



Highly efficient reusable polymer-supported Pd catalysts of general use for the Suzuki reaction

Stéphane Schweizer, Jean-Michel Becht*, Claude Le Drian

Institut de Science des Matériaux de Mulhouse, LRC-CNRS 7228, ENSCMu, 3 rue Alfred Werner, F-68093 Mulhouse Cedex, France

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ABSTRACT

Short and efficient syntheses of various polymer-supported Pd catalysts are reported. The reactivity of these catalysts has been determined for the Suzuki reaction. It turned out that the (*tert*-butylphenylphosphinomethyl)polystyrene-supported Pd catalyst **2'a** is highly efficient for versatile Suzuki reactions from aryl chlorides. These couplings are performed in the presence of low amounts (4 mequiv) of supported Pd, the catalyst can be reused more than seven times without loss of efficiency and the Pd leaching is extremely low (<0.1% of the initial amount).

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1. Introduction

Transition metal catalyzed cross-couplings are fundamental transformations in modern organic synthesis.¹ Among them, the Pd catalyzed Suzuki reaction is very efficient for the formation of aryl–aryl bonds,^{2,3} and therefore finds widespread applications for the synthesis of molecules possessing interesting pharmacological or physical properties.⁴ These couplings proceed generally in high yields under very mild and non-anhydrous reaction conditions and tolerate the presence of many functional groups. Usually, they are performed in the presence of a homogeneous (soluble) Pd catalyst,¹ the major drawbacks being the impossibility to recover for direct reuse these expensive catalysts and the difficulties frequently encountered to avoid the presence of Pd in waste and, even more importantly, in the reaction products. During the last decade, extensive work has been devoted to the development of reusable Pd catalysts for C–C bond forming reactions: the precious metal is generally grafted on inorganic⁵ or polymeric supports.⁶ For example, Pd can be encapsulated⁷ or incarcerated⁸ in a polymeric matrix or bound to polymer-supported carbene⁹ or phosphine ligands.^{10,11}

Concerning the Suzuki reaction, an additional challenge is the development of Pd catalysts allowing the use of aryl chlorides instead of the more reactive but much more expensive aryl bromides or iodides. Several homogeneous Pd catalysts have been developed for the Suzuki coupling of aryl chlorides,¹² but only few efficient heterogeneous Pd catalysts, which are of general use for this reaction have been reported.¹³ Compared to their homogeneous analogues, heterogeneous Pd catalysts often suffer from a lower

reactivity, which moreover could decrease,^{13c} or even disappear, after use.^{13d}

In a previous report, we have described reusable (diarylphosphinomethyl)polystyrene-supported Pd catalysts for Suzuki reactions of aryl bromides.^{11b} Besides this first family of catalysts, we developed a second family by replacing, on the polymer, the (diarylphosphinomethyl) substituents by (aryl-*tert*-butylphosphinomethyl) substituents.^{11c,14} This modification brought a considerable improvement: the catalysts are either highly efficient and of general use for Suzuki reactions from aryl chlorides. We present here the detailed results of the Suzuki coupling.

2. Results and discussion

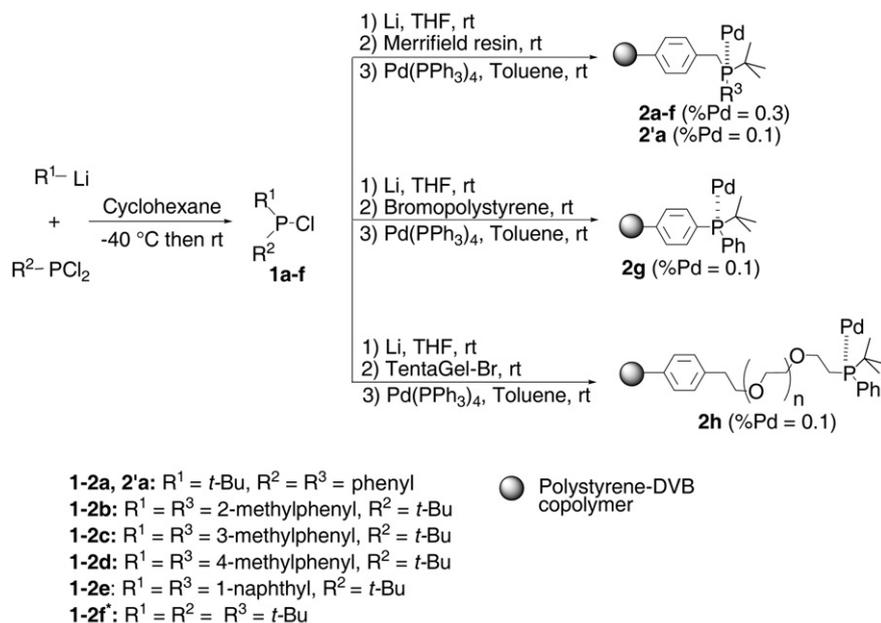
2.1. Preparation of the heterogeneous polymer-supported Pd catalysts

The Pd catalysts were prepared from two types of commercially available halogenated polymers: Merrifield resin for catalysts **2a–g** and Tentagel-Br resin for catalyst **2h**.

