salt
1	PI/CB Rh/Co **II-1**	$CoCl_2$
2	PI/CB Rh/Ru **III-1**	$Ru_2(cymene)_2Cl_2$
3[a]	PI/CB Rh/Ag **IV-1**	$AgSbF_6$
4	PI/CB Rh/Cu **V**	$Cu(PPh_3)_2NO_3$
5	PI/CB Rh/Au **VI-1**	$AuClPPh_3$
6	PI/CB Rh/Pt **VII**	$Na_2PtCl_6 \cdot 6H_2O$

[a] $Rh_2(OAc)_4$ was used instead of $Rh(PPh_3)_3Cl$

Table 1-2-4. Screening of bimetallic catalysts

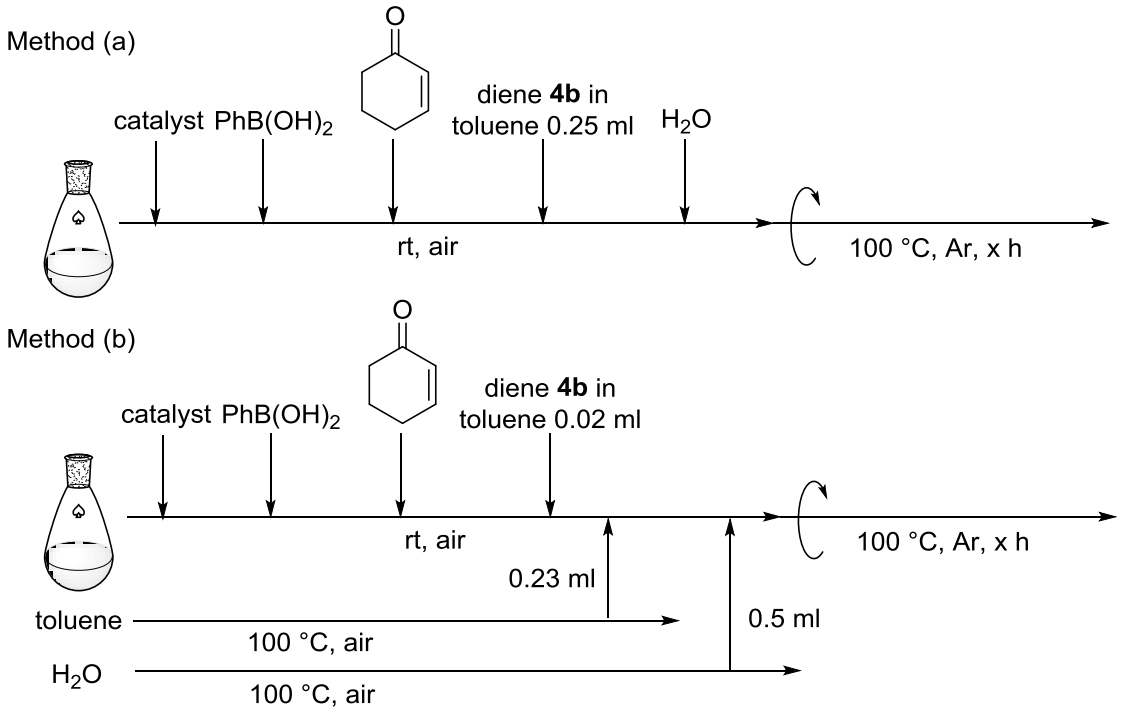


entry	cat.	conv. (%)[a]	yield (%)[a]	Rh leaching (%)[b]	ee (%)[c]
1	PI/CB Rh **I-1**	86	79	5.7	-
2	PI/CB Rh/Co **II-1**	96	quant.	ND	98
3	PI/CB Rh/Ru **III-1**	97	94	ND	98
4	PI/CB Rh/Ag **IV-1**	98	90	ND	98
5	PI/CB Rh/Cu **V**	89	83	1.7	-
6	PI/CB Rh/Au **VI-1**	>99	26	0.85	-
7	PI/CB Rh/Pt **VII**	>99	46	ND	-

0.2 mmol scale. ND = under detection limit (<0.2~0.3%). "-" = Not measured. [a] Determined by GC analysis. [b] Determined by ICP analysis. [c] Determined by HPLC analysis.

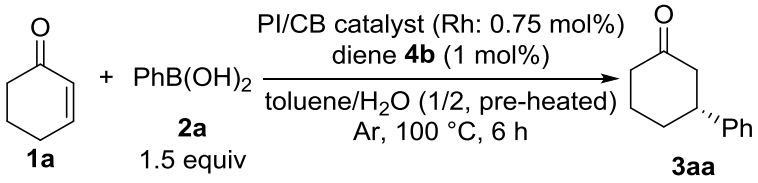
The above mentioned reactions were always conducted by the method (a), which started heating at 100 ˚C after all materials were combined (Scheme 1-2-5). However, the time until temperature rose from room temperature to 100 ˚C was not ignorable in this method (a). Therefore, the method (b) involved the addition of pre-heated solvents at 100 ˚C to the mixture was considered (Scheme 1-2-5). The reactions almost finished within 2 hours by the method (b) in the case of PI/CB Rh/Co **II-1** (Table 1-2-5, entry 1); however, the small amount of leaching of Rh was observed. At this stage, it could not be judged whether it was the problem of reproducibility or that of method (b). Receiving these results, Rh/Ru catalyst and Rh/Ag catalyst were examined again employing the method (b) and the product was obtained in ca. 90% yield without leaching of Rh in 6 hours in both cases (entries 2 and 4). To confirm reproducibility, PI/CB Rh/Ru **III-1** (lot B) and Rh/Ag **IV-1** (lot B) were prepared again by the same method and tested under the same conditions; however, around 1% of leaching was obtained in both cases (entries 3 and 5).

Scheme 1-2-5. Reaction procedure using "pre-heated" solvents



It was assumed that the metal leaching from newly prepared catalysts might occur from remaining cationic Rh salts.[71] To complete the reduction process, the catalysts (lot B) were treated with $NaBH_4$ by the method shown in Scheme 1-2-6. After this treatment, these catalysts showed high activity and did not cause leaching in both Rh/Ru and Rh/Ag (Table 1-2-6, entries 2 and 4). On the other hands, the leaching was still observed with PI/CB Rh/Co **II-1** even after this treatment (entry 6).

Table 1-2-5. Reproducibility tests by method (b)



entry	cat.	Lot	time (h)	conv. (%)[a]	yield (%)[a]	Rh leaching (%)[b]	ee (%)[c]
1[d]	PI/CB Rh/Co **II-1**	-	2	96	98	2.7	98
2	PI/CB Rh/Ru **III-1**	A	6	93	91	ND	97
3	PI/CB Rh/Ru **III-1**	B	6	94	88	1.5	-
4	PI/CB Rh/Ag **IV-1**	A	6	96	93	ND	98
5	PI/CB Rh/Ag **IV-1**	B	6	57	54	1.5	-

0.2 mmol scale. ND = under detection limit (<0.2~0.3%). "-" = Not measured.

[a] Determined by GC analysis. [b] Determined by ICP analysis and no leaching of Ru and Ag were observed (<0.17% as a detection limit of Ru, <2.7% as a detection limit of Ag). [c] Determined by HPLC analysis. [d] The reaction time was 2 h.

Scheme 1-2-6. Reduction treatment of PI/CB catalysts

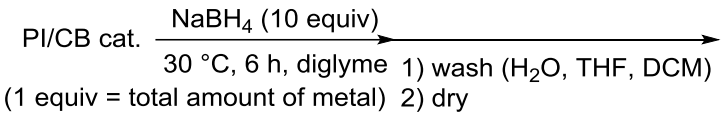
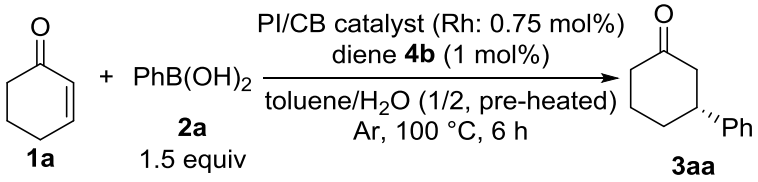


Table 1-2-6. 1,4-Addition reaction with various activated catalysts in method (b)



entry	cat.	Lot	conv. (%)[a]	yield (%)[a]	Rh leaching (%)[b]	activation of the catalyst
1	Rh/Ru **III-1**	B	94	88	1.5	-
2[c]	Rh/Ru **III-1**	B	91	87	ND	Reduction with $NaBH_4$
3	Rh/Ag **IV-1**	B	57	54	1.5	-
4[c]	Rh/Ag **IV-1**	B	95	89	ND	Reduction with $NaBH_4$
5[d]	Rh/Co **II-1**		96	98	2.7	-
6[c,d]	Rh/Co **II-1**		97	93	1.2	Reduction with $NaBH_4$

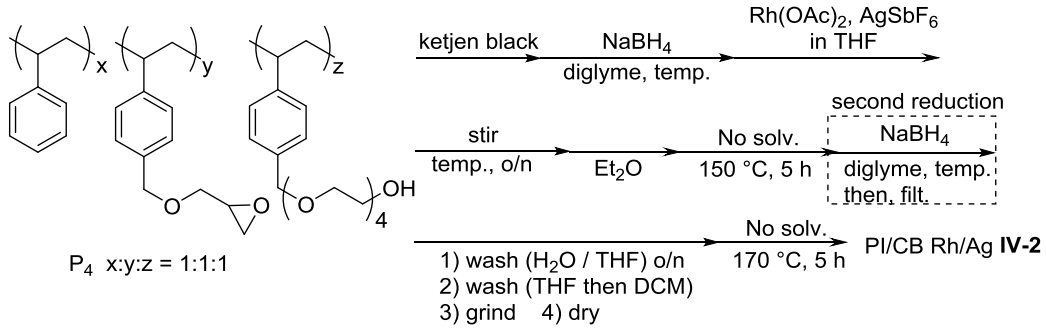
0.2 mmol scale. ND = under detection limit (<0.2~0.3%). "-" = Not measured.

[a] Determined by GC analysis. [b] Determined by ICP analysis and no leaching of Ru and Ag

were observed (<0.17% as a detection limit of Ru, <2.7% as a detection limit of Ag). [c] The catalyst was reduced again by the method shown in Scheme 1-2-6. [d] The reaction time was 2 h.

As it was considered that the key to suppress the leaching was completing the reduction, the preparation method of PI/CB Rh/Ag was revised by introduction of "second reduction" step to obtain good reproducibility (Table 1-2-7). It was realized that the temperature during the reduction step of the catalyst B was lower than that for the preparation of the previous catalyst A and in the revised procedure the reduction step was conducted at 30 ˚C (entries 3-5). Three batches of PI/CB Rh/Ag **IV-2** were prepared by the same method and the activities of these catalysts were tested (Table 1-2-8). All catalysts could suppress the leaching completely (entries 3-5). From these results, the procedure that includes the second reduction step was selected for the further investigation. In this way, the reliable method to prepare PI/CB Rh/Ag **IV-2** was established during my master course study.

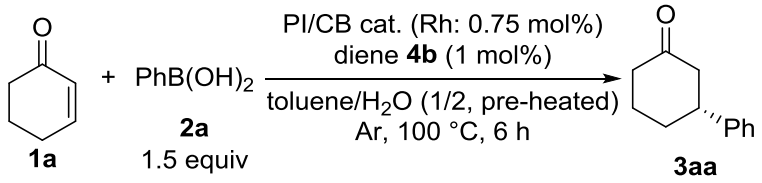
Table 1-2-7. Preparation of PI/CB Rh/Ag with "second reduction"



entry	catalyst	Lot	temp. (˚C)	second reduction	actual loading(mmol/g)[a]
1	Rh/Ag **IV-1**	A	rt (>25)	no	Rh: 0.215, Ag: 0.181
2	Rh/Ag **IV-1**	B	rt (<15)	no	Rh: 0.175, Ag: 0.180
3	Rh/Ag **IV-2**	A	30	yes	Rh: 0.145, Ag: 0.166
4	Rh/Ag **IV-2**	B	30	yes	Rh: 0.166, Ag: 0.170
5	Rh/Ag **IV-2**	C	30	yes	Rh: 0.164, Ag: 0.169

[a] Determined by ICP analysis. The target loadings were 0.2 mmol/g for each metal.

Table 1-2-8. Effect of second reduction for the reproducibility



entry	catalyst	Lot	conv. (%)[a]	yield (%)[a]	Rh leaching (%)[b]
1	Rh/Ag **IV-1**	A	96	93	ND
2	Rh/Ag **IV-1**	B	57	54	1.5
3	Rh/Ag **IV-2**	A	95	quant.	ND
4	Rh/Ag **IV-2**	B	81	89	ND
5	Rh/Ag **IV-2**	C	89	96	ND

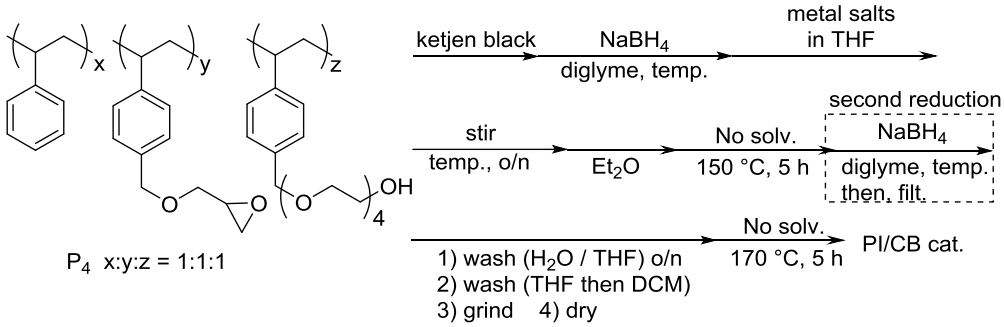
0.2 mmol scale. ND = under detection limit (<0.2~0.3%). "-" = Not measured.

[a] Determined by GC analysis. [b] Determined by ICP analysis and no leaching of Ag was observed (<2.7% as a detection limit of Ag).

Examination of bimetallic catalysts for the reactions with acyclic substrate 1b

As only PI/CB Rh/Ag was prepared from rhodium acetate as a rhodium salt while the other Rh catalysts (includes bimetallic catalysts) were prepared from Wilkinson complex, PI/CB Rh **I-2** and Rh/Co **II-3** were prepared from rhodium acetate by the revised method (Table 1-2-9) and examined for asymmetric 1,4-addtion reaction as control experiments (Table 1-2-10). PI/CB Rh **I-2** and Rh/Co **II-3** which were prepared from rhodium acetate did not cause leaching indicating that no bimetallic effect for the leaching exists (entries 1 vs. 2 and 6). When (*S*)-BINAP was used in the reaction with PI/CB Rh **I-2**, significant amount of the leaching was observed again, indicating that a choice of ligand is important factor to prevent the leaching even in this case. Judging from the fact that (*S*)-BINAP caused significant amount of leaching, phosphine ligands from Wilkinson complexes might remain in the catalyst and might cause leaching due to their strong coordination ability. In the case of PI/CB Rh/Co, regardless of the metal precursor, the leaching was suppressed when the catalysts were prepared by the revised method (entries 4 vs. 5 and 6). The loading of Ag could be increased to the twice amount of Rh without significant loss of activity and leaching (entries 7 vs. 8).

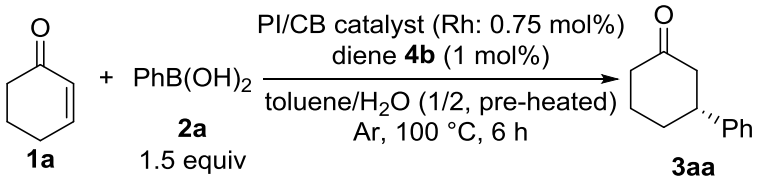
Table 1-2-9. Preparation of various catalysts with the revised method



entry	name	Rh salt	second metal salt	actual loading (mmol/g)[a]
1	PI/CB Rh **I-2**	$Rh_2(OAc)_4$	-	Rh: 0.149
2	PI/CB Rh/Co **II-2**	$Rh(PPh_3)_3Cl$	$CoCl_2$	Rh: 0.171, Co: 0.198
3	PI/CB Rh/Co **II-3**	$Rh_2(OAc)_4$	$CoCl_2$	Rh: 0.081, Co: 0.182
4	PI/CB Rh/Ag **IV-2**	$Rh_2(OAc)_4$	$AgSbF_6$	Rh: 0.145, Ag: 0.166
5[b]	PI/CB Rh/Ag **IV-3**	$Rh_2(OAc)_4$	$AgSbF_6$	Rh: 0.152, Ag: 0.326

[a] Determined by ICP analysis. The target loadings were 0.2 mmol/g for each metal. [b] The target loading of Ag was 0.4 mmol/g.

Table 1-2-10. Activity test of the catalysts which were prepared from rhodium acetate

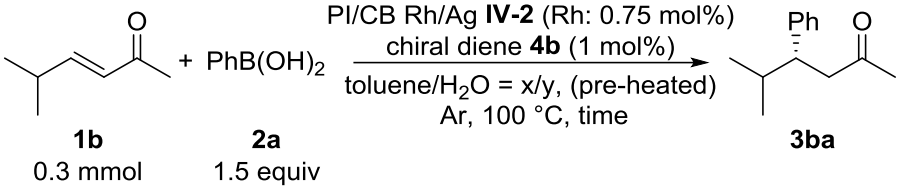


entry	catalyst	conv. (%)[a]	yield (%)[a]	leaching (%)[b]
1[c]	Rh **I-1** (from $RhCl(PPh_3)_3$)	96	94	7.4
2	Rh **I-2** (from $[Rh(OAc)_2]_2$)	94	96	ND
3[c]	Rh **I-2** (from $[Rh(OAc)_2]_2$)	28	16	7.2
4[d]	Rh/Co **II-1** (from $RhCl(PPh_3)_3$)	96	98	2.7
5	Rh/Co **II-2** (from $RhCl(PPh_3)_3$)	98	99	ND
6	Rh/Co **II-3** (from $[Rh(OAc)_2]_2$)	98	quant.	ND
7	Rh/Ag **IV-2**	95	quant.	ND
8	Rh/Ag **IV-3**	93	91	ND

0.2 mmol scale. [a] Determined by GC analysis. [b] Determined by ICP analysis. [c] (*S*)-BINAP was used instead of diene **4b**. [d] 2 h.

The reaction using acyclic substrate **1b**, which was less reactive than cyclic substrate **1a**, was examined (Table 1-2-11). In the presence of PI/CB Rh/Ag **IV-2**, the moderate yield and around 2% of leaching were observed (entry 1). Neither prolonged reaction time, high concentration nor the change of solvent ratio improved the yield (entries 2-4).

Table 1-2-11. Optimization of the reaction conditions with 5-methylhex-3-en-2-one



1b 0.3 mmol | **2a** 1.5 equiv | **3ba**

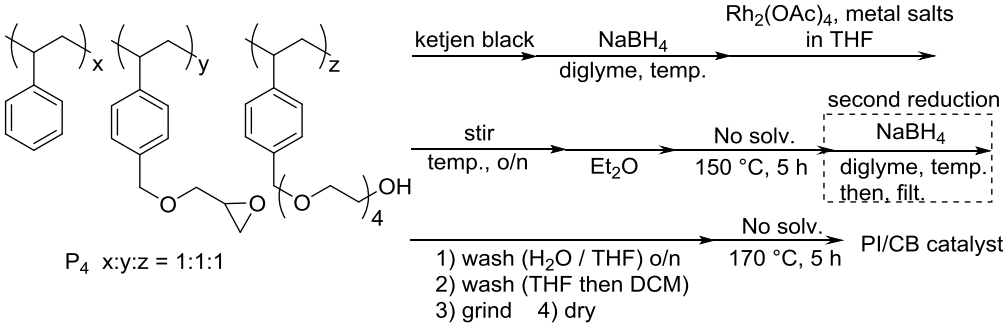
entry	x/y (ml/ml)	time (h)	conv. (%)[a]	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	0.375/0.75	6	67	60	92	2.3
2	0.375/0.75	24	68	64	-	1.4
3	0.25/0.5	6	63	59	-	1.3
4	0.375/0.375	6	38	32	-	ND

ND = under detection limit (<0.2~0.3%). "-" = Not measured.

[a] Determined by GC analysis. [b] Calculated from the amount of isolated product from 70% amount of the reaction mixture. [c] Determined by HPLC. [d] Determined by ICP analysis with 30% amount of the reaction mixture.

To improve the result, various bimetallic or trimetallic catalysts were prepared from rhodium acetate (Table 1-2-12) and tested for the reaction with **1b** (Table 1-2-13). Monometallic catalyst showed poor activity (entry 2) compared with several bimetallic catalysts such as Rh/Ag **IV-2**, Rh/Co **II-2**, **3** and Rh/Ru **III-2** (entries 1, 3, 4 and 5). The metal leaching was observed when the relatively high active catalysts were employed (entries 1 and 5). The catalytic activity of PI/CB Rh/Ru **III-3** that was prepared from rhodium acetate was very low (entry 6) as well as Rh/Pd **VIII** and Rh/Au **VI-2** (entries 7 and 8). As it was known that both Pd nanoparticle and Au nanoparticle could react with arylboronic acid,[72] Pd or Au might promote side reactions with phenylboronic acids, such as decomposition to benzene, and lead the poor yield. PI/CB Rh/Ag **IV-4**, which possessed the different ratio between Rh and Ag, were examined and the silver rich catalyst gave the better results in term of both yield and leaching and PI/CB Rh/Ag **IV-4**, which was composed of 1:3 ratio of Rh and Ag, was determined as the best catalyst for this reaction (entries 9-12). Trimetallic catalyst could not improve the result (entry 13). Moreover, the reaction with commercially available Rh on carbon was carried out as a control and low yield was observed (entry 14).

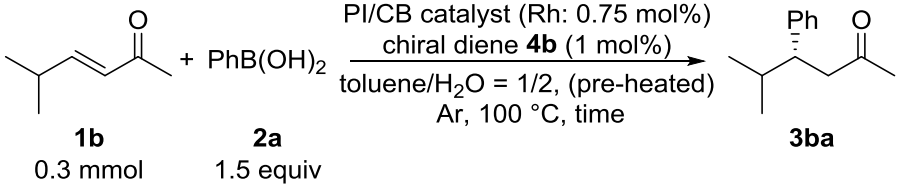
Table 1-2-12. Preparation of various catalysts with the revised method



entry	catalyst	second metal salt	actual loading (mmol/g)[a]
1	Rh/Ru **III-3**	$Ru_2(cymene)_2Cl_2$	Rh: 0.185, Ru: 0.175
2	Rh/Pd **VIII-2**	$Pd(OAc)_2$	Rh: 0.153, Pd: 0.160
3[b]	Rh/Au **VI-2**	$Au(PPh_3)Cl$	Rh: 0.241, Au: 0.222
4[c]	Rh/Ag **IV-4**	$AgSbF_6$	Rh: 0.150, Ag: 0.413
5[d]	Rh/Ag **IV-5**	$AgSbF_6$	Rh: 0.150, Ag: 0.596
6	Rh/Ag/Co **IX**	$AgSbF_6$	Rh: 0.156, Ag: 0.158
		$Co(acac)_2 \cdot 2H_2O$	Co: 0.150

[a] Determined by ICP analysis. The target loadings were 0.2 mmol/g for each metal [b] The target loadings were 0.28 mmol/g for each metal. [c] The target loading of Ag was 0.6 mmol/g. [d] The target loading of Ag was 0.8 mmol/g.

