Bis[*N*,*N′*-(2-indanolyl)]-1,5-diazacyclooctane as Unique Metal Ligand: Self-Assembly of Palladium Nanoparticles and Catalytic Reactivity on C–C Bond Formation

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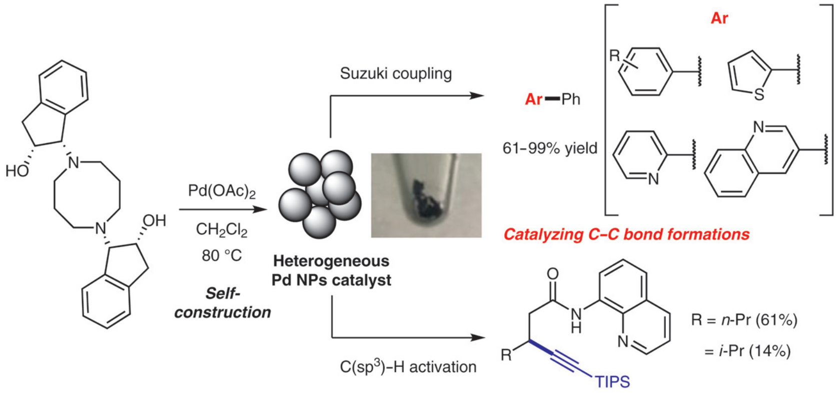

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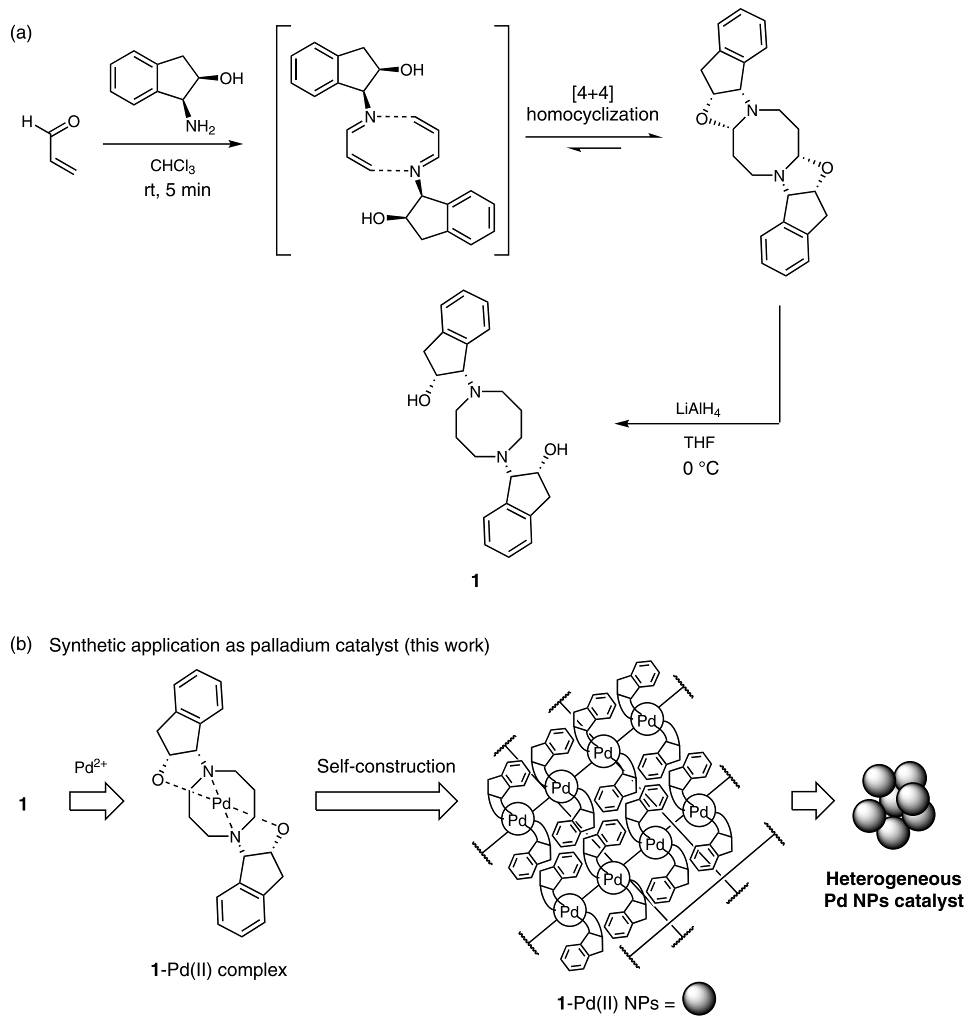
Abstract A previously unreported 1,5-diazacyclooctane-palladium(II) complex was synthesized using bis[*N*,*N′*-(2-indanolyl)]-1,5-diazacyclooctane, which was readily prepared via a novel [4+4] homocyclization of the unsaturated imine intermediate generated from acrolein and 1-amino-2-indanol. Interestingly, the 1,5-diazacyclooctane-palladium(II) complex self-assembled to form palladium nanoparticles. This approach readily provided palladium nanoparticles simply by heating a mixture of palladium(II) acetate and bis[*N*,*N′*-(2-indanolyl)]-1,4-diazacyclooctane in dichloroethane at mild temperatures. The 1,5-diazacyclooctane-derivative-palladium nanoparticles were successfully deployed in synthetic applications as a heterogeneous catalyst, facilitating Suzuki coupling and a challenging C–C bond formation via C(sp^3)–H activation under low catalyst loading conditions.

