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Highly Active Catalyst for the Heterogeneous Suzuki−Miyaura Reaction: Assembled Complex of Palladium and Non-Cross-Linked Amphiphilic Polymer

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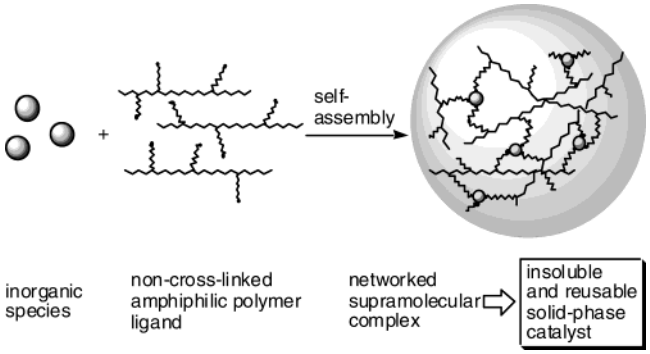
An assembled insoluble catalyst, PdAS, prepared from palladium ($(NH_4)_2PdCl_4$ (**1**)) and non-cross-linked amphiphilic copolymer poly(*N*-isopropylacrylamide-*co*-4-diphenylstyrylphosphine) (**2**) was developed. It was found that PdAS is an excellent catalyst for the Suzuki−Miyaura reaction on three points: (1) The use of 8×10^{-7} to 5×10^{-4} mol equiv of PdAS afforded the coupling products efficiently after easy workup, with the turnover number reaching up to 1 250 000. (2) The catalyst was reusable many times without loss of catalytic activity. (3) PdAS showed good stability in any reaction medium (i.e., water or aqueous or anhydrous organic solvents). Analytical study of PdAS indicates that the phosphines in **2** coordinate to palladium to form $PdCl_2(PPh_2Ar)_2$ species.

Introduction

Development of immobilized and insoluble metal catalysts has been of great interest in recent organic chemistry.[1,2] 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 leach away from their supports. Taking these into consideration, we decided to concentrate on developing insoluble metal catalysts which are highly active and stable. Our goal was that they still be effective in the use of ppm mol equiv, and in being recycled many times in any reaction medium. To achieve the challenging theme, we have focused on amphiphilic insoluble catalysts based on a novel concept (Scheme 1).

SCHEME 1. Concept for the Preparation of an Assembled Catalyst of Inorganic Species and a Non-Cross-Linked Amphiphilic Polymer Ligand



We investigated a self-assembly process between non-cross-linked amphiphilic polymer ligands and an inorganic species.[3] This process should afford a networked supramolecular complex where the polymers are cross-linked together by the inorganic species. Such an insoluble complex was expected to act as a highly reactive catalyst because the polymers and the inorganic species could construct effective catalytic sites with high affinity to both hydrophilic and hydrophobic reagents. This implies that they work with efficiency in both water and organic solvents. In addition, the cross-linked complex has a characteristic high surface-to-volume ratio, and the many mesopores formed by the cross-linking will be able to capture reagents easily. Hence, higher efficiency of the

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(2) For recent reviews of immobilized palladium catalysts, see: (a) de Miguel, Y. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4213−4221. (b) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035−1074. (c) Loch, J. A.; Crabtree, R. H. *Pure Appl. Chem*. **2001**, *73*, 119−128. (d) Corain, B.; Kralik, M. *J. Mol. Catal A: Chem*. **2001**, *173*, 99−115. (e) Bergbreiter, D. E. *Curr. Opin. Drug Discovery Dev*. **2001**, *4*, 736−744. (f) Cameron, J. H. In *Solid State Organometallic Chemistry Methods and Applications*; Gielen, M., Willem, R., Wrackmeyer, B., Eds.; Wiley: Chichester, U.K., 1999.

(3) (a) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Org. Lett*. **2001**, *3*, 1837−1841. (b) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett*. **2002**, *43*, 3431−3434. (c) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Org. Lett*. **2002**, *4*, 3371−3374. (d) Yamada, Y. M. A.; Tabata, H.; Takahashi, H.; Ikegami, S. *Synlett* **2002**, 2031−3034.

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catalytic cycle will be reached. On the basis of such a hypothesis, we developed a tungsten catalyst, PWAA, formed from $H_3PW_{12}O_{40}$ and poly{[3-(acryloylamino)-propyldodecyldimethylammonium nitrate]-*co*-(*N*-isopropylacrylamide)$_{12}$} for oxidation.[3a,d] Since this self-assembled catalyst exhibited great potential, we next extended this methodology to a palladium catalyst applicable to the Suzuki−Miyaura reaction, which is the palladium-catalyzed cross-coupling reaction of halides or triflates with boronic acids or their esters. This reaction is one of the most important, powerful, and versatile tools for the synthesis of biologically active compounds and liquid crystals.[4] Although many heterogeneous catalysts, including Pd/C, have been applied to the Suzuki−Miyaura reaction,[5] homogeneous catalytic systems still have advantages in catalytic activity.

In this paper, we describe the development of an assembled catalyst, PdAS, prepared from $(NH_4)_2PdCl_4$ (**1**) and non-cross-linked amphiphilic polymer poly[(*N*-isopropylacrylamide)-*co*-(4-diphenylstyrylphosphine)] (**2**) and its application to the heterogeneous Suzuki−Miyaura reaction. The coupling of aryl and alkenyl halides with arylboronic and alkenylboronic acids was efficiently catalyzed by 8×10^{-7} to 5×10^{-4} mol equiv of PdAS. It should be noted that the highest turnover number (TON (= mol of product/mol of catalyst)) of PdAS reached up to 1 250 000. To our knowledge, this is the highest TON value by a reusable catalyst for the Suzuki−Miyaura reaction. PdAS showed outstanding stability in any reaction medium such as water or aqueous or anhydrous organic solvents and was reused 10 times without loss of activity.