Table 1-2-13. Screening of the catalysts in the reaction with **1b**



entry	catalyst	time (h)	conv. (%)[a]	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	Rh/Ag **IV-2**	6	67	60(57)	92	2.3
2	Rh **I-2**	6	36	18	-	ND
3	Rh/Co **II-2**	6	71	71	92	1.2
4	Rh/Co **II-3**	6	63	42	-	ND
5	Rh/Ru **III-2**	6	58	61	-	3.9
6	Rh/Ru **III-3**	12	21	2	-	ND
7	Rh/Pd **VIII-2**	12	21	trace	-	ND
8	Rh/Au **VI-2**	12	25	3	-	ND
9	Rh/Ag **IV-3**	6	65	60(57)	92	ND
10	Rh/Ag **IV-3**	24	71	61	-	0.5

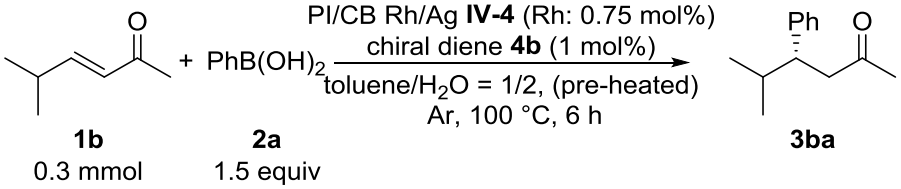
11	Rh/Ag **IV-4**	6	71	77	-	ND
12	Rh/Ag **IV-5**	6	58	63	-	ND
13	Rh/Ag/Co **IX**	6	58	54	-	1.1
14	Rh/C (5 wt%)[e]	12	29	11	-	ND

ND = under detection limit (<0.2~1%). "-" = Not measured.

[a] Determined by GC analysis. [b] Determined by GC analysis and the yield in parenthesis was calculated from the amount of isolated product from 70% amount of the reaction mixture. [c] Determined by HPLC analysis. [d] Determined by ICP analysis with 30% amount of the reaction mixture. [e] Purchased from TCI Co., LTD.

The reaction conditions were further optimized with PI/CB Rh/Ag **IV-4** (Table 1-2-14). While the increase of the amount of the catalyst and the ligand could not improve the yield (entry 2), the increase of the amount of the catalyst, the ligand and phenylboronic acid improved the yield (entry 3). Finally, excellent yield was achieved when the reaction time was prolonged to 12 h under the same conditions of entry 3 (entry 4). Use of ^{t}AmOH instead of toluene was examined with the two types of the ratio of alcohol and water; however, the yields were low (entries 5 and 6).

Table 1-2-14. Optimization of the reaction conditions with 5-methylhex-3-en-2-one



entry	Optimized point	conv. (%)[a]	yield (%)[a]	ee (%)[b]	Rh leaching (%)[c]
1	Standard conditions	71	77	92	ND
2	1.5% of Rh, 2 mol% of **4b**	64	58	-	ND
3	1.5% of Rh, 2 mol% of **4b**, 2 equiv of **2a**	85	89	92	ND
4[d]	1.5% of Rh, 2 mol% of **4b**, 2 equiv of **2a**	95	91	92	ND
5	^{t}AmOH (instead of toluene) : H_2O = 1:2	24	23	-	ND
6	^{t}AmOH (instead of toluene) : H_2O = 2:1	18	18	-	detected

ND = under detection limit (<0.2~1%). "-" = Not measured.

[a] Determined by GC analysis. [b] Determined by HPLC analysis. [c] Determined by ICP analysis with 30% amount of the reaction mixture. [d] The reaction time was 12 h.

To clarify the bimetallic effect on Rh/Ag for the catalytic activity and the leaching, scanning transmission electron microscopy (STEM) analyses and energy-dispersive X-ray spectroscopy (EDS) mappings were conducted. While the formation of small

nanoparticles and good dispersion were observed in the STEM images of PI/CB Rh **I-1**, which was made from Wilkinson complex (Figure 1-2-1), small nanoparticles (ca. 3 nm) were assembled on one area and not dispersed widely over the support in the case of PI/CB Rh **I-2**, which was made from rhodium acetate (Figure 1-2-2). In contrast, although the size of nanoparticles was not uniform, the nanoparticles in PI/CB Rh/Ag **IV-2** were dispersed well over the support (Figure 1-2-3) and EDS mapping confirmed the formation of bimetallic alloy nanoparticles (Figure 1-2-4). EDS line analyses of those alloy nanoparticles (Figure 1-2-5) revealed that the ratio between Rh and Ag in the nanoparticles was random (1:2−2:1). A dope of Ag could change the structure of nanoparticles and the higher activity of Rh/Ag bimetallic catalysts might be explained by the size effect. Increase of the amount of Ag could generate silver rich nanoparticles (Figures 1-2-6~14) and probably relatively larger nanoparticles might be difficult to leach out. When too much amount of Ag was immobilized, aggregation of nanoparticles might easily occur and decreased the surface area of nanoparticles and the catalytic activity.

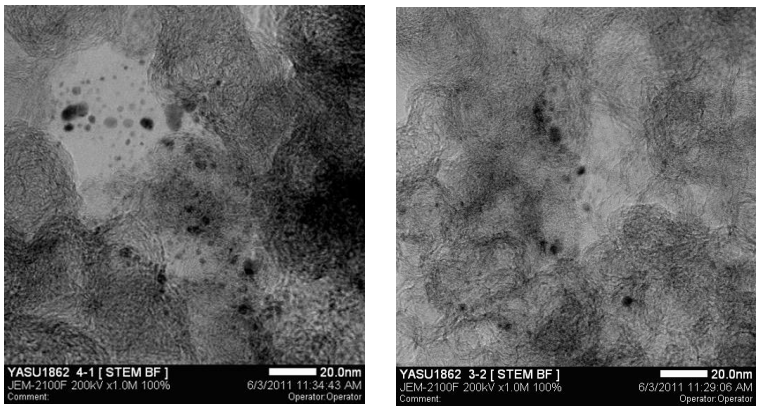


Fig. 1-2-1. TEM images of PI/CB Rh **I-1**

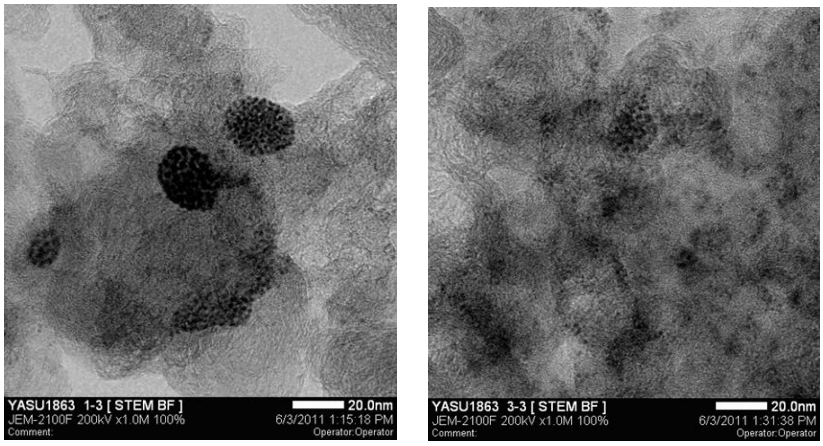


Fig. 1-2-2. TEM images of PI/CB Rh **I-2**

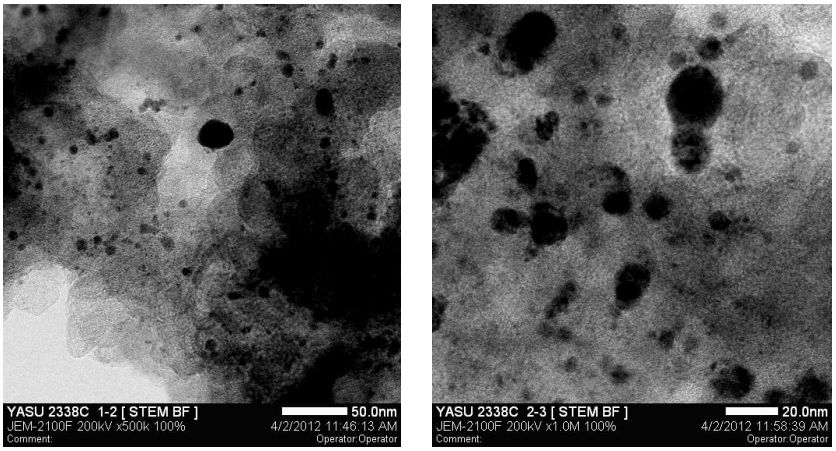


Fig. 1-2-3. STEM images of PI/CB Rh/Ag **IV-2**

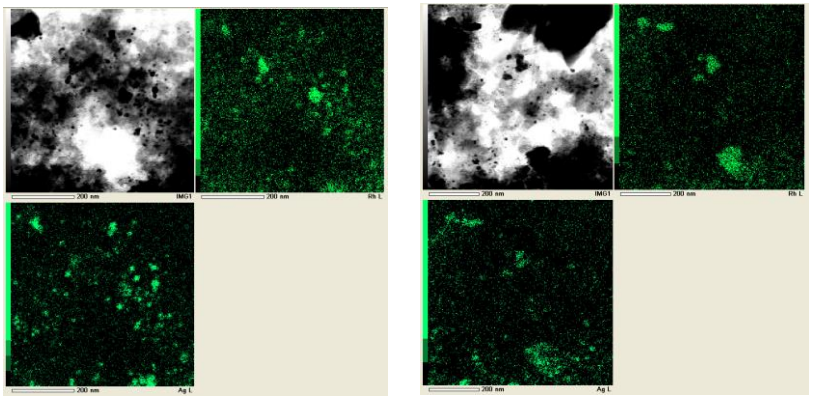


Fig. 1-2-4. EDS analyses of PI/CB Rh/Ag **IV-2**

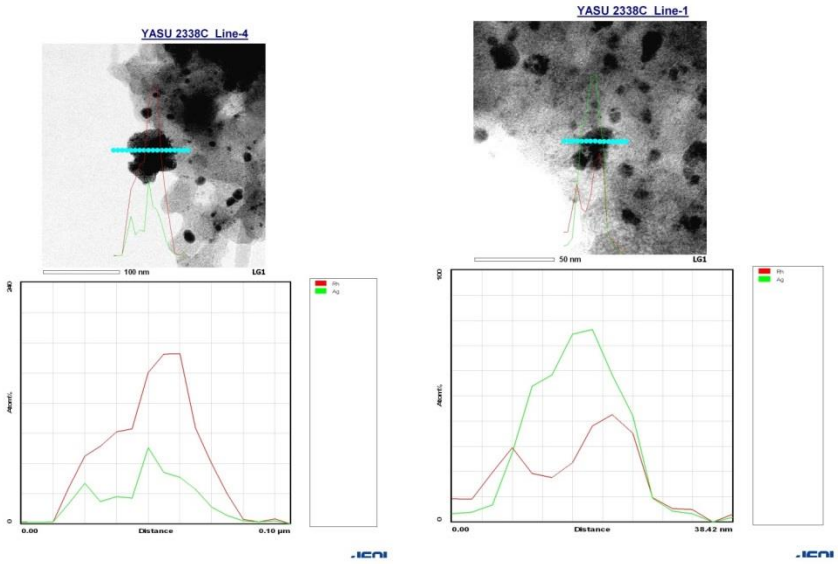


Fig. 1-2-5. Line analyses of PI/CB Rh/Ag **IV-2**

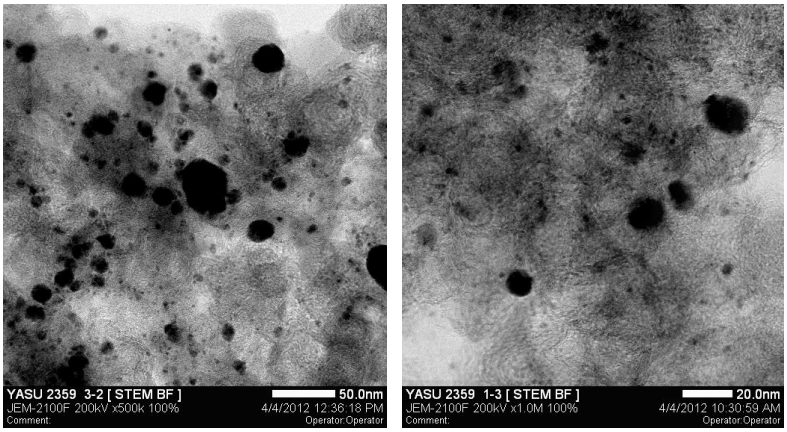


Fig. 1-2-6. STEM images of PI/CB Rh/Ag **IV-3**

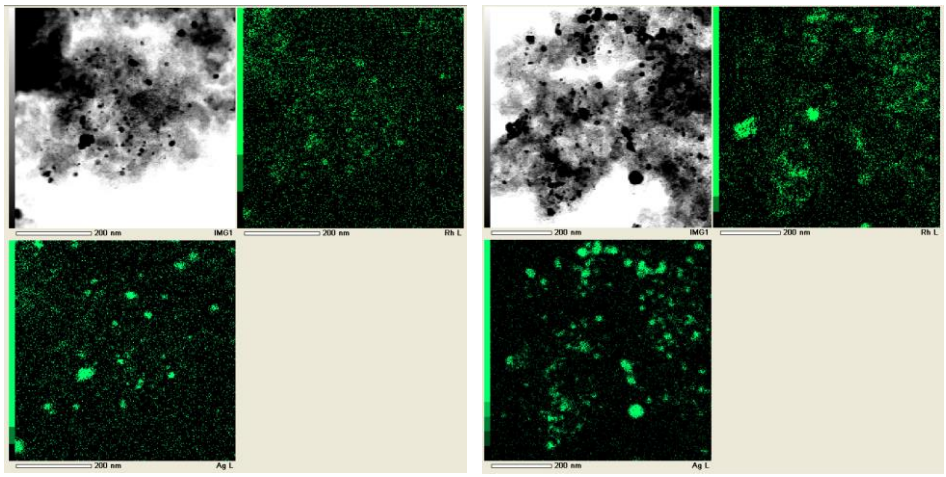


Fig. 1-2-7. EDS analyses of PI/CB Rh/Ag **IV-3**

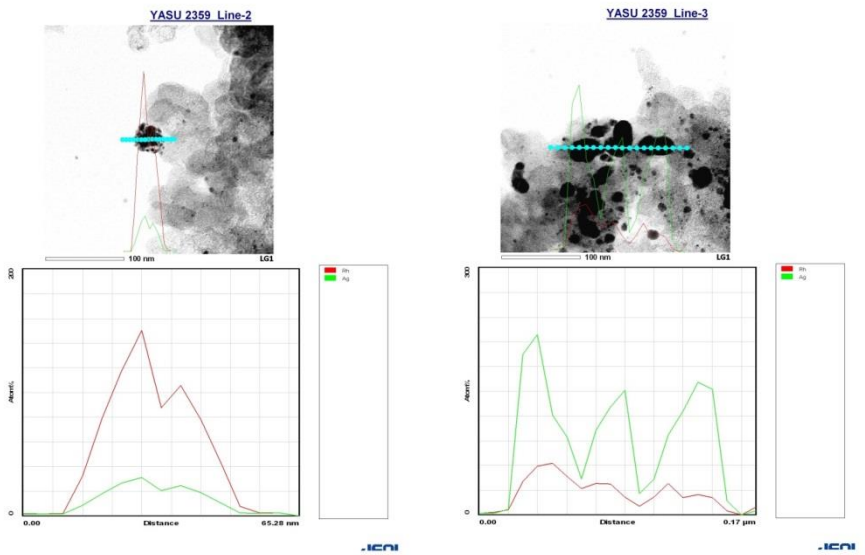


Fig. 1-2-8. Line analyses of PI/CB Rh/Ag **IV-3**

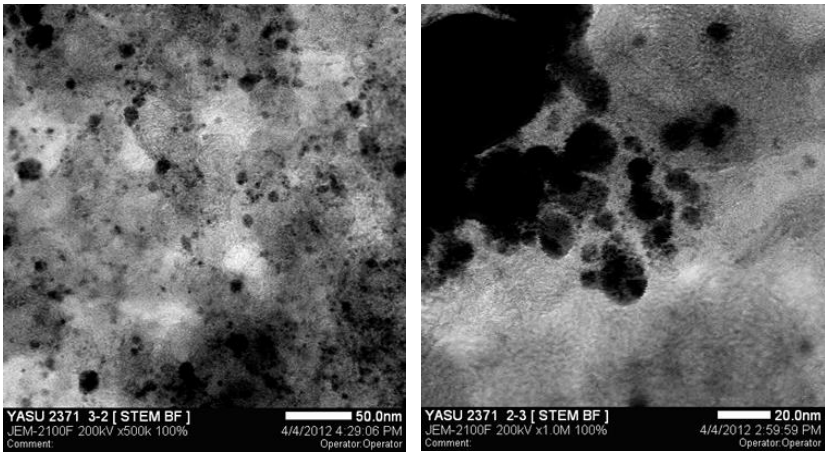


Fig 1-2-9. STEM images of PI/CB Rh/Ag **IV-4**

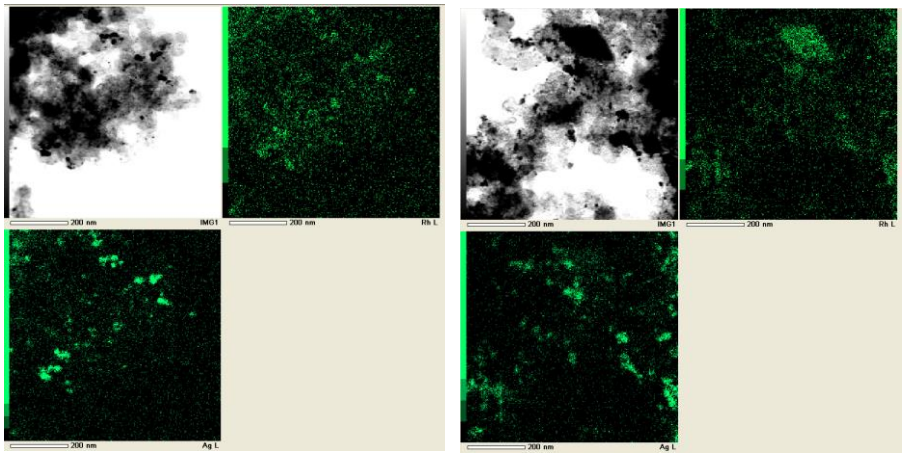


Fig 1-2-10. EDS analyses of PI/CB Rh/Ag **IV-4**

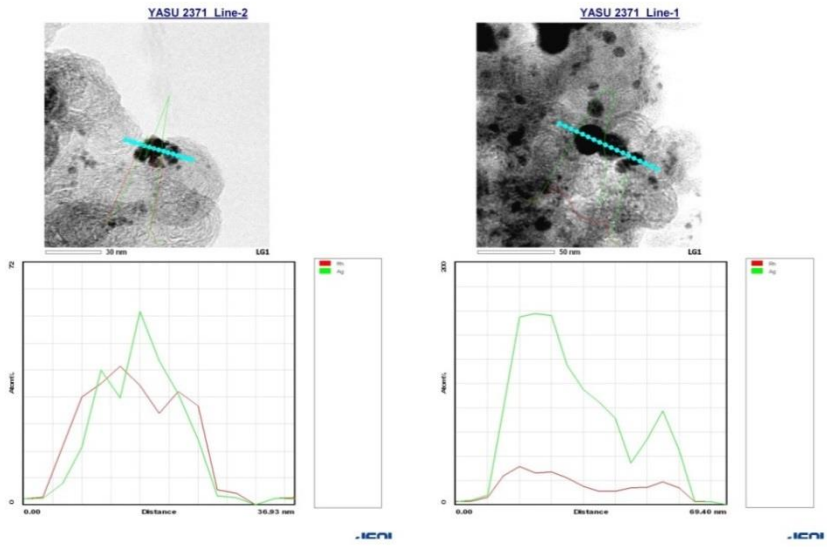


Fig 1-2-11. Line analyses of PI/CB Rh/Ag **IV-4**

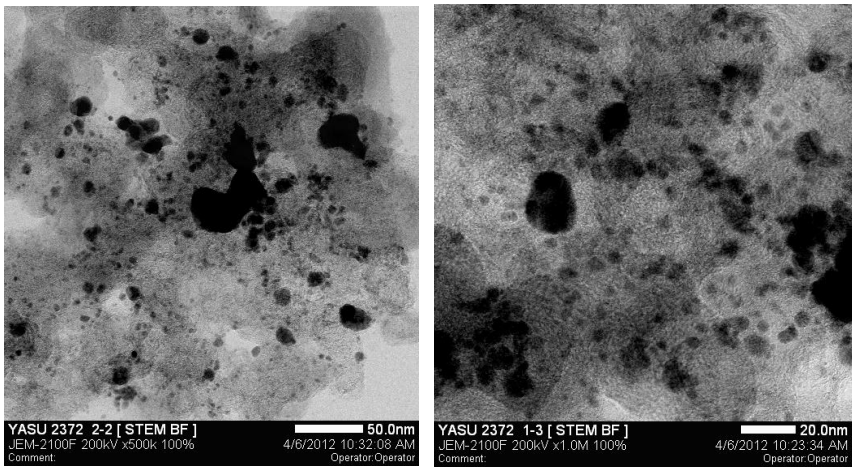


Fig 1-2-12. STEM images of PI/CB Rh/Ag **IV-5**

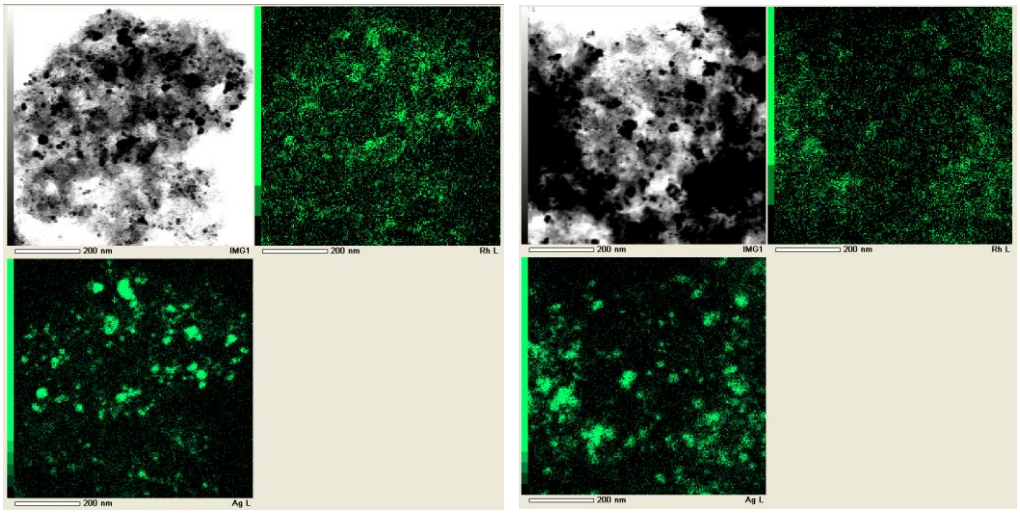


Fig. 1-2-13. EDS analyses of PI/CB Rh/Ag **IV-5**

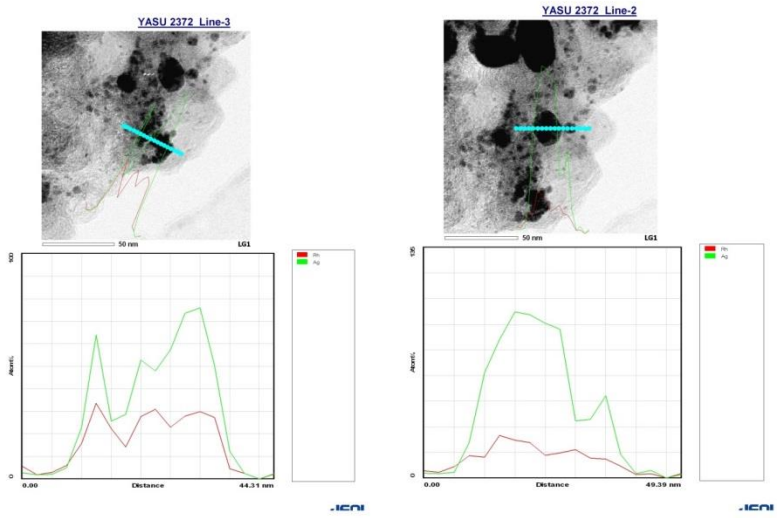
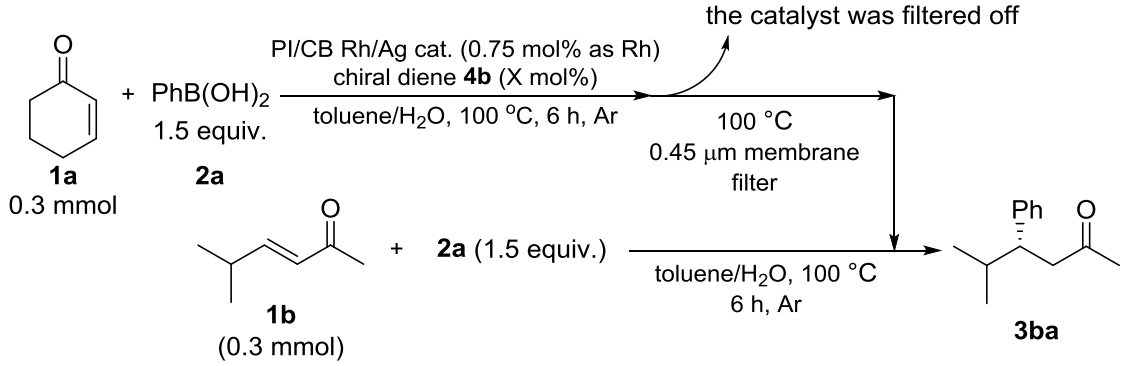