Key words 1,5-diazacyclooctane, palladium nanoparticles, heterogeneous catalyst, chiral ligand, Suzuki coupling, C(sp^3)–H activation

Transition-metal-catalyzed C–C bond-forming reactions have played an important role in organic synthesis.[1] In recent decades, metal nanoparticles (NPs) have received attention as heterogeneous metal catalysts.[2] Metal NPs provide a high catalytic reactivity in synthetic applications, even without the addition of a ligand, they can be reused several times to enable metal-catalyzed reactions,[3] and can be easily removed from the reaction mixture. These advantages enable the replacement of homogeneous palladium catalysts with Pd NP catalysts in Pd NP-catalyzed reactions, such as hydrogenation,[4] cross-coupling,[5] and C–H activation.[6] Metal NPs are typically immobilized on a stabilizing substrate, such as a polymer[7] or an inorganic material.[8] The reactivity of the metal NP catalyst can then be tuned by the electronic and structural effects of the NP-supporting material. Support materials modified with metal ligand structures, such as phosphine[9] and N-heterocyclic carbene (NHC),[10] enhance the reactivity of a NP catalyst and enable coupling reactions on low-reactivity substrates. Metal NPs supported by a chiral ligand, xylose-backbone-modified colloidal Pd-NPs, were prepared by Chaudret and co-workers by reducing tris(dibenzylideneacetone)dipalladium(0) via hydrogenation in the presence of the chiral ligand xylofuranoside diphosphite.[11] The introduction of these ligand motifs into a support material, however, required several time-consuming chemical synthesis steps. The facile preparation of metal NPs supported by simple ligands, including chiral ligands, would be synthetically useful.

Our group has focused on previously unrecognized reactions of unsaturated imine derivatives.[12] We recently identified a unique [4+4] homocyclization of an imine intermediate derived from unsaturated aldehyde derivatives and hydroxyl group-containing amine substrates.[13] Bis[*N*,*N′*-(2-indanolyl)]-1,5-diazacyclooctane **1** having a (1*S*,2*R*)-(–)-*cis*-1-amino-2-indanol moiety, was produced by the formal [4+4] homocyclization between acrolein and (1*S*,2*R*)-(–)-*cis*-1-amino-2-indanol, followed by hydride reduction (Scheme 1, a). 1,5-Diazacyclooctane **1**, which includes two hydroxyl groups on indanol moieties, positioned at the N atoms of the 1,5-diazacyclooctane core, suggested utility as a metal ligand capable of forming a robust metal complex by coordination through the two hydroxyl groups and the two endocyclic nitrogen atoms in the 1,5-diazacyclooctane skeleton. This structure is similar to that of sparteine,[14] an effective 1,5-diazacyclooctane skeleton-containing ligand used as a lithium organometallic reagent. Here, we report the preparation of a **1**-Pd(II) complex as the first example of a 1,5-diazacyclooctane derivative Pd complex. The complex was found to self-assemble to form Pd NPs (Scheme 1, b).

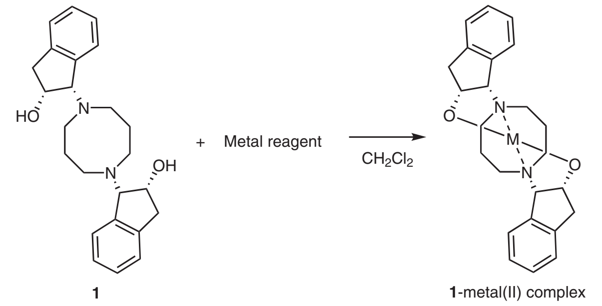


Scheme 1 1,5-Diazacyclooctane **1** and its applications to metal catalyst chemistry: (a) The formal [4+4] homocyclization reaction developed here using an intermediate unsaturated imine formed from acrolein and (1*S*,2*R*)-(–)-*cis*-1-amino-2-indanol; and (b) access to a **1**-Pd(II) complex and self-assembled **1**-Pd nanoparticles.

The Pd NPs were found to be useful as a heterogeneous catalyst, displaying catalytic reactivity in Suzuki coupling and C–C bond formation reaction via $C(sp^3)$–H activation.

