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Arylation of Terminal Alkynes by Aryl Iodides Catalyzed by a Parts per Million Loading of Palladium Acetate

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ABSTRACT: Arylation of terminal alkynes (16 varieties) by aryl iodides (28 varieties) was achieved with a mol ppm loading level of palladium catalyst, where a variety of functional groups including heteroarenes were tolerated. Thus, the arylations were carried out in the presence of palladium acetate at ppm loadings and potassium carbonate in ethanol at 80 ºC to give the corresponding internal alkynes in good to excellent yields. Synthesis of 2-phenyl-3-(phenylalkynyl)benzofuran was achieved by iterative use of the alkyne arylation under mol ppm catalytic conditions. Reaction-rate analysis, transmission electron microscopic examination of the reaction mixture, and mercury-amalgamation test were performed to gain insight into the active species of the highly active ppm catalytic species. Transmission electron microscopic (TEM) examination of the reaction mixture revealed that palladium nanoparticles were generated in situ under the reaction conditions, and their cluster size was variable during the catalytic reaction. A variation in size of palladium particles suggested that the composition-decomposition process of Pd aggregates should take place in situ via monomeric palladium(0) species and/or fine palladium(0) clusters which might be real catalytic species in this reaction.

KEYWORDS: Arylation, Alkynes, Aryl Iodides, Palladium, Parts per Million

INTRODUCTION

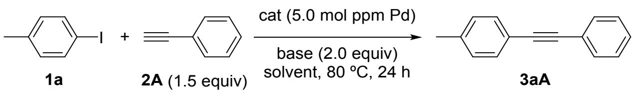
Palladium-catalyzed cross-coupling reactions are recognized as useful and important methods for synthesizing a variety of pharmaceuticals, agrochemicals, organic functional materials, etc.[1] However, these reactions often require mole percent levels of palladium species, based on the starting materials, to obtain the target compounds efficiently, resulting in potential contamination of the products by metallic residues. These palladium contaminants have to be removed from the products, because transition metals tend to be toxic toward living species and can impair the performance of organic functional materials.[2,3] In addition, some transition-metal species are limited resources on this planet and must be conserved to achieve sustainable development. Decreasing the catalyst loading provides a simple and straightforward solution to these difficulties. Consequently, organic chemists have attempted to develop highly efficient catalytic systems.[4–6] In this context, we also have developed efficient catalytic systems based on a palladium NNC-pincer complex for arylation of allyl esters and alkenes.[7,8]

The palladium-catalyzed arylation of terminal alkynes is a method commonly used for the synthesis of internal alkynes. Pioneering works on this reaction were independently reported in 1975 by Dieck and Heck,[9] Cassar,[10] and Sonogashira and co-workers.[11] Among these reactions, the Sonogashira reaction, in which a catalytic quantity of a copper salt and a stoichiometric amount of an amine as a base are used, proceeds efficiently under mild conditions with a broad tolerance of functional groups. Further studies on this protocol for the arylation of terminal alkynes have shown that the reaction proceeds in the absence of a copper salt;[12,13] however, a mole percent loading of the catalyst is still required to obtain the desired internal alkynes efficiently within reasonable reaction times. Although several research groups have investigated the arylation of terminal alkynes in the presence of part per million loadings of palladium catalysts, the catalytic systems were generally complicated and involved, for example, special palladium catalysts, bases, or solvents.[14] Furthermore, the substrate scope in the presence of parts per million loadings of palladium catalysts remains limited. The reaction would therefore be more useful if it could be promoted by a parts per million loading of a simple palladium catalyst and if it could be applied to a variety of the substrates under mild conditions. Very recently, highly efficient ppm palladium-catalyzed copper-free Sonogashira coupling was developed by Handa and Lipsutz.[15-17] Clearly, while pioneering strides have been made, additional studies on ppm palladium protocols using a highly accessible palladium source are warranted. In this report, we describe the arylation of various terminal alkynes with aryl iodides containing diverse functional groups in the presence of a parts per million loading of $Pd(OAc)_2$ and K_2CO_3 in ethanol to give the corresponding internal alkynes in good to excellent yields (52 examples). We also examined the nature of the catalytically active species in this system by using reaction-rate analysis, transmission electron microscopic measurements, and a mercury-amalgamation experiment.

RESULTS AND DISCUSSION

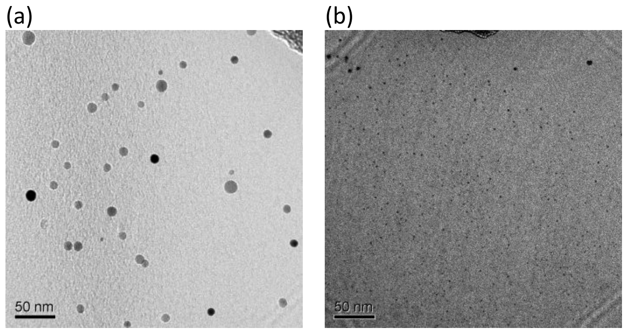
Initially, we screened the conditions for the coupling of 4-iodotoluene (**1a**) with ethynylbenzene (**2A**) (Table 1). The reaction was carried out in the presence of 5 mol ppm palladium acetate and 1.5 equivalents of potassium carbonate in a variety of solvents. The reaction did not proceed at all in water or methanol (Table 1, entries 1 and 2) but it proceeded efficiently in ethanol to give 1-methyl-4-(2-phenylethynyl)benzene (**3aA**) in 95% yield (entry 3). When propan-1-ol, isopropyl alcohol, or butan-1-ol was used as the solvent, **3aA** was obtained in yields of 50, 30, and 52%, respectively (entries 4–6). Ethylene glycol, 1,4-dioxane, and tetrahydrofuran were not suitable solvents for this reaction (entries 7–9). These results therefore showed that ethanol is the best solvent in this reaction. We next tested a variety of bases. However, the reaction did not proceed efficiently in the presence of other inorganic or organic bases [sodium carbonate, cesium carbonate, potassium acetate, potassium phosphate, potassium fluoride, sodium hydroxide, triethylamine, piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or 1,4-diazabicyclo[2.2.2]octane (DABCO)] (entries 10–19). We also optimized the amount of potassium carbonate (entries 20 and 21) and found that three equivalents were optimal for this reaction. The loading of palladium acetate could be decreased to 2.3 mol ppm (entry 22). Screening of the palladium catalyst was also performed. The use of tetrakis(triphenylphosphine)palladium, palladium–allyl chloride, palladium chloride, or palladium nitrite gave **3aA** in yields of 72, 75, 58, and 45%, respectively (entries 23–26). Palladium acetate was therefore the most effective catalyst among the palladium catalysts studied. The reaction did not proceed at all in the absence of a palladium catalyst (entry 27). The use of anhydrous ethanol as the solvent led to an increase in the yield of **3aA** (entry 28). A further decrease in the catalyst loading to 1.0 mol ppm gave the lower yield of **3aA** (entry 29). We also examined the transmission electron microscopic (TEM) analysis of the reaction mixtures of selected entries (Figure 1). While big size clusters of palladium (ϕ = ca. 10-18) were observed in the reaction mixtures using H_2O and THF (Figure 1a and 1c) which showed little catalytic activity for the coupling reaction, fine nanoparticles of palladium having *ca.* 2.1 nm of average diameter were generated in situ in EtOH in the presence of K_2CO_3 at 80 °C (Figure 1b) to promote the reaction efficiently (see also Table 1, entries 1, 3, and 9). In contrast, use of Et_3N in EtOH gave catalytically inactive giant clusters during the reaction as shown in Figure 1d. Thus, EtOH/K_2CO_3 were essential to generate highly catalytically active fine nanoparticles under the reaction conditions.

