An Active and Recyclable Polystyrene-Supported N-Heterocyclic Carbene–Palladium Catalyst for the Suzuki Reaction of Arylbromides with Arylboronic Acids under Mild Conditions

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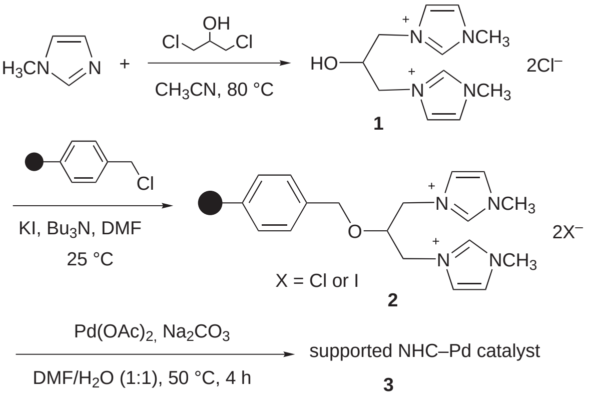
Abstract: A novel polymer-supported imidazolium salt has been prepared from a bisimidazolium salt and cross-linked chloromethyl polystyrene. The polymer-supported N-heterocyclic carbene–palladium complex, generated from the supported bisimidazolium salt and Pd(OAc)$_2$, efficiently catalyzed the Suzuki coupling reaction of aryl bromides and arylboronic acids under air in aqueous DMF solution at room temperature, giving biaryls in good to excellent yields. The catalyst could be reused several times still retaining high activity.

Key words: Suzuki reaction, N-heterocyclic carbene–palladium complex, polymer-supported catalyst, recyclable catalyst

Suzuki cross-coupling reaction is one of the most efficient, popular, and convenient methods for synthesizing unsymmetrical biaryls.[1] As the biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products as well as in conducting polymers and liquid crystalline materials, development of new efficient ligands and improved conditions for Suzuki reaction has received much attention.[2] Due to their versatile processing capabilities, ease of separation and recycling, polymer-supported catalysts offer many advantages for industrial applications. Many immobilized Pd catalysts based on polymer-supported phosphine or amine ligands have been developed for Suzuki reaction.[3] However, the activity of those catalysts decreased in recycling experiments because of Pd leaching from their supports. Generally, mild conditions and strong interactions between Pd and ligands are in favor of avoiding Pd leaching.

In recent years, the stable N-heterocyclic carbene (NHC) complexes of Pd^{II} or Pd^0 have been used as catalysts for Suzuki reactions.[4] In contrast to the widely used phosphine complexes,[5] they have shown remarkable stability towards heat, oxygen and moisture, and represent a remarkable improvement with respect to the catalytic activity. The NHC ligands bind to both Pd^0 and Pd^{II} centers substantially stronger than phosphine ligands, and are highly suitable for attachment to solid supports owing to anticipated low level of metal leaching.[6] So far, only a few examples of heterogeneous catalysts by anchoring NHC–Pd complexes for Suzuki reaction have been reported.[7] Zhang's group[7a] has recently reported a SiO$_2$-supported NHC–Pd catalyst that could only be used for 2–3 times since the NHC–Pd complex was physically absorbed on solid surface. The polymer-supported NHC–Pd catalysts developed by Lee's group required heating condition and more active aryliodide as substrate in most cases, and the reuse of those catalysts was not satisfactory. Herein, we report an active polystyrene-supported NHC–Pd catalyst that enables the Suzuki couplings of aryl bromides and arylboronic acids at room temperature without the need of inert gas protection. The catalyst showed outstanding stability in air, water and organic solvents, and was reused five times still retaining high activity.



