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Copper-free Sonogashira cross-coupling reaction catalyzed by polymer-supported *N*-heterocyclic carbene palladium complex

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Abstract—A core-shell type of polymer-supported *N*-heterocyclic carbene (NHC) palladium catalyst was applied to Sonogashira cross-coupling reactions without copper cocatalyst under ambient atmosphere. This supported NHC–palladium complex efficiently catalyzed the copper-free Sonogashira reaction of various aryl iodides and bromides with terminal alkynes; the reaction exhibited high dependency on the temperature and the amount of base as well as its nature. In addition, this heterogeneous catalyst exhibited good reusability for the copper-free Sonogashira reaction.

The Sonogashira reaction cocatalyzed by palladium and copper is a powerful and straightforward method for the construction of arylated internal alkyne compounds,[1] C(sp^2)–C(sp) bond, which are important intermediates in organic synthesis including natural products,[2] biologically active molecules,[3] molecular electronics[4] and polymers.[5] The original Sonogashira reaction was generally performed in the presence of large amounts of palladium and copper(I) iodide as a cocatalyst under inert conditions, which were economically and environmentally malignant. This protocol has recently been improved by several modifications such as reaction in aqueous media, ionic liquid or under microwave irradiation[6] and the use of promoters (Zn, Mg, Sn) or effective ligands.[7] Especially, the most significant improvement has focused on the omission of copper(I) iodide,[8] because it can induce oxidative homocoupled by-products of acetylenes that are difficult to separate from the desired product and copper acetylides can be explosive.[9] Besides, the use of copper(I) iodide has also been shown to inhibit the Sonogashira reaction.[10]

However, most of the above reactions were carried out homogeneously and, thus, had intrinsic problems such as difficulties in recovery, separation and recycling of the expensive, toxic catalysts and contamination of the ligand residue into the final product, except ionic liquid-mediated system.[6c] In order to avoid these drawbacks, several heterogeneous catalyst systems have also been reported.[11] Nevertheless, there is still a need for an efficient heterogeneous catalyst that is air and moisture stable and applicable to a wide range of Sonogashira reactions without copper cocatalyst.

Herein, we report the copper-free, heterogeneous Sonogashira reactions catalyzed under ambient atmosphere by a novel type of polymer-supported *N*-heterocyclic carbene (NHC) palladium complex that we recently developed,[12] in which NHC is an emerging alternative as an air and moisture stable ligand against phosphines.[13]

As shown in Scheme 1, this polymer-supported NHC precursor bead has imidazolium on its surface and a bidentic NHC–palladium complex (**1**) forms on the beads.

We first investigated the effect of various solvents on the model reaction of iodobenzene with phenylacetylene catalyzed by 1 mol % of supported NHC–palladium without copper iodide at ambient atmosphere. Cesium carbonate (Cs_2CO_3) was used as a base in this reaction. As shown in Table 1, a solution of DMF/H_2O (3:1) gave the highest yield (entry 1, 85%) after 3 h at 60 °C in the copper-free reaction of iodobenzene with phenylacetylene. The yield of cross-coupled product was reduced as the polarity of organic solvents decreased. In

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Keywords: Polymer-supported catalyst; *N*-Heterocyclic carbene (NHC); Heterogeneous catalysis; Palladium (Pd); Sonogashira reaction; Copper-free.

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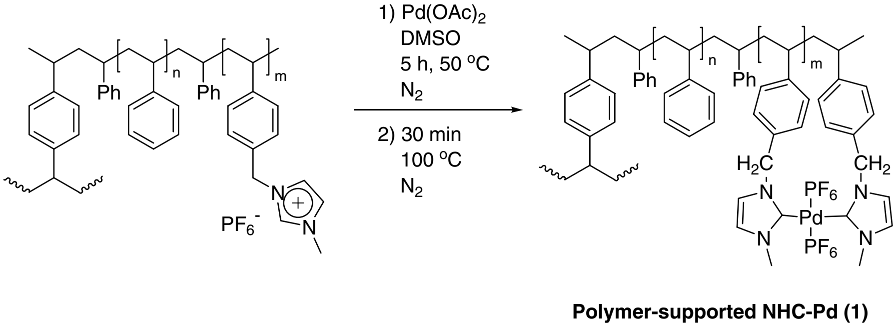
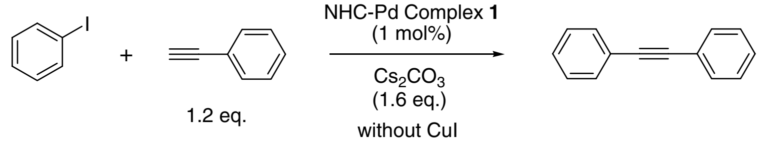


Scheme 1. Core-shell type of polymer-supported NHC–Pd catalyst (**1**).

