

Copper-free Sonogashira coupling reaction catalyzed by MCM-41-supported thioether palladium(0) complex in water under aerobic conditions

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Abstract

The MCM-41-supported thioether palladium(0) complex is a highly active catalyst for the copper-free Sonogashira coupling of aryl iodides with terminal alkynes in water at room temperature under aerobic conditions. This phosphine-free heterogeneous palladium catalyst can be easily recovered from the products and reused many times without loss of activity.

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1. Introduction

The Sonogashira coupling reaction of terminal alkynes with aryl or vinyl halides provides a powerful tool for carbon–carbon bond formation, which has been widely applied to diverse areas such as natural product synthesis and material science [1–3]. The reaction generally proceeds in the presence of a homogeneous palladium catalyst such as Pd(PPh₃)₄ and a cocatalyst. The most widely employed cocatalysts are copper salts, which mediates homocoupling of terminal alkynes and might result in high copper contamination of the product [4]. The homocoupling of terminal alkynes as a side reaction is problematic when the terminal alkynes are difficult to obtain. The other cocatalysts such as zinc, tin, boron, aluminum, Ag₂O, and AgOTf have also proven to be efficient, but additional steps are needed to make these agents [5–8]. Recently, significant progress has been made in the Sonogashira reaction to give diminished homocoupling [9–11]. Many of the coupling reactions were performed without copper salts [12–15], which provides the opportunity to develop the Sonogashira coupling reaction under aerobic conditions, because the copper-mediated oxidative homocoupling of alkynes is prevented [4]. Very recently, Yang et al. reported the first copper-free Sonogashira cou-

pling reaction with PdCl₂ in water under aerobic conditions [16].

While these examples contributed to the improvement of the Sonogashira coupling reaction, they remained based on homogeneous palladium complex catalyst, which make the separation and the recovery of the catalysts tedious if not impossible and might result in unacceptable palladium contamination of the products. A way to overcome these difficulties would be the use of a heterogeneous palladium catalyst. Although a great deal of effort has been made to carry out the coupling reaction using immobilized palladium catalysts [17–24], what seems to be lacking is the efficiency of the catalytic systems. It is obvious that the heterogeneous catalytic systems exhibit generally lower activity than the homogeneous ones and the activity of the catalysts decreases gradually in the recycled systems because the palladium leaches away from their supports. Besides, the heterogeneous palladium-catalyzed Sonogashira reactions need degassed organic solvents and have to be carried out under an inert atmosphere, copper salts are usually used as cocatalyst. This is particularly inconvenient when the reactions are carried out in multiple vessels for library generation. Therefore, the development of a convenient method is an important objective in this effort. Taking these into consideration, we decided to concentrate on developing a novel supported palladium catalyst which is highly active and stable. Our goal was that it still be effective in the absence of copper salts as a cocatalyst and can be recycled many times in water as solvent under aerobic

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conditions. In this paper, we develop a mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal alkynes in water under aerobic conditions with the MCM-41-supported thioether palladium(0) complex [MCM-41-S-Pd(0)] as catalyst.

2. Experimental

All chemicals were reagent grade and used as purchased. IR spectra were determined on a Perkin-Elmer 683 instrument. ^1H NMR spectra were recorded on a Bruker AC-P400 (400 MHz) spectrometer with TMS as an internal standard in CDCl_3 as solvent. ^{13}C NMR spectra were recorded on a Bruker AC-P400 (100 MHz) spectrometer with TMS as an internal standard in CDCl_3 as solvent. Microanalyses were measured using a Yanaco MT-3 CHN microelemental analyzer. X-ray powder diffraction (XRD) was obtained on Damx-rA (Rigaku). X-ray photoelectron spectra (XPS) were recorded on XSAM 800 (Kratos). The MCM-41-supported thioether palladium(0) complex [MCM-41-S-Pd(0)] was prepared as previously described [25], the sulfur and palladium content was 0.72 and 0.35 mmol/g, respectively.

