



Accepted Article

Title: A Convoluted Polyvinylpyridine-Palladium Catalyst for Suzuki– Miyaura Coupling and C-H Arylation

Authors: Aya Ohno, Takuma Sato, Toshiaki Mase, Yasuhiro Uozumi, and Yoichi M. A. Yamada

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Adv. Synth. Catal. 10.1002/adsc.202000742

Link to VoR: https://doi.org/10.1002/adsc.202000742

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

A Convoluted Polyvinylpyridine-Palladium Catalyst for Suzuki–Miyaura Coupling and C-H Arylation

Aya Ohno,^a Takuma Sato,^a Toshiaki Mase,^b Yasuhiro Uozumi,^{*b} and Yoichi M. A. Yamada^{*a}

^a RIKEN Center for Sustainable Resource Science, Hirosawa, Wako, Saitama 351-0198, Japan. [phone: +81-(0)48-467-9404, fax: +81-(0)48-467-1423, e-mail: ymayamada@riken.jp]

Institute for Molecular Science (IMS), Myodaiji, Okazaki, Aichi 444-8787, Japan. [phone: +81-(0)564-59-5571, fax: +81-(0)564-59-5574, e-mail: uo@ims.ac.jp]

[pnone. + 01-(0)304-39-3371, 1ax. + 01-(0)304-39-3374, e-mail. u0@mail.

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201#######.

Abstract. The development of highly active and reusable supported catalysts for Suzuki-Miyaura coupling and catalytic C-H arylation is important for fundamental and applied chemistry, with these reactions being used to produce medical compounds and functional materials. Herein, we found that a mesoporous composite made of a linear poly(4-vinylpyridine) and tetrachloropalladate acted as a dual-mode catalyst for a variety of cross-coupling reactions, with both Pd nanoparticles and a Pd complex catalyst being observed under different conditions. The polyvinylpyridine-palladium composite 1 was readily prepared via the molecular convolution of poly(4-vinylpyridine) and sodium tetrachloropalladate to provide a hardly soluble polymermetal composite. The Suzuki-Miyaura coupling and the C-H arylation of aryl chlorides and bromides with arylboronic acids, thiophenes, furans, benzene, and anisole proceeded in the presence of 0.004 mol% (40 mol ppm) to 1 mol% Pd of $\mathbf{1}$ to afford the corresponding coupling products in high yields.

Furthermore, the catalyst was reused without an appreciable loss of activity. Pharmaceutical compounds and function: 1 materials were synthesized via the coupling reactions. N₂ ga adsorption/desorption analysis indicated that the catalyst had a mesoporous nature, which played a crucial role in the catalysis. In the Suzuki-Miyaura couplings, *in situ* generated palladium nanoparticles in the polymer matrix were catalytically active, while a polymeric Pd(II) complex was crucial in the C-H arylations. These catalytic species were investigated via XAFS, XPS, far-infrared absorption, and Raman spectroscopies, as well as DFT calculations.

Keywords: Molecular Convolution; Polymeric Palladiun poly(4-vinylpyridine); Suzuki-Miyaura coupling; C-H Arylation

Introduction

The use of both C-H arylations and Suzuki-Miyaura to prepare (hetero)aromatic couplings biarvl compounds is important not only for fundamental catalytic chemistry but also for the production of functional materials and pharmaceutical compounds.^{[1-} ³ In recent years, many homogeneous catalysts for these reactions have been reported that utilize precious transition metals such as palladium,^[4-7] rhodium,^[8] ruthenium,^[9] copper,^[10] and iridium.^[11] Converting such systems from homogeneous to heterogeneous catalysis is desirable because it would allow these precious transition metal species to be readily recovered and reused. While heterogeneous catalysts including crosslinked polymeric resin-supported palladium catalysts have been reported for Suzuki-Miyaura coupling,^[12-21] heterogeneous catalysts for couplings using C-H bonds are still limited. Felpin^[22]

and MacGlacken^[23] have both covered the topic of direct Csp²-H arylation using heterogeneous palladium catalysts in their useful reviews. Catalysts used for this purpose include Pd/C, ^[24,25] $Pd(OH)_2/C$, ^[26] Pd on metal oxides,^[27] Pd nanoparticles on supports,^[28-32] and polymer-supported palladium catalysts;^[33,34] however, the reusability of these catalysts has not been investigated in depth. Although we acknowledge thes pioneering works, we decided to develop highly active and reusable polymeric palladium catalysts for the direct C-H arylation of various substrates, including heteroaromatic systems. Additionally, development of highly active and reusable heterogeneous catalysts for Suzuki–Miyaura coupling of aryl chlorides are still in progress. We believe that cutting-edge concepts are important for the development of highly active and reusable polymeric palladium.

We have developed a convolution methodology to overcome the issues with the preparation of more highly active and reusable immobilized metal catalysts than polymeric resin (cross-linked polymer)-supported ones (Figure 1a).^[16,17,35-37] For example, we have already reported a poly(*N*-isopropylacrylamide-*co-N*vinylimidazole) palladium dichloride catalyst (aka MPPI-Pd) for the Suzuki–Miyaura coupling. MPPI-Pd was a highly active catalyst for the coupling of some aryl chlorides.^[17] However, when using less reactive electron-rich aryl chlorides such as chloroanisole, 0.1 mol% Pd of MPPI-Pd was required. Additionally, MPPI-Pd was unsuitable for C-H arylations. Since highly active and reusable palladium catalysts for the Suzuki–Miyaura coupling of aryl chlorides and C-H arylations are desired, we have developed polymeric palladium catalysts for these reactions.