Results and Discussion

Development of an Assembled Catalyst, PdAS. We examined self-assembly between various palladium species and non-cross-linked amphiphilic polymers with phosphine ligands and found that the complexation of **1** and **2** afforded a novel palladium−polymer catalyst, PdAS (Pd−acrylamide−styrylphosphine). As shown in Scheme 2,[6] random copolymerization of 4-diphenylstyrylphosphine (**4**) with 12 mol equiv of *N*-isopropylacrylamide (**5**) in the presence of 4 mol % AIBN gave **2** in 89% yield. The ratio of the phosphine to the amide units in **2** 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, 1/10, was reproducible in several experiments. The molecular weight of **2** was wide-ranging (ca. 5000−70000) as a result of gel-permeation chromatography relative to polystyrene standards. Self-assembly of **1** and **2** was investigated under conditions similar to those for the preparation of $PdCl_2(PPh_3)_2$.[7] To a well-stirred solution of **2** (3 mol equiv in phosphine) in THF was added a solution of **1** (1 mol equiv) in H_2O. The mixture was stirred for 62 h at room temperature, and a precipitate was formed. After water was added to the suspension, THF was removed at 80 °C for 4 h with 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 the suspension was dried in vacuo, a dark red solid, PdAS (**3**), 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.

To obtain information on the structure of the catalyst, **3** was characterized by gel-phase ^{31}P NMR in $CDCl_3$. While a peak of **2** was observed at −2.9 ppm ($ArPh_2P$), two broad peaks of **3** 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 **2** coordinated with palladium to form a Pd(II) complex. In our preliminary experiments, it was elucidated that the complexation of **1** and poly(*N*-isopropylacrylamide) without phospine units afforded no precipitates. Considering these results, it could be confirmed that the phosphine ligands of **2** cross-linked with palladium (Scheme 2).

Catalytic Activity of PdAS for the Suzuki−Miyaura Reaction. The catalytic activity of PdAS for the heterogeneous Suzuki−Miyaura reaction was investigated. (Table 1). Since "water" is the most safe and easily available solvent, numerous attempts have been made in utilizing it in organic reactions.[8] While the development of catalytic systems in water has been confronted with many difficulties, PdAS will be a key to developing an efficient system in water owing to its amphiphilicity. Therefore, all the reactions in Tables 1−3 and Scheme 3 were performed in water under organic-solvent-free conditions. The reaction of iodobenzene (**6a**)

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(6) For an example of the Suzuki−Miyaura reaction catalyzed by homogeneous palladium catalysts prepared from poly(*N*-isopropylacrylamide) polymers as soluble and thermoresponsive catalysts, see: Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058−9064. For an example of (*N*-isopropylacrylamide)-polymer-protected palladium nanoparticles for hydrogenation, see: (b) Chen, C.-W.; Akashi, M. *Polym. Adv. Technol.* **1999**, *10*, 127−133.

(7) Mann, F. G.; Purdie, D. *J. Chem. Soc.* **1935**, 1549−1563.

(8) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023−2035. (b) Grieco, P. A., Ed. *Organic Synthesis in Water*; Blackie Academic & Professional: London, 1998.

SCHEME 2. Preparation of an Assembled Catalyst, PdAS, for the Suzuki−Miyaura Reaction and Its Working Model

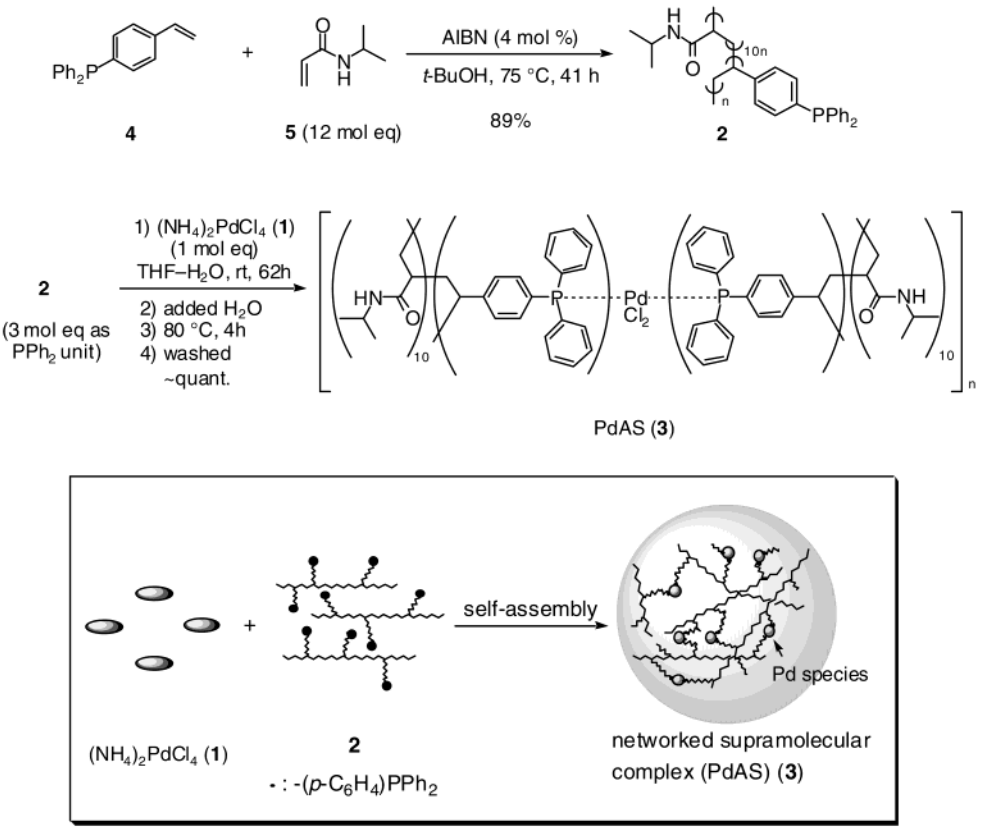
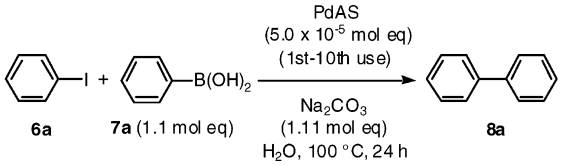