Table 1. Screening of Conditions for the Reaction of 4-Iodotoluene (1a) with Ethynylbenzene (2A)[a]



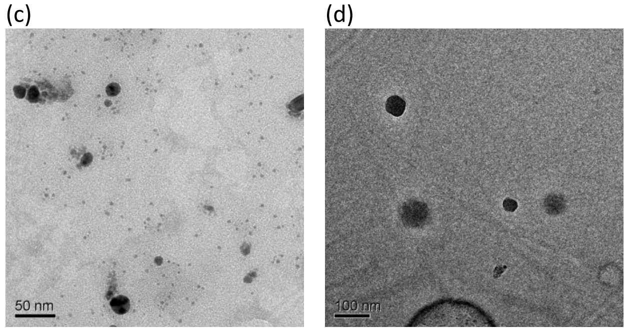
Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	K_2CO_3	H_2O	0
2	$Pd(OAc)_2$	K_2CO_3	MeOH	0
3	$Pd(OAc)_2$	K_2CO_3	EtOH	95
4	$Pd(OAc)_2$	K_2CO_3	PrOH	50
5	$Pd(OAc)_2$	K_2CO_3	^{i}PrOH	30
6	$Pd(OAc)_2$	K_2CO_3	BuOH	52
7	$Pd(OAc)_2$	K_2CO_3	ethylene glycol	0
8	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	0
9	$Pd(OAc)_2$	K_2CO_3	THF	0
10	$Pd(OAc)_2$	Na_2CO_3	EtOH	17
11	$Pd(OAc)_2$	Cs_2CO_3	EtOH	0
12	$Pd(OAc)_2$	KOAc	EtOH	0
13	$Pd(OAc)_2$	K_3PO_4	EtOH	0
14	$Pd(OAc)_2$	KF	EtOH	0
15	$Pd(OAc)_2$	NaOH	EtOH	0
16	$Pd(OAc)_2$	Et_3N	EtOH	0
17	$Pd(OAc)_2$	piperidine	EtOH	0
18	$Pd(OAc)_2$	DBU	EtOH	0
19	$Pd(OAc)_2$	DABCO	EtOH	24
20	$Pd(OAc)_2$	K_2CO_3[c]	EtOH	93
21	$Pd(OAc)_2$	K_2CO_3[d]	EtOH	100
22	$Pd(OAc)_2$[e]	K_2CO_3[d]	EtOH	91
23	$Pd(PPh_3)_4$[e]	K_2CO_3[d]	EtOH	72
24	$[PdCl(C_3H_5)]_2$[e]	K_2CO_3[d]	EtOH	75
25	$Pd(NO_3)_2$[e]	K_2CO_3[d]	EtOH	45
26	$PdCl_2$[e]	K_2CO_3[d]	EtOH	58
27	none	K_2CO_3[d]	EtOH	0
28[f]	$Pd(OAc)_2$[e]	K_2CO_3[d]	EtOH[g]	100 (93)[h]
29[f]	$Pd(OAc)_2$[i]	K_2CO_3[d]	EtOH[g]	21

[a] *Reaction conditions*: **1a** (0.5 mmol), **2A** (0.75 mmol), catalyst (2.5×10^{-6} mmol), base (1.0 mmol), solvent (2 mL), 80 °C, 24 h. [b] NMR yield. [c] K_2CO_3 (1.5 equiv, 0.75 mmol). [d] K_2CO_3 (3.0 equiv, 1.5 mmol). [e] Catalyst (2.3 mol ppm). [f] **2A** (1.1 equiv, 0.55 mmol). [g] Anhyd EtOH. [h] Isolated yield. [i] Catalyst (1 mol ppm).



In H_2O with K_2CO_3 (Table 1, entry 1)
Average diameter = ca. 9.8 nm.

In EtOH with K_2CO_3 (Table 1, entry 3)
Average diameter = ca. 2.1 nm.



In THF with K_2CO_3 (Table 1, entry 9)
Average diameter = ca. 18 nm.

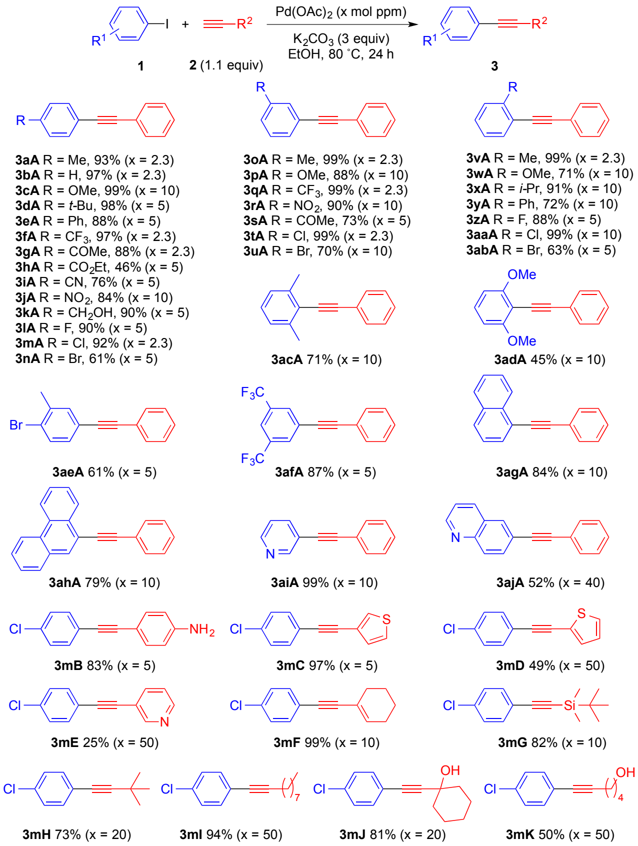
In EtOH with Et_3N (Table 1, entry 16)
Average diameter = ca. 46 nm.

Figure 1. TEM images for the reaction of **1a** and **2A** under the conditions shown in Table 1.

Having optimized the reaction conditions, we next examined the substrate scope of this reaction (Scheme 1). The reaction of ethynylbenzene (**2a**) with iodobenzene substrates **1** with various *para*-substituents, including electron-donating or -withdrawing groups, in the presence of 2.3–10 mol ppm palladium acetate gave the corresponding diphenylalkynes **3aA**–**3nA** in isolated yields of 46–99%. With our catalytic system, *meta*- and *ortho*-substituted iodobenzenes **1o**–**1ab** also participated in the reaction to give the desired diphenylalkynes **3oA**–**3abA** in isolated yields of 70–99%. Fluoro (**1l** and **1z**), chloro (**1m**, **1t**, **1aa**, and **1ae**), and bromo (**1n**, **1u**, and **1ab**) groups remained intact after the reaction.[18] Sterically hindered 2,6-disubstituted iodobenzenes **1ac** and **1ad** reacted with **2A** to afford the corresponding diphenylalkynes **3acA** and **3adA** in yields of 71 and 45%, respectively. Our catalytic system could also be applied to the reactions of 3,5-bis(trifluoromethyl)iodobenzene (**1af**), 2-iodonaphthalene (**1ag**), and 9-iodophenanthrene (**1ah**). Iodinated N-heteroaromatics **1ai** and **1aj** also underwent the reaction in the presence of a mol ppm loading of palladium acetate to give the corresponding internal alkynes **3aiA** and **3ajE** in yields of 99 and 52%, respectively.

The reaction of 1-chloro-4-iodobenzene (**1m**) with a variety of terminal alkynes **2** was next examined. The reaction with (4-ethynylphenyl)amine (**2B**) gave {4-[(4-chlorophenyl)ethynyl]phenyl}amine (**3mB**) in 83% yield. The catalytic system could also be applied in the reactions of several ethynylhetarenes. The reaction of **1m** with 3-ethynylthiophene (**2C**) proceeded efficiently in the presence of 5 mol ppm palladium acetate to afford the desired internal alkyne **3mC** in 97% yield. In the reactions of 2-ethynylthiophene (**2D**) or 3-ethynylpyridine (**2E**), 50 mol ppm of palladium acetate was required to promote the reaction and the yields of the desired products **3mD** and **3mE** were relatively low (49 and 25%, respectively). 1-Ethynylcyclohexene (**3F**) reacted to give 1-chloro-4-(cyclohex-1-en-1-ylethynyl)benzene (**3mF**) in 99% yield. The reaction with a silylated acetylene, *tert*-butyl(ethynyl)dimethylsilane (**2G**), gave the silylated ethynylbenzene **3mG** in 51% yield. Our catalytic system could also be used in the reactions of aliphatic alkynes. The reaction of **1m** with 3,3-dimethylbut-1-yne (**2H**) or dec-1-yne (**2I**) in the presence of 20 or 50 mol ppm of palladium acetate, respectively, gave the corresponding coupling products **3mH** and **3mI** in yields of 73 and 94% yields, respectively. The hydroxylated cyclic and linear aliphatic terminal alkynes **2J** and **2K** similarly gave the desired internal alkynes **3mJ** and **3mK** in yields of 81 and 50%, respectively.

