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# The Cross-Coupling Reaction of Arylboronic Acids with Chloropyridines and Electron-Deficient Chloroarenes Catalyzed by a Polymer-Bound Palladium Complex

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**Abstract**—The cross-coupling reaction of tolylboronic acids (1.3 equiv.) with chloropyridines, chloroquinoline, or activated chloroarenes having an electron-withdrawing group was carried out in toluene at 80°C in the presence of a polymer-bound $PdCl_2$ catalyst (3 mol%) and aqueous 2 M $K_3PO_4$ (2.6 equiv.). The palladium–phosphine complex supported on a polystyrene–$PPh_2$ resin was reused with no significant decrease in activity. 

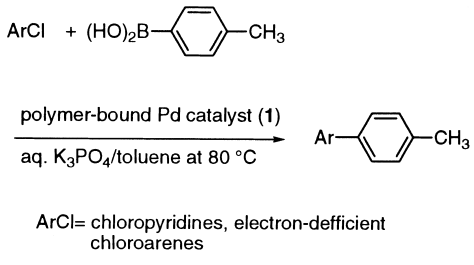
## Introduction

Both palladium and nickel complexes catalyze the cross-coupling reaction of arylboronic acids with haloarenes to yield biaryls.[1] However, the nickel-catalyzed cross-coupling reaction of arylboronic acids has an advantage over that using palladium/phosphine catalysts because of their high catalyst activity for aryl chlorides[2] and mesylates,[3] and the economy which does not require recycling of the catalyst. Thus, the biaryl coupling of arylboronic acids by using $NiCl_2$(dppf) or $NiCl_2(PPh_3)_2$ in the presence of $K_3PO_4{\cdot}nH_2O$ was recently developed for a large-scale synthesis not only in industry but also in the laboratory.[2] However, 2-chloropyridine and its derivatives strongly reluctant to the nickel-catalyzed coupling, presumably due to chelation of the nitrogen atom to the nickel(II) metal center, though the palladium–phosphine complexes catalyze the reaction efficiently.[4] The polymer-bound palladium complexes are a new class of catalyst designed to solve the basic problems of homogeneous catalysts, namely, the separation and recycling of the catalysts.[5] These catalysts are also advantageous in as much as contamination of the phosphine ligand to the products is avoided. The palladium complex supported on polystyrene resin has indeed achieved excellent results in the cross-coupling of arylboronic acids with iodo- and bromoarenes.[6] The phosphine supported on a graft copolymer of styrene and ethylene glycol is another ligand efficient in a single aqueous media, which can be recovered from the reaction mixture and reused with no decrease in activity.[7]Although cross-coupling reaction of arylboronic acids catalyzed by a polystyrene-bound palladium complexes was previously studied by Zhang[6a] and Drian[6b] for the synthesis of biaryls from iodo- and bromoarenes, we reinvestigated the efficiency of the catalyst in the reaction with chloropyridines, their derivatives, and activated chloroarenes having an electron-withdrawing group (Scheme 1).

## Results and Discussion

### Reaction conditions

The palladium catalyst was prepared by the reported procedures (Scheme 2).[7,8] The chloromethylation of 1% cross-linked polystyrene with $ClCH_2OCH_3/SnCl_4$,[8] followed by the substitution with $LiPPh_2$[9] gave a polystyrene–diphenylphosphine ligand (**4**) with a 2.86 mmol/g phosphine incorporation. Stirring a mixture of **4** and $PdCl_2$(cod) (P/Pd=9.53) in benzonitrile at 100°C for 3 h provided an air-stable, bright yellow resin of polystyrene–$PdCl_2$ complex (**1**). Judging from the disappearance of yellow color of the palladium complex and elemental analysis, $PdCl_2$ was quantitatively supported on the resin. The




**Scheme 1.** Biaryl coupling of arylboronic acids with chloroarenes catalyzed by polymer-bound palladium complex.

*Keywords*: coupling reactions; boron compounds; biaryl; polymer support.
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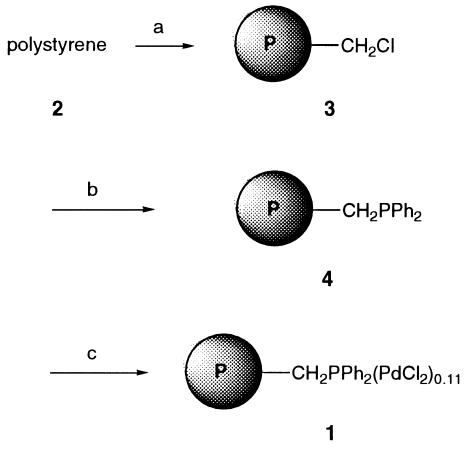



