July 2005 *Chem. Pharm. Bull.* **53**(7) 723—739 (2005) 723

Review

Self-Assembled Complexes of Non-cross-linked Amphiphilic Polymeric Ligands with Inorganic Species: Highly Active and Reusable Solid-Phase Polymeric Catalysts

Yoichi M. A. YAMADA

Institute for Molecular Science; Myodaiji, Okazaki, Aichi 444–8787, Japan.

Received March 16, 2005

I present herein the development of highly active and reusable polymeric catalysts produced by self-assembly process of non-cross-linked amphiphilic polymeric ligands with inorganic species. Thus, PWAA 1 prepared from $H_3PW_{12}O_{40}$ and poly[(*N*-isopropylacrylamide)-*co*-(acrylamide with ammonium salt)] is suitable for oxidation of alcohols, amines, and sulfides in aqueous hydrogen peroxide. PdAS 2 produced by self-organization of $(NH_4)_2PdCl_4$ and poly[(*N*-isopropylacrylamide)$_{10}$-*co*-diphenylphosphinostyrene] is an excellent recyclable catalyst for Suzuki–Miyaura reaction in water, water-organic solvent, and organic solvent. It is commercially available from Tokyo Kasei Kogyo (TCI). PdAS-V 3 assembled from $(NH_4)_2PdCl_4$ and poly[(*N*-isopropylacrylamide)$_5$-*co*-diphenylphosphinostyrene] provides recycling system of itself for Mizorogi–Heck reaction. TiSS 4 made from Ti(O-*i*-Pr)$_4$ and poly(styryl-linked binaphtholate-*co*-styrene) promotes an enantioselective carbonyl-ene reaction as a recyclable catalyst.

Key words immobilized polymeric catalyst; reusable solid-phase catalyst; self-assembly; tungsten; palladium; titanium

1. Introduction

Development of immobilized and insoluble metal catalysts is of great interest in recent organic chemistry.[1—9] The simple recovery of catalysts by filtration and their reuses resulted in enhancing the economical evaluation of the reaction. At the same time, there is a prospect that the environmental pollution caused by residual metals in the waste fluid will be decreased. Although a great deal of effort has been made to carry out such ideal reactions using immobilized metal catalysts, what seems to be lacking is the efficiency of the catalytic systems. It is obvious that the heterogeneous catalytic systems exhibit generally lower activity than the homogeneous ones. Besides, it is expected that the activity of the catalysts decreases gradually in the recycled systems because the metal species leaches away from their supports. Taking these into consideration, we decided to concentrate on developing insoluble metal catalysts which are highly active and stable. We designed that they were still effective in the use of ppm mol eq, and in the recycled use of many times in any reaction media. To achieve the challenging theme, we have focused on the amphiphilic insoluble catalysts based on a novel concept (Chart 1).

Over the past few decades, a considerable numbers of study have been made on solid-phase catalysts which were immobilized with cross-linked polystyrene resins, silica gels or metals. These catalytic systems, however, generally resulted in lower catalytic activity compared with their soluble counterparts, and were often obliged to use hazardous chlorohydrocarbon solvents.[10—15] Besides, reuse of these catalysts was often difficult owing to the gradual decline of the catalytic activity. These problems made them less practical.

In traditional triphase catalysts, as I have mentioned before, a catalytic species was anchored to a linker that was immobilized to a polymer resin or silica gel (Chart 1, above). In

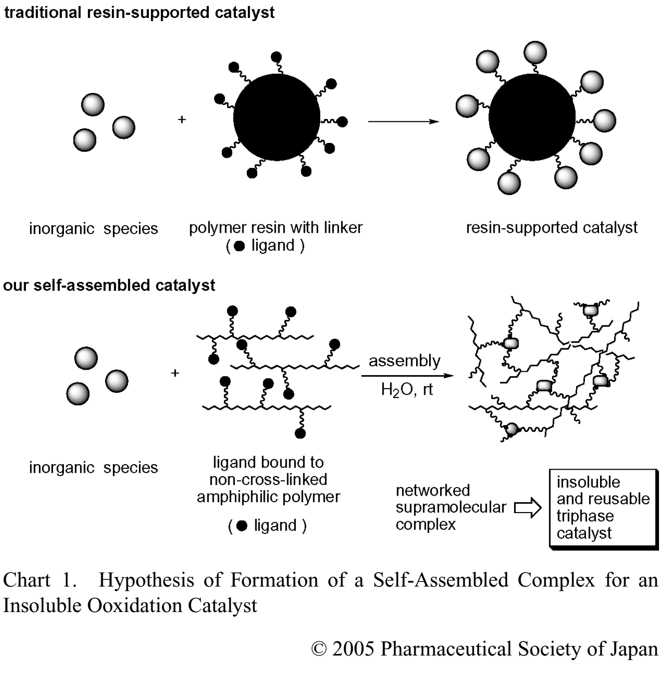


Chart 1. Hypothesis of Formation of a Self-Assembled Complex for an Insoluble Ooxidation Catalyst

e-mail: yyamada@ims.ac.jp

our approach, however, the insoluble catalysts were constructed from self-assembly process of non-cross-linked amphiphilic copolymer ligands and inorganic species. This process would promote the cross-linking of the copolymer by the inorganic species to provide networked, supramolecular, and insoluble complexes (Chart 1, below). They might possess many mesopores where the inorganic species would be tightly supported by many ligands not to be dissociated. We expected such complexes should act as highly active catalysts based on the following points: 1) the complexes have a characteristic high-to-volume ratio to react with a substrate and a reagent, 2) they can capture these reagents effectively by their mesopores, and 3) the amphiphilic copolymers and the inorganic species might construct effective catalytic sites with high affinity to both hydrophobic and hydrophilic reagents.

In this review, I describe the development of self-assembled catalysts PWAA (poly{$PW_{12}O_{40}^{3-}$[(*N*-isopropylacrylamide)-*co*-(acrylamide with ammonium salt)]$_3$}) (**1**), PdAS (poly{$PdCl_2$[(*N*-isopropylacrylamide)$_{10}$-*co*-diphenylphosphinostyrene]$_2$}) (**2**), PdAS-V (poly{$PdCl_2$[(*N*-isopropylacrylamide)$_5$-*co*-diphenylphosphinostyrene]$_2$}) (**3**), and TiSS (poly(Ti styryl-linked binaphtholate-*co*-styrene)) (**4**) prepared from metal ions and non-cross-linked amphiphilic (except **4**) polymers, and their application to the heterogeneous organic synthetic reactions. These catalysts showed outstanding stability in any reaction media such as water, aqueous or anhydrous organic solvents and was reused as follows.[16—23]

2. Development of a Novel Solid-Phase Tungsten Catalyst PWAA and Its Application to Oxidation

2.1. Preparation of a Triphase Catalyst PWAA PWAA **1** was prepared as shown in Chart 2. Ammonium salt **7** was synthesized from commercially available *N*-[3-(dimethylamino)propyl]acrylamide with 1-bromododecane in 92% yield. Random copolymerization of **5** with 12 mol eq of **6** were performed in the presence of 0.04 mol eq of AIBN in *t*-BuOH at 75 °C for 48 h, resulting in that non-cross-linked polymer **7-Br** was formed. It was an amphiphilic polymer that was soluble in water, *t*-BuOH, and CH_2Cl_2. The ratio of the *N*-isopropylacryl amide unit to the ammonium unit to be 12/1 was determined by ^{1}H-NMR. The bromide **7-Br** was ion-exchanged to the nitrate **7-NO$_3$**.[24)] The molecular weight of **7-NO$_3$** was wide-ranging (thousands to tens of thousands) as a result of gel-permeation chromatography relative to polystyrene standards. Thus, complexation to form PWAA was carried out according to the procedure for the preparation of $[\pi\text{-}C_5H_5N(CH_2)_{15}CH_3]_3PW_{12}O_{40}$.[25)] A self-assembly process of **8** with **7-NO$_3$** (3 mol eq of an ammonium unit) in water at room temperature resulted in the formation of white insoluble precipitates simultaneously. After stirring for 7 d at the same temperature, the resulted precipitate was washed and dried to give PWAA as white lumps. PWAA were insoluble in H_2O and organic solvents such as MeOH, EtOH, *i*-PrOH, AcOEt, Me_2CO, CH_2Cl_2, toluene, Et_2O and hexane. Addition of **8** to poly(*N*-isopropylacrylamide) afforded no precipitates. This result indicated that the existence of the ammonium salt units in **7** was essential for cross-linking the polymers through phosphotungstates.

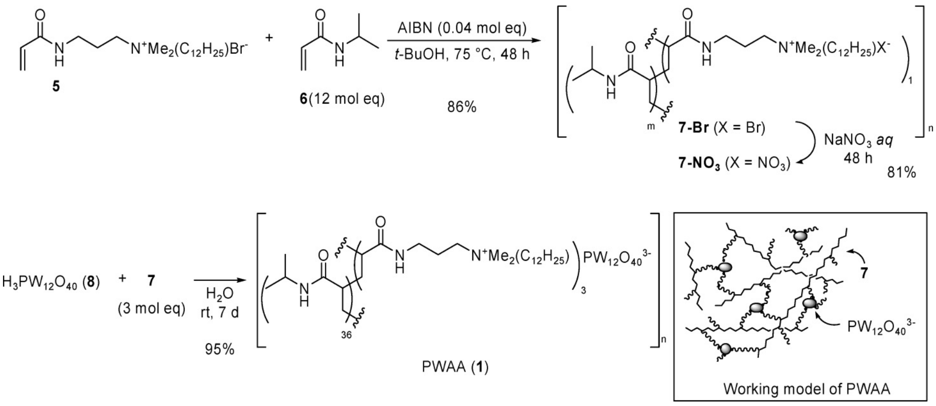


Chart 2. Preparation of PWAA **1**

Yoichi M. A. Yamada was born in 1970 in Tokyo, Japan. He received his bachelor's degree from the University of Tokyo in 1994 under the direction of Professor Masakatsu Shibasaki, and awarded his Ph. D. degree from the University of Tokyo in 1999 under the supervision of Professor Masakatsu Shibasaki. In 1999—2003, he had joined the group of Professor Shiro Ikegami (ex-chairperson of Pharmaceutical Society of Japan) in Teikyo University as an assistant professor, and he moved to Prof. K. C. Nicolaou's group in Scripps Research Institute as a research associate (2003—2004). After returning to Japan, he joined Prof. Yasuhiro Uozumi's group in Institute for Molecular Science as an assistant professor. He has received the Dainippon Ink and Chemicals Award in Synthetic Organic Chemistry (1999), the Inoue Research Award for Young Scientists (2000), and the Pharmaceutical Society Award for Young Scientists (2005).

Yoichi M. A. Yamada

To elucidate the structure of PWAA, several spectroscopic measurements were examined. The elementary analysis showed that one complex unit of **1**·$22H_2O$. The infrared spectrum of PWAA exhibited strong vibrations at 1080 (P=O), 978 (W=O), 897 and 818 cm^{-1}, while that of **8** exhibited them at 1080, 982, 893 and 808 cm^{-1}. Viewed in this light, the structure of the phosphotungstic acid unit of PWAA can be regarded as that of **8**.

Furthermore, we analyzed PWAA by gel-phase ^{31}P-NMR; a broad singlet peak was detected at -13 ppm (Fig. 1). Since it was reported that the signals of $H_3PW_{12}O_{40}$ and $[\pi\text{-}C_5H_5N(CH_2)_{15}CH_3]_3PW_{12}O_{40}$ were observed at the similar frequency (-14.7 ppm[26] and -14.5 ppm[27] respectively), it would be supported that phosphotungstate in PWAA maintained the heteropoly acidic structure such as the Keggin type ($PW_{12}O_{40}^{3-}$).[28,29]

A scanning electron microscope (SEM) of PWAA was also investigated (Fig. 2). PWAA was treated with gold vapor by the sputter-coating method. It was observed that PWAA possessed many pores, whose diameter was about 1—10 μm (left) and hundreds nanometer or less (center). Further magnification (×50000) showed many projections those lengths were less than 100 nm (right); All these things make it clear that PWAA has a high surface-to-volume ratio and many reactive sites.

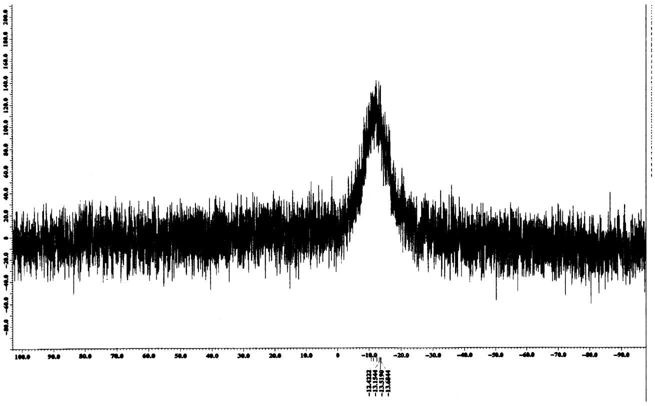


Fig. 1. A Gel-Phase ^{31}P-NMR Chart of PWAA

2.2. Epoxidation of Allylic Alcohols Catalyzed by PWAA

With the insoluble complex PWAA in hand, the epoxidation of allylic alcohols with aq. H_2O_2 under the organic solvent-free conditions was examined.[30—42] We were pleased to find that PWAA showed a very high catalytic activity on epoxidation. In the presence of 2.7×10^{-5} mol eq of PWAA, the reaction of phytol (**9a**) with 2 mol eq of 30% aq. H_2O_2 resulted in the corresponding epoxy alcohol **10a** in 94% yield (Chart 3). TON of PWAA was approximately 35000. This result showed that PWAA has a superior catalytic activity compared with the precedent.