Scheme 1. Substrate Scope in the Reaction of Iodobenzenes 1 with Terminal Alkynes 2[a]

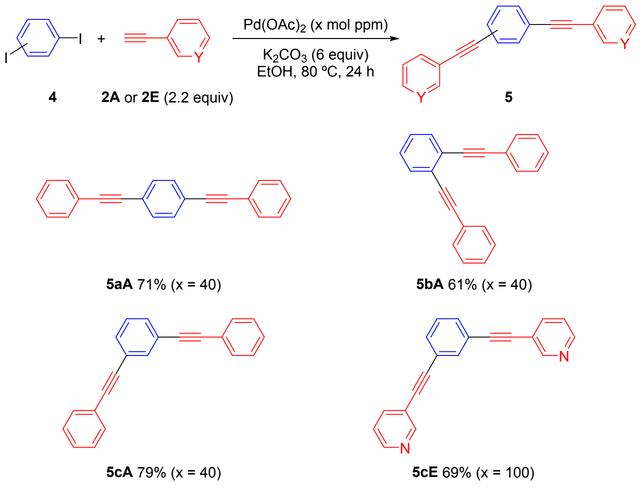


[a] *Reaction conditions*: **1** (0.5 mmol), **2** (1.1 equiv, 0.55 mmol), $Pd(OAc)_2$ (2.3–50 mol ppm), K_2CO_3 (3.0 equiv, 1.5 mmol), anhyd EtOH (2 mL), 80 °C, 24 h, isolated yield.

Next, we applied our catalytic system to the dialkynylation of diiodobenzenes **4** (Scheme 2). The reaction of 1,4-diiodobenzene (**4a**) with ethynylbenzene (**2A**) in the presence of 40 mol ppm palladium acetate and potassium carbonate in anhydrous ethanol gave 1,4-bis(phenylethynyl)benzene (**5aA**) in 71% yield. Similarly, 1,2-diiodobenzene (**4b**) and 1,3-

diiodobenzene (**4c**) also participated in the reaction to afford 1,2-bis(ethynylphenyl)benzene (**5bA**) and 1,3-bis(ethynylphenyl)benzene (**5cA**) in yields of 61 and 79%, respectively. 3,3'-[1,3-Phenylenebis(ethyne-2,1-diyl)]dipyridine (**5cE**), which has been used as a ligand for the formation of metallomacrocyles,[19] was obtained in 69% yield by the reaction of **4c** with 3-ethynylbenzene (**2E**) in the presence of 100 mol ppm palladium acetate.

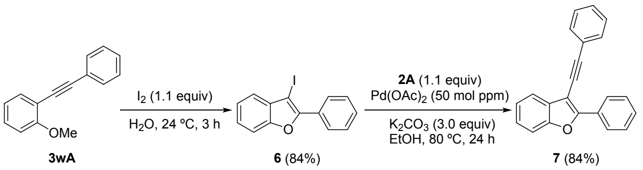
Scheme 2. Dialkynylation of Diiodobenzenes 4 with Ethynylbenzene (2A) Or 3-Ethynylpyridine (2E)[a]



[a] *Reaction conditions*: **4** (0.5 mmol), **2** (2.2 equiv, 1.1 mmol), Pd(OAc)$_2$ (40–100 mol ppm), K$_2$CO$_3$ (6.0 equiv, 3.0 mmol), anhyd EtOH (2 mL), 80 °C, 24 h. Isolated yields are reported.

Derivatization of an internal alkyne product was also tested (Scheme 3). Cyclization of 1-methoxy-2-(phenylethynyl)benzene (**3wA**) with iodine in water afforded 3-iodo-2-phenylbenzofuran (**6**) in 84% yield.[20] The iodo compound **6** reacted further with **2A** under the coupling conditions in the presence of a 40 mol ppm of palladium acetate to give 2-phenyl-3-(phenylethynyl)benzofuran (**7**), also in 84% yield. [21]

Scheme 3. Synthesis of a Disubstituted Benzofuran 7[a]



[a] *Reaction conditions*: **4** (0.5 mmol), **2** (2.2 equiv, 1.1 mmol), Pd(OAc)$_2$ (40–100 mol ppm), K$_2$CO$_3$ (6.0 equiv, 3.0 mmol), anhyd EtOH (2 mL), 80 °C, 24 h. Isolated yields are reported.

To understand the nature of the catalytically active species in our reaction, we performed the reaction-rate analysis as well as TEM analysis in a snapshot manner for the reaction of 4-iodotoluene (**1a**) with ethynylbenzene (**2A**) (Figures 2 and 3, and also see Figure S1 in the Supporting Information)). When palladium acetate was added into an ethanol solution of **1a** and **2A** under the standard reaction conditions, the reaction did not proceed during the initial 2 hours, showing that there is an induction period in this reaction and that palladium acetate is a precursor of the actual catalytic species. We also examined the reaction mixture by transmission electron microscopy (TEM) (Figure 3), where a variation in size of palladium nanoparticles was observed. After heating of the standard mixture of palladium acetate, **1a**, **2A**, and potassium carbonate in ethanol at 80 °C for 2 h (0% conversion), TEM showed the generation of nanoparticles of palldium of average diameter 2.0 ± 0.7 nm (Figure 3a). In contrast,when the reaction time was prolonged to 4 hours (42% conversion), larger nanoparticles (average diameter 4.4 ± 1.0 nm) were generated (Figure 3b). The particle size gradually decreased with increasing conversion. When the reaction time was 8 hours, the conversion was 91% and the size of the palladium nanoparticles was 3.2 ± 0.8 nm (Figure 3c). After completion of the reaction, the palladium nanoparticles were of a similar size (2.2 ± 0.5 nm; Figure 3d) to those generated during the induction period (2.0 ± 0.7 nm; Figure 3a). These results suggest that palladium species (monomeric palladium and/or fine palladium clusters) are liberated from the palladium nanoparticles during the reaction proceeded (Scheme 4).

We also performed a poisoning experiment (Scheme 5).[22] Four hours after the start of the reaction (24% conversion), mercury was added to the mixture, completely stopping the reaction. The above experimental results show that a monomeric palladium(0) species and/or fine palladium(0) clusters generated from palladium acetate might be an actual catalytically active species in this reaction.[23]