TABLE 1. Heterogeneous Suzuki−Miyaura Reaction of 6a with 7a Catalyzed by 5×10^{-5} mol equiv of the Recycled Catalyst PdAS



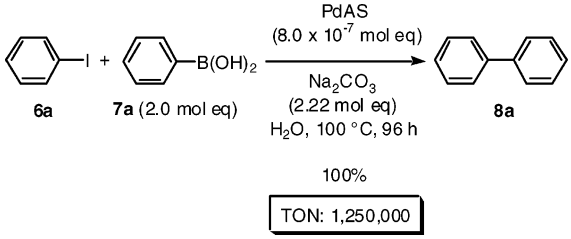
entry	catalyst cycle	yield[a] (%)	TON
1	1st	95%	19 000
2	10th	93%	18 600
3	1st to10th consecutive	av 95%	total of 190 000

[a] Isolated by crystallization under organic-solvent-free conditions.

with phenylboronic acid (**7a**) (1.1 mol equiv) in the presence of 5×10^{-5} mol equiv of PdAS proceeded efficiently to give biphenyl (**8a**) in 95% yield (entry 1), with the TON of PdAS reaching approximately 20 000. Leaching of catalytically active species from the supports was often a crucial problem generally.[9] 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.[10]

More importantly, the workup of this reaction was perfectly performed under organic-solvent-free conditions, where water was the only solvent used. After the reaction was complete, the liquid reaction mixture was filtrated with boiling water under an argon atmosphere (see the Supporting Information, Figure S-1). PdAS was recovered on a glass filter,[11] and the filtrate was cooled to room temperature to give **8a** as white crystals with high purity.

SCHEME 3. Heterogeneous Suzuki-−Miyaura Reaction Catalyzed by 8.0×10^{-7} mol equiv of PdAS



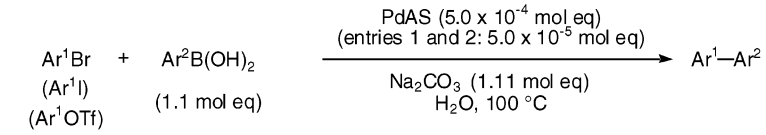
To examine the activity of PdAS as a recyclable catalyst, 5×10^{-5} mol equiv of PdAS was reused 10 times in the reaction of **6a** and **7a**. All the reactions were worked up under organic-solvent-free conditions as mentioned above. It is noteworthy that PdAS maintains its catalytic activity after many reuses (Table 1). The reaction in the 10th cycled run gave **8a** in 93% yield (entry 2). The average yield of **8a** in consecutive runs was 95% (entry 3), and the total TON of PdAS in the 1st to the 10th cycled reactions reached 190 000.

(9) Davies, I. W.; Matty, L.; Hughes, D. L. *J. Am. Chem. Soc.* **2001**, *123*, 10139−10140.

(10) 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.

(11) PdAS was reused after being dried in vacuo.

TABLE 2. Heterogeneous Suzuki–Miyaura Reaction of Aryl Iodides and Bromides and an Aryl Triflate with Arylboronic Acids Catalyzed by PdAS