Since the catalytic activity of PWAA was evaluated, a series of epoxidation of several allylic alcohols was performed in the presence of 5.0×10^{-4} mol eq of PWAA (Table 1). Hydrophobic substrates of **9a** and farnesol (**9b**) were converted to the corresponding epoxides in high yields. Epoxidation of **9a** proceeded in 7 h at room temperature to give **10a** in 96% yield with TON reaching approximately 2000 (entry 1). In

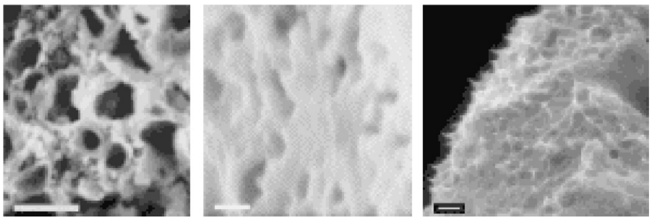


Fig. 2. Scanning Electron Micrographs (SEM) of PWAA

Left: scale bar, 10 μm; center: scale bar, 500 nm, right; scale bar: 100 nm.

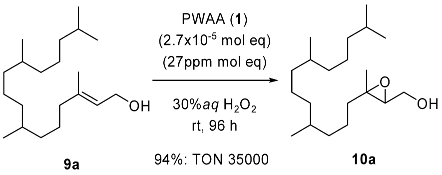
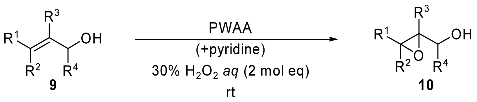
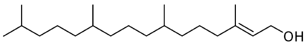
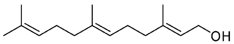
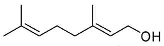
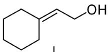
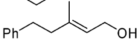
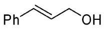
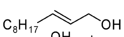
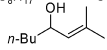


Chart 3. Epoxidation of Phytol (**9a**) Promoted by PWAA

Table 1. Epoxidation of Allylic Alcohols Promoted by PWAA



Entry	Substrate		PWAA **1** (mol eq)	Pyridine (mol eq)	Time (h)	Yield (%)[a]
1		**9a**	5.0×10^{-4}	—	7	**10a**: 96
2		**9b**	5.0×10^{-4}	—	13	**10b**: 84
3		**9c**	5.0×10^{-4}	6.0×10^{-3}	15	**10c**: 80
4		**9d**	5.0×10^{-4}	6.0×10^{-3}	12	**10d**: 83
5		**9e**	5.0×10^{-4}	6.0×10^{-3}	13	**10e**: 96
6		**9f**	2.0×10^{-3}	9.6×10^{-2}	30	**10f**: quant
7		**9g**	2.0×10^{-3}	2.4×10^{-2}	33	**10g**: quant
8		**9h**	2.0×10^{-3}	9.6×10^{-2}	85	**10h**: 73 (*threo* : *erythro*=91 : 9)

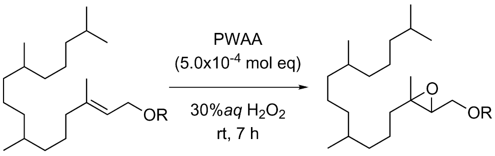
a) Isolated yields.

the reaction of **9b**, 2,3-epoxy alcohol **10b** was obtained in 84% yield (entry 2). In this case, other trialkylsubstituted alkene moieties were intact. Although the epoxidation of less hydrophobic geraniol (**9c**) was messy to afford **10c** in 12% yield owing to acidic hydrolysis of the epoxide, we found that the addition of a trace amount of pyridine was effective to reduce an acidity in this system and thus to prevent the epoxide-opening reactions (entry 3).[43] The reaction of **9c** in the presence of PWAA and 6.0×10^{-3} mol eq of pyridine for 15 h resulted in the formation of **10c** in 80% yield (entry 4), where the C(6)–(7) double bond was not affected. Under identical conditions, trisubstituted allylic alcohols such as an exocyclic allylic alcohol **9d** and a linear one **9e** provided the corresponding epoxides in high yields (entries 4, 5). Although disubstituted allylic alcohols were less reactive, they were converted to the corresponding epoxides in quantitative yields by using 2.0×10^{-3} mol eq of PWAA (entries 6, 7). Besides, the diasteroselective epoxidation of 2-methyl-2-octen-4-ol (**9h**) furnished the *threo*-selective epoxy alcohol **10h** in 73% yield (*threo*/*erythro* (91 : 9)) (entry 8).

The proximity effect of allylic alcohol was also investigated (Chart 4). Epoxidation of a phytol-methyl ether, a phytol-acetyl ester and a phytol-pivaloyl ester under identical conditions did not proceed at all. Besides, the mixture of phytol (**9a**) and cyclohexene resulted in the quantitative conversion of phytol and the no reaction of cyclohexene under the identical conditions (Chart 5). Considered these results, epoxidation was promoted by the interaction of hydroxyl group of allylic alcohol with PWAA which is similar to early transition metal catalyses.[44]

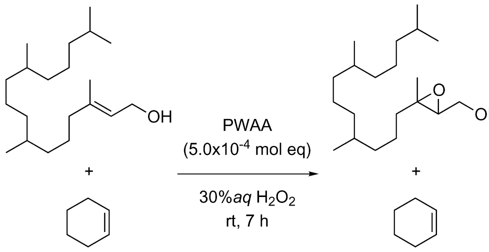
Moreover, recycling of PWAA in case of **9a** was examined as shown in Chart 6. It was found that PWAA was reused three times; in the 1st to 3rd cycle runs, the product **10a** was given in 96, 93, and 97% yields respectively. The activity of PWAA was unchanged under the oxidation conditions through the consecutive runs although PWAA was pulverized through runs.

2.3. Oxidation of Amines Catalyzed by PWAA Since PWAA efficiently promoted the epoxidation of allylic alcohols, we applied this oxidation system to secondary amines.[45—56] Oxidation of secondary amines is the most straightforward method and the direct route to prepare nitrones, which are important substrates for the synthesis of nitrogen-containing bioactive compounds. It was beforehand confirmed that no oxidation of dibenzylamine (**11a**) with hydrogen peroxide was observed at room temperature. On the contrary, addition of 2×10^{-3} mol eq of PWAA to this reaction system promoted oxidation to give the corresponding nitrone (**12a**) in 86% yield (Table 2, entry 1).[57] Bis(*p*-substituted benzyl)amines were also converted to the corresponding oximes under similar conditions. The reaction of bis[(4-trifluoromethyl)benzyl]amine (**11b**) proceeded smoothly to afford **12b** in 90% yield. TON of PWAA in this oxidation reached 450. However, bis(4-chlorobenzyl)amine (**11c**) and bis(4-methoxybenzyl)amine (**11d**) were converted to **12c** and **d** in moderate yields. We further examined the regioselective oxidations of bis(*p*-substituted benzyl)amines. Although it seemed reasonable that the deprotonation took place at more acidic benzylic position selectively, the reactions gave nitrones in 71—94% yield albeit with low regioselectivity (1.3/1—1.7/1) (entries 5—7).[58] Turning to cyclic secondary amines, tetrahydroisoquinoline (**11i**) was converted to **12i**, which is the useful substrate for the synthesis of isoquinoline alkaloids, in 70% yield (entry 9). Oxidation of tetrahydroquinoline (**11j**) provided **12j** instead of the corresponding nitrone (entry 10).



R = H: 96%
Me: no reaction
Ac: no reaction
Piv: no reaction

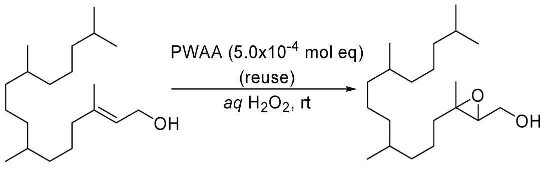
Chart 4. The Epoxidation of Phytol Derivatives



(1 : 1 mixture)

conversion: phytol 100%
cyclohexene 0% (determined by ^{1}H NMR)

Chart 5. Epoxidation of the Mixture of Phytol and Cyclohexene Promoted by PWAA



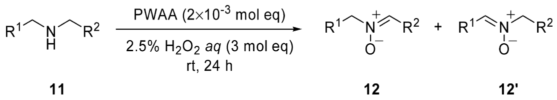
9a **10a**

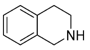
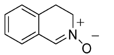
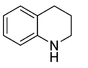
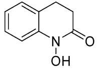
1st use: 96%; 2nd use: 93%; 3rd use: 97%
(isolated yields)

Chart 6. Epoxidation of Phytol (**9a**) Catalyzed by Recycled PWAA

2.4. Oxidation of Sulfides Catalyzed by PWAA Next, we turned our attention to oxidation of sulfides to sulfones (Table 3).[59—67] Sulfones have been utilized as the syntons for total synthesis of bioactive natural compounds. As depicted in parenthesis in Table 3, oxidation of **13a**—**k** with hydrogen peroxide in the absence of PWAA proceeded sluggishly to give mainly the corresponding sulfoxides **14a**—**k** in low to moderate yields[68] rather than sulfones **15a**—**k**. Meeting our expectations, PWAA efficiently promoted the oxidation of sulfides to give sulfones under similar conditions. In the presence of 2×10^{-3} mol eq of PWAA, **13a** was converted into **15a** in 97% yield (entry 1). TON of PWAA reached approximately 500. The substituted aryl methyl sulfides were also converted to the corresponding sulfones in high yields (84—90%) (entries 3, 5, 7). Similarly, oxidation of alkyl thiophenols also provided the corresponding sulfones in high yields (entries 9, 15, 17, 19). It is notable that the catalytic system tolerates a wide variety of functional group. For example, methylthio benzothiazole (**13f**) that is a useful nucle-

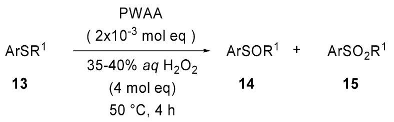
Table 2. Oxidation of Secondary Amines by PWAA

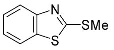
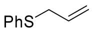
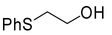
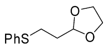


Entry	Amines	R^1	R^2	Temp (°C)	Time (h)	Nitrone	Yield (%)a)
1	**11a**	Ph	Ph	rt	24	**12a**	86
2	**11b**	*p*-CF_3-C_6H_4	*p*-CF_3-C_6H_4	rt	24	**12b**	90
3	**11c**	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	rt	24	**12c**	56
4	**11d**	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	rt	48	**12d**	62
5	**11e**	*p*-MeO-C_6H_4	*p*-CF_3-C_6H_4	rt	24	**12e**+**12e′**	94 (**12e**+**12e′**=1.7/1)
6	**11f**	Ph	*p*-CF_3-C_6H_4	rt	24	**12f**+**12f′**	80 (**12f**+**12f′**=1.3/1)
7	**11g**	Ph	*p*-CN-C_6H_4	40	24	**12g**+**12g′**	71 (**12g**+**12g′**=1.5/1)
8	**11h**	$(CH_3)_3$	Ph	rt	24	**12h**	34
9	**11i**			rt	12	**12i** 	70
10	**11j**			rt	12	**12j** 	30

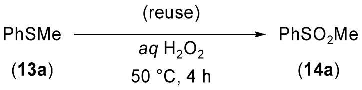
a) Isolated yields.

Table 3. Oxidation of Sulfides to Sulfones with and without PWAA



Entry	**13**	Catalyst	**14** (%)a)	**15** (%)a)
1b)	PhSMe (**13a**)	PWAA	3	97
2b)	**13a**	—	(74)	(26)
3	*p*-Me-C_6H_4SMe (**13b**)	PWAA	9	90
4	**13b**	—	(71)	(22)
5	*p*-Br-C_6H_4SMe (**13c**)	PWAA	12	87
6	**13c**	—	(70)	(15)
7	*p*-MeO-C_6H_4SMe (**13d**)	PWAA	6	84
8	**13d**	—	(76)	(24)
9	PhSEt (**13e**)	PWAA	3	91
10	**13e**	—	(75)	(17)
11c)	 (**13f**)	PWAA	17	78
12c)	**13f**	—	(9)	(0)
13	*p*-CHO-C_6H_4SMe (**13g**)	PWAA	—	86
14	**13g**	—	(53)	(33)
15c)	 (**13h**)	PWAA	3	81
16c)	**13h**	—	(80)	(10)
17	 (**13i**)	PWAA	—	Quant
18	**13i**	—	(80)	(13)
19	 (**13j**)	PWAA	11	71
20	**13j**	—	(54)	(Trace)
21	PhSPh (**13k**)	PWAA	10	6
22	**13k**	—	4	(0)

The yields of the oxidations without PWAA were in parentheses. *a*) Isolated yields. *b*) 3 mol eq of H_2O_2 was used. *c*) The reaction was performed for 7 h.