2.1. General procedure for the Sonogashira coupling reaction

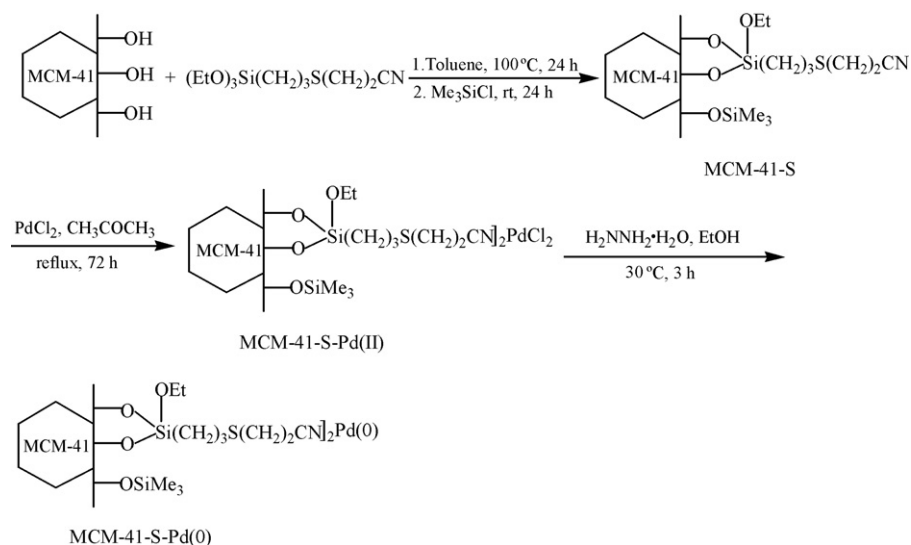
Aryl iodide (1.0 mmol), MCM-41-S-Pd(0) (14 mg, 0.005 mmol Pd), piperidine (8.0 mmol), and H_2O (1.2 ml) were added to a flask under aerobic conditions, and the resulting mixture was stirred at 50°C for 15 min, then cooled to 25°C . To this suspension was added terminal alkyne (1.5 mmol), and the reaction mixture was stirred at 25°C for 12–24 h. The mixture was dissolved in Et_2O (40 ml). The MCM-41-S-Pd(0) catalyst was separated from the mixture by filtration, washed with distilled water (2×10 ml), EtOH (3×10 ml) and Et_2O (2×10 ml) and reused in the next run. The ethereal solution was washed with water (2×10 ml) and dried over MgSO_4 .

The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel to give the desired product. The isolated products were analyzed by IR, ^1H NMR, and ^{13}C NMR and compared with authentic samples.

3. Results and discussion

Recent developments on the mesoporous material MCM-41 provided a new possible candidate for a solid support for immobilization of homogeneous catalysts [26]. MCM-41 has a regular pore diameter of *ca.* 50 Å and a specific surface area $>700\text{ m}^2\text{ g}^{-1}$ [27]. Its large pore size allows passage of large molecules such as organic reactants and metal complexes through the pores to reach to the surface of the channel [28–30]. To date, a few palladium complexes on functionalized MCM-41 support have been prepared and successfully used in organic reactions [31–34]. Very recently, we have reported the synthesis of the first MCM-41-supported thioether palladium(0) complex [MCM-41-S-Pd(0)] and its catalytic behavior in Heck reaction [25]. It was found that the MCM-41-S-Pd(0) complex is highly active and stereoselective catalyst for Heck arylation reaction of olefins with aryl iodides and bromides. The MCM-41-supported thioether palladium(0) complex [MCM-41-S-Pd(0)] can be conveniently prepared from 3-(2-cyanoethylsulfanyl) propyltriethoxysilane via immobilization on MCM-41, followed by reacting with palladium chloride in acetone, and then the reduction with hydrazine hydrate in ethanol according to our previous procedure (Scheme 1).

