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Efficient Recycling in Suzuki–Miyaura Reactions of Aryl Chlorides with Arylboronic Acids using Polymer-Supported Aryldicyclohexylphosphine

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Abstract: The synthesis of polymer-supported aryldicyclohexylphosphines has been developed. The catalytic performance of these ligands has been demonstrated in the Suzuki–Miyaura cross-coupling reaction of aryl chlorides with arylboronic acids. Concerning the recycling of the catalyst, the ligand based on copolymer polyethylene glycol/polystyrene showed a very high activity which was maintained during 6 runs.

Keywords: aryl chlorides; catalyst recycling; cross-coupling; phosphane ligands; polymer supports; Suzuki–Miyaura reaction

Introduction

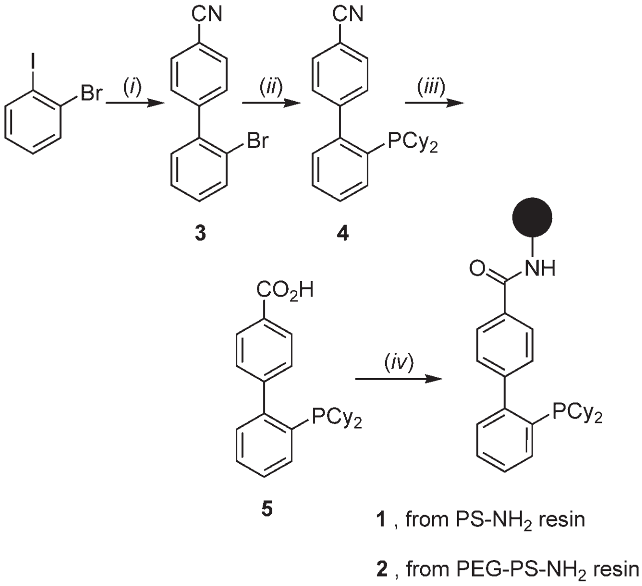
Biaryl derivatives constitute important building blocks for the synthesis of pharmaceuticals, herbicides, polymers, materials, liquid crystals and ligands, with some applications being extended on an industrial scale.[1] One of the most important routes for the preparation of biaryl compounds is certainly the palladium-catalyzed cross-coupling reactions between aryl halides and arylboronic acids, the so-called Suzuki–Miyaura reaction.[2] In recent years, the main effort has been focused on the development of efficient recycling catalyst systems. In the industrial field, one possibility is to use immobilized catalysts, which offer more environmentally benign protocols, and simplified experimental parts can be considered using heterogeneous catalysts. Many approaches to heterogenic a homogeneous catalyst have been published.[3] In heterogenised systems using organic or inorganic supports, there are several ways for the binding of the ligand: physisorption or entrapment, adsorption, ion pair formation, or covalent binding. The last one offers many advantages, the main one being in that of avoiding leaching.

Many anchored Pd catalysts based on polymer-supported mono- or diphosphine,[4] olefin,[5] salen[6] or N-heterocyclic carbene[7] have been described. Generally, the yields in the cross-coupling reactions between aryl iodides or aryl bromides with arylboronic acids are higher than 90%. When aryl iodides or aryl bromides were used, the catalyst could be recycled over 10 and 5 times, respectively, without loss of activity. Due to their low cost and ready accessibility, aryl chlorides are more interesting substrates from the industrial point of view. However, their reactivities are lower than those of aryl bromides, and the key to their successful coupling is the use of electron-rich and sterically hindered phosphines.[8] Only few examples of such phosphines based on an organic polymer are described in the literature. Miyaura[9] described one of the first cross-coupling reaction between activated chloroarenes or chloropyridine derivatives and 4-tolylboronic acid using a polystyrene-PPh_2 as ligand. Buchwald[10] presented Merrifield resin-supported dicyclohexylphosphinobiphenyl ligands used in the Suzuki–Miyaura reactions between some aryl chlorides and arylboronic acids. However, in the latter case, the catalyst recycling was studied using only aryl bromides. The Suzuki–Miyaura coupling-recycling experiments using aryl chlorides has been described by Plenio,[11] who used soluble monomethyl polyethylene glycol (MeOPEG)-tagged palladium phosphine complexes.