It was envisioned that some polymeric ligands should activate palladium species and accelerate the targeted coupling reactions. After screening a variety of polymeric ligands, we found a simple, linear, and commercially available linear polymer, poly(4vinylpyridine), showed the greatest increase in

palladium species activity. Herein, we report the development of the polyvinylpyridine-palladium catalyst 1, and its application to the C-H arylation of thiophenes, furans, and benzenes with aryl chlorides and bromides, as well as the Suzuki–Miyaura coupling of aryl chlorides. The use of heterogeneous catalyst 1 loaded with 40 mol ppm Pd (0.004 mol% Pd) mediated the Suzuki–Miyaura coupling to give the corresponding biaryl products, and **1** loaded with 100 mol ppm Pd (0.01 mol% Pd) promoted the C-H arylations to give their corresponding products. The catalyst was reused without significant loss of catalytic activity. Moreover, we found that the catalytically active species in these couplings were different from each other, with polymer-stabilized palladium nanoparticles being present in the Suzuki-Miyaura coupling, while a polymeric Pd(II) complex was active in the C-H arylations. This shows that 1 acted as a dual-mode catalyst for these cross-coupling reaction (Figure 1b).



Figure 1. Suzuki-Miyaura coupling and C-H arylation by heterogeneous (supported) polymeric Pd dual-mode catalysts. [al Molecular convolution for the preparation of polymeric metal catalysts. [b] Dual mode catalyses of **1**.

Results and Discussion

Preparation of polymeric pyridine palladium catalyst 1

The poly(4-vinylpyridine)-palladium catalyst 1 was prepared from commercially available materials in one step via our molecular convolution methodology (Fig. 2a). An aqueous solution of Na₂PdCl₄ (**3**) was added

to a solution of poly(4-vinylpyridine) (2) (3 mol equiv based on a monomer) in 2-propanol, after which composite 1 quantitatively precipitated as a yellow solid (Figure 2b) that was hardly soluble in water, 2propanol, ethyl acetate, dichloromethane, and hexane (checked by treatment of 1 in these solvents at 90 °C for 5 d). Polymeric Pd catalysts 1' and 1'' were also prepared from 3 (1 mol equiv Pd) and 2 (2 and 5 mol equiv of N, respectively). Polarized light imaging of 1

(a)

suggested that the material was homogeneously dispersible and non-crystalline in nature (Figure 2c). The structure of 1 was investigated using several spectroscopic methods, including X-ray absorption fine structure (XAFS). The oxidation state of palladium in 1 was +2, as shown in the X-ray absorption near edge structure (XANES) of the Pd Kedge (Figure S8). Elemental analysis indicated that the molar ratio of Pd:Cl:N was 1:2:3, which is very consistent with the quantitative formation of 1 under the preparation conditions used (Pd:N ratio = 1:3). Therefore, the local structure of 1 was proposed as *trans*-PdCl₂L₂ (L = pyridine unit of polymer), and the optimized geometry of trans-PdCl₂(4methylpyridine)₂ was obtained by DFT using the PBE0 functional with the polarized triple-zeta basis set (Figures 3a and 3b). A fitting analysis of the extended X-ray absorption fine structure (EXAFS) of 1 with the DFT-calculated model indicated the validity of this local Pd structure. Thus, the best fit was obtained and the Pd-N and Pd-Cl bond lengths were estimated to be 2.026 and 2.302 Å, respectively (Figure 3c). The trans-configuration of the palladium center was confirmed from the absorption pattern of the Cl-Pd-Cl stretching vibrations in the far-infrared (FIR) region and the corresponding Raman spectrum (Figure S16). Curve fitting analysis of the X-ray photoelectron spectroscopy (XPS) spectrum indicated the existence of free pyridine units as a minor peak component as well as coordinating pyridines as the main peak with a positive binding energy shift (Figures S18 and S19).

Na₂PdCL -PrOH/H2O (1:1)25 °C, 20 h 3 (3 mol equiv N) (1 mol equiv Pd) i-PrOH/H2O (2 mol equiv N) (1 mol equiv Pd) (1:1)25 °C, 20 h 2 3 i-PrOH/H2O (5 mol equiv N) (1 mol equiv Pd) (1:1)25 °C, 20 h



Figure 2. (a) Preparation of polyvinylpyridine-PdCl₂ catalysts **1**, **1'**, and **1''**. (b) Visual appearance of **1** (yellow solid). (c) Polarized microscopy image of **1**.



Figure 3. (a) Plausible polymeric structure of **1** (Pd:N =1:3). (b) DFT-optimized structure of *trans*-PdCl₂(4-

methylpyridine)₂ as a model for EXAFS analysis. (c) Fourier-transform of k^3 -weighted Pd K-edge EXAFS of **1** and the best fit. R factor: 0.014, *k*-range: 3-15 Å⁻¹, *R*-range: 1.2-2.2 Å, *R*(Pd-N) = 2.026(16) Å, *R*(Pd-Cl) = 2.302(10) Å, σ^2 (Pd-N) = 0.00304(121) Å², σ^2 (Pd-Cl) = 0.00347(55) Å².

Polyvinylpyridine-palladium composite-catalyzed Suzuki-Miyaura coupling of aryl chlorides

Suzuki-Miyaura couplings were investigated using a variety of catalysts, including our polymeric palladium composites (poly(4-vinylpyridine)-palladium 1, 1', and 1") as heterogeneous catalysts and several Pd (II) complexes as homogeneous catalysts (Table 1). We chose an electron-rich and unreactive aryl chloride, 4chloroanisole (4a), as a widely used benchmark substrate. When the reaction of 4a with phenylboronic acid (5a; 1.2 mol equiv) was performed using 1 (0.004 mol% = 40 mol ppm, Pd:N = 1:3), K_3PO_4 (3.0 mol equiv), and tetrabutylammonium bromide (TBAB; 1.0 mol equiv) in H₂O at 95 °C for 20 h, the desired coupling product, 4-methoxybiphenyl (6a) was obtained in 93% yield (Table 1, entry 1). The turnover number and the turnover frequency in this catalytic reaction reached 20,000, and 1162 h⁻¹, respectively. Note that the molar ratio of Pd to N (polymeric ligand) in the polyvinylpyridine-palladium catalyst was critical in terms of the yield of the product. Thus, using a similar polyvinylpyridine-palladium composite 1' (Figure 2a, Pd:N = 1:2) promoted the coupling to give 6a in 74% yield (Table 1, entry 2), while the use of catalyst 1" (Figure 2a, Pd:N = 1:5) gave less than 1% of the product (Table 1, entry 3).