Synthetic applications of 1,5-diazacyclooctane **1** were sought by synthesizing the **1**-metal complex. We focused on transition-metal catalysts, such as Ni and Pd, due to their synthetic utility in a variety of catalytic coupling reactions. The air-stable divalent Ni and Pd reagents were selected as easy-to-use metal sources. Initially, the synthesis of a Ni complex with **1** was attempted (Table 1). Nickel(II) chloride hexahydrate was treated with **1** in dichloromethane, which showed good solubility in the presence of **1** at room temperature; however, a **1**-Ni(II) complex was not obtained, and **1** was recovered (Table 1, entry 1). A reaction of **1** with palladium(II) acetate produced a palladium(II) complex with **1** in good yield (84%) after precipitation by addition of diethyl ether and then filtration (entry 2; see Supporting Information). Electrospray ionization mass spectrometry (ESI-MS) analysis of the product clearly identified the presence of a single product corresponding to the mass of **1**-Pd(II) (Figure 1, a). Our synthesis of **1**-Pd(II) is the first example of a Pd complex involving a 1,5-diazacyclooctane skeleton ligand. The obtained **1**-Pd(II) complex was found to be bench stable; thus, decomposition did not occur, even after several months at room temperature under air atmosphere. The thermal stability of **1** was tested by mixing with palladium acetate and heating at 80 °C (entry 3). As shown in Figure 1 (b and c), the yellow solution of **1** and palladium(II) acetate turned to a black suspension after 12 hours and then to a Pd NP suspension (vide infra) in a 55% yield [calculated as assembly of **1**-Pd(II)], which was easily isolated as a black solid by centrifuging (Figure 1, d). It should be noted that our preparation conditions were mild and did not require the presence of a reductant (the addition of a reducing reagent in most metal NP preparations is necessary to form metal NPs). By contrast, heating a dichloroethane solution of palladium(II) acetate in the absence of **1** at 80 °C did not produce Pd NPs (see the Supporting Information). The production of NPs was confirmed by collecting transmission electron microscopy (TEM) images of the obtained complex product, as shown in Table 1, entry 3. TEM imaging revealed the construction of NPs (Figure 1, e), 4 nm in diameter (Figure 1, f). The production of the small NPs was attributed to the bulk of ligand **1**, which prevented the extensive aggregation of **1**-Pd NPs via steric hindrance.[15]

Table 1 Synthesis of the **1**-Transition Metal Complexes



Entry	Metal reagent	Time (h)	Temp	Result (Yield)
1	$NiCl_2{\cdot}6H_2O$	3	r.t.	recovered **1**
2	$Pd(OAc)_2$	1.5	r.t.	**1**-Pd(II) (84%)
3[a]	$Pd(OAc)_2$	12	80 °C	**1**-Pd NPs (55%)

[a] Dichloroethane was used as a chlorinated solvent.

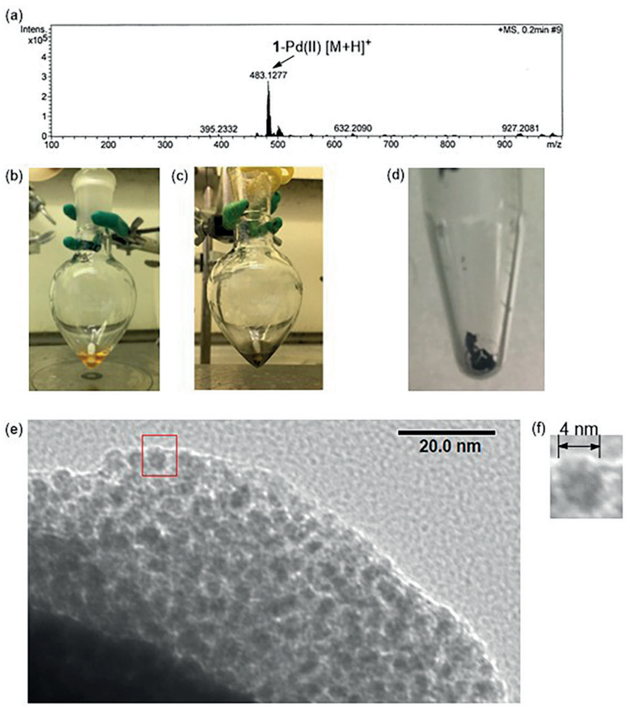
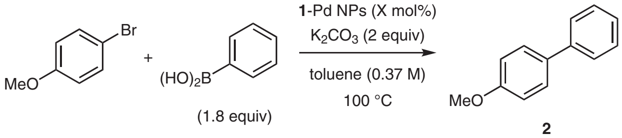


Figure 1 (a) ESI-MS spectrum of **1**-Pd. The reaction mixtures listed in entry 3 of Table 1, at (b) 0 h and (c) 12 h, and (d) as isolated **1**-Pd NPs. (e) TEM image of the **1**-Pd nanoparticles, and (f) expanded image of a single nanoparticle, as indicated by the square.