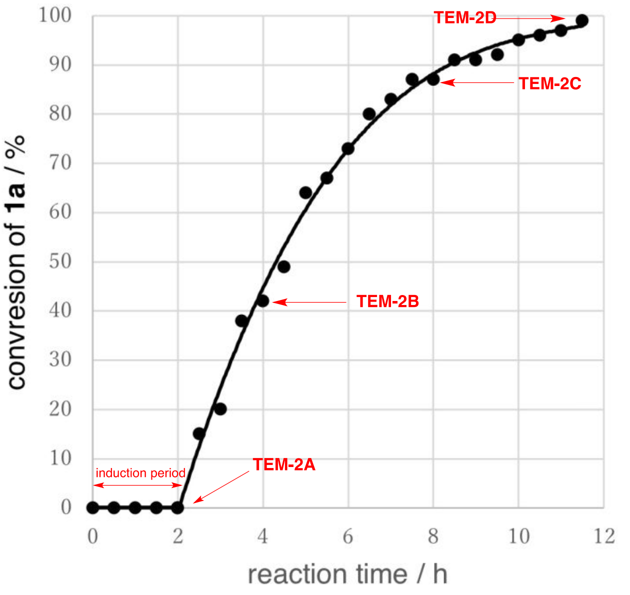
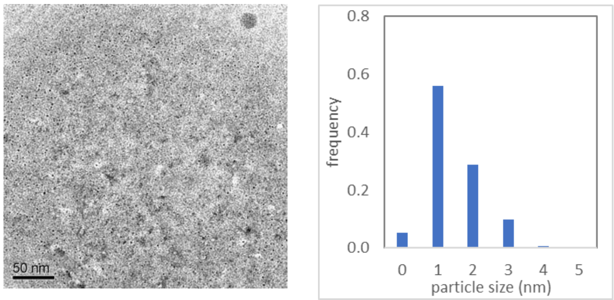
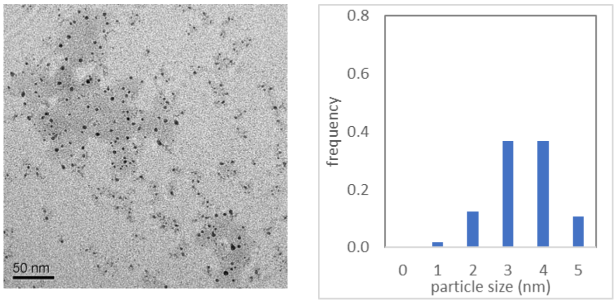


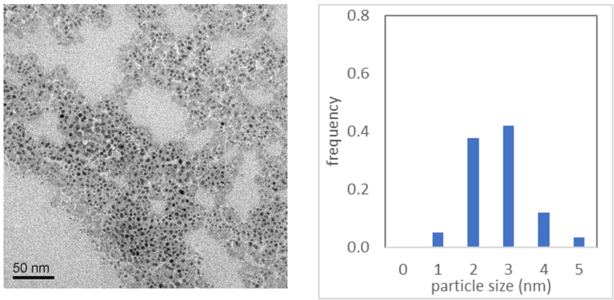
Figure 2. Analysis of the rate of reaction of 4-iodotoluene (**1a**) with ethynylbenzene (**2A**) in the presence of palladium acetate. *Reaction conditions*: **1a** (0.5 mmol), **2A** (0.75 mmol), Pd(OAc)$_2$ (2.5 × 10^{-6} mmol), K$_2$CO$_3$ (1.5 mmol), anhyd EtOH (2 mL), 80 °C.



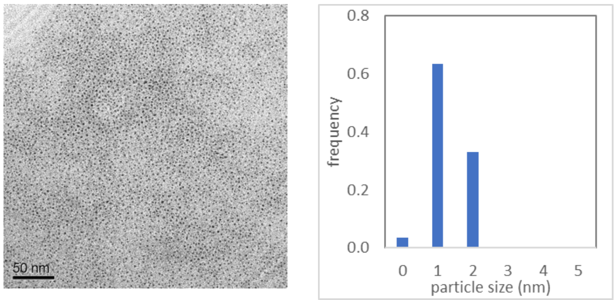
(a) **TEM-2A**: After 2 h, $\phi = 2.0 \pm 0.7$ nm



(b) **TEM-2B**: After 4 h, $\phi = 4.4 \pm 1.0$ nm



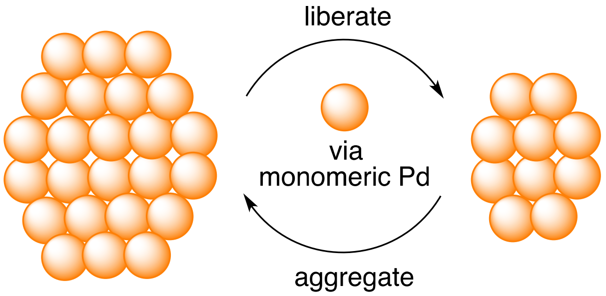
(c) **TEM-2C**: After 8 h, $\phi = 3.2 \pm 0.8$ nm



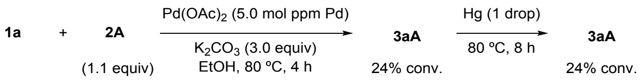
(d) **TEM-2D**: After 10 h, $\phi = 2.2 \pm 0.5$ nm

Figure 3. TEM images and size distribution histograms in the reaction shown in Figure 2.

Scheme 4. Schematic Proposal for Variation in Size of Pd Nanoparticles during the Reaction.



Scheme 5. Mercury-Amalgamation Test



CONCLUSION

In summary, we found that palladium acetate is a good catalyst precursor for the arylation of terminal alkynes by aryl iodides. The reaction of aryl iodides with terminal alkynes was carried out in the presence of 2.3–100 mol ppm of palladium acetate and potassium carbonate in ethanol at 80 °C to give the corresponding internal alkynes in good to excellent yields. Reaction-rate analysis, TEM analysis, and a mercury-amalgamation experiment suggested that monomeric palladium(0) and/or fine palladium(0) clusters might be the actual catalytically active species in this reaction.

ASSOCIATED CONTENT

Supporting Information

General experimental methods, TEM images, and NMR and Mass data of products (PDF). This material is available free of charge on the ACS Publication website at DOI: XXXXXXXXXXXXX.

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NOTE

The authors declare no competing financial interest.

Author Contributions

The manuscript was written through contributions of all authors.

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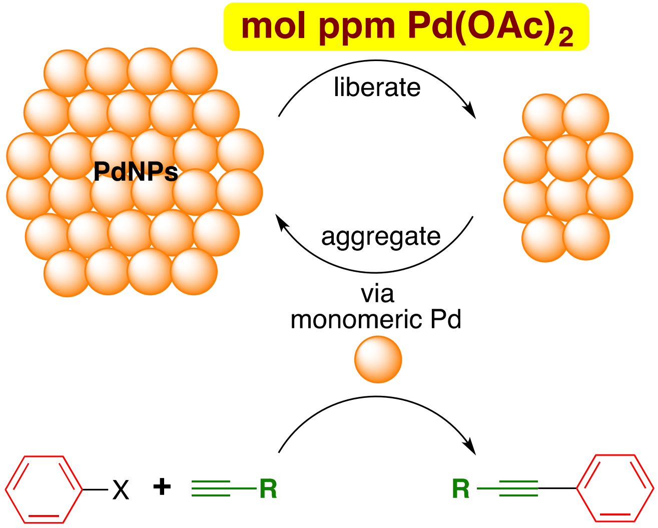
TOC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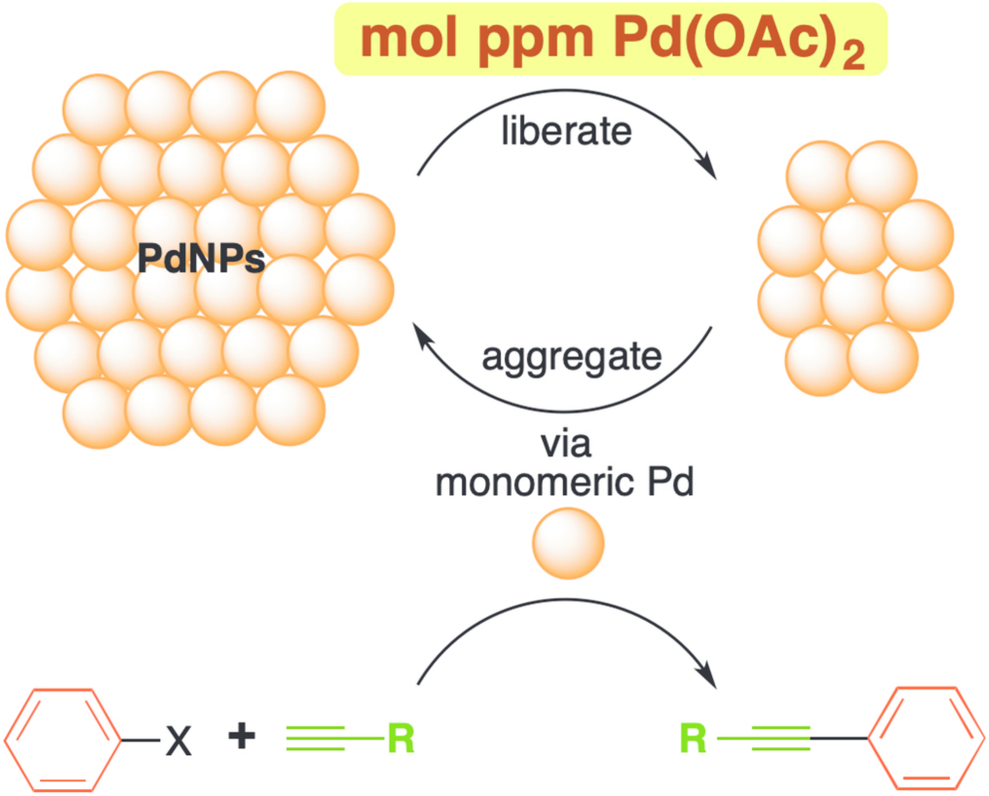
liberate
aggregate
PdNPs
via
monomeric Pd
X
+
R
R