Interestingly, gas adsorption/desorption isotherms revealed that the 1:2 and 1:3 composites had mesoporous features (type IV isotherms with H₂ hysteresis), whereas the 1:5 composite and the starting polymer (i.e., poly(4-vinylpyridine) powder) were non-porous (Figures S1-S7). The Barrett-Joyner-Halenda (BJH) plot of 1 (Pd:N = 1:3) shows that its pore size distribution peaked at around 19 nm (Figure $\hat{4}$). The specific surface areas of 1 (Pd:N = 1:3), 1' (Pd:N = 1:2), 1" (Pd:N = 1:5), and poly(4vinylpyridine) 2 were 366 (N₂), 350 (N₂), 4.7 (Kr), and 2.6 (Kr) m²g⁻¹, respectively, based on their Brunauer-Emmett-Teller (BET) plots. Therefore, the morphology and catalytic activity the of polyvinylpyridine-palladium composites strongly depended on the Pd:N ratio, even though the local palladium structures were intrinsically identical as indicated by XAFS (trans-PdCl₂L₂, Figure S9).

For comparison, poly(vinylimidazole)₂PdCl₂ and our polymeric Pd catalysts, MPPI-Pd¹⁷ (composite of poly(*N*-isopropylacrylamide-*co*-*N*-vinylimidazole) and PdCl₂, Pd:imidazole = 1:2) and PA-TAP-Pd¹⁶ (composite of poly(*N*-isopropylacrylamide-*co*-*N*-diphenylstyrylphosphine) and PdCl₂, Pd:P = 1:2) gave **6a** in 38%, 47%, and 10% yields, respectively (Table1, entries 4–6). The catalytic activities of their homogeneous counterparts, (NH₄)₂PdCl₄, *trans*-

 $PdCl_2(pyridine)_2$, and a mixture of $(NH_4)_2PdCl_4$ and pyridine (Pd:pyridine = 1:3), were also much lower, affording **6a** in 18%, <1%, and 28% yields, respectively (Table 1, entries 7–9). The synergistic combination of an appropriate polymeric ligand and a palladium salt can therefore be seen to provide a much higher catalytic activity when coupling this less reactive substrate.





^{a)} Conditions: **4a** (1.5 mmol), **5a** (1.8 mmol), Pd catalyst (60 nmol), K₃PO₄ (4.5 mmol), TBAB (1.5 mmol), H₂O (0.6 mL), 95 °C, 20 h, mixing at 800-900 rpm.



Figure 4. Barrett-Joyner-Halenda (BJH) pore size distribution plot of **1** (Pd:N = 1:3) derived from the N_2 desorption branch of the isotherm.

Table 2. Suzuki–Miyaura couplings of a variety of aryl Chlorides (4) with arylboronic acids (5) catalyzed by 40 mol ppm of $\mathbf{1}^{a}$

	ci + (HO)-8	1 (0.004 mol% P (40 mol ppm Pd)	
4	5 (1.2 mol equiv)	K ₃ PO ₄ (3.0 mol equiv) TBAB	6
		(1.0 mol equiv) H ₂ O 95 °C, 20 h	
Entry	4 R ¹ , X	5 R ²	Yield of 6 (%)
1	4b 4-Me, Cl	5a	6b 99
2	4c 2-Me, Cl	5a	6c 92
3	4d 3,5-(MeO)2, Cl	5a	6d 98
4	4e 4-Ac, Cl	5a	6e 92
5	4f 4-CF ₃ , Cl	5a	6f 99
6 ^{b)}	4g 4-NO ₂ , Cl	5a	6g 81
7 ^{b)}	4b	5b 4-	6h 89
		MeO	
8	4e	5b	6i 99
9	4b	5c 4-	6j 98
		Ac	-
10 ^{b)}	4 e	5c	6k 90
11 ^{c)}	4e	5d 4-	61 75
		Ph	
12 ^{d)}	4a-Br 4-MeO, Br	5a	6a 94
13 ^{d)}	4b-Br 4-Me, Br	5a	6b 99
14 ^{d)}	4b-I 4-Me, I	5a	6b 99

^{a)}conditions: **4** (1.5 mmol), **5** (1.8 mmol), **1** (60 nmol), K₃PO₄ (4.5 mmol), TBAB (1.5 mmol), H₂O (0.6 mL), 95 °C, 20 h, mixing at 800-900 rpm; ^{b)} 40 h; ^{c)} in H₂O-4-methyl-2pentanone (0.6 mL each); d) without TBAB in 5 h

Since 1 exhibited high catalytic activity for the coupling of 4a to 5a, the Suzuki-Miyaura coupling of a variety of aryl chlorides with different arylboronic acids was performed with 0.004 mol% (40 mol ppm) Pd of 1 (Table 2). Both electron-poor and rich aryl chlorides and arylboronic acids were suitable substrates and reactants in the polyvinylpyridinepalladium 1-catalyzed cross-coupling, affording the corresponding biaryl compounds in yields of up to 99%. The reaction of arylbromides, and iodotoluene was also carried out with 1 (0.004 mol% Pd) to give the corresponding products 6a-b in 94-99% yields (Entries 12-14). Evangelisti and co-workers reported palladium nanoparticles supported on poly(4vinylpyridine) cross-linked with divinylbenzene (also cross-linked known as polyvinylpyridine Pd nanoparticles) for the Suzuki-Miyaura coupling.^[15] In their report, the reaction of arylbromides and -iodides was performed with 0.15 mol% Pd in DMA/H₂O. The reaction of 4-nitrochlorobenzene, an activated aryl chloride, was shown as the reaction of aryl chlorides to give 4-nitrobiphenyl in 16% yield.

A heteroaromatic chloride as well as di- and trichlorobenzenes were also suitable substrates for this reaction (Scheme 1). Various functional materials were readily produced under similar conditions in 98-99% yields. Polyvinylpyridine-palladium 1 was recovered and reused without significant loss of catalytic activity, and no detectable amount of Pd was found in the reaction mixture as confirmed by inductively coupled plasma mass spectrometry (ICP-MS) analysis (see Supporting Information for details). Moreover, fenbufen (6p), a nonsteroidal antiinflammatory drug (NSAID), was directly synthesized without any functional group protection in 95% yield. For large-scale synthesis, a 0.5-mol-scale reaction was investigated (Scheme 2): The reaction of **4b** (63 g) with 5a (73 g) was performed with 1 (10 mg) in water to produce 79 g of the biaryl compound 6b (94% yield).