Table 1. Effect of the solvent on the reaction of iodobenzene with phenylacetylene without copper iodide[a]



Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	DMF/water (3:1)	60	3	85
2	CH_3CN/water (3:1)	60	3	45
3	THF/water (3:1)	60	3	5
4	Dioxane/water (3:1)	60	3	25

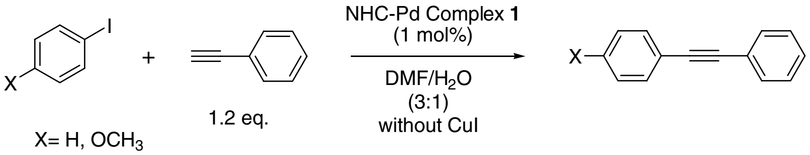
[a] Iodobenzene (0.5 mmol), phenylacetylene (0.6 mmol), supported NHC–Pd (1 mol %), Cs_2CO_3 (0.8 mmol), without CuI.

[b] Isolated by column chromatography.

addition, no homocoupled by-product was formed under any solvent conditions.

After selecting a DMF/H_2O (3:1) solution as the optimal solvent, we investigated the influence of various bases on the copper-free Sonogashira reaction of electron-neutral iodobenzene and electron-rich 4-iodoanisole with phenylacetylene using 1 mol % of supported NHC–palladium catalyst at ambient atmosphere. We found that the copper-free Sonogashira reaction was highly dependent on the amount of base as well as its nature. According to the results shown in Table 2, Cs_2CO_3 gave excellent yield (entry 1, 85%) in the reaction of electron-neutral iodobenzene with phenylacetylene under mild conditions (3 h at 60 °C). Piperidine also produced a similar yield (entry 4, 79%) to Cs_2CO_3. However, the results with the deactivated substrate, electron-rich 4-iodoanisole, were different from the electron-neutral one. An inorganic base, Cs_2CO_3, gave poor conversion of 4-iodoanisole to the corresponding product (entry 5, 20% yield) for 2 h at 80 °C. Other inorganic bases such as NaOAc and NaOH also provided low transformation of deactivated aryl iodide to the desired product (Table 2, entries 7 and 8). The best result for electron-rich 4-iodoanisole was obtained using 1.6 equiv of piperidine for 2 h at 80 °C (Table 2, entry 11, 51%). However, a 29% yield of the side product was formed from the desired product under the above conditions with 1.6 equiv of piperidine; this side product was not observed in the copper-free reaction of electron-neutral and deficient aryl iodides, even at high temperature. We identified the phenylacetylene-added side product as ((*Z*)-1-(4-methoxyphenyl)-4-phenylbut-1-en-3-yn-2-l)-benzene.[14] This kind of side reaction was previously reported by Djakovitch et al.,[11c] who hypothesized that the side product originated from the thermal coupling of the desired product with excess phenylacetylene at temperatures above 80 °C. In our study, however, this side product also formed at lower temperature (60 °C). This finding led us to more intensively investigate the base for the copper-free reaction of electron-rich aryl iodide. First, we investigated the influence of the amount of piperidine used in the copper-free Sonogashira reaction. As illustrated in Table 2, when larger amounts of base were used, less side product was obtained. When 5 equiv of piperidine was used, the yield of the side product declined to 14% (Table 2, entry 12), while the conversion into desired product was maintained. In addition, the formation of side product was completely suppressed when 10 equiv of piperidine was used, and the desired coupling product formed cleanly (Table 2, entry 13). However, neither the desired product nor the side product was synthesized when 15 equiv of piperidine was used in the copper-free reaction of 4-iodoanisole with phenylacetylene (Table 2, entry 14). These results indicate that excess amount of the base, piperidine, suppresses not only the side reaction, but also the desired reaction. We speculate that the large excess

Table 2. Effect of the base on the reaction of iodobenzene and 4-iodoanisole with phenylacetylene without copper iodide[a]