In this paper, we describe the synthesis of aryldicyclohexylphosphine supported on polystyrene (PS) or on polyethylene glycol/polystyrene copolymer (PEG-PS, TentaGel®). This copolymer consists of a low cross-linked polystyrene matrix on which polyethylene glycol is grafted. The applications of these polymer-supported ligands in the cross-coupling reaction of aryl chlorides with arylboronic acids, as well as the experiments involving the recycling of the catalyst are described.

Results and Discussion

The synthesis of aryldicyclohexylphosphine based on polystyrene (PS) **1** or on copolymer polyethylene glycol/polystyrene (PEG-PS) **2** is shown in Scheme 1.



Scheme 1. Synthesis of solid-supported PS-phosphine **1** and PEG-PS-phosphine **2**. *Reagents and conditions:* (*i*) 4-cyanophenylboronic acid, $Pd(OAc)_2$/TPPTS, Et_3N, CH_3CN/H_2O, 45 °C, 48 h; (*ii*) *n*-BuLi at −100 °C during 1 h, then Cy_2PCl at −100 °C and room temperature during 15 h; (*iii*) HCl, 110 °C; (*iv*) PS-NH_2 or PEG-PS-NH_2 resin, EDC·HCl, HOBT, DMF, room temperature, 24 h.

According to the procedure described in the literature for 1,2-dibromobenzene,[12,13] the palladium-catalysed coupling of 2-iodobromobenzene with 3-cyanophenylboronic acid gave 2′-bromobiphenyl-4-carbonitrile **3** in 80 % yield. A lithiation-phosphorylation of the C–Br bond of the biaryl derivative **3** afforded 2′-(dicyclohexylphosphino)biphenyl-4-carbonitrile **4** in 80 % yield. Acidic hydrolysis of this biaryl derivative **4** gave 2′-(dicyclohexylphosphino)biphenyl-4-carboxylic acid **5** in 45 % yield after purification. Following a standard method for the solid-phase amide bond formation,[14] the condensation of carboxylic acid **5** with PS-NH_2 or PEG-PS-NH_2 in DMF solution in the presence of 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl), and 1-hydroxybenzotriazole (HOBT), afforded the polymer-supported PS-phosphine **1** or PEG-PS-phosphine **2**, respectively. In order to assay the efficiency of coupling, the phosphorus loading in PS-phosphine **1** and PEG-PS-phosphine **2** was determined for each condensation reaction. Concerning PS-phosphine **1**, the synthesis was performed three times, and the phosphorus analyses were 1.89 %, 2.00 %, and 2.12 % P, respectively. The capacity of PS-NH_2 is given by Fluka Company as 0.8–1.2 mmoles per gram, which approximates at 1.0 mmol per gram, thus, the percentage of coupling in PS-phosphine **1** was about 62 %, 65 %, and 68 %, respectively. Concerning PEG-PS-phosphine **2**, the synthesis was performed four times, the phosphorus analyses being 0.68 %, 0.69 %, 0.80 %, and 0.89 %, respectively. The capacity of PEG-PS-NH_2 is given as 0.4 mmole per gram, thus, the percentage of coupling in PEG-PS-phosphine **2** was about 55 %, 55 %, 65 %, and 72 %, respectively. The $^{31}P\{^1H\}$ NMR spectra of resin-supported phosphines **1** and **2** were recorded using standard solution-phase spectroscopic parameters and equipment. Regardless of the solvent used (chloroform, toluene, DMSO, water), the PS-phosphine **1** showed significantly broadened signals. Uozumi[14c] observed also this phenomenon, and explained it by the insolubility of the polymer in the used solvents. From the PEG-PS-phosphine **2**, a narrow signal at $\delta = -12.3$ in chloroform was recorded.