Fig 1-2-14. Line analyses of PI/CB Rh/Ag **IV-5**

To confirm the heterogeneity of the current chiral PI/CB Rh/Ag system, hot filtration test[32a] with two different substrates was conducted (Table 1-2-15). After the asymmetric 1,4-addition reaction with **1a** and **2a** was completed under the standard conditions, the catalyst was filtered off through a membrane filter and the filtrate was directly transferred to the other flask that contained **1b** and additional **2a**. Very small amount of the product **3ba** was obtained by using PI/CB Rh/Ag **IV-2** or PI/CB Rh **I-2** (entries 1 and 2). When PI/CB Rh/Ag **IV-4** was tested under the same experimental procedure, only trace amount of **3ba** was observed and the results were reproduced (entries 3-1, 3-2 and 3-3), indicating that no catalytic active species existed in the filtrate in thr course of the reaction. Decrease of the amount of the ligand could suppress the formation of **3ba** even in the presence of PI/CB Rh/Ag **IV-2** (entries 4-5).

Table 1-2-15. Hot filtration test with two different substrates



entry	cat.	diene X (mol%)	yield (**3ba**) (%)[a]
1	Rh/Ag **IV-2**	1	4
2	Rh **I-2**	1	5
3-1	Rh/Ag **IV-4**	1	1
3-2	Rh/Ag **IV-4**	1	2
3-3	Rh/Ag **IV-4**	1	1
4	Rh/Ag **IV-4**	0.15	trace
5	Rh/Ag **IV-2**	0.075	<1

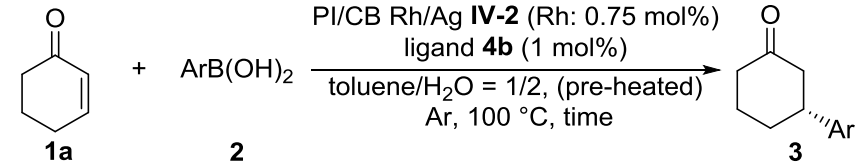
[a] Determined by GC analysis.

Substrate generality

With the optimized reaction conditions in hand, substrate generality was examined. Firstly, various arylboronic acids were tested using 2-cyclohexenone as a substrate in the presence of PI/CB Rh/Ag **IV-2** (Table 1-2-16). It turned out that ortho-substituted arylboronic acids, including 1-naphtylboronic acid, were less reactive (entries 1-3 and 11) and the twice amount of the catalyst and the ligand and 2.0 equiv of arylboronic acid

were required to achieve high yield (entries 4 and 12). The reaction with arylboronic acids bearing substitution at meta position proceeded smoothly (entries 5, 6 and 13). Both arylboronic acids with electron donating groups at any positions and arylboronic acids with electron withdrawing groups at para position could be used and they provided the desired products with high yield and high enantioselectivity (entries 9, 10, 13-15). As the reaction with 4-*tert*-butyl phenylboronic acid caused the leaching (entry 7), the catalyst was changed to PI/CB Rh/Ag **IV-4**. In this case, high yield and enantioselectivity were achieved without the leaching (entry 8).

Table 1-2-16. Substrate generality of arylboronic acids



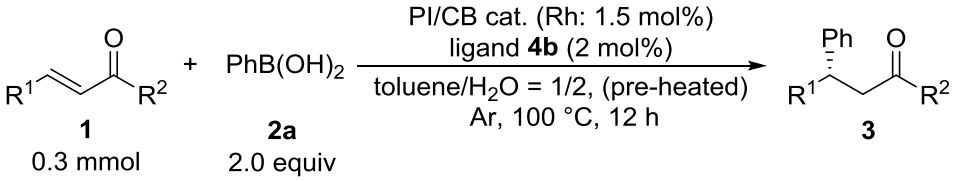
entry	Ar	product	time (h)	conv. (%)[a]	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	(2-Me)C_6H_4	**3ab**	24	94	74		ND
2[e]	(2-Me)C_6H_4	**3ab**	24	74	-	-	ND
3[f]	(2-Me)C_6H_4	**3ab**	24	66	-	-	ND
4[e,f]	(2-Me)C_6H_4	**3ab**	24	91	81	96	ND
5	(3-Me)C_6H_4	**3ac**	9	>99	99	96	ND
6	(3,5-diMe)C_6H_4	**3ad**	11	99	96	97	ND
7	(4-^{t}Bu)C_6H_4	**3ae**	6	43	40	-	1.4
8[g]	(4-^{t}Bu)C_6H_4	**3ae**	24	98	89	97	ND
9	(4-F)C_6H_4	**3af**	24	90	87	98	ND
10	(4-Ph)C_6H_4	**3ag**	10	99	quant.	98	ND
11	1-napthyl	**3ah**	23	83	77	93	ND
12[e,f]	1-napthyl	**3ah**	12	-	90	95	ND
13	(2-OMe)C_6H_4	**3ai**	7	99	95	93	ND
14	(3-OMe)C_6H_4	**3aj**	10	-	93	98	ND
15	(4-OMe)C_6H_4	**3ak**	7	93	82	97	ND

ND = under detection limit (<0.2~1%). "-" = Not measured.

[a] Determined by GC analysis. [b] Calculated from the amount of isolated product from 70% amount of the reaction mixture. [c] Determined by HPLC analysis. [d] Determined by ICP analysis with 30% amount of the reaction mixture. [e] 1.5 mol% of Rh and 2.0 mol% of **4b** were used. [f] 2.0 equiv of arylboronic acid was used. [g] PI/CB Rh/Ag **IV-4** was used.

Substrate scope with enones was performed (Table 1-2-17). Cyclopentenone **1c** could be converted to the product with high yield and good enantioselectivity under the optimized conditions for cyclic substrate **1a** (entry 2). For the reaction with other acyclic enones, PI/CB Rh/Ag **IV-4** was used and the optimized conditions for **1b** (entry 1) was utilized; however, the leaching was observed in the reactions with **1d-f** (entries 3-5). Catalyst screening for the reaction with **1f** was conducted (entries 6-7) and it was found that PI/CB Rh **I-2** did not cause the leaching although the yield was slightly lower than the case of Rh/Ag **IV-4** (entry 6).

Table 1-2-17. Substrate generality of enones



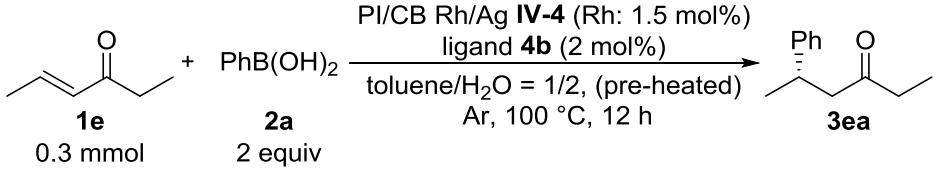
entry	R^1	R^2	product	cat.	conv. (%)[a]	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	^{i}Pr	Me	**3ba**	Rh/Ag **IV-4**	95	91	92	ND
2[e]	$-(CH_2)_2-$		**3ca**	Rh/Ag **IV-2**		86	74	ND
3	Ph	Me	**3da**	Rh/Ag **IV-4**	-	83	92	2.4
4	Me	Et	**3ea**	Rh/Ag **IV-4**	>99	84	90	1.6
5	n-C_5H_{11}	Me	**3fa**	Rh/Ag **IV-4**	-	92	95	1.2
6	n-C_5H_{11}	Me	**3fa**	Rh **I-2**	-	83	95	ND
7	n-C_5H_{11}	Me	**3fa**	Rh/Co **II-3**	-	83	95	<0.1

ND = under detection limit (<0.2~1%). "-" = Not measured.

[a] Determined by GC analysis. [b] Determined by GC analysis and the yield in parenthesis was calculated from the amount of isolated product from 70% amount of the reaction mixture. [c] Determined by HPLC analysis. [d] Determined by ICP analysis with 30% amount of the reaction mixture. [e] PI/CB Rh/Ag **IV-2** (0.75 mol%), **4b** (1.0 mol%) and **2a** (1.5 equiv) were used and the reaction time was 7 h.

The conditions for the reaction with **1e** were optimized in order to suppress the leaching completely (Table 1-2-18). Unlike the case of **1f**, PI/CB Rh **I-2** and PI/CB Rh/Co **II-3** could not maintain high catalytic activity (entries 1 vs. 2-3). Increase of Ag loading (entry 4), change of the amount of diene (entries 6 and 7), increase of the amount of phenylboronic acid (entry 8), change of the concentration (entries 9 and 10) and change of the ratio of solvent (entries 11 and 12) could not prevent the leaching. Use of *tert*-amyl alcohol as a proton source instead of water completely inhibited the reaction (entry 13).

Table 1-2-18. Optimization of the reaction condition with substrate **1e**

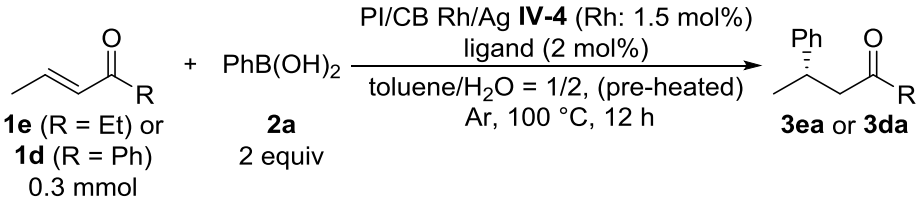


entry	toluene (ml)	H_2O (ml)	yield (%)[a]	ee (%)[b]	Rh leaching (%)[c]	Optimized point
1	0.375	0.75	84	90	1.6	-
2	0.375	0.75	<18	-	ND	PI/CB Rh **I-2**
3	0.375	0.75	<26	-	ND	PI/CB Rh/Co **II-3**
4	0.375	0.75	85	91	1.4	PI/CB Rh/Ag **IV-5**
5	0.375	0.75	85	90	3.6	0.5 equiv. of K_2CO_3
6	0.375	0.75	89	90	4.4	1 mol% of diene
7	0.375	0.75	81	91	3.4	3 mol% of diene
8	0.375	0.75	83	89	2.6	3 equiv of $PhB(OH)_2$
9	0.75	1.5	31	92	2.8	conc.*1/2
10	0.188	0.375	89	91	2.5	conc.*2
11	0.56	0.56	84	91	1.9	solvent ratio = 1:1
12	0.28	0.84	87	91	4.2	solvent ratio = 1:3
13	0.375	0.75	ND	-	ND	^{t}AmOH (instead of H_2O)

[a] The yield was calculated from the amount of isolated product from 70% amount of the reaction mixture. [b] Determined by HPLC analysis. [c] Determined by ICP analysis from 30% amount of the reaction mixture and the figures represent the amount of leached Rh with respect to initial amount of Rh added.

The chiral diene **4a** was then examined (Table 1-2-19). Though diene **4a** gave the lower ee (~80%) in the case of cyclic substrate **1a**, the ee was improved to 95% when substrate **1e** was used (entries 1 vs. 2). The ee decreased when substrate **1d** was used (entries 3 vs. 4). The leaching could not be suppressed in both cases.

Table 1-2-19. Screening of chiral dienes

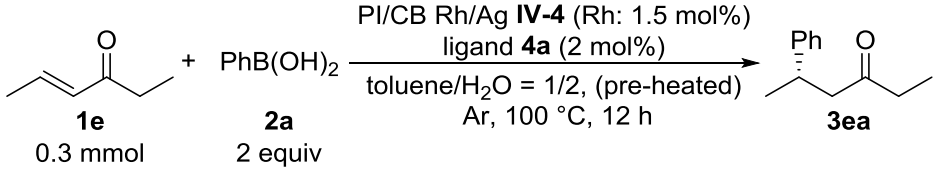


entry	**1**	ligand	yield (%)[a]	ee (%)[b]	Rh leaching (%)[c]
1	**1e**	**4b**	84	90	1.6
2	**1e**	**4a**	89	95	1.8
3	**1d**	**4b**	83	92	2.4
4	**1d**	**4a**	78	90	4.0

[a] The yield was calculated from the amount of isolated product from 70% amount of the reaction mixture. [b] Determined by HPLC analysis. [c] Determined by ICP analysis from 30% amount of the reaction mixture.

The recovered catalyst, which was obtained from the reaction shown in Table 1-2-19, entry 2, provided the less amount of the leaching (Table 1-2-20, entry 1) and it suggests that there might be the Rh nanoparticles that cause the leaching to some Rh species easily in the first cycle. For example, relatively smaller nanoparticles are assumed to be omitted from the polymer matrix readily. To remove such small nanoparticles, the catalyst was heated at 150 ˚C in mesitylene for 5 h before use (named as "mesitylene treatment") because it was reported that this operation makes the size of nanoparticles bigger.[10b] After this treatment, the catalyst was used with chiral diene **4a** and finally, the leaching was completely suppressed with a slight loss of the yield (entry 2). Receiving result, PI/CB Rh/Ag **IV-6** was prepared by the revised method in which a first heating procedure was conducted in mesitylene (Scheme 1-2-7). PI/CB Rh/Ag **IV-6** also prevented the leaching completely under the same conditions; however, the yield significantly decreased (Table 1-2-20, entry 3). The heating procedure in mesitylene at an early stage of the catalyst preparation might cause rapid aggregations to generate too big nanoparticles and as a consequence, the lower activity was observed. To support this hypothesis, STEM analyses and EDS mappings were conducted with PI/CB Rh/Ag **IV-4** after mesitylene treatment and PI/CB Rh/Ag **IV-6**. In the former case, the number of small size nanoparticle decreased compared with the PI/CB Rh/Ag **IV-4** before mesitylene treatment (Figures 1-2-9 vs. 1-2-15). On the other hand, in the images of PI/CB Rh/Ag **IV-6**, nanoparticles were much aggregated and big size nanoparticles (~50 nm) were observed (Figure 1-2-18). Rh and Ag still composed alloy nanoparticles in both cases (Figures 1-2-16, 1-2-17, 1-2-19 and 1-2-20). Judging from these results, the size of nanoparticles may affect the catalytic activity and the leaching.

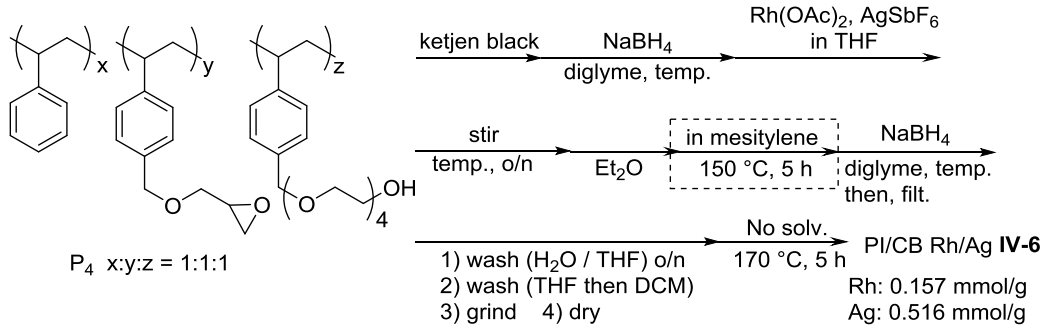
Table 1-2-20. Effect of "mesitylene treatment"



entry	yield (%)[a]	ee (%)[b]	Rh leaching (%)[c]	Optimized point
1	88	96	0.3	Recovered catalyst (from Table 1-2-19, entry 2) was used
2	82	96	ND	The catalyst was heated at 150 ˚C in mesitylene for 5 h before use
3	52	-	ND	PI/CB Rh/Ag **IV-6** was used

[a] The yield was calculated from the amount of isolated product from 70% amount of the reaction mixture. [b] Determined by HPLC analysis. [c] Determined by ICP analysis from 30% amount of the reaction mixture.