Scheme 1 Preparation of the polystyrene-supported NHC–Pd catalyst **3**

Our work focused on the use of an ether linkage to attach the bisimidazolium salt **1** to the Merrifield resin (2% cross-linked with divinylbenzene, 100–200 mesh size, 2.7 mmol Cl/g; Scheme 1). The bisimidazolium salt **1** was prepared in 60% yield by heating one equivalent of 1,3-dichloro-2-propanol and two equivalents of 1-methylimidazole in MeCN at 80 °C for four days.[8] The polystyrene-supported bisimidazolium salt **2** was readily prepared by reacting **1** with chloromethyl polystyrene in the presence of KI.[9] The loading of the imidazolium groups was determined by means of the nitrogen content obtained from elementary analysis (N, 1.4%, 0.5 mmol imidazolium/g).

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The polystyrene-supported NHC–Pd catalyst **3** was produced by mixing $Pd(OAc)_2$ and **2** in DMF–H_2O (1:1, v/v) with Na_2CO_3 as the base at 50 °C for 4 hours.[10] The Pd loading was 0.1 mmol/g as measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES) suggesting only partial imidazolium groups in the support participated in the formation of NHC–Pd complex. It is not clear whether both of the imidazolium groups in each bisimidazolium salt took part in the formation of NHC–Pd complex.

The swelling properties of the polystyrene-supported bisimidazolium salt **2** and the catalyst **3** in various solvents were measured (Table 1).[11] The swelling studies are important for identifying the suitable reaction medium to perform reaction on polymer supports. As can be seen from Table 1, the polymeric supports have high swelling volumes in water, MeOH and DMF. In these solvents, the catalyst **3** would be able to capture reagents easily, and higher efficiency of the catalytic cycle would be reached.

Table 1 Swelling Properties of the Polymer-Supported Bisimidazolium Salt **2** and the Catalyst **3**

Polymeric support	Swelling volume in solvent (mL/g polymeric support)						
	Dry	H_2O	MeOH	DMF	CH_2Cl_2	THF	Dioxane
2	1.8	4.0	4.4	5.0	3.5	2.3	2.9
3	1.8	4.0	4.4	5.0	3.5	2.3	2.9

The catalytic activity of the polymer-supported NHC–Pd catalyst **3** was investigated by coupling 4-bromoanisole and phenylboronic acid.[12] As illustrated in Table 2, the presence of water appears to be essential in order to perform the reactions (entries 7–14). The conversion of 4-bromoanisole was very low when DMF, dioxane or water each was used as solvent (entries 1–6). Among the solvents tested, the DMF–water (v/v 1:1) gave the best result, which is likely attributed to the better solubility of both the reactants and the base in the co-solvent.

Several bases were examined to indicate the base effect on the reaction. It seems that carbonate bases are more effective in activating the palladium catalyst. No detectable coupling products were observed when NaOH was used as a base (entry 3). When the reaction was carried out in DMF–water (v/v 1:1), both Na_2CO_3 and K_2CO_3 gave excellent yields (entries 9, 10, 12–14). Higher yields were observed by prolonging the reaction time (entries 12–14). The product formation was almost quantitative after 24 hours (entry 14).

The recycling of the catalyst **3** was also investigated for the reaction of 4-bromoanisole with phenylboronic acid (Table 3). The catalyst **3** was stable to air and moisture, and the reactions could be carried out under air by using technical grade solvents. After separation and washing, the catalyst was reused under the same reaction conditions as for the initial run without any need for regeneration. The catalyst **3** was used 5 times and still remained highly active.

Table 2 Coupling of 4-Bromoanisole and Phenylboronic Acid Catalyzed by **3**[a]

Entry	Solvent (v:v)	Base	Time (h)	Yield (%)[b]
1	DMF	Na_2CO_3	12	23
2	DMF	K_2CO_3	12	21
3	DMF	NaOH	12	0
4	DMF	Na_3PO_4	12	20
5	Dioxane	Na_2CO_3	12	13
6	H_2O	Na_2CO_3	12	24
7	DMF–H_2O (2:1)	Na_2CO_3	12	79
8	DMF–H_2O (1:2)	Na_2CO_3	12	75
9	DMF–H_2O (1:1)	Na_2CO_3	12	88
10	DMF–H_2O (1:1)	K_2CO_3	12	87
11	DMF–H_2O (1:1)	Na_3PO_4	12	75
12	DMF–H_2O (1:1)	Na_2CO_3	16	93
13	DMF–H_2O (1:1)	Na_2CO_3	20	96
14	DMF–H_2O (1:1)	Na_2CO_3	24	99

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.6 mmol), base (2.5 mmol), solvent (4 mL), catalyst **3** (20 mg, 2 μmol Pd), r.t.