Different cross-coupling reactions were investigated using various aryl halides with two arylboronic acids: phenylboronic acid and 4-methylphenylboronic acid. The results are summarized in Table 1. Two reaction media were used: toluene and a 3/2/2 toluene/EtOH/H_2O mixture. Water is known to influence favourably the activity of the Suzuki–Miyaura catalyst.[15] Plenio[11c] found that addition of small amounts of water to the reaction medium increased significantly the activity of the catalyst. Before testing the potential of the two polymer-supported ligands **1** and **2**, we studied the Suzuki–Miyaura cross-coupling of 1-bromo-4-nitrobenzene (Table 1, entries 1 and 2) or 1-chloro-4-nitrobenzene (Table 1, entries 3 and 4) with 1.1 equivalents of phenylboronic acid using a "ligandless" palladium catalyst. In the case of 1-bromo-4-nitrobenzene, the yields of the coupling reaction were 89 % and 97 % in toluene and in the mixture of solvents, respectively, while no reaction occurred in both media when 1-chloro-4-nitrobenzene was used as the aryl halide. It is well known that ligand-free $Pd(OAc)_2$ is able to catalyse the coupling reaction of aryl iodides and activated or deactivated aryl bromides;[1d,h,16] however, in the case of aryl chlorides, temperatures higher than 150 °C or microwave assistance are necessary in order to perform efficiently this cross-coupling reaction.[17]

In the presence of polymer-supported ligands **1** and **2** (Table 1, entries 5–20), the reactions were carried out in the two media (toluene or a 3/2/2 toluene/

Table 1. Suzuki–Miyaura cross-coupling of aryl halides and boronic acids with $Pd(OAc)_2$/**1** or **2**.[a]

$$\text{Ar-X} + \text{Ar'-B(OH)}_2 \longrightarrow \text{Ar-Ar'}$$

Entry	Ar-X	Ar′-B(OH)$_2$	L	Solvent[b]	Yield [%][c]
1	1-Bromo-4-nitrobenzene	Phenylboronic acid	no	Toluene	89
2			no	Toluene/EtOH/H_2O	97
3	1-Chloro-4-nitrobenzene	Phenylboronic acid	no	Toluene	0
4			no	Toluene/EtOH/H_2O	0
5			**1**	Toluene	60
6			**1**	Toluene/EtOH/H_2O	20
7			**2**	Toluene	86
8			**2**	Toluene/EtOH/H_2O	96
9	4-Chlorobenzonitrile	Phenylboronic acid	**1**	Toluene	90
10			**1**	Toluene/EtOH/H_2O	20
11			**2**	Toluene/EtOH/H_2O	65
12	4-Chlorobenzaldehyde	Phenylboronic acid	**1**	Toluene	91
13			**1**	Toluene/EtOH/H_2O	15
14			**2**	Toluene/EtOH/H_2O	92
15	1-Chloro-4-methylbenzene	Phenylboronic acid	**1**	Toluene	30
16			**1**	Toluene/EtOH/H_2O	0
17			**2**	Toluene/EtOH/H_2O	0
18	1-Chloro-4-nitrobenzene	4-Methylphenylboronic acid	**1**	Toluene	90
19			**1**	Toluene/EtOH/H_2O	18
20			**2**	Toluene/EtOH/H_2O	0

[a] *Reaction conditions:* [aryl halide] = 0.07 M; [aryl halide]/[boronic acid]/[base]/[$Pd(OAc)_2$]/[L] = 1/1.1/3/0.002/0.006; the reaction time was 20 h.

[b] In the case of toluene, the base was K_3PO_4 and the reaction temperature was 100 °C; in the case of toluene/EtOH/H_2O (3/2/2), the base was Na_2CO_3 and the reaction temperature was 80 °C.

[c] Isolated chemical yield after column chromatography.

EtOH/H_2O mixture) in the presence of the catalyst formed *in situ* from 0.2 % M of $Pd(OAc)_2$ and 0.6 % M of polymer-supported ligand, in the presence of K_3PO_4 (3 equivs.) or Na_2CO_3 (3 equivs.) as the base, and with an aryl chloride/arylboronic acid ratio of 1 to 1.1. When the reaction was performed in toluene, K_3PO_4 was used as the base and the applied temperature was 100 °C, whereas in a 3/2/2 toluene/EtOH/H_2O mixture, Na_2CO_3 was used as the base and the applied temperature was 80 °C. It is to be noticed that the presence of EtOH did not allow us to perform the Suzuki–Miyaura reaction at a temperature higher than 80 °C.