Scheme 1-2-7. Preparation of PI/CB Rh/Ag **IV-6**



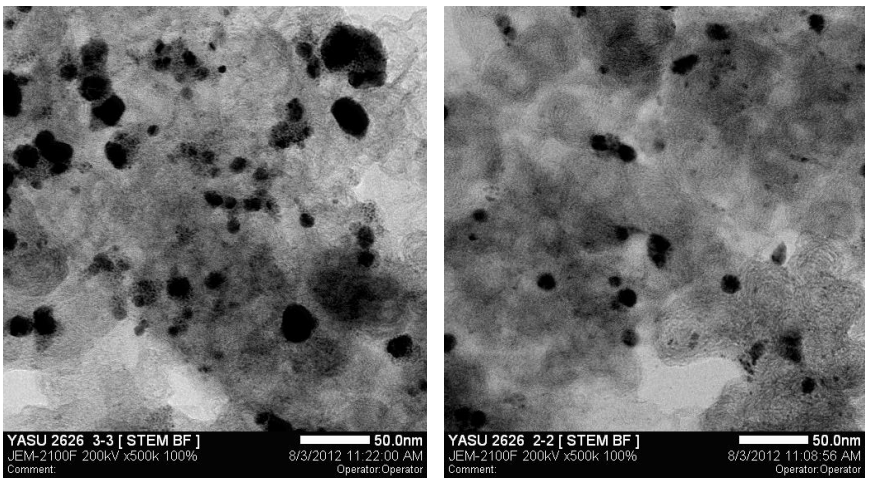


Fig. 1-2-15. STEM images of PI/CB Rh/Ag **IV-4** after mesitylene treatment

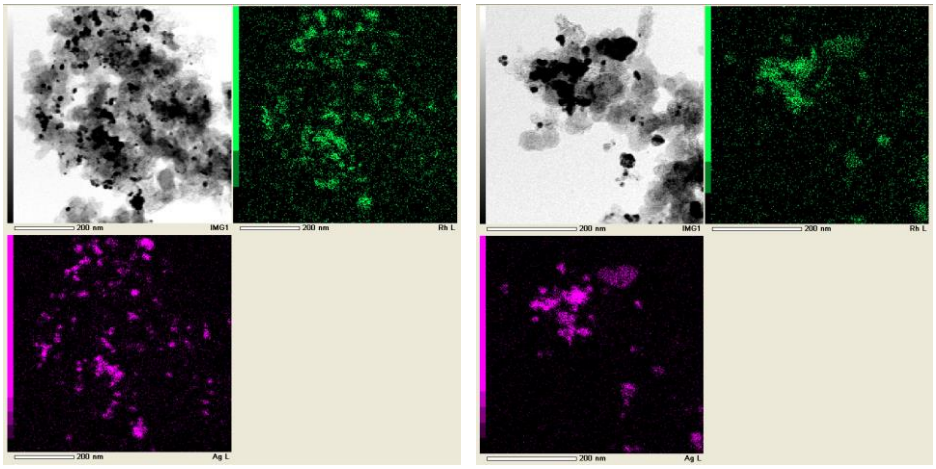


Fig. 1-2-16. EDS analyses of PI/CB Rh/Ag **IV-4** after mesitylene treatment

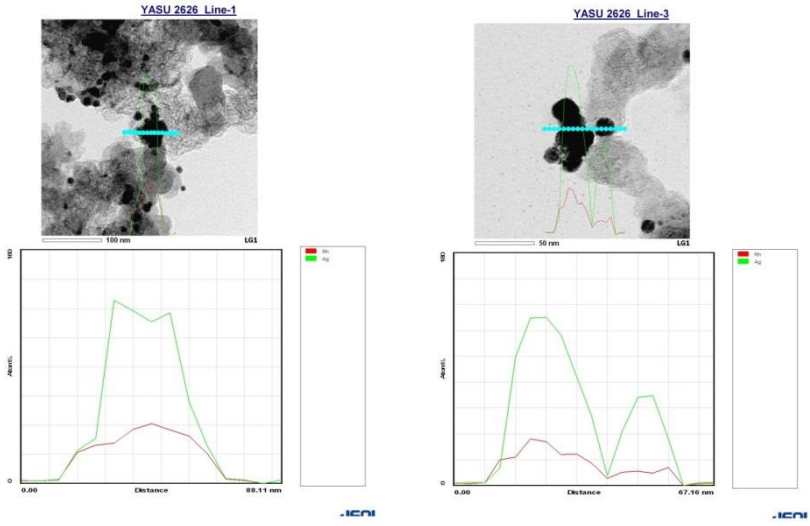


Fig. 1-2-17. Line analyses of PI/CB Rh/Ag **IV-4** after mesitylene treatment

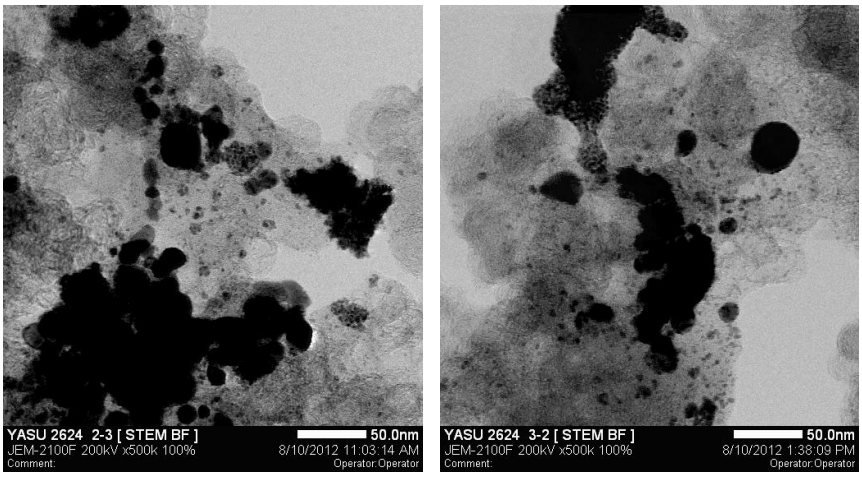


Fig. 1-2-18. STEM images of PI/CB Rh/Ag **IV-6**

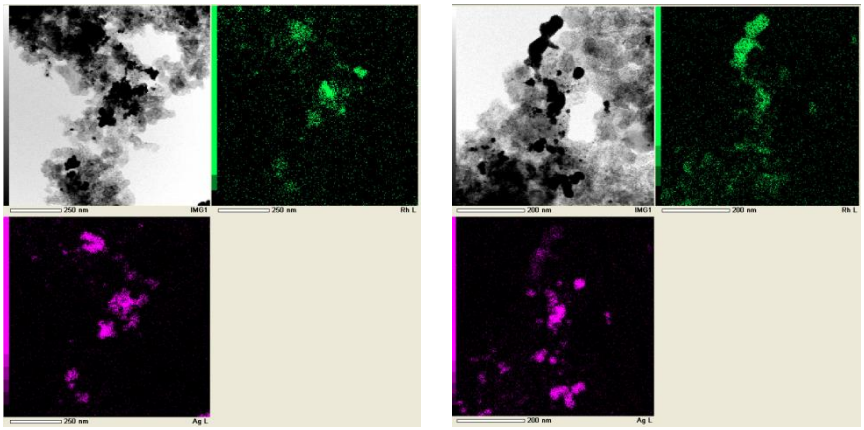


Fig. 1-2-19. EDS analyses of PI/CB Rh/Ag **IV-6**

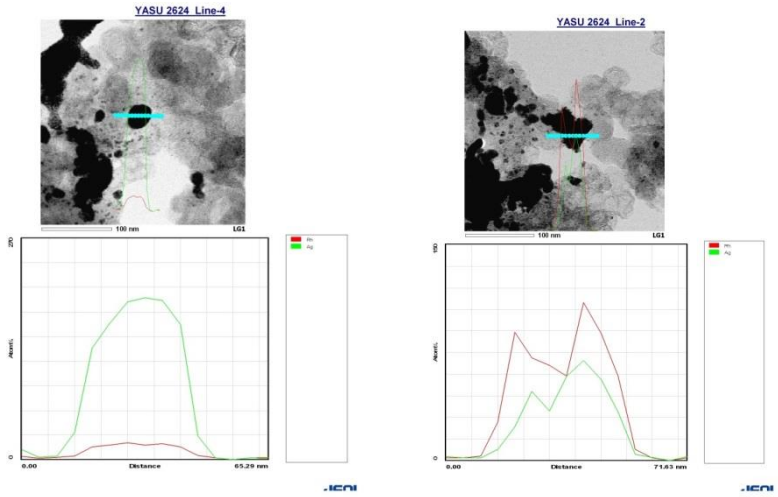
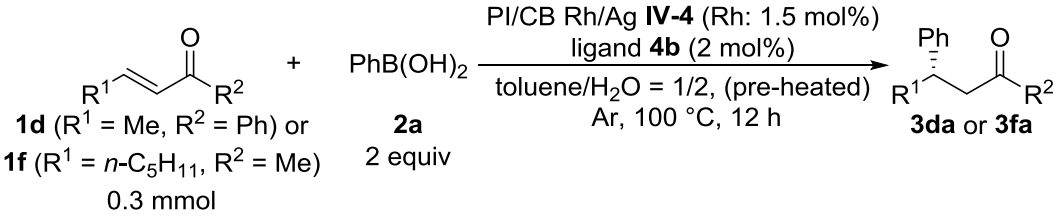


Fig. 1-2-20. Line analyses of PI/CB Rh/Ag **IV-6**

Table 1-2-21. Effect of "mesitylene treatment" for the reactions with **1d** or **1f**



entry	**1**	mesitylene treatment[a]	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	**1d**	-	83	92	2.4
2	**1d**	+	72	92	ND
3	**1f**	-	92	95	1.2
4	**1f**	+	70	95	ND

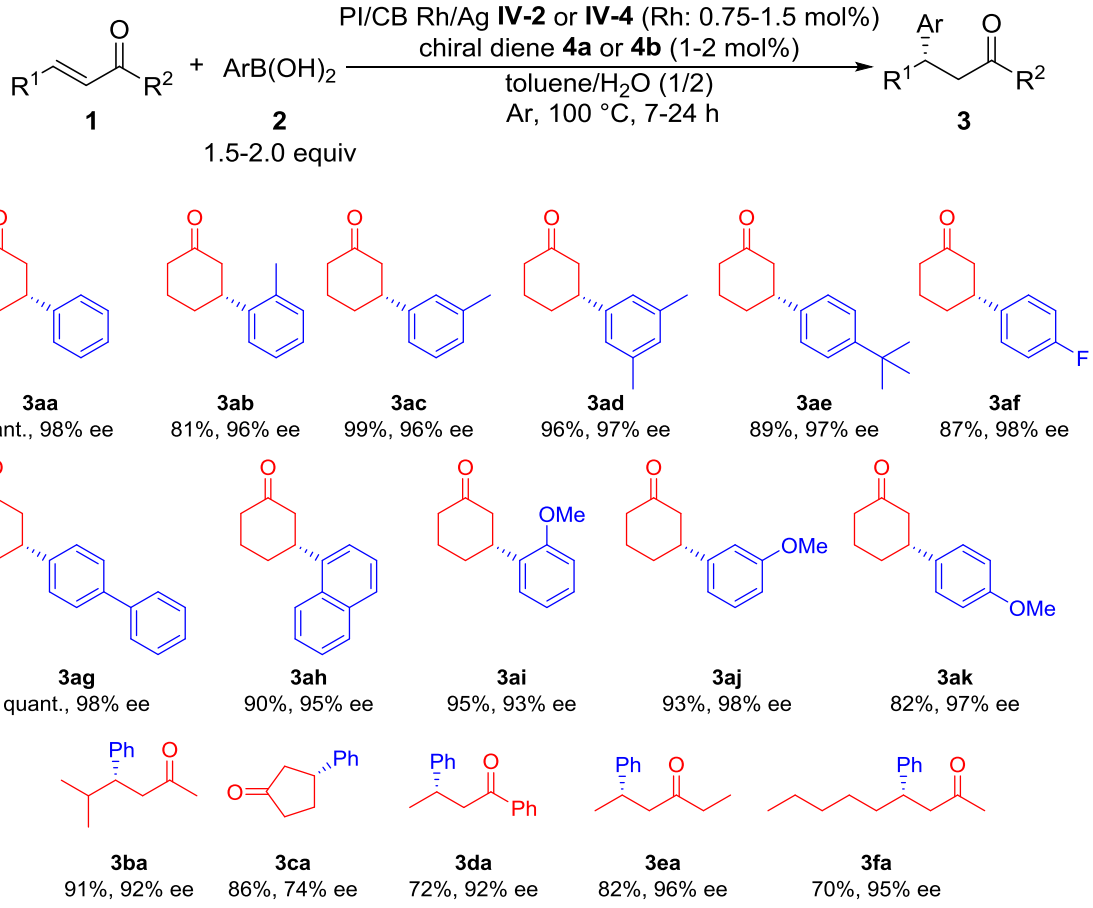
[a] "Mesitylene treatment" is that the catalyst was heated at 150 ˚C in mesitylene for 5 h before use. [b] The yield was calculated from the amount of isolated product from 70%

amount of the reaction mixture. [c] Determined by HPLC analysis. [d] Determined by ICP analysis from 30% amount of the reaction mixture.

Mesitylene treatment was applied for the asymmetric 1,4-addition reactions using substrate **1d** or **1f** with chiral diene **4b** (Table 1-2-21) and the leaching was suppressed completely in both cases while the yield decreased.

In this way, wide substrate generality was demonstrated and high yield and enantioselectivities were achieved without leaching in all cases in asymmetric 1,4-addition of arylboronic acids to enones catalyzed by PI/CB Rh/Ag with chiral diene (Scheme 1-2-8).

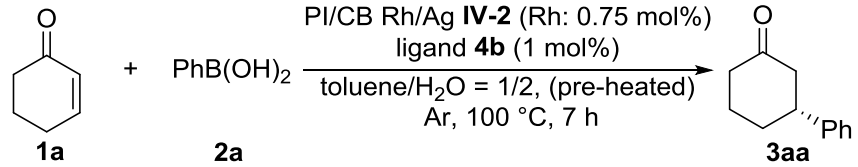
Scheme 1-2-8. Summary of substrate generality



Recovery and reuse

Recovery and reuse of the catalysts were examined (Table 1-2-21). The catalysts could be recovered by a simple filtration without significant loss (only 1~2 mg due to the technical loss) and reused for the next cycle with a new portion of chiral diene after the recovered catalyst was washed with water and THF and dried. High catalytic activity was maintained to produce the product in high yield until run 8 (runs 1-8). In run 9, yield decreased and the similar lower yield was obtained in run 10 when no special treatment for the recovered catalyst was performed (runs 9-10). In run 11, the recovered catalyst was heated at 170 ˚C for 4 h before use and the catalytic activity was revived (run 11). STEM analyses and EDS mappings of the recovered catalyst revealed that no significant structural changes before use, after the run 10, or after heating were observed (Figures 1-2-3~5 vs. 1-2-21-24). As many small nanoparticles (<2 nm) still remained in the recovered catalyst after run 10 and heating, the loss of catalytic activity, derived from decrease of total surface area of Rh nanoparticles due to an aggregation, might hardly occur in this system. Thus, the heating treatment might remove impurities, such as small amount of solvent, product or side-products that were adsorbed on the surface of nanoparticles. The high catalytic activity was maintained until run 14 without any special treatment for the catalyst (runs 12-14). These results proved the robustness of PI/CB Rh/Ag system.

Table 1-2-21. Recovery and reuse



run	yield (%)[a]	ee (%)[b]	Rh leaching (%)[c]	run	yield (%)[a]	ee (%)[b]	Rh leaching (%)[c]
1	quant.	98	ND	8	94	98	ND
2	97	98	ND[e]	9	67	98	ND
3	quant.	98	ND	10	60	98	ND
4	95	98	ND	11[d]	97	98	ND
5	quant.	98	ND	12	97	98	ND
6	94	98	ND	13	92	98	ND
7	quant.	98	ND	14	90	98	ND

ND = under detection limit (<0.15~0.4%). [a] Determined by GC analysis. [b] Determined by HPLC analysis. [c] Determined by ICP analysis with 40% amount of the reaction mixture. [d] The catalyst was heated at 170 ˚C for 4 h before use.

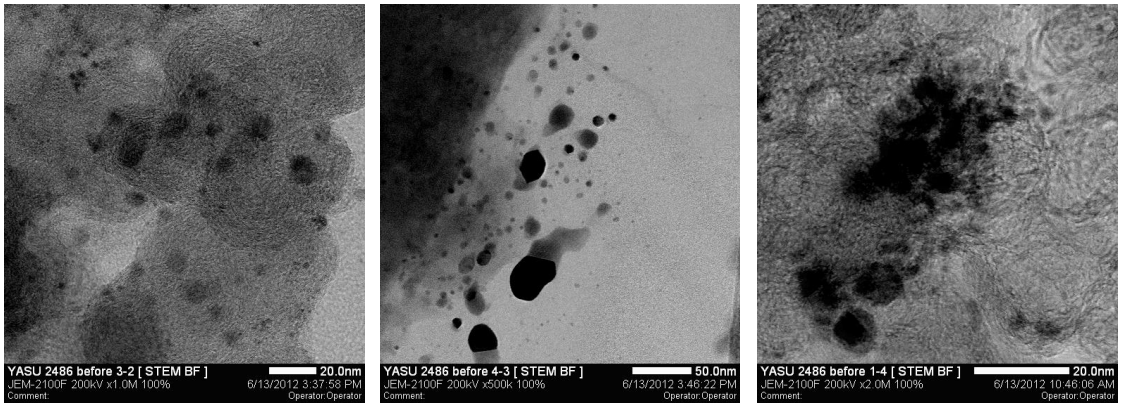


Fig. 1-2-21. STEM images of PI/CB Rh/Ag **IV-2** (after 10th use, before heating)

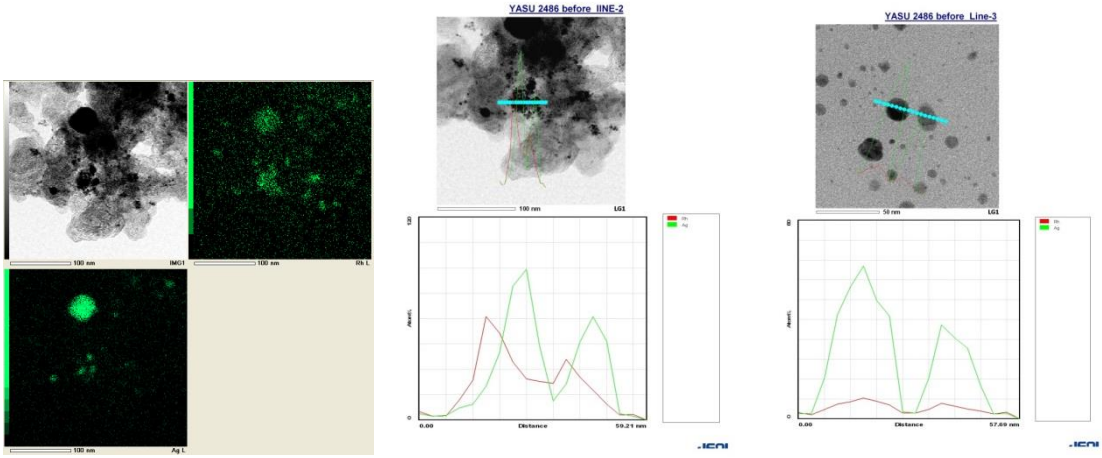


Fig. 1-2-22. EDS mapping and line analyses of PI/CB Rh/Ag **IV-2** (after 10th use, before heating)

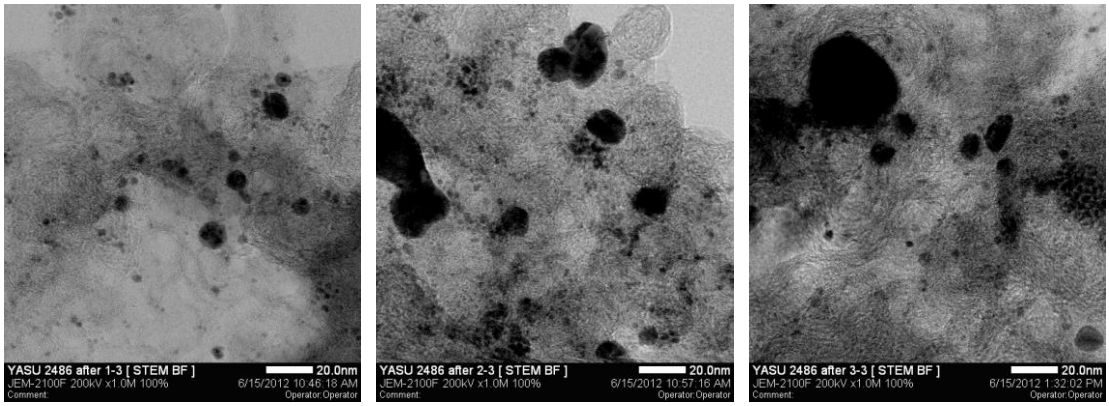


Fig. 1-2-23. STEM images of PI/CB Rh/Ag **IV-2** (after 10th use and heating)

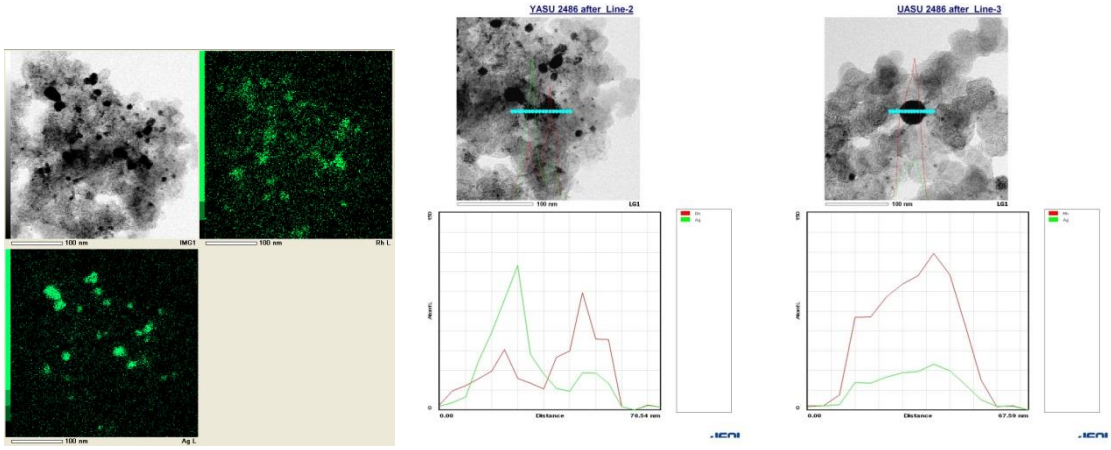
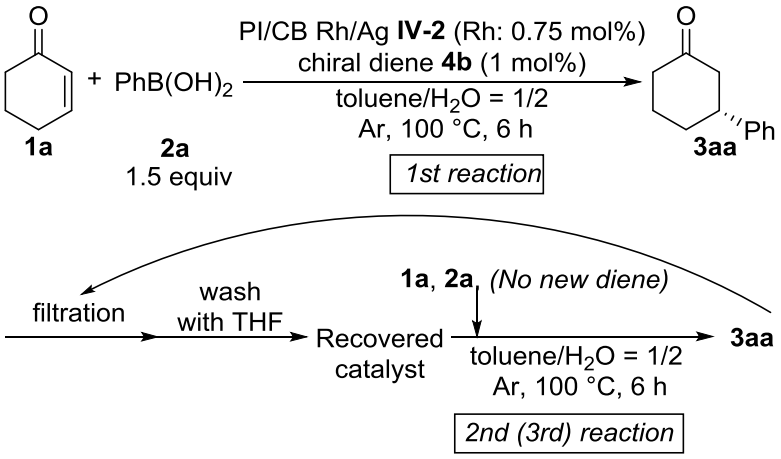


Fig. 1-2-24. EDS mapping and line analyses of PI/CB Rh/Ag **IV-2** (after 10th use and heating)

The reaction using the recovered catalyst was conducted without adding a new portion of chiral diene in order to examine whether the chiral diene could be recovered or not (Table 1-2-22). After run 1 in the presence of chiral diene and the catalyst, the catalyst was filtered, washed with THF several times and dried. This recovered catalyst was used for run 2 without adding a new portion of chiral diene and this process was performed in two different batches. Although it was difficult to reproduce the same result in this procedure, the reaction could proceed in spite of the lower yield in both batches indicating that the chiral diene remained in the polymer matrix was recovered. Enantioselectivity also gradually decreased whenever the catalyst was reused and it implied that a part of the recovered chiral diene decomposed or structure change of the chiral diene occurred.

Table 1-2-22. Recovery and reuse of the catalyst without addition of new chiral diene



	Batch 1			Batch 2		
	1st	2nd	3rd	1st	2nd	3rd
yield[a]	>95	62	~10	>95	41	trace
ee[b]	98	-	73	98	95	-

[a] Determined by GC analysis. [b] Determined by HPLC analysis.

To develop the method to recover the catalyst and the chiral diene from the reaction system, recovery of chiral diene from a simple toluene/water solvent system was examined (Scheme 1-2-9). After the mixture of the catalyst and chiral diene was heated at 100 ˚C for 30 minutes in toluene and water, the catalyst was filtered, washed with hexane several times and dried. The asymmetric 1,4-addition reaction was conducted with this recovered catalyst without adding a new portion of chiral diene and the desired product was obtained in only 50% yield. To estimate how much amount of the chiral diene remained in the catalyst, the reactions with less amount of chiral diene were performed (Table 1-2-23). In the presence of PI/CB Rh/Ag **IV-2**, the loading of ligand could be reduced to 0.0375 mol% without loss of activity (entries 1-5). On the other hand, in the presence of PI/CB Rh/Ag **IV-4**, the yield dramatically decreased when the loading of ligand was reduced to 0.075 mol% (entries 6-8). These experiments showed that the chiral diene could be partially recovered but it was very small amount and probably not pure. To maintain the catalytic activity, another recovery method and/or a new designed ligand, which has high affinity with polymer or metal nanoparticles, were required.

Scheme 1-2-9. Recovery of chiral diene from toluene/water media

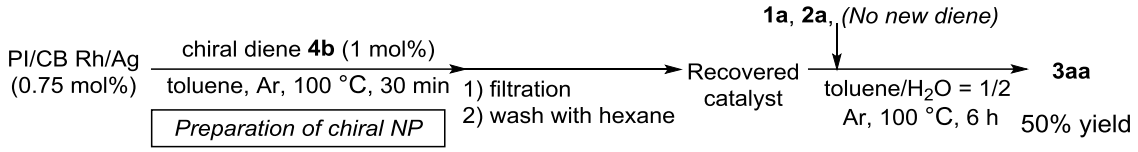
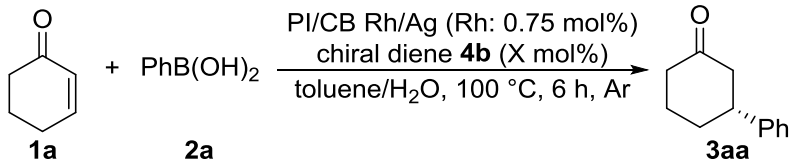


Table 1-2-23. Effect of the amount of chiral diene



entry	catalyst	diene X (mol%)	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	**IV-2**	1	>99	98	ND
2	**IV-2**	0.25	95	98	ND
3	**IV-2**	0.15	96	98	ND
4	**IV-2**	0.075	>99	98	ND
5	**IV-2**	0.0375	>99	98	ND
6	**IV-4**	1	>95	98	ND
7	**IV-4**	0.15	87	98	ND
8	**IV-4**	0.075	9	98	ND

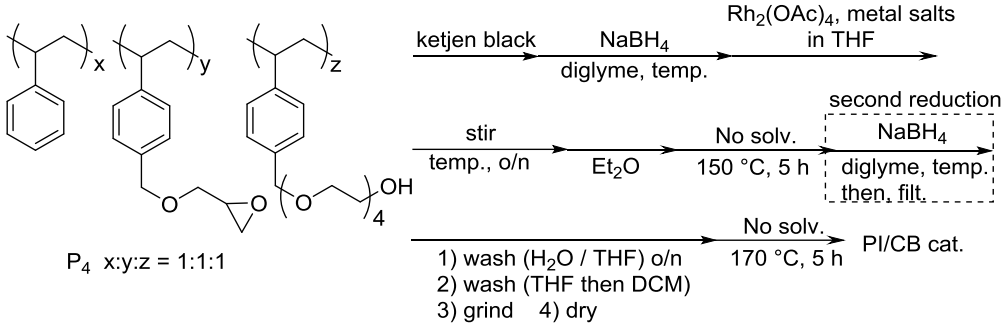
ND = under detection limit of ICP equipment (< 0.003–0.005 ppm). "–" = Not determined. [a] Reaction conditions: 100 °C, 1a (0.2 mmol), 2a (0.3 mmol), toluene (0.25 ml), water (0.5 ml) [b] Determined by GC analysis. [c] Determined by HPLC analysis. [d] Determined by ICP analysis; the figures represent the amount of leached Rh with respect to the initial amount of Rh added.