Inspired by the development of **1**-Pd NPs through the preparation protocol described above, we examined synthetic applications of the **1**-Pd NPs as a practical heterogeneous catalyst. **1**-Pd NPs were used to conduct a Suzuki coupling, which is a useful Pd-catalyzed reaction.[16] As shown in Table 2, Suzuki coupling between 4-bromoanisole and phenylboronic acid was investigated in the presence of catalytic amounts of the **1**-Pd NPs. The coupling reaction was performed with 10 mol% **1**-Pd NPs, revealing that the **1**-Pd NPs exhibited catalytic reactivity under these Suzuki coupling conditions and gave the coupled product **2** in modest yield (42%, Table 2, entry 1). Unexpectedly, increasing the catalyst loading to 20 mol% diminished the yield of **2** (18%, entry 2). These results suggested that the aggregation of **1**-Pd NPs competed with the catalytic activity at higher catalyst loading levels, thereby deactivating the **1**-Pd NPs. Consistent with this hypothesis, reducing the **1**-Pd NPs loading to 2 mol% prevented deactivation of the catalytic reactivity, and the coupling reaction was catalyzed to afford **2** in 90% yield (entry 3). Catalyst loading in the context of the coupling reaction was further optimized by testing much lower catalyst loading levels of **1**-Pd NPs. Even a 0.5 mol% **1**-Pd NPs loading provided a good catalytic reactivity, and the product was obtained in 89% yield (entry 4). Performing the coupling reaction in the presence of 0.05 mol% **1**-Pd NPs provided good catalytic reactivity; consequently, **2** was produced in 64% yield (entry 5). A highest turnover number (TON) of 1275 was obtained. These results enabled Suzuki coupling on the hundreds of milligram scale. These results were compared with those obtained from ligand-free conditions by carrying out the coupling reaction in the presence of 10 or 0.5 mol% palladium acetate, in place of the **1**-Pd NPs. The coupled product **2** was produced in 76% yield with a 10 mol% loading palladium acetate (entry 6). Reducing the **1**-Pd NP loading to 0.5 mol% produced **2** in 20% yield (entry 7). These results indicated that **1** stabilized the active species of the **1**-Pd NP catalyst and prolonged the catalytic lifetime.

The substrate diversity of the **1**-Pd NP-catalyzed Suzuki coupling reaction was explored by testing a variety of aromatic bromides in a coupling reaction involving phenylboronic acid (Table 3). The coupling reactions were conducted under the optimized conditions of 0.5 mol% catalyst loading. When applied to an electron-deficient substrate comprising 4-acetylbromobenzene, the coupling reaction proceeded completely to give the coupled product **3a** in 99% yield (Table 3, entry 1). It could be noted that **1**-Pd NPs

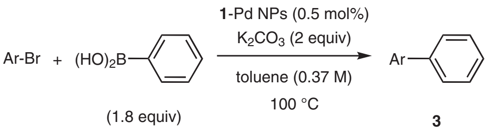
Table 2 Investigation of **1**-Pd NP-Catalyzed Suzuki Coupling Reaction

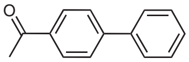
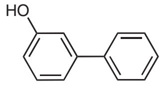
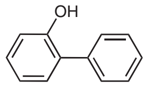
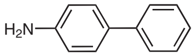
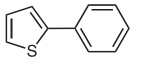
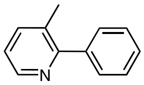
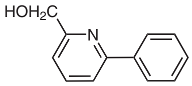
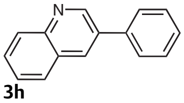
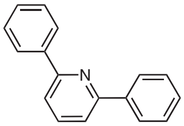


Entry	X	Time (h)	Yield (%)	TON[a]
1	10	6	42	
2	20	18	18	
3	2	5	90	9
4	0.5	5	89	178
5[b]	0.05	21	64	1275
6[c]	$Pd(OAc)_2$ (10 mol%)	8	76	
7[c]	$Pd(OAc)_2$ (0.5 mol%)	8	20	

[a] Turnover number.
[b] 4-Bromoanisole (660 mg, 3.5 mmol) was used.
[c] Coupling reaction was conducted without the addition of the ligand.

Table 3 Substrate Scope on the **1**-Pd NP-Catalyzed Suzuki Coupling Reaction



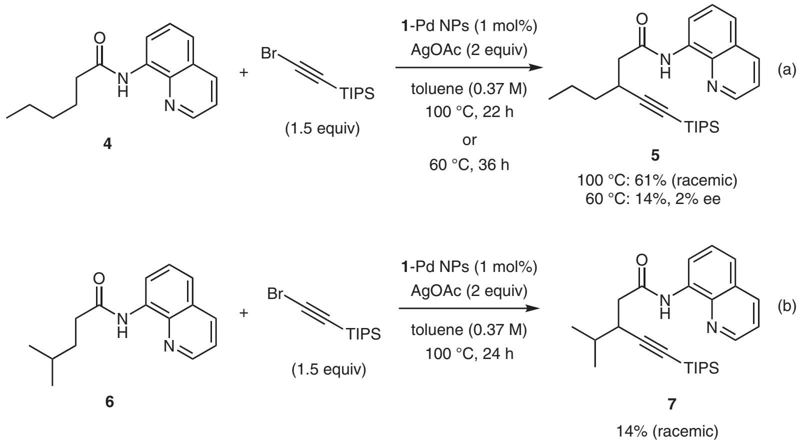
Entry	Coupled product	Time (h)	Yield (%)
1	 **3a**	4	99
2	 **3b**	4	75
3	 **3c**	4	75
4	 **3d**	13	93
5	 **3e**	6	68
6	 **3f**	24	67
7	 **3g**	6	78
8	 **3h**	15	21 (61)[a]
9[b]	 **3i**	8	74