Using PS-phosphine **1** as the ligand, aryl chlorides bearing electron-withdrawing groups reacted with phenylboronic acid affording the corresponding biaryl compounds in low yields (15–20 %) when the reaction was performed in the 3/2/2 toluene/EtOH/H_2O mixture (Table 1, entries 6, 10 and 13). However, moving to toluene as the solvent gave quite good yields (60–91 %) of the biaryl derivatives (Table 1, entries 5, 9 and 12). 1-Chloro-4-methylbenzene bearing an electron-donating group gave a very low yield in toluene (30 %) and no reaction at all in the mixture of solvents (Table 1, entries 15 and 16). Reaction of 4-methylphenylboronic acid with 1-chloro-4-nitrobenzene gave a high yield of coupling product in toluene (90 %) and a very low yield in the other medium (18 %) (Table 1, entries 18 and 19). Generally, elevated temperature is necessary in order to obtain good yields.[8] The difference in the efficiency of the studied coupling in the two media could be explained by the difference in their polarity. In fact, the polystyrene support presents hydrophobic properties, and for the same volume of solvent and for the same quantity of PS-phosphine **1**, the resin swells more in toluene than in a 3/2/2 toluene/EtOH/H_2O mixture. The better swelling of polymer should give a better accessibility of the reagents to the palladium complexes, and so a higher conversion.

In the case of PEG-PS-phosphine **2**, the organic resin presents hydrophobic and hydrophilic properties. In comparison to polystyrene, the swelling volumes of this copolymer in water and in EtOH are not negligible. And so, the swelling of the copolymer in both media should be similar; consequently, the yields in cross-coupling products in toluene or in a 3/2/2 toluene/EtOH/H_2O mixture should be very close. In the case of reaction between 1-chloro-4-nitrobenzene and phenylboronic acid (Table 1, entries 7 and 8), the yields in biaryl compounds were 86 % in toluene and 96 % in the mixture of solvents, in agreement with these properties. Two other aryl chlorides bearing electron-withdrawing groups, namely 4-chlorobenzonitrile and 4-chlorobenzaldehyde, were used in the cross-coupling reaction with phenylboronic acid. With the first aryl chloride, the yield in biaryl derivative was 65% (Table 1, entry 11), and with the second one, the yield was 92% (Table 1, entry 14). Using 1-chloro-4-methylbenzene, bearing an electron-donating group with phenylboronic acid, or 1-chloro-4-nitrobenzene with 4-methylphenylboronic acid gave no reaction at all (Table 1, entries 17 and 20).

The recycling of the catalysts derived from polymer-supported ligands **1** or **2** and $Pd(OAc)_2$ was then studied in this reaction. The main results of the recycling experiments are summarized in Table 2. After the first run performed under the same conditions as reported before, the polymer-supported palladium complex was filtered, and washed with CH_2Cl_2 when K_3PO_4 was used as the base, or with ethyl acetate and water when Na_2CO_3 was used as the base. Then the complex was used in the next Suzuki–Miyaura reaction without any addition of palladium catalyst. Using the PS-phosphine **1** in toluene, the yields of coupling between 4-chlorobenzaldehyde and phenylboronic acid, or 1-chloro-4-nitrobenzene and 4-methylphenylboronic acid, decreased drastically for the second run from 91% to 50%, or from 90% to 46%, respectively (Table 2, entries 1 and 2). Using the PEG-PS-phosphine **2** in toluene, the yield of the coupling product of 1-chloro-4-nitrobenzene and phenylboronic acid decreased from 86% to 30% for the third run (Table 2, entry 3). However, when the 3/2/2 toluene/EtOH/H_2O mixture was used as the solvent, the chemical yield remained the same (91–100%) during four runs, and decreased slightly in the fifth and the sixth run to 80% and 79% yield, respectively (Table 2, entry 4). Apparently, the efficiency of the studied recycling-coupling reaction is strongly influenced by the nature of the used solvent and the base.

