Heterogeneous copper-free Sonogashira coupling reaction of terminal alkynes with aryl halides over a quinoline-2-carboimine palladium complex immobilized on MCM-41

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A R T I C L E   I N F O

A B S T R A C T

Heterogeneous Sonogashira coupling of terminal alkynes with aryl halides was studied over a quinoline-2-carboimine palladium complex immobilized on MCM-41 (Pd-2QC-MCM) catalyst. The cross-coupling reaction occurred within 3 h at 80 °C by adding a piperidine in *N*-methyl-2-pyrolidone (NMP) solvent. By varying the combination of alkynes and aryl halides, Pd-2QC-MCM showed effective catalytic activities to produce corresponding tolane derivatives with moderate to excellent yields. Pd-2QC-MCM can be reused without significant loss of its catalytic activity until the fourth recycle under aerobic conditions because of negligible leaching of palladium metal and a high turnover number (∼2850) in the reaction of phenyl acetylene with iodobenzene. The excellent catalytic performance of Pd-2QC-MCM indicates that the reactions effectively occurred by a palladium complex immobilized on mesoporous silica.

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1. Introduction

Sonogashira coupling reaction of terminal alkynes with aryl halides catalyzed over a Pd(0)/Cu(I) system is a powerful tool in organic synthesis because the reaction directly provides unique organic compounds having the $C(sp^2)$–$C(sp)$ bond [1–6]. A number of studies have been reported on homogeneously catalyzed reactions [7]. In Sonogashira coupling reaction, copper salts usually play an important role in assisting the oxidative addition of acetylene to palladium metal; this method has drawbacks, though, including waste production and the necessity of separation after the reaction. Recently, some successful examples of copper-free homogeneous Sonogashira coupling reactions have been reported for the reduction of the drawbacks for the use of copper salts [8–14]. The use of amines such as piperidine or pyrrolidine [8,9], and amides such as *N,N*-dimethylformamide or *N,N*-dimethylacetoamide [10], and quaternary ammonium salts [11,12] have been proposed as copper-free methodologies in Pd(0) and Pd(II) complexes. Other examples are a dendritic Pd(II) complex bearing bidentate phosphorous ligand and [Pd{*t*-Bu₂PCH₂N(CH₂Ph)CH₂P*t*-Bu₂}(OAc)₂] complex in triethylamine [13,14]. Genêt et al. have proposed that

the reactions using water-soluble Pd complexes in homogeneous organic–aqueous solvent systems are also effective copper-free procedures [15,16].

The use of heterogeneous catalysts for Sonogashira coupling reaction has paid much attention to reducing waste, thus working toward an environmentally benign chemical process. Particularly, there have been many efforts on the development of copper-free methodologies [17–23]. Macquarrie and coworkers have reported the effectiveness of N,P-chelated Pd(II) complexes immobilized on silica gel under solvent-free conditions [17]. Choudary et al. have proposed layered double hydroxide supported nanopalladium works as the Heck-type reactions including Sonogashira coupling [18]. The palladium-supported Y zeolite ([Pd(NH₃)₄]²⁺/(NH₄)Y) catalyst was developed by Djakovitch et al. [19–21]. Köhler and coworkers found the use of *N*-methyl-2-pyrolidone as a solvent with an additive such as piperidine proved to be effective for a heterogeneous copper-free procedure over Pd/C catalyst [22].

Our strategy for developing a versatile heterogeneous catalyst is based on the concept of immobilizing an organometallic complex onto mesoporous silica. This is because the usage of mesoporous silica often offers enhanced catalytic activity due to its high surface area, and a palladium complex immobilized of robustly coordinated ligands stable under aerobic conditions through the silanol groups can be expected to have negligible leaching of precious metal species and high catalytic activity rather than bulk metal.

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Actually, we recently reported a Heck-type vinylation and Suzuki coupling over Pd, Rh, and Pt complexes bearing a quinoline-2-carboimine ligand immobilized on mesoporous silica (FSM-16) and found that these immobilized complexes exhibited high catalytic performance even at a low concentration of metal species, and they can be easily recovered and reused without loss of catalytic activity without any special air-manipulation [24,25]. We consider that these high activities are due to the performance of the transition metals as an 'organometallic complex' on the large surface area of mesoporous silica. Thus, these results encouraged us to develop a further application toward sophisticated chemical transformations, especially carbon–carbon bond forming reactions. Djakovitch and coworkers [21] and Cai et al. [23] have also focused on the use of mesoporous silicas as a reliable support matrix in Sonogashira coupling reaction.

Here, we report the heterogeneous copper-free Sonogashira coupling reaction of terminal alkynes with aryl halides over a quinoline-2-carboimine palladium complex immobilized on MCM-41 (Pd-2QC-MCM) catalyst without special air-manipulation, and discuss scope and limitations of the catalyst.