Entry	X	Base	Temperature (°C)	Time (h)	Yield[b] (%)
1	H	Cs_2CO_3	60	3	85
2	H	TEA	60	3	75
3	H	TBAOAc	60	3	60
4	H	Piperidine	60	3	79
5	OCH_3	Cs_2CO_3	80	2	20 (14)[c]
6	OCH_3	TEA	80	2	46 (23)[c]
7	OCH_3	NaOAc	80	2	20 (50)[c]
8	OCH_3	NaOH	80	2	7
9	OCH_3	DMAP	80	2	0
10	OCH_3	Pyridine	80	2	0
11	OCH_3	Piperidine (0.8 mmol)	80	2	51 (29)[c]
12	OCH_3	Piperidine (2.5 mmol)	80	2	47 (14)[c]
13	OCH_3	Piperidine (5 mmol)	80	2	43 (0)[c]
14	OCH_3	Piperidine (7.5 mmol)	80	2	0 (0)[c]
15	OCH_3	Piperidine (5 mmol)	100	2	85 (0)[c]

[a] Aryl iodides (0.5 mmol), phenylacetylene (0.6 mmol), supported NHC–Pd (1 mol %), base (0.8 mmol), DMF/H_2O (3:1), without CuI.

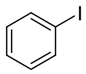
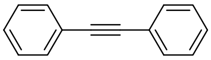
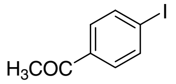
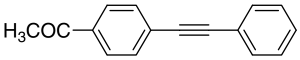
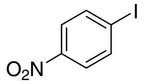
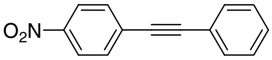
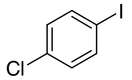
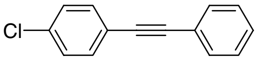
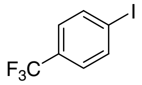
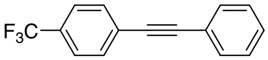
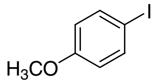
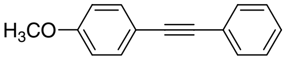
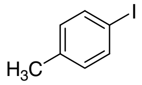
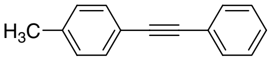
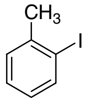
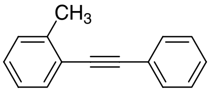
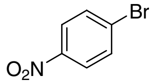
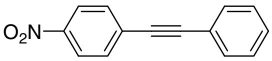
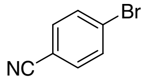
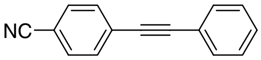
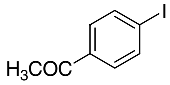
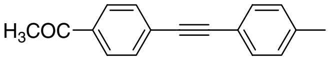
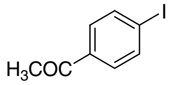
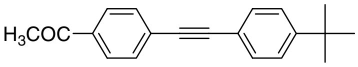
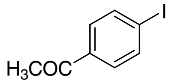
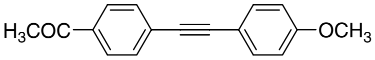
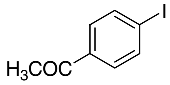
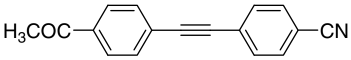
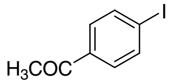
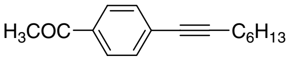
[b] Isolated by column chromatography.

[c] The yield in the round bracket is for the side product induced from the desired product.

of piperidine prohibits the acetylenes from coordinating to palladium in copper-free Sonogashira reaction, resulting in no progress in the reactions. In order to optimize the copper-free reaction further, reaction temperature was then varied. As the temperature increased up to 100 °C in the copper-free reaction of 4-iodoanisole with phenylacetylene using 10 equiv of piperidine as a base, the yield of the desired product sharply increased to 85% after 2 h. No side product was induced from the desired product and no homocoupled by-product from terminal alkynes was also observed, even at high temperature (Table 2, entry 15). Based on the results thus far, we found that the amount of base, as well as its nature, such as basicity and steric bulkiness, and the temperature were critical for the copper-free Sonogashira reaction of deactivated aryl iodides, 4-iodoanisole and 4-iodotoluene, which is directly correlated with the reaction of electron-deficient and rich aryl bromides.

