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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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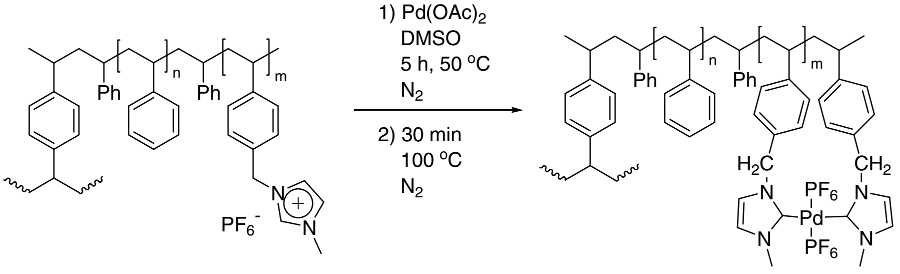
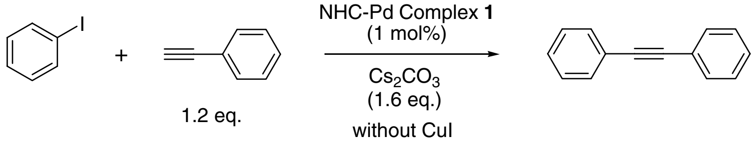


Polymer-supported NHC-Pd (1)

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