2. Experimental

2.1. Materials

Mesoporous MCM-41 was synthesized in our laboratory according to a procedure reported in literature [26]. 3-Aminopropyltrimethoxysilane, 4-ethynyltoluene, 4-ethynylanisole, and 4-ethynyl-1-bromobenzene were purchased from Aldrich Japan, Tokyo, Japan. Pd(OAc)$_2$, RuCl$_3$·xH$_2$O, H$_2$PtCl$_6$·6H$_2$O, RhCl$_3$·3H$_2$O, N-methyl-2-pyrolidone (NMP), and N,N-dimethylformamide (DMF) were purchased from Wako Pure Chem. Ind. Ltd., Tokyo, Japan. Piperidine and triethylamine (TEA) were purchased from Nacalai Tesque, Kyoto, Japan. Quinoline-2-carboxaldehyde (2QC), phenylacetylene and 1-hexyne were purchased from Tokyo Kasei Kogyo Ltd., Tokyo, Japan. All chemicals were used as received without further purification.

2.2. Preparation of the catalyst

Immobilization of metal complexes on MCM-41 consists of the following scheme as illustrated in Scheme 1 [24,25]:
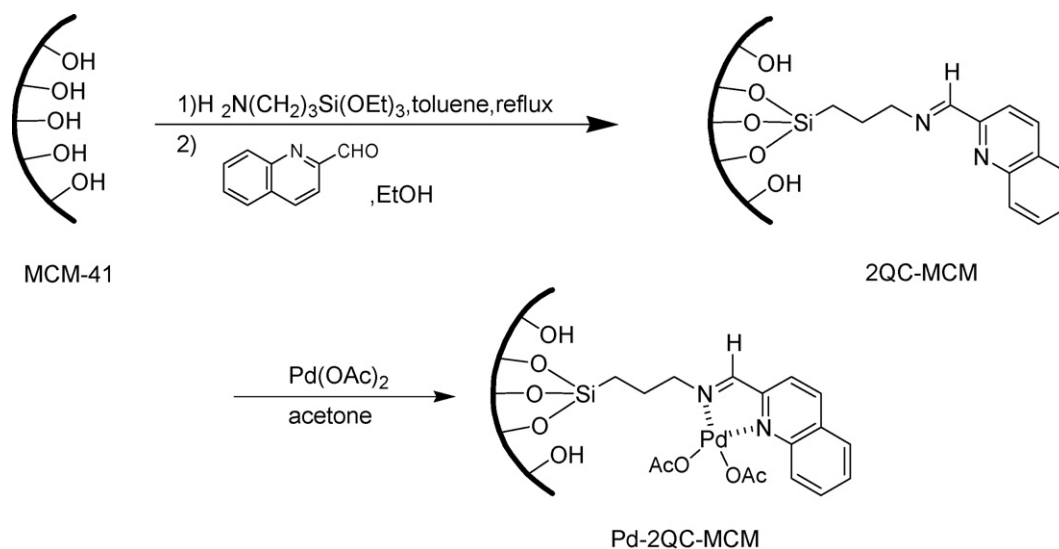
(a) Surface modification of MCM-41 with 3-aminopropyl-trimethoxysilane: In a 100 ml round-bottom flask containing a magnetic stirring bar, calcined MCM-41 (1.0 g) was dispersed in toluene (30 ml) and refluxed for 30 min. After cooling to ambient temperature, 3-aminopropyltrimehoxysilane (0.26 g, 1.4 mmol) was added to the mixture. Then, the resulting mixture was refluxed with removing periodically the methanol formed during modification. After 3 h, the reaction mixture was cooled to room temperature, and the white solid was separated by filtration and washed well with toluene. Aminopropyl-moiety immobilized MCM-41 (AP-MCM) was obtained by drying under reduced pressure.

(b) Preparation of quinoline-2-carboimine ligand on MCM-41 (2QC-MCM): In a 50 ml round-bottom flask containing a magnetic stirring bar, 2QC (0.23 g, 1.5 mmol) was resolved in distilled EtOH (20 ml). Then, AP-MCM (1.0 g) was added to the solution, and the resulting mixture was stirred for 24 h at room temperature. The resulting pale yellow powder was filtrated, washed thoroughly with EtOH and dried *in vacuo* to produce 2QC-MCM. The amount of the 2QC ligand of 2QC-MCM based on the weight loss by TG analysis is estimated as 0.359 mmol/g.

(c) Preparation of a quinoline-2-carboimine palladium complex immobilized on MCM-41 (Pd-2QC-MCM): In a 50 ml round-bottom flask, palladium acetate (24 mg, 0.11 mmol) was resolved in distilled acetone (20 ml). Then, 2QC-MCM was dispersed in this solution and stirred for 24 h at ambient temperature. The resulting brown powder was filtrated and washed well with acetone to give Pd-2QC-MCM. The palladium content of Pd-2QC-MCM based on ICP analysis is estimated to be 0.0905 mmol/g.

2.3. Characterization of the catalyst

Powder XRD patterns were recorded on a XRD-6000 diffractometer with Cu Kα radiation (λ = 0.15418 nm) (Shimadzu Corp., Kyoto, Japan). Nitrogen adsorption isotherms were obtained at 77 K using a Belsorp 28SA apparatus (Bel Japan Inc., Osaka, Japan). TG/DTA measurements were performed on a Shimadzu DTG-50 apparatus with temperature programmed rate of 10 °C/min in the air stream. FT-IR spectra were recorded on a Nexus 470 FT-IR spectrometer (Thermo Electron, MA, U.S.A.) by the KBr technique. Elemental analysis by ICP was performed using a JICP-PS-1000 UV

Scheme 1.

spectrophotometer (Teledyne Leeman Labs Inc., NH, U.S.A.). ^{1}H and ^{13}C NMR spectra were measured by a ECA-500 FT-NMR spectrometer (JEOL Ltd., Tokyo, Japan).