TOC

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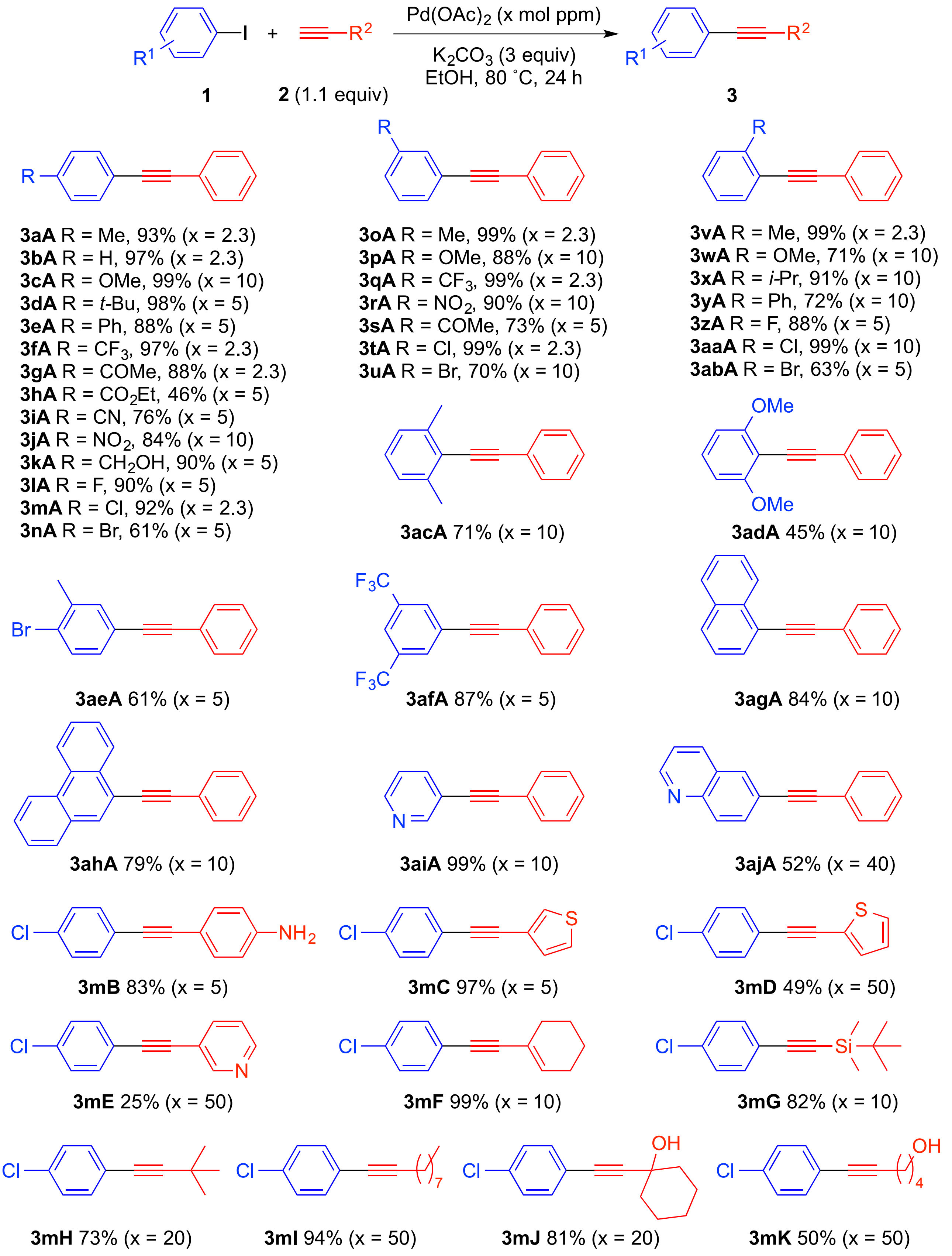
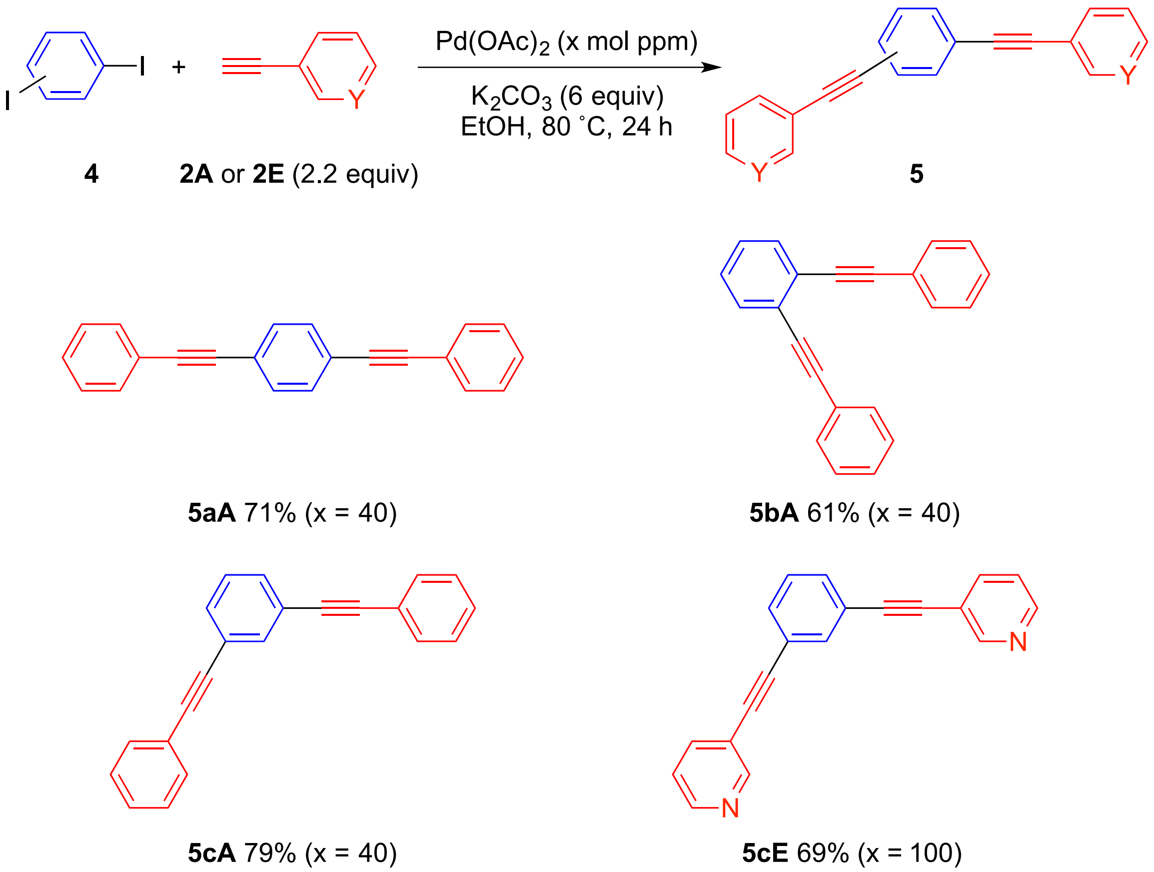
Scheme 1