Inspired by our previous work,¹¹ the heterogeneous Pd catalysts were prepared in two steps: lithiation of the (aryl-*tert*-butyl)- or di(*tert*-butyl)-chlorophosphines **1a–f** followed by substitution of the halogen atoms of the polymer and then introduction of the precious metal (Scheme 1).

Chlorophosphine **1a** was obtained from *tert*-butyllithium and dichlorophenylphosphine, whereas chlorophosphines **1b–e** were generated from the reactions of aryllithiums with *tert*-butyldichlorophosphine.¹⁵ Since the air- and moisture-sensitive chlorophosphines **1a–e** were obtained with a purity (determined by ³¹P and ¹H NMR) already above 90%, they were directly reacted with lithium without further purification.¹⁶ By reaction of the

* Corresponding author. Tel.: +33 3 89 33 67 20; fax: +33 3 89 33 68 60.
E-mail address: jean-michel.becht@uha.fr (J.-M. Becht).



Scheme 1. Syntheses of polymer-supported Pd catalysts.

phosphinololithiums with halogenated polymers, the desired aryl-*tert*-butyl- or di-*tert*-butylphosphino-polymers were obtained: when a halomethyl group was present on the starting polymer, 99% of the halogen atoms were removed, however only ca. 80% of the theoretical amount of phosphino groups were introduced in **2a–f**, **2h**, and **2'a**. In the case of catalyst **2g**, 98% of the bromine atoms disappeared but only 25% of them were replaced by phosphino groups. The polymer-supported Pd catalysts **2a–h** and **2'a** were then obtained via an exchange reaction with Pd(PPh₃)₄ as a soluble Pd source.^{11b} During the synthesis of catalyst **2'a**, we have shown that 4 equiv of PPh₃ were recovered. Elemental analysis of the reaction medium (performed according to Section 4.4. of the Experimental section) proved that more than 99% of the amount of Pd used was grafted on the resins. The Pd content of the catalyst was confirmed according to Section 4.5. of the Experimental section and by conventional elemental analysis (see General remarks of the Experimental section). Comparable P/Pd ratios were obtained for all catalysts **2a–f** (for further details see Experimental section). It is important to note that these catalysts could easily be prepared on a 20 g scale. Besides, they are air- and moisture-stable and can therefore be easily stored and handled.

2.2. Suzuki reactions of aryl chlorides

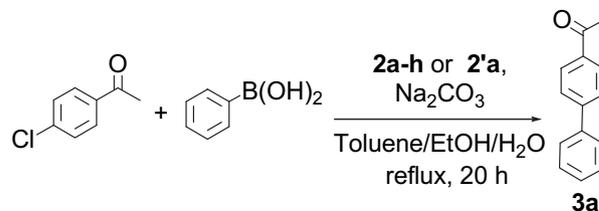
The reactivity of catalysts **2a–h** and **2'a** was then determined for the Suzuki reaction using 4-chloroacetophenone and phenylboronic acid as model substrates (Table 1). This coupling was initially performed in the presence of Na₂CO₃ in a 5:1:1 mixture of toluene/EtOH/H₂O (Table 1).

In the presence of the polystyrene-supported Pd catalyst **2a** containing 0.3% of Pd, the desired biaryl **3a** was obtained in an excellent 99% yield with 2 mequiv of supported Pd (entry 1). A lower 73% yield was observed by using only 1 mequiv of supported Pd (entry 2). Except catalysts **2c** and **2d**, which gave excellent yields of **3a** with 2 mequiv of Pd (entries 4–5), the other polystyrene-supported Pd catalysts **2b**, **2e–g** afforded **3a** in lower yields (entries 3, 6–7, 11). The Pd/P ratio seems to have a notable influence since considerable improvement was achieved by using catalyst **2'a** (%Pd=0.1), which afforded an almost quantitative yield of **3a** with

only 0.2 mequiv of Pd (entries 8 and 9). We studied also the influence of the polymeric support: replacing the Merrifield resin by a Tentagel resin brought a considerable improvement since in the presence of only 0.05 mequiv of supported Pd a 87% yield of **3a** was still obtained (entry 13).