2.4. Sonogashira coupling reaction

The typical reaction was carried out with terminal alkyne (1.0 mmol), aryl iodide (1.3 mmol), amine (2.0 mmol), and Pd-2QC-MCM (0.02 g, 1.8 μmol based on Pd) in NMP (3.0 ml). The mixture was stirred for 3 h at 80 °C under a nitrogen atmosphere. After cooling the reaction mixture, the catalyst was separated from the liquid product by filtration. An aliquot of filtrate was analyzed by a Shimadzu Gas Chromatograph 14A equipped with capillary column (Ultra-1: 25 m × 0.2 mm and 0.33 μm thick layer) to determine the yield of the product. Catalytic activity was estimated by the conversion of terminal alkyne using biphenyl as an internal standard. Purification of product was performed by column chromatography using EtOAc/hexane (8/2) as an eluent. The structure of the product was assigned by ^{1}H and ^{13}C NMR spectra.

2.5. Reuse of the catalyst

The reaction was carried out with terminal alkyne (6.0 mmol), aryl halide (6.3 mmol), piperidine (12 mmol), and Pd-2QC-MCM (0.01 g, 0.9 μmol based on Pd) in NMP (9 ml). The mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. After cooling the reaction mixture, the catalyst was separated from the liquid product by filtration. An aliquot of filtrate was analyzed by gas chromatography to determine the yield of the product. The recovered catalyst was washed with acetone without any special air-manipulation in inert atmosphere, dried at room temperature overnight under aerobic conditions, and then reused for the next reaction under the same conditions mentioned above.

3. Results and discussion

3.1. Characterization of Pd-2QC-MCM

Fig. 1 shows powder XRD patterns of MCM-41 (A) and Pd-2QC-MCM (B). The peaks corresponding to MCM-41 were observed in the low-angle region indexed on a hexagonal unit cell (A); however, the slight decrease in peak intensities associated with (1 0 0), (1 1 0)
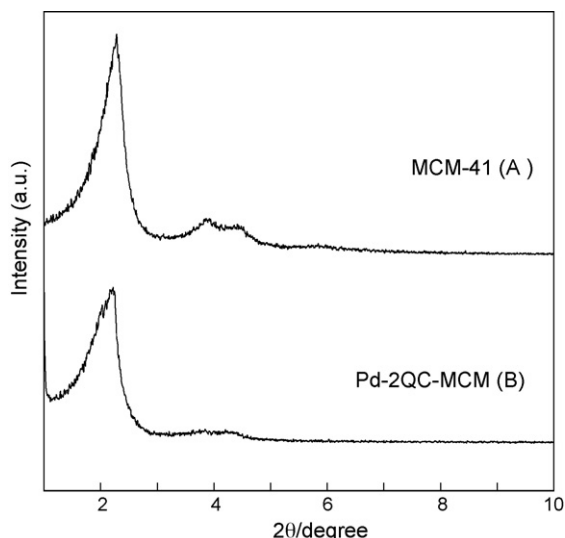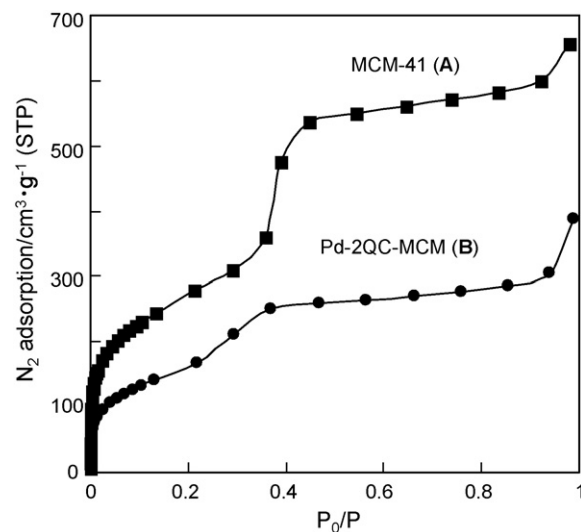

Fig. 2. N_2 adsorption isotherms of MCM-41 (A) and Pd-2QC-MCM (B).

and (2 0 0) reflections was observed after immobilization of the Pd complex onto MCM-41 (B).

Fig. 2 shows the nitrogen adsorption isotherms of MCM-41 (A) and Pd-2QC-MCM (B). They showed typical type-IV isotherms although the surface area decreased by the immobilization of the palladium complex from 950 to 642 m^2/g.

