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Preparation of polymer-supported palladium/*N*-heterocyclic carbene complex for Suzuki cross-coupling reactions

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Abstract—A novel polymer-supported *N*-heterocyclic carbene (NHC) was prepared from chloromethyl polystyrene (CM PS) resin using a simple procedure, and was used as the ligand for palladium (Pd) catalysts. The polymer-supported Pd–NHC complexes efficiently catalyzed the Suzuki cross-coupling of aryl halides and phenylboronic acid in good yields and excellent purities under aqueous conditions.

Transition-metal catalyzed cross-coupling reactions are versatile and highly useful transformations, which yield a wide variety of organic compounds. In particular, the Suzuki cross-coupling reaction, which is the palladium(Pd)-catalyzed cross-coupling reaction of organic halides with organoboron compounds, represents one of the most important methods of forming sp^2–sp^2 carbon–carbon bonds in synthetic chemistry, as well as in industrial applications.[1] In the past few years, many attempts have been made to develop effective Pd complexes, which can act as highly active catalysts for this reaction.[2]

In general, specific ligands, such as electron-rich and sterically hindered phosphines, are necessary to promote these Pd-catalyzed cross-coupling reactions. Since they were first introduced independently by Öfele and Wanzlick, transition-metal complexes containing *N*-heterocyclic carbenes (NHCs) have attracted considerable attention as effective ligands for transition metals in homogeneous catalysis.[3] These NHCs can bind to any transition metal irrespective of their oxidation states. Furthermore, compared with many other ligands, such as phosphine ligands, they show very high dissociation energies, which have been quantified by theoretical calculations for different metals.[4] Therefore, the bonding between the NHC and the transition metal is much stronger and is chemically and thermally more inert toward cleavage than that of any other complexes.

Although there have been many successful demonstrations of homogeneous catalysis using this NHC as a ligand for transition metal, heterogeneous systems still remain practically useful catalysts.[5] Due to their versatile processing capabilities and ease of separation and recycling, polymer-supported catalysts offer many advantages for industrial applications. These catalysts can prevent the contamination of the ligand residue in the products. With these concerns, several kinds of polymer-supported NHC were developed recently by anchoring the Pd–NHC complex onto Wang resin[6] or modifying the nitrile groups in PAN fiber into imidazoline groups.[7]

These trends of heterogeneous catalysis inspired us to design a novel polymer-supported ligand that can form effective complexes with Pd. Herein, we report on the preparation of a novel polymer-supported Pd–NHC complex, which has water-compatibility, from chloromethyl polystyrene (CM PS) resin, and its application to the Pd-catalyzed Suzuki cross-coupling of various aryl halides and phenylboronic acid in the aqueous phase.

As shown in Figure 1, the imidazolium-loaded polymeric support (**1**) for Pd catalyst was prepared by treating chloromethyl polystyrene (CM PS) resin with 1-methylimidazole using a simple procedure.[8] A mixture of CM PS resin and an excess amount of 1-methylimidazole was agitated in NMP at 80 °C for 12 h.

Keywords: Polymer-supported *N*-heterocyclic carbene (NHC); Heterogeneous catalysis; Palladium (Pd); Suzuki cross-coupling.
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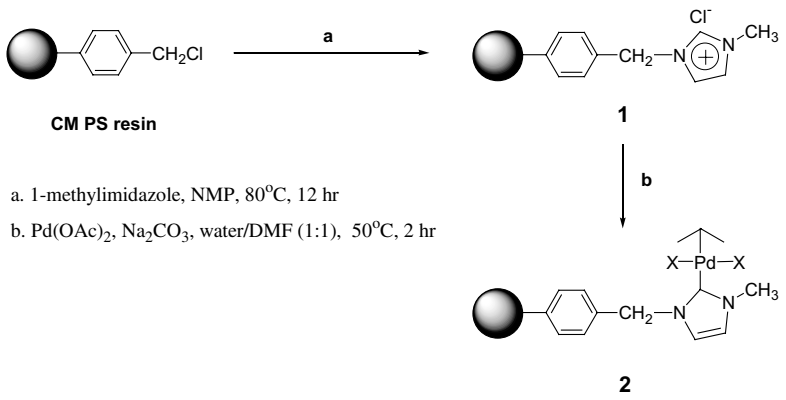


Figure 1. Preparation of imidazolium-loaded polymeric support (**1**) and the formation of polymer-supported Pd–NHC complexes (**2**).