[a] **1**-Pd NP used: 2 mol%.
[b] **1**-Pd NPs used: 1 mol%; and 3.6 equiv $PhB(OH)_2$ and 4 equiv K_2CO_3 were added.

could be reused for 4 times of Suzuki coupling reaction with 4-acetylbromobenzene, although the catalytic activity decreased after each reaction (See Supporting Information). Bromobenzene derivatives substituted with free functional groups were next investigated. The hydroxyl group of 3-bromophenol did not inhibit the catalyst to provide the coupled products **3b** in 75% yield (entry 2). The 2-bromophenol coupling proceeded smoothly to give **3c** in good yield (75%, entry 3). Coupling of an aniline substrate with phenylboronic acid under the optimal coupling conditions furnished **3d** in 93% yield (entry 4). 2-Bromothiophene was examined as a heteroaromatic bromide (entry 5). Although Pd catalysts are typically deactivated by sulfur poisoning, the coupling proceeded smoothly to afford **3e** in 68% yield. 2-Bromopyridine, which contained a sterically hindering methyl group at the 3-position, was investigated. The reaction time was extended, and the product **3f** was obtained in 67% yield (entry 6). 6-Hydroxylmethylbromopyridine was reactive to produce **3g** in good yield (78%, entry 7).

A coupling reaction employing 3-bromoquinoline with a 0.5 mol% catalyst loading gave **3h** in low yield (21%), although a 2 mol% catalyst loading improved the yield to 61% (Table 3, entry 8). Dibromopyridine was treated with 3.5 equivalents of phenylboronic acid in the presence of 1 mol% **1**-Pd NPs and 4 equivalents of potassium carbonate, and the product substituted with two phenyl groups **3i** was successfully obtained in 74% yield (entry 9).

The development of the **1**-Pd NP-catalyzed Suzuki coupling reaction suggested further applications of the **1**-Pd NPs to challenging C–C bond-forming reactions via $C(sp^3)$–H activation. The **1**-Pd NPs were tested in the Pd(II)-catalyzed ethynylation of a $C(sp^3)$–H bond on an alkyl chain with a quinoline directing group.[17] After optimizing the conditions, the 8-[(hexanoyl)amino]quinoline (**4**) was ethynylized with 2-silylacetynyl bromide in the presence of 2 equivalents of silver(I) acetate and the **1**-Pd NPs upon heating at 100 °C. The enantioselectivity of the ethynylated products was analyzed using normal-phase high-performance liquid chromatography (HPLC) equipped with a chiral column. Interestingly, the **1**-Pd NPs catalyzed the ethynylation to give the 3-ethynylated product **5** in 61% yield, even if the ethynylation was carried out in 1 mol% the



Scheme 2 1-Pd NP-catalyzed ethynylation through C(sp^3)–H activation

catalyst loading (Scheme 2, a). Performing the reaction at 60 °C revealed enantioselectivity, albeit to a very small degree. Ethynylation of the relatively sterically hindered substrate **6** also proceeded to produce **7** in 14% yield with a racemic form (Scheme 2, b).

In summary, we have reported the first synthesis of a 1,5-diazacyclooctane core derivative palladium(II) complex, **1**-Pd(II) using bis[*N*,*N*′-(2-indanolyl)]-1,4-diazacyclooctane prepared via a novel [4+4] homocyclization. The unique properties of the complex were harnessed to synthesize chiral ligand-coordinated Pd NPs, **1**-Pd NPs, through a concise preparation procedure. Synthetic applications of the NPs were explored by demonstrating **1**-Pd NP-catalyzed C–C bond formation reactions, Suzuki coupling, and ethynylation via C(sp^3)–H activation, a challenging C–C bond-forming reaction. This success demonstrated the potential utility of the NPs as a practical heterogeneous Pd NP catalyst. Further studies of asymmetric reactions catalyzed by **1**-Pd NPs as heterogeneous chiral catalysts are ongoing. Other metal NP catalysts based on a series of 1,5-diazacyclooctane derivatives synthesized through our [4+4] homocyclization reaction will be disclosed in due course.