Conclusions

The synthesis of an aryldicyclohexylphosphine based on polystyrene (PS-phosphine) and on a copolymer polyethylene glycol/polystyrene (PEG-PS-phosphine) *via* a dicyclohexylphosphinobenzoic acid has been described. The efficiency of these polymer-supported ligands has been demonstrated in palladium-catalyzed coupling reactions between aryl chlorides and arylboronic acids under smooth conditions. With only 1.1 equivalents of arylboronic acid in relation to aryl chloride, the chemical yields are generally high using PS-phosphine-palladium complexes in toluene as the solvent, or PEG-PS-phosphine-palladium complexes in a 3/2/2 toluene/EtOH/H_2O mixture. We have shown the high efficiency of PEG-PS-phosphine in the 3/2/2 toluene/EtOH/H_2O mixture for recycling palladium in the cross-coupling reaction of 1-chloro-4-nitrobenzene with 1.1 equivalent of phenylboronic acid. This study is currently being extended to other aryl chlorides, as well as to the binding of the phosphinocarboxylic acid to other natural aminopolymers.

Experimental Section

General Remarks

Solvents were purified by standard methods and dried if necessary. All commercially available reagents were used as received. All manipulations involving palladium catalyst were performed under the usual inert atmosphere techniques in Schlenk tubes. Conversion was determined by GC using a Quadrex OV1 column (30 m × 0.25 mm). Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). NMR spectra were recorded with a Bruker AC 300 spectrometer and referenced as follows: ^{1}H (300 MHz), internal $SiMe_4$ at $\delta = 0.00$ ppm, ^{13}C (75 MHz), internal $CDCl_3$ at $\delta = 77.2$ ppm, and ^{31}P (121 MHz), external 85% H_3PO_4 at $\delta = 0.00$ ppm.

Preparation of 2′-Bromobiphenyl-4-carbonitrile (3)

A mixture of $Pd(OAc)_2$ (16.8 mg, 0.075 mmol) and trisodium salt of trisulfonated triphenylphosphine (TPPTS, 90 mg, 0.15 mmol) in water (1.50 mL) was stirred at room temperature for 30 min. A mixture of 2-iodobromobenzene (849 mg, 3 mmol), 4-cyanophenylboronic acid (534 mg, 3.63 mmol), triethylamine (1.05 mL, 759 mg, 7.5 mmol), and acetonitrile

Table 2. Recycling experiments for Suzuki–Miyaura cross-coupling.[a]

Entry	Ar-Cl	Ar′-B(OH)$_2$	L	Yield (%)[b] – Run					
				1	2	3	4	5	6
1[c]	4-Chlorobenzaldehyde	Phenylboronic acid	**1**	91	50				
2[c]	1-Chloro-4-nitrobenzene	4-Methylphenylboronic acid	**1**	90	46				
3[c]	1-Chloro-4-nitrobenzene	Phenylboronic acid	**2**	86	76	30			
4[d]	1-Chloro-4-nitrobenzene	Phenylboronic acid	**2**	96	94	91	100	80	79

[a] *Reaction conditions:* [aryl halide] = 0.07 M; [aryl halide]/[boronic acid]/[base]/[$Pd(OAc)_2$]/[L] = 1/1.1/3/0.002/0.006; the reaction time was 20 h.

[b] Isolated chemical yield after column chromatography.

[c] Toluene, K_3PO_4, 100 °C; after each run the polymer was washed with CH_2Cl_2.

[d] Toluene/EtOH/H_2O (3/2/2), Na_2CO_3, 80 °C; after each run the polymer was washed with EtOAc and water.

(7.5 mL) was then added. The resulting mixture was stirred at 45 °C for 48 h, then the reaction mixture was cooled at room temperature and filtered on Celite. After evaporation of the solvent, the crude mixture was purified by flash chromatography on silica gel [petroleum ether (PE)/ethyl acetate (EA), 10/1] to give compound **3** as a white solid; yield: 620 mg (80 %). R_f = 0.45 (PE/EA, 10/1); ^{1}H NMR (CDCl$_3$): δ = 7.75 (d, J = 8.0 Hz, 2 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.54 (d, J = 8.0 Hz, 2 H), 7.43 (dd, J = 8.0, 8.0 Hz, 1 H), 7.35–7.25 (m, 2 H), in agreement with the literature.[12]

Preparation of 2′-(Dicyclohexylphosphino)-biphenyl-4-carbonitrile (4)