Application to tandem reactions

Tandem reaction system or one-pot reaction system are attractive systems from the viewpoint of green chemistry due to several advantages: 1) purification steps can be reduced, 2) toxic and/or unstable intermediate can be generated *in situ* and need not to be isolated.[73] Tandem reaction systems using two different catalysts are expected to produce compounds with complicated structures efficiently[73a]; however, undesired interactions between two catalysts to deactivate the activities each other are usually problematic. I considered that robust heterogeneous nanoparticles system probably overcome this problem[74] and applied PI/CB Rh/Ag system to one-pot aerobic oxidation/asymmetric 1,4-addition process. Gold nanoparticle catalysts were chosen as

catalysts for aerobic oxidation reaction and allylic alcohols was chosen as starting materials. Initially, trimetallic catalysts including Au nanoparticles and Rh nanoparticles were prepared by the same preparation method for PI/CB Rh/Ag (Table 1-2-24). The catalytic activity of these catalysts for the aerobic oxidation of **1a** was confirmed (Table 1-2-25). PI/CB Au/Ru/Rh **X** produced the desired unsaturated ketone in high yield while the reaction hardly proceeded in the presence of PI/CB Au/Rh/Ag **XI** (entries 1-2).

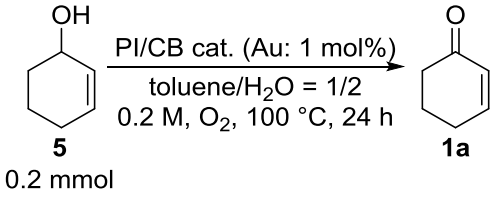
Table 1-2-24. Preparation of trimetallic catalysts from Rh acetate



entry	name	metal salt	actual loading (mmol/g)[a]
1	PI/CB Au/Rh/Ru **X**	$AuPPh_3Cl$ $[Ru(cymene)Cl_2]_2$	Au: 0.168, Rh: 0.161 Ru: 0.169
2	PI/CB Au/Rh/Ag **XI**	$AuPPh_3SbF_6$ $AgSbF_6$	Au: 0.158, Rh:0.162 Ag: 0.183

[a] Determined by ICP analysis.

Table 1-2-25. Oxidation of 2-cyclohexenone catalyzed by trimetallic catalyst



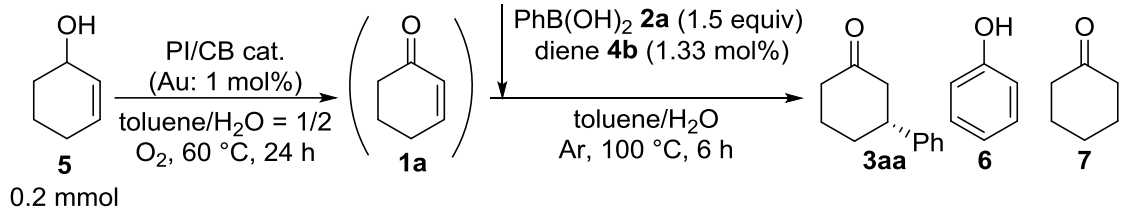
entry	catalyst	conv. (%)[a]	yield (%)[a]
1	Au/Rh/Ru **X**	>99	87
2	Au/Rh/Ag **XI**	-	5

[a] Determined by GC analysis.

One-pot aerobic oxidation of alcohol to ketone/asymmetric 1,4-addition to unsaturated ketone was then performed with these catalysts (Table 1-2-26). To avoid several undesired reactions, such as oxidative homocoupling of arylboronic acid and isomerization of allylic alcohol, chiral diene and arylboronic acid were decided to

combine after the oxidation reactions completed. However, the desired product **3aa** hardly formed in both cases and phenol and cyclohexanone were obtained instead. As the yield of phenol and cyclohexanone were similar, a disproportionation reaction from **1a** might occur to form these side products.[75]

Table 1-2-26. One-pot reaction using trimetallic catalyst and chiral diene

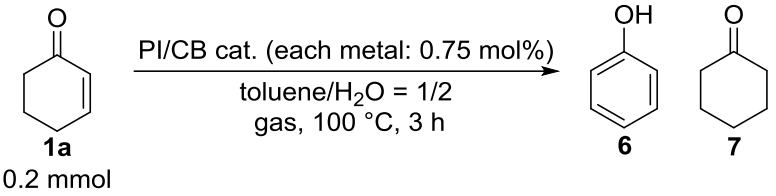


entry	PI/CB M	conv. (%)[a]	yield **3aa** (%)[a]	**1a** (%)[a]	**6** (%)[a]	**7** (%)[a]
1	Au/Rh/Ru **X**	>99	2	0	49	39
2	Au/Rh/Ag **XI**	-	7	22	32	40

[a] Determined by GC analysis.

Though this phenol formation reaction is undesirable for the one-pot reaction, further investigation was continued to know the nature of this reaction (Table 1-2-27). The yields of these two compounds were always same regardless of the presence of molecular oxygen in the presence of PI/CB Au/Rh **VI-2** (entries 1-3). On the other hand, in the presence of only PI/CB Au **XII** or Rh **I-2**, the reaction did not proceed and it showed that two metals were required to promote this phenol formation reaction (4-8). In addition, the reaction did not proceed in the presence of both PI/CB Au **XII** and PI/CB Rh **I-2**, demonstrating that the presence of bimetallic nanoparticles is essential for this reaction (entry 9). This reaction was also suppressed by introduction of Ag as a third metal (entry 10) and Au rich catalyst could not catalyze this reaction (entry 11). Probably, a certain composition ratio of Au/Rh alloy nanoparticles showed a specific activity for this reaction and a dopant of Ag might change the structure of active nanoparticles. Further catalyst screening showed that several combinations of multi-metallic nanoparticle catalyst and even monometallic nanoparticle catalyst, such as Pt or Pd, could also promoted this reaction and the same amount of phenol and cyclohexanone were always obtained (entries 12-20).

Table 1-2-27. Catalyst and gas screening of phenol formation reaction

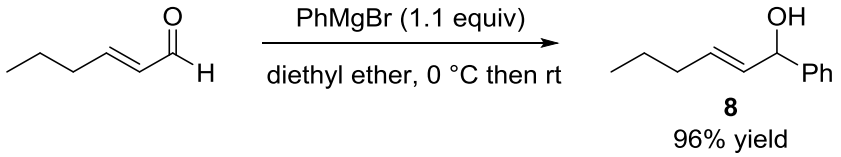


entry	cat.[a]	gas	conv. (%)[b]	yield 1 (%)[b]	yield 2 (%)[b]
1	Au/Rh **VI-2**	Ar	92	41	40
2	Au/Rh **VI-2**	air	92	43	41
3	Au/Rh **VI-2**	O_2	95	46	48
4	Au **XII**	Ar	8	0	0
5	Au **XII**	air	5	0	0
6	Au **XII**	O_2	3	0	0
7[c]	Au **XII**	O_2	5	0	0
8	Rh **I-2**	Ar	4	0	0
9	Au **XII** & Rh **I-2**	Ar	8	trace	0
10	Au/Rh/Ag **XI**	Ar	7	0	0
11[d]	Au/Rh **VI-2**	O_2	NR	-	-
12	Au/Rh/Ru **X**	Ar	92	43	41
13	Au/Pd **XIII**	O_2	>99	47	44
14	Au/Pt **XIV**	O_2	>99	47	45
15[e]	Au/Pt/Rh **XV**	O_2	71	37	29
16	Au/Pt/Rh **XV**	O_2	>99	48	47
17	Au/Rh/Pd **XVI**	O_2	>99	47	45
18	Pt **XVII**	O_2	>99	49	45
19	Pd **XVIII**	O_2	>99	48	47
20	Pt/Pd **XIX**	O_2	>99	49	48

[a] All the bimetallic or trimetallic catalysts had an equal target metal loading for each metal. [b] Determined by GC analysis. [c] Chiral diene (1 mol%) was used and reaction time was 16 h. [d] The ratio of Au and Rh was 4:1. [e] 0.5 ml of toluene and 1.0 ml of water were used.

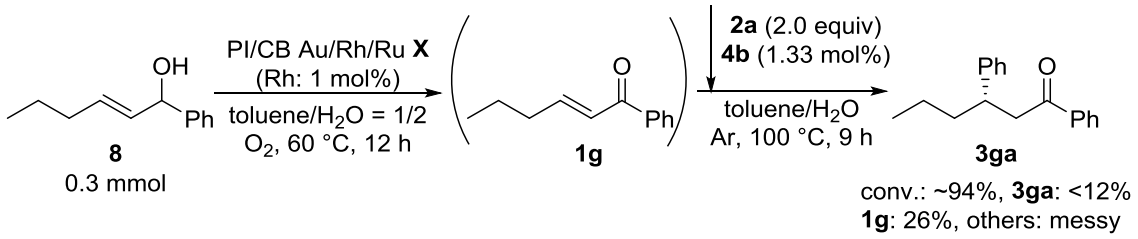
Because of the difficulty to suppress the undesired phenol formation reaction, the model substrate for the one-pot reaction was changed to the acyclic allyl alcohol **8** that is easily prepared from Grignard reagent or alkyllithium (Scheme 1-2-10).

Scheme 1-2-10. Preparation of 1-phenylhex-2-en-1-ol **8**

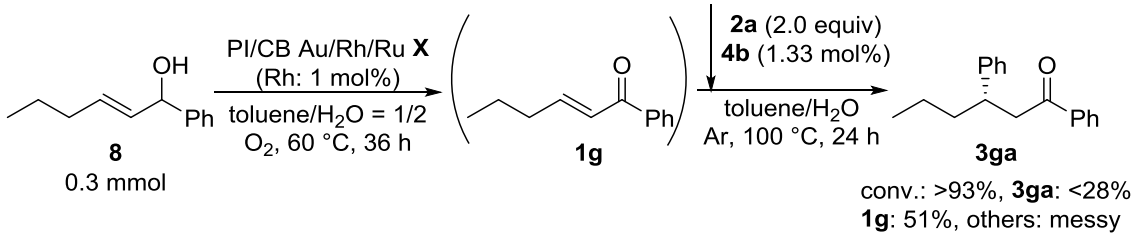


The one-pot reaction using **8** was conducted by the same procedure of previous one-pot reaction (Scheme 1-2-11). Though the desired product was observed on GC-MS and ^{1}H NMR spectra, the crude mixture was too messy to isolate it purely. Even if the reaction time was prolonged to 60 h (total), ketone **1g** still remained and several by-products generated (Scheme 1-2-12). As one of the major by-products was 1-phenylhexan-1-one **9** (Scheme 1-2-13), which might be isomerized product from starting material, the oxidation step was not completed. In addition, it is possible that hydrogens on starting materials can be transferred to the surface of Au nanoparticles and they may reduce the chiral diene.

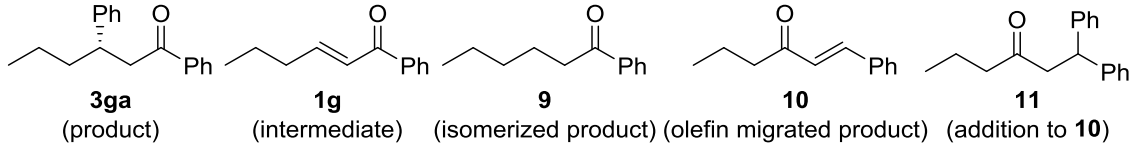
Scheme 1-2-11. One-pot reaction using **8**



Scheme 1-2-12. One-pot reaction using **8** (long reaction time)



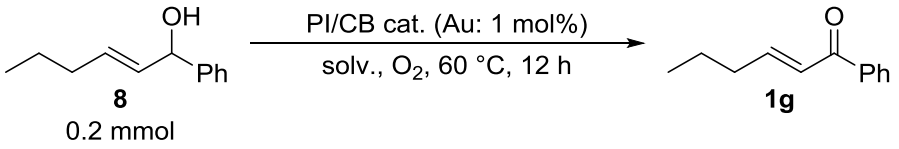
Scheme 1-2-13. List of by-products



To complete the oxidation step before the second step, the conditions for the oxidation step were examined (Table 1-2-28). The reaction did not finish in 12 h or even in 36 h at 60 ˚C in the presence of PI/CB Au/Rh/Ru **X** (entries 1 and 2) and the

temperature could not be raised to 100 ˚C because too many decomposed products, which might be the isomerized product **9** or olefin migrated product **10**, were observed (entry 3). The several bimetallic or trimetallic catalysts were examined; however, no catalyst showed higher activity than PI/CB Au/Rh/Ru **X** (entries 4-6). The solvent system was screened and the higher concentration was examined. When the reaction was conducted in high concentration, the side reactions occurred and more than two side products were obtained in toluene toluene/water or THF (entries 7-9). As the only 9:1 ratio of THF/water media prevented these side reactions (entry 10), the catalysts were screened again and monometallic PI/CB Au **XII** showed the highest yield (entries 11-13). Though the additional Rh catalyst was required if PI/CB Au **XII** was used for the one-pot reaction, first of all, the optimization of the oxidation conditions was examined with PI/CB Au **XII**.

Table 1-2-28. Catalyst and solvent screening for aerobic oxidation of **8**



8
0.2 mmol

1g

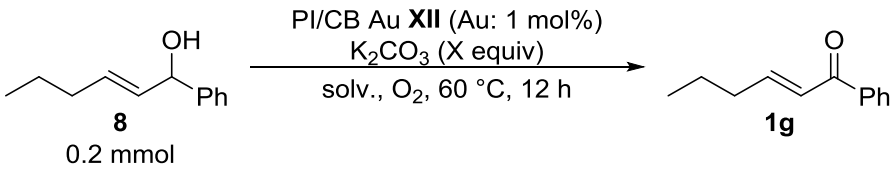
entry	cat.	solv. (ml/ml)	conv. (%)[a]	yield **1g** (%)[a]
1	Au/Rh/Ru **X**	PhMe (0.25) / H_2O (0.5)	38	39
2[b]	Au/Rh/Ru **X**	PhMe (0.25) / H_2O (0.5)	74	69
3[c]	Au/Rh/Ru **X**	PhMe (0.25) / H_2O (0.5)	~88	4
4	Au/Pt **XIV**	PhMe (0.25) / H_2O (0.5)	18	18
5	Au/Rh/Pt **XV**	PhMe (0.25) / H_2O (0.5)	24	16
6	Au/Pd **XIII**	PhMe (0.25) / H_2O (0.5)	21	18
7	Au/Rh/Ru **X**	PhMe (0.2)	64	~1
8	Au/Rh/Ru **X**	PhMe (0.1) / H_2O (0.1)	87	19
9	Au/Rh/Ru **X**	THF (0.25)	23	2
10	Au/Rh/Ru **X**	THF (0.18) / H_2O (0.02)	34	34
11	Au/Pd **XIII**	PhMe (0.18) / H_2O (0.02)	10	7
12	Au/Pd **XIII**	THF (0.18) / H_2O (0.02)	26	24
13	Au **XII**	THF (0.18) / H_2O (0.02)	52	52

[a] Determined by GC analysis. [b] 36 h. [c] At 100 ˚C.

The effect of base was examined (Table 1-2-29) and 0.5 equiv of K_2CO_3 accelerated the oxidation reaction to give the excellent yield in THF/water media (entry 2). In toluene/water media or only water, K_2CO_3 worked well and the excellent yield was obtained (entries 3 and 4). The high yield was maintained when the amount of K_2CO_3

was decreased to 0.1 equiv (entry 5). It was noted that the moderate yield was obtained in the presence of K_2CO_3 at 30 ˚C (entry 6).

Table 1-2-29. Effect of base for aerobic oxidation of **8**

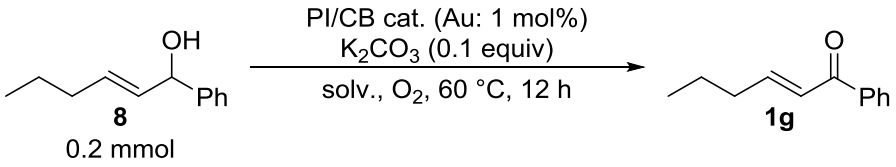


entry	X (equiv)	solv. (ml/ml)	conv. (%)[a]	yield **1g** (%)[a]
1	0	THF (0.18) / H_2O (0.02)	52	52
2	0.5	THF (0.18) / H_2O (0.02)	94	97
3	0.5	MePh (0.2) / H_2O (0.2)	99	97
4	0.5	H_2O (0.4)	96	91
5	0.1	MePh (0.2) / H_2O (0.2)	99	quant.
6[b]	0.5	MePh (0.2) / H_2O (0.2)	59	61

[a] Determined by GC analysis. [b] 30 ˚C.

Using the best conditions for the oxidation step in the presence of PI/CB Au **XII**, the catalytic activities of trimetallic catalysts were tested again (Table 1-2-30). In the case of Au/Rh/Ru **X**, the side reactions, such as isomerization to ketone **9**, occurred and the low yield of unsaturated ketone **1g** was obtained (entry 2). In the case of Au/Rh/Ag **XI**, the selectivity was improved and the lower catalytic activity was observed (entry 3).

Table 1-2-30. Aerobic oxidation of **8** catalyzed by trimetallic catalysts



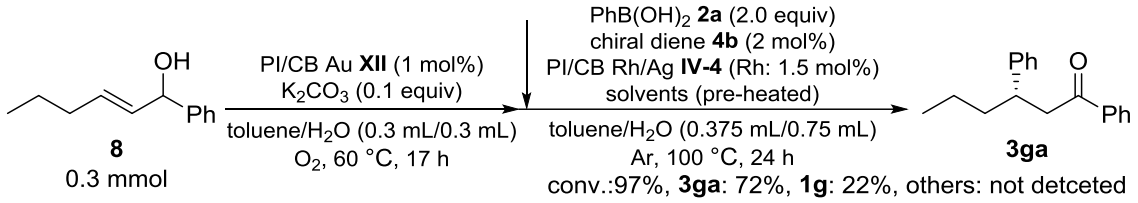
entry	cat.	X (equiv)	solv. (ml/ml)	conv. (%)[a]	yield **1g** (%)[a]
1	Au **XII**	0.1	MePh (0.2) / H_2O (0.2)	99	quant.
2	Au/Rh/Ru **X**	0.1	MePh (0.2) / H_2O (0.2)	97	24
3	Au/Rh/Ag **XI**	0.1	MePh (0.2) / H_2O (0.2)	68	58

[a] Determined by GC analysis.

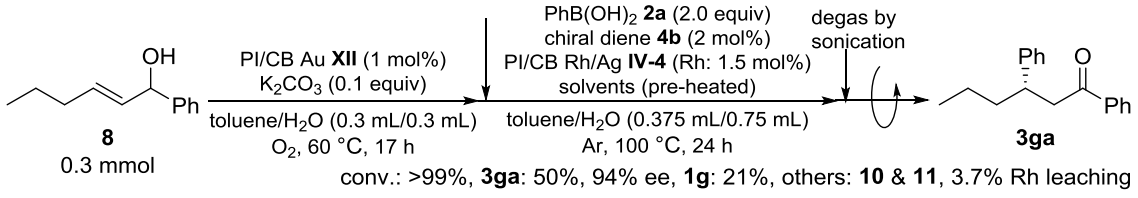
Given that, the one-pot process using two different catalysts was examined. The procedure was shown in Scheme 1-2-14; 1) allylic alcohol **8**, PI/CB Au **XII** and K_2CO_3

were combined in toluene/water co-solvent system and stirred under molecular oxygen atmosphere at 60 ˚C, 2) phenylboronic acid, chiral diene **4b**, PI/CB Rh/Ag **IV-4** and additional solvents were added and the reaction mixture was stirred at 100 ˚C under Ar atmosphere. The desired product was obtained in 72% yield and unsaturated ketone **1g** was recovered by this method. Though any other side products derived from starting material **8** were not detected, the small amount of biphenyl generated from the oxidative homocoupling reaction of phenylboronic acids was observed probably due to the remained molecular oxygen in the solvent. To prevent the generation of biphenyl, the reaction mixture was degased after the addition of whole reagents and the reaction was continued (Scheme 1-2-15). However, the desired product was obtained in the lower yield and 1,3-migrated by-product **10**, **11** generated by the 1,4-addition of phenyl group to **10** (Scheme 1-2-13) and biphenyl were observed. As it is important to keep high reaction temperature in the second step, the reaction mixture was cooled during degassing process and it might cause the decomposition of phenylboronic acid to benzene to give the lower yield of the product **3ga**. The former method (Scheme 1-2-14) was determined as the best procedure.

Scheme 1-2-14. One-pot oxidation/1,4-addition reaction (method 1)



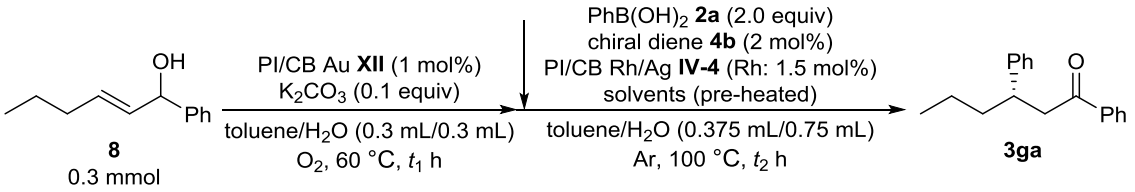
Scheme 1-2-15. One-pot oxidation/1,4-addition reaction (method 2)



Several reaction conditions were then examined (Table 1-2-31). The reason why the second reaction produced in the moderate yield might be the decomposition of all phenylboronic acid or chiral diene before full conversion of **1g** was achieved. To examine the latter possibility, the amount of the chiral diene was increased; however, no improvement was observed and the amount of the leaching was increased (entry 2). As the decomposition of chiral diene, if it occurred, might be caused by the reduction of double bond with Au-H spices, the reaction was conducted under air in order to remove Au-H spices by molecular oxygen (entry 3); however, no improvement was observed. These results may indicate that the possibility of the decomposition of chiral diene is not feasible reason of the moderate yield. When the amount of base (entry 4) or the amount of both base and the PI/CB Au **XII** (entry 5) were changed, the side product **10** and **11**

were somehow detected as a significant loss of starting materials although it had been confirmed that the aerobic oxidation could be accomplished without formation of olefin migrated product under this condition at 0.2 mmol scale (Table 1-2-29, entry 3). By the way, it was noted that the leaching was prevented when the amount of base was increased (entries 4 and 5).