The XRD and N_2 adsorption of Pd-2QC-MCM obviously indicate that the meso-array structure was not destroyed during modification. The decreases in peak intensity of XRD and surface area of Pd-2QC-MCM are due to the immobilization of the palladium complex on MCM-41. The amount of the 2-QC ligand of 2QC-MCM is estimated as 0.359 mmol/g based on the weight loss from 150 to 500 °C in TG/DTA analysis. The palladium content of Pd-2QC-MCM based on ICP analysis is estimated as 0.0905 mmol/g.

Fig. 3 shows the FT-IR spectra of 2QC-MCM (A) and Pd-2QC-MCM (B) in the range of 1250–2000 cm^{-1}. The characteristic band assignable to the C=N double bond of 2QC moiety immobilized on MCM-41 was observed at 1645 cm^{-1} (A in Fig. 3). After immobilization of Pd on 2QC-MCM, this band was shifted to 1634 cm^{-1} (Fig. 3B), suggesting bond formation between Pd and ligand (C=N).
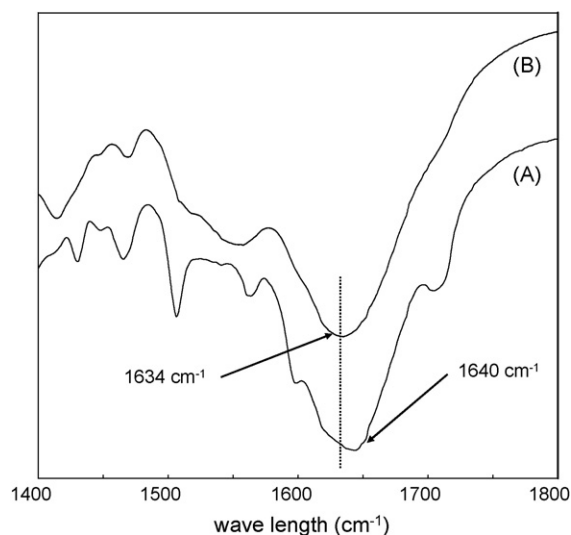

Fig. 1. Powder XRD patterns of MCM-41 (A) and Pd-2QC-MCM (B).

Fig. 3. IR spectra of 2QC-MCM (A) and Pd-2QC-MCM (B).

Table 1
The influence of metal species in the Sonogashira coupling reaction of phenyl acetylene with iodobenzene

Entry	Catalyst	Conversion (%)[a]
1	Pd-2QC-MCM[b]	69.4
2	Pd-2QC-MCM[c]	64.2
3	Ru-2QC-MCM[d]	0
4	Pt-2QC-MCM[e]	0
5	Rh-2QC-MCM[f]	0

Reaction conditions: Iodobenzene (1.0 mmol), phenyl acetylene (1.3 mmol), biphenyl (0.2 mmol, as an internal standard), triethylamine (2.0 mmol), catalyst (0.02 g) and DMF (3 ml) at 80 °C for 7 h.

[a] Based on consumed phenyl acetylene.
[b] Pd(OAc)$_2$ as a precursor.
[c] PdCl$_2$ as a precursor.
[d] RuCl$_3$·xH$_2$O as a precursor.
[e] H$_2$PtCl$_6$·6H$_2$O as a precursor.
[f] RhCl$_3$·3H$_2$O as a precursor.

A similar band shift in the IR spectrum has been also observed in our previous studies [24,25]. These results indicate that the palladium species are effectively immobilized on mesoporous silica as a 2QC-palladium complex.

3.2. Sonogashira coupling reaction over Pd-2QC-MCM

Table 1 shows the influences of metal species on Sonogashira coupling reaction of phenyl acetylene (**1a**) with iodobenzene (**2a**) over some transition metal complexes immobilized on 2QC-MCM-41. All reactions were performed at 80 °C for 7 h using TEA as an additive in DMF solvent without copper salt. Pd-2QC-MCM prepared from PdCl$_2$ and Pd(OAc)$_2$ showed good catalytic activity in the absence of copper compounds, yielding tolane efficiently without formation of by-products such as dialkyne (entries 1 and 2). However, Ru-, Pt- and Rh-2QC-MCM are not effective for the Sonogashira coupling reaction (entries 3–5), although they had good catalytic activity for Heck vinylation [25]. From these results, we chose the Pd(OAc)$_2$ as a metal precursor for further research.

The influence of solvents on the Sonogashira coupling reaction of **1a** with **2a** was examined over Pd-2QC-MCM catalyst as shown in Table 2. High catalytic activity was observed in NMP and DMF among polar solvents (entries 1 and 2). NMP has often been used as a solvent in Pd-catalyzed organic synthesis [27–32]. We also reported the effectiveness of NMP solvent in Heck vinylation over Pd-2QC supported on FSM-16 due to the stabilization of active palladium species [24,29]. However, the reaction in NMP produced trace amounts of homo-coupled dialkyne (entry 2). Dimethylsulfoxide (DMSO) and 1,4-dioxane were less effective with yields of 47.3% and 39.1%, respectively (entries 3 and 4). Reaction in toluene also showed good conversion with a yield of 53.9% although

Table 2
The influence of the solvent in the Sonogashira coupling reaction of phenyl acetylene with iodobenzene over Pd-2QC-MCM-41

Entry	Solvent	Conversion (%)[a]	Yield (%)[a,b]
1	DMF	63.5	63.5
2	NMP	67.4	67.2 (0.1)
3	DMSO	41.5	41.1
4	1,4-Dioxane	37.4	37.1
5	Toluene	56.5	56.3 (0.1)
6	NMP/H$_2$O	80.9	80.9

Reaction conditions: Iodobenzene (1.3 mmol), phenyl acetylene (1.0 mmol), triethylamine (2.0 mmol), catalyst (Pd-2QC-MCM, 0.02 g), and solvent (3 ml) at 80 °C for 7 h.