The possibility to reuse catalysts **2'a** and **2h** was then examined. For this purpose, the catalyst was recovered by filtration on a membrane and directly reused in a second run (for further details see Experimental section). Unfortunately, the first reuse of catalyst **2'a** resulted in a significantly lower 35% yield of **3a**. For **2h**, the first reuse was satisfactory, however the subsequent reuses led to decreasing yields (Table 2).

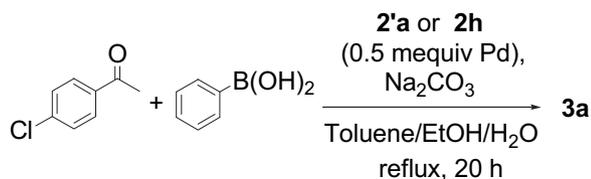
Table 1
Suzuki reactions of 4-chloroacetophenone and phenylboronic acid



Entry ^a	Catalyst	Pd (mequiv.)	Yield ^b (%)
1	2a	2	99
2	2a	1	73
3	2b	2	14
4	2c	2	95
5	2d	2	90
6	2e	2	33
7	2f	2	74
8	2'a	0.5	99
9	2'a	0.2	98
10	2'a	0.1	47
11	2g	2	58
12	2h	0.1	99
13	2h	0.05	87

^a Reactions performed with 1.0 equiv (0.65 mmol) of 4-chloroacetophenone, 1.1 equiv of phenylboronic acid, 1.2 equiv of Na₂CO₃.

^b Yields were calculated by comparison of the ¹H NMR integrations of the constituents of crude reaction mixtures.

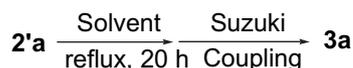
Table 2
Recycling tests

Run ^a	Yield ^b (%) 2'a	Yield ^b (%) 2h
1	98	99
2	35	94
3	—	83
4	—	53

^a Reactions performed with 1.0 equiv (0.65 mmol) of 4-chloroacetophenone, 1.1 equiv of phenylboronic acid, 1.2 equiv of Na₂CO₃.

^b Yields were calculated by comparison of the ¹H NMR integrations of the constituents of crude reaction mixtures.

It should be noted that the loss of Pd during the first use of catalyst **2'a** was only 1% of the initial amount, proving that the deactivation of **2'a** is not caused by a loss of the metal. Moreover, TEM images of the catalyst before and after use showed no significant difference. We have therefore no explanation for this deactivation of the catalyst. Then, we examined if catalyst **2'a** was stable in a 5:1:1 mixture of toluene/EtOH/H₂O. For this purpose, three independent experiments were performed (Table 3): **2'a** was respectively refluxed for 20 h in toluene, in a 5:1 mixture of toluene/EtOH and in a 5:1:1 mixture of toluene/EtOH/H₂O. Then, **2'a** was recovered by filtration and directly reacted in a Suzuki reaction using the previous reaction conditions. It turned out that no deactivation of **2'a** was observed in toluene since the desired coupling product was obtained in 98% yield (entry 1), but that heating **2'a** in a mixture of toluene and an protic solvent was detrimental to its reactivity (entries 2 and 3).

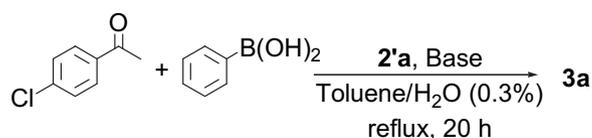
Table 3
Stability tests of catalyst **2'a**

Entry ^a	Solvent	Yield ^b (%)
1	Toluene	98
2	Toluene/EtOH 5:1	46
3	Toluene/EtOH/H ₂ O 5:1:1	38

^a Reactions performed with 1.0 equiv (0.65 mmol) of 4-chloroacetophenone, 1.1 equiv of phenylboronic acid, 1.2 equiv of Na₂CO₃.

^b Yields were calculated by comparison of the ¹H NMR integrations of the constituents of crude reaction mixtures.

We had therefore to reoptimize the reaction conditions in order to recover a reusable catalyst. The Suzuki reaction was run in conditions avoiding protic solvents. We tried several bases in anhydrous toluene (Table 4): Cs₂CO₃ gave good results (entries 3 and 4). However erratic yields were sometimes obtained. We found that traces of H₂O insured reproducibility and we always introduced 0.3% of H₂O, an arbitrary amount, which turned out to have no detrimental side-effect. It turned out that 2 mequiv of supported Pd and a slight excess of boronic acid and base were necessary to get a 99% yield. Unfortunately, during the first reuse of catalyst **2'a** only a lower 75% yield of **3a** was obtained. We could therefore conclude that the presence of important amounts of protic solvent was not the only factor preventing reusability of the catalyst. Replacement of Cs₂CO₃ by CsF, which is known to be a very efficient base in anhydrous media also gave very good results during the first use (entries 5 and 6) and moreover allowed an excellent reusability of the catalyst, which still afforded a 98% yield in the seventh use (Table 5).