Table 1-2-31. Optimization of the reaction conditions in the one-pot reaction



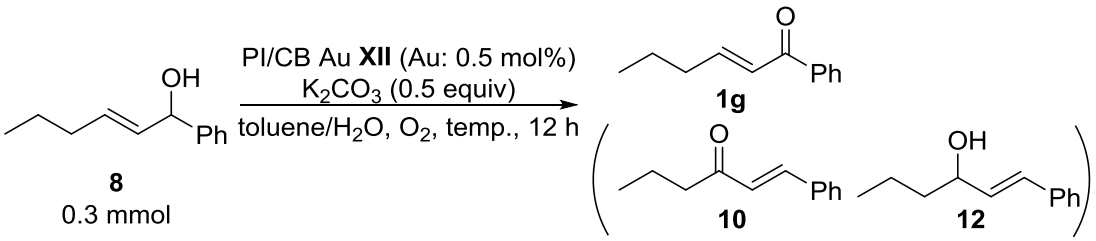
entry	t_1 (h)	t_2 (h)	conv. **8** (%)[a]	yield **3ga** (%)[b]	**1g** (%)[a]	**9** (%)[a]	**10** (%)[a]	**11** (%)[a]	ee (%)[c]	leaching (%)[d]
1	17	24	97	72	22	0	0	0	94	2.6
2[e]	18	16	98	65	24	0	0	0	95	4.0
3[f]	16	18	>99	~40	trace	0	+	+	-	1.5
4[g]	16	18	97	25	51	trace	+	trace	94	ND
5[g,h]	16	18	>99	49	12	0	+	24	94	ND

ND = under detection limit (<0.2%). "-" = Not measured. "+" = detected. [a] Determined by GC analysis. [b] Calculated from the amount of isolated product from 70% amount of the reaction mixture. [c] Determined by HPLC analysis. [d] Determined by ICP analysis with 30% amount of the reaction mixture. [e] Diene **4b** (3 mol%) was used. [f] Second step was conducted under air. [g] K_2CO_3 (0.5 equiv) was used. [h] PI/CB Au **XII** (0.5 mol%) was used.

Thus, the reproducibility of the oxidation step was confirmed in 0.3 mmol scale (Table 1-2-32). 1,3-Migrated product **10** was obtained under the same optimized condition at 60 ˚C with 0.5 or 0.25 mol% of the catalyst (entries 2 and 3). 1,3-Migrated allylic alcohol **12** was also generated when the reaction was conducted under Ar atmosphere (entry 4). The side products were observed in the reaction conducted at 30 ˚C (entries 6 and 7) while any reactions hardly occurred in the absence of the base or the catalyst at 30 ˚C (entries 8 and 9). As the reaction proceeded slowly at 30 ℃, the same control experiments were conducted at 60 ˚C. The side products were observed even in the absence of the base or the catalyst at 60 ˚C (entries 10 and 11) and finally, it was confirmed that the side reactions occurred as background reactions at 60 ˚C (entry 12) while they did not occur at 30 ˚C in the absence of the catalyst and the base (entry 13). It was noted that in the absence of water, the side reactions were suppressed (entry 14) while the side reactions were promoted in the absence of the organic solvent (entry 15). These results indicated that the amount of water might be

essential for the side reactions and the amounts of solvents were examined to prevent the side reactions (entries 16-20). In the absence of water, the oxidation reaction proceeded very slowly and the significant amount of starting material was lost (entry 17). Finally, the desired product was obtained in high yield and good reproducibility was confirmed when the 2:1 ratio of toluene and water were used (entries 18 and 18-2).

Table 1-2-32. Aerobic oxidation of **8** to obtain good reproducibility

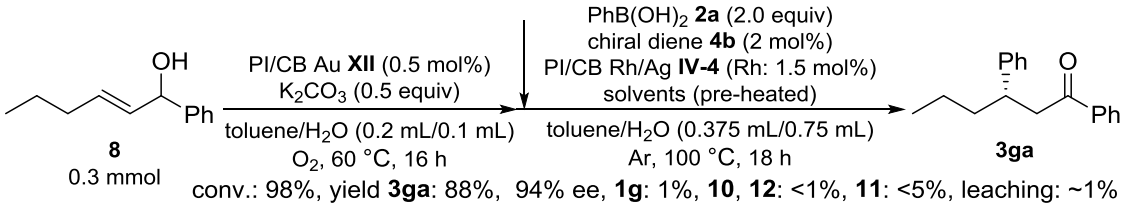


entry	Au	K_2CO_3	temp. (℃)	toluene (ml)	H_2O (ml)	conv. (%)[a]	yield **1g** (%)[a]	**10** (%)[a]	**12** (%)[a]
1[c]	+	+	60	0.2	0.2	99	97	0	0
2	+	+	60	0.3	0.3	>99	54	38	0
3	+[d]	+	60	0.3	0.3	92	36	36	0
4[e]	+	+	60	0.3	0.3	86	12	detected	53[f]
5[c]	+	+	30	0.2	0.2	59	61	0	0
6	+	+	30	0.15	0.15	52	27	detected	detected
7	+	+	30	0.15	0.3	61	29	detected	detected
8	+	−	30	0.3	0.3	17	6	0	0
9	−	+	30	0.3	0.3	4	0	0	0
10	+	−	60	0.3	0.3	>99	5	78	1
11	−	+	60	0.3	0.3	36	0	0	36
12	−	−	60	0.3	0.3	15	0	0	15
13	−	−	30	0.3	0.3	4	0	0	0
14	−	−	60	0.3	-	35	trace	0	<5
15	−	−	60	-	0.3	52	0	0	33
16	+	+	60	0.15	0.15	>99	92	detected	0
17	+	+	60	0.3	-	50	6	trace	trace
18	+	+	60	0.2	0.1	99	95	trace	0
18-2	+	+	60	0.2	0.1	96	91	trace	0
19	+	+	60	0.25	0.05	95	70	detected	0
20	+	+	60	0.27	0.03	30	22	0	0

[a] Determined by GC analysis. [b] 30 ˚C. [c] 0.2 mmol scale (previous data). [d] 0.25 mol%.
[e] Reaction was conducted under Ar atmosphere. [f] Isolated yield.

The revised best conditions for the oxidation reaction was applied to the one-pot reaction and the desired product was finally obtained in high yield and excellent enantioselectivity (Scheme 1-2-16).

Scheme 1-2-16. One-pot reaction in the best conditions



I attempted to expand the application of PI/CB Rh/Ag system for other tandem reactions and examined one-pot esterification/asymmetric 1,4-addtion (Scheme 1-2-17). First of all, each step was examined individually. The asymmetric 1,4-addition reaction of methyl 2-hexenoate **13** was carried out under the optimized conditions for the asymmetric 1,4-addition of acyclic unsaturated ketones (Table 1-2-33). The desired product was obtained in high yield without the leaching of Rh by using PI/CB Rh/Ag **IV-2** or Rh/Ag **IV-4**; however, low enantioselectivity was observed. When chiral diene **4b** was used instead of **4b**, the enantioselectivity was improved and the yield dropped (Scheme 1-2-18). The dehydrogenated product **15** and the saturated ester **16** were also obtained as byproducts.

Scheme 1-2-17. Concept of tandem esterification/asymmetric 1,4-addtion

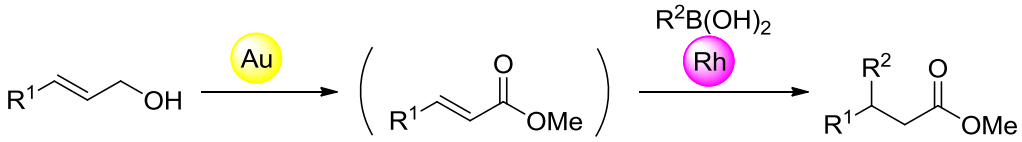
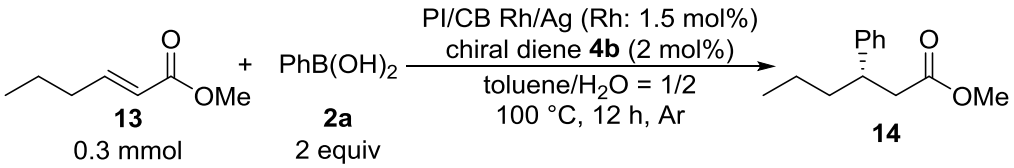


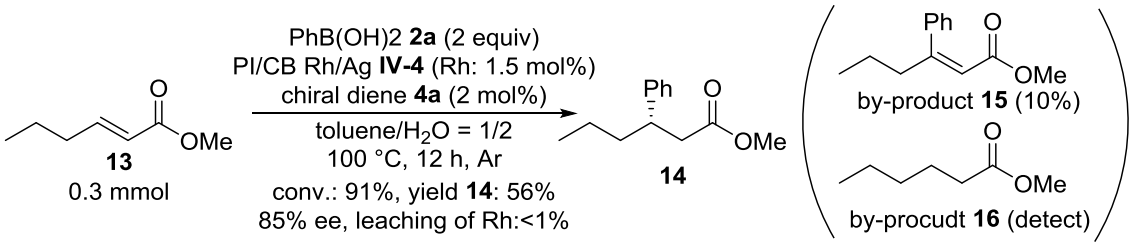
Table 1-2-33. Asymmetric 1,4-addition to unsaturated ester **13**



entry	cat.	conv. (%)[a]	yield (%)[b]	ee (%)[c]	Rh leaching (%)[d]
1	Rh/Ag **IV-2**	87	80	66	ND
2	Rh/Ag **IV-4**	91	87	66	ND

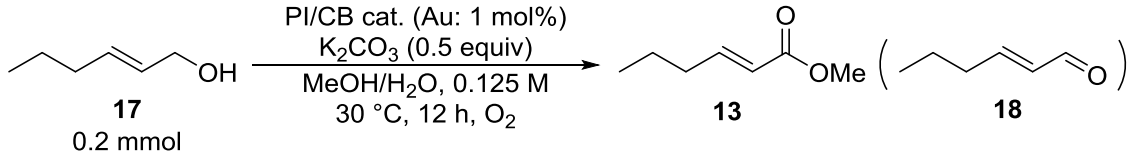
[a] Determined by GC analysis. [b] The yield was calculated from the amount of isolated product from 70% amount of the reaction mixture. [c] Determined by HPLC analysis. [d] Determined by ICP analysis from 30% amount of the reaction mixture.

Scheme 1-2-18. Asymmetric 1,4-addition to unsaturated ester **13** with ligand **4a**



The first step, methyl esterification of 2-hexenol **17**, was also examined (Table 1-2-34). The ester was hardly obtained under the previously reported conditions (entries 1 and 2).[10c] The bimetallic catalysts and high temperature could not afford the desired ester (entries 3-7), in spite of high conversion. No major side products were detected except 2-hexenal **18** by GC analyses.

Table 1-2-34. Methyl esterification of unsaturated alcohol **17**

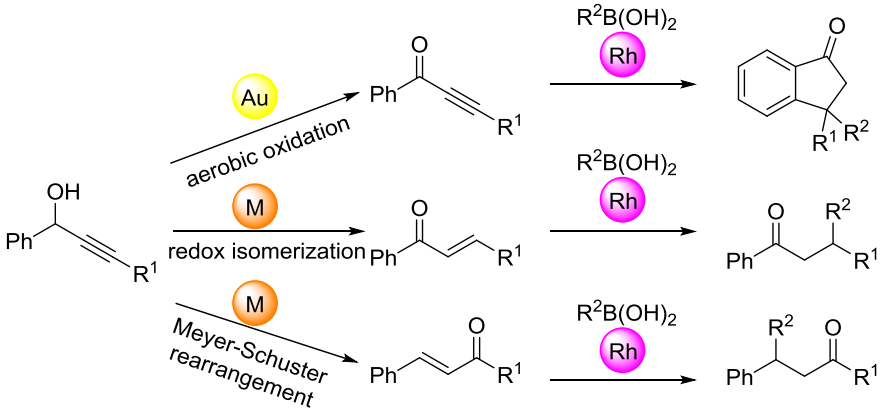


entry	cat.	solv. (MeOH:H_2O)	conv. (%)[a]	yield **13** (%)[a]	**18** (%)[a]
1	Au **XII**	500:1	-	0	0
2	Au **XII**	1:1	-	3	0
3	Au/Pt **XIV**	1:1	68	0	12
4	Au/Pd **XIII**	1:1	>99	0	11
5	Au/Ru **XX**	1:1	29	0	0
6[b]	Au **XII**	MeOH only	48	trace	1
7[b]	Au **XII**	1:1	95	2	6

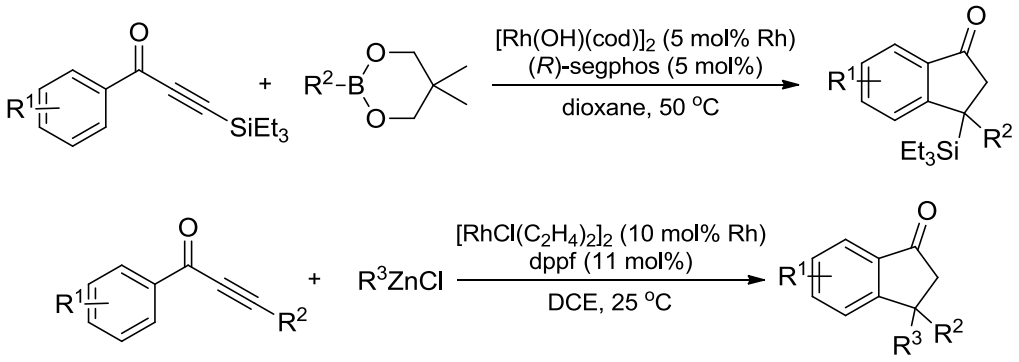
[a] Determined by GC analysis. [b] The reaction was conducted at 60 ˚C

Propargyl alcohol is also good candidate as a starting material for tandem reaction involving Rh catalyzed asymmetric 1,4-addition reaction (Scheme 1-2-19). Hayashi reported that indanone derivatives can be obtained from ynone via sequential 1,4-addition, 1,4-hydrogen shift and intramolecular 1,4-addition (Scheme 1-2-20).[76] Alternatively, redox isomerization[77] or Meyer-Schuster rearrangement[77c,78] convert propargyl alcohols to unsaturated ketones that can be further transformed to arylated product by asymmetric 1,4-addition reaction in one-pot process. Inspired by these reports, firstly the tandem oxidation/indanone formation reaction was examined.

Scheme 1-2-19. Concept of tandem reaction from propargyl alcohol

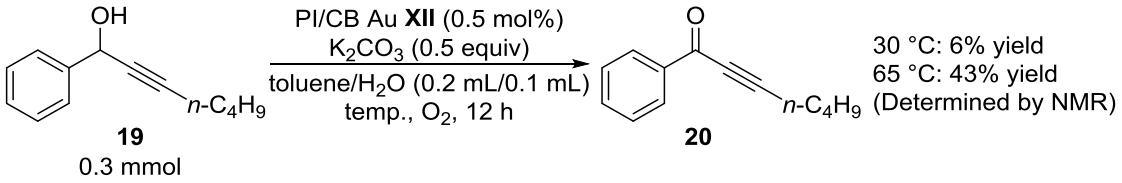


Scheme 1-2-20. Examples of Rh catalyzed indanone synthesis from ynone



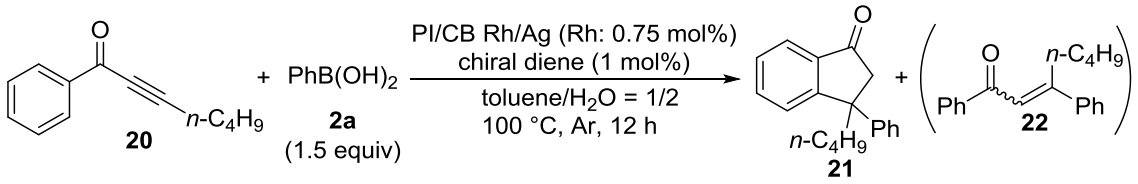
The first oxidation step was examined in the presence of PI/CB Au **XII** under the optimized conditions for the oxidation of allylic alcohol in toluene/water solvent system (Scheme 1-2-21). The reaction proceeded slowly and the low or moderate yield was observed at 30 or 65 ˚C after 12 h respectively. The results suggested that the strong interaction between triple bond and gold nanoparticles delayed the reaction.

Scheme 1-2-21. Aerobic oxidation of propargyl alcohol **19** to ynone **20**



The second step was examined from ynone **20** with several catalysts and ligands (Table 1-2-35). However, only first 1,4-addition occurred with poor *E*/*Z* selectivity and the significant amount of Rh leaching was observed in all cases.

Table 1-2-35. Examination of indanone synthesis in PI/CB Rh/Ag system

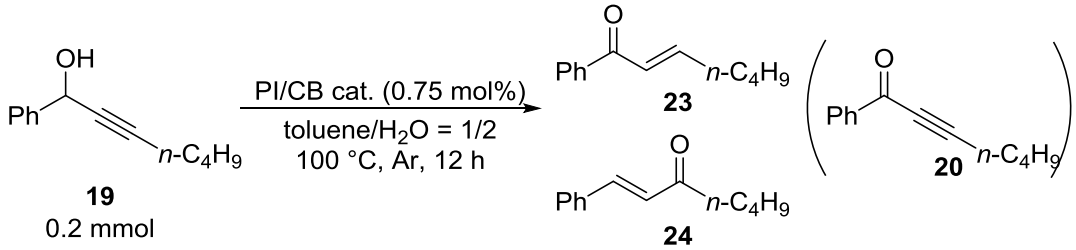


entry	cat.	diene	conv. (%)[a]	yield **21** (%)[a]	(*E*)-**22** (%)[a]	(*Z*)-**22** (%)[a]	Rh leaching (%)[b]
1	Rh/Ag **IV-2**	**4b**	44	0	19	22	18.5
2	Rh/Ag **IV-4**	**4b**	<10	0	5	7	4.6
3	Rh/Ag **IV-4**	**4a**	<10	0	4	5	3.3

[a] Determined by NMR analysis. [b] Determined by ICP analysis from 30% amount of the reaction mixture.

As the step of 1,4-addition to ynone seems to be difficult at this stage, I examined the second or third strategy of the tandem reaction from propargyl alcohol (Table 1-2-36). At this stage, either isomerized product **23** or Meyer-Schuster rearrangement adduct **24** is desirable if they can be obtained selectively. While Rh or bimetallic catalysts including Rh could not convert **19** to any other products (entries 2-4), PI/CB Au **XII** gave Meyer-Schuster rearrangement adduct **24** without generation of **23** (entries 5-6). Though this reaction was conducted under Ar atmosphere, the oxidized product **20** was also obtained.

Table 1-2-36. Reaction with propargyl alcohol



entry	cat.	conv. (%)[a]	yield **23** (%)[a]	yield **24** (%)[a]	**20** (%)[a]
1	none	~0	-	-	-
2	Rh/Ag **IV-2**	~0	-	-	-
3	Rh/Ru **III-3**	~0	-	-	-
4	Rh/Pd **IV-2**	~0	-	-	-
5	Au **XII**	28	0	7	11
6[b]	Au **XII**	12	0	12	6

[a] Determined by NMR analysis. [b] 10 mol% of *p*-toluic acid was added.

Section 3: Conclusion

In this chapter chiral ligand modified Rh nanoparticle catalysts (chiral Rh nanoparticle catalyst systems) were developed and asymmetric 1,4-addition of arylboronic acids to enones were investigated. A choice of chiral ligand is crucial to suppress the leaching of metal and chiral dienes are found to be the best ligands in terms of reactivity, enantioselectivity and prevention of the leaching. Dopant of Ag enhanced the catalytic activity and STEM analyses and EDS mappings revealed that Ag affected the structure of Rh nanoparticles by formation of alloy nanoparticles. Wide substrate generality including various arylboronic acids and acyclic enones was demonstrated with high yields and excellent enantioselectivities without the leaching. The catalyst could be easily recovered and reused for several cycles without loss of catalytic activity and it was found that simple heating process revived the activity of the deactivated catalyst. Moreover, an one-pot aerobic oxidation/asymmetric 1,4-addition reaction from an allylic alcohol and an arylboronic acid was achieved by combination of PI/CB Au **XII** and PI/CB Rh/Ag **IV-4**. Highly active and robust chiral diene modified heterogeneous nanoparticles systems developed here clearly showed a great potential of heterogeneous chiral metal nanoparticle catalysts.

Chapter 2: Development of bifunctional chiral Rh nanoparticle catalysts

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 3: Development of biomass derived polymer supported chiral nanoparticle catalysts

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。

Experimental section

General

- Melting point was determined on a standard melting point apparatus and is uncorrected.
- JEOL JMN-LA400, 500 or 600 spectrometers were used for NMR measurement. Chloroform (δ = 7.24) was used as an internal standard for ^{1}H NMR and $CDCl_3$ (δ = 77.0) for ^{13}C NMR. Structures of known compounds were confirmed by comparison with commercially available compounds or data shown in literature.
- IR spectra were measured on a JASCO FT/IR-610 spectrometer.
- Specific rotations were recorded with JASCO P-1010 or P-2100.
- Preparative thin-layer chromatography was carried out using Wakogel B-5F.
- ICP analysis was performed on Shimadzu ICPS-7510 equipment.
- GC analysis was performed on Shimadzu GC-2010 apparatus (**Condition A :** Column = GL Science, TCWAX, 0.25 mm ID, 0.25 μm, 60.0 m; Gas pressure: 214.2 kPa; Total flow: 90.6 mL/min; Column flow: 1.86 mL/min; Velocity: 30.8 cm/sec; Purge flow: 3.0 mL/min; Sprit ratio: 46.0; Injector: 250 ˚C, FID: 250 ˚C; Column program: starting from 50.0 ˚C, 10 min hold, 10 ˚C/min to 220 ˚C, 15 min hold) (**Condition B :** column = J & W SCIENTIFIC DB-1 0.25 mm ID, 0.25 μm, 60.0 m; Gas pressure: 157.5 kPa, Total flow: 41.3 mL/min, Column folw: 0.93 mL/min, Velocity: 21.1 cm/sec; Purge flow: 3.0 mL/min; Sprit ratio: 40.1; Injector: 300 ˚C, FID: 300 ˚C; Column program: starting from 100 ˚C, 10 ˚C/min to 300 ˚C, 10 min hold).
- HPLC analysis was performed on Shimadu LC-20AB, SPD-M20A and $DGU\text{-}20A_3$.
- The absolute configuration of reported compounds was determined by comparison to literature and that of other products was assumed by analogy.
- STEM/EDS images were obtained using a JEOL JEM-2100F instrument operated at 200 kV. All STEM specimens were prepared by placing a drop of the solution on carbon-coated Cu grids and allowed to dry in air (without staining).
- $Rh_2(OAc)_4$ was purchased from Strem Chemical Inc.
- $[Rh(C_2H_4)_2Cl]_2$ was purchased from Wako Pure Chemical Company.
- $AgSbF_6$ complex was purchased from Sigma-Aldrich Co., Ltd..
- Other Au, Rh, Ru, Pt and Pd complexes were purchased from Strem Chemical Inc.
- Rhodium 5% on Carbon (Rh/C) was purchased from Tokyo Kasei Kogyo Co., Ltd..
- $NaBH_4$ was purchased from Wako Pure Chemical Company and recrystallized from diglyme by heating according to the literature and stored in a glove box.[126] It is important to manipulate all operations under Ar atmosphere during recrystallization.
- Ketjen black EC300J was purchased from Lion Corporation. SEM images of Ketjen black EC300J was described in W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am.*

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- Toluene was purchased in dried grade from Wako Pure Chemical Company and used without further purification.
- Deionized water from a MILLIPORE MilliQ machine (Gradient A 10) was used as solvent without further treatment.
- Other solvents were purchased in dried grade from Wako Pure Chemical Company and used without further purification.
- Enones were purchased from Tokyo Kasei Kogyo Co., Ltd..
- Aliphatic unsaturated esters and cinnamate were purchased from Tokyo Kasei Kogyo Co., Ltd..
- Aryl unsaturated esters except cinnamate were prepared by following the literature.[127]
- Arylboronic acids were purchased from Wako Pure Chemical Company or prepared from the corresponding Grignard reagent. The ratio of boronic acid to boroxine was determined by ^{1}H NMR analysis before use.
- Chiral diene **4a**, **4c**, **4f**, and **S1**were prepared by following the literatures.[70a]
- Chiral diene **4b** and **4i** were prepared by following the literatures.[70b]
- Asymmetric 1,4-addition reactions and other reactions in small scale (<1 mmol scale) were conducted with Carousel^{TM}.
- Cellulose, Powder, through 38μm (400mesh) was purchased from Wako Pure Chemical Company and dried *in vacuo* by heating with a heat gun before use.
- Amylopectin Hydrate (Amylose free), from Waxy Corn was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as received.
- Unless otherwise stated, all reactions were carried out under argon atmosphere.
- 0.45 μm PTFE membrane filter (Whatman^{TM} cat. No. 6784-2504) was used for filtration of solid catalysts.