1st use: 97%; 2nd use: 86%; 3rd use: 83%
4th use: 88%; 5th use: 82%
(isolated yields)

Chart 7. Oxidation of **11a** Catalyzed by Recycled PWAA

ophile for the Julia olefination69) was converted to the sulfone **15f** in 78% yield (entry 11). In this reaction, benzothiazole ring was unaffected through the reaction. The chemoselective oxidation of methylthiobenzaldehyde (**13g**) proceeded to give **15g** in 86% yield with intactness of formyl group (entry 13). Besides, the oxidation of **13h** and **i** proceeded efficiently to give **15h** and **i** in high yields, where the olefin and alcohol were tolerated and *β*-elimination of the alcohol was not observed (entries 15, 17). Sulfide **13j** with a cyclic acetal in the structure was converted to **15j**, which was the substrate for the preparation of the prostaglandin analogue, in 71% yield (entry 19).70,71) On the other hand, the reaction of diphenyl sulfide **13k** hardly proceeded (entry 21).

The recycled activity of PWAA in the oxidation of sulfide **13a** was evaluated (Chart 7). The oxidation of **13a** was performed under identical conditions, affording **15a** in 97% yield. In the repeated use of the recovered catalyst, PWAA mediated the 2nd to 5th cycled runs to give **15a** in 82—88% yields. The reason to reduce yields in the 2nd cycled run was unclear. One explanation for this might be that PWAA was pulverized and adsorbed onto the reaction vessel so that the efficiency of the reaction was reduced physically. In this respect, it was confirmed that the pulverization did not affect the intrinsic activity of PWAA: the recovered PWAA was analyzed by gel-phase ^{31}P-NMR to show a broad peak at −13 ppm as well as the PWAA before use.72)

As stated above, all the reactions were performed under organic solvent-free conditions. PWAA was insoluble and stable in both aqueous and organic solvents. We expected that PWAA should efficiently catalyze the oxidation in any media. Hence, the activity of PWAA in an organic solvent was investigated. The reactions of **13a** to **15a** were carried out with various organic solvents as depicted in Table 4. Similar to the oxidation without organic solvent completed in 4 h to give **15a** in 97% yield (entry 1), the reaction with aprotic hydrophobic solvents [toluene, CH_2Cl_2, THF, and Et_2O (entries 2—5)], hydrophilic solvent [DMF (entry 6)], and protic solvent [EtOH (entry 7)] progressed smoothly to furnish **15a** in high yields. On the contrary, the reaction in toluene proceeded slower to give **15a** in 75%. It seems reasonable that both organic solvent-free and -containing systems were effective for this oxidation.

3. Development of a Novel Solid-Phase Palladium Catalyst PdAS and Its Application to Suzuki–Miyaura Reaction

3.1. Preparation of an Assembled Catalyst PdAS We examined a self-assembly between various palladium species and non-cross-linked amphiphilic polymers with phosphine ligands and found that the complexation of $(NH_4)_2PdCl_4$ (**18**) and poly(*N*-isopropylacrylamide-*co*-4-diphenylstyrylphosphine) (**17**) afforded a novel palladium-polymer catalyst PdAS (<u>Pd</u>-<u>a</u>crylamide-<u>s</u>tyrylphosphine). As shown in Chart 8,[73,74] random copolymerization of 4-diphenylstyrylphosphine (**16**) with 12 mol eq of *N*-isopropylacrylamide (**6**) in the presence of 4 mol% of AIBN gave **17** in 89% yield. The ratio of the phosphine to the amide units in **17** was determined by ^{1}H-NMR measurements in $CDCl_3$ to be 1/10, and the phosphine unit was hardly oxidized in this polymerization as shown by ^{31}P-NMR. This ratio of the phosphine to the amide units as 1/10 was reproducible in several experiments. The molecular weight of **17** was wide-ranging (*ca.* 5000—70000) as a result of gel-permeation chromatography relative to polystyrene standards. A self-assembly of **17** and **18** was investigated under similar conditions to those for the preparation of $PdCl_2(PPh_3)_2$.[75] To a well-stirred solution of **17** (3 mol eq of phosphine) in THF was added a solution of **18** (1 mol eq) in H_2O. The mixture was stirred for 62 h at room temperature and the precipitates were formed. After water was added to the suspension, THF was removed at 80 °C for 4 h with the Dean–Stark equipment. For removal of a trace amount of unreacted palladium species and polymers, the suspension was stirred at 100 °C successively in H_2O, in THF, and in H_2O. After drying *in vacuo*, a dark red solid PdAS **2** was obtained in almost quantitative yield. It was insoluble in water and organic solvents such as acetone, CH_3OH, CH_2Cl_2, AcOEt, THF, and hexane.

Table 4. Solvent Effect on the Oxidation Catalyzed by PWAA

$$\mathbf{13a} \xrightarrow[\substack{\text{30\% } H_2O_2\ aq\text{, 50 °C, 4 h} \\ \text{solvent (1.0M soln of } \mathbf{13a}\text{)}}]{\text{PWAA (2.0x}10^{-3}\text{ mol eq)}} \mathbf{14a} + \mathbf{15a}$$

Entry	Solvent	**12a**[a]	**13a**[a]
1	— (Neat)	3	97
2	Toluene	3	75
3	CH_2Cl_2	8	90
4	THF	8	91
5	Et_2O	—	96
6	DMF	—	100
7	EtOH	—	99

[a] Isolated yields.

To obtain information on the structure of the catalyst, PdAS **2** was characterized by gel-phase ^{31}P-NMR in $CDCl_3$. While a peak of **17** was observed at −2.9 ppm ($ArPh_2\underline{P}$), two broad peaks of PdAS **2** were detected at 32.5 and 26.1 ppm, which must be assigned to the signals of $ArPh_2P{=}O$ and $PdCl_2(PPh_2Ar)_2$, respectively, *i.e.*, the phosphines in **17** coordinated with palladium to form a Pd(II). In our preliminary experiments, it was elucidated that the complexation of **1** and poly(*N*-isopropylacrylamide) without phosphine units afforded no precipitations. Considering these results, it could be confirmed that the phosphine ligands of **2** were the cross-linked structure with palladium (Chart 8).

3.2. Catalytic Activity of PdAS for the Suzuki–Miyaura Reaction The catalytic activity of PdAS for the heterogeneous Suzuki–Miyaura reaction[76—89] was investigated (Table 5). Since "water" is the most safe, non-toxic, and easily available solvent, numerous attempts have been made in utilizing it to the organic reactions.[90,91] While the development of the catalytic system in water has been confronted with many difficulties, PdAS will be a key to develop an efficient system in water owing to its amphiphilicity. Therefore, all the reactions in Tables 5—7 and Chart 9 were performed in water under organic solvent-free conditions. The reaction of iodobenzene (**19a**) with phenylboronic acid

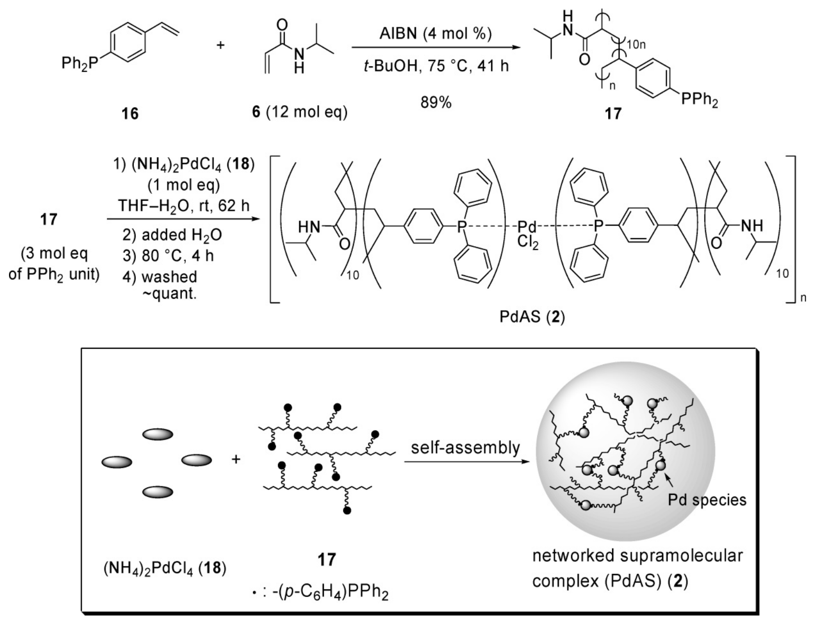
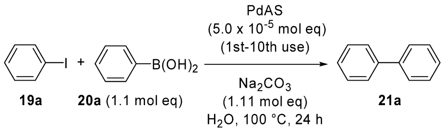


Chart 8. Preparation of an Assembled Catalyst PdAS for the Suzuki–Miyaura Reaction and Its Working Model

Table 5. The Heterogeneous Suzuki–Miyaura Reaction of Iodobenzene (**19a**) with Phenylboronic Acid (**20a**) Catalyzed by 5×10^{-5} mol eq of the Recycled Catalyst PdAS



Entry	Catalyst (cycle)	Yield[a]	Turnover number (TON)
1	1st cycle	95%	19000
2	10th cycle	93%	18600
3	1st—10th consecutive cycle	Ave: 95%	A total of 190000

a) Isolated by crystallization under organic solvent-free conditions.

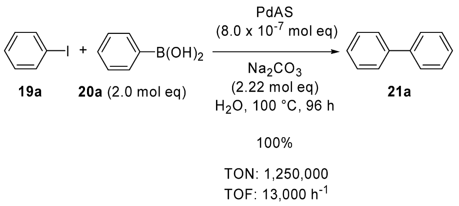


Chart 9. The Heterogeneous Suzuki–Miyaura Reaction Catalyzed by 8.0×10^{-7} mol eq of PdAS

(**20a**) (1.1 mol eq) in the presence of 5×10^{-5} mol eq of PdAS proceeded efficiently to give biphenyl (**21a**) in 95% yield (entry 1) with the TON of PdAS reaching approximately 20000. Leaching of catalytically active species from the supports was often a crucial problem generally.[92)] In our case, however, the resulting filtrate separated from the reaction mixture had no catalytic activity under identical reaction conditions. Thus, it was confirmed that the catalytic activity observed was due to PdAS itself.[93)]

More importantly, the work-up of this reaction was perfectly performed under organic solvent-free conditions, where water was the only solvent used. After the reaction was completed, the liquid reaction mixture was filtrated with boiling water under an argon atmosphere. PdAS was recovered on a glass filter,[94)] and the filtrate was cooled to room temperature to give **21a** as white crystals with high purity.

In order to examine the activity of PdAS as recyclable catalyst, 5×10^{-5} mol eq of PdAS was reused 10 times in the reaction of **19a** and **20a**. All the reactions were worked up under organic solvent-free conditions as mentioned above. It is noteworthy that PdAS maintains its catalytic activity after reuses (Table 5). The reaction in the 10th cycled run gave **21a** in 93% yield (entry 2). The average yield of **21a** in consecutive runs was 95% (entry 3), and the total of TON of PdAS in the 1st to the 10th cycled reactions reached 190000.

We further investigated the limitation of its catalytic activity and found that in less than 1 ppm mol eq of PdAS still catalyzed the reaction efficiently as depicted in Chart 9. Treatment of **19a** with **20a** in the presence of 8×10^{-7} mol eq of PdAS afforded **21a** quantitatively with high purity. In this case, the turnover number reached 1250000.

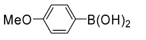
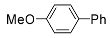
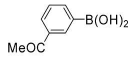
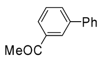
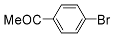
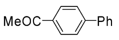
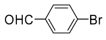
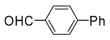
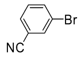
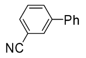
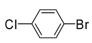
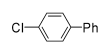
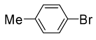
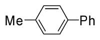
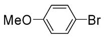
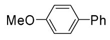
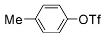
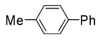
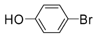
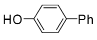
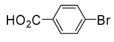
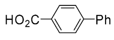
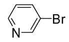
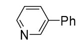
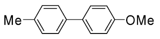
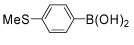
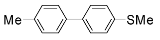
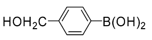
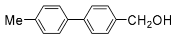
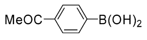
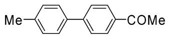
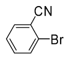
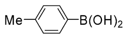
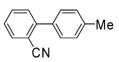
3.3. The Coupling of Aryl Halides with Arylboronic Acids in Water In order to establish the scope of the sequence, we next examined the reaction of various aryl iodides, aryl bromides, and an aryl triflate with arylboronic acids as depicted in Table 6. The following reactions except entry 1 were worked up by the traditional method using an organic solvent.[95)] The reaction of **19a** with the electron-rich (**20b**) or the electron-deficient (**20c**) arylboronic acids catalyzed by 5×10^{-5} mol eq of PdAS afforded the corresponding biaryls **21b** and **c** in almost quantitative yields (entries 1, 2). The reaction of electron-deficient aryl bromides **22a**—**d** with **20a** proceeded smoothly in the presence of 5×10^{-4} mol eq of PdAS to give the biaryls **21d**—**g** in 94—98% yields (entries 3—6). This system was applicable to the electron-rich aryl bromides **22e** and **f** (entries 7, 8) and an aryl triflate **22g** (entry 9). 4-Bromophenol (**20h**), 4-bromobenzoic acid (**20i**) and 3-bromopyridine (**20j**) were easily converted to the corresponding biaryls (entries 10—12). The reactions using **22h** and **i**, which were soluble in water, were completed in 4 h to give **21i** and **j** in 91 and 95% yield, respectively (entries 10, 11). It is notable that the reaction in entry 10 could be performed at room temperature under identical reaction conditions to afford **21i** in 80% yield. Substituted arylboronic acids can be used as reactants (entries 13—16). The reaction of the sulfur-containing boronic acid **20d** also proceeded smoothly to afford **21m** in 95% yield (entry 14). In general, when the reaction of electron-deficient arylboronic acid is performed in the presence of Na_2CO_3 as a base, a critical hydrolysis of arylboronic acid occurs to decrease the yield of the corresponding biaryl.[96)] However, it was found that the use of 1.1 mol eq of the electron-deficient arylboronic acid **20f** with **22e** resulted in the biaryl **21o** in 84% yield (entry 16). Furthermore, the product **21p** that is an important intermediate in the synthesis of the angiotensin II antagonists[97—99)] was prepared by the reaction of 2-bromobenzonitrile (**22k**) with *p*-tolylboronic acid (**20g**) (entry 17).