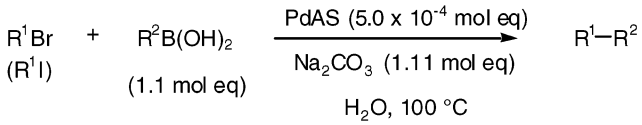


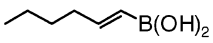
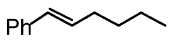
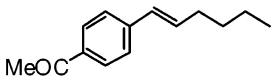
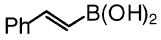
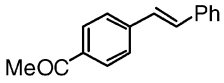
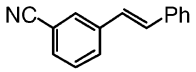
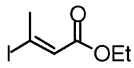
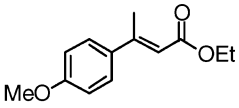
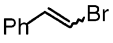
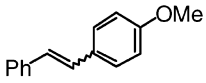
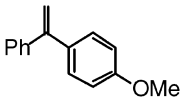
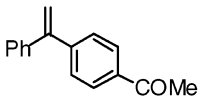
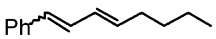
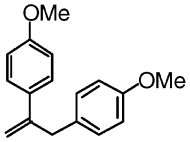
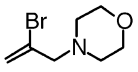
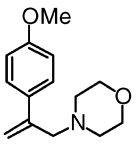
Entry	Ar^1Br (Ar^1OTf)		$Ar^2B(OH)_2$		Time	Product	Yield
1	PhI	**6a**	MeO–$B(OH)_2$	**7b**	24 h	MeO–Ph	**8b**: 97%
2	**6a**		MeOC–$B(OH)_2$	**7c**	24 h	MeOC–Ph	**8c**: 98%
3	MeOC–Br	**9a**	**7a**		24 h	MeOC–Ph	**8d**: 98%
4	OHC–Br	**9b**	**7a**		9 h	OHC–Ph	**8e**: 97%
5	NC–Br	**9c**	**7a**		9 h	NC–Ph	**8f**: 98%
6	Cl–Br	**9d**	**7a**		12 h	Cl–Ph	**8g**: 94%
7	Me–Br	**9e**	**7a**		9 h	Me–Ph	**8h**: 95%
8	MeO–Br	**9f**	**7a**		24 h	MeO–Ph	**8b**: 87%
9	Me–OTf	**9g**	**7a**		9 h	Me–Ph	**8h**: 93%
10	HO–Br	**9h**	**7a**		4 h (24 h at rt)	HO–Ph	**8i**: 91% (80% at rt)
11	HO_2C–Br	**9i**	**7a**		4 h	HO_2C–Ph	**8j**: 95%
12	N–Br	**9j**	**7a**		9 h	N–Ph	**8k**: 99%
13	**9e**		**7b**		9 h	Me–OMe	**8l**: 91%
14	**9e**		MeS–$B(OH)_2$	**7d**	9 h	Me–SMe	**8m**: 95%
15	**9e**		HOH_2C–$B(OH)_2$	**7e**	9 h	Me–CH_2OH	**8n**: 87%
16	**9e**		MeOC–$B(OH)_2$	**7f**	9 h	Me–COMe	**8o**: 84%
17	CN, Br	**9k**	Me–$B(OH)_2$	**7g**	24 h	Me, CN	**8p**: 93%

We further investigated the limitation of its catalytic activity and found that less than 1 ppm mol equiv of PdAS still catalyzed the reaction efficiently as depicted in Scheme 3. Treatment of **6a** with **7a** in the presence of 8×10^{-7} mol equiv of PdAS afforded **8a** quantitatively with high purity.[12] In this case, the turnover number reached 1 250 000.

(12) A ^{1}H NMR chart of **8a** in this reaction is available in the Supporting Information.

TABLE 3. Heterogeneous Suzuki−Miyaura Reaction of Alkenyl Halides and Alkenylboronic Acids Catalyzed by PdAS



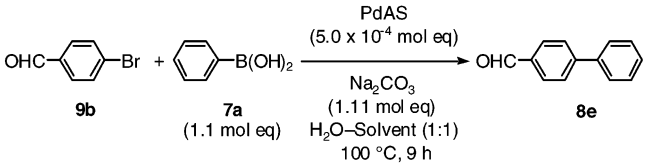
Entry	Halide	Boronic Acid	Time	Product	Yield
1	**6a**	 **10a**	9 h		**11a**: 91%
2	**9a**	**10a**	9 h		**11b**: 86%
3	**9a**	 **10b**	6 h		**11c**: 82%
4	**9c**	**10b**	6 h		**11d**: 82%
5	 **12a**	**7b**	6 h		**11e**: 96%
6	 **12b** (*E* : *Z* (10 : 1))	**7b**	24 h		**11f**: 91%
7	 **12c**	**7b**	9 h		**11g**: 90%
8	**12c**	**7f**	9 h		**11h**: 92%
9	**12b** (*E* : *Z* (6 : 1))	**10a**	5 h		**11i**: 81% (*E* : *Z* (5 : 1))
10[b]	 **12d**	**7b**[a]	24 h		**11j**: 70%
11[b]	 **12e**	**7b**	9 h		**11k**: 81%

[a] 3.0 mol equiv of **7b**. [b] The reaction temperature was 80 °C, and 2.0 × 10^{-3} mol equiv of PdAS was used.

Coupling of Aryl Halides with Arylboronic Acids in Water. 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 2.[13] The following reactions except that in entry 1 were worked up by the traditional method

(13) The coupling of these substrates was reviewed in ref 4a.

TABLE 4. Effect of Organic Solvents as Cosolvents on the Heterogeneous Suzuki−Miyaura Reaction Catalyzed by PdAS in Water



entry	solvent	yield (%)	entry	solvent	yield (%)
1		95	5	1,4-dioxane	95
2	THF	91	6	2-butanone	89
3	toluene	92	7	2-butanol	87
4	DMF	94	8	EtOH−DME (1:4)	90