Scheme 1. Suzuki-Miyaura couplings of 3-pyridyl chloride (4h), 1,4-dichlorobenzene (4i), and 1,3,5-trichlorobenzene (**4j**), and reusability of **1**.



Scheme 2. The 0.5-mol-scale Suzuki-Miyaura coupling.

Polyvinylpyridine-palladium composite 1catalyzed C-H arylation of thiophenes, furans, benzene, and anisole

Since **1** exhibited high catalytic activity and reusability when used for the Suzuki-Miyaura coupling, C-H arylation of various thiophene and furan derivatives, benzene, and anisole using polyvinylpyridinepalladium 1 was investigated. While there are many reports on homogeneous catalysis of this reaction,^{[5-} ^{7,38} the development of heterogeneous alternatives is still in progress.^[22,23] Especially, the C-H arylation with aryl chlorides,^[7,39,40] less reactive reactants as compared with aryl bromides and iodides, with heterogeneous catalysts is still challenging although the reaction is important for preparation of organic functional materials and pharmaceutical compounds. Since 1 exhibited high catalytic activity for the Suzuki-Miyaura coupling with reusability, we challenged to develop C-H arylation of thiophenes, furans, benzene, and anisole by using 1. The reaction of 2hexylthiophene (7a) and bromobenzene (8a) was carried out with K₂CO₃, pivalic acid (PivOH), and 0.1 mol% Pd of 1 in dimethylacetamide (DMA) at 120 °C for 20 h to afford the corresponding phenylated thiophene 9a in 93% yield (Table 3, entry 1). The catalytic loading of 1 was decreased to 500, 200, and 100 mol ppm (0.05, 0.02, and 0.01 mol%), affording **9a** in yields of 91–83% (table 3, entries 2–4), and then to 30 mol ppm (0.003 mol%), where turnover number and frequency of 15000 and 780 h⁻¹ were achieved (Table3, entry 5). The arylation with o-, m-, and p-8b-d gave substituted bromotoluenes the corresponding products 9b-d in up to 97% yield (Table3, entries 6-8). The reaction of a variety of thiophenes and aryl bromides proceeded smoothly to give the corresponding coupling products 9e–9l in up to 89% vield, with chloro- and t-Bu-NHSO₂ moieties remaining intact (Table 3, entries 9-18). Of particular note is product 91, which is an intermediate for the synthesis of AR-C123196, a candidate compound for the treatment of inflammatory and allergic conditions such as asthma and rhinitis.^[41,42] As control experiments, the reactions of 7a and 8a were performed with 1' and 1'' (0.05 mol% Pd) to give 9a in 83% and 77% yield, respectively (Entries 19 and 20). The catalyst **1** is also the best in the C-H arylation (vs. Entry 2).

Table 3. C-H arylations of a variety of thiophenes (7) with arylbromides (8) catalyzed by 0.003-0.1 mol% Pd of 1^{a}



2	7a	8a	0.05	9a 91
3 ^{b),c)}	7a	8a	0.02	9a 88
4 ^{d),e)}	7a	8a	0.01	9a 83
5 ^{d),e)}	7a	8a	0.003	9a 47
6	7a	8b 2-Me	0.1	9b 83
7 ^{d)}	7a	8c 3-Me	0.1	9c 79
8 ^{d)}	7a	8d 4-Me	0.1	9d 97
9 ^{d)}	7a	8e 4-CF ₃	0.1	9e 82
10	7b Me	8a	0.1	9f 89
11 ^{c)}	7b	8a	0.05	9f 81
12 ^{c),d)}	7b	8a	0.02	9f 73
13	7b	8b	0.1	9g 88
14 ^{d)}	7b	8d	0.1	9h 78
15 ^{c),d)}	7b	8f 4-OMe	0.2	9i 74
16 ^{b),c)}	7b	8g 4-Cl	0.1	9j 70
17	7c Cl	8a	0.1	9k 58
18	7d	8f	0.1	91 87
	t-Bu-			
	NH-SO ₂			
19 ^{f)}	7a	8a	0.05	9a 83
20 ^{g)}	7a	8a	0.05	9a 77

^{a)} conditions: **7** (1.0 mmol), **8** (2.0 mmol), **1** (as described), K₂CO₃ (1.5 mmol), PivOH (0.3 mmol), DMA (3 mL), Ar, 120 °C, 20 h, mixing at 1000 rpm; ^{b)} 130 °C; ^{c)} 40 h; ^{d)}140 °C; ^{e)} 65 h; f) **1'** was used; g) **1''** was used.



Scheme 3. Application of C-H arylation to the synthesis of functional materials.

Several functional materials were prepared using **1**, as shown in Scheme 3. 2,5-Bis(4-chlorophenyl)thiophene (**9m**), hexyl 4T (**9n**), ^[43] and 2-phenylbenzo[*b*]thiophenes (**9o** and **9p**) were readily synthesized in one step with yields of 73–85%.

Table 4. C-H arylations of various thiophenes (7) with aryl chlorides (4) catalyzed by 1^{a}

√ _S ∕∼H + CI— 7 4(2.0	mol equiv)	KOAc (2.0 mol eq TBAB (1.0 mol eq DMA 130 °C, 20 h	uiv) uiv)	R ¹ /S	
Entry	7 R ¹	4 R ²	1(mol % Pd)	Yield of 9 (%)	
1 ^{b)}	7b	41 H ^{c)}	1.0	9f 75	
	Me	(10)	0.4	0.0 (7	
2 ^(b),d)	7b	4I ^{c)}	0.1	9f 67	
$3 (1^{st} use)^{e}$	7b	4m 2-CN	1.0	9g 82	
$4 (2^{nd} use)^{e}$	7b	4 m	1.0	9g 81	
5 ^{b)}	7a	4I ^{c)}	1.0	9a 60	
	$C_{6}H_{13}$				
6	7a	4 m	1.0	9r 86	
7	7a	4 m	0.1	9r 90	
8	7a	4 m	0.05	9r 76	
9 ^{d),f)}	7a	4 m	0.02	9r 61	
10	7a	4f 4-CF ₃	1.0	9e 84	
11	7a	4g 4-NO ₂	1.0	9s 72	
12	7a	4n 4-CN	1.0	9t 80	
13	7a	4o 4-	1.0	9u 74	
		СНО			
14	7a	4p 4- COPh	1.0	9v 98	