3.4. The Coupling of Alkenyl Halides and Alkenylboronic Acids At this point, we turned our attention to the coupling of alkenyl halides and alkenylboronic acids (Table 7).[13)] In the presence of 5×10^{-4} mol eq of PdAS, hexenylboronic acid (**23a**) was successfully cross-coupled with **19a** and **22a** to afford **24a** and **b** in 91 and 86% yield (entries 1, 2). The reaction of aryl bromides **22a** and **c** with *trans*-2-phenylvinylboronic acid (**23b**) also proceeded efficiently (entries 3, 4). Similarly, ethyl *cis*-3-iodomethacrylate **25a** was converted to the corresponding coupling product **24e** in 96% yield (entry 5). It is interesting to note that β-bromostyrene (**25b**) ($E/Z=10/1$) was reacted with **20b** to afford **24f** in 91% yield without no isomerization (entry 6). α-Bromostyrene (**25c**) was converted to disubstituted styrene derivatives **24g** and **h** in 90 and 92% yield respectively (entries 7, 8). The coupling of an alkenyl halide with an alkenylboronic acid was successful; conjugated diene **24i** was synthesized from **25b** and **23a** in 81% yield (entry 9). Both vinyl and allylic bromides in 2,3-dibromopropene (**25d**) reacted with 3 mol eq of **20b** to afford the double coupling product **24j** in 70% yield (entry 10). A screening compound for several GABA uptake inhibitors **24k**[100,101)] was synthesized from **25e** and **20b** in 81% yield (entry 11).

3.5. Stability of PdAS in Organic Solvent Now that we are sure that all the reactions were successfully performed under organic solvent-free conditions, we next deal with sta-

Table 6. The Heterogeneous Suzuki–Miyaura Reaction of Aryl Iodides, Bromides and Triflate with Arylboronic Acids Catalyzed by PdAS

$$\begin{matrix}\mathrm{Ar^1Br}\\(\mathrm{Ar^1I})\\(\mathrm{Ar^1OTf})\end{matrix} + \begin{matrix}\mathrm{Ar^2B(OH)_2}\\(1.1\ \mathrm{mol\ eq})\end{matrix} \xrightarrow[\mathrm{Na_2CO_3}\ (1.11\ \mathrm{mol\ eq})\ \mathrm{H_2O},\ 100\ ^\circ\mathrm{C}]{\mathrm{PdAS}\ (5.0\times10^{-4}\ \mathrm{mol\ eq})\ (\text{entries 1 and 2: } 5.0\times10^{-5}\ \mathrm{mol\ eq})} \mathrm{Ar^1{-}Ar^2}$$

Entry	Ar^{1}Br (Ar^{1}OTf)	Ar^{2}B(OH)$_2$	Time	Product	Yield
1	PhI **19a**	 **20b**	24 h		**21b**: 97%
2	**19a**	 **20c**	24 h		**21c**: 98%
3	 **22a**	**20a**	24 h		**21d**: 98%
4	 **22b**	**20a**	9 h		**21e**: 97%
5	 **22c**	**20a**	9 h		**21f**: 98%
6	 **22d**	**20a**	12 h		**21g**: 94%
7	 **22e**	**20a**	9 h		**21h**: 95%
8	 **22f**	**20a**	24 h		**21b**: 87%
9	 **22g**	**20a**	9 h		**21h**: 93%
10	 **22h**	**20a**	4 h (24 h at rt)		**21i**: 91% (80% at rt)
11	 **22i**	**20a**	4 h		**21j**: 95%
12	 **22j**	**20a**	9 h		**21k**: 99%
13	**22e**	**20a**	9 h		**21l**: 91%
14	**22e**	 **20d**	9 h		**21m**: 95%
15	**22e**	 **20e**	9 h		**21n**: 87%
16	**22e**	 **20f**	9 h		**21o**: 84%
17	 **22k**	 **20g**	24 h		**21p**: 93%

bility of PdAS in organic solvents. During the study on characterization of PdAS, we have observed that PdAS swelled in $CDCl_3$. Therefore we examined the effect of organic solvents on its activity. It was found that all the reactions with several aqueous co-solvents proceeded efficiently (Table 8). While the coupling of **22b** with **20a** in water afforded **21e** in 95% yield (entry 1), the reactions in aqueous aprotic solvents (THF, toluene, DMF, 1,4-dioxane, 2-butanone (entries 2—6)), a protic solvent (2-butanol (entry 7)), and a mixed solvent (ethanol–dimethoxyethane (entry 8)) progressed smoothly, furnishing **21e** in approximately 90% yields. These results indicated that PdAS maintains its catalytic activity in organic solvents.

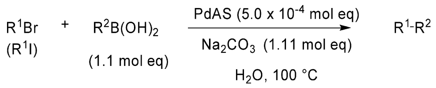
3.6. The Coupling of Alkyl-9-BBNs in Anhydrous Organic Solvents

We further examined the reaction in anhydrous organic solvents. Since the coupling reaction of alkyl-9-BBNs is very useful for organic syntheses, we focused on the Suzuki–Miyaura reaction of *sp*^{3}-boranes in anhydrous media. Alkyl-9-BBNs were prepared from an alkene with 9-BBN-H in anhydrous THF and used without any purification.[102] It is notable that PdAS also worked effectively even in anhydrous conditions. As shown in Table 9, the reaction of octyl-9-BBN (**26a**), prepared from 1-octene and 9-BBN-H in THF, with aryl iodides **19a** and **b** were performed in THF–1,4-dioxane (1 : 1),[103] furnishing 1-aryloctanes **27a** and **b** in 95 and 88% yield, respectively (entries 1, 2). Electron-deficient and -rich aryl bromides, and alkenyl bromides **22a**, **d**, **k**, and **25b** were also adequate substrates (entries 3—6). The reactions of phenyethyl-9-BBN gave the corresponding coupling products in more than 90% yields (entries 7, 8). Besides, the coupling of an alkenyl halide with an alkyl-9-BBN is among the most important reactions for natural product synthesis.[104] Thus, it is noteworthy that the coupling of alkenyl bromides **25b** (entry 6), **25e** (entry 9), and **25f** (entry 10) proceeded efficiently to provide the corresponding products in high yields.

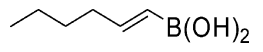
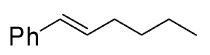
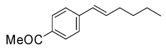
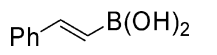
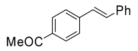
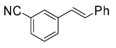
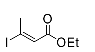
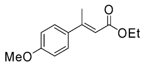
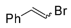
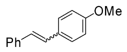
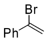
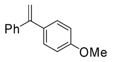
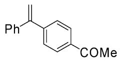
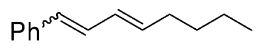
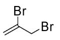
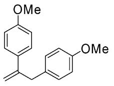
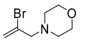
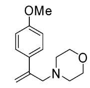
3.7. The Coupling of Benzylic Chlorides

Since the catalyst worked efficiently for *sp*^{3}-borane systems, attention was turned to the coupling of *sp*^{3}-halides such as benzylic halides (Table 10). Until now, there are only a few reported

Table 7. The Heterogeneous Suzuki–Miyaura Reaction of Alkenyl Halides and Alkenylboronic Acids Catalyzed by PdAS

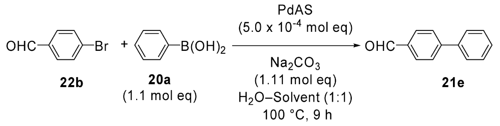


$$\underset{(R^1I)}{R^1Br} + \underset{(1.1\text{ mol eq})}{R^2B(OH)_2} \xrightarrow[\substack{Na_2CO_3\ (1.11\text{ mol eq})\\ H_2O,\ 100\ °C}]{\text{PdAS }(5.0 \times 10^{-4}\text{ mol eq})} R^1\text{-}R^2$$

Entry	Halide	Boronic acid	Time	Product	Yield
1	**19a**	 **23a**	9 h		**24a**: 91%
2	**22a**	**23a**	9 h		**24b**: 86%
3	**22a**	 **23b**	6 h		**24c**: 82%
4	**22c**	**23b**	6 h		**24d**: 82%
5	 **25a**	**20b**	6 h		**24e**: 97%
6	 **25b** (E : Z (10 : 1))	**20b**	24 h		**24f**: 91%
7	 **25c**	**20b**	9 h		**24g**: 90%
8	**25c**	**20f**	9 h		**24h**: 92%
9	**25b** (E : Z (6 : 1))	**23a**	5 h		**24i**: 81% (E : Z (5 : 1))
10[b]	 **25d**	**20b**[a]	24 h		**24j**: 70%
11[b]	 **25e**	**20b**	9 h		**24k**: 81%

a) 3.0 mol eq of **20b**. *b*) The reaction temperature was 80 °C and 2.0×10^{-3} mol eq PdAS was used.

Table 8. The Effects of Organic Solvents as a Co-solvent on the Heterogeneous Suzuki–Miyaura Reaction Catalyzed by PdAS in Water



Entry	Co-solvent	Yield (%)
1	—	95
2	THF	91
3	Toluene	92
4	DMF	94
5	1,4-Dioxane	95
6	2-Butanone	89
7	2-Butanol	87
8	EtOH–DME (1 : 4)	90

examples of the Suzuki–Miyaura reactions of benzylic halides even in the homogeneous system.[105—108] The reaction of benzyl chloride with 1.1 mol eq of boronic acids was performed in the presence of 5×10^{-4} mol eq of PdAS with 3.0 mol eq of KF in DME. The coupling of benzyl chloride (**28a**) with **20b** was accomplished in 9 h to give **29a** in 95% yield (entry 1).[109] This result indicated that oxidative addition of a benzylic chloride to PdAS proceeded smoothly. The same reaction of **15a** with 2.0 mol eq of **20b** in the presence of 2×10^{-3} mol eq of PdAS completed in 1 h to afford **29a** in 92% yield. The reaction of electron-deficient and -rich arylboronic acids were also converted to the coupling products in more than 90% yields (entries 2, 3). A series of substituted benzyl chlorides also proved to be good substrates (entries 4—7). It is notable that the reaction of 4-chlorobenzyl chloride (**28b**) with **20b** afforded **29d** in 72% yield and a biscoupling product **29d′** in 9% yield; it is assumed that the oxidative addition of a less reactive aryl chloride to PdAS occurred in this conditions. Furthermore, alkenylboronic acid **23a** was coupled with benzylic chloride smoothly (entry 7).