All commercially available reagents were used without further purification. All anhydrous solvents were purchased from Wako Pure Chemical Industries Ltd., and Pd(OAc)$_2$ was purchased from Wako Pure Chemical Industries Ltd. 1,5-Diazacyclooctane **1** was prepared according to our report.[13] For Suzuki coupling, all aromatic bromides were purchased from Tokyo Chemical Industry Co., Ltd. and Sigma-Aldrich, and phenylboronic acid was purchased from Sigma-Aldrich. K_2CO_3 was purchased from Nacalai Tesque Inc. For the typical procedure of 4-methoxybiphenyl (**2**) (Table 2, entry 3), **1**-Pd NPs (3.6 mg) were prepared by repeating the procedure of **1**-Pd NPs. For C–C bond-forming reaction via C(sp^3)–H activation, 8-aminoquinoline and trimethylsilylacetylene were purchased from Tokyo Chemical Industry Co. 8-(*N*-Acylamino)quinolones **4** and **6** were prepared according to the reported procedures.[18] (Bromoethynyl)triisopropylsilane was prepared according to the literature.[19] Silica gel 60 (0.015–0.040 mm) was used for column chromatography. For preparative TLC, PLC glass plate Silica gel 60 F254, 0.5 or 1 mm (Merck-Millipore) was used. HPLC grade hexane and *i*-PrOH from Wako Pure Chemical Industries Ltd. were used for HPLC analysis. Normal phase HPLC analysis on enantiomeric excess of ethynylated products **5** and **7** was performed on a Shimadzu Prominence® system equipped with a CHIRALPAK (DAICEL Corporation) (AS-3, 4.6 × 250 mm), with isocratic elution of hexane and *i*-PrOH (95:5). The mobile phase for HPLC were HPLC grade hexane (Buffer A) and HPLC grade *i*-PrOH (Buffer B). Simultaneous monitoring of the eluent at 220 and 254 nm by UV detector was performed.

The amount of **1**-Pd NPs used for the coupling reactions was estimated by the mole number of **1**-Pd NPs, which was same as that of **1**-Pd(II) precursor (MW: 482.92). NMR spectra of the compounds produced by **1**-Pd NPs-catalyzed coupling reactions were in accordance with the reported data (see details and references in Supporting Information).

1-Pd(II)

In a frame dried flask, 1,5-diazacyclooctane **1** (104 mg, 0.27 mmol) and Pd(OAc)$_2$ (62 mg, 0.27 mmol) were dissolved in anhyd CH_2Cl_2 (2.5 mL) under N_2 atmosphere and then stirred for 1.5 h at r.t. To the reaction mixture was added Et_2O to form a precipitate. The obtained precipitate was filtered, washed with Et_2O, and dried under low pressure to afford **1**-Pd(II) (112 mg, 84%) as a light yellow powder.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{29}N_2O_2Pd$ 483.1268; found: 483.1277.

1-Pd NPs

In a frame-dried flask, 1,5-diazacyclooctane **1** (1.4 mg, 0.0062 mmol) and Pd(OAc)$_2$ (2.3 mg, 0.0060 mmol) were dissolved in anhyd dichloroethane (0.5 mL) under N_2 atmosphere and heated at 80 °C for 12 h without stirring. After cooling to r.t., the reaction mixture was transferred into an Eppendorf tube and centrifuged for a second to give a black precipitate. Supernatant solvent was removed, then hexane and a very small amount of CH_2Cl_2 were added, and centrifuged again. After removal of supernatant solvent, the obtained black precipitate was dried in vacuo to afford **1**-Pd NPs (1.6 mg, 55%) as a black powder. Production of NPs was analyzed by TEM.

Note: In a larger scale preparation, the yield of **1**-Pd NPs was decreased. **1**-Pd NPs were therefore prepared for each reaction under the conditions described above; for example, 1,5-diazacyclooctane **1** (6.0 mg, 0.015 mmol) and $Pd(OAc)_2$ (3.5 mg, 0.015 mmol) were dissolved in anhyd dichloroethane (1.3 mL) under N_2 atmosphere. After heating at 80 °C for 12 h without stirring and subsequent isolation by centrifugation, **1**-Pd NPs (2.3 mg, 30%) was obtained.

4-Methoxybiphenyl (2); Typical Procedure

1-Pd NPs (3.6 mg, 0.0075 mmol) was added to a frame-dried flask and filled with N_2. To the flask were added phenylboronic acid (83 mg, 0.68 mmol), K_2CO_3 (106 mg, 0.76 mmol), 4-bromoanisole (47 μL, 0.37 mmol), and anhyd toluene (1.0 mL), then the reaction mixture was heated at 100 °C. After stirring for 5 h, the mixture was cooled to r.t., filtered, extracted with hexane, and the combined hexane layers were washed with brine, dried (Na_2SO_4), and evaporated. The crude material was purified by silica gel column chromatography (hexane to hexane/EtOAc 100:1) to give **2** (62 mg, 90%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.56–7.50 (m, 4 H), 7.41 (dd, J = 7.5, 7.2 Hz, 2 H), 7.32–7.27 (m, 1 H), 6.97 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3.

4-Acetylbiphenyl (3a)

According to the typical procedure, **1**-Pd NPs (0.85 mg, 0.0017 mmol), phenylboronic acid (78 mg, 0.64 mmol), K_2CO_3 (98 mg, 0.70 mmol), 4-bromoacetophenone (71 mg, 0.35 mmol), and anhyd toluene (0.94 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 4 h. Purification by preparative TLC (hexane/EtOAc 4:1) provided **3a** (71 mg, 99%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.03 (d, J = 8.4 Hz, 2 H), 7.68 (d, J = 8.4 Hz, 2 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.51–7.37 (m, 3 H), 6.97 (dt, J = 8.7, 1.8 Hz, 2 H), 2.63 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.7, 145.7, 139.8, 135.8, 128.91, 128.88, 128.20, 127.23, 127.18, 26.6.