^{a)} conditions: **7** (1.0 mmol), **8** (2.0 mmol), **1** (as described), KOAc (2.0 mmol), TBAB (1.0 mmol), DMA (3 mL), Ar, 130 °C, 20 h, mixing at 1000 rpm; ^{b)} without DMA; ^{c)} **4** (5.0 mmol); ^{d)} 65 h; ^{e)} 140 °C; ^{f)} 120 °C.

The C-H arylation of thiophenes with aryl chlorides by heterogeneous catalysis was also attempted (Table 4). The reaction of 2-methylthiophene (7b) and chlorobenzene (41), a non-reactive aryl chloride, was carried out using 1. We were pleased to find that the reaction proceeded with 1.0 mol% and even 0.1 mol% Pd of 1 to afford 2-methyl-5-phenylthiophene (9f) in 75% and 67% yield, respectively (Table 4, entries 1 and 2). The reaction of 7b with electron-deficient 2chlorobenzonitrile (4b) gave the product 9g in 82% yield, and the catalyst was reused to afford 9g in 81% yield (Table 4, entry 3 and 4). The reaction between 7a and 4m gave 9r in a 86% yield (Table 4, entry 6), and when the catalyst loading was reduced to 0.1, 0.05, and 0.02 mol% Pd, the achieved yields were 90%, 76%, and 61%, respectively, with a turnover number of 3,000 (Table 4, entries 7–9). Substituted chlorobenzenes 4f, 4g, 4n, 4o, and 4p were also suitable reactants in the conversion, affording their corresponding products in 72%–98% yield (Table 4, entries 10-14).

Table 5. C-H arylations of a variety of furans (10) with aryl chlorides (4) catalyzed by 1^{a}



6^{c)}

7^{d)}

8

9

10

11

12^{e)}

10a

10a

10a

10a

10a

10a

10b

41

41

4b 4-Me

4g 4-NO2

4m 2-CN

40 4-CHO

4p 4-COPh

H	531)
^{a)} conditions: 10 (1.0 mmol), 4 (2.0 mmol), 1 (a)	as described),
K ₂ CO ₃ (1.5 mmol), PivOH (0.3 mmol), TBAB	3 (1.0 mmol), "
DMA (3 mL), Ar, 100 °C, 20 h, mixing at	1000 rpm; ^{b)}
110 °C; ^{c)} 40 h; ^{d)} 120 °C; ^{e)} conditions: 10 (0.6	mmol), 4 (2.4
mmol), 1 (1.7 mol%), K ₂ CO ₃ (1.8 mmol),	PivOH (0.36
mmol), TBAB (0.6 mmol), DMA (3 mL), Ar,	110 °C, 20 h,
mixing at 1000 rpm; ^{f)} yield of 2,5-diphenylfu	ran.



Scheme 4. C-H arylations of benzene and anisole.

The C-H arylation of furans is rather difficult owing to their instability. However, 2-butylfuran (**10a**) reacted with chlorobenzene (**4l**) to give 2-butyl-5-phenylfuran (**11a**) in 67% yield when using **1** as a catalyst (Table 5, entry 1). The catalyst was reused without loss of catalytic activity (Table 5, entries 2 and 3). Various furans and aryl chlorides were coupled to give the corresponding arylated furans **11b–g** in 53–82% yield (Table 5, entries 4–12). The C-H arylations of benzene and anisole are among the most difficult C-H bond functionalizations.^[11,44] The reaction of 4-tolylbromide (**8d**) with benzene (**12a**) was carried out with **1** to give 4-methylbiphenyl (**6b**) in 58% yield (Scheme 4). The

11a 62

11b 70

11c 78

11e 82

11f 75

11g

11d 69

0.1

1.0

0.4

1.0

1.0

1.0

1.7

reaction of bromobenzene (8a) and anisole (12b) was also performed with 1 to give a mixture of methoxybiphenyls with a combined yield of 53%.

Reusability and structure of the recovered catalyst from the Suzuki-Miyaura coupling



Figure 5. Time course experiments of (a) the Suzuki-Miyaura coupling of **4b** and **5a** (Table 1. Entry 1) and (b) the C-H arylation of **7a** and **8a** (Table 3, Entry 1).

During time course experiments of the Suzuki-Miyaura coupling of **4b** and **5a** (Table 1. Entry 1) and the C-H arylation of **7a** and **8a** (Table 3, Entry 1), induction period was obserbed in the Suzuki-Miyaura coupling (Figure 5). We also found that the colors of **1** when used in the Suzuki-Miyaura coupling and the C-H arylation were different. While the as-prepared **1** was yellow, the catalysts recovered from Suzuki-Miyaura couplings and C-H arylations were black and yellowish brown, respectively. We built a hypothesis that **1** worked as a polymeric Pd nanoparticle catalyst in the Suzuki-Miyaura coupling and as a polymeric Pd complex catalyst in the C-H arylation, i.e., as a dualmode catalyst. This hypothesis was tested as outlined below. The black color of the recovered catalyst powder from the Suzuki-Miyaura coupling suggested the in situ reduction of Pd(II) complexes to Pd(0) nanoparticles. The Catalyst was reused without loss of its catalytic activity (Scheme 1; An SEM image of the recovered catalyst is shown in Figure S23.). Transmission electron microscopy (TEM) observations of the recovered **1** showed the formation of nanoparticles with mean diameters of 3.7±1.0 nm (Figures S21 and S22). The oxidation state of Pd in the recovered catalyst from the Suzuki-Miyaura coupling was zero (i.e., metallic), as shown by Pd K-edge XANES (Figure S8). According to EXAFS, the coordination number of Pd decreased from 12 in bulk Pd to 7.8 after use, which supports the formation of metallic nanoclusters and nanoparticles whose Pd-Pd bond lengths are estimated to be 2.794 Å (Figure 6). Curve fitting analysis of the N 1s XPS spectrum revealed three peak components: (a) free pyridine, (b) +1.6 eVand (c) +3.1 eV (Figure 7). We assigned the main peak (b) and the minor peak component (c) to face-to-face $(\eta^6 - \kappa C, N)$ and edge-to-face $(\eta^1 - \kappa N)$ interactions of pyridine with the surface of the metallic palladium nanoparticles, respectively, as supported by DFT calculations on a model Pd20 cluster and 4methylpyridine system (Figure 8, see Supporting Information Figures S8-S16 for details).^[45] In other words, Pd nanoparticles prefer to interact with poly(4vinylpyridine) in a face-to-face manner.