4. Development of a Novel Solid-Phase Palladium Catalyst PdAS-V and Its Application to Mizorogi–Heck Reaction

4.1. PdAS-V *vs.* PdAS Since PdAS was a highly active and reusable catalyst, we focused on its application to the efficiently recycled system of the Heck reaction. The Heck reaction, the coupling of *sp*^{2}-halides with alkenes promoted by palladium catalysts, is an important reaction for the synthesis of natural products and bioactive compounds as

Table 9. The Heterogeneous Suzuki–Miyaura Reaction of Alkyl-9-BBNs Catalyzed by PdAS

$$\underset{(X = I,\ Br)}{R^1\text{-}X} + \underset{\mathbf{26}\ (1.1\ \text{mol eq})}{R^2\text{-9-BBN}} \xrightarrow[\substack{K_3PO_4\ (3.0\ \text{mol eq}) \\ \text{THF, 1,4-dioxane (1:1)} \\ 100\ ^\circ C}]{\text{PdAS}\ (5.0 \times 10^{-4}\ \text{mol eq})} \underset{\mathbf{27}}{R^1\text{-}R^2}$$

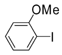
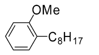
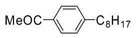
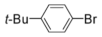
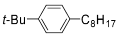
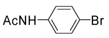
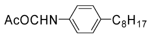
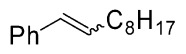
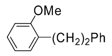
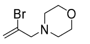
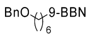
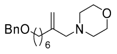
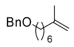
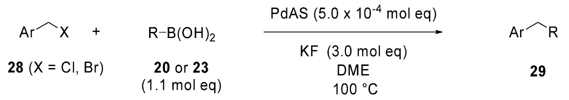
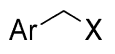
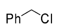
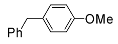
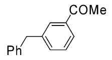
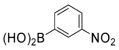
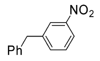
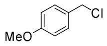
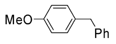
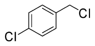
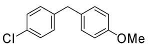
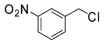
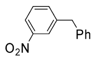
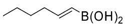
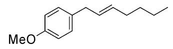
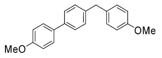
Entry	R^1-X	R^2-9-BBN	Time	Product	Yield
1	**19a**	C_8H_{17}-9-BBN	1.5 h	Ph-C_8H_{17}	**27a**: 95%
2	 **19b**	**26a**	1.5 h		**27b**: 88%
3	**22a**	**26a**	1.5 h		**27c**: 91%
4	 **22d**	**26a**	10 h		**27d**: 91%
5	 **22k**	**26a**	10 h		**27e**: 93%
6	**25b**	**26a**	1.5 h		**27f**: 97% (E : Z (8 : 1))
7	**19a**	Ph(CH_2)$_2$-9-BBN **26b**	10 h	Ph–(CH_2)$_2$Ph	**27g**: 93%
8	**19b**	**26b**	10 h		**27h**: 91%
9	 **25e**	 **26c**	15 h		**27i**: 77%
10	 **25f**	**26c**	15 h		**27j**: 86%

Table 10. The Heterogeneous Suzuki–Miyaura Reaction of Benzyl Halides Catalyzed by PdAS



Entry		R-B(OH)$_2$	Time	Product	Yield
1	 **28a**	**20b**	9 h (1 h)		**29a**: 95% (92%)$^{a)}$
2	**28a**	**20c**	9 h		**29b**: 92%
3	**28a**	 **20h**	9 h		**29c**: 95%
4	 **28b**	**20a**	12 h		**29a**: 98%
5	 **28c**	**20b**	12 h		**29d**: 72% (+**29d′**: 9%)
6	 **28d**	**20a**	12 h		**29c**: 92%
7	**28b**	 **23a**	5 h		**29e**: 99%

a) The reaction was performed with 2.0 mol eq of **20b** in the presence of 2×10^{-3} mol eq of PdAS. **29d′**  .

well as for the industrial process chemistry.[110—113] Although many efforts to prepare solid-phase catalysts for the Heck reaction have been made, homogeneous catalytic systems have advantages on catalytic activity.[114—122] In fact, it was known that designing recyclable system for the Heck reaction was more challenging than that for the Suzuki–Miyaura reaction. These catalysts were less stable under the Heck reaction condition, and thus often decompose physically or chemically. For example, resulting salts accumulated in the reaction lead to degradation of the catalytic system and choke of catalysts under the Heck conditions. Besides, the reductive elimination of phosphonium cation causes depletion of phosphine-containing palladium catalysts.

While a preliminary investigation by using PdAS **2** was carried out, it was concluded that PdAS was not so effective owing to its pulverization under the recycled condition of the Heck reaction. We supposed that cross-linking in PdAS was not sufficient to preserve physical strength for the Heck reaction. This hypothesis struck us that a more cross-linked palladium catalyst should enhance the physical strength and the

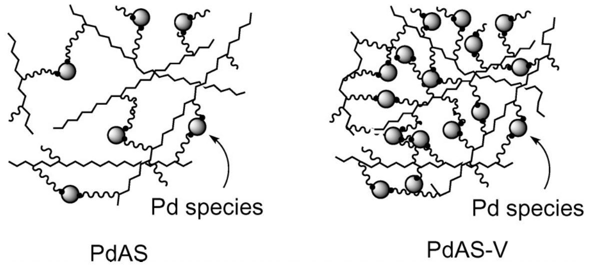


Fig. 3. Working Model of PdAS and PdAS-V

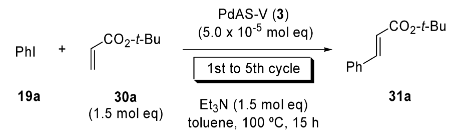
stability. Based on our working hypothesis, I present here the detail of the development of PdAS-V and a highly efficient and recyclable system for the heterogeneous Heck reaction. It is found that PdAS-V showed good stability not only in toluene but also in water, and thus both solvents were suitable for this reaction of versatile substrates such as alkylacrylates, styrenes, and acrylic acid with aryl iodides. It is noteworthy that employment of 8.0×10^{-7}—5.0×10^{-5} mol eq of PdAS-V facilitated the recycled system of the Heck reaction with TON up to 1150000 and TOF up to 12000 h^{-1}. PdAS-V was reused five times without any decrease in its activity. Furthermore, the efficient synthesis of resveratrol, a promising COX-II inhibitor, was achieved *via* the PdAS-V-promoted Heck reaction.

The difference of PdAS-V and PdAS was that the ratio of the *N*-isopropylacrylamide unit to the phosphine unit was 5/1 in PdAS-V while that in PdAS was 10/1. Theoretically, the polymers in PdAS-V were cross-linked eight-fold more than those in PdAS per unit volume, and thus the amount of palladium in PdAS-V increased eight-fold over PdAS per unit content (Fig. 3). This implied that physical strength of PdAS-V was superior to that of PdAS, so that PdAS-V was expected to be prevented from pulverization under the Heck reaction conditions.

4.2. The Catalytic Activity of PdAS-V To check the potency of PdAS-V for the Heck reaction, PdAS-V was treated with the reaction of **19a** with 1.5 mol eq of **30a** in the presence of Et_3N in toluene at 100 °C (Table 1). The results agreed with our working hypothesis that PdAS-V was a highly active and reusable catalyst; the employment of 5.0×10^{-5} mol eq of PdAS-V in the 5th cycled run afforded **31a** in 95% yield with TON being 19000 (entry 5). PdAS-V was recycled five times without any loss of its activity. The average yield of five runs was 94%. A total turnover number of PdAS-V in the 1st to the 5th cycled runs was 94000, and the average of TOF was 1250 h^{-1}.

Since the recycled ability and high TON of PdAS-V was achieved in the Heck reaction, we further investigate the limitation of its catalytic activity. It was found that less than 1 ppm mol eq of PdAS-V catalyzed the coupling efficiently as shown in Chart 10. The employment of 8×10^{-7} mol eq of PdAS-V in the coupling of **19a** (1.37 mol; 153 ml) with **30b** (2.06 mol; 186 ml) for 96 h provided **31b** (1.27 mol; 205 g) in 92% yield, isolated by crystallization. It is notable that PdAS-V promoted the reaction on a scale of more than one mol with TON and TOF in its reaction reaching 1150000 and 12000 h^{-1} respectively. That is, PdAS-V was the most active solid-phase catalyst for the Heck reaction. As far as we know, this is the highest TON value by the reusable catalysts for the Heck reaction.

Table 11. Recycling of PdAS-V for the Heck Reaction



Entry	Cycle	Yield (%)	TON	TOF (h^{-1})
1	1st cycle	92	18400	1230
2	2nd cycle	93	18600	1240
3	3rd cycle	95	19000	1270
4	4th cycle	94	18800	1250
5	5th cycle	95	19000	1270
	A total TON:	94000	Av. TOF:	1250

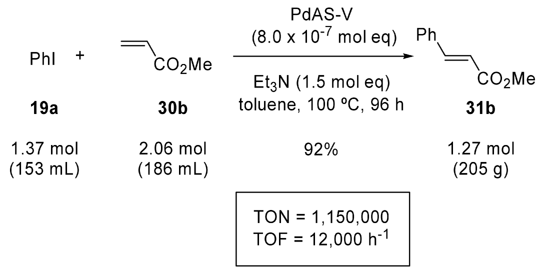


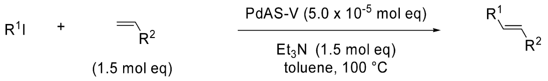
Chart 10. The Heterogeneous Heck Reaction Catalyzed by 8×10^{-7} mol eq of PdAS-V

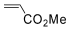
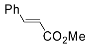
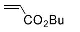
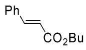
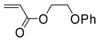
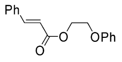
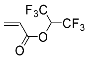
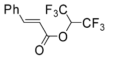
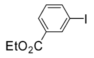
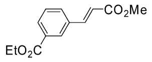
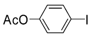
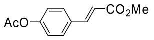
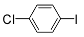
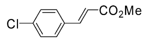
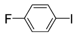
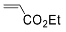
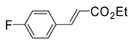
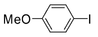
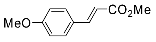
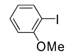
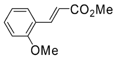
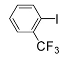
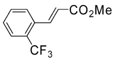
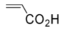
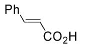
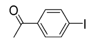
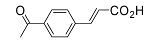
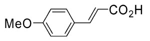
The product **31b** was purified by crystallization.

4.3. The Heck Reaction of Aryl Iodides with Acrylates in Toluene In order to establish the scope of the sequence as depicted in Table 12, the coupling of various aryl halides with acrylates was investigated. All the reactions in Table 12 were performed under identical conditions as in Table 11: aryl iodide (1 mol eq), alkene (1.5 mol eq), PdAS-V (5.0×10^{-5} mol eq), Et_3N (1.5 mol eq) in toluene at 100 °C. Full conversions were achieved for these couplings in the presence of PdAS-V to afford cinnamic esters in high yields with TON and TOF of PdAS-V reached approximately 20000 and 1000 h^{-1}, respectively. The reaction of **19a** with alkylacrylates **30b**—**e** proceeded in 5—20 h to give the corresponding couplings in 93—98% yields (entries 1—4). It is notable that the coupling of hexafluoroisopropyl acrylate (**31d**), an electron-deficient olefin, proceeded much faster and completed in 5 h to furnish **31e** in 95% yield (entry 4). Electron-deficient aryl iodides such as ethoxycarbonyl-, acetoxy-, chloro-, and fluoro-substituted iodobenzenes were also converted to **31f**—**i** in more than 90% yields (entries 5—8). The reaction system was applicable to the reaction of an electron-rich iodoarene (entry 9). Moreover, the coupling of *ortho*-substituted aryl iodides, sterically hindered substrate, proceeded to afford the corresponding products in high yields while it was slower (entries 10, 11). Interestingly, the reactions of acrylic acid (**32**) in toluene were faster than that of alkyl acrylates to afford cinnamic acids **33a** and **b** in 93% and 90% yields.

4.4. The Heck Reaction of Aryl Iodides with Styrenes in Toluene PdAS-V was applicable to the coupling of styrene derivatives. The reaction conditions were identical with that in the reaction of acrylates. Aryl iodides with styrenes were also converted smoothly to the corresponding

Table 12. The Heck Reaction of Aryl Iodides with Acrylates



Entry	R^1I			Time	Product	Yield
1	**19a**		**30b**	12 h		**31b**: 93%
2	**19a**		**30c**	20 h		**31c**: 98%
3	**19a**		**30d**	20 h		**31d**: 97%
4	**19a**		**30e**	5 h		**31e**: 95%
5	 **19b**	**30b**		20 h		**31f**: 95%
6	 **19c**	**30b**		20 h		**31g**: 92%
7	 **19d**	**30b**		20 h		**31h**: 95%
8	 **19e**		**30f**	20 h		**31i**: 93%
9	 **19f**	**30b**		20 h		**31j**: 92%
10	 **19g**	**30b**		40 h		**31k**: 90%
11	 **19h**	**30b**		60 h		**31l**: 82%
12	**19a**		**32**	5 h		**33a**: 93%[a]
13	 **19i**	**32**		4 h		**33b**: 90%[a]
14	**19f**	**32**		8 h		**33c**: 87%[a]

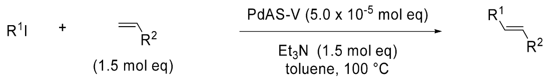
a) The product was purified by recrystallization without column chromatography.

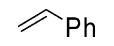
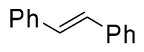
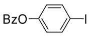
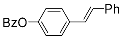
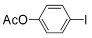
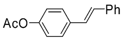
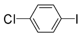
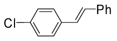
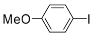
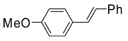
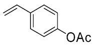
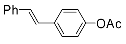
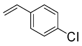
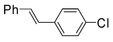
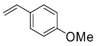
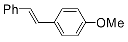
stilbenes in high yields with TON and TON being approximately 20000 and 1000 h^{-1} (Table 13). When the reaction of iodobenzene (**19a**) with styrene (**34a**) was carried out, stilbene (**35a**) was obtained in 90% yield. Both electron-deficient (entries 2—4) and -donating (entry 5) aryl iodides were efficiently coupled with **34a** to provided the corresponding coupling products **35b**—**e** in high yields. Besides, the electron-deficient and -donating styrenes **34b**—**d** were also useful reactants to give **35c**—**e** in approximately 90% yields (entries 6—8).

