

論文の内容の要旨

Development of Heterogeneous Rh Catalysts

for Asymmetric Arylation Reactions

(不均一系 Rh 触媒の開発と不斉アリール化反応)

氏名 呉本 達哉

1. Introduction

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

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

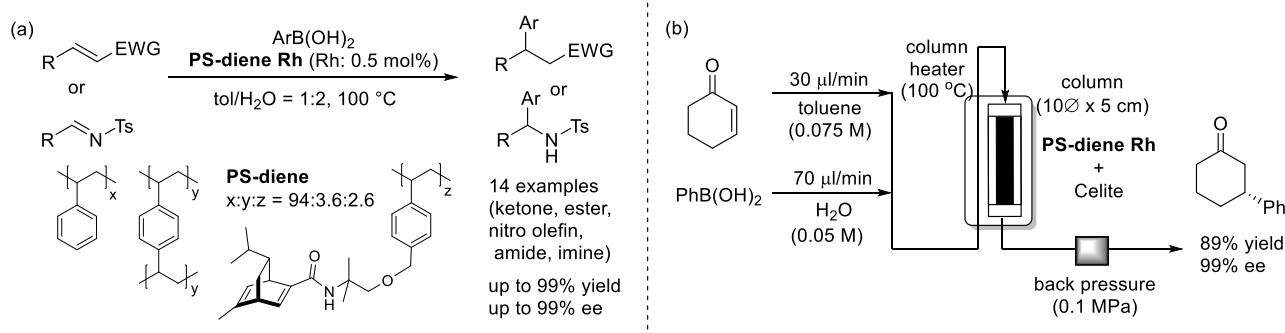
Asymmetric arylation catalyzed by Rh is highly useful in synthetic organic chemistry because it can create new C–C bonds with high enantioselectivities. This reaction can transform readily available materials into chiral molecules, and applications to the synthesis of active pharmaceutical ingredients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

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

To apply the catalyst to flow reactions, activation methods of the catalyst were investigated. It was found that the treatment of **PS-diene Rh** with a base could enhance the catalytic activity significantly. The continuous-flow reaction was then conducted with the base-treated **PS-diene Rh** (Scheme 1 (b)). A toluene solution of a substrate

and an aqueous solution of phenylboronic acid were mixed in a T-shape joint and the biphasic flow was passed through a column packed with the catalyst. The product was continuously obtained in high yield with excellent enantioselectivity.

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

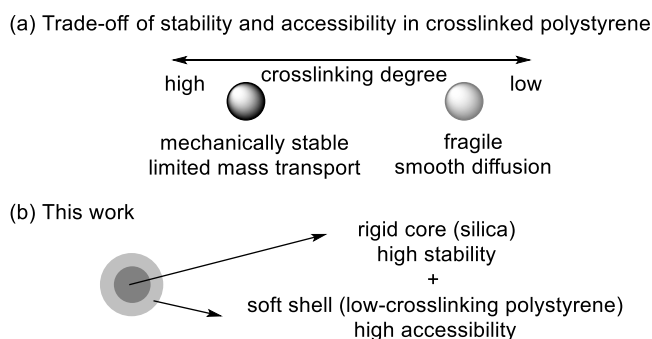


3. Development of Core/Shell-Type Supports for Catalyst Immobilization without Loss in Kinetics

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

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

Figure 1. (a) Trade-off of stability and accessibility in cross-linked polystyrene and (b) general concept of this work.



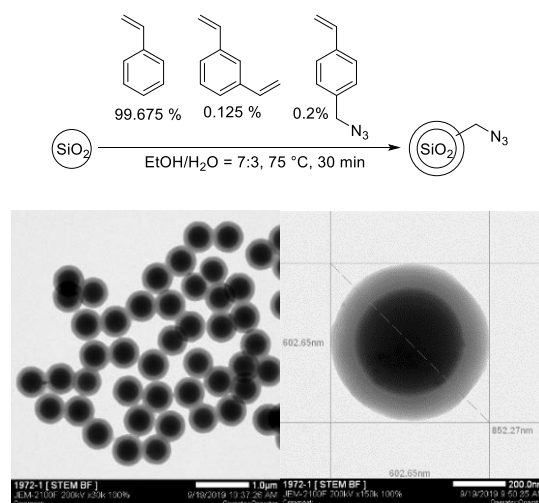
(a)). This trade-off has long been known since the first report of solid-phase synthesis. To address the issue, I have designed a core/shell-type support in which low-cross-linking degree PS is attached on a rigid core material to keep high mass transport efficiency and make the whole support insoluble,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