**Scheme 2.** Polymer-bound $PdCl_2$ catalyst.

elemental analysis of **1** revealed that the resin contains 2.32 mmol/g of P and 0.256 mmol/g of Pd. On the other hand, the addition of $Pd(PPh_3)_4$, $Pd(dba)_2$, or $PdCl_2(PPh_3)_2$ to the resin in toluene at 80°C for 24 h[6a] was unsuccessful due to incomplete complexation to the resin, precipitation of palladium-black, or contamination of triphenylphosphine in the resin.

The effects of the base, solvent, and reaction time on the yields of the coupling reaction of tolylboronic acid with 2-chloropyridine at 80°C are summarized in Table 1.

The reactions were very slow in polar solvents such as $CH_3CN$ and DMF, alcohols, and ethers (entries 1–4), but it was interesting that the reaction was faster in a heterogeneous three-phase system using toluene, an aqueous base, and a solid polymer-bound catalyst (entries 5–8). $K_3PO_4$ gave better results than $Na_2CO_3$, but NaOH resulted in a low yield, presumably due to the side-reaction yielding 2-hydroxypyridine[10] (entries 5, 7 and 9). The $PdCl_2$ supported on the resin was in situ reduced to the corresponding palladium(0) complex during heating the mixture at 80°C, analogously to other cross-coupling reactions of organoboron compounds. This process may involves a double transmetalation of arylboronic acid to the $PdCl_2$ complex, leading to a Pd(0)/phosphine complex and a biaryl or the displacement of the Pd–Cl bond with a base leading to a Pd(0)/phosphine complex, $O{=}PPh_3$, and two $Cl^-$.[11] Thus, the palladium(0) catalyst obtained by the reduction of **1** with $NH_2NH_2$ afforded essentially the same results to those obtained with the direct use of palladium(II) complex **1** without treatment.

**Table 1.** Reaction conditions for the coupling of 2-chloropyridine with 4-tolylboronic acid (all reactions were carried out at 80°C in the presence of 2-chloropyridine (1.0 mmol), 4-tolylB$(OH)_2$ (1.3 mmol), a base (2 M solution in $H_2O$, 2 mmol), and a catalyst (**5**, 3 mol%) in a solvent (5 ml))

| Entry | Base | Solvent | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 2 M $Na_2CO_3$ | $CH_3CN$ | 16 | 30 |
| 2 | 2 M $Na_2CO_3$ | DMF | 16 | 50 |
| 3 | 2 M $Na_2CO_3$ | EtOH | 16 | 50 |
| 4 | 2 M $Na_2CO_3$ | DME | 16 | 40 |
| 5 | 2 M $Na_2CO_3$ | toluene | 16 | 58 |
| 6 | 2 M $K_3PO_4$ | toluene | 9 | 51 |
| 7 | 2 M $K_3PO_4$ | toluene | 16 | 87 |
| 8 | 2 M $K_3PO_4$ | toluene | 24 | 88 |
| 9 | 2 M NaOH | toluene | 16 | 43 |

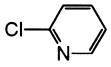
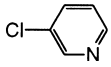
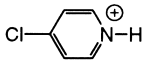
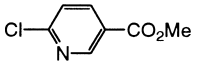
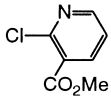
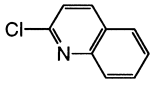
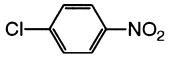
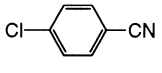
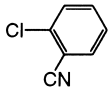
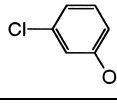
[a] GC yields.

## Scope and limitation

The synthesis of biaryls via the cross-coupling reaction of the representative chloropyridines, its derivatives, and activated chloroarenes having an electron-withdrawing group is summarized in Table 2.