Chapter 1

Section 2

1-2-1. Preparation of PI/CB catalysts[10g,15]

1-2-1-1. Preparation of 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol: To sodium hydride (60% in mineral oil, 5.7 g) suspended in THF (150 mL), tetraethyleneglycol (22.5 g) was added at 0 ˚C. After the reaction mixture was stirred for 20 min at room temperature, 1-(chloromethyl)-4-vinylbenzene (13.3 g) was added and the mixture was further stirred for 2 h. The mixture was cooled to 0 ˚C and diluted with diethyl ether. Saturated aqueous ammonium chloride was added to quench the reaction and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol ether (21.6 g, 80%). ^{1}H NMR ($CDCl_3$) δ = 2.55-2.59 (m, 1H), 3.59-3.73 (m, 16H), 4.55 (s, 2H), 5.25 (d, 1H, *J* = 6.4 Hz), 5.53 (d, 1H, *J* = 18 Hz), 6.71 (dd, 1H, *J* = 11.0, 17.9 Hz), 7.22-7.27 (m, 3H), 7.31-7.39 (m, 2H); ^{13}C NMR δ = 61.8, 69.5, 70.5, 70.69, 70.74, 72.6, 73.0, 113.8, 126.3, 128.0, 136.0, 137.1, 138.0.

1-2-1-2. Preparation of 4-Vinylbenzyl glycidyl ether: To sodium hydride (60% in mineral oil, 4.0 g) suspended in DMF (200 mL), glycidol (6.6 mL) was added at 0 ˚C. After the reaction mixture was stirred for 1 h at 0 ˚C, 1-(chloromethyl)-4-vinylbenzene (7 mL) was added and the mixture was further stirred for 5 h at room temperature. The mixture was cooled to 0 ˚C and diluted with diethyl ether. Saturated aqueous ammonium chloride was added to quench the reaction and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography to afford 4-vinylbenzyl glycidyl ether (7.0 g, 74%). ^{1}H NMR ($CDCl_3$) δ = 2.60 (dd, 1H, *J* = 2.8, 4.8 Hz), 2.78 (dd, 1H, *J* = 4.0, 4.8 Hz), 3.17 (m, 1H), 3.42 (dd, 1H, *J* = 5.6, 11.2 Hz), 3.74 (dd, 1H, *J* = 2.8, 11.2 Hz), 4.56 (dd, 2H, *J* = 10.8, 17.6 Hz), 5.22 (t, 1H, *J* = 10.3 Hz), 5.74 (t, 1H, *J* = 15.5 Hz), 6.66-6.72 (m, 1H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.39 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ = 40.2, 50.7, 70.7, 72.9, 113.8, 126.2, 127.9, 136.4, 137.0, 137.4.

1-2-1-3. Preparation of Copolymer: Styrene (2.1 g), 4-vinylbenzyl glycidyl ether (4.1 g), 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol (6.0 g) and 2, 2'-azobis(4-methoxy)-2,4-dimethylvaleronitrile (V-70, 181.2 mg) were combined in chloroform (11.0 mL). The mixture was stirred for 48 h at room temperature. The resulting polymer solution was slowly poured into ether. Solvent was removed by decantation and remaining precipitated polymers were washed with ether several times.

Polymers were dissolved in THF, repeated to precipitate for 2 times and dried *in vacuo* to afford the desired copolymer (6.86 g, 56 % yield). The molar ratio of the components was determined by ^{1}H NMR analysis (*x: y: z* = 29: 35: 36).

1-2-1-4. Preparation of PI/CB Rh I-1 (Scheme 1-2-1): Copolymer (100.0 mg), ketjen black EC300J (100.0 mg) and $NaBH_4$ (10.6 mg, 0.28 mmol) were combined in diglyme (6 mL) at room temperature. To this solution was slowly added the solution of chlorotris(triphenylphosphine)rhodium(I) (51.8 mg, 0.056 mmol) in THF (2 mL). The mixture was stirred overnight under air at room temperature and diethyl ether (50 mL) was slowly added to the mixture at room temperature. After the catalysts, which were black powders, were filtered and ground, they were washed with diethyl ether several times and dried *in vacuo*. The catalysts were heated at 150 ˚C for 5 h without solvent and were stirred in 1:1 ratio of THF/water co-solvent overnight. The catalysts were filtered, washed with water, THF and dichloromethane and dried *in vacuo* to afford black powder. This powder was heated at 170 ˚C for 5 h without solvent to afford PI/CB Rh **I-1**. PI/CB Rh **I-1** (10-20 mg) was heated in the mixture of sulfuric acid and nitric acid at 200 ˚C, and the mixture was cooled to room temperature. The amount of Rh in the resulting solution was measured by ICP analysis to determine the loading of Rh.

1-2-1-5. Preparation of other PI/CB bimetallic catalysts (Table 1-2-3): The procedures for the preparation of each catalyst were same as the procedure shown in **1-2-1-4**. The metal precursors were listed in Table 1-2-3 and dissolved in an appropriate amount of THF. In all cases, 0.04 mmol of each metal was used for 200 mg scale (target loading = 0.2 mmol/g).

1-2-1-6. Reduction treatment of PI/CB catalysts (Scheme 1-2-6): To the solution of $NaBH_4$ (13.4 mg, 0.355mmol) in diglyme (3 mL), PI/CB catalyst (100 mg, 0.0355 mmol of metals contained) was added and the mixture was stirred for 6 h at 30 ˚C. The catalysts were filtered, washed with water, THF and dichloromethane and dried *in vacuo*.

1-2-1-7. Preparation of PI/CB Rh/Ag IV-2 with "second reduction" (Table 1-2-7, entries 3-5): Copolymer (500.0 mg), ketjen black EC300J (500.0 mg) and $NaBH_4$ (113.5 mg, 3.0 mmol) were combined in diglyme (30 mL) at room temperature and the mixture was stirred for several minutes. To this solution was slowly added the solution of rhodium(II) acetate dimer (44.2 mg, 0.1 mmol) and silver hexafluoroantimonate (68.7 mg, 0.2 mmol) in THF (~20 mL). The mixture was stirred under air for 6 h or overnight at room temperature and diethyl ether (200 mL) was slowly added to the mixture at room temperature. After the catalysts, which were black powders, were filtered and ground, they were washed with diethyl ether several times and dried *in vacuo* at room temperature. The catalysts were heated at 150 ˚C for 5 h without solvent.

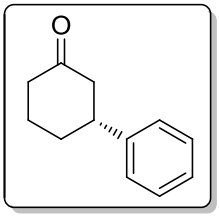
The catalysts were transferred to the solution of $NaBH_4$ (113.5 mg, 3.0 mmol) in diglyme (30 mL) and this suspension was stirred under air at room temperature for 6 h. The catalysts were filtered and stirred in 1:1 ratio of THF/water co-solvent overnight. The catalysts were filtered, washed with water, THF and dichloromethane and dried *in vacuo* to afford black powder. This powder was heated at 170 ˚C for 5 h without solvent to afford PI/CB Rh/Ag **IV-2**. PI/CB Rh/Ag **IV-2** (10-20 mg) was heated in the mixture of sulfuric acid and nitric acid at 200 ˚C and the mixture was cooled to room temperature. The amount of each metal in the resulting solution was measured by ICP analysis to determine the loading of each metal.

1-2-1-8. Preparation of other PI/CB multi metallic catalysts with "second reduction" (Table 1-2-9 and 1-2-12): The procedures for the preparation of each catalyst were same as the procedure shown in **1-2-17**. The metal precursors were listed in Table 1-2-3 and dissolved in an appropriate amount of THF. In all cases, $[Rh(OAc)_2]_2$ was used as Rh precursor and 0.04 mmol of each metal was used for 200 mg scale (target loading = 0.2 mmol/g).

1-2-2. Asymmetric 1,4-addition reactions catalyzed by PI/CB catalyst

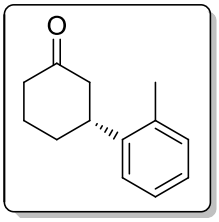
1-2-2-1. A typical procedure of asymmetric 1,4-addition of arylboronic acids to enones catalyzed by PI/CB catalyst (for example, Table 1-2-8): 2-Cyclohexenone (28.8 mg, 0.3 mmol), phenylboronic acid (54.9 mg, 0.45 mmol), PI/CB Rh/Ag **IV-2** (Rh: 0.75 mol%) and chiral diene **4b** (0.03 mL of 22.0 mg/mL solution of toluene) were combined in Carousel^{TM} tube and toluene (0.345 mL) and water (0.75 mL), which were pre-heated at 100 ˚C, were added to the mixture. After the mixture was stirred for 7 h under Ar atmosphere at 100 ˚C, ethylbenzene (15~20 mg) as an internal standard and THF were added to the mixture. The mixture was picked up with a syringe and transferred to a volumetric flask through a membrane filter in order to remove the residual solids and diluted to 10 mL solution by THF. The filtrate (3 mL) was taken by a volumetric pipette and the solvent was removed *in vacuo*. The residual crude mixture was heated in the mixture of sulfuric acid (1 mL) and nitric acid at 200 ˚C until all nitric acid was evaporated, the mixture was cooled to room temperature and aqua regia (1 mL) was added. The solution was diluted to 50 mL solution by pure water and the resulting solution was measured by ICP analysis to determine the amount of Rh that leached out. Another filtrate (7 mL) and water were transferred to a separating funnel and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and the conversion of 2-cyclohexenone and the yield of 3-phenylcyclohexanone were determined by GC analysis with reference to an internal standard (IS = ethylbenzene). After sodium sulfate was filtered, the solvent was removed *in vacuo* and the residue was purified by preparative TLC to afford 3-phenylcyclohexanone (**3aa**). The ee value of the product was determined by chiral HPLC analysis.

(*R*)-3-phenylcyclohexanone (3aa)[128]:



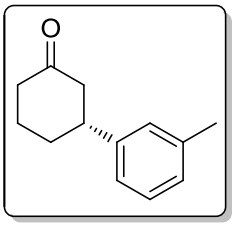
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.72-1.87 (m, 2H), 2.06-2.16 (m, 2H), 2.33-2.60 (m, 4H), 2.99 (tt, 1H, *J* = 12.0, 3.9 Hz), 7.20-7.23 (m, 3H), 7.31 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.4, 32.6, 41.0, 44.6, 48.8, 126.4, 126.5, 128.5, 144.2, 210.9. The ee value of the product was determined on Daicel Chiralpak AD column with hexane/2-propanol = 49/1, flow = 0.5 mL/min by HPLC analysis. Retention times: 18.8min [(*S*)-enantiomer], 23.0 min [(*R*)-enantiomer], 98% ee.

(*R*)-3-(*o*-tolyl)cyclohexanone (3ab)[129]:



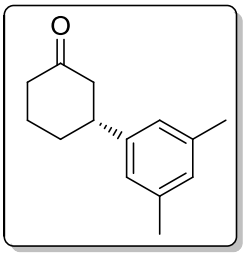
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.74-1.86 (m, 2H), 1.98-2.00 (m, 1H), 2.14-2.18 (m, 1H), 2.31 (s, 3H), 2.36-2.52 (m, 4H), 3.17-.322 (m, 1H), 7.10-7.15 (m, 2H), 7.18-7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 19.2, 25.8, 32.0, 40.3, 41.3, 48.3, 125.1, 126.38, 126.43, 130.6, 135.1, 142.3, 211.1. The ee value of the product was determined on Daicel Chiralpak AD-3 column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 17.7 min [(*S*)-enantiomer], 21.3 min [(*R*)-enantiomer], 96% ee.

(*R*)-3-(*m*-tolyl)cyclohexanone (3ac)[129]:



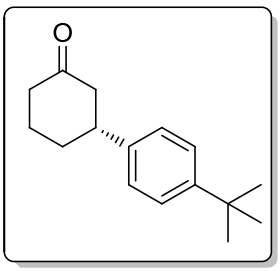
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.71-1.86 (m, 2H), 2.04-2.07 (m, 1H), 2.11-2.16 (m, 1H), 2.33 (s, 3H), 2.31-2.58 (m, 4H), 2.95 (tt, 1H, *J* = 12.0, 4.0 Hz), 6.99-7.04 (m, 3H), 7.20 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ =21.4, 25.5, 32.8, 41.2, 44.7, 48.9, 123.5, 127.3, 127.4, 128.5, 138.2, 144.3, 211.1. The ee value of the product was determined on Daicel Chiralpak AS-H column with hexane/2-propanol = 49:1, flow = 1.0 mL/min by HPLC analysis. Retention times: 24.5 min [(*S*)-enantiomer], 29.5 min [(*R*)-enantiomer], 96% ee.

(*R*)-3-(3,5-dimethylphenyl)cyclohexanone (3ad)[129]:



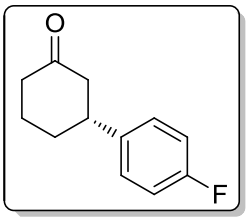
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.73-1.85 (m, 2H), 2.02-2.15 (m, 2H), 2.29 (s, 6H), 2.32-2.57 (m, 4H), 2.91 (tt, 1H, *J* = 12.0, 3.8 Hz), 6.82 (s, 2H), 6.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.3, 25.6, 32.9, 41.2, 44.7, 49.0, 124.4, 128.3, 138.2, 144.4, 211.1. The ee value of the product was determined on Daicel Chiralpak OD-H column with hexane/2-propanol = 99:1, flow = 1.0 mL/min by HPLC analysis. Retention times: 11.0 min [(*R*)-enantiomer], 18.6 min [(*S*)-enantiomer], 97% ee.

(*R*)-3-(4-(tert-butyl)phenyl)cyclohexanone (3ae)[130]:



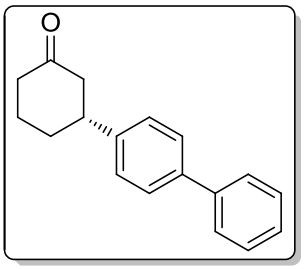
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.30 (s, 9H), 1.73-1.86 (m, 2H), 2.03-2.15 (m, 2H), 2.33-2.59 (m, 4H), 2.97 (tt, 1H, *J* = 12.0, 3.8 Hz), 7.13 (d, 2H, *J* = 8.2 Hz), 7.33 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.5, 31.3, 32.8, 34.4, 41.2, 44.2, 49.0, 125.5, 126.2, 141.3, 149.4, 211.2. The ee value of the product was determined on Daicel Chiralpak AS-H column with hexane/2-propanol = 49:1, flow = 1.0 mL/min by HPLC analysis. Retention times: 21.1 min [(*S*)-enantiomer], 25.9 min [(*R*)-enantiomer], 97% ee.

(*R*)-3-(4-fluorophenyl)cyclohexanone (3af)[130]:



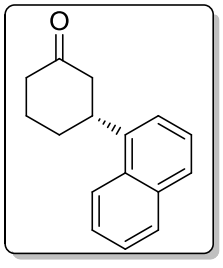
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.72-1.83 (m, 2H), 2.04-2.15 (m, 2H), 2.32-2.57 (m, 4H), 2.98 (tt, 1H, *J* = 11.7, 3.8 Hz), 6.97-7.01 (m, 2H), 7.15-7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.4, 32.9, 41.1, 44.0, 49.0, 115.4 (d, 2C, *J* = 20.2 Hz), 128.0 (d, 2C, *J* = 7.2 Hz), 140.0 (d, 1C, *J* = 3.3 Hz), 161.5 (d, 1C, *J* = 244 Hz), 210.6. The ee value of the product was determined on Daicel Chiralpak AS-H column with hexane/2-propanol = 49:1, flow = 1.0 mL/min by HPLC analysis. Retention times: 28.9 min [(*S*)-enantiomer], 31.9 min [(*R*)-enantiomer], 98% ee.

(*R*)-3-([1,1'-biphenyl]-4-yl)cyclohexanone (3ag)[129]:



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.77-1.91 (m, 2H), 2.10-2.19 (m, 2H), 2.36-2.64 (m, 4H), 3.05 (tt, 1H, *J* = 12.0, 3.9 Hz), 7.28 (d, 2H, *J* = 8.2 Hz), 7.33 (t, 1H, *J* = 7.2 Hz), 7.42 (t, 2H, *J* = 7.6 Hz), 7.54-7.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.5, 32.8, 41.2, 44.4, 48.9, 127.0, 127.2, 127.4, 128.7, 139.7, 140.7, 143.4, 210.9. The ee value of the product was determined on Daicel Chiralpak AS-H column with hexane/2-propanol = 49:1, flow = 1.0 mL/min by HPLC analysis. Retention times: 32.9 min [(*S*)-enantiomer], 54.0 min [(*R*)-enantiomer], 98% ee.

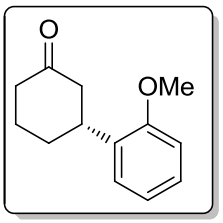
(*R*)-3-(naphthalen-1-yl)cyclohexanone (3ah)[129]:



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.89-2.03 (m, 2H), 2.17-2.22 (m, 2H), 2.42-2.76 (m, 4H), 3.84 (tt, 1H, *J* = 11.3, 3.6 Hz)), 7.38 (d, 1H, *J* = 7.6 Hz), 7.44-7.53 (m, 3H), 7.74 (d, 1H, *J* = 8.2 Hz), 7.86 (t, 1H, *J* = 8.2 Hz), 8.02 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ =25.6, 32.3, 39.4, 41.4, 48.6, 122.4, 122.7, 125.5, 125.6, 126.2, 127.2, 129.0, 130.9, 133.95, 140.02, 211.2. The ee value of the product was determined on Daicel Chiralpak AS-H column with

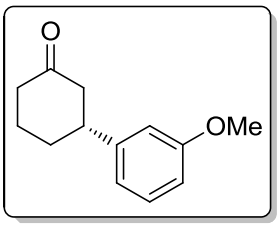
hexane/2-propanol = 49:1, flow = 1.0 mL/min by HPLC analysis. Retention times: 19.4 min [(*S*)-enantiomer], 34.9 min [(*R*)-enantiomer], 95% ee.

(*R*)-3-(2-methoxyphenyl)cyclohexanone (3ai)[129]:



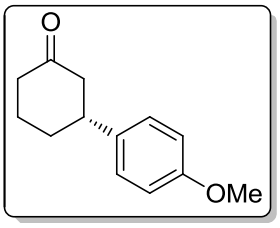
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.75-1.89 (m, 2H), 1.98-2.13 (m, 2H), 2.32-2.58 (m, 4H), 3.40 (tt, 1H, *J* = 11.9, 3.8 Hz), 3.80 (s, 3H), 6.85 (d, 1H, *J* = 7.9 Hz), 6.93 (td, 1H, *J* = 7.4, 1.1 Hz), 7.16-7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.6, 31.0, 37.9, 41.4, 47.5, 55.2, 110.5, 120.6, 126.5, 127.5, 132.5, 156.7, 211.7. The ee value of the product was determined on Daicel Chiralpak AD-H column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 20.4 min [(*S*)-enantiomer], 22.4 min [(*R*)-enantiomer], 93% ee.

(*R*)-3-(3-methoxyphenyl)cyclohexanone (3aj)[131]:



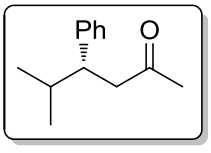
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.73-1.84 (m, 2H), 2.05-2.16 (m, 2H), 2.32-2.59 (m, 4H), 2.96 (tt, 1H, *J* = 11.7, 3.8 Hz), 3.79 (s, 3H), 6.75-6.77 (m, 2H), 6.79 (d, 1H, *J* = 7.6 Hz), 7.21-7.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.5, 32.7, 41.2, 44.7, 48.9, 55.2, 111.6, 112.7, 118.9, 129.7, 146.0, 159.8, 211.0. The ee value of the product was determined on Daicel Chiralpak AD-H column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 28.8 min [(*S*)-enantiomer], 31.2 min [(*R*)-enantiomer], 98% ee.

(*R*)-3-(4-methoxyphenyl)cyclohexanone (3ak)[70b,132]:



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.71-1.83 (m, 2H), 2.03-2.13 (m, 2H), 2.32-2.57 (m, 4H), 2.95 (tt, 1H, *J* = 12.0, 3.8 Hz), 3.77 (s, 3H), 6.83-6.86 (m, 2H), 7.10-7.13 (m, 2H), ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.5, 33.0, 41.1, 43.9, 49.2, 55.2, 114.0, 127.4, 136.5, 158.2, 211.2. The ee value of the product was determined on Daicel Chiralpak AD-H column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 28.2 min [(*S*)-enantiomer], 29.7 min [(*R*)-enantiomer], 97% ee.

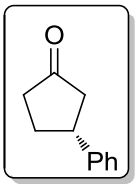
(*R*)-5-methyl-4-phenylhexan-2-one (3ba)[48,70b]:



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 0.72 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.2 Hz), 1.78-1.83 (m, 1H), 1.95 (s, 3H), 2.74-2.80 (m, 2H), 2.89-2.91 (m, 1H), 7.11-7.17 (m, 3H), 7.25 (t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.3, 20.7, 30.5, 33.3, 47.7, 48.1, 126.3, 128.2, 128.3, 143.3, 208.3. The ee value of the product was determined on Daicel Chiralpak OD-H column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis.

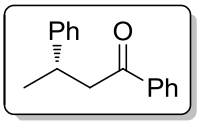
Retention times: 13.1 min [(*S*)-enantiomer], 15.0 min [(*R*)-enantiomer], 92% ee.

(*R*)-3-phenylcyclopentanone (3ca)[48]:



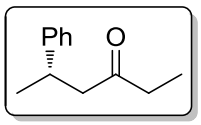
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.98 (tt, 1H, *J* = 13.1, 4.4 Hz), 2.26-2.36 (m, 2H), 2.41-2.48 (m, 2H), 2.66 (dd, 1H *J* = 17.9, 7.6 Hz), 3.41 (tt, 1H, *J* = 10.7, 5.3 Hz), 7.22-7.25 (m, 3H), 7.33 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 31.1, 38.8, 42.1, 45.7, 126.7, 128.6, 143.0, 218.3. The ee value of the product was determined on Daicel Chiralpak AS-H column with hexane/2-propanol = 99:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 55.9 min [(*R*)-enantiomer], 61.3 min [(*S*)-enantiomer], 74% ee.