[a] Based on consumed phenyl acetylene.
[b] Values in parenthesis is a yield of homo-coupled dialkyne.

Table 3
The influence of the base in the Sonogashira coupling reaction of phenyl acetylene with iodobenzene over Pd-2QC-MCM-41

Entry	Base	Conversion (%)[a]	Yield (%)[a,b]
1	None	0	–
2	Piperidine	100	99.2 (0.4)
3	Piperidine[c]	67.8	67.4 (0.2)
4	TEA	67.4	66.8 (0.3)
5	Pyridine	0	–
6	Indoline	0	–
7	Na$_2$CO$_3$	55.3	55.2
8	NaOAc	52.6	52.1
9	K$_2$CO$_3$	4.1	3.9

Reaction conditions: Iodobenzene (1.3 mmol), phenyl acetylene (1.0 mmol), base (2.0 mmol), biphenyl (0.2 mmol, as an internal standard), catalyst (Pd-2QC-MCM, 0.02 g) and NMP (3 ml) at 80 °C for 7 h.

[a] Based on consumed phenyl acetylene.
[b] Values in parenthesis is a yield of homo-coupled dialkyne.
[c] 1.0 mmol of piperidine was used.

dialkyne was accompanied (entry 5). These results show that NMP is the most suitable solvent for Sonogashira coupling reaction over Pd-2QC-MCM.

The reactions were carried out in NMP and in a mixture of NMP and water (NMP/water, 8/2 (v/v)) to elucidate the influence of water. The conversion was increased by adding water (67.4–80.9%) (entry 6). Similar enhancements of catalytic activity in Sonogashira coupling reaction were also observed in previous reports [18,19,33].

The absorption of hydrogen halide by the addition of organic or inorganic bases is a key of Pd-catalyzed Heck-type reactions, such as vinylation, carbonylation, and Heck-Mizorogi and Suzuki-Miyaura coupling reactions [32]. In the Sonogashira coupling reaction, it is also known that the base is not only important for absorption of hydrogen halide, but also plays a role in inhibiting a homo-coupling product (Glaser-type reaction) [9,12–14,17,19]. Table 3 shows the influence of base in the cross-coupling of **1a** with **2a** over Pd-2QC-MCM. No coupling reaction occurred in the absence of base (entry 1). The addition of two-fold molar piperidine against phenyl acetylene resulted in excellent conversion (100%; entry 1); however, the addition of equimolar piperidine gave lower conversion (67.8%, entry 2). This means that excess addition of piperidine significantly enhances catalytic activity. The cross-coupling reaction was also enhanced by the addition of TEA (conversion: 67%; entry 4), although a small amount of dialkyne was accompanied. Pyridine and indoline were inert due to their low basicities (entries 5 and 6). The addition of inorganic bases such as Na$_2$CO$_3$ and NaOAc resulted in moderate conversions (entries 7 and 8), whereas the conversion was very low by adding K$_2$CO$_3$ (entry 9). These results indicate that organic amines are more favorable than inorganic ones because they effectively trap hydrogen halide formed in the reaction. It is interesting that the addition of the amine plays an important role in the enhancement of catalysis as well as in the absorption of hydrogen halide.

Fig. 4 shows the influence of reaction temperature on Sonogashira coupling reaction of **1a** with **2a** over Pd-2QC-MCM. The reaction was performed for 3 h in the presence of two-fold molar piperidine against **1a** in NMP solvent. Catalytic activity was decreased with decreasing reaction temperature: it was not detectable at temperatures below 40 °C. However, the conversion was enhanced by elevating the reaction temperature, and the reaction was completed over 3 h at 70–80 °C.

The combination of terminal alkynes and aryl halides was investigated to elucidate scope and limitations of Pd-2QC-MCM catalyst. The aromatic terminal alkynes phenyl acetylene (**1a**), 4-ethynyltoluene (**1b**), 4-ethynylanisole (**1c**), and 4-ethynylbromobenzene (**1d**); an aliphatic terminal alkyne, 1-
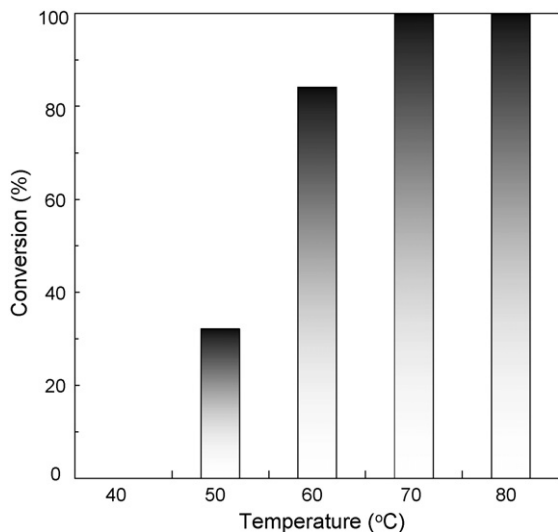
Fig. 4. The influence of reaction temperature on Sonogashira coupling reaction over Pd-2QC-MCM. *Reaction conditions*: Catalyst (0.02 g); iodobenzene (1.3 mmol); phenyl acetylene (1.0 mmol); piperidine (2.0 mmol); NMP (3 ml); temperature: 3 h.