3-Phenylphenol (3b)

According to the typical procedure, **1**-Pd NPs (1.0 mg, 0.0022 mmol), phenylboronic acid (98 mg, 0.80 mmol), K_2CO_3 (123 mg, 0.89 mmol), 3-bromophenol (77 mg, 0.44 mmol), and anhyd toluene (1.2 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 4 h. Purification by silica gel column chromatography (hexane/EtOAc 20:1 to toluene/EtOAc 30:1) provided **3b** (56 mg, 75%) as a light orange solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.68–7.55 (m, 2 H), 7.45–7.40 (m, 2 H), 7.37–7.25 (m, 2 H), 7.18–7.15 (m, 1 H), 7.07–7.05 (m, 1 H), 4.86 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.7, 142.9, 140.6, 129.9, 128.7, 127.47, 127.08, 119.8, 114.17, 114.07.

2-Phenylphenol (3c)

According to the typical procedure, **1**-Pd NPs (0.85 mg, 0.0017 mmol), phenylboronic acid (76 mg, 0.62 mmol), K_2CO_3 (97 mg, 0.70 mmol), 2-bromophenol (41 μL, 0.35 mmol), and anhyd toluene (0.94 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 4 h. Purification by preparative TLC (hexane/EtOAc 5:1) provided **3c** (45 mg, 75%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.45 (m, 4 H), 7.41–7.37 (m, 1 H), 7.26–7.23 (m, 2 H), 7.01–6.97 (m, 2 H), 5.18 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.3, 137.0, 130.2, 129.25, 129.12, 129.06, 128.0, 115.8.

4-Aminobiphenyl (3d)

According to the typical procedure, **1**-Pd NPs (0.7 mg, 0.0014 mmol), phenylboronic acid (63 mg, 0.51 mmol), K_2CO_3 (80 mg, 0.58 mmol), 4-bromoaniline (49 mg, 0.29 mmol), and anhyd toluene (0.76 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 13 h. Purification by silica gel column chromatography (hexane/EtOAc 4:1) provided **3d** (46 mg, 93%) as a light brown solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.54–7.51 (m, 2 H), 7.42–7.38 (m, 4 H), 7.36–7.22 (m, 1 H), 6.74 (d, J = 8.4 Hz, 2 H), 3.70 (br s, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 145.7, 141.1, 131.5, 128.6, 127.9, 126.3, 126.2, 115.3.

2-Phenylthiophene (3e)

According to the typical procedure, **1**-Pd NPs (0.6 mg, 0.0012 mmol), phenylboronic acid (55 mg, 0.45 mmol), K_2CO_3 (68 mg, 0.49 mmol), 2-bromothiophene (24 μL, 0.25 mmol), and anhyd toluene (0.66 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 6 h. Purification by silica gel column chromatography (hexane/EtOAc 50:1) provided **3e** (27 mg, 68%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62–7.59 (m, 2 H), 7.37 (td, J = 7.2, 2.0 Hz, 2 H), 7.31–7.25 (m, 3 H), 7.08–7.06 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.4, 134.4, 1128.8, 127.9, 127.4, 125.9, 124.8, 123.0.

3-Methyl-2-phenylpyridine (3f)

According to the typical procedure, **1**-Pd NPs (0.6 mg, 0.0012 mmol), phenylboronic acid (53 mg, 0.43 mmol), K_2CO_3 (67 mg, 0.48 mmol), 2-bromo-3-methylpyridine (28 μL, 0.25 mmol), and anhyd toluene (0.66 mL) were added to a N_2-filled flask, the reaction mixture was heated at 100 °C for 24 h. Purification by preparative TLC (hexane/EtOAc 3:1) provided **3f** (28 mg, 67%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.53 (dd, J = 4.8, 0.8 Hz, 1 H), 7.57 (dd, J = 7.6, 0.8 Hz, 1 H), 7.54–7.50 (m, 2 H), 7.47–7.42 (m, 2 H), 7.41–7.36 (m, 1 H), 7.17 (dd, J = 7.6, 4.8 Hz, 1 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.6, 146.9, 140.6, 138.4, 130.7, 128.9, 128.1, 127.8, 122.0, 20.0.

6-Phenyl-2-pyridinemethanol (3g)

According to the typical procedure, **1**-Pd NPs (0.3 mg, 0.0006 mmol), phenylboronic acid (28 mg, 0.23 mmol), K_2CO_3(34 mg, 0.25 mmol), 2-bromo-6-(hydroxymethyl)pyridine (24 mg, 0.12 mmol), and anhyd toluene (0.33 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 6 h. Purification by preparative TLC (hexane/EtOAc 15:1) provided **3g** (18 mg, 78%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (d, J = 6.8 Hz, 2 H), 7.75 (t, J = 7.6 Hz, 1 H), 7.64 (d, J = 7.6 Hz, 1 H), 7.48–7.43 (m, 3 H), 7.47–7.42 (m, 2 H), 7.16 (d, J = 7.2 Hz, 1 H), 4.82 (s, 2 H), 4.14 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.4, 156.0, 138.5, 137.6, 129.2, 128.7, 126.9, 119.2, 118.7, 63.9.