Recently, aqueous phase reactions have been one of the major interests in organic synthesis, because water is a readily available, safe, and environment-friendly solvent.[9] In order to apply this polymer-supported Pd–NHC complex to reactions in the aqueous phase, the swelling property in water or the water-compatibility of the polymeric support is an important factor. Therefore, we prepared several kinds of polymeric support with different imidazolium loadings by adjusting the initial concentration of 1-methylimidazole, and measured the swelling properties in various solvents (Table 1).[10] In contrast to conventional polystyrene-based polymeric supports, we observed that all of the imidazolium-loaded polymeric supports were water-compatible, even though the imidazolium loading was low (entry 1). As the imidazolium loading of the polymeric support increased, its swelling volumes increased in polar solvents, such as water and MeOH, and decreased in nonpolar solvents, such as DCM, THF, and toluene. In particular, when the imidazolium loading was high (entry 3), the polymeric support showed a dramatic increase of swelling in water (4.2 mL/g) and in MeOH (7.4 mL/g).

We used a polymeric support containing a high imidazolium loading (1.91 mmol/g) as the ligand for the Pd catalysts. The complexes formed between the Pd metals and the imidazolium groups were obtained by mixing $Pd(OAc)_2$ in DMF/water (1:1, v/v) at 50 °C for 2 h.[11] In order to bring about the deprotonation of the imidazolium groups to form the Pd–NHC complexes, we added Na_2CO_3 as a base to the reaction mixture. After filtration, the polymer-supported Pd–NHC complex was colored dark brown, and the Pd loading was as high as 0.29 mmol/g, as measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES). This means that 29.2% of the initial Pd content was loaded on the polymeric support, and 15.0% of the imidazolium groups in the polymeric support participated in the formation of Pd complexes. This rather low loading of Pd, which occurred via the formation of Pd–NHC complexes, can be explained by the difficulty for the Pd metal to diffuse into the core of the polymeric support, with the result that the majority of the complex formed between the Pd and the imidazolium groups may be located within the surface layer of the polymeric support.

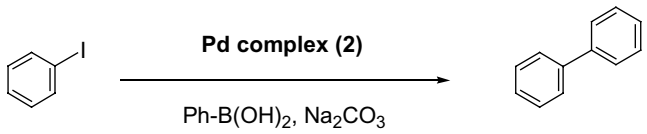
The catalytic activity of the polymer-supported Pd–NHC complexes (**2**) was investigated in detail for the Pd-catalyzed Suzuki cross-coupling of aryl halides with phenylboronic acid. To determine the optimal reaction conditions, the coupling of iodobenzene (0.5 mmol) and phenylboronic acid (0.6 mmol) as a model reaction was carried out using the polymer-supported Pd–NHC complexes (1.2 mol%) in aqueous solution of Na_2CO_3 (2.5 mmol).[12] We surveyed several kinds of reaction variables, such as the temperature and reaction time, in different solvents, and the results are summarized in Table 2.

Table 1. Swelling properties of the imidazolium-loaded polymeric supports (**1**)

Entry	Loading of imidazolium (mmol/g)[a]	Swelling volume in solvent (mL/g polymeric support)[b]						
		Dry	Water	MeOH	DMF	DCM	THF	Toluene
1	0.24[c]	1.6	2.0	2.1	5.4	6.3	5.8	5.6
2	1.12[d]	1.8	2.1	2.4	5.9	6.1	2.2	2.9
3	1.91[e]	1.8	4.2	7.4	5.2	4.6	2.5	2.8

[a] The loading of imidazolium was determined by means of the nitrogen content obtained from elementary analysis.
[b] The swelling volumes were measured by the protocol shown in Ref. 10.
[c] A mixture of CM PS resin (1.0 g, 1.1 mmol/g) and 1-methylimidazole (0.6 mmol, 50 μL) in NMP was reacted at 80 °C for 6 h.
[d] A mixture of CM PS resin (1.0 g, 1.1 mmol/g) and 1-methylimidazole (11.0 mmol, 880 μL) in NMP was reacted at 80 °C for 12 h.
[e] A mixture of CM PS resin (1.0 g, 2.3 mmol/g) and 1-methylimidazole (23.0 mmol, 1.8 mL) in NMP was reacted at 80 °C for 12 h.