hexyne (**1e**); and aryl halides having electron withdrawing or donating groups (**2a–h**) were chosen as substrates (Scheme 2).

Table 4 shows typical results of the reactions of **1a** with aryl halides (**2a–h**) over Pd-2QC-MCM. The reaction of **2a** gave tolane (**3aa**) in quantitative yield (entry 1). Aryl iodides having an electron-donating group such as 4-iodotoluene (**2b**), 4-iodoanisole (**2c**) and

4-iodoaniline (**2d**) and 1-iodonaphthalene (**2e**) gave corresponding cross-coupling products (**3ab**–**ae**) with high yields, although trace amounts of homo-coupled dialkyne were accompanied as a by-product (entries 2–5). The dialkyne formation was due to the dialkynylpalladium intermediate during catalysis [17]. On the other hand, reactions of 4-iodoacetophenone (**2f**) and 1-iodo-4-nitrobenzene (**2g**) having an electron-withdrawing group gave only tolane derivatives with quantitative yields (entries 6 and 7). However, no coupling product was obtained in the reaction of less reactive bromobenzene (**2h**). This means that the Pd-2QC-MCM catalyst is less active for aryl bromides.

Table 5 shows the Sonogashira coupling reaction of terminal alkynes (**1b**–**e**) with aryl halides (**2a–g**) over Pd-2QC-MCM. All reactions of terminal alkynes **1b** and **1c** having an electron-donating group gave the corresponding cross-coupling products (**3ba**–**bg** and **3ca**–**cg**) in high yields (entries 1–15); however, the reaction of 1-iodonaphthalene (**1e**) showed slightly lower yields: this may be due to its steric hindrance and/or electronic factor [20] (entries 5 and 13). In coupling reactions of **1b**, a higher activity was observed in reactions with electron-withdrawing aryl iodides, **2f** and **2g**. Reactions of **1c** gave quantitative yields of cross-coupling products, except for **2e**. However, no coupling product was obtained in reactions of **2h** with **1b** or **1c** (entries 8 and 16).

The use of an electron-withdrawing alkyne **1d** also showed the excellent catalytic activity to afford desired cross-coupling products (**3da**–**df**) in quantitative yields with no formation of homo-coupling product (Table 5, entries 17–20). This is due to an easier release of a terminal proton, compared to that of **1a**–**c**, to accelerate the coordination to the palladium complex.
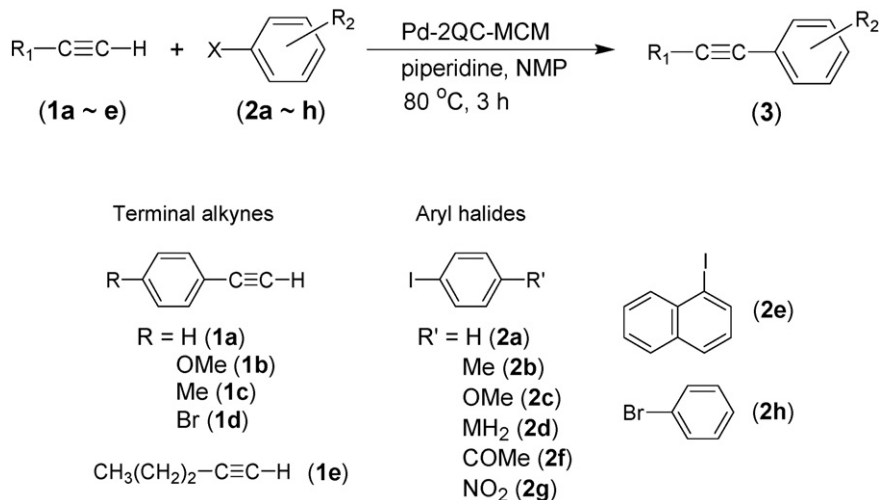
Table 4
Sonogashira coupling reaction of phenyl acetylene (**1a**) with aryl halides over Pd-2QC-MCM-41

Entry	Aryl halide	Product	Conversion (%)[a]	Yield (%)[a,b]
1	Iodobenzene (**2a**)	**3aa**	100	99.2 (0.4)
2	4-Iodotoluene (**2b**)	**3ab**	95.9	94.9 (0.5)
3	4-Iodoanisole (**2c**)	**3ac**	97.3	96.3 (0.5)
4	4-Iodoaniline (**2d**)	**3ad**	94.7	94.5 (0.1)
5	Iodonaphthalene (**2e**)	**3ae**	85.2	84.4 (0.4)
6	4-Iodoacetophenone (**2f**)	**3af**	100	99.6 (0.2)
7	1-Iodo-4-nitrobenzene (**2g**)	**3ag**	100	99.8 (0.1)
8	Bromobenzene (**2h**)	**3ah**	2.7	0 (1.3)

Reaction conditions: Aryl halide (1.3 mmol), phenyl acetylene (1.0 mmol), piperidine (2.0 mmol), catalyst (Pd-2QC-MCM, 0.02 g), and NMP (3 ml) at 80 °C for 3 h.
[a] Based on consumed phenyl acetylene.
[b] Values in parenthesis is a yield of homo-coupled dialkyne.