using an organic solvent.[14] The reaction of **6a** with an electron-rich (**7b**) or electron-deficient (**7c**) arylboronic acid catalyzed by 5×10^{-5} mol equiv of PdAS afforded the corresponding biaryls **8b** and **8c** in almost quantitative yields (entries 1 and 2). The reaction of electron-deficient aryl bromides **9a**−**d** with **7a** proceeded smoothly in the presence of 5×10^{-4} mol equiv of PdAS to give the biaryls **8d**−**g** in 94−98% yields (entries 3−6). This system was applicable to the electron-rich aryl bromides **9e**,**f** (entries 7 and 8) and an aryl triflate, **9g** (entry 9). 4-Bromophenol (**9h**), 4-bromobenzoic acid (**9i**), and 3-bromopyridine (**9j**) were easily converted to the corresponding biaryls (entries 10−12). The reactions using **9h** and **9i**, which were soluble in water, were complete in 4 h to give **8i** and **8j** in 91% and 95% yield, respectively (entries 10 and 11). It is notable that the reaction in entry 10 could be performed at room temperature under identical reaction conditions to afford **8i** in 80% yield. Substituted arylboronic acids can be used as reactants (entries 1, 2, and 13−17). The reaction of the sulfur-containing boronic acid **7d** also proceeded smoothly to afford **8m**[15] 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.[16] However, it was found that the use of 1.1 mol equiv of the electron-deficient arylboronic acid **7f** with **9e** resulted in the biaryl **8o** in 84% yield (entry 16). Furthermore, the product **8p**, which is an important intermediate in the synthesis of the angiotensin II antagonists[17] (see the Supporting Information, Scheme S-1), was prepared by the reaction of 2-bromobenzonitrile (**9k**) with *p*-tolylboronic acid (**7g**) (entry 17).

Coupling of Alkenyl Halides and Alkenylboronic Acids. At this point, we turned our attention to the coupling of alkenyl halides and alkenylboronic acids (Table 3).[13] In the presence of 5×10^{-4} mol equiv of PdAS, hexenylboronic acid (**10a**) was successfully cross-coupled with **6** and **9a** to afford **11a**[18] and **11b**[19] in 91% and 86% yield (entries 1 and 2). The reaction of aryl bromides **9a** and **9c** with *trans*-2-phenylvinylboronic acid (**10b**) also proceeded efficiently (entries 3 and 4). Similarly, ethyl *cis*-3-iodomethacrylate (**12a**) was converted to the corresponding coupling product **11e** in 96% yield (entry 5). It is interesting to note that *β*-bromostyrene (**12b**) (*E*/*Z* = 10/1) was reacted with **7b** to afford **11f** in 91% yield without isomerization (entry 6). α-Bromostyrene (**12c**) was converted to disubstituted styrene derivatives **11g** and **11h**[20] in 90% and 92% yield, respectively (entries 7 and 8). The coupling of an alkenyl halide with an alkenylboronic acid was successful; conjugated diene **11i**[21] was synthesized from **12b** and **10a** in 81% yield (entry 9). Both vinyl and allylic bromides in 2,3-dibromopropene (**12d**) reacted with 3 mol equiv of **7b** to afford the double coupling product **11j** in 70% yield (entry 10). A screening compound for several GABA uptake inhibitors, **11k**,[22] was synthesized from **12e** and **7b** in 81% yield (entry 11).

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 the stability of PdAS in organic solvents. During the study on the characterization of PdAS, we 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 cosolvents proceeded efficiently (Table 4). While the coupling of **9b** with **7a** in water afforded **8e** in 95% yield (entry 1), the reactions in 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 **8e** in approximately 90% yield. These results indicated that PdAS maintains its catalytic activity in organic solvents.[23]

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.[24] It is notable that PdAS also worked effectively even in anhydrous conditions. As shown in Table 5, the reactions of octyl-9-BBN (**13a**), prepared from 1-octene and 9-BBN−H in THF, with aryl

(14) These reactions afforded 300−400 mg (2.25 mmol) of the products, so it was difficult to isolate the products efficiently under organic-solvent-free conditions. See the Experimental Section.

(15) Lane, G. M., Jr.; Momde, K.; Tomita, Y.; Iwashita, T.; Nakanishi, K.; McDermott, A. E. *J. Magn. Reson.* **2001**, *152*, 1−6.

(16) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210.

(17) (a) 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.* **1993**, *36*, 2182−2195. (b) 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.* **1991**, *34*, 2525−2547. (c) 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.* **1991**, *34*, 2919−2922.

(18) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *123*, 5600−5601.

(19) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(20) Heidenreich, R.; Kohler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118−1122.

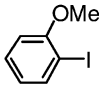
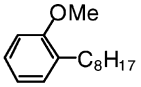
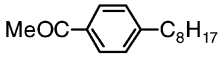
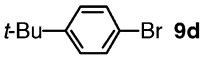
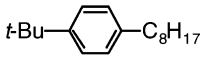
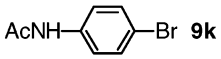
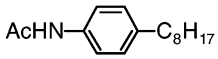
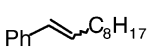
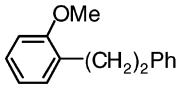
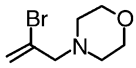
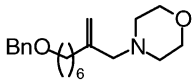
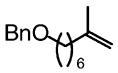
(21) Kobayashi, Y.; Watatani, K.; Tokoro, Y. *Tetrahedron Lett.* **1998**, *39*, 7533−7536.

(22) (a) Organ, M. G.; Mayhew, D. M.; Cooper, J. T.; Dixon, C. E.; Lavorato, D. J.; Kaldor, S. W,; Siegel, M. G. *J. Comb. Chem.* **2001**, *3*, 64−67. (b) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288−1294.

(23) As for the recycling of PDAS in organic media, we have shown that it maintains catalytic activity in the Heck reaction, which will be reported in another full paper.

(24) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Org. Synth.* **1993**, *71*, 89−96.