3-Phenylquinoline (3h)

According to the typical procedure, **1**-Pd NPs (0.2 mg, 0.0004 mmol), phenylboronic acid (4.7 mg, 0.038 mmol), K_2CO_3 (5.5 mg, 0.039 mmol), 3-bromoquinoline (2.8 μL, 0.021 mmol), and anhyd toluene

(0.15 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 15 h. Purification by preparative TLC (hexane/EtOAc 5:2) provided **3h** (2.6 mg, 62%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.19 (d, J = 2.1 Hz, 1 H), 8.31 (d, J = 2.4 Hz, 1 H), 8.15 (d, J = 8.4 Hz, 1 H), 7.89 (d, J = 8.4 Hz, 1 H), 7.76–7.70 (m, 3 H), 7.61–7.51 (m, 3 H), 7.47–7.42 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.9, 147.3, 137.9, 133.2, 129.4, 129.21, 129.16, 128.1, 128.00, 127.99, 127.4, 127.0.

2,6-Diphenylpyridine (3i)

According to the general procedure, **1**-Pd NPs (0.5 mg, 0.001 mmol), phenylboronic acid (45 mg, 0.37 mmol), K_2CO_3 (59 mg, 0.43 mmol), 2,6-dibromopyridine (24 mg, 0.10 mmol), and anhyd toluene (0.27 mL) were added to a N_2-filled flask, and the reaction mixture was heated at 100 °C for 8 h. Purification by preparative TLC (hexane/EtOAc 10:1) provided **3i** (18 mg, 74%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.15 (dt, J = 7.6, 5.2 Hz, 4 H), 7.82, 7.80 (d, d, J = 7.2, 7.2 Hz, 1 H), 7.69 (d, J = 7.2 Hz, 2 H), 7.51–7.48 (m, 4 H), 7.45–7.40 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.8, 139.5, 137.5, 128.9, 128.7, 127.0, 118.6.

8-{[3-(Triisopropylethynyl)hexanoyl]amino}quinoline (5); Typical Procedure

1-Pd NPs (0.4 mg, 0.0008 mmol) was added to a frame-dried flask and filled with N_2. To the flask were added 8-[*N*-(hexanoyl)amino]quinoline (**4**; 19 mg, 0.080 mmol), (bromoethynyl)triisopropylsilane (30 μL, 0.12 mmol), AgOAc (28 mg, 0.17 mmol), and anhyd toluene (0.22 mL), then the reaction mixture was heated at 100 °C. After stirring for 22 h, the mixture was cooled to r.t., filtered, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The crude material was purified by preparative TLC (hexane/EtOAc 5:1) to give **5** (21 mg, 61%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.87 (br s, 1 H), 8.80–8.78 (m, 2 H), 8.15 (dd, J = 8.4, 1.6 Hz, 1 H), 7.53–7.50 (m, 2 H), 7.49–7.43 (m, 1 H), 3.13 (br s, 1 H), 2.75, 2.68 (q each, J = 7.6, 7.2 Hz, 2 H), 1.64–1.51 (m, 4 H), 0.97–0.87 (m, 24 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.5, 148.0, 138.3, 136.2, 134.4, 127.8, 127.3, 121.49, 121.45, 116.5, 110.4, 82.0, 44.4, 36.9, 29.8, 20.4, 18.4, 13.8, 11.1.

8-{[3-(Triisopropylethynyl)-4-methylpentanoyl]amino}quinoline (7)

According to the procedure for **5**, **1**-Pd NPs (0.3 mg, 0.0006 mmol), 8-[(3-methylpentanoyl)amino]quinoline (**6**; 15 mg, 0.064 mmol), (bromoethynyl)triisopropylsilane (23 μL, 0.096 mmol), and AgOAc (21 mg, 0.12 mmol) in anhyd toluene (0.17 mL) were heated at 100 °C for 24 h. Purification by preparative TLC (hexane/EtOAc 5:1) gave **7** (3.7 mg, 14%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.88 (br s, 1 H), 8.81–8.79 (m, 2 H), 8.16 (dd, J = 8.4, 1.6 Hz, 1 H), 7.55–7.44 (m, 3 H), 3.13–3.08 (m, 1 H), 2.72–2.69 (m, 2 H), 1.88–1.86 (m, 1 H), 1.10–1.07 (m, 6 H), 0.94–0.90 (m, 21 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.9, 148.0, 138.3, 136.3, 134.4, 127.8, 127.4, 121.50, 121.45, 116.5, 108.3, 42.3, 36.8, 31.1, 21.3, 18.5, 17.8, 11.1.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590956.

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