4.5. The Heck Reaction in Water All the reactions above mentioned were performed in toluene. Since PdAS-V was composed of an amphiphilic polymer, it was expected that PdAS-V was also stable and work in water. Water is inexpensive, nontoxic, nonflammable, and easily available solvent. It nowadays receives much attention as a reaction solvent, although it has not been commonly used because palladium catalysts were generally unstable in water and hydrophobic substrates were insoluble. Thus, the heterogeneous Heck reaction in water was investigated as shown in Table 14.[123—126] We were fueled by finding that PdAS-V has a good stability and activity even in water. The coupling of **19a** with acrylic acid (**32**) proceeded smoothly in 6 h to result in the formation of cinnamic acid (**33a**) in 95% yield (entry 1). Substituted aryl iodides including an *ortho*-substituted aryl iodide were also appropriate substrates in these couplings (entries 2—7). It was notable that styrene (**34a**) was also a useful reactant in water while both aryl iodides and styrene were not dissolved in water (entries 8, 9). This result suggested that dispersion of reagents in water might be effective for promoting the reaction.

4.6. Efficient Synthesis of Resveratrol *via* the Heck Reaction by PdAS-V To demonstrate the utility of PdAS-V for the synthesis of bioactive compounds, resveratrol (**33h**) was synthesized *via* the heterogeneous Heck reaction. Resveratrol is a new type antitumor agent that can inhibit all three stages of cancer by inducing quinone reductase activity, inhibiting cyclooxygenase-2 (COX-2), and inducing the expression of nitroblue tetazolium reduction activity. Furthermore, it can inhibit the development of cardiovasacular disease through its ability as an antioxidant to inhibit platelet aggregation and eicosanoid synthesis and its ability to modulate lipoprotein metabolism.[127—130] However, it is isolated from natural sources in trace amounts,[130] so that efficient chemical syntheses of **33h** are required.[131,132] The starting materials 4-iodophenol (**19j**) and 3,5-dihydroxystyrene (**34e**)[133] were protected by benzoyl group to afford **19k** and **34f** in 82 and 87% yield respectively. The heterogeneous Heck reaction[12] of aryl iodide **19k** and alkene **34f** proceeded smoothly in the presence of PdAS-V to furnish the coupling

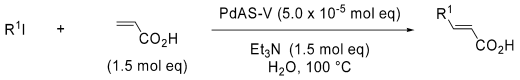
Table 13. The Heck Reaction of Aryl Iodides with Styrenes

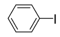
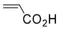
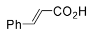
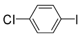
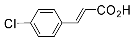
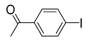
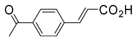
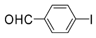
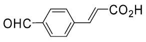
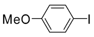
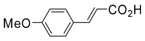
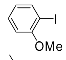
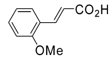
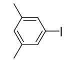
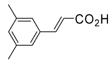
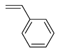
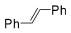
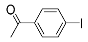
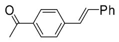


Entry	R^1I	$=\!\!\backslash_{R^2}$	Time	Product	Yield
1	**19a**	 **34a**	12 h		**35a**: 90%
2	 **19j**	**34a**	20 h		**35b**: 86%[a]
3	 **19c**	**34a**	20 h		**35c**: 75%[a]
4	 **19d**	**34a**	20 h		**35d**: 87%[a]
5	 **19f**	**34a**	20 h		**35e**: 92%[a]
6	**19a**	 **34b**	20 h		**35c**: 95%[a]
7	**19a**	 **34c**	20 h		**35d**: 88%[a]
8	**19a**	 **34d**	20 h		**35e**: 93%[a]

[a] These products were purified by recrystallization without column chromatography.

Table 14. The Heck Reaction in Water



Entry	R^1I	$=\!\!\backslash_{R^2}$	Time	Product	Yield[a]
1	 **19a**	 **32**	6 h		**33a**: 94%
2	 **19d**	**32**	6 h		**33d**: 91%
3	 **19i**	**32**	4 h		**33b**: 91%
4	 **19k**	**32**	6 h		**33e**: 94%
5	 **19f**	**32**	24 h		**33c**: 88%
6	 **19g**	**32**	24 h		**33f**: 95%
7	 **19l**	**32**	8 h		**33g**: 92%
8	**19a**	 **34a**	36 h		**33a**: 76%
9	 **19i**	**34a**	30 h		**33f**: 97%

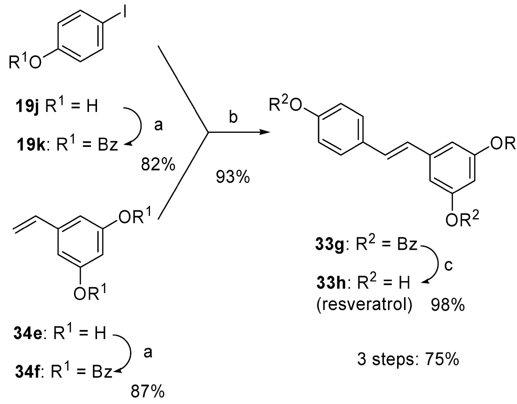
[a] These products were purified by crystallization without column chromatography.

33g in 93% yield. Deprotection of **33g** over NaOMe in THF and MeOH provided resveratrol (**33h**) in 98% yield. The total yield of resveratrol from commercially available **19j** was 75% in 3 steps.

5. Development of a Novel Solid-Phase Asymmetric Titanium Catalyst TiSS and Its Application to Enantioselective Carbonyl-ene Reaction

Since this self-assembled catalyst exhibited great potentiality, we tried applying this concept to asymmetric synthesis (Chart 12).[134—137] Hereby, I present development of new chiral catalysts by our methodology and their application to an asymmetric carbonyl-ene reaction.[138—140] It is noteworthy that one of the catalysts can be reused five times with retention of its activity and enantioselectivity.

Recently, Nakai and co-authors reported an excellent asymmetric carbonyl-ene reaction catalyzed by a bimetallic titanium complex, in which two binaphthols were bridged by μ-oxodititanium **36** (Fig. 4).[138] They noted that the reaction of α-methylstyrene with methyl glyoxylate was carried out in



Reagents and conditions: a) BzCl, pyridine, CH_2Cl_2, 0 °C; (b) **19k** (1 mol eq), **34f** (1.5 mol eq), PdAS-V (5×10^{-4} mol eq), Et_3N (1.5 mol eq), toluene, 100 °C, 12 h; (c) NaOMe, THF-MeOH, 50 °C, 5 h.

Chart 11. Efficient Synthesis of Resveratrol *via* the Heck Reaction by PdAS-V

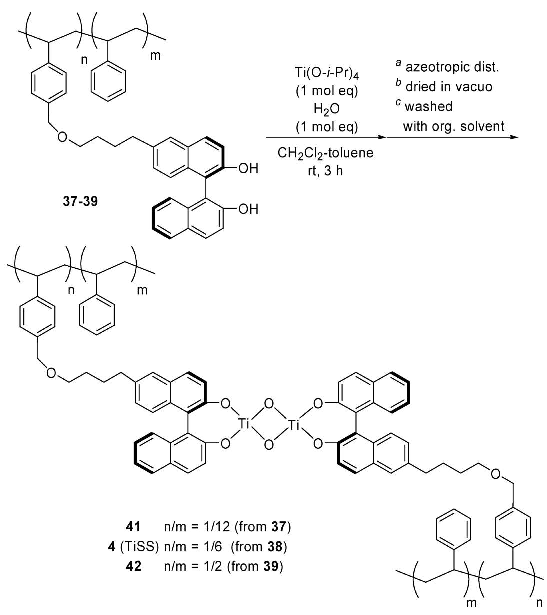


Chart 12

the presence of 5 mol% of the titanium complex in CH_2Cl_2 at −30 °C for 3 h to provide the corresponding product in 93% yield with 98% ee. We envisioned that this homogeneous catalyst would be applicable to the self-assembled and insoluble counterpart, wherein binaphthol moieties bound to non-cross-linked copolymer backbones would be crossbridged by μ-oxodititanium. Therefore, we selected (*R*)-1,1′-bi-2-naphthol (BINOL) as a chiral ligand moiety. First, a titanium catalyst was made from poly(*N*-isopropylacrylamide) with (*R*)-BINOL. However, the carbonyl-ene reaction in the presence of this catalyst provided the corresponding product in low yield with poor ee. This result suggested that a component of the non-cross-linked copolymer backbones might affect the catalytic activity and enantioselectivity. Thus, after investigating several non-cross-linked copolymer backbones, we found the polystyrene copolymers **37**—**39** to be effective. These **37**—**39** were prepared from **40** *via* etherification with 4-vinylbenzyl chloride, random copolymerization with styrene, and deprotection of the methoxymethyl groups, successively. They were easily soluble polymers in CH_2Cl_2, and the ratio of n/m of **37**—**39** could be determined by ^{1}H-NMR in $CDCl_3$.

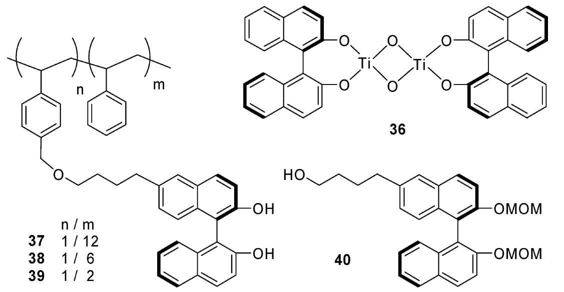
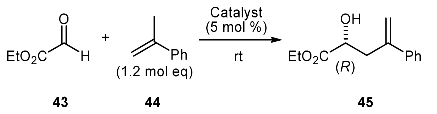


Fig. 4

Table 15. Surveying Potency of Complexes **41**, **4**, and **42** as Chiral Catalysts for an Enantioselective Carbonyl-ene Reaction



Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	ee (%)[b]
1	**41**	CH_2Cl_2	48	49	49
2	**4**	CH_2Cl_2	60	55	58
3	**42**[c]	CH_2Cl_2	14	87	56
4	**4**	THF	60	Trace	N.D.[d]
5	**4**	PhMe	60	56	59
6	**4**	Et_2O	60	68	84

a) Isolated yield after purification by column chromatography. *b*) Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AS. *c*) Compound **45** was obtained in 26% yield with 36% ee by reused **42** which was recovered after the reaction in entry 3.[141] *d*) N.D.=not determined.

With the chiral copolymers in hand, catalysts **41**, **4** (TiSS), and **42** were prepared by a self-assembly of **37**—**39**, Ti(O-*i*-Pr)$_4$, and H_2O based on Nakai's conditions for **36**[138] (Chart 12). Experimental procedure for the synthesis of TiSS was as follows: To a solution of **38** (0.120 mmol as a BINOL unit) in CH_2Cl_2 (2.0 ml) was added a solution of Ti(O-*i*-Pr)$_4$ (0.120 mmol) in toluene (1.2 ml) and H_2O (0.120 mmol) in CH_2Cl_2 (12 ml). The solution was stirred at room temperature for 3 h to give reddish precipitates. The solvents were removed by azeotropic distillation at 110 °C for 1 h, and evaporated at 110 °C under reduced pressure for 1 h. The residue was dried *in vacuo* at room temperature for 14 h, and washed with Et_2O (2×2 ml) to give dark reddish lumps **4**. As predicted, **41**, **4**, and **42** were insoluble in organic solvents such as CH_2Cl_2, THF, PhMe and Et_2O.

To survey the potency of complexes **41**, **4**, and **42** as catalysts, we applied these catalysts to a catalytic enantioselective carbonyl-ene reaction (Table 15). When the reaction of ethyl glyoxylate (**43**) and 1.2 mol eq of α-methylstyrene (**44**) was carried out with 5 mol% of **41**, **4**, and **42** in CH_2Cl_2 at −30 °C, the Nakai reaction conditions,[138] only a trace amount of **45** was yielded. However, we were pleased to find that the reaction proceeded rather easily at room temperature to give **45** in moderate yield with modest ee (entries 1—3). It was found that the solvents influenced the enantioselectivity in this reaction (entries 2, 4—6). When diethyl ether was used as a solvent, **45** was obtained in 68% yield with 84% ee

Table 16. Recyclable Catalysis Promoted by **4** (TiSS)

$$\mathbf{43} + \underset{(1.2\ \text{mol eq})}{\mathbf{44}} \xrightarrow[\text{Et}_2\text{O, rt, 72 h}]{\text{Catalyst } \mathbf{4}\ \text{(TiSS)}\ (20\ \text{mol }\%)} (R)\text{-}\mathbf{45}$$

Entry	Catalyst	Yield (%)	ee (%)
1	1st use	85	88[a]
2	2nd use	83	88
3	3rd use	79	87
4	4th use	77	85
5	5th use	86	81

a) $[\alpha]_D^{26}$ −20.1° ($CHCl_3$, c=0.75) (lit. $[\alpha]_D^{20}$ −22.2° ($CHCl_3$, c=1.9, 96.3% ee)).[144]

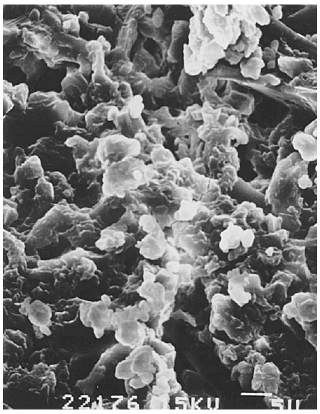


Fig. 5. A Scanning Electron Micrograph (SEM) of TiSS

Scale bar: 5 μm.