To synthesize a core/shell-type support, I selected a spherical silica particle as a core material because rigid and highly monodisperse particles can be obtained by application of the well-established Stöber method. The surface of the silica particles was functionalized with 3-(trimethoxysilyl)propyl methacrylate to attach low cross-linking degree PS shell covalently. Copolymerization of styrene, *meta*-divinylbenzene, and azidomethylstyrene in the presence of the core silica particles was conducted based on a reported procedure to afford spherical concentric core/shell particles (Scheme 2). Formation of uniform thin shell confirmed using scanning transfer electron microscopy analysis. The chiral ligand **L1**,

bearing bicyclo[6.1.0]nonyne (BCN) for immobilization, was synthesized as shown in Scheme 3. Readily available BCN **I** was converted into bromide **II**, which was treated with diene **A** in the presence of a phase-transfer catalyst. The immobilization by strain-promoted alkyne-azide cycloaddition was conducted in the presence of an excess amount of **L1** to convert the azide moiety fully into the ligand. The excess amount of **L1** could be recovered without any noticeable degradation. The immobilized ligand was mixed with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ to give the target immobilized chiral catalyst (SiO_2/PS -diene Rh) as a fine powder.

This SiO_2/PS -diene Rh and other control catalysts, those are corresponding homogeneous catalyst, the catalyst on Merrifield resin, and PS-diene Rh without core shown above, were evaluated in the asymmetric 1,4-addition of phenylboronic acid **2a** to α,β -unsaturated ester **1a**. Notably, plots of reaction progress clearly show that the core/shell-type catalyst has

Scheme 2. Synthesis of SiO_2/PS core/shell particles



Scheme 3. Synthesis of SiO_2/PS core/shell particles

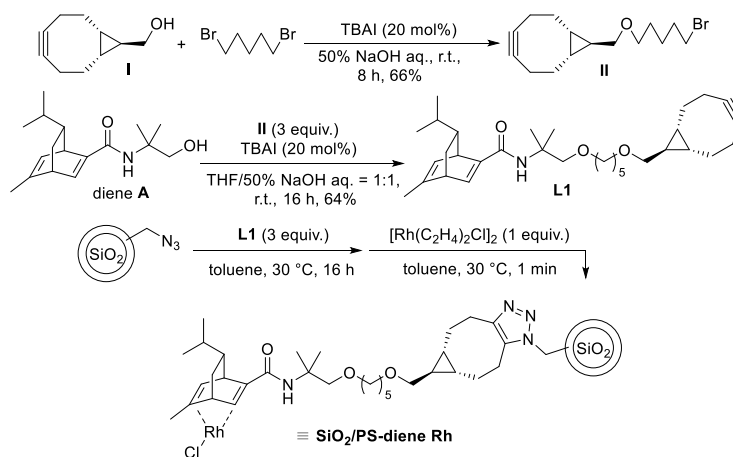
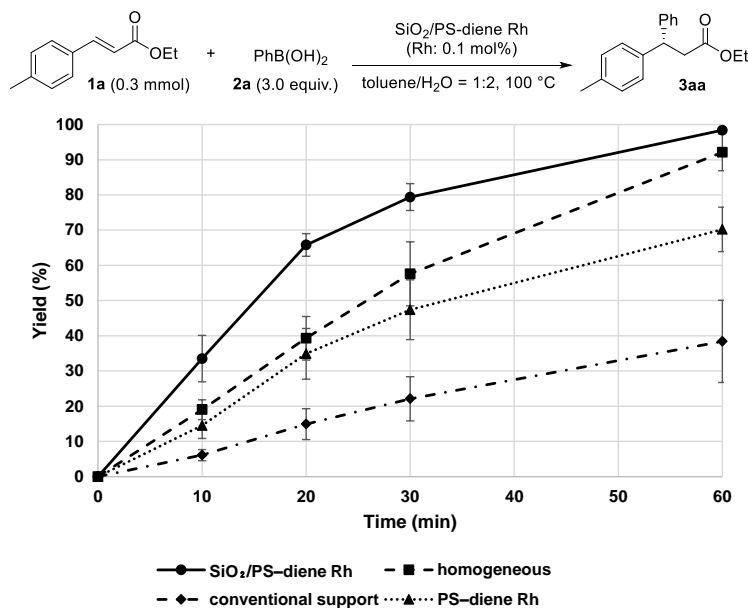


Figure 2. Comparison of the reaction rates.



much better performance than conventional catalysts and confirmed that even better reaction rate than the homogeneous catalyst was achieved. Substrate generality including ketone, ester, amide, nitroolefin, imine, and arylboronic acids was confirmed with high yields and excellent enantioselectivities. Continuous-flow reactions using the core/shell-type catalyst were also conducted, where high efficiency (TOF >150 h⁻¹) was maintained until 260 min, where TON reached over 500.

4. Conclusion

In my Ph.D studies, I have developed heterogeneous **PS-diene Rh** catalyst to achieve high yields and excellent enantioselectivities for broad substrates. Furthermore, I designed a core/shell-type support with extremely low cross-linking degree PS shell, which enables the immobilization without adversely affecting the kinetics while maintaining its heterogeneity and ease of handling. As a proof of concept, I have developed **SiO₂/PS-diene Rh**, which showed significantly higher catalytic activity than those on conventional supports, and even better than the corresponding homogeneous catalyst. This strategy would be applicable to other immobilized catalysts and the catalytic activity could be improved.

5. References

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