Since “water” is the most safe and easily available solvent, numerous attempts have been made in utilizing it in organic reactions [35,36]. While the development of catalytic systems in water has been confronted with many difficulties, the MCM-41-S-Pd(0) complex will be a key to developing an efficient system in water owing to its amphiphilicity. To realize our goal, we screened a variety of coupling conditions and were pleased to find that the Sonogashira coupling reaction proceeded very smoothly using MCM-41-S-Pd(0) in water in the presence of



Scheme 1. Preparation of the MCM-41-S-Pd(0).

Table 1

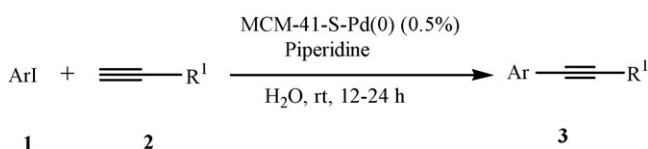
Effect of base, amount of the catalyst, and temperature on Sonogashira coupling reaction of phenylacetylene with iodobenzene^a

Entry	Base	Temperature (°C)	MCM-41-S-Pd(0) (mol%)	Time (h)	Yield (%) ^b
1	Et ₃ N	25	0.5	24	82
2	Pyridine	25	0.5	24	75
3	BuNH ₂	25	0.5	20	85
4	Pyrrolidine	25	0.5	18	89
5	Piperidine	25	0.5	18	92
6	Piperidine	50	0.5	18	87
7	Piperidine	80	0.5	18	82
8	Piperidine	25	0.3	24	90
9	Piperidine	25	0.1	32	87
10	Piperidine	25	0.8	13	91
11	Piperidine	25	1.0	10	89

^a All reactions were performed using 1.0 mmol of iodobenzene, 1.5 mmol of phenylacetylene, and 8.0 mmol of base in 1.2 ml of H₂O under aerobic conditions.^b Isolated yield based on the iodobenzene used.

piperidine under aerobic conditions without copper salts. We then investigated the effect of various reaction parameters (base, the amount of palladium catalyst, temperature) on the outcome of the coupling reaction with phenylacetylene and iodobenzene as the substrates (Table 1). It was found that among the bases used [Et₃N, pyridine, BuNH₂, pyrrolidine, and piperidine], piperidine proved to be the most efficient. Among the amounts of MCM-41-S-Pd(0) tested [0.1, 0.3, 0.5, 0.8, and 1.0 mol%], the use of 0.5 mol% MCM-41-S-Pd(0) was the best choice. Increasing the amount of palladium catalyst could shorten the reaction time, but did not increase the yield of 1,2-diphenylacetylene. For the temperatures evaluated [25, 50, and 80 °C], 25 °C gave the best result. Taken together, excellent result was obtained when the reaction was carried out with 0.5 mol% MCM-41-S-Pd(0) in water at 25 °C in the presence of piperidine as base under aerobic conditions.

To examine the scope for this coupling reaction, a variety of terminal alkynes were coupled with different phenyl iodides (Scheme 2). The experimental results are summarized in Table 2. As shown in Table 2, the Sonogashira coupling reactions of aryl iodides with a variety of terminal alkynes proceeded smoothly at 25 °C in water under aerobic conditions giving the corresponding coupling products in high yields. However, the coupling reaction of phenyl iodide with a hydrophilic terminal alkyne was very slow under the same conditions, only trace of coupling product was obtained after 24 h of reaction time (entry 20). So, the hydrophobic property of the coupling products is important to this Sonogashira reaction in water. The coupling reactions of heteroaryl iodides such as 3-iodopyridine and 2-iodothiophene with terminal alkynes could also proceed smoothly under the same conditions affording the corresponding coupling products in good yields after 24 h of reaction time (entries 21, 22). The optimized catalyst system is quite general and tolerant of a range



Scheme 2. Sonogashira coupling reaction catalyzed by MCM-41-S-Pd(0).

of functionalities. For the electron-deficient phenyl iodides, the coupling reactions were completed within 12 h, and the others required slightly longer reaction times. In all reactions only 0.5 mol% of MCM-41-S-Pd(0) based on the aryl iodides was used, the molar turnover numbers are larger than those in the corresponding coupling reaction catalyzed by other heterogeneous catalysts reported [17–24].