A solution of **3** (353.5 mg, 1.37 mmol) in THF (7 mL) was cooled at −100 °C. A solution of *n*-BuLi (1 mL, 1.6 mmol) at 1.6 M in hexane was added drop by drop, and the reaction mixture was stirred at −100 °C for 1 hour. Then a solution of Cy$_2$PCl (0.31 mL, 326 mg, 1.4 mmol) in THF (1 mL) was slowly added. The reaction mixture was stirred for 1 hour at −100 °C, then at room temperature for 15 h. After evaporation of the solvents, ethyl acetate (20 mL) and a 1/1 mixture of water and brine (12 mL) were added. After separation, the aqueous phase was washed with ethyl acetate. The organic phases were dried over MgSO$_4$, and after evaporation of the solvent, the residue was purified by flash-chromatography on silica gel (PE/EA, 15/1) to give compound **4** as a white solid; yield: 410 mg (80 %). R_f = 0.65 (PE/EA, 10/1); ^{1}H NMR (CDCl$_3$): δ = 7.66 (d, J = 8.1 Hz, 2 H, H$_{arom}$), 7.65–7.59 (m, 1 H, H$_{arom}$), 7.50–7.35 (m, 4 H, H$_{arom}$), 7.28–7.18 (m, 1 H, H$_{arom}$), 1.92–1.79 (m, 2 H, PCH), 1.75–1.45 (m, 10 H, CH$_2$), 1.36–0.97 (m, 10 H, CH$_2$); ^{31}P NMR (CDCl$_3$): δ −12.2. These data are in agreement with the literature.[12]

Preparation of 2′-(Dicyclohexylphosphino)-biphenyl-4-carboxylic Acid (5)

A mixture of **4** (400 mg, 1.06 mmol) and HCl 33 % (7.5 mL) was heated at 110 °C for 4 h. After concentration at 80 °C under reduced pressure, the residue was dissolved in CH$_2$Cl$_2$ (30 mL) and Et$_3$N (0.15 mL, 107.3 mg, 1.2 mmol), and the mixture was stirred at room temperature. The organic phase was washed with brine (2 × 10 mL), dried over MgSO$_4$ and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate as the eluent to give compound **5** as a white solid; yield: 190 mg (45 %). R_f = 0.43 (CH$_2$Cl$_2$/MeOH, 10/1); ^{1}H NMR (CDCl$_3$): δ = 8.12 (d, J = 8.1 Hz, 2 H, H$_{arom}$), 7.67–7.57 (m, 1 H, H$_{arom}$), 7.48–7.36 (m, 4 H, H$_{arom}$), 7.35–7.20 (m, 1 H, H$_{arom}$), 1.95–1.80 (m, 2 H, PCH), 1.80–1.50 (m, 10 H, CH$_2$), 1.47–0.92 (m, 10 H, CH$_2$); ^{13}C NMR (CDCl$_3$): δ = 172.4, 150.4 (d, J = 28.5 Hz), 149.5 (d, J = 6.2 Hz), 134.7 (d, J = 21.7 Hz), 133.9 (d, J = 2.5 Hz), 131.6 (d, J = 4.3 Hz), 130.6 (d, J = 5.6 Hz), 130.2, 129.2, 128.5, 127.9, 35.4 (d, J = 13.6 Hz), 31.2 (d, J = 17.4 Hz), 30.0 (d, J = 8.7 Hz), 28.0 (d, J = 12.4 Hz), 27.9 (d, J = 7.4 Hz), 27.2; ^{31}P NMR (CDCl$_3$): δ = −12.0; HR-MS: *m/z* = 395.2150, calcd. for C$_{25}$H$_{32}$O$_2$P [M + H]$^+$: 395.2140.

Preparation of Solid-Supported PS-Phosphine (1) or PEG-PS-Phosphine (2)

A mixture of resin (0.3 mmol of NH$_2$ group), carboxylic acid **5** (118 mg, 0.3 mmol), EDC·HCl (93 mg, 0.48 mmol), HOBT (87 mg, 0.6 mmol), and DMF (5 mL), was stirred at room temperature for 24 h. Then the polymer was filtered, and washed with DMF (3 × 2 mL) and CH$_2$Cl$_2$ (4 × 2 mL). The resin was dried under reduced pressure to give PS-phosphine **1** or PEG-PS-phosphine **2**, respectively.

Solid-supported PS-phosphine **1**: Analysis: P 1.89 %, 2.00 %, or 2.12 %.