Figure 6. Fourier-transform of k^3 -weighted Pd K-edge EXAFS of the recovered catalyst from the Suzuki-Miyura coupling and the best fit. R factor: 0.003, *k*-range: 3–19 Å⁻¹, *R*-range: 2.0–2.9 Å, mean coordination number = 7.8(5), *R* = 2.794(2) Å, $\sigma^2 = 0.00482(21)$ Å². The spectrum was measured in transmission mode at 10 K.







Figure 8. Face-to-face (left) and edge-to-face (right) interactions based on a model system using a Pd_{20} cluster and 4-methylpyridine at the level of M06/LANL2DZ (for Pd) + 6-31G(d,p). Palladium atoms are partially omitted for clarity.



(recovered catalyst: black)



Scheme 5. Reusability of 1 in C-H arylations.

These results suggest that the coordination-like interaction between pyridine and Pd(0) nanoparticles maintains the insoluble polymer matrix of the catalyst even after the completion of the reaction. Since the catalyst is highly active and reusable (Scheme 1), insitu generated palladium nanoparticles work as the heterogeneous catalyst for the Suzuki-Miyaura coupling. Pd nanoparticles were dispersed in the polymer matrix, and no detectable leaching of Pd was observed in the solution phase of the reaction by ICP-MS analysis (less than the limit of the detection of ICP-MS, <0.06 ppb).

Reusability and structure of the recovered catalys. from the C-H arylation

The molar ratio of the (hetero)arenes and aryl halides used as starting materials for the C-H arylation drastically affected the reusability of the catalyst. For example, the reaction of 2-methylthiophene (7b; 1 mol equiv) with bromobenzene (8a; 2 mol equiv) proceeded in the presence of polyvinylpyridinepalladium 1 (1 mol% Pd) to give the corresponding product **9f** in excellent yield with good reusability: 1st use, 89%; 2nd use, 93%; 3rd use, 95%; 4th use, 93% yield (Scheme 5a; An SEM image of the recovered catalyst is shown in Figure S24.). Note that the recovered catalyst under these conditions was yellowish brown, and so it (SEM images of the recovered catalyst are shown in Figure S24.) was supposed that it acted as a polymeric Pd complex in this reaction. However, reactions under similar conditions but with the molar ratio of the starting materials swapped gave the product in 85% (1st use) and 5% yields (2nd use) (Scheme 5b). In this case, the catalyst powder turned black after the first use, which suggests that metallic nanoparticles formed during the 1st use and were no longer very active for the catalysis of the C-H arylation. For this reason, we focused on the analysis of the catalyst recovered from reactions using excess aryl halides, i.e., where the catalyst was reusable (Scheme 5a). In fact, the Pd K-edge XANES

spectrum of the recovered catalyst that was catalytically active for the C-H arylation indicated that the oxidation state of palladium was +2. Elemental analysis suggested that the Pd:Br ratio was nearly 1:1. Therefore, it is proposed that the structure of the recovered catalyst was $PdBrPhL_2$ (L = pyridine unit of polymer), which is the final product of the oxidative addition of bromobenzene to a presumed Pd(0)intermediate. The fitting result of Pd K-edge EXAFS based on the DFT-optimized (PBE0 functional with polarized triple-zeta basis set) geometry of trans-PdBrPh(4-methylpyridine)₂ showed good agreement with the experimental data (Figures 9a and 9b). Pd-N, Pd-C, and Pd-Br bond lengths were estimated to be 1.976, 2.024, and 2.438 Å, respectively. Because it is hard to strictly distinguish between N and C using we also performed IR EXAFS, absorption measurements after a deuterium labeling experiment using bromobenzene- d_5 as a reagent in order to confirm the incorporation of the phenyl group into the complex (Scheme S2 and Figure S17, see Supporting Information for experimental details). Moreover, Br K-edge EXAFS also suggested the existence of a Pd-Br bond with an interatomic distance of 2.438 Å (Figure S14). Notably, this structure corresponds to a precursor state for the concerted metalationdeprotonation mechanism in Pd-catalyzed C-H arylations under homogeneous conditions, as proposed in pioneering works by Fagnou et al.^{46,47} Considering the above, the in situ generated PdBrPhL₂ structure should be an active species in C-H arylations using **1**. Figure 10 summarizes the structural changes that the catalyst undergoes in the studied reactions. The Suzuki-Miyaura coupling and the C-H arylation reactions were catalyzed by polymer-stabilized palladium nanoparticles and organopalladium(II) species, respectively. The in situ generated active catalysts were recoverable and reusable without significant loss of activity. From the above, it is concluded that 1 acted as a dual-mode catalyst for the Suzuki-Miyaura coupling and C-H arylation reactions.



Figure 9. (a) DFT-optimized structure of trans-PdBrPh(4methylpyridine)₂ as a model for EXAFS analysis. (b) Fourier-transform of k^3 -weighted Pd K-edge EXAFS of the recovered catalyst from the C-H arylation and the best fit. R factor: 0.013, k-range: 3-15 Å⁻¹, R-range: 1.2-2.4 Å, R(Pd-C) = 1.976(26) Å, R(Pd-N) = 2.024(26) Å, R(Pd-Br) =2.438(15) Å, σ^2 (Pd-C) = 0.00384(410) Å², σ^2 (Pd-N) = $0.00369(124) \text{ Å}^2$, $\sigma^2 (\text{Pd-Br}) = 0.00806(71) \text{ Å}^2$.