R^1
I
+
R^2
$Pd(OAc)_2$ (x mol ppm)
K_2CO_3 (3 equiv)
EtOH, 80 ˚C, 24 h
1
2 (1.1 equiv)
3
R
3aA R = Me, 93% (x = 2.3)
3bA R = H, 97% (x = 2.3)
3cA R = OMe, 99% (x = 10)
3dA R = *t*-Bu, 98% (x = 5)
3eA R = Ph, 88% (x = 5)
3fA R = CF_3, 97% (x = 2.3)
3gA R = COMe, 88% (x = 2.3)
3hA R = CO_2Et, 46% (x = 5)
3iA R = CN, 76% (x = 5)
3jA R = NO_2, 84% (x = 10)
3kA R = CH_2OH, 90% (x = 5)
3lA R = F, 90% (x = 5)
3mA R = Cl, 92% (x = 2.3)
3nA R = Br, 61% (x = 5)
3oA R = Me, 99% (x = 2.3)
3pA R = OMe, 88% (x = 10)
3qA R = CF_3, 99% (x = 2.3)
3rA R = NO_2, 90% (x = 10)
3sA R = COMe, 73% (x = 5)
3tA R = Cl, 99% (x = 2.3)
3uA R = Br, 70% (x = 10)
3vA R = Me, 99% (x = 2.3)
3wA R = OMe, 71% (x = 10)
3xA R = *i*-Pr, 91% (x = 10)
3yA R = Ph, 72% (x = 10)
3zA R = F, 88% (x = 5)
3aaA R = Cl, 99% (x = 10)
3abA R = Br, 63% (x = 5)
3acA 71% (x = 10)
OMe
OMe
3adA 45% (x = 10)
Br
3aeA 61% (x = 5)
F_3C
F_3C
3afA 87% (x = 5)
3agA 84% (x = 10)
3ahA 79% (x = 10)
N
3aiA 99% (x = 10)
N
3ajA 52% (x = 40)
Cl
NH_2
3mB 83% (x = 5)
Cl
S
3mC 97% (x = 5)
Cl
S
3mD 49% (x = 50)
Cl
N
3mE 25% (x = 50)
Cl
3mF 99% (x = 10)
Cl
Si
3mG 82% (x = 10)
Cl
3mH 73% (x = 20)
Cl
7
3mI 94% (x = 50)
Cl
OH
3mJ 81% (x = 20)
Cl
OH
4
3mK 50% (x = 50)

Scheme 2



4 **2A** or **2E** (2.2 equiv) **5**

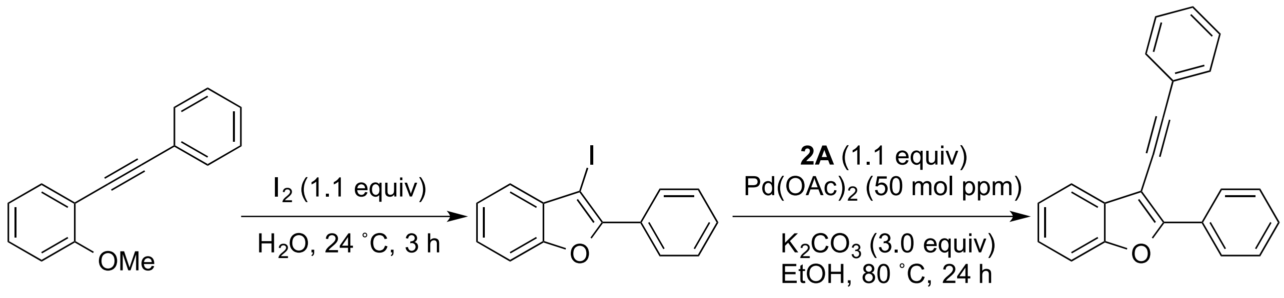
5aA 71% (x = 40)

5bA 61% (x = 40)

5cA 79% (x = 40)

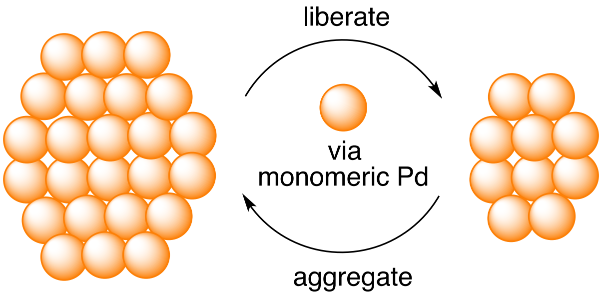
5cE 69% (x = 100)

Scheme 3



3wA **6** (84%) **7** (84%)

Scheme 4

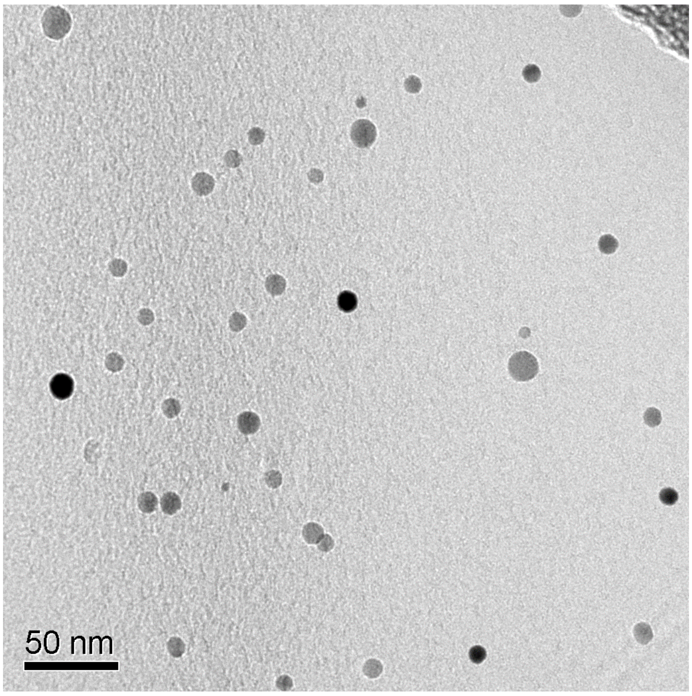


Scheme 5

$$\mathbf{1a} + \underset{(1.1\ \text{equiv})}{\mathbf{2A}} \xrightarrow[\substack{\text{K}_2\text{CO}_3\ (3.0\ \text{equiv})\\ \text{EtOH, 80 °C, 4 h}}]{\text{Pd(OAc)}_2\ (5.0\ \text{mol ppm Pd})} \underset{24\%\ \text{conv.}}{\mathbf{3aA}} \xrightarrow[\text{80 °C, 8 h}]{\text{Hg (1 drop)}} \underset{24\%\ \text{conv.}}{\mathbf{3aA}}$$

Figure 1 (a) (b)

(a)



(b)