We next investigated the copper-free reactions of a variety of aryl iodides and bromides with several alkynes catalyzed by 1 mol % of polymer-supported NHC–palladium complex under ambient atmosphere.[15] As summarized in Table 3, 1.6 equiv of Cs_2CO_3 was effective as a base for electron-neutral and deficient aryl iodides because its reactivity was sufficient to obtain the desired products in high yields. Also, Cs_2CO_3 was easily removed in the extraction step after the reaction. Electron-neutral iodobenzene was converted to the corresponding product in 95% yield after 4 h at 60 °C. Aryl iodides with electron-withdrawing groups such as *p*-$COCH_3$ and *p*-NO_2 were more smoothly converted to the products in high yields (94% and 95%) under mild conditions, after 1 h at 60 °C (Table 3, entries 2 and 3). However, the above reaction conditions (60 °C, Cs_2CO_3) were poor for aryl iodides with electron-donating groups such as *p*-OCH_3 and *p*-CH_3, in which the phenylacetylene-added side product of the internal alkyne of the desired product was also observed even at low temperature. Therefore, piperidine was used as a base for copper-free reactions of electron-rich aryl iodides and aryl bromides at the elevated temperature (100 °C). Thus, 4-iodoanisole and 4-iodotoluene clearly gave the corresponding products in 90% and 91% yields, respectively, after 2.5 h at 100 °C using 10 equiv of piperidine, and did not produce any side products. In addition, the steric hindrance of the substituent did not influence the product yield in the copper-free Sonogashira reaction of deactivated aryl iodides using the polymer-supported NHC–palladium catalyst (Table 3, entry 8). The polymer-supported NHC–palladium catalyzed the copper-free reactions so rapidly that all of the electron-rich aryl iodides were converted to the desired products within 2.5 h, which is excellent catalytic efficiency compared to the results of the previous heterogeneous system. When less reactive aryl bromides with electron-withdrawing groups were used in the copper-free reaction, the coupling products were also obtained in excellent yields after longer reaction times (Table 3, entries 9 and 10) and without any side products. We next examined the copper-free reactions of several kinds of terminal alkynes catalyzed by 1 mol % of polymer-supported NHC–palladium, as shown in Table 3. The reactions of phenylacetylenes that had electron-donating groups with 4′-iodoacetophenone gave the desired products in good yields after longer reaction times at 60 °C than those required for phenylacetylene. There was no homocoupled by-product induced from terminal alkynes (Table 3, entries 11–13). The less reactive aliphatic alkyne, 1-octyne, was also converted to the desired

Table 3. Copper-free Sonogashira reaction of various aryl iodides and bromides with terminal alkynes[a]

Entry	Aryl halide	Base	Product	Temperature (°C)	Time (h)	Yield[b] (%)
1		Cs_2CO_3		60	4	95
2		Cs_2CO_3		60	1	94
3		Cs_2CO_3		60	1	95
4		Cs_2CO_3		60	3	93
5		Cs_2CO_3		60	3	94
6[c]		Piperidine		100	2.5	90
7[c]		Piperidine		100	2.5	91
8[c]		Piperidine		100	2.5	92
9		Piperidine		100	5	91
10		Piperidine		100	7	92
11		Cs_2CO_3		60	4	96
12		Cs_2CO_3		60	5	92
13		Cs_2CO_3		60	5	94
14		Cs_2CO_3		60	1.5	90
15		Cs_2CO_3		60	8	80

[a] Aryl halide (0.5 mmol), terminal alkyne (0.6 mmol), supported NHC–Pd catalyst **1** (1 mol %), base (0.8 mmol), DMF/H_2O (3:1), without CuI.

[b] Isolated by column chromatography.

[c] 10 equiv of piperidine (5 mmol) were used.

product with 80% yield under mild conditions, at 60 °C for 8 h (Table 3, entry 15).

Finally, we explored the reusability of the polymer-supported NHC–palladium catalyst for the copper-free Sonogashira reaction of 4′-iodoacetophenone with phenylacetylene after 1 h at 60 °C using 1.6 equiv of Cs_2CO_3 as a base. After the first run, the catalyst (1 mol %) was filtered and extensively washed with DMF and DCM and then reused under the same conditions. The product was obtained in 93%, 93% and 94% yields for the second, third and forth runs, respectively, indicating that the polymer-supported NHC–palladium catalyst had consistent activity for copper-free Sonogashira reaction after recycling. The recovered catalyst was analyzed by an inductively coupled plasma-atomic emission spectrometer (ICP-AES) and no significant decrease in palladium content on polymer beads was observed.

In summary, the polymer-supported NHC–palladium complex efficiently catalyzed the copper-free Sonogashira cross-coupling reactions of various aryl iodides and bromides with terminal alkynes under ambient atmosphere; these reactions were highly dependent on the amount and nature of the base as well as on the temperature. The catalyst also maintained its catalytic activity for copper-free Sonogashira reaction after recycling four times. This supported NHC–palladium catalyst system offers many advantages such as complete recovery and reuse of the catalyst, easy work-up procedure, reactions under ambient conditions and no copper cocatalyst.