Figure 10. Suzuki-Miyaura coupling and C-H arylation using 1.

Conclusion

We developed a polyvinylpyridine-palladium catalyst 1 for the Suzuki-Miyaura coupling of aryl chlorides and the C-H arylation of (hetero)arenes with aryl halides. The reactions proceeded in the presence of 0.004 mol% (40 mol ppm) to 1 mol% of 1 to afford the corresponding products in high yields, and the catalyst showed good reusability. Using X-ray absorption fine structure (XAFS) analysis, we found that the composite 1 was a dual-mode catalyst that allowed the in situ generation of Pd(0) nanoparticles dispersed in a polymer matrix that were catalytically active in the Suzuki-Miyaura coupling, while a polymeric Pd(II) complex was an active species in the C-H arylation (Figure 9). Moreover, we also found that the final state of the catalyst and its reusability depended on the initial molar ratio of the starting materials in case of C-H arylations. This means that the reusability of heterogeneous catalysts is potentially affected by the consumption of one of the starting materials from the solution phase after the completion of the reaction.

Experimental Section

Experimental Details

Preparation of 1 (Pd:N = 1:3): An aqueous solution of Na₂PdCl₄ was prepared by mixing PdCl₂ (236 mg, 1.33 mmol) and NaCl (779 g, 13.3 mmol) in water (100 mL) at 60 °C for 30 min. The Na₂PdCl₄ solution was cooled to room temperature, and added dropwise to the solution of poly(4-vinylpyridine) (average Mw ~160000, purchased from Aldrich, 420 mg, 4.0 mmol) in 2-propanol (100 mL). The mixture was stirred for 20 h at 25 °C to give yellow powder. The insoluble material was collected by filtration, washed with water and 2-propanol, and dried under reduced pressure for overnight to give **1** (680 mg). Pd content: 20 wt%. Anal. Calcd for (C₇ H₇N)_{2.8}(PdCl₂)_{1.0}·3.5H₂O: C, 44.02; H, 5.01; N, 7.34; Cl, 13.26; Pd, 19.46. IR (ATR): 3066, 2931, 1615, 1557, 1497, 1430, 1221, 1068, 994, 832 cm⁻¹.

General Procedure for the Suzuki-Miyaura Reaction (Table1, entry1 and Table 2): 1 (0.03 mg, 0.06 μ mol, 40 mol ppm of Pd), 4 (1.5 mmol), 5 (1.8 mmol), K₃PO₄ (955 mg, 4.5 mmol), TBAB (481 mg, 1.5 mmol), and water (0.6 mL) were added to a 4-mL glass vessel. The mixture was stirred at 95 °C for 20 h, and cooled to room temperature. The mixture was diluted with water and extracted with EtOAc for several times. The combined organic layer was washed with water and brine, and dried over MgSO₄, then evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: mixture of hexane and EtOAc) to give product 6.

General Procedure for the C-H Arylation of Thiophenes with Aryl Bromides (Table3): 1 (0.51 mg, 1.0 μ mol, 0.1 mol% Pd), 8 (2.0 mmol), 7 (1.0 mmol), K₂CO₃ (207 mg, 1.5 mmol), pivalic acid (31 mg, 0.3 mmol), and DMA (3.0 mL) were added to a 15-mL glass vessel. The reaction mixture was stirred at 120 °C for 20h under Ar atmosphere then cooled to room temperature. The reaction mixture was diluted with water, and extracted with EtOAc for several times. The combined organic layer was washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: mixture of hexane and EtOAc) to give product 9.

Acknowledgements

We thank Dr. Tetsuo Honma (JASRI, SPring-8) for assistance with the XAFS studies (SPring-8, BL14B2). We would like to thank RIKEN for assistance with the XPS (Dr. Aiko Nakao, RIKEN), elemental analysis (materials characterization support team, CEMS, RIKEN), and ESI-MS (molecular structure characterization unit, CSRS, RIKEN) measurements.

We gratefully acknowledge financial support from the JST ACT-C (#JPMJCR12ZC), the JST ACCEL (#JPMJAC1401), the JSPS (#24550126, #20655035, and #15K05510), AMED (#19ak0101115h), the Takeda Science Foundation, the Naito Foundation, and RIKEN.

References

- [1] D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930.
- [2] J. Magano and J. R. Dunetz, Chem. Rev. 2011, 111, 2177-2250.
- [3] A. J. Burke and C. S. Marques in C-H Bond Activatio for Arylation, MacCaig, N. In Catalytic Arylation Methods: From the Academic Lab to Industria' Processes, Eds.; Wiley-VCH, Weinheim, 2015, pp 173-246.
- [4] I. Hussain, J. Capricho and M. A. Yawer, Adv. Synth. Catal. 2016, 358, 3320-3349.
- [5] L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826
- [6] T. W. Lyons and M. S. Sanford, *Chem. Rev.* 2010, 110, 1147-1169.
- [7] S. Mao, H. Li, X. Shi, J. F. Soulé, and H. Doucet, *ChemCatChem* 2019, 11, 269-286.
- [8] D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.* 2010, 110, 624-655.
- [9] P. Nareddy, F. Jordan and M. Szostak, ACS Catal. 2017, 7, 5721-5745.
- [10] X. -X. Guo, D. -W. Gu, Z. Wu and W. Zhang, *Chem. Rev.* 2015, 115, 1622-1651.
- [11] B. Join, T. Yamamoto and K. Itami, *Angew. Chem. Int. Ed.* **2009**, *48*, 3644-3647
- [12] a) G. Shore, S. Morin and M. G. Organ, Angew. Chem. Int. Ed. 2006, 45, 2761-2766; b) T. Wakamatsu, K. Nagao, H. Ohmiya and M. Sawamura, Angew. Chem. Int. Ed. 2013, 52, 11620-11623; c) S. Pathak, M. T. Greci, R. C. Kwong, K. Mercado, G. K. S. Prakash and G. A. Olah, Chem. Mater. 2000, 12, 1985-1989.