[b] Isolated yields were based on bromide.

Table 4 summarizes the coupling of different arylboronic acids with various arylbromides catalyzed by catalyst **3**. The results reveal the wide scope of this method that is compatible with nitro, methoxy, trifluoromethyl, and carbonyl in bromides. It was observed that bromides with electron-rich groups to electron-poor groups reacted efficiently affording the corresponding products in high yields. Arylboronic acids with *ortho* substituents led to lower, but still good yields (entries 15–17).

It is noteworthy that all crossing-coupling reactions listed in Table 2, Table 3 and Table 4 were carried out under air and no visible palladium black formation was observed during the course of the reaction.

Table 3 Recycling of the Catalyst **3**[a]

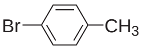
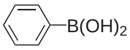
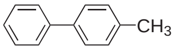
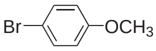
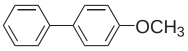
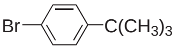
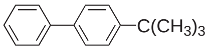
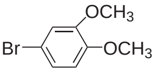
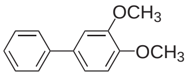
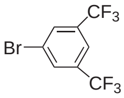
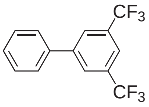
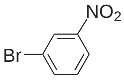
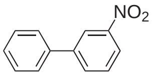
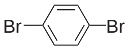
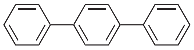
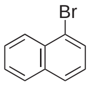
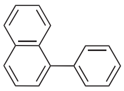
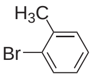
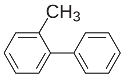
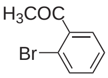
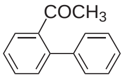
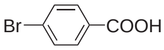
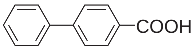
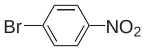
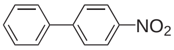
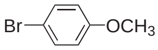
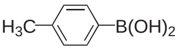
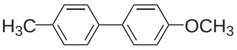
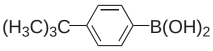
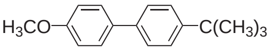
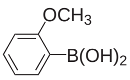
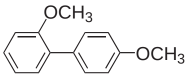
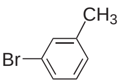
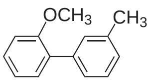
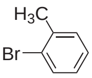
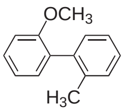
Run	1	2	3	4	5
Yield (%)[b]	99	96	95	95	94

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.6 mmol), catalyst **3** (20 mg, 2 μmol Pd), Na_2CO_3 (2.5 mmol), DMF (2 mL), H_2O (2 mL), r.t., 24 h.

[b] Isolated yields were based on bromide.

In conclusion, we have developed an active, reusable polymer-supported NHC–Pd catalyst prepared from $Pd(OAc)_2$ and the polystyrene-supported bisimidazolium salt **2**. The catalyst was highly active in catalyzing the Suzuki reaction of aryl bromides with arylboronic acids affording biaryls in high yields. The Suzuki reaction was carried out under extremely mild conditions: room temperature, aqueous DMF solution, Na_2CO_3 as the base, and without the need of inert gas protection. Using very low catalyst loading, the catalyst **3** could be reused several times still retaining its activity.

Table 4 Coupling Reactions of Various Arylbromides with Different Arylboronic Acids Catalyzed by Polystyrene-Supported NHC–Pd Catalyst **3**[a]

Entry	Arylbromide	Arylboronic acid	Product	Yield (%)[b]
1				98
2				99
3				97
4				95
5				94
6				73
7				89
8				87
9				97
10				73
11				98
12				92
13				99
14				97
15				85
16				85
17				77

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[a] Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), catalyst **3** (20 mg, 2 mmol Pd), Na_2CO_3 (2.5 mmol), DMF (2 mL), H_2O (2 mL), r.t., 24 h.