Solid-supported PEG-PS-phosphine **2**: ^{31}P NMR (CDCl$_3$): δ = −12.3; Analysis: P 0.68 %, 0.69 %, 0.80 %, or 0.89 %.

Typical Cross-Coupling Procedure in Toluene

Pd(OAc)$_2$ (1.3 mg, 6 μmol), polymer-supported ligand (18 μmol of phosphine), K$_3$PO$_4$ (1.91 g, 9.0 mmol) and toluene (12 mL) were placed in a flask under argon. The solution was stirred for 30 min. A mixture of aryl halide (3.0 mmol), and arylboronic acid (3.3 mmol) in toluene (30 mL) was then added. The resulting mixture was stirred at 100 °C for 20 h. The mixture was cooled at room temperature, the heterogeneous solution was filtered, and the filtrate was concentrated under reduced pressure to give the corresponding crude biaryl compound, which was purified by flash chromatography on silica gel to afford the pure coupling product.

Typical Cross-Coupling Procedure in a 3/2/2 Toluene/EtOH/H$_2$O Mixture

Pd(OAc)$_2$ (1.3 mg, 6 μmol), polymer-supported ligand (18 μmol of phosphine), and toluene (6 mL), were placed in a flask under argon. The solution was stirred for 30 min. Aryl halide (3 mmol) and arylboronic acid (3.3 mmol) in a mixture of toluene (6 mL) and EtOH (12 mL) were then added in the flask, followed by Na$_2$CO$_3$ (0.95 g, 9 mmol) in water (12 mL). The resulting mixture was stirred at 80 °C for 20 h. After being cooled at room temperature, the heterogeneous solution was filtered, and the two phases were separated. The EtOH/H$_2$O layer was washed twice with toluene, and the organic phases were dried over MgSO$_4$. Evaporation of the solvents under reduced pressure gives the corresponding crude biaryl compound, which was purified by flash chromatography on silica gel to afford the pure coupling product.

Recycling Cross-Coupling Procedure

For the first run, the same experimental conditions than described above were used. After filtration, the polymer-supported complex was washed with CH$_2$Cl$_2$ (2 × 5 mL) when K$_3$PO$_4$ was used as the base, and with ethyl acetate (2 × 5 mL), with water (2 × 5 mL), and then ethyl acetate (2 × 5 mL) when Na$_2$CO$_3$ was used as the base. After drying the polymer under vacuum, a mixture of aryl halide (3 mmol), arylboronic acid (3.3 mmol), base (9 mmol), and 14 mL of solvent, was added to this polymer.

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References

[1] H. H. Szmant, *Organic Building Blocks of the Chemical Industry*, Wiley, New York **1989**.

[2] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim **1998**; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; d) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; e) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11–59; f) J. Hassan, M. Sévignon, C. Gozzi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469; g) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633–9695; h) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419–2440.

[3] a) *Chiral Catalyst Immobilization and Recycling*, (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim **2000**; b) R. Haag, S. Roller, *Top. Curr. Chem.* **2004**, *242*, 1–42; c) Y. Uozumi, *Top. Curr. Chem.* **2004**, *242*, 77–112; d) D. E. Bergbreiter, *Top. Curr. Chem.* **2004**, *242*, 113–176; e) N. End, K.-U. Schöning, *Top. Curr. Chem.* **2004**, *242*, 241–271.

[4] a) S.-B. Jang, *Tetrahedron Lett.***1997**, *38*, 1793–1797; b) I. Fenger, C. Le Drian, *Tetrahedron Lett.* **1998**, *39*, 4287–4290; c) Y. Uozumi, H. Danjo, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 3384–3388; d) A. N. Cammidge, N. J. Baines, R. K. Bellingham, *Chem. Commun.* **2001**, 2588–2589; e) Y. Uozumi, *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 1063–1068; f) Y. Uozumi, Y. Nakai, *Org. Lett.* **2002**, *4*, 2997–3000; g) Y. M. A. Yamada, K. Takeda, H. Takahashi, S. Ikegami, *J. Org. Chem.* **2003**, *68*, 7733–7741.

[5] J. Cortés, M. Moreno-Mañas, R. Pleixats, *Eur. J. Org. Chem.* **2000**, 239–243.