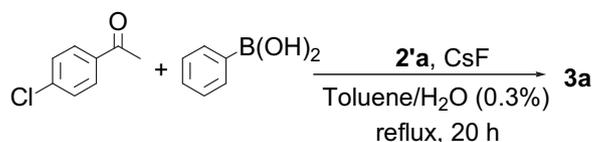
Table 4
Screening of bases

Entry ^a	Base	Pd (mequiv.)	Yield ^b (%)
1	Na ₂ CO ₃	0.5	3
2	Ag ₂ CO ₃	0.5	Traces
3	Cs ₂ CO ₃	0.5	66
4	Cs ₂ CO ₃	2	93 (99) ^c
5	CsF	0.5	45
6	CsF	4	88 (99) ^c

^a Reactions performed with 1.0 equiv (0.65 mmol) of 4-chloroacetophenone, 1.1 equiv of phenylboronic acid, 1.2 equiv of base.

^b Yields were calculated by comparison of the ¹H NMR integrations of the constituents of crude reaction mixtures.

^c Reactions performed with 1.4 equiv of phenylboronic acid and 1.5 equiv of base.

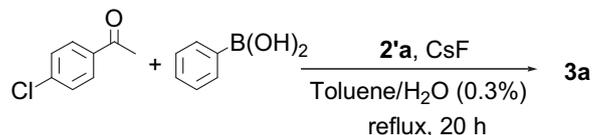
Table 5
Recycling test of catalyst **2'a**

Run ^a	1	2	3	4	5	6	7
Yield ^b (%)	99	95	99	98	99	98	98

^a Reactions performed with 1.0 equiv (0.65 mmol) of 4-chloroacetophenone, 1.4 equiv of phenylboronic acid, 1.5 equiv of CsF.

^b Yields were calculated by comparison of the ¹H NMR integrations of the constituents of crude reaction mixtures.

We then thought necessary to examine the reactivity of catalysts **2a–f** and **2'a** under these notably different conditions and to compare them with commercially available heterogeneous Pd EnCat TPP30 and Pd EnCat NP30 (Table 6). It turned out that the catalysts **2a** and **2'a** were still the most reactive and that **2'a** was more efficient than **2a** (entries 1–7). Decreasing the amount of supported Pd (entry 8), the excess of phenylboronic acid, or the temperature, afforded only lower yields of **3a**. The Pd EnCat TPP30

Table 6
Suzuki reactions under the reoptimized conditions

Entry ^a	Catalyst	Pd (mequiv.)	Yield ^b (%)
1	2a	4	84
2	2b	4	29
3	2c	4	74
4	2d	4	83
5	2e	4	31
6	2f	4	36
7	2'a	4	99
8	2'a	3	87
9	Pd EnCat TPP30	4	No reaction ^c
10	Pd EnCat NP30	4	No reaction ^c

^a Reactions performed with 1.0 equiv (0.65 mmol) of 4-chloroacetophenone, 1.4 equiv of phenylboronic acid, 1.5 equiv of CsF.

^b Yields were calculated by comparison of the ¹H NMR integrations of the constituents of crude reaction mixtures.

^c The starting materials were recovered unchanged.

and Pd Encat NP30 catalysts were found to be totally inactive, 4-chloroacetophenone being recovered unchanged (entries 9–10). The catalysts of the first family developed in our laboratory, where the polymer bears diarylphosphino groups, are only slightly active: even in the presence of 20 mequiv of supported Pd, only a low yield (19%) of **3a** could be obtained.^{11b}

A hot filtration test was then performed using catalyst **2'a** in order to figure out if soluble Pd species are present in the reaction medium: after 20 min of reaction (Table 6, entry 7), **2'a** was removed by filtration (yield of **3a** at that point: 73%), and the filtrate was refluxed for another 20 h after which the yield reached only 74%. This result proves the absence of any soluble catalytic entity. Moreover, the amount of Pd present in the filtrate was less than 0.1% of the initial amount. Finally, catalyst **2'a** was studied by transmission electron microscopy (TEM), which showed only very scarce Pd aggregates. Interestingly, many aggregates appeared in **2'a** very quickly after the beginning of the reaction: they were already found after only 20 min. Neither their size (up to ca. 15 nm) nor their abundance changed significantly thereafter, even after seven uses. The exact nature of the catalytic sites remains to be studied. The Pd contents of the fresh catalyst and of the catalyst recovered after seven uses were found to be identical within experimental error.