(entry 6), whereas CH_2Cl_2 and PhMe gave **45** with moderate ee, and THF afforded only a trace amount of **45**.[142] It is interesting that the highest enantioselectivity was achieved at room temperature by using TiSS **4**.

Furthermore, TiSS **4** was found to be recoverable and reusable (Table 16): when the reaction of **43** and 1.2 mol eq of **44** was performed in the presence of 20 mol% of **4** at room temperature for 72 h, **45** was given in 85% yield with 88% ee (entry 1). The catalyst was reused without further treatment after recovery by filtration. In the repeated use of the recovered catalyst, **45** was obtained in 83% yield with 88% ee (entry 2). Again, the recovered catalyst was reused; that is, the third, fourth and fifth reactions afforded **45** in 79% yield with 87% ee, in 77% yield 85% ee, and in 86% yield with 81% ee, respectively (entries 3—5).[143]

A scanning electron microscope (SEM) study was made to obtain further information on the catalyst (Fig. 5). TiSS was treated with gold vapor by a sputter coating method. The SEM picture showed the presence of many prominences, which were approximately 1—10 μm in length. The surface of **4** is now being investigated to clarify the structure and recognition mechanism.

6. Conclusion

Highly active and reusable catalysts have been successfully developed by self-assembly process of linear amphiphilic polymer ligands with inorganic species, affording insoluble supramolecular complexes. Thus, PWAA **1** prepared from $H_3PW_{12}O_{40}$ and poly[(*N*-isopropylacrylamide)-*co*-(acrylamide with ammonium salt)] is suitable for oxidation of alcohols, amines, and sulfides in aqueous hydrogen peroxide. PdAS **2** produced by self-organization of $(NH_4)_2PdCl_4$ and poly[(*N*-isopropylacrylamide)$_{10}$-*co*-diphenylphosphinostyrene] is an excellent recyclable catalyst for Suzuki–Miyaura reaction in water, water-organic solvent, and organic solvent, is commercially available from Tokyo Kasei Kogyo (TCI) (Fig. 6). PdAS-V **3** assembled from $(NH_4)_2PdCl_4$ and poly[(*N*-isopropylacrylamide)$_5$-*co*-diphenylphosphinostyrene] provides recycling system of itself for Mizorogi–Heck reaction. TiSS **4** made from Ti(O-*i*-Pr)$_4$ and poly(styryl-linked binaphtholate-*co*-styrene) promotes an enantioselective carbonyl-ene reaction as a recyclable catalyst. I believe that this concept for the preparation of highly active and reusable catalysts apply not only for other catalytic systems but also for other supramolecular chemistry, so that I would like to expand this new world for 21st century chemistry.

Fig. 6. Commercially Available PdAS from TCI

Acknowledgements The research presented here was performed at Faculty of Pharmaceutical Sciences, Teikyo University. I would like to express my deep gratitude to Prof. Shiro Ikegami for his kind and great help during the research and for his financial support. I am very thankful to Dr. Hideyo Takahashi for her suitable advice and kind help. I also thank Mr. Masato Ichinohe, Mr. Hidetsugu Tabata, and Mr. Koji Takeda for their good co-working. They worked very hard with me to develop the aforementioned projects. I also thank Ms. Junko Shimode, Ms. Maroka Kitsukawa, and Mr. Kiyoshi Abe for spectroscopic measurement. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Technology. I also thank the Inoue Foundation for Science (IFS) for Inoue Research Award for Young Scientists, and Dainippon Ink and Chemicals, Inc. Award in Synthetic Organic Chemistry, Japan.

References and Notes

1) Anastas P. T., Warner J. C., "Green Chemistry: Theory and Practice," Oxford Univ. Press, Oxford, 1998.
2) Tundo P., Anastas P., Black D. S., Breen J., Collins T., Memoli S., Miyamoto J., Polyakoff M., Tumas W., *Pure Appl. Chem.*, **72**, 1207—1228 (2000).
3) de Miguel Y. R., *J. Chem. Soc., Perkin Trans. 1*, **2000**, 4213—4221 (2000).
4) Shuttleworth S. J., Allin S. M., Wilson R. D., Nasturica D., *Synthesis*, **2000**, 1035—1074 (2000).
5) Loch J. A., Crabtree R. H., *Pure Appl. Chem.*, **73**, 119—128 (2001).
6) Corain B., Kralik M., *J. Mol. Catal A: Chem.*, **173**, 99—115 (2001).
7) Bergbreiter D. E., *Curr. Opin. in Drug Discovery & Development*, **4**, 736—744 (2001).
8) Cameron J. H., "Solid State Organometallic Chemistry Methods and Applications," ed. by Gielen M., Willem R., Wrackmeyer B., Wiley, Chichester, 1999.
9) Buchmeiser M. R., "Polymer Materials in Organic Synthesis and

Catalysis," Wiley-VCH, Weinheim, 2003.

10) Centi G., Cavani F., Trifiro F., "Selective Oxidation by Heterogeneous Catalysis (Fundamental and Applied Catalysis)," Kluwer Academic Pubs, Norwell, MA, 2000.
11) Hodnett K., "Heterogeneous Catalytic Oxidation," Wiley, New York, 2000.
12) Bunin B. A., "The Combinatorial Index," Academic Press, San Diego, 1998.
13) "Reactions on Polymers," ed. by Moore J. A., Redel, Boston, 1973.
14) "Solid Phase Synthesis," ed. by Blossey E. C., Neckers D. C., Dowden, Hutchinson and Ross, Pennsylvania, 1975.
15) Corma A., García H., *Chem. Rev.*, **102**, 3837—3892 (2002).
16) Yamada Y. M. A., Ichinohe M., Takahashi H., Ikegami S., *Org. Lett.*, **3**, 1837—1841 (2001).
17) Yamada Y. M. A., Ichinohe M., Takahashi H., Ikegami S., *Tetrahedron Lett.*, **43**, 3431—3434 (2002).
18) Yamada Y. M. A., Takeda K., Takahashi H., Ikegami S., *Org. Lett.*, **4**, 3371—3374 (2002).
19) Yamada Y. M. A., Tabata H., Takahashi H., Ikegami S., *Synlett*, **2002**, 2031—2034 (2002).
20) Yamada Y. M. A., Takeda K., Takahashi H., Ikegami S., *Tetrahedron Lett.*, **44**, 2379—2382 (2003).
21) Yamada Y. M. A., Takeda K., Takahashi H., Ikegami S., *J. Org. Chem.*, **68**, 7733—7741 (2003).
22) Yamada Y. M. A., Tabata H., Ichinohe M., Takahashi H., Ikegami S., *Tetrahedron*, **60**, 4087—4096 (2004).
23) Yamada Y. M. A., Takeda K., Takahashi H., Ikegami S., *Tetrahedron,* **60**, 4097—4105 (2004).
24) Jacobs and co-workers reported the Amberlite IRA-900-supported Venturello catalyst converted into NO_3^- was effective for the enhancement of selectivity of epoxidation, see: Villa A. L., Sels B. F., de Vos D. E., Jacobs P. A., *J. Org. Chem.*, **64**, 7267—7270 (1999).
25) Ishii Y., Yamawaki K., Ura T., Yamada H., Yoshida T., Ogawa M., *J. Org. Chem.*, **53**, 3587—3593 (1988).
26) Massart R., Contant R., Fruchart J.-M., Ciabrini J.-P., Fournier M., *Inorg. Chem.*, **16**, 2916—2921 (1977).
27) Ishii Y., Tanaka H., Nishiyama Y., *Chem. Lett.*, **1994**, 1—4 (1994).
28) Keggin J. F., *Proc. R. Soc. London, Ser. A*, **144**, 75—100 (1934).
29) Brown G. M., Noe-Spirlet M.-R., Busing W. R., Levy H. A., *Acta Cryst. B*, **33**, 1038—1046 (1977).
30) Ogata Y., Sawaki Y., "Organic Syntheses by Oxidation with Metal Compounds," ed. by Mijs W. J., De Jonge C. R. H. I., Plenum Press, New York, 1986, pp. 839—876.
31) Sato K., Aoki M., Noyori R., *Science*, **281**, 1646—1647 (1998).
32) Venturello C., Gambaro M., *J. Org. Chem.*, **56**, 5924—5931 (1991).
33) Venturello C., Gambaro M., *Synthesis*, **1989**, 295—297 (1989).
34) Bortolini O., Conte V., Di Furia F., Modena G., *J. Org. Chem.*, **51**, 2661—2663 (1986).
35) Villa A. L., Sels B. F., De Vos D. E., Jacobs P. A., *J. Org. Chem.*, **64**, 7267—7270 (1999).
36) Hoegaerts D., Sels B. F., de Vos D. E., Verpoort F., Jacobs P. A., *Catal. Today*, **60**, 209—218 (2000).
37) Gelbard G., Breton F., Quenard M., Sherrington D. C., *J. Mol. Catal. A: Chem.*, **153**, 7—18 (2000).
38) Sakamoto T., Pac C., *Tetrahedron Lett.*, **41**, 10009—10012 (2000).
39) Briot E., Piquemal J.-Y., Vennat M., Brégeault J.-M., Chottard G., Manoli J.-M., *J. Mater. Chem.*, **10**, 953—958 (2000).
40) Ichihara J., *Tetrahedron Lett.*, **42**, 695—697 (2001).
41) De Bos D. E., Wahlen J., Sels B. F., Jacobs P. A., *Synlett*, **2002**, 367—380 (2002).
42) de Vos D. E., Jacobs P. A., *J. Org. Chem.*, **64**, 7267—7270 (1999).
43) It was reported that pH control in aqueous media was important for the tungsten-catalyzed epoxidation, see ref. 33, 34 and 36.
44) Haines A. H., "Methods for the Oxidation of Organic Compounds," Academic Press, London, 1985.
45) Herrmann W. A., Fridgen J., Haider J. J., "Peroxide Chem.," ed. by Adam W., Wiley, Weinheim, 2000, pp. 406—432.
46) Ogata Y., Tomizawa K., Maeda H., *Bull. Chem. Soc. Jpn.*, **53**, 285—286 (1980).
47) Murahashi S., Mitsui H., Shiota T., Tsuda T., Watanabe S., *J. Org. Chem.*, **55**, 1736—1744 (1990).
48) Murahashi S., Oda T., Sugahara T., Masui Y., *J. Org. Chem.*, **55**, 1744—1749 (1990).
49) Sakaue S., Sakata Y., Ishii Y., *Chem. Lett.*, **1992**, 289—292 (1992).
50) Marcantoni E., Petrini M., Polimanti O., *Tetrahedron Lett.*, **36**, 3561—3562 (1995).
51) Ballistreri F. P., Barbuzzi E. G. M., Tomaselli G. A., *J. Org. Chem.*, **61**, 6381—6387 (1996).
52) Reddy J. S., Jacobs P. A., *J. Chem. Soc. Perkin Trans. 1*, **1993**, 2665—2666 (1993).
53) Joseph R., Sudalai A., Ravindranathan T., *Synlett*, **11**, 1177—1178 (1995).
54) Joseph R., Ravindranathan T., Sudalai A., *Tetrahedron Lett.*, **36**, 1903—1904 (1995).
55) Delaude L., Laszlo P., *J. Org. Chem.*, **61**, 6360—6370 (1996).
56) Dewkar G. K., Nikalje M. D., Ali I. S., Paraskar A. S., Jagtap H. S., Sudalai S., *Angew. Chem. Int. Ed.*, **40**, 405—408 (2001).
57) The reaction oxidized by more concentrated H_2O_2 aqueous solution was less successful because dimerization of the substrates occurred. Besides, recycling of PWAA in case of **11a** was not efficient to afford **12a** in lower yield.
58) These oxidations were controlled kinetically, and the regioselectivity for the formation of nitrones was determined at the oxidation stage of dibenzyl hydroxyamines to nitrones. It was assured by the following results: no isomerization between **12e** and **e**′ was observed in the reaction of **12e** or **e**′ in the presence of PWAA and 2.5% H_2O_2, the reaction of **11e** in CH_2Cl_2 at room temperature provided **12e** and **e**′ in 95% yield with the same regioselectivity (**12e**/**12e**′ = 1.76/1), even in the reaction of **12e** or **e**′ with CH_2Cl_2 under identical conditions, isomerizations were hardly observed.
59) Schultz H. S., Freyermuth H. B., Buc S. R., *J. Org. Chem.*, **28**, 1140—1142 (1963).
60) Stec Z., Zawadiak J., Skibinski A., Pastuch G., *Polish J. Chem.*, **70**, 1121—1123 (1996).
61) Neumann R., Juwiler D., *Tetrahedron*, **52**, 8781—8788 (1996).
62) Gresley N. M., Griffith W. P., Laemmel A. C., Nogueira H. I. S., Perkin B. C., *J. Mol. Catal.*, **117**, 185—198 (1997).
63) Collins F. M., Lucy A. R., Sharp C., *J. Mol. Catal.*, **117**, 397—403 (1997).
64) Yasuhara Y., Yamaguchi S., Ichihara J., Nomoto T., Sasaki Y., *Phosphorus Res. Bull.*, **11**, 43—46 (2000).
65) Sato K., Hyodo M., Aoki M., Zheng X.-Q., Noyori R., *Tetrahedron*, **57**, 2469—2476 (2001).
66) Dell'Anna M. M., Mastrorilli P., Nobile C. F., *J. Mol. Catal. A: Chem.*, **108**, 57—62 (1996).
67) Alcon M. J., Corma A., Iglesias M., Sanchez F., *J. Mol. Catal. A: Chem.*, **178**, 253—266 (2002).
68) Noyori *et al.* reported that the oxidation of sulfides to sulfoxides proceeded efficiently in hydrogen peroxide without catalysts, so that we have not examined the selective oxidation to sulfoxide. See ref. 65.
69) Baudin J. B., Hareau G., Julia S. A., Ruel O., *Tetrahedron Lett.*, **32**, 1175—1178 (1991).
70) Kondo K., Tunemoto D., *Tetrahedron Lett.*, **17**, 1397—1400 (1975).
71) Caton M. P. L., Coffee E. C. J., Watkins G. L., *Tetrahedron Lett.*, **9**, 773—774 (1972).
72) Brégault *et al.* reported that heteropoly acidic structure easily decomposed in the presence of hydrogen peroxide under the homogeneous conditions, see: Salles L., Aubry C., Thouvenot R., Robert F., Dorémieux-Morin C., Chottard G., Ledon H., Jeannin Y., Brégault J., *Inorg. Chem.*, **33**, 871—878 (1994). On the other hand, Ishii *et al.* proved that $[\pi\text{-}C_5H_5N^+(CH_2)_{15}CH_3]_3PW_{12}O_{40}^{3-}$ maintained the structure closed to Keggin unit after treatment with hydrogen peroxide. See ref. 27.
73) For an example of the Suzuki–Miyaura reaction used by homogeneous palladium catalysts prepared from poly(*N*-isopropylacrylamide) polymers as soluble and thermoresponsive catalysts: Bergbreiter D. E., Osburn P. L., Wilson A., Sink E. M., *J. Am. Chem. Soc.*, **122**, 9058—9064 (2000).
74) For an example of (*N*-isopropylacrylamide)polymer-protected palladium nanoparticles for hydrogenation, see: Chen C.-W., Akashi M., *Polym., Adv. Technol.*, **10**, 127—133 (1999).
75) Mann F. G., Purdie D., *J. Chem. Soc.*, **1935**, 1549—1563 (1935).
76) Miyaura N., Suzuki A., *Chem. Rev.*, **95**, 2457—2483 (1995).
77) Suzuki A., *J. Organomet. Chem.*, **576**, 147—168 (1999).
78) "Organometallics in Synthesis A Manual," ed. by Schlosser M., Miley, West Sussex, 2002.
79) Stanforth S. P., *Tetrahedron*, **54**, 263—303 (1998).
80) Thompson L. A., Ellman J. A., *Chem. Rev.*, **96**, 555—600 (1996).