TABLE 5. Heterogeneous Suzuki−Miyaura Reaction of Alkyl-9-BBNs Catalyzed by PdAS

Entry	R^1—X	R^2—9-BBN	Time	Product	Yield
1	**6a**	C_8H_{17}−9-BBN **13a**	1.5 h	Ph−C_8H_{17}	**14a**: 95%
2	 **6b**	**13a**	1.5 h		**14b**: 88%
3	**9a**	**13a**	1.5 h		**14c**: 91%
4	 **9d**	**13a**	10 h		**14d**: 91%
5	 **9k**	**13a**	10 h		**14e**: 93%
6	**12b**	**13a**	1.5 h		**14f**: 97% (*E* : *Z* (8 : 1)
7	**6a**	$Ph(CH_2)_2$-9-BBN **13b**	10 h	Ph−$(CH_2)_2$Ph	**14g**: 93%
8	**6b**	**13b**	10 h		**14h**: 91%
9	 **12e**	 **13c**	15 h		**14i**: 77%
10	 **12f**	**13c**	15 h		**14j**: 86%

iodides **6a** and **6b** were performed in THF−1,4-dioxane (1:1),[25] furnishing 1-aryloctanes **14a** and **14b** in 95% and 88% yield, respectively (entries 1 and 2). Electron-deficient and -rich aryl bromides and alkenyl bromides **9a**, **9d**, **9k**, and **12b** were also adequate substrates (entries 3−6). The reactions of phenyethyl-9-BBN gave the corresponding coupling products in more than 90% yield (entries 7 and 8). Besides, the coupling of an alkenyl halide with an alkyl-9-BBN is among the most important reactions for natural product synthesis.[26] Thus, it is noteworthy that the coupling of alkenyl bromides **12b** (entry 6), **12e** (entry 9), and **12f** (entry 10) proceeded efficiently to provide the corresponding products in high yields.

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 6). Until now, there have been only a few reported examples of the Suzuki−Miyaura reactions of benzylic halides even in the homogeneous system.[27] The reaction of benzyl chloride with 1.1 mol equiv of boronic acid was performed in the presence of 5×10^{-4} mol equiv of PdAS with 3.0 mol equiv of KF in DME. The coupling of benzyl chloride (**15a**) with **7b** was accomplished in 9 h to give **16a** in 95% yield (entry 1).[28] This result indicated that oxidative addition of a benzylic chloride to PdAS proceeded smoothly. The same reaction of **15a** with 2.0 mol equiv of **7b** in the presence of 2×10^{-3} mol equiv of PdAS was complete in 1 h to afford **16a** in 92% yield. Electron-deficient and -rich arylboronic acids were also converted to the coupling products in more than 90% yield (entries 2 and 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 (**15b**) with **7b** afforded **16d** in 72% yield and a biscoupling product, **16d′**, in 9% yield; it is assumed that the oxidative addition of a less reactive aryl chloride to PdAS occurred in these conditions. Furthermore, alkenylboronic acid **10a** was coupled with benzylic chloride smoothly (entry 7).

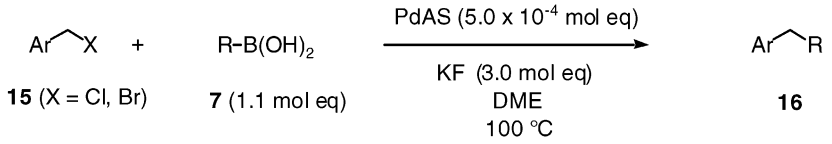
(25) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691−694.

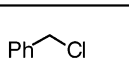
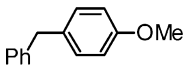
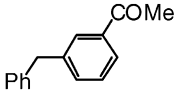
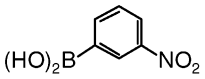
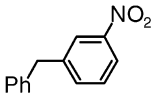
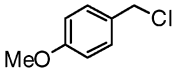
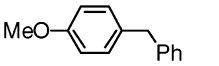
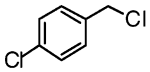
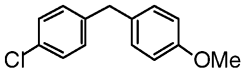
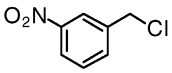
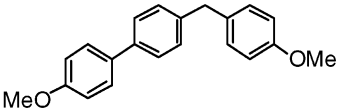
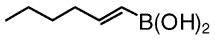
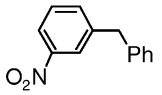
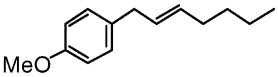
(26) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568.

(27) (a) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501−6503. (b) Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599−7603. (c) Juteau, H.; Gareau, Y.; Labelle, M.; Lamontagne, S.; Tremblay, N.; Carriére, M.-C.; Sawyer, N.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 747−749. (d) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179−181.

(28) When the reaction of benzyl bromide with **7b** (1.5 mol equiv) with PdAS (5×10^{-4} mol equiv) and KF (3 mol equiv) in H_2O was performed for 24 h, **16a** was obtained in 65% yield with a significant amount of anisole that was produced by hydrolysis of **7b**.

TABLE 6. Heterogeneous Suzuki−Miyaura Reaction of Benzyl Halides Catalyzed by PdAS



Entry	Ar X		R-B(OH)$_2$		Time	Product	Yield
1		**15a**	**7b**		9 h (1 h)		**16a**: 95% (92%)[a]
2	**15a**		**7c**		9 h		**16b**: 92%
3	**15a**			**7h**	9 h		**16c**: 95%
4		**15b**	**7a**		12 h		**16a**: 98%
5		**15c**	**7b**		12 h		**16d**: 72%
6		**15d**	**7a**				(+**16d'**: 9%)
7	**15b**			**10a**	12 h		**16c**: 92%
					5 h		**16e**: 99%

[a] The reaction was performed with 2.0 mol equiv of **7b** in the presence of 2×10^{-3} mol equiv of PdAS.