The cross-coupling of various aryl chlorides and arylboronic acids were performed in the presence of catalyst **2'a** (Table 7) and very good yields were obtained in the presence of either electron-rich or electron-deficient substituents on each reactant. Noteworthy, sterically crowded 2-substituted, 2,6-disubstituted and even 2,6,2'-trisubstituted biaryls could be prepared in good yields (entries 3, 10–12, 16). 1,4-Dichlorobenzene reacted with 1.1 equiv of phenylboronic acid to give the monosubstituted biaryl **3h** in 66% yield (entry 8). However, in the presence of 2.8 equiv of phenylboronic acid and 3.1 equiv of CsF, *p*-terphenyl was obtained in 86% yield.

Finally, **2'a** can be successfully used for cross-couplings involving heterocyclic aryl chlorides or heterocyclic arylboronic

acids. The reaction between 3-thiopheneboronic acid and 4-chloroacetophenone gave the expected biaryl **3r** in 64% isolated yield, whereas the cross-coupling of 2-chloropyridine and phenylboronic acid afforded 2-phenylpyridine (**3s**) in 88% isolated yield.

3. Conclusions

Short and efficient syntheses of air- and moisture-stable, easy to recover and reuse, polymer-supported Pd catalysts have been developed. In particular, the (*tert*-butylphenylphosphinomethyl)polystyrene-supported Pd catalyst **2'a** was highly reactive for Suzuki couplings of aryl chlorides. It can easily be reused more than seven times without any loss of efficiency. Remarkably, less than 4 mequiv of Pd are lost during this reaction. Therefore, the crude biaryls obtained contain only a negligible amount of Pd contaminants, which considerably simplifies their purification procedures. Moreover, the environment-related preoccupation to preserve scarce natural resources is fulfilled.

4. Experimental section

4.1. General remarks

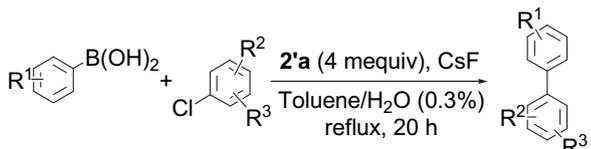
The reagents were obtained from commercial sources and were used without further purifications. Dichlorophenylphosphine, *tert*-butyldichlorophosphine and di-*tert*-butylchlorophosphine were purchased from Sigma–Aldrich. The Merrifield resin was purchased from Polymer Laboratories (PL-CMS Resin, 0.86 mmol/g, 75–150 μm). The Tentagel-Br and the bromopolystyrene resins were purchased from Fluka. THF and cyclohexane were distilled from sodium/benzophenone. The syntheses of chlorophosphines **1a–e**, catalysts **2a–h** and **2'a** were performed in dry glassware under an atmosphere of argon. Since aryl-*tert*-butylchlorophosphines **1a–e** were air-, water- and heat-sensitive (they are only stable for some hours at 0 °C), they were used directly and attempts to get analytical samples were, as expected, unfruitful. Catalysts **2a–h** and **2'a** were air- and moisture-stable. The reaction mixtures were filtered on a polytetrafluoroethylene Whatman membrane (0.2 μm). ¹H- and ³¹P NMR spectra were recorded using a 400 MHz instrument in CDCl₃. Chemical shifts are reported in parts per million (δ) downfield from TMS. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), and m (multiplet). The ¹H NMR spectra of biaryls **3a–s** and the melting points of solid biaryls were in accordance with literature reports (see below). Elemental analyses were performed by the Service Central d'Analyses du CNRS, Solaize (France).

4.2. Syntheses of the polymer-supported Pd catalysts

4.2.1. Synthesis of *tert*-butylchlorophenylphosphine (1a**).** Dichlorophenylphosphine (27.1 mL, 0.2 mol, 1.0 equiv) was added in small portions to a mixture of a 1.5 M solution of *tert*-butyllithium in pentane (160 mL, 0.24 mol, 1.2 equiv) and anhydrous cyclohexane (700 mL) at –40 °C under an atmosphere of argon. The reaction mixture was successively stirred at –40 °C for 1 h, warmed to rt for 20 h and centrifuged (3000 t/min for 3 min) under an atmosphere of argon to remove the inorganic salts. The organic solvents were distilled off under an atmosphere of argon. The residue was dried under vacuum (0.1 mbar) for 20 h. The resulting yellowish oil (34.9 g, 87%) contained **1a** (purity > 90%) and no dichlorophenylphosphine was left. ¹H NMR (400 MHz, CDCl₃): δ 0.91 (d, ³J(H,P)=13.6 Hz, 9H), 7.28 (m, 3H), 7.49 (m, 2H). ³¹P NMR (162 MHz, CDCl₃): δ 109.5.