The coupling to 3-chloropyridine resulted in a slightly reduced yield, but almost quantitative conversions and yields were achieved for 2-chloropyridine and 4-chloropyridine when the mixture was heated at 80°C for 24 h in the presence of 3 mol% of the catalyst (entries 1–3). The complete separation of the organic and basic phases using toluene and aqueous $K_3PO_4$ allowed the coupling of chloronicotinic esters without saponification of the ester group (entries 4 and 5). The reaction was accompanied with less than 1% of bitolyl, but filtration of the catalyst followed by evaporation of the solvent yielded almost pure biaryls since

**Table 2.** Biaryl coupling (Scheme 1) (all reactions were carried out in toluene (5 ml) at 80°C for 24 h in the presence of ArCl (1.0 mmol), 4-tolylB$(OH)_2$ (1.3 mmol), aq. $K_3PO_4{\cdot}nH_2O$ (2 M in $H_2O$, 2 mmol), and a catalyst (**1**, ca. 3 mol%))

| Entry | ArCl | Yield[a] (%) |
|---|---|---|
| 1 |  | 91 |
| 2 |  | 72 |
| 3 |  | 90[b] |
| 4 |  | 92 |
| 5 |  | 90 |
| 6 |  | 91 |
| 7 |  | 89 |
| 8 |  | 89 |
| 9 |  | 91 |
| 10 |  | 35 |

[a] Isolated yields.
[b] The base (3 mmol) was used.

neither the phosphine ligand nor the palladium metal was contaminated in the products. Both nickel(II) complexes[2] and palladium complexes catalyze the coupling reaction of 2-chloroquinoline, but palladium catalysts may give more reliable results (entry 6). The palladium complexes catalyze the coupling reaction of activated chloroarenes having an electron-withdrawing groups, which have been successfully used in the industrial-scale synthesis of *o*-tolylbenzonitrile.[12] The polymer-bound catalyst also achieved quantitative conversions for 4-chloronitrobenzene, 4-chlorobenzonitrile, and 2-chlorobenzonitrile (entries 6–8). However, all attempts at the coupling with more electron-rich chloroarenes were unsuccessful due to their slow oxidative addition to palladium(0) complex (entry 10).[13]

The resin catalyst was easily recovered by filtration in air and reused for the next coupling reaction of with 2-chloropyridine. The yellow catalyst changed to a gray resin during the repeated use, but high yields in a range of 86–96% were reproducible by the recovered catalyst in 6 repeated runs.

## Experimental

### Reagents

Polystyrene cross-linked with 1% of divinylbenzene (Bio-Beads SX-1, 200–400 mesh) was purchased from Bio-Rad Laboratories. 4-Tolylboronic acid and chloroarenes were commercially available. $K_3PO_4{\cdot}nH_2O$ ($n$=2–3) from Nakalai Tesque Co. was used directly.

### Polystyrene ligand (4)

The polymer ligand was synthesized following by the literature procedures. The reaction of 1% cross-linked polystyrene beads (Bio-Beads SX-1, 200–400 mesh) (45 g) and chloromethyl methyl ether (225 ml) in the presence of $SnCl_4$ (5 ml) at room temperature for 30 min, followed by 2 h at the refluxing temperature afforded **3** (64 g).[8] To the suspension of the above beads **3** (8.7 g) in THF (300 ml) was added $Ph_2PCl$ (25 g) and lithium sliced to a small pieces (1.8 g), and the mixture was then stirred for 20 h at room temperature.[9] The beads thus obtained was filtered and successively washed with methanol, $CHCl_3$/methanol (2/3, 3/1, and 9/1), and finally with pure chloroform. The beads were dried in vacuo (0.1 mm Hg) under nitrogen at 100°C for 6 h to give the (diphenylphosphinomethyl)polystyrene **4**. The beads thus obtained weighted 16.84 g. After the decomposition of the resin with acid ($H_2SO_4/HNO_3$), phosphine and palladium were determined by ICP-AES. The analysis showed that the beads contains 2.86 mmol/g (8.85 wt.%) of phosphine.

### Catalyst (1)

A mixture of **4** (2 g, 5.72 mmol of $Ph_2P$ group on the resin) and $PdCl_2$(cod) (0.172 g, 0.6 mmol) in benzonitrile (30 ml) was heated to 100°C for 3 h under nitrogen. The yellow color of solution faded completely to yield a bright yellow beads. The beads were filtered, washed with acetone (20 ml×6), $CH_2Cl_2$ (20 ml×5), and ether (20 ml×3), and finally freed of traces of solvent for 5 h at 60°C in vacuo. Elemental analysis of the resin by ICP-AES: C, 75.1; H, 5.9; P, 7.2; Pd, 2.7.