[6] a) N. T. S. Phan, D. H. Brown, P. Styring, *Tetrahedron Lett.* **2004**, *45*, 7915–7919; b) N. T. S. Phan, J. Khan, P. Styring, *Tetrahedron* **2005**, *61*, 12065–12073.

[7] a) P. G. Steel, C. W. T. Teasdale, *Tetrahedron Lett.* **2004**, *45*, 8977–8980; b) J.-H. Kim, J.-W. Kim, M. Shokouhimehr, Y.-S. Lee, *J. Org. Chem.* **2005**, *70*, 6714–6720; c) T. Kang, Q. Feng, M. Luo, *Synlett* **2005**, 2305–2308.

[8] a) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388; c) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561; d) X. Bei, H. W. Turner, W. H. Weinberg, A. S. Guram, *J. Org. Chem.* **1999**, *64*, 6797–6803; e) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem. Int. Ed.* **2000**, *39* 4153–4155; f) A. Zapf, M. Beller, *Chem. Eur. J.* **2000**, *6*, 1830–1833; g) S.-Y. Liu, M. J. Choi, G. C. Fu, *Chem. Commun.* **2001**, 2408–2409; h) J. F. Jensen, M. Johannsen, *Org. Lett.* **2003**, *5*, 3025–3028; i) F. X. Roca, C. J. Richards, *Chem. Commun.* **2003**, 300–3003; j) C. Baillie, L. Zhang, J. Xiao, *J. Org. Chem.* **2004**, *69*, 7779–7782; k) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876.

[9] K. Inada, N. Miyaura, *Tetrahedron* **2000**, 56, 8661–8664.

[10] C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, 66, 3820–3827.

[11] a) A. Datta, H. Plenio, *Chem. Commun.* **2003**, 1504–1505; b) A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, *22*, 4685–4691; c) M. van der Heiden, H. Plenio, *Chem. Eur. J.* **2004**, *10*, 1789–1797.

[12] M. Nishimura, M. Ueda, N. Miyaura, *Tetrahedron* **2002**, *58*, 5779–5787.

[13] A. Konovets, A. Penciu, E. Framery, N. Percina, C. Goux-Henry, D. Sinou, *Tetrahedron Lett.* **2005**, *46*, 3205–3208.

[14] a) B. A. Bunin, in: *Combinatorial Index*, Academic Press, London, **1998**; b) D. Obrecht, J. M. Villalgordo, in: *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Tetrahedron Organic Chemistry Series Vol. 17, Elsevier, Oxford, **1998**; c) H. Danjo, D. Tanaka, T. Hayashi, Y. Uozumi, *Tetrahedron* **1999**, *55*, 14341–14352.

[15] R. B. Bedford, C. S. J. Cazin, S. J. Coles, T. Gelbrich, P. N. Horton, M. E. Hursthouse, M. E. Light, *Organometallics* **2003**, *22*, 987–999.

[16] a) E. M. Campi, W. R. Jackson, S. M. Maruccio, C. G. M. Naeslund, *J. Chem. Soc., Chem. Commun.* **1994**, 2395–2395; b) D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170–7173; c) N. A. Bumagin, V. V. Bykov, *Tetrahedron* **1997**, *53*, 14437–14450; d) J. C. Bussolari, D. C. Rehborn, *Org. Lett.* **1999**, *1*, 965–967; e) L. M. Klingensmith, N. E. Leadbeater, *Tetrahedron Lett.* **2003**, *44*, 765–768; f) X. Tao, Y. Zhao, D. Shen, *Synlett* **2004**, 359–361.

[17] a) N. E. Leadbeater, M. Marco, *Org. Lett.* **2002**, *4*, 2973–2976; b) R. K. Arvela, N. E. Leadbeater, *Org. Lett.* **2005**, *7*, 2101–2104; c) G. Miao, P. Ye, L. Yu, C. M. Baldino, *J. Org. Chem.* **2005**, *70*, 2332–2334; d) L Liu, Y. Zhang, Y. Wang, *J. Org. Chem.* **2005**, *70*, 6122–6125; e) G. Cravotto, M. Beggiato, A. Penoni, G. Palmisano, S. Tollari, J.-M. Lévêque, W. Bonrath, *Tetrahedron Lett.* **2005**, *46*, 2267–2271.