4.2.2. General procedure for the syntheses of aryl-*tert*-butylchlorophosphines **1b–e.** A 1.5 M solution of *tert*-butyllithium in pentane (12.6 mL, 18.9 mmol, 2.2 equiv) was added dropwise at 0 °C to solutions of aryl bromides (9.46 mmol, 1.1 equiv) in

Table 7
Syntheses of biaryls



Entry ^a	R ¹	R ²	R ³	Product	Yield ^b (%)
1	H	4-Ac	H	3a	90
2	H	3-Ac	H	3b	78
3	H	2-Ac	H	3c	90
4	H	4-NO ₂	H	3d	86
5	H	H	H	3e	98
6	H	4-Me	H	3f	86
7	H	4-OMe	H	3g	72
8 ^c	H	4-Cl	H	3h	66
9	H	3-Me	H	3i	79
10	H	2-Me	H	3j	82
11	H	2-Me	6-Me	3k	88
12	2-Me	2-Me	6-Me	3l	61
13	4-OMe	4-Ac	H	3m	93
14 ^d	3-NH ₂	4-Ac	H	3n	69
15	4-Me	4-Ac	H	3o	90
16	2-Me	4-Ac	H	3p	86
17 ^d	3-NO ₂	4-Ac	H	3q	78

^a Reactions performed with 1.0 equiv (0.65 mmol) of aryl chloride, 1.4 equiv of arylboronic acid, 1.5 equiv of CsF.

^b Isolated yields after flash chromatography of the crude reaction mixture on silica gel.

^c Reaction performed with 1.0 equiv (0.65 mmol) of 1,4-dichlorobenzene, 1.1 equiv of phenylboronic acid and 1.2 equiv of CsF in toluene/H₂O.

^d Reactions performed in the presence of EtOH.

anhydrous cyclohexane (20 mL) under an atmosphere of argon. The resulting suspensions were then warmed to rt for 20 h. A solution of *tert*-butyldichlorophosphine (1.37 g, 8.6 mmol, 1.0 equiv) in anhydrous cyclohexane (20 mL) was then added dropwise at 0 °C. The resulting suspensions were stirred at 0 °C for 15 min then warmed to rt for 1 h. The reaction mixtures were centrifuged (3000 t/min for 3 min) under an atmosphere of argon to remove the inorganic salts. The organic solvents were distilled off under an atmosphere of argon. The residues were dried under vacuum (0.1 mbar) for 20 h. The resulting yellowish oils contained **1b–e** (purities >90%) and no *tert*-butyldichlorophosphine was left.

4.2.2.1. *tert*-Butylchloro-(2-methylphenyl)phosphine (1b). 86% yield (1.59 g). Yellowish oil. ¹H NMR (400 MHz, CDCl₃): δ 1.02 (d, ³J(H,P)=13.6 Hz, 9H), 2.48 (s, 3H), 7.10 (m, 1H), 7.21 (m, 2H), 7.69 (m, 1H). ³¹P NMR (162 MHz, CDCl₃): δ 102.1.

4.2.2.2. *tert*-Butylchloro-(3-methylphenyl)phosphine (1c). 87% yield (1.61 g). Yellowish oil. ¹H NMR (400 MHz, CDCl₃): δ 0.95 (d, ³J(H,P)=13.8 Hz, 9H), 2.30 (s, 3H), 7.14 (m, 1H), 7.21 (m, 1H), 7.33 (m, 2H). ³¹P NMR (162 MHz, CDCl₃): δ 109.5.

4.2.2.3. *tert*-Butylchloro-(4-methylphenyl)phosphine (1d). 86% yield (1.59 g). Yellowish oil. ¹H NMR (400 MHz, CDCl₃): δ 1.04 (d, ³J(H,P)=13.6 Hz, 9H), 2.39 (s, 3H), 7.23 (d, ³J(H,H)=8.0 Hz, 2H), 7.53 (d, ³J(H,H)=³J(H,P)=8.0 Hz, 2H). ³¹P NMR (162 MHz, CDCl₃): δ 109.4.

4.2.2.4. *tert*-Butylchloro-(1-naphthyl)phosphine (1e). The same procedure as above was followed on a small scale (2.37 mmol of 1-bromonaphthalene). The residue was dried under vacuum (0.1 mbar) for 20 h to give 480 mg (89%) of **1e** as a yellowish oil (purity >90%, no *tert*-butyldichlorophosphine was left). ¹H NMR (400 MHz, CDCl₃): δ 1.11 (d, ³J(H,P)=13.8 Hz, 9H), 7.54 (m, 3H), 7.89 (m, 2H), 8.01 (m, 1H), 8.59 (m, 1H). ³¹P NMR (162 MHz, CDCl₃): δ 103.7.