Table 2. Suzuki cross-coupling of iodobenzene and phenylboronic acid with the polymer-supported Pd–NHC complex (**2**)[a]



Entry	Solvent	Temperature (°C)	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	Water	30	12	30.0	22.3
2	Water	50	3	33.4	25.8
3	Water	50	12	52.1	48.2
4	Water/DMF	30	3	34.4	30.5
5	Water/DMF	30	12	46.1	40.8
6	Water/DMF	50	3	89.6	85.1
7	Water/DMF	50	12	95.6	93.3
8[d]	Water/DMF	50	3	81.9	77.8
9[e]	Water/DMF	50	3	77.8	75.7

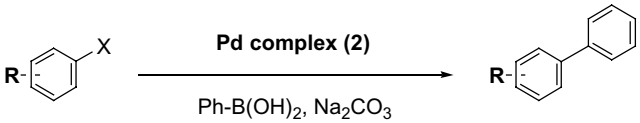
[a] All of the reactions were carried out with the mole ratio of Ph–I:Ph–$B(OH)_2$:Na_2CO_3:Pd = 0.5:0.6:2.5:0.006. The imidazolium loading of starting polymeric support was 1.91 mmol/g (Table 1, entry 3).
[b] The conversions of the starting iodobenzene were determined by GC–MS analysis using an internal standard.
[c] Isolation yields were calculated from the mass of the biphenyl product after separation by column chromatography.
[d] The repeat experiment with the polymeric support catalyst of entry 6 under the same conditions (the second use).
[e] The repeat experiment with the polymeric support catalyst of entry 8 under the same conditions (the third use).

First of all, the reaction in a co-solvent consisting of water and DMF showed better results than that in an aqueous only phase. Since the starting iodobenzene and the biphenyl product had poor solubility in water, the addition of DMF might be helpful to solve these solubility problems, and accelerate the reaction. In addition, a higher temperature (50 °C) and longer reaction time (12 h) were generally favorable to the reaction. However, when the reaction was carried out in water/DMF at 50 °C, the result obtained after 3 h was comparable to that obtained after 12 h (entries 6 and 7). Meanwhile, the catalytic activity of the recovered catalyst decreased slightly in its second and the third use under the same reaction conditions, due to partial Pd leaching (entries 8 and 9).

With an optimal protocol for the Suzuki cross-coupling reaction in hand, we next examined the combinatorial coupling of various aryl halides with phenylboronic acid in the aqueous phase. Eight kinds of aryl iodides and aryl bromides were subjected to the cross-coupling reaction in water/DMF (1:1, v/v) containing an excess of Na_2CO_3 at 50 °C for 12 h in the presence of the polymer-supported Pd–NHC complexes (1.2 mol %).[12]

As shown in Table 3, all the combinations of aryl halides and phenylboronic acid afforded satisfactory yields and excellent purities under the given conditions. On the whole, the relatively reactive aryl iodides showed better results than the aryl bromides. In the cross-coupling reactions of aryl iodides, the conversion of the starting and the isolated yield of the product were more than 90%. Especially, the cross-coupling reaction using iodophenol, which has a phenolic hydroxyl group, proceeded smoothly exhibiting tolerance toward the presence of other functional groups under these reaction conditions (entry 5).

Table 3. Combinatorial cross-couplings of aryl halide derivatives and phenylboronic acid with the polymer-supported Pd–NHC complex (**2**)[a]



Entry	R	X	Conversion (%)[b]	Yield (%)[c]
1	H	I	95.6	93.3
2	Me	I	91.9	90.7
3	OMe	I	91.8	90.2
4	COPh	I	99.9	98.0
5	OH	I	72.7	69.1
6	H	Br	93.0	90.3
7	Me	Br	81.9	80.2
8	OMe	Br	70.8	68.5

[a] All of the reactions were carried out with the mole ratio of Ph–I:Ph–$B(OH)_2$:Na_2CO_3:Pd = 0.5:0.6:2.5:0.006 in water/DMF (1:1, v/v) at 50 °C for 12 h. The imidazolium loading of starting polymeric support was 1.91 mmol/g (Table 1, entry 3).
[b] The conversions of the starting iodobenzene were determined by GC–MS analysis using an internal standard.
[c] Isolation yields were calculated from the mass of the product after separation by column chromatography. All of the isolated products showed more than 99% of GC purity.