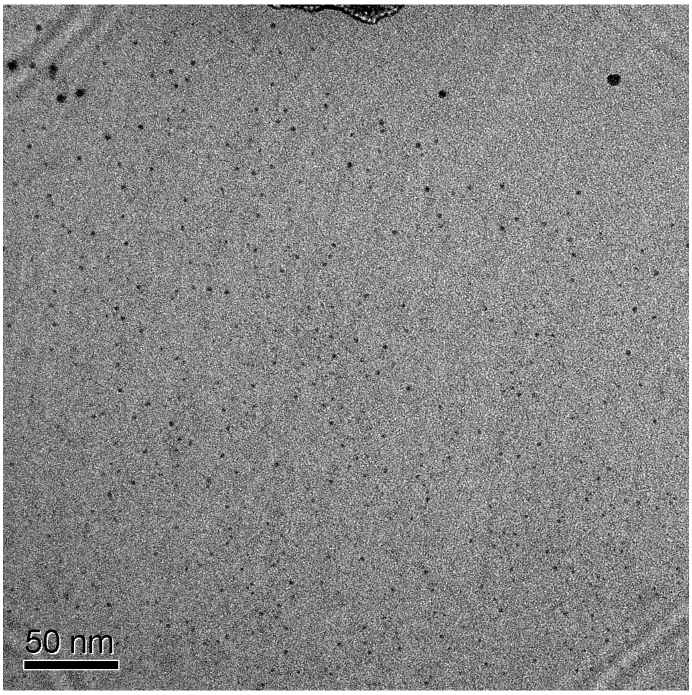
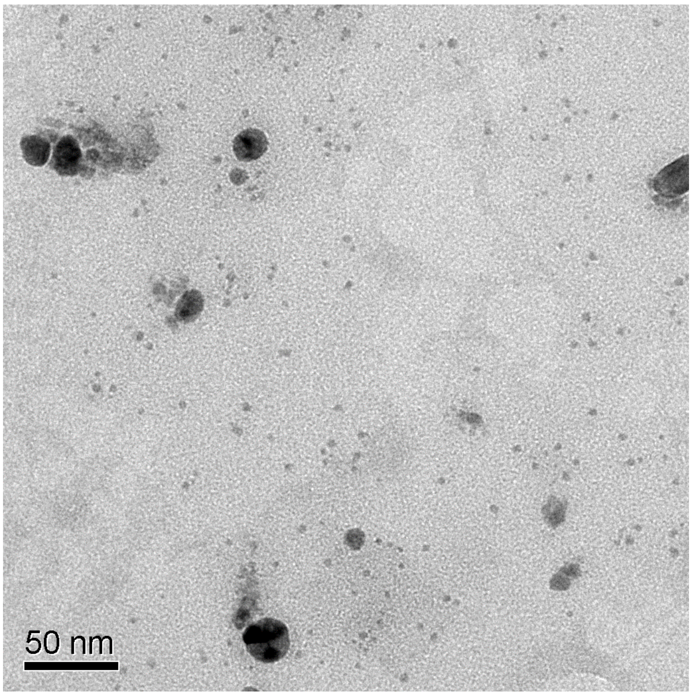


Figure 1 (c) (d)

(c)



(d)

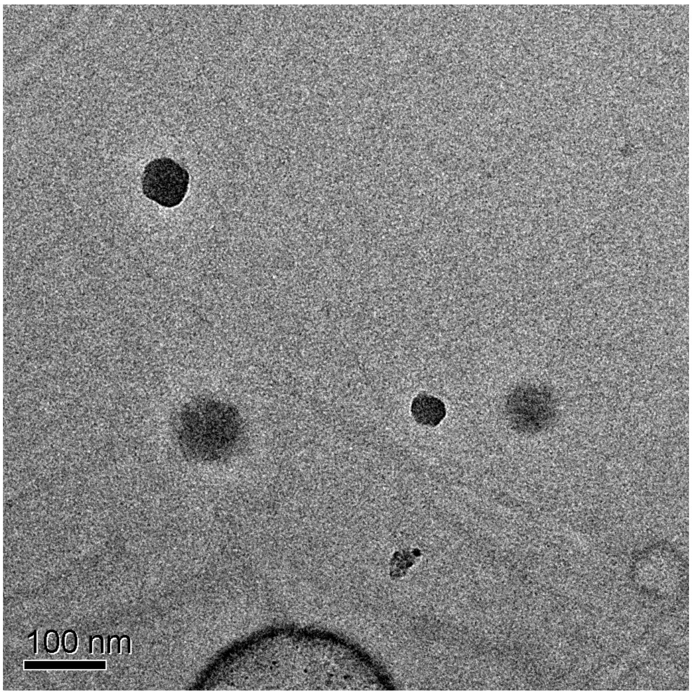


Figure 2

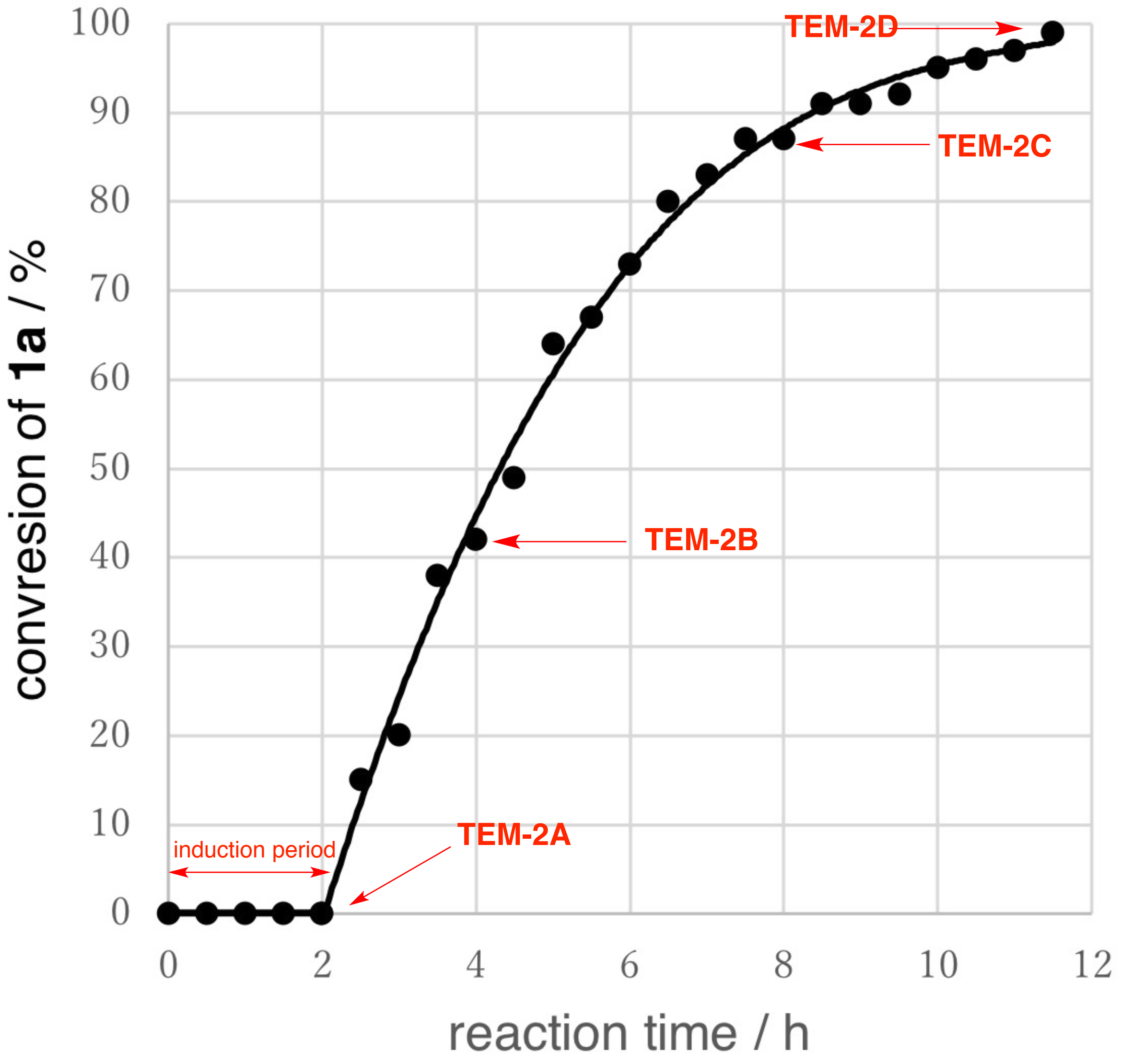
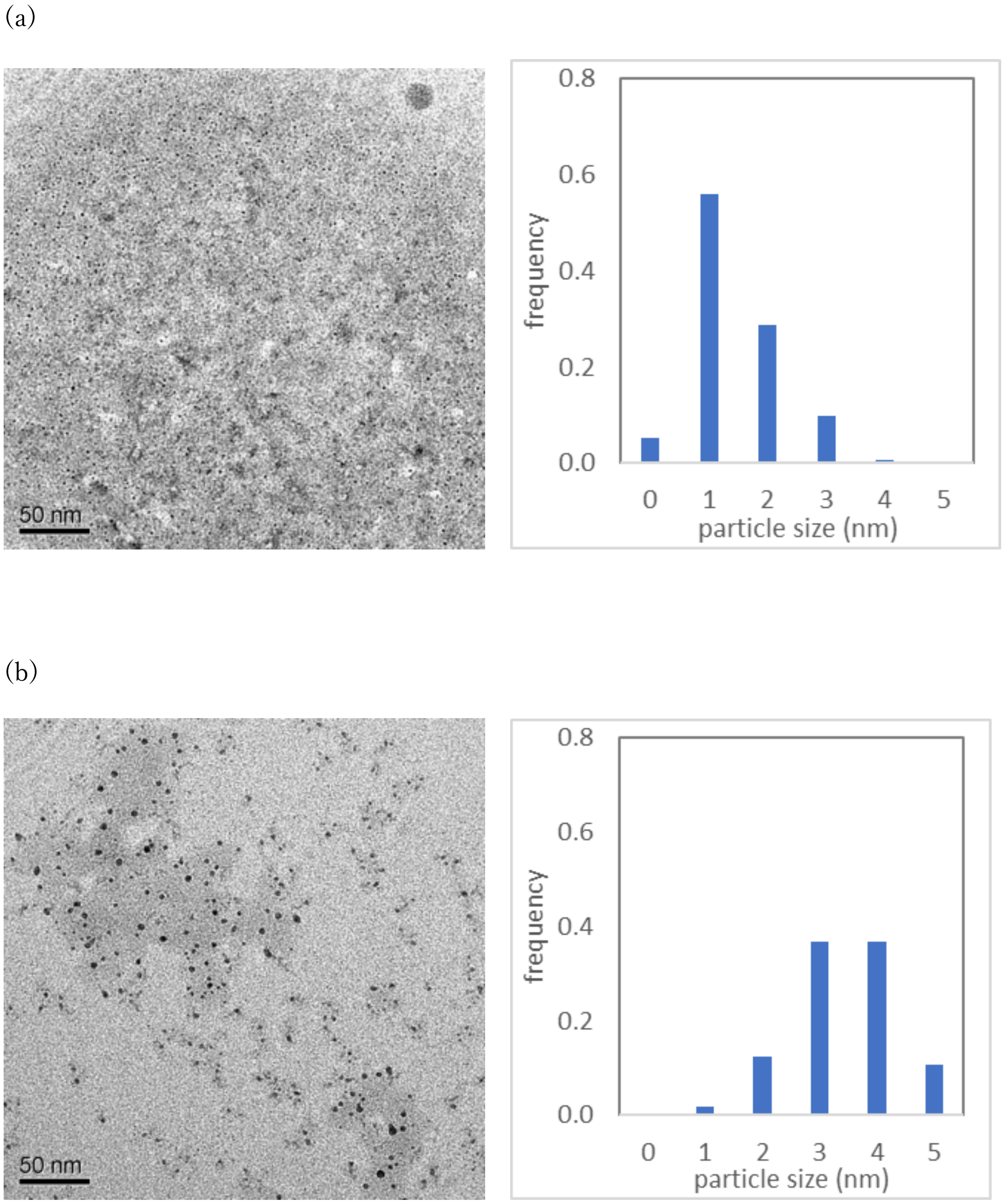