4.2.3. General procedure for the syntheses of (aryl-*tert*-butylphosphinomethyl)polystyrene-supported Pd catalysts 2a–f. Lithium wires (180 mg, 25.9 mmol, 30 equiv) were added to solutions of **1a–f** (8.60 mmol, 10 equiv) in anhydrous THF (20 mL) under an atmosphere of argon. The reaction mixtures were stirred at rt for 15 h. The resulting dark red solutions were added in small portions to suspensions of a Merrifield resin (1.0 g, 0.86 mmol of Cl) in anhydrous THF (30 mL) under an atmosphere of argon. The reaction mixtures were stirred at rt for 72 h then quenched by addition of a 2:1 mixture of acetone/H₂O (30 mL). These reaction mixtures were stirred for 30 min, the white resins were filtered under vacuum and washed successively with H₂O (3×30 mL), acetone (3×30 mL), CHCl₃ (3×30 mL), toluene (3×30 mL), and Et₂O (3×30 mL). The resins were then refluxed in a 3:1 mixture of EtOH/toluene (20 mL) for 20 h, then cooled to rt, filtered under vacuum, washed successively with toluene (30 mL), Et₂O (30 mL) and finally dried under vacuum (0.1 mbar) for 20 h. Pd(PPh₃)₄ (32.6 mg, 28.2 μmol) was then added in portions at rt to suspensions of these resins (1.0 g) in anhydrous toluene (50 mL) under an atmosphere of argon. The reaction mixtures were degassed with argon and stirred at rt for 20 h. The resins **2a–f** were filtered under vacuum and washed with toluene (3×20 mL) and Et₂O (3×20 mL). These resins were finally dried under vacuum (0.1 mbar) for 20 h.

4.2.3.1. (*tert*-Butylphenylphosphinomethyl)-polystyrene-supported Pd catalyst (2a). Yellow resin. Elemental analysis (%): P, 1.84; Pd, 0.26.

4.2.3.2. (*tert*-Butyl-[2-methylphenyl]phosphinomethyl)-polystyrene-supported Pd catalyst (2b). Yellow resin. Elemental analysis (%): P, 1.70; Pd, 0.30.

4.2.3.3. (*tert*-Butyl-[3-methylphenyl]phosphinomethyl)-polystyrene-supported Pd catalyst (2c). Yellow resin. Elemental analysis (%): P, 1.90; Pd, 0.29.

4.2.3.4. (*tert*-Butyl-[4-methylphenyl]phosphinomethyl)-polystyrene-supported Pd catalyst (2d). Yellow resin. Elemental analysis (%): P, 1.99; Pd, 0.31.

4.2.3.5. (*tert*-Butyl-[1-naphthyl]phosphinomethyl)polystyrene-supported Pd catalyst (2e). Yellow resin. Elemental analysis (%): P, 0.93; Pd, 0.30.

4.2.4. Synthesis of (*tert*-butylphenylphosphinomethyl)-polystyrene-supported Pd catalyst (2'a). Lithium wires (3.6 g, 0.52 mol, 30 equiv) were added to a solution of **1a** (0.17 mol, 10 equiv) in anhydrous THF (400 mL) under an atmosphere of argon. The reaction mixture was stirred at rt for 15 h. The resulting dark red solution was added in small portions to a suspension of a Merrifield resin (20 g, 17.2 mmol of Cl) in anhydrous THF (600 mL) under an atmosphere of argon. The reaction mixture was stirred at rt for 72 h then quenched by addition of a 2:1 mixture of acetone/H₂O (600 mL). This reaction mixture was stirred for 30 min, the white resin was filtered under vacuum and washed with H₂O (3×600 mL), acetone (3×600 mL), CHCl₃ (3×600 mL), toluene (3×600 mL), and Et₂O (3×600 mL). The resin was then refluxed in a 3:1 mixture of EtOH/toluene (400 mL) for 20 h, then cooled to rt, filtered under vacuum, washed successively with toluene (600 mL), Et₂O (600 mL) and finally dried under vacuum (0.1 mbar) for 20 h. Pd(PPh₃)₄ (0.22 g, 0.19 mmol) was then added at rt to a suspension of this resin (20 g) in anhydrous toluene (1 L) under an atmosphere of argon. The reaction mixture was degassed with argon and stirred at rt for 20 h. The resin **2'a** was filtered under vacuum and washed successively with toluene (3×400 mL) and Et₂O (3×400 mL). These filtrates were combined and evaporated to dryness. The amount of Pd was then determined after complete mineralization (see below) and found to be 13 μg (0.3%). The white resin was finally dried under vacuum (0.1 mbar) for 20 h to give 20.9 g of **2'a**. Elemental analysis (%): P, 1.57; Pd, 0.10.