81) Tsuji J., "Palladium Reagents and Catalysts: Innovations in Organic Synthesis," Wiley, Chichester, 1995.
82) Akiyama R., Kobayashi S., *Angew. Chem. Int. Ed.*, **40**, 3469—3471 (2001).
83) Cammidge A. N., Baines N. J., Bellingham R. K., *Chem. Commun.*, **2001**, 2588—2589 (2001).
84) LeBlond C. R., Andrew A. T., Sun Y., Sowa J. R., Jr., *Org. Lett.*, **3**, 1555—1557 (2001).
85) Gordon R. S., Holmes A. B., *Chem. Commun.*, **2002**, 640—641 (2002).
86) Kim S.-W., Kim M., Lee W. Y., Hyeon T., *J. Am. Chem. Soc.*, **124**, 7642—7643 (2002).
87) Uozumi Y., Nakai Y., *Org. Lett.*, **4**, 2997—3000 (2002).
88) Sakurai H., Tsukuda T., Hirao T., *J. Org. Chem.*, **67**, 2721—2722 (2002).
89) Mori K., Yamaguchi K., Hara T., Mizugaki T., Ebitani K., Kaneda K., *J. Am. Chem. Soc.*, **124**, 11572—11573 (2002).
90) Li C.-J., *Chem. Rev.*, **93**, 2023—2035 (1993),
91) Grieco P. A. (ed.), "Organic Synthesis in Water," Blackie Academic & Professional, London, 1998.
92) Davies I. W., Matty L., Hughes D. L., *J. Am. Chem. Soc.*, **123**, 10139—10140 (2001).
93) It was ascertained that thorough washing with water and THF in preparing PdAS was essential for removing a trace amount of active and homogeneous catalytic species from PdAS.
94) PdAS was reused after dried *in vacuo*.
95) These reactions afforded 300 to 400 mg (2.25 mmol) of the products, so that it was difficult to isolate the products efficiently under organic solvent-free conditions.
96) Watanabe T., Miyaura N., Suzuki A., *Synlett*, **1992**, 207—210 (1992).
97) For the synthesis of candesartan, see: Kubo K., Kohara Y., Imamiya E., Sugiura Y., Inada Y., Furukawa Y., Nishikawa K., Naka T., *J. Med. Chem.*, **36**, 2182—2195 (1993).
98) For the synthesis of losartan, see: Carini D. J., Duncia J. V., Aldrich P. E., Chiu A. T., Johnson A. L., Pierce M. E., Price W. A., Santella J. B., III, Wells G. J., Wexler R. R., Wong P. C., Yoo S.-E., Timmermans P. B. M. W. M., *J. Med. Chem.*, **34**, 2525—2547 (1991).
99) For the synthesis of L-158809, see: Mantlo N. B., Chakravarty P. K., Ondeyka D. L., Siegl P. K. S., Chang R. S., Lotti V. J., Faust K. A., Chen T.-B., Schorn T. W., Sweet C. S., Emmert S. E., Patchett A. A., Greenlee W. J., *J. Med. Chem.*, **34**, 2919—2922 (1991).
100) Organ M. G., Mayhew D. M., Cooper J. T., Dixon C. E., Lavorato D. J., Kaldor S. W, Siegel M. G., *J. Comb. Chem.*, **3**, 64—67 (2001).
101) Organ M. G., Arvanitis E. A., Dixon C. E., Cooper J. T., *J. Am. Chem. Soc.*, **124**, 1288—1294 (2002).
102) Ishiyama T., Miyaura N., Suzuki A., *Org. Synth.*, **71**, 89—96 (1993).
103) Ishiyama T., Abe S., Miyaura N., Suzuki A., *Chem. Lett.*, **1992**, 691—694 (1992).
104) Chemler S. R., Trauner D., Danishefsky S. J., *Angew. Chem. Int. Ed.*, **40**, 4544—4568 (2001).
105) Maddaford S. P., Keay B. A., *J. Org. Chem.*, **59**, 6501—6503 (1994).
106) Chowdhury S., Georghiou P. E., *Tetrahedron Lett.*, **40**, 7599—7603 (1999).
107) Juteau H., Gareau Y., Labelle M., Lamontagne S., Tremblay N., Carriére M.-C., Sawyer N., Denis D., Metters K. M., *Bioorg. Med. Chem. Lett.*, **11**, 747—749 (2001).
108) Botella L., Nájera C., *Angew. Chem. Int. Ed.*, **41**, 179—181 (2002).
109) When the reaction of benzyl bromide with **20b** (1.5 mol eq) with PdAS (5×10^{-4} mol eq) and KF (3 mol eq) in H$_2$O was performed for 24 h, **29a** was obtained in 65% yield with a significant amount of anisole that was produced by hydrolysis of **20b**.
110) Beletskaya I. P., Cheprakov A. V., *Chem. Rev.*, **100**, 3009—3066 (2000).
111) Whitcombe N. J., Hii K. K. (M.), Gibson S. E., *Tetrahedron*, **57**, 7449—7476 (2001).
112) Biffis A., Zecca M., Basato M., *J. Mol. Catal. A: Chem.*, **173**, 249—274 (2001).
113) Uozumi Y., Hayashi T., "Handbook of Combinatorial Chemistry," ed. by Nicolaou K. C., Hanko R., Hartwig W., Wiley, Weinheim, 2002.
114) Zhou J., Zhou R., Mo L., Zhao S., Zheng X., *J. Mol. Catal. A: Chem.*, **178**, 289—292 (2002).
115) Gordon R. S., Holmes A. B., *Chem. Commun.*, **2002**, 640—641 (2002).
116) Dams M., Drijkoningen L., De Vos D., Jacobs P., *Chem. Commun.*, **2002**, 1062—1063 (2002).
117) Galow T. H., Drechsler U., Hanson J. A., Rotello V. M., *Chem. Commun.*, **2002**, 1076—1077 (2002).
118) Heidenreich R. G., Köhler K., Krauter J. G. E., Pietsch J., *Synlett*, **2002**, 1118—1122 (2002).
119) Chandrasekhar V., Athimoolam A., *Org. Lett.*, **4**, 2113—2116 (2002).
120) Dell'Anna M. M., Mastrorilli P., Muscio F., Nobile C. F., Suranna G. P., *Eur. J. Org. Chem.*, **2002**, 1094—1099 (2002).
121) Mori K., Yamaguchi K., Hara T., Mizugaki T., Ebitani K., Kaneda K., *J. Am. Chem. Soc.*, **124**, 11572—11573 (2002).
122) The homogeneous Heck reaction catalyzed by poly(*N*-isopropylacrylamide)-palladium complex under soluble and thermomorphic conditions, see: Bergbreiter D. E., Osburn P. L., Wilson A., Sink E. M., *J. Am. Chem. Soc.*, **122**, 9058—9064 (2000).
123) Buchmeiser M. R., Lubbad S., Mayr M., Wurst K., *Inorg. Chim. Acta*, **345** 145—153 (2002).
124) Uozumi Y., Kimura T., *Synlett*, **2002**, 2045—2048 (2002).
125) Kogan V., Aizenshtat Z., Popovitz-Biro R., Neumann R., *Org. Lett.*, **4**, 3529—3532 (2002).
126) Mukhopadhyay S., Rothenberg G., Joshi A., Baidossi M., Sasson Y., *Adv. Synth. Cat.*, **344**, 348—354 (2002).
127) Jang M., Cai L., Udeani G. O., Slowing K. V., Thomas C. F., Beecher C. W. W., Fong H. H. S., Farnsworth N. R., Kinghorn A. D., Mehta R. G., Moon R. C., Pezzuto J. M., *Science*, **275**, 218—220 (1997).
128) Subbaramaiah K., Dannenberg A. J., *Adv. Experi. Med. Biol.*, **492**, 147—157 (2001).
129) Ciolino H. P., Yeh G. C., *Adv. Experi. Med. Biol.*, **492**, 183—193 (2001).
130) Sovak M., *J. Med. Food*, **4**, 93—105 (2001).
131) Orsini F., Pelizzoni F., Bellini B., Miglierini G., *Carbohydr. Res.*, **301**, 95—109 (1997).
132) Recently, Gruiso reported syntheses of resveratrol *via* the homogeneous Heck reaction (70% yield) using Pd(OAc)$_2$ and PPh$_3$, used in 1×10^{-2} mol eq, see: Guiso M., Marra C., Farina A., *Tetrahedron Lett.*, **43**, 597—598 (2002).
133) Reek J. N. H., Priem A. H., Engelkamp H., Rowan A. E., Elemans J. A. A. W., Nolte R. J. M., *J. Am. Chem. Soc.*, **119**, 9956—9964 (1997).
134) Lipshutz B. H., Shin Y.-J., *Tetrahedron Lett.*, **41**, 9515—9521 (2000).
135) Yang X.-W., Sheng J.-H., Da C.-S., Wang H.-S., Su W, Wang R., Chan A. S. C., *J. Org. Chem.*, **65**, 295—296 (2000).
136) Sellner H., Faber C., Rheiner P. B., Seebach D., *Chem. Eur. J.*, **6**, 3692—3705 (2000).
137) Jayaprakash D., Sasai H., *Tetrahedron: Asymmetry*, **12**, 2589—2595 (2001).
138) Kitamoto D., Imma H., Nakai T., *Tetrahedron Lett.*, **36**, 1861—1864 (1995).
139) Terada M., Mikami K., *J. Chem. Soc. Chem. Commun.*, **1994**, 833—834 (1994).
140) Annunziata R., Benaglia M., Cinquini M., Cozzi F., Pitillo M., *J. Org. Chem.*, **66**, 3160—3166 (2001).
141) This result would indicate that the self-assembly of **39** and Ti(O-*i*-Pr)$_4$ was not successful.
142) It is unclear why the reaction in THF did not proceed. The strong Lewis basicity of THF would reduce a Lewis acidity of the titanium catalyst.
143) The preparation of the catalyst was reproducible. A different batch of the catalyst was independently prepared from a different batch of the polymer, and showed identical activity and enantioselectivity in this reaction.
144) Cavorot M., Byrne J. J., Chavant P. Y., Pardillos-Guindet J., Vallée Y., *Tetrahedron: Asymmetry*, **9**, 3889—3894 (1998).