### Synthesis of biaryls (Table 2)

The cross-coupling reaction of 2-chloropyridine with 4-tolylboronic acid is representative. A flask equipped with a condenser, a septum inlet, and a mechanical stirrer was charged with a polymer-supported palladium catalyst (**1**, 0.10 g, 2.47 mmol of $PdCl_2$ on the resin) and 4-tolylboronic acid (0.177 g, 1.3 mmol) and was flushed with nitrogen. Toluene (3 ml), 2-chloropyridine (0.114 g, 1.0 mmol), and 2 M $K_3PO_4$ in $H_2O$ (1.0 ml, 2 mmol) were added. The resulting mixture was then stirred for 24 at 80°C. Chromatography over silica gel gave 2-(4-methylphenyl)-pyridine (91%) as a pale yellow liquid; IR (Nujol) 1590, 1560 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$); $\delta$ 2.40 (s, 3H), 7.20 (dd, $J$=4.8, 6.6 Hz, 1H), 7.27 (d, $J$=8.3 Hz, 2H), 7.67–7.72 (m, 2H), 7.88 (d, $J$=8.3 Hz, 2H), 8.67 (d, $J$=4.8 Hz, 1H); MS $m/z$ 77 (5), 78 (6), 83 (14), 91 (11), 154 (10), 169 ($M^+$, 100); exact mass calcd for $C_{12}H_{11}N$ 169.0891, found 169.0891.

The following biaryls were prepared by the above general procedure, unless otherwise noted.

**3-(4-Methylphenyl)pyridine.** IR (Nujol) 1550 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.41 (s, 3H), 7.29 (d, $J$=8.1 Hz, 2H), 7.34 (dd, $J$=4.9, 7.9 Hz,), 7.48 (d, $J$=8.1 Hz, 2H), 7.85 (d, $J$=7.9 Hz, 1H), 8.57 (d, $J$=4.9 Hz, 1H), 8.84 (s, 1H); MS $m/z$ 91 (2), 154 (6), 169 ($M^+$, 100); exact mass calcd for $C_{12}H_{11}N$ 169.0891, found 169.0875.

**4-(4-Methylphenyl)pyridine.** IR (Nujol) 1600, 1540 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.42 (s, 3H), 7.30 (d, $J$=8.1 Hz, 2H), 7.50 (d, $J$=5.1 Hz, 2H), 7.55 (d, $J$=8.1 Hz, 2H), 8.64 (d, $J$=5.1 Hz, 2H); MS $m/z$ 91 (2), 154 (3), 169 ($M^+$, 100); exact mass calcd for $C_{12}H_{11}N$ 169.0891, found 169.0876.

**5-Methoxycarbonyl-2-(4-methylphenyl)pyridine.** IR (Nujol) 1730, 1290, 1110 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.42 (s, 3H), 3.97 (s, 3H), 7.31 (d, $J$=8.1 Hz, 2H), 7.79 (d, $J$=8.3 Hz, 1H), 7.96 (d, $J$=8.1 Hz, 2H), 8.32 (dd, $J$=1.9, 8.3 Hz, 1H), 9.26 (d, $J$=1.9 Hz, 1H); MS $m/z$ 77 (1), 91 (1), 168 (13), 196 (59), 227 (100); exact mass calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0941.

**3-Methoxycarbonyl-2-(4-methylphenyl)pyridine.** IR (Nujol) 1740, 1560, 1540, 1280, 1130 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.40 (s, 3H), 3.72 (s, 3H), 7.24 (d, $J$=7.9 Hz, 2H), 7.30 (dd, $J$=4.7, 7.8 Hz, 1H), 7.45 (d, $J$=7.9 Hz, 2H), 8.07 (dd, $J$=7.8, 1.8 Hz, 1H), 8.76 (dd, $J$=1.8 and 4.7 Hz, 1H); 167 (11), 196 (11), 212 (100), 227 (19); exact mass calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0940.

**2-(4-Methylphenyl)quinoline.** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.44 (s, 3H), 7.33 (d, $J$=8.1 Hz, 2H), 7.49–7.53 (m, 1H), 7.70–7.74 (m, 1H), 7.81 (d, $J$=8.1 Hz, 1H), 7.86 (d, $J$=8.5 Hz, 1H), 8.07 (d, $J$=8.1 Hz, 2H), 8.16 (d, $J$=8.5 Hz, 1H), 8.20 (d, $J$=8.5 Hz, 1H); Ms $m/z$ 95 (5),

109 (6), 204 (7), 219 ($M^+$, 100), 220 (18); exact mass calcd for $C_{16}H_{13}N$ 219.1048, found 219.1049.

The synthesis of 4-(4-methylphenyl)nitrobenzene, 4-(4-methylphenyl)benzonitrile, 2-(4-methylphenyl)benzonitrile, and 3-(4-methylphenyl)anisole was previously reported.[2b]

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