Conclusion

In summary, we have developed a new reusable heterogeneous catalyst, PdAS, prepared from a self-assembly of **1** and **2**. It efficiently catalyzed the heterogeneous Suzuki−Miyaura reaction of aryl and alkenyl halides and benzylic chlorides with arylboronic and alkenylboronic acids and alkyl-9-BBNs. It should be noted that the highest TON reached over one million. PdAS showed outstanding stability in any reaction medium such as water or aqueous or anhydrous organic solvents and was reused 10 times without any decrease in its catalytic activity.

Experimental Section

Poly(*N*-isopropylacrylamide-*co*-4-diphenylstyrylphosphine) (2). To a solution of **4** (2.5 mmol) in *t*-BuOH (50 mL), after treatment of ultrasonication for 3 h to degass and dissolve **4** in *t*-BuOH, was added **5** (30 mmol), and the mixture was degassed by ultrasonication for 20 min. To the solution was added AIBN (0.10 mmol), and the resulting solution was again degassed by ultrasonication for 2 × 25 min, stirred at 75 °C for 41 h, and evaporated at 75 °C to give a crude polymer. It was purified by precipitation (3×) from CH_2Cl_2 and Et_2O and dried in vacuo (ca. 0.08 mmHg) to afford **2** in 89% yield: IR (KBr, cm^{-1}) ν 3306, 2973, 2934, 1653, 1537, 1458, 1172, 1130, 747, 698; ^{1}H NMR (400 MHz, $CDCl_3$ with a trace of D_2O) δ 1.14 (br, 60H), 1.35−1.80 (br, 20H), 2.13 (br, 10H), 3.99 (br, 10H), 7.02−7.65 (br, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 41.3, 42.4, 128.3, 128.5, 133.4, 133.6, 174.2; ^{31}P NMR (243 MHz, $CDCl_3$) δ −3.0 (br, Ar_2PhP). Anal. Calcd for $C_{80n}H_{137n}O_{15n}N_{10n}P_n$ as **2**·5nH$_2$O: C, 63.635; H, 9.145; N, 9.276. Found: C, 63.417; H, 9.469; N, 8.944.

Poly[dichlorobis(*N*-isopropylacrylamide-*co*-4-diphenylstyrylphosphine)palladium] (PdAS) (3). All solvents were degassed by ultrasonication and argon substitution prior to use. To a well-stirred solution of **2** (0.36 mmol in phosphine) in THF (72 mL) was added a solution of **1** (0.12 mmol) in H_2O (30 mL), and the mixture was again degassed. After the mixture was stirred for 62 h at room temperature, a yellow precipitate was formed. Water (30 mL) was added to the suspension, and THF was removed at 80 °C for 4 h with Dean−Stark equipment to give a red precipitate. This precipitate was stirred at 100 °C successively in H_2O (100 mL) for 12 h, in THF (100 mL) for 3 h, and in H_2O (100 mL) for 12 h to wash the unreacted palladium species and polymers. After the precipitate was dried in vacuo (ca. 0.08 mmHg), a dark red solid, **3**, was obtained in almost quantitative yield: IR (KBr, cm^{-1}) ν 3304, 2973, 2932, 1651, 1537, 1458, 1173, 1130, 747, 694; gel-phase ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.1−2.5 (br),

3.0−4.2 (br), 5.4−8.8 (br); gel-phase ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.5, 41.3, 42.4, 128.5, 128.5, 132.0, 174.3; gel-phase ^{31}P NMR (243 MHz, $CDCl_3$) δ 26.1 (br), 32.5 (br). Anal. Calcd for $C_{240n}H_{395n}O_{37n}N_{30n}Pd_{1n}Cl_{2n}$ as PdAS·7$n$$H_2O$: C, 63.172; H, 8.725, N, 9.208. Found: C, 62.940; H, 9.324; N, 9.801.

Recycling of PdAS for the Suzuki−Miyaura Reaction (Organic-Solvent-Free Workup) (Table 1). A mixture of **6a** (22.5 mmol), **7** (24.8 mmol), and Na_2CO_3 (25.0 mmol) in water (75 mL) was degassed by untrasonication for 30 min. To the solution was added PdAS (1.13 μmol), and the resulting suspension was stirred at 100 °C for 24 h. After the reaction mixture was filtered with hot water, the glass filter was washed with hot water. At that time, PdAS was recovered on the filter. The filtrate was cooled to room temperature to afford crystals of **8a**. It was isolated on the filter and dried in vacuo to give **8a**. The recovered PdAS was dried in vacuo and reused.

General Procedure for the Suzuki−Miyaura Reaction Catalyzed by PdAS (Traditional Workup) (Tables 2 and 3). The reactions, except that in entry 1, were worked up with organic solvents as follows: A mixture of halide (or an aryl triflate) **6** (22.5 mmol) or **9** or **12** (2.25 mmol), boronic acid **7** or **10** (in **6**, 24.8 mmol; in **9** or **12**, 2.48 mmol), Na_2CO_3 (in **6**, 25.0 mmol; in **9** or **12**, 2.50 mmol), and PdAS (1.13 μmol) in water (in **6**, 75 mL; in **9** or **12**, 7.5 mL) was stirred at 100 °C. After the reaction was complete and the reaction mixture was cooled to room temperature, AcOEt was added. The mixture was filtered through a glass filter, and the filtrate was separated. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, dried in vacuo, and purified by column chromatography to give the corresponding product.