(*S*)-1,3-diphenylbutan-1-one (3da)[133]:



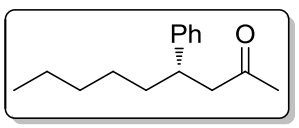
^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.31 (d, 3H, *J* = 6.9 Hz), 3.13-3.17 (m, 1H), 3.26 (dd, 1H, *J* = 16.5, 5.5 Hz), 3.44-3.49 (m, 1H), 7.14-7.17 (m, 1H), 7.21-7.27 (m, 4H), 7.40 (t, 2H, *J* = 7.6 Hz), 7.49-7.51 (m, 1H), 7.88-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.8, 35.6, 47.0, 126.3, 126.8, 128.1, 128.51, 128.53, 132.9, 137.3, 146.6, 199.0. The ee value of the product was determined on Daicel Chiralpak AD column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 14.2 min [(*S*)-enantiomer], 17.0 min [(*R*)-enantiomer], 92% ee.

(*S*)-5-phenylhexan-3-one (3ea)[134]:



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 0.97 (t, 3H, *J* = 7.6 Hz), 1.24 (d, 3H, *J* = 6.9 Hz), 2.23-2.36 (m, 2H), 2.61 (dd, 1H, *J* = 15.8, 7.6 Hz), 2.70 (dd, 1H, *J* = 16.2, 6.5 Hz), 3.27-3.33 (m, 1H), 7.16-7.19 (m, 3H), 7.27 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 7.6, 21.9, 35.5, 36.6, 50.8, 126.2, 126.7, 128.5, 146.3, 210.4. The ee value of the product was determined on Daicel Chiralpak AD-3 column with hexane/2-propanol = 99:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 10.7 min [(*S*)-enantiomer], 11.7 min [(*R*)-enantiomer], 96% ee.

(*S*)-4-phenylnonan-2-one (3fa)[129]:



^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.80 (t, 3H, *J* = 6.8 Hz), 1.08-1.22 (m, 6H), 1.49-1.61 (m, 2H), 1.99 (s, 3H), 2.64-2.73 (m, 2H), 3.06-3.12 (m, 1H), 7.14-7.18 (m, 3H), 7.26 (t, 2H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.0, 22.5, 27.0, 30.6, 31.7, 36.4, 41.3, 51.0, 126.3, 127.5, 128.4, 144.6, 208.0. The ee value of the product was determined on Daicel Chiralpak OJ column with hexane/2-propanol = 99:1, flow = 0.25 mL/min by HPLC analysis. Retention times: 28.2 min [(*S*)-enantiomer], 31.4 min [(*R*)-enantiomer], 95% ee.

1-2-2-2. A typical procedure for preparation of racemic sample: 2-Cyclohexenone (19.2 mg, 0.2 mmol), phenylboronic acid (48.8 mg, 0.4 mmol), PI/CB Rh **I-1** (Rh: 0.75 mol%) and *rac*-BINAP (1.2 mg, 1 mol%) were combined in Carousel^{TM} tube and toluene (0.25 mL) and water (0.5 mL), which were pre-heated at 100 ˚C, were added to the mixture. After the mixture was stirred for 18 h under Ar atmosphere at 100 ˚C, the catalyst was collected by filtration and washed with dichloromethane using KIRIYAMAROHTO$^{®}$ funnel. The aqueous layer of the filtrate was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate. After sodium sulfate was filtered, the solvent was removed *in vacuo* and the residue was purified by preparative TLC to afford racemic 3-phenylcyclohexanone (**3aa**).

1-2-2-3. Hot filtration test with two different substrates (Table 1-2-15, entry 3): 2-Cyclohexenone (**1a**, 28.8 mg, 0.3 mmol), phenylboronic acid (**2a**, 54.9 mg, 0.45 mmol), PI/CB Rh/Ag **IV-4** (Rh: 0.75 mol%) and chiral diene **4b** (0.03 mL of 22.0 mg/mL solution of toluene) were combined in Carousel^{TM} tube and toluene (0.345 mL) and water (0.75 mL), which were pre-heated at 100 ˚C, were added to the mixture. After the mixture was stirred for 6 h under Ar atmosphere at 100 ˚C, the mixture was picked up with a syringe and solid catalyst was removed through a membrane filter keeping 100 ˚C. The filtrate was transferred to another Carousel^{TM} tube, which contained 5-methylhex-3-en-2-one (**1b**, 33.7 mg, 0.3 mmol) and phenylboronic acid (**2a**, 54.9 mg, 0.45 mmol). After the mixture was stirred for 6 h under Ar atmosphere at 100 ˚C, the mixture and water were transferred to separating funnel and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and the conversion of 5-methylhex-3-en-2-one **1b** (~1%) and the yield of 5-methyl-4-phenylhexan-2-one **3ba** (trace) were determined by GC analysis with reference to an internal standard (IS = ethylbenzene). The result showed that the asymmetric 1,4-addition hardly occurred in the filtrate and it indicated that the catalytic active spices are not homogeneous leached spices.

1-2-2-4. Mesitylene treatment (Table 1-2-20, entry 2): PI/CB Rh/Ag **IV-4** was suspended in mesitylene and heated at 100 ˚C for 5 h under air. The catalyst was filtered, washed with dichloromethane and dried *in vacuo*.

1-2-2-5. A typical procedure of asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexenone catalyzed by PI/CB catalyst and recovery of the catalyst (Table 1-2-21): 2-Cyclohexenone (57.6 mg, 0.6 mmol), phenylboronic acid (109.8 mg, 0.9 mmol), PI/CB Rh/Ag **IV-2** (Rh: 0.75 mol%) and chiral diene **4b** (0.06 mL of 22.0 mg/mL solution of toluene) were combined in Carousel^{TM} tube and toluene (0.69 mL) and water (1.5 mL), which were pre-heated at 100 ˚C, were added to the mixture. After the mixture was stirred for 6 h under Ar atmosphere at 100 ˚C and ethylbenzene (15~20 mg) as an internal standard was added to the mixture, the catalyst was collected by

filtration and washed with THF using KIRIYAMAROHTO® funnel. While the collected catalyst was dried *in vacuo* and reused for the next reaction, the filtrate was picked up with a syringe, transferred to a volumetric flask through a membrane filter in order to remove the residual solids and diluted to 25 mL solution by THF. The filtrate (10 mL) was taken by a volumetric pipette and the solvent was removed *in vacuo*. The residual crude mixture was heated in mixture of sulfuric acid (1 mL) and nitric acid at 200 ˚C until all nitric acid was evaporated, the mixture was cooled to room temperature and aqua regia (1 mL) was added. The solution was diluted to 50 mL solution by pure water and the resulting solution was measured by ICP analysis to determine the amount of Rh that leached out. Another filtrate (15 mL) was dried over sodium sulfate and the conversion of 2-cyclohexenone and the yield of 3-phenylcyclohexanone were determined by GC analysis with reference to an internal standard (IS = ethylbenzene). The solvent was removed *in vacuo* and the residue was purified by preparative TLC to afford 3-phenylcyclohexanone. The ee value of the product was determined on Daicel Chiralpak AD column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 18.8 min [(*S*)-enantiomer], 23.0 min [(*R*)-enantiomer], 98% ee.

1-2-3. One-pot reaction

1-2-3-1. Preparation of PI/CB-Au XII[15]: Copolymer (500.0 mg), ketjen black EC300J (500.0 mg) and $NaBH_4$ (53.0 mg) were combined in diglyme (30 mL) at room temperature, to this solution was slowly added the solution of chlorotriphenylphosphine gold (I) (53.0 mg) in THF (2 mL). The mixture was stirred for 3 h at room temperature and diethyl ether (500 mL) was slowly added to the mixture at room temperature. After the catalysts, which were black powders, were filtered and ground, they were washed with diethyl ether several times and dried *in vacuo* at room temperature. The catalysts were heated at 150 ˚C for 5 h without solvent. The prepared solid was washed with water, THF and dichloromethane and dried *in vacuo* to afford black powder. This powder was heated at 170 ˚C for 5 h without solvent to afford PI/CB-Au **XII**. PI/CB-Au **XII** (10-20 mg) was heated in the mixture of sulfuric acid and nitric acid at 200 ˚C, the mixture was cooled to room temperature and aqua regia was added. The amount of gold in the resulting solution was measured by ICP analysis to determine the loading of gold.

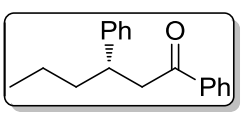
1-2-3-2. Preparation of other PI/CB catalysts for aerobic oxidations (used in Table 1-2-27, such as Au, Pt, Pd, Au/Pt, Au/Pd, Pt/Pd): The procedures for the preparation of each catalyst were same as the procedure shown in **1-2-3-1**. The metal precursors were listed in Table 1-2-3 for the listed metals and $Pd(OAc)_2$ was used for the source of Pd. The metal salts were dissolved in an appropriate amount of THF. In all cases, 0.28 mmol of each metal was used for 1.0 g scale (target loading = 0.28 mmol/g).

1-2-3-3. Preparation of 1-phenylhex-2-en-1-ol (8)[135]: To magnesium (402 mg, 16.5

mmol) suspended in diethylether (5 mL), bromobenzene (2.71 g, 17.25 mmol) in diethylether (12.5 ml) was added through the dropping funnel to generate Grignard reagent. After the reaction mixture was cooled to 0 ˚C, hex-2-enal (1.47 g, 15 mmol) in diethylether (5 ml) was added through the dropping funnel at 0 ˚C and the mixture was further stirred for 2 h at room temperature. 1 M HCl solution was added to quench the reaction and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography (ethyl acetate: hexane = 1:10) to afford 1-Phenylhex-2-en-1-ol (2.47 g, 96% yield). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 0.86-0.89 (m, 3H), 1.37-1.43 (m, 2H), 1.87 (d, 1H, J = 4.1 Hz), 2.00-2.04 (m, 2H), 5.14-5.15 (m, 1H), 5.63-5.67 (m, 1H), 5.72-5.76 (m, 1H) 7.23-7.26 (m, 1H), 7.32-7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 13.6, 22.2, 34.2, 75.2, 126.1, 127.4, 128.4, 132.4, 132.6, 143.4.

1-2-3-4. A typical procedure of one-pot reactions using allylic alcohol (Scheme 1-2-16): 1-Phenylhex-2-en-1-ol **8** (52.9 mg, 0.3 mmol), PI/CB Au **XII** (Au: 0.5 mol%), potassium carbonate (20.7 mg, 0.15 mmol), toluene (0.2 mL) and water (0.1 mL) were combined in Carousel^{TM} tube. After the mixture was stirred for 16 h under molecular oxygen atmosphere at 60 ˚C, phenylboronic acid (72.6 mg, 0.6 mmol), PI/CB Rh/Ag **IV-2** (Rh: 1.5 mol%) and chiral diene **4b** (0.06 mL of 22.0 mg/mL solution of toluene as 2 mol%) were added under air. Toluene (0.115 mL) and water (0.65 mL), which were pre-heated at 100 ˚C, were added to the mixture and the mixture was stirred for 18 h under Ar atmosphere at 100 ˚C. The mixture, which was diluted by THF, was picked up with a syringe and transferred to a volumetric flask through a membrane filter in order to remove the residual solids and diluted to 10 mL solution by THF. The filtrate (3 mL) was taken by a volumetric pipette and the solvent was removed *in vacuo*. The residual crude mixture was heated in the mixture of sulfuric acid (1 mL) and nitric acid at 200 ˚C until all nitric acid was evaporated, the mixture was cooled to room temperature and aqua regia (1 mL) was added. The solution was diluted to 50 mL solution by pure water and the resulting solution was measured by ICP analysis to determine the amount of Rh that leached out. Another filtrate (7 mL) and water were transferred to separating funnel and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate. After sodium sulfate was filtered, the solvent was removed *in vacuo* and the residue was purified by preparative TLC to afford 1,3-diphenylhexan-1-one **3ga**.

(*S*)-1,3-diphenylhexan-1-one (3ga)[136]:



^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.83 (t, 3H, J = 7.4 Hz), 1.13-1.24 (m, 2H), 1.59-1.69 (m, 2H), 3.18-3.34 (m, 3H), 7.16 (t, 1H, J = 7.4 Hz), 7.15-7.27 (m, 4H), 7.41 (t, 2H, J = 7.9 Hz), 7.51 (t, 1H, J = 7.4 Hz), 7.88 (d, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 14.0,

20.6, 38.6, 41.1, 45.9, 126.2, 127.6, 128.0, 128.4, 132.9, 137.3, 145.0, 199.2. The ee value of the product was determined on Daicel Chiralpak AD column with hexane/2-propanol = 49:1, flow = 0.5 mL/min by HPLC analysis. Retention times: 15.4 min [(*S*)-enantiomer], 19.1 min [(*R*)-enantiomer], $[\alpha]^{28}_{D}$ +4.7 (*c* 1.0, EtOH, 94% ee).

1-2-3-5. A typical procedure of aerobic oxidations of alcohols (Table 1-2-32, entry 18): 1-Phenylhex-2-en-1-ol **8** (52.9 mg, 0.3 mmol), PI/CB Au **XII** (Au: 0.5 mol%), potassium carbonate (20.7 mg, 0.15 mmol), toluene (0.2 mL) and water (0.1 mL) were combined in Carousel^{TM} tube and the mixture was stirred for 16 h under molecular oxygen atmosphere at 60 ˚C. The conversion of **8** and the yields of **1g**, **10** and **12** were determined by GC analysis with reference to an internal standard (IS = ethylbenzene).

1-2-3-6. A typical procedure of aerobic oxidative methyl esterifications of allylic alcohol 17 (Table 1-2-34, entry 1): (*E*)-Hex-2-en-1-ol **17** (20.0 mg, 0.2 mmol), PI/CB Au **XII** (Au: 0.5 mol%), potassium carbonate (13.8 mg, 0.1 mmol), methanol (1.6 mL) and water (0.0032 mL) were combined in Carousel^{TM} tube and the mixture was stirred for 12 h under molecular oxygen atmosphere at 30 ˚C. The conversion of **17** and the yields of the desired ester **13** and aldehyde **18** were determined by GC analysis with reference to an internal standard (IS = ethylbenzene).

1-2-3-7. A typical procedure of asymmetric 1,4-additions of phenylboronic acid to ynone catalyzed by PI/CB catalyst (Table 1-2-35, entry 1): 1-Phenylhept-2-yn-1-one **20** (55.9 mg, 0.3 mmol), phenylboronic acid (54.9 mg, 0.45 mmol), PI/CB Rh/Ag **IV-2** (Rh: 0.75 mol%) and chiral diene **4b** (0.03 mL of 22.0 mg/mL solution of toluene) were combined in Carousel^{TM} tube and toluene (0.345 mL) and water (0.75 mL), which were pre-heated at 100 ˚C, were added to the mixture. After the mixture was stirred for 7 h under Ar atmosphere at 100 ˚C, THF were added to the mixture. The mixture was picked up with a syringe and transferred to a volumetric flask through a membrane filter in order to remove the residual solids and diluted to 10 mL solution by THF. The filtrate (3 mL) was taken by a volumetric pipette and the solvent was removed *in vacuo*. The residual crude mixture was heated in the mixture of sulfuric acid (1 mL) and nitric acid at 200 ˚C until all nitric acid was evaporated, the mixture was cooled to room temperature and aqua regia (1 mL) was added. The solution was diluted to 50 mL solution by pure water and the resulting solution was measured by ICP analysis to determine the amount of Rh that leached out. Another filtrate (7 mL) and water were transferred to a separating funnel and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and the conversion of **20** and the yield of **21**, (*E*)-**22** and (*E*)-**22** were determined by ^{1}H NMR analysis with reference to an internal standard (IS = tetrachloroethane).

1-2-3-8. A typical procedure of the reactions with propargyl alcohol (Table 1-2-36,

entry 5): 1-Phenylhept-2-yn-1-ol **19** (37.7 mg, 0.2 mmol), PI/CB Au **XII** (Au: 0.5 mol%), toluene (0.25 mL) and water (0.5 mL) were combined in Carousel^{TM} tube and the mixture was stirred for 12 h under Ar atmosphere at 100 ˚C. The conversion of **19** and the yields of **23**, **24** and **20** were determined by ^{1}H NMR analysis with reference to an internal standard (IS = tetrachloroethane).

Chapter 2

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 3

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。

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List of publications

[Publications related to the thesis]

1. "Polymer-Incarcerated Chiral Rh/Ag Nanoparticles for Asymmetric 1,4-Addition Reactions of Arylboronic Acids to Enones: Remarkable Effects of Bimetallic Structure on Activity and Metal Leaching" T. Yasukawa, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 16963.

2. "Chiral metal nanoparticle-catalyzed asymmetric C–C bond formation reactions" T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Soc. Rev.* **2014**, *43*, 1450.

3. "Chiral Bifunctional Metal Nanoparticle systems as Heterogeneous Catalysts beyond Homogeneous Catalyst Systems for Asymmetric Carbon–Carbon Bond-Forming Reactions", T. Yasukawa, A. Suzuki, H. Miyamura, K. Nishino, S. Kobayashi, *J. Am. Chem. Soc.* Submitted.

[Publications not related to the thesis]

1. "Aerobic Oxidative Esterification of Alcohols Catalyzed by Polymer-incarcerated Gold Nanoclusters under Ambient Conditions" H. Miyamura, T. Yasukawa, S. Kobayashi, *Green. Chem.* **2009**, *12*, 776.

2. "Rate-Acceleration in Gold-Nanocluster-Catalyzed Aerobic Oxidative Esterification Using 1,2- and 1,3-Diols and Their Derivative" T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Asian. J.* **2011**, *6*, 621.

3. "Copper-Catalyzed, Aerobic Oxidative Cross-Coupling of Alkynes with Arylboronic Acids: Remarkable Selectivity in 2,6-Lutidine Media", T. Yasukawa, H. Miyamura, S. Kobayashi, *Org. Biomol. Chem.* **2011**, *9*, 6208.

4. "A heterogeneous layered bifunctional catalyst for the integration of aerobic oxidation and asymmetric C–C bond formation", H. Miyamura, G. C. Y. Choo, T. Yasukawa, W.-J. Yoo, S. Kobayashi, *Chem. Commun.* **2013**, *49*, 9917.

5. "Preparation of polymer incarcerated gold nanocluster catalysts (PI-Au) and their application to aerobic oxidation reactions of boronic acids, alcohols, and silyl enol ethers", H. Miyamura, T. Yasukawa, S. Kobayashi, *Tetrahedron* **2014**, *70*, 6039.

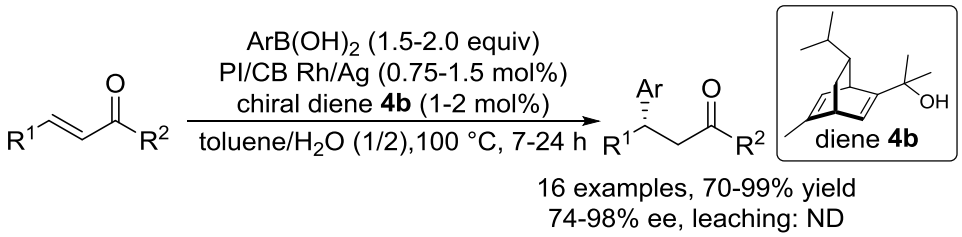
6. "Simple Homopolymer-Incarcerated Gold Nanoclusters Prepared by Self-Assembled Encapsulation with Aluminum Reagents as Crosslinkers: Catalysts for Aerobic Oxidation Reactions", T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Lett.* **2015**, *44*, 50.

Summary

Since conventional chiral metal complex catalysts or immobilized ones have limitations in terms of reusability and/or reduced activity, an alternative concept of asymmetric catalysis was required to develop a truly efficient and practical heterogeneous catalyst system. I focused on a chiral nanoparticle and postulated that it would be a promising approach to direct a next stage of asymmetric catalysis. I investigated chiral Rh nanoparticle catalytic systems as heterogeneous catalysts and the introduction of several strategies to these systems, such as bifunctional chiral modifiers and use of sustainable materials, finally establish a sophisticated asymmetric catalysis with significant advantages and usability. Numerous unique aspects and insights of chiral nanoparticles were also recognized during this research.

In chapter 1, I discovered that the chiral diene **4b** modified heterogeneous Rh/Ag nanoparticle catalytic system was effective for asymmetric 1,4-additions of aryl boronic acids to enones and achieved substrate generality with excellent enantioselectivities (Scheme 4-1). Such a high performance for various substrates is a rare example of chiral nanoparticle catalysis. The catalyst could be easily recovered and reused several times without loss of activity and the deactivated catalysts could be revived by heating. The fundamental factor to construct a robust chiral nanoparticle system in this case is a choice of ligands, as it affected both a chiral environment and a stability of chiral nanoparticles. In fact, no metal leaching was observed in the presence of a chiral diene as a modifier. Moreover, a dopant of second metal changed the structure of Rh nanoparticles and enhanced the catalytic activity. These studies clearly proved the great potential of chiral nanoparticle catalytic system as a practically useful asymmetric catalyst. However, the loadings of the catalyst and the ligand were not satisfactory level, and substrates were only limited to enones at this stage.

Scheme 4-1. Chiral Rh nanoparticle systems for asymmetric 1.4-addition to enones



(５年以内に雑誌等で刊行予定のため、該当箇所にあたる内容を一部略)

Chiral nanoparticle systems offer engineering flexibility and have the potential to be applied to other asymmetric catalysis and even industrial scale synthesis. I believe the concept of chiral nanoparticle systems as heterogeneous chiral catalysts opens the door to a new generation of asymmetric catalysis. The observations of unique nature in the heterogeneous nanoparticle system also provided precious scientific knowledge to aid a construction of new chiral nanoparticle catalytic systems and an elucidation of a reaction mechanism.

Acknowledgement

The author expressed his sincere thanks to Prof. Shu Kobayashi, The University of Tokyo, for his valuable suggestions, enthusiastic discussions and support ranging over many subjects throughout the course of this work.

He also gratefully thanks Dr. Hiroyuki Miyamura for fruitful suggestions and helpful discussions, hands-on instructions and continuous encouragement throughout the course of this work.

He also deeply thanks to Mr. Noriaki Kuramitsu for electronic microscopy analysis and Mr. Kenju Takasugi for solid state NMR analysis.

He also truly thanks to Mr. Gerald Choo Chong Yu, Ms. Aya Suzuki, Mr. Kohei Nishino and Yuki Saito for their countless contributions.

He also thanks Dr. Yasuhiro Yamashita, Dr. Yuichiro Mori, Dr. Masaharu Ueno, Dr. Woo-Jin Yoo and Tetsu Tsubogo for beneficial advice and discussions.

He is also grateful to all the member of the synthetic organic chemistry laboratory for various help, discussion and motivation.

He also thanks the Japan Society for Promoting Science for their financial support.

He also expressed his hearty thanks to his grandparents, parents, sister, wife and friends who have always warmly supported him.

At last, he is thankful to the grandfathers who watched over him warmly from Heaven.

January, 2015

Tomohiro YASUKAWA
The University of Tokyo