In summary, the polymer-supported Pd–NHC complex was prepared from CM PS resin using a simple procedure, and the complexes formed between the Pd metal and the imidazolium of the polymeric support resulted in the formation of the Pd–NHC complexes under aqueous basic conditions. The high activity of the Pd–NHC complexes on the polymeric support provided satisfactory yields and excellent purities from the Suzuki cross-coupling reactions in the aqueous phase. This heterogeneous Pd catalyst can be used as a promising

system for the combinatorial synthesis of substituted aromatics. More detailed investigations of different protocols, which can be used for Pd loading and measurements of the catalytic activity of further cross-coupling reactions, are in progress.

Acknowledgements

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8. A typical procedure for the preparation of an imidazolium-loaded polymeric support (**1**). The imidazolium-loaded polymeric support (**1**) was prepared from commercially available chloromethyl polystyrene (CM PS) resin cross-linked with 1% DVB (100–200 mesh, BeadTech Inc.). A mixture of CM PS resin (1.0 g, 2.3 mmol Cl/g polymeric support) and 1-methylimidazole (1.8 mL, 23.0 mmol) in NMP (100 mL) was slowly agitated at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered, and the polymeric support was washed with NMP (20 mL × 3), 0.1 N aq HCl (20 mL × 3), and methanol (20 mL × 3), followed by drying under reduced pressure to give **1**. The loading of the imidazolium groups was determined by means of the nitrogen content obtained from elementary analysis.
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10. A typical procedure for measuring the swelling properties of the imidazolium-loaded polymeric supports (**1**). The swelling volumes of the imidazolium-loaded polymeric support in various solvents were measured in a fritted column (ID 0.8 cm, length 20 cm). The polymeric support (1.0 g) was swollen in a solvent at room temperature for 30 min, and then washed with a 10-fold volume of each solvent. After filtering out the solvent, the volume of the polymeric support was measured.
11. A typical procedure for preparing the polymer-supported Pd–NHC complexes (**2**) with the imidazolium-loaded polymeric support (**1**). A mixture of the imidazolium-loaded polymeric support **1** (100 mg, 1.91 mmol/g) and $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) was suspended in DMF (2 mL). To this suspension was added an aqueous solution (2 mL) of Na_2CO_3 (106 mg, 1.0 mmol). The mixture was sonicated at room temperature for 30 min, and then agitated for 2 h at 50 °C in a shaking incubator. After filtration, the polymeric support was washed vigorously with distilled water (10 mL × 5), MeOH (10 mL × 5), and dried under reduced pressure to give **2**. To measure the amount of Pd loaded on the polymeric support, the polymeric support (10 mg) was treated with a mixture (5 mL) of hydrochloric acid and nitric acid (1:1, v/v) at room temperature for 30 min. After the orange-colored solution was filtered, the polymeric support was washed with distilled water (2.5 mL × 2), and then, the filtrate and the washing solution were combined to determine the amount of Pd by inductively coupled plasma-atomic emission spectrometry (ICP-AES).
12. A typical procedure for Pd-catalyzed Suzuki cross-coupling in the aqueous phase (Table 2, entry 7). The polymer-supported Pd–NHC complex **2** (20 mg, 5.8 μmol Pd) was suspended with DMF (2 mL). After a mixture of iodobenzene (57 μL, 0.5 mmol), phenylboronic acid (75 mg, 0.6 mmol), and Na_2CO_3 (265 mg, 2.5 mmol) in distilled water (2 mL) was added, the reaction mixture was agitated in a shaking incubator at 50 °C for 12 h. The coupling reactions were carried out under an air atmosphere. The reaction mixture was filtered and washed with distilled water (4 mL × 5) and diethyl ether (4 mL × 5). After the organic portion was separated and dried over Na_2SO_4 followed by evaporation under reduced pressure, the conversion of the starting iodobenzene was determined by GC–MS analysis with an appropriate internal standard (anisole). The chemical identification of the product was performed by GC–MS from the mass database library (WILEY 275), showing good similarity (>95%) with authentic data. After the biphenyl product was isolated by column chromatography (eluent; *n*-hexane), the isolation yield was calculated from the mass of the product (71.9 mg, 93.3% yield), and the purity of the isolated product was determined by GC analysis (99.5% GC purity).