[b] Isolated yields were based on bromide.

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(8) **Procedure for the Preparation of the Bisimidazolium Salt 1.**
In a dry nitrogen atmosphere, a mixture of 1,3-dichloro-2-propanol (1.29 g, 10 mmol) and 1-methylimidazole (1.72 g, 21 mmol) was stirred in MeCN (20 mL) at 80 °C for 4 d in an oil bath. The solvent was removed completely under vacuum. Then, CH_2Cl_2 was added to the residue to give a white solid, which was filtered and dried under vacuum affording the salt **1** in 60% yield. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.88 (s, 6 H, NC*H*$_3$), 4.20 (m, 1 H, C*H*OH), 4.22–4.51 (br, 4 H, NC*H*$_2$), 7.79 (s, 2 H, NC*H*), 7.87 (s, 2 H, NC*H*), 9.36 (s, 2 H, NC*H*N). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 36.23 (N*C*H$_3$), 52.17 (*C*HOH), 68.21 (N*C*H$_2$), 123.44 (N*C*H), 123.77 (N*C*H), 137.74 (N*C*HN). HRMS (ESI): *m/z* calcd for $C_{11}H_{18}Cl_2N_4O$ [M – 2Cl]$^{2+}$: 111.0741; found: 111.0729.

(9) **Procedure for the Preparation of Polystyrene-Supported Bisimidazolium Salt 2.**
A mixture of Merrifield polymer (200 mg 2.7 mmol Cl/g), KI (30 mg, 0.18 mmol), tributylamine (0.3 g, 1.62 mmol) and the bisimidazolium salt **1** (158 mg, 0.54 mmol) dissolved in DMF (10 mL) was stirred for 4 d at r.t. The polymer was filtered off and washed with DMF (6 × 10 mL), MeOH (6 × 10 mL), H_2O (6 × 10 mL), and then dried under vacuum. The loading of the imidazolium groups was determined by means of the nitrogen content obtained from elemental analysis (N, 1.4%, 0.5 mmol imidazolium/g).

(10) **Procedure for the Preparation of Polystyrene-Supported NHC–Pd Complex 3.**
In a dry nitrogen atmosphere, a mixture of the imidazolium loaded polymeric support **2** (200 mg, 0.5 mmol imidazolium/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 stirred at r.t. for 30 min, and then agitated for 4 h at 50 °C in an oil bath. After filtration, the polymeric support was washed vigorously with distilled H_2O (10 × 10 mL), MeOH (10 × 10 mL), and dried under reduced pressure to give **3**. ICP-AES: 100 μmol Pd/g.

(11) **Procedure for Measuring the Swelling Properties of the Polystyrene-Supported Bisimidazolium Salt 2 and the Catalyst 3.**
The swelling volumes of polymeric supports 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 r.t. for 2 h, and then washed with a 10-fold volume of each solvent. After filtration, the volume of the polymeric support was measured.

(12) **Representative Procedure for Suzuki Reaction (Table 2, Entry 14).**
The catalyst **3** (20 mg, 2 μmol Pd) was suspended with DMF (2 mL). After a mixture of 4-bromoanisole (63 μL, 0.5 mmol), phenylboronic acid (75 mg, 0.6 mmol), and Na_2CO_3 (265 mg, 2.5 mmol) in distilled H_2O (2 mL) was added, the reaction mixture was stirred at r.t. for 24 h without the protection of inert gas. The catalyst was filtered and washed with distilled H_2O (5 × 4 mL) and Et_2O (5 × 4 mL), and dried in vacuo for use in the next run. The organic portion was dried over $MgSO_4$ and evaporated under reduced pressure. The biphenyl product (91 mg, yield 99%) was isolated by column chromatography (eluent: *n*-hexane).