Scheme 2.

Table 5
Sonogashira coupling reaction of alkynes and aryl halides over Pd-2QC-MCM

Entry	Alkyne	Arylhalide	Product	Yield (%)[a]
1		**2a**	**3ba**	94.5
2		**2b**	**3bb**	93.8
3		**2c**	**3bc**	93.1
4		**2d**	**3bd**	94.1
5	4-Ethynyltoluene (**1b**)	**2e**	**3be**	81.3
6		**2f**	**3bf**	99.2
7		**2g**	**3bg**	100
8		**2h**	**3bh**	0
9		**2a**	**3ca**	100
10		**2b**	**3cb**	100
11		**2c**	**3cc**	100
12		**2d**	**3cd**	100
13	4-Ethynylanisole (**1c**)	**2e**	**3ce**	90.3
14		**2f**	**3cf**	100
15		**2g**	**3cg**	100
16		**2h**	**3ch**	0
17		**2a**	**3da**	100
18	4-Ethynylbromobenzene (**1d**)	**2b**	**3db**	87.6
19		**2g**	**3dg**	100
20		**2f**	**3df**	93.9
21		**2a**	**3ea**	60.1
22		**2b**	**3eb**	50.7
23		**2c**	**3ec**	54.3
24		**2d**	**3ed**	50.2
25	1-Hexyne (**1e**)	**2e**	**3ee**	43.8
26		**2f**	**3ef**	59.5
27		**2g**	**3eg**	64.3
28		**2h**	**3eh**	0

Reaction conditions: Aryl halide (1.3 mmol), terminal alkyne (1.0 mmol), piperidine (2.0 mmol), catalyst (Pd-2QC-MCM, 0.02 g), and NMP (3 ml) at 80 °C for 3 h.

[a] Based on consumed terminal alkyne.

An aliphatic alkyne (**1e**) gave moderate yields of cross-coupling product in reactions with aryl halides (**2a**–**h**) with no formation of homo-coupling product (entries 23–28). These moderate catalytic activities are due to lower acidity of terminal proton of **1e**, compared to that of aromatic alkynes (**1a**–**d**), resulting in slow insertion of **1e** to aryl palladium intermediate to form aryl alkynyl palladium species.

We investigated turnover number (TON) in the reaction of **1a** with **2a** over Pd-2QC-MCM. In order to estimate the maximum catalytic performance, the reaction was carried out: **1a** (4 mmol), **2a** (5.2 mmol), piperidine (8.0 mmol), catalyst (10 mg of catalyst, 9.1×10^{-4} mmol of Pd), and 12 ml of NMP at 80 °C. TON value was 2850 calculated from 64.8% yield over 48 h. This TON value is the highest among heterogeneous Sonogashira coupling reaction in previous reports [17,20,22]. The excellent catalytic performance of Pd-2QC-MCM can be explained by the catalyst effectively being employed as a palladium complex on the high surface area of MCM-41.

Immobilized metal complex catalysts often suffer from leaching of metal species during the reaction. In particular, the trace amount of leached metal species sometimes works as an active catalyst. Fig. 5 shows leaching experiment during the reaction over Pd-2QC-MCM catalyst. The conversion of **1a** reached 100% within 3 h as shown in Fig. 5A. To know the catalytic activity of the filtrate, the catalyst was removed after the reaction during 30 min under aerobic condition (conversion of phenyl acetylene was 43.4%), and resulting filtrate was subjected to heating for further reaction. It is obvious that there was no significant increase in conversion (49% after 3 h) as shown in Fig. 5B. These results mean that the catalysis by leached palladium is negligible. The efficient catalytic performance is due to a Pd complex immobilized on MCM-41, not to naked bulk metal species.
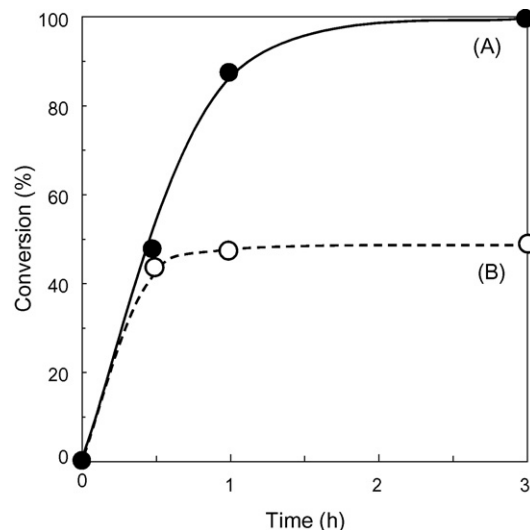

Fig. 5. Leaching experiment of Pd-2QC-MCM in Sonogashira coupling reaction. (A) Usual reaction (●). (B) The further reaction of the filtrate removing the catalyst after 30 min reaction (○). *Reaction conditions*: Catalyst (0.02 g); iodobenzene (1.3 mmol); phenyl acetylene (1.0 mmol); piperidine (2.0 mmol); NMP (3 ml); temperature: 80 °C. The filtration of the catalyst was carried out under aerobic conditions.