- [13] A. M. Caporusso, P. Innocenti, L. A. Aronica, G. Vitulli, R. Gallina, A. Biffis, M. Zecca and B. Corain, J. *Catal.* 2005, 234, 1-13.
- [14] W. Solodenko, K. Mennecke, C. Vogt, S. Gruhl and A. Kirschning, Synthesis 2006, 11, 1873-1881.
- [15] G. Fusini, F. Rizzo, G. Angelici, E. Pitzalis, C. Evangelisti, and A. Carpita, *Catalysts* **2020**, *10*, 330-341.
- [16] Y. M. A. Yamada, K. Takeda, H. Takahashi and S. Ikegami, J. Org. Chem. 2003, 68, 7733-7741.
- [17] Y. M. A. Yamada, S. M. Sarkar and Y. Uozumi, J. Am. Chem. Soc. 2012, 134, 3190-3198.
- [18] R. Hudson, H. R. Zhang, A. LoTemplio, G. Benedetto, G. Hamasaka, Y. M. A. Yamada, J. L. Katz and Y. Uozumi, *Chem. Commun.* **2018**, *54*, 2878-2881.
- [19] L. Yin and J. Liebscher, Chem. Rev. 2007, 107, 133-173.
- [20] Á. Molnár, Chem. Rev. 2011, 111, 2251-2320.
- [21] P. P. Mpungose, Z. P. Vundla, G. E. M. Maguire and H. B. Friedrich, *Molecules* 2018, 23, 1676-1699.
- [22] L. Djakovitch and F. –X. Felpin, *ChemCatChem* 2014, 6, 2175-2187.
- [23] R. Cano, A. F. Schmidt and G. P. McGlacken, *Chem. Sci.* 2015, 6, 5538-5346.
- [24] D. –T. Tang, K. D. Collins and F. Glorius, J. Am. Chem. Soc. 2013, 135, 7450-7453.
- [25] D. –T. Tang, k. D. Collins, J. B. Ernst and F. Glorius, Angew. Chem. Int. Ed. 2014, 53, 1809-1813.
- [26] M. Parisien, D. Valette and K. Fagnou, J. Org. Chem. 2005, 70, 7578-7584.
- [27] S. Byun, J. Chung, J. Kwon and B. M. Kim, *Chem. Asian J.* 2015, 10, 982-988.
- [28] L. Wang, W. –B. Yi and C. Cai, *Chem. Commun.* 2011, 47, 806-808.
- [29] Y. Huang, Z. Lin and R. Cao, Chem. Eur. J. 2011, 17, 12706-12712.
- [30] G. Park, S. Lee, S. J. Son and S. Shin, *Green Chem.* 2013, 15, 3468-3473.
- [31] Y. M. A. Yamada, Y. Yuyama, T. Sato, S. Fujikawa and Y. Uozumi, *Angew. Chem. Int. Ed.* 2014, 53, 127-131.

- [32] S. M. McAfee, J. S. J. McCahill, C. M. Macaulay, A.
 D. Hendsbee and G. C. Welch, *RSC Adv.* 2015, *5*, 26097-26106.
- [33] V. A. Zinovyeva, M. A. Vorotyntsev, I. Bezverkhyy, D. Chaumont and J. –C. Hierso, *Adv. Funct. Mater.* 2011, 21, 1064-1075.
- [34] M. Beaupérin, R. Smaliy, H. Cattey, P. Meunier, J. Ou, P. H. Toy and J. –C. Hierso, *Chem. Commun.* 2014, 50, 9505-9508.
- [35] S. M. Sarkar, Y. Uozumi and Y. M. A. Yamada, *Angew. Chem. Int. Ed.* **2011**, *50*, 9437-9441.
- [36] Y. M. A. Yamada, T. Watanabe, A. Ohno and Y. Uozumi, *ChemSusChem* **2012**, *5*, 293-299.
- [37] T. Sato, A. Ohno, S. M. Sarkar, Y. Uozumi and Y. M. A. Yamada, *ChemCatChem* 2015, 7, 2141-2148.
- [38] J. Roger, F. Požgan and H. Doucet, *Green Chem.* **2009**, *11*, 425-432.
- [39] D. Roy, S. Mom, M. Beaupérin, H. Doucet and J.-C. Hierso, Angew. Chem. Int. Ed. 2010, 49, 6550-6554.
- [40] D. Ghosh and H. M. Lee, Org. Lett. 2012, 14, 5534-5537.
- [41] G. L. Allsop, A. J. Cole, M. E. Giles, E. Merifield, A. J. Noble, M. A. Pritchett, L. A. Purdie and J. T. A. Singleton, *Org. Process Res. Dev.* **2009**, *13*, 751-759.
- [42] C. Karmel, Z. Chen and J. F. Hartwig, J. Am. Chem. Soc. 2019, 141, 7063-7072.
- [43] A. Facchetti, M.-H. Yoon, C. L. Stern, G. R. Hutchison, M. A. Ratner and T. J. Marks, *J. Am. Chem Soc.* 2004, *126*, 13480-13501.
- [44] M. Lafrance and K. Fagnou, J. Am. Chem. Soc. 2006, 128, 16496-16497.
- [45] Oxidative addition of chlorobenzene on Pd₂₀ and Au/Pd clusters has been theoretically studied by Ehara and Sakurai.; R. N. Dhital, C. Kamonsatikul, E. Somsook, K. Bobuatong, M. Ehara, S. Karanjit and H. Sakurai, J. Am. Chem. Soc. 2012, 134, 20250-20253.
- [46] D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.* 2007, *129*, 6880-6886.
- [47] S. I. Gorelsky, D. Lapointe and K. Fagnou, J. Am. Chem. Soc. 2008, 130, 10848-10849.

12

FULL PAPER

A Convoluted Polyvinylpyridine-Palladium Catalyst for Suzuki–Miyaura Coupling and C-H Arylation

Adv. Synth. Catal. Year, Volume, Page - Page

Aya Ohno, Takuma Sato, Toshiaki Mase, Yasuhiro Uozumi,* and Yoichi M. A. Yamada*