Effect of Organic Solvent on the Suzuki−Miyaura Reaction Catalyzed by PdAS (Table 4). A mixture of **9b** (2.25 mmol), **7a** (2.48 mmol), Na_2CO_3 (2.50 mmol), PdAS (1.13 μmol) in water (7.5 mL), and organic solvent (7.5 mL) was stirred for 9 h at 100 °C. After the reaction was cooled to room temperature, AcOEt was added. The mixture was filtered through a glass filter, and the filtrate was separated. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, dried in vacuo, and purified by column chromatography to give the corresponding product.

Reaction of Alkyl-9-BBNs (Table 5). To alkene **13** was added 0.5 M 9-BBN−H (2.75 mmol) in THF (5.5 mL), and the resulting mixture was stirred at room temperature for 17 h to give **13** in THF.[13] To a suspension of alkene **6**, **9**, or **12** (2.25 mmol), K_3PO_4 (6.75 mmol), and PdAS (1.13 μmol) in 1,4-dioxane (13.5 mL) was added **13** in THF (5.5 mL) and THF (8 mL), and the resulting mixture was stirred at 100 °C. After the reaction was complete, the reaction mixture was cooled to room temperature, and AcOEt was added. The mixture was filtered through a glass filter, and the filtrate was separated. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, dried in vacuo, and purified by column chromatography to give the corresponding product.

Data for 1-*tert*-butyl-4-octylbenzene (14e): oil; IR (neat, cm^{-1}) ν 2959, 2924, 2855, 1516, 1464, 1364, 831; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.24−1.36 (m, 10H), 1.31 (s, 9H), 1.60 (m, 2H), 2.56 (t, J = 7.9 Hz, 2H), 7.28 (m, 2H), 7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.8, 29.4, 29.6, 29.6, 31.6, 31.6, 32.0, 34.4, 35.6, 125.0, 127.9, 139.7, 148.1; MS (EI) m/z 246 (M^+), 231 (bp, $M^+ - CH_3$), 147 (t-$BuC_6H_4CH_2^+$), 91 ($PhCH_2^+$), 57 (t-Bu^+); HRMS (EI) m/z calcd for $C_{18}H_{30}$ 246.2347, found 246.2357.

Data for 4-[2-(6-benzyloxyhexyl)-2-propenyl]morpholine (14i): oil; IR (neat, cm^{-1}) ν 3069, 3032, 2936, 2853, 2805, 1455, 1361, 1118, 1073, 899, 868, 734, 698; ^1H NMR ($CDCl_3$) δ 1.29−1.48 (m, 6H), 1.58−1.66 (m, 2H), 2.05 (t, J = 7.6 Hz, 2H), 2.36 (m, 4H), 2.85 (s, 2H), 3.46 (t, J = 6.6 Hz, 2H), 3.69 (t, J = 4.6 Hz, 4H), 4.50 (s, 2H), 4.85 (m, 1H), 4.90 (m, 1H), 7.35−7.25 (m, 5H); ^{13}C NMR (CDCl3) δ 26.1, 27.5, 29.2, 29.7, 34.1, 53.6, 64.4, 67.0, 70.5, 72.9, 112.1, 127.5, 127.6, 128.3, 138.7, 146.0; MS (EI) m/z 317 (M^+); HRMS (EI) m/z calcd for $C_{20}H_{31}O_2N$ 317.2355, found 317.2355.

Data for 8-benzyloxy-2-methyl-1-octene (14j): oil; IR (neat, cm^{-1}) ν 3067, 3032, 2932, 2857, 1455, 1364, 1101, 887, 735, 696; ^1H NMR ($CDCl_3$) δ 1.26−1.47 (m, 6H), 1.57−1.66 (m, 2H), 1.70 (s, 3H), 2.00 (t, J = 7.4 Hz, 2H), 3.47 (t, J = 6.6 Hz, 2H), 4.50 (s, 2H), 4.66 (m, 1H), 4.68 (m, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.5, 26.2, 27.6, 29.3, 29.8, 34.2, 37.9, 53.7, 70.5, 72.9, 109.5, 127.3, 127.5, 128.2, 138.5, 146.0; MS (EI) m/z 232 (M^+), 91 (bp, $PhCH_2^+$); HRMS (EI) m/z calcd for $C_{16}H_{24}O$ 232.1827, found 232.1829.

Reaction of Benzyl Halides (Table 6). A mixture of benzyl halide **15** (2.25 mmol), boronic acid **7** (2.48 mmol), KF (6.75 mmol), and PdAS (1.13 μmol) in DME (7.5 mL) was stirred at 100 °C. After the reaction was complete and the reaction mixture was cooled to room temperature, AcOEt was added. The mixture was filtered through a glass filter, and the filtrate was separated. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, dried in vacuo, and purified by column chromatography to give the corresponding product.

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Supporting Information Available: A figure showing the recycled system of the heterogeneous Suzuki−Miyaura reaction, a scheme showing the angiotensin II antagonists, ^1H, ^{13}C, and ^{31}P NMR spectra of polymer **2** and **3**, and ^1H and ^{13}C NMR spectra of the new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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