We also investigated the reuse of catalyst in the reaction of **1a** with **2a**. The reaction was carried out in a low palladium concentration (**1a**/Pd = 600 (molar ratio)) to elucidate the maximum catalytic performance of Pd-2QC-MCM. The catalyst was recovered by filtration and reused after washing with acetone and drying at room temperature. All recycling procedures were carried out under aerobic conditions without any special air-manipulation. The yield of **3aa** was gradually decreased from 68.7% in the first run to 60.1% in the fourth recycle as shown in Fig. 6. Considering the loss of the catalyst during the recycling, there is no significant loss of catalytic activity during the experiment, and the catalysts are air-stable during the reaction and recycling. These results show that Pd-2QC-MCM is a versatile catalyst for Sonogashira coupling reaction with good reusability.

Catalytic activities were enhanced in the presence of water in NMP solvent, as mentioned in the previous section. However, the
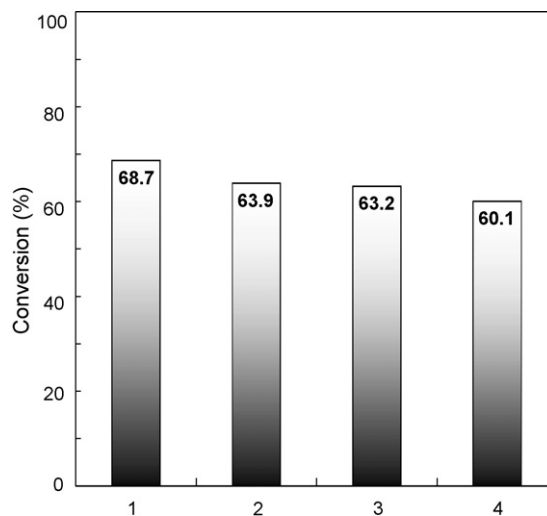

Fig. 6. Reusability of Pd-2QC-MCM in the Sonogashira coupling reaction. *Reaction conditions*: Catalyst (0.01 g); iodobenzene (6.3 mmol); phenyl acetylene (6.0 mmol); piperidine (12 mmol); NMP (9 ml); temperature: 80 °C. The catalyst was recovered without any special air-manipulation.

Table 6
Influences of water addition on the reuse of Pd-2QC-MCM in the Sonogashira coupling reaction of phenyl acetylene with iodobenzene

Solvent	Conversion (%)[a]				Pd content (wt%)[b]	
	1st	2nd	3rd	4th	Fresh	4th used
NMP	68.4	66.8	65.7	60.3	1.24	1.13
NMP/H_2O (8/2)	80.9	51.5	43.5	39.6	1.24	0.75

Reaction conditions: Iodobenzene (1.3 mmol), phenylacetylene (1.0 mmol), triethylamine (2.0 mmol), catalyst (Pd-2QC-MCM, 0.02 g), biphenyl (0.2 mmol, as an internal standard) and solvent (3 ml) at 80 °C for 7 h.

[a] Based on consumed phenyl acetylene.

[b] Pd contents of fresh and 4th used catalyst were determined by ICP analysis.

conversion decreased significantly after reuse of Pd-2QC-MCM catalyst, though such a decrease did not occur in NMP solvent (Table 6). ICP analyses of used catalyst clearly indicated leaching of palladium metal during the reaction (1.24–1.13 wt% in NMP and 1.24–0.75 wt% in NMP/water). The leaching may occur via exchange of ligands with highly polar water molecule.

4. Conclusion

Quinoline-2-carboimine Pd complex immobilized on MCM-41 (Pd-2QC-MCM) showed excellent catalytic activity in Sonogashira coupling reaction. The addition of two-fold amount of piperidine and the use of NMP as a solvent effectively promoted the reaction even in the absence of copper salt. Reactions of various terminal alkynes with aryl halides gave excellent yields of the corresponding cross-coupling products; however, moderate catalytic activity was observed in reactions of an aliphatic alkyne due to the lower acidity of its terminal proton. The dialkyne formation was observed in some cases as a by-product. The turnover number of Pd-2QC-MCM was the highest among previously reported heterogeneous catalysts in Sonogashira coupling reaction. Pd-2QC-MCM had good reusability under aerobic conditions without loss of catalytic activity. The excellent catalytic performance of Pd-2QC-MCM is ascribed to effective catalysis by the quinoline-2-carboimine palladium complex on MCM-41 with high surface area and to the high air-stability of the catalyst.

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