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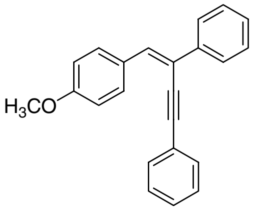
14. The side product induced from the desired product; [(Z)-1-(4-methoxyphenyl)-4-phenylbut-1-en-3-yn-2-yl]benzene. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.81 (s, 3H, $\mathrm{OCH_3}$), 7.08 (d, 2H, m-$\mathrm{C{=}C{-}C_6H_4{-}OMe}$), 7.46 (m, 9H, o-$\mathrm{C{=}C{-}C_6H_4{-}OMe}$, m and p-$\mathrm{C{\equiv}C{-}C_6H_5}$, m and p-$\mathrm{C{=}C{-}C_6H_5}$), 7.61 (m, 2H, o-$\mathrm{C{\equiv}C{-}C_6H_5}$), 7.84 (d, 1H, o-$\mathrm{C{=}C{-}C_6H_5}$), 8.08 (d, 1H, o-$\mathrm{C{=}C{-}C_6H_5}$). ^{13}C NMR (500 MHz, DMSO-d_6): δ (ppm) 55.25 ($\mathrm{CH_3}$), 88.62 ($\mathrm{C{\equiv}C{-}C{=}C}$, alkyne), 96.39 ($\mathrm{C{\equiv}C{-}C_6H_5}$, alkyne), 113.95 ($m$-C=C, $\mathrm{C{=}C{-}C_6H_4{-}OMe}$, benzene carbon), 120.02 ($\mathrm{C{-}C{\equiv}C}$, $\mathrm{C_6H_5}$, benzene carbon), 122.39 ($\mathrm{HC{=}C{-}C{\equiv}C}$), 125.87 ($o$-C=C, $\mathrm{HC{=}C{-}C_6H_5}$, benzene carbon), 127.72 (o-C=C, $\mathrm{C{=}C{-}C_6H_4{-}OMe}$, benzene carbon), 127.82 ($\mathrm{C{-}C{=}C}$, $\mathrm{C{=}C{-}C_6H_4{-}OMe}$, benzene carbon), 128.53 (p-C=C, $\mathrm{HC{=}C{-}C_6H_5}$, benzene carbon), 128.84 (m-C=C, $\mathrm{C{\equiv}C{-}C_6H_5}$, benzene carbon), 128.91 (p-C=C, $\mathrm{C{\equiv}C{-}C_6H_5}$, benzene carbon), 129.04 (m-C=C, $\mathrm{HC{=}C{-}C_6H_5}$, benzene carbon), 130.61 (o-C=C, $\mathrm{C{\equiv}C{-}C_6H_5}$, benzene carbon), 131.32 (o-C=C, $\mathrm{C{\equiv}C{-}C_6H_5}$, benzene carbon), 138.62 ($\mathrm{HC{=}C{-}C_6H_5}$, benzene carbon), 141.80 ($\mathrm{HC{=}C{-}C_6H_5}$, alkene), 159.60 ($\mathrm{CH_3O{-}C{=}C}$, benzene carbon). GC–MS: m/z 310.



15. General procedure for copper-free Sonogashira cross-coupling reaction: The polymer-supported NHC–Pd complex (50 mg, 1 mol % Pd, 0.11 mmol-Pd/g) was suspended in DMF/water (3:1, 4 mL), and then aryl halides (0.5 mmol) and terminal acetylenes (0.6 mmol, 1.2 equiv) were added to the bead dispersion. After a suitable base, such as Cs_2CO_3 (0.8 mmol, 1.6 equiv) for activated aryl halides or piperidine (5 mmol, 10 equiv) for deactivated aryl halides, was added to the reaction vessel, the reaction mixture was agitated in a shaking incubator at 60 °C or at 100 °C for certain period of time. All of the coupling reactions were performed under ambient atmosphere. The resulting reaction mixture was filtered and washed with distilled water (4 mL × 5) and diethyl ether (4 mL × 5). The organic phase was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The final product was isolated by column chromatography and identified by gas chromatography/mass spectroscopy (GC–MS) and nuclear magnetic resonance spectroscopy (NMR). The isolation yield was calculated from the mass value of the product.