This MCM-41-supported thioether palladium(0) catalyst can be easily recovered by simple filtration. In an attempt to show that the MCM-41-S-Pd(0) can be recycled, the coupling reactions of different phenyl iodides with a range of terminal alkynes were repeated five times using the same batch of supported catalyst. The experimental results are summarized in Table 3. As shown in Table 3, the average yield of **3a**, **3o**, and **3j** in con-

Table 2

Copper-free Sonogashira reactions of terminal alkynes with aryl iodides catalyzed by MCM-41-S-Pd(0) in water^a

Entry	Ar	R ¹	Time (h)	Product	Yield (%) ^b
1	Ph	Ph	18	3a	92
2	4-CH ₃ C ₆ H ₄	Ph	18	3b	90
3	4-ClC ₆ H ₄	Ph	12	3c	92
4	4-O ₂ NC ₆ H ₄	Ph	12	3d	93
5	3-O ₂ NC ₆ H ₄	Ph	12	3e	91
6	4-CH ₃ COC ₆ H ₄	Ph	12	3f	90
7	2-CF ₃ C ₆ H ₄	Ph	12	3g	92
8	3-CNC ₆ H ₄	Ph	12	3h	93
9	Ph	Me ₃ Si	18	3i	90
10	4-CH ₃ OC ₆ H ₄	Me ₃ Si	24	3j	89
11	4-ClC ₆ H ₄	Me ₃ Si	12	3k	91
12	Ph	CH ₃ OCH ₂	18	3l	89
13	4-ClC ₆ H ₄	CH ₃ OCH ₂	12	3m	90
14	Ph	<i>n</i> -C ₄ H ₉	18	3n	93
15	4-O ₂ NC ₆ H ₄	<i>n</i> -C ₄ H ₉	12	3o	95
16	3-CNC ₆ H ₄	<i>n</i> -C ₄ H ₉	12	3p	93
17	2-CF ₃ C ₆ H ₄	<i>n</i> -C ₄ H ₉	12	3q	92
18	Ph	4-CH ₃ OC ₆ H ₄	20	3r	88
19	4-CH ₃ C ₆ H ₄	4-BrC ₆ H ₄	18	3s	91
20	Ph	HOCH ₂	24	3t	Trace
21	3-Pyridyl	Ph	24	3u	81
22	2-Thienyl	<i>n</i> -C ₄ H ₉	24	3v	78

^a All reactions were performed using 1.0 mmol of **1**, 1.5 mmol of **2**, and 8.0 mmol of piperidine in 1.2 ml of H₂O under aerobic conditions.^b Isolated yield based on **1** used.

Table 3
Sonogashira reactions of aryl iodides with terminal alkynes catalyzed by recycled catalyst^a

Entry	Ar	R ¹	Product	Catalyst cycle	Yield (%) ^b
1	Ph	Ph	3a	1st	92
2	Ph	Ph	3a	2nd	91
3	Ph	Ph	3a	3rd	92
4	Ph	Ph	3a	4th	90
5	Ph	Ph	3a	5th	90
6	4-O ₂ NC ₆ H ₄	<i>n</i> -C ₄ H ₉	3o	1st	95
7	4-O ₂ NC ₆ H ₄	<i>n</i> -C ₄ H ₉	3o	2nd	95
8	4-O ₂ NC ₆ H ₄	<i>n</i> -C ₄ H ₉	3o	3rd	93
9	4-O ₂ NC ₆ H ₄	<i>n</i> -C ₄ H ₉	3o	4th	94
10	4-O ₂ NC ₆ H ₄	<i>n</i> -C ₄ H ₉	3o	5th	93
11	4-CH ₃ OC ₆ H ₄	Me ₃ Si	3j	1st	89
12	4-CH ₃ OC ₆ H ₄	Me ₃ Si	3j	2nd	88
13	4-CH ₃ OC ₆ H ₄	Me ₃ Si	3j	3rd	87
14	4-CH ₃ OC ₆ H ₄	Me ₃ Si	3j	4th	86
15	4-CH ₃ OC ₆ H ₄	Me ₃ Si	3j	5th	86