TEM-2D
TEM-2C
TEM-2B
TEM-2A
induction period
convresion of **1a** / %
reaction time / h
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12

Figure 3 (a) (b)


(a)
50 nm
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0.4
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1
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4
5
particle size (nm)
(b)
50 nm
frequency
0.8
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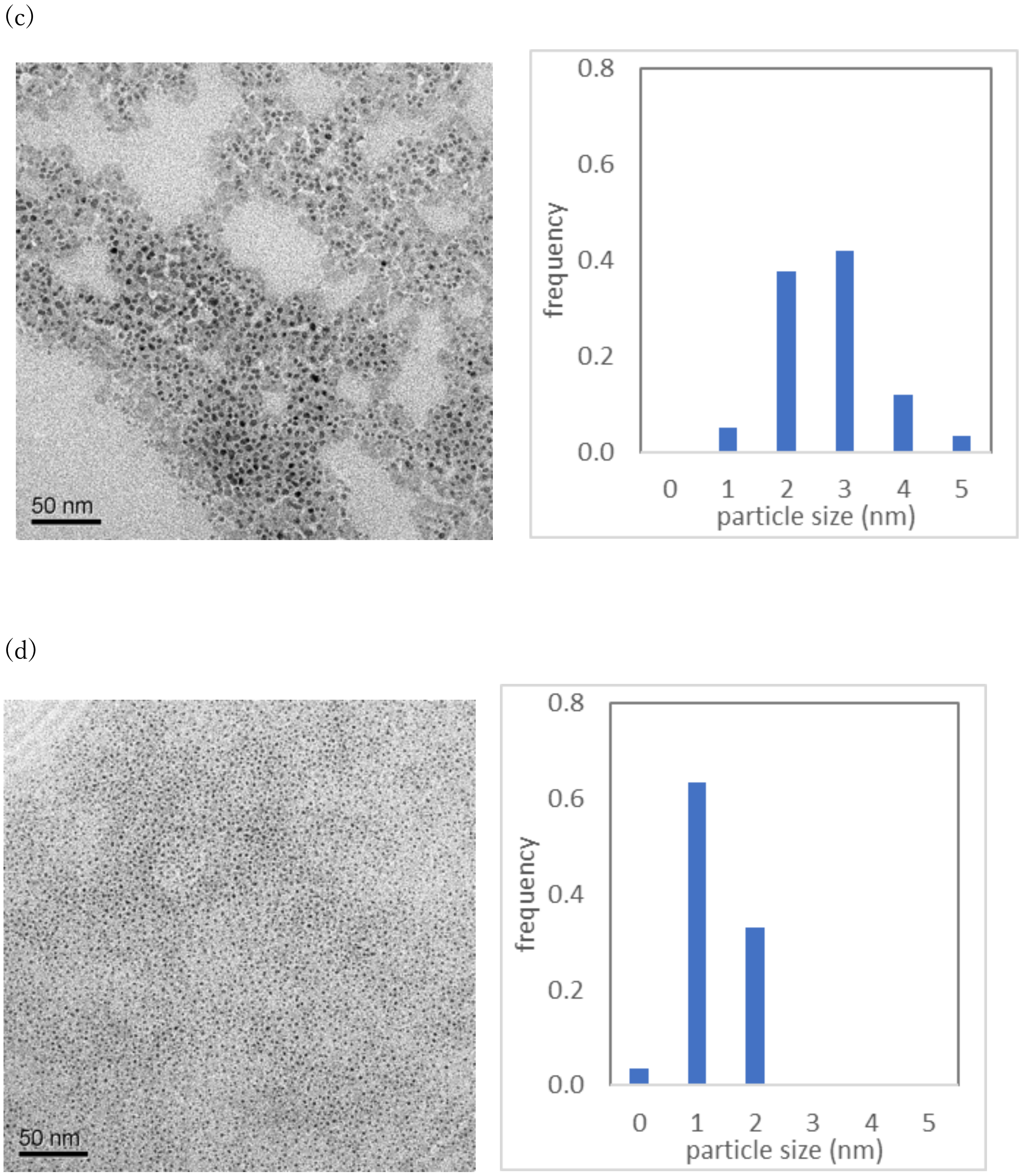
0
1
2
3
4
5
particle size (nm)

Figure 3 (c) (d)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(d)
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0.0
frequency
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particle size (nm)