^a All reactions were performed using 5.0 mmol of aryl iodide, 7.5 mmol of terminal alkyne, 0.025 mmol of MCM-41-S-Pd(0), and 40.0 mmol of piperidine in 6.0 ml of H₂O under aerobic conditions.

^b Isolated yield based on aryl iodide used.

secutive reactions promoted by the 1st through the 5th recycled catalyst was 91%, 94%, and 87%, respectively. The XPS data for the used catalyst after the fifth cycle and the fresh catalyst are listed in Table 4. It can be seen that the binding energies of Pd_{3d5/2}, S_{2p}, N_{1s}, Si_{2p}, and O_{1s} of the used MCM-41-S-Pd(0) after the fifth cycle are similar to those of the fresh MCM-41-S-Pd(0). Small angle X-ray powder diffraction of the used MCM-41-S-Pd(0) gave peaks similar to those of the fresh one. The intensity of the (100), (110) and (200) reflections was found to be almost same in the used MCM-41-S-Pd(0) after the fifth cycle and in the fresh MCM-41-S-Pd(0). These results indicate that the MCM-41-S-Pd(0) complex has high stability and excellent reusability. A further objective of our studies was to determine whether the catalysis was due to the MCM-41-S-Pd(0) complex or to a homogeneous palladium complex that comes off the support during the reaction and then returns to the support at the end. To test this, we focused on the coupling reaction of phenylacetylene with iodobenzene. We filtered off the MCM-41-S-Pd(0) complex after 2 h of reaction time and allowed the filtrate to react further. We found that, after this filtration, no further reaction was observed and the absence of Pd in the filtrate was determined by AAS. The palladium content of the catalyst was found to be almost same in the fresh catalyst and in the used catalyst after the fifth cycle by elemental analyses. This clearly rules out the possibility of leaching of palladium from the MCM-41 support. The result is important from a practical point

Table 4
XPS data for the used catalyst after the fifth cycle and the fresh catalyst^a

Sample	Pd _{3d5/2}	S _{2p}	N _{1s}	Si _{2p}	O _{1s}
MCM-41-S-Pd(0) (used)	336.6	164.4	400.4	103.3	533.0
MCM-41-S-Pd(0) (fresh)	336.7	164.3	400.5	103.2	532.9

^a The binding energies are referenced to C_{1s} (284.6 eV) and the energy differences were determined with an accuracy of ±0.2 eV.

of view. Although a number of Sonogashira coupling reactions that were carried out in aqueous media were reported previously with CuI as a cocatalyst [37–42], this copper-free Sonogashira reaction in aqueous media has some attractive advantages such as its insensitivity to air, its production of only trace amounts of homocoupling products of terminal alkynes, easy recovery and reuse of the palladium catalyst.

4. Conclusion

We have developed a mild copper-free heterogeneous Sonogashira coupling reaction of aryl iodides with terminal alkynes in water using piperidine as base under aerobic conditions. The advantages of our heterogeneous catalytic system over others are: (1) the preparation of the phosphine-free heterogeneous MCM-41-S-Pd(0) catalyst is rather simple and convenient from commercially available and cheap reagents, (2) the reaction conditions are very mild, i.e., only 0.5 mol% palladium catalyst, room temperature, water as the solvent, air atmosphere and without CuI, (3) excellent performance and reusability of the catalyst. Current work in our laboratory is focused on extending the synthetic scope.

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