4.2.5. Synthesis of (*tert*-butylphenylphosphino)polystyrene-supported Pd Catalyst 2g. Lithium wires (260 mg, 37.5 mmol, 30 equiv) were added to a solution of **1a** (2.51 g, 12.5 mmol, 10 equiv) in anhydrous THF (20 mL) under an atmosphere of argon. The reaction mixture was stirred at rt for 15 h. The resulting dark red solution was added in small portions to a suspension of a bromopolystyrene resin (1.0 g, 1.25 mmol of Br) in anhydrous THF (20 mL) under an atmosphere of argon. The reaction mixture was stirred at rt for 72 h then quenched by addition of a 2:1 mixture of acetone/H₂O (30 mL). This reaction mixture was stirred for 30 min, the white resin was filtered under vacuum and washed successively with H₂O (3×30 mL), acetone (3×30 mL), toluene (3×30 mL), and Et₂O (3×30 mL). The resin was then refluxed in a 3:1 mixture of EtOH/toluene (20 mL) for 20 h, then cooled to rt, filtered under vacuum, washed successively with toluene (30 mL), Et₂O (30 mL) and finally dried under vacuum (0.1 mbar) for 20 h. Pd(PPh₃)₄ (10.9 mg, 9.4 μmol) was then added in portions at rt to a suspension of this resin (1.0 g) in anhydrous toluene (50 mL) under an atmosphere of argon. The reaction mixture was degassed with argon and stirred at rt for 20 h. The resin **2g** was filtered under vacuum and washed successively with toluene (3×20 mL) and Et₂O (3×20 mL). The resin was finally dried under vacuum (0.1 mbar) for 20 h to give 0.99 g of **2g**. Elemental analysis (%): P, 0.93; Pd, 0.10.

4.2.6. Synthesis of (*tert*-butylphenylphosphino)polystyrene-polyethyleneoxide-supported Pd catalyst 2h. Lithium wires (100 mg, 14.4 mmol, 30 equiv) were added to a solution of **1a** (960 mg,

4.8 mmol, 10 equiv) in anhydrous THF (12 mL) under an atmosphere of argon. The reaction mixture was stirred at rt for 15 h. The resulting dark red solution was added in small portions to a suspension of a Tentagel-Br resin (1.0 g, 0.48 mmol of Br) in anhydrous THF (12 mL) under an atmosphere of argon. The reaction mixture was stirred at rt for 72 h then quenched by addition of a 2:1 mixture of acetone/H₂O (30 mL). This reaction mixture was stirred for 30 min, the white resin was filtered under vacuum and washed successively with H₂O (3×30 mL), acetone (3×30 mL), toluene (3×30 mL), and Et₂O (3×30 mL). The resin was then refluxed in a 3:1 mixture of EtOH/toluene (20 mL) for 20 h, then cooled to rt, filtered under vacuum, washed successively with toluene (30 mL), Et₂O (30 mL) and finally dried under vacuum (0.1 mbar) for 20 h. Pd(PPh₃)₄ (10.9 mg, 9.4 μmol) was then added in portions at rt to a suspension of this resin (1.0 g) in anhydrous toluene (50 mL) under an atmosphere of argon. The reaction mixture was degassed with argon and stirred at rt for 20 h. The resin **2h** was filtered under vacuum and washed successively with toluene (3×20 mL) and Et₂O (3×20 mL). The resin was finally dried under vacuum (0.1 mbar) for 20 h to give 1.01 g of **2h**. Elemental analysis (%): P, 1.69; Pd, 0.10.

4.3. Syntheses of biaryls 3a–s

4.3.1. General procedure for the syntheses of biaryls 3a–g, 3i–m, 3o–p and 3r–s. Catalyst **2'a** (277 mg, 4 mequiv of Pd) was added to a solution of aryl chloride (0.65 mmol, 1.0 equiv), arylboronic acid (0.91 mmol, 1.4 equiv), CsF (149 mg, 0.98 mmol, 1.5 equiv) in a mixture of toluene (3.5 mL) and H₂O (10 μL). The reaction mixture was degassed with argon and heated at reflux for 20 h. After cooling to rt, **2'a** was filtered under vacuum on a 0.2 μm membrane. The catalyst was washed with AcOEt (3×10 mL). The combined organic phase was washed with H₂O (20 mL), dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel to afford pure biaryls after drying under vacuum.

4.3.1.1. 1-(4-Biphenyl)ethanone (3a). Elution with AcOEt/Cyclohexane 10:90 afforded 115 mg (90% yield) of a white solid. Mp 123–124 °C (lit. mp 122–123 °C).¹⁷ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.66 (s, 3H), 7.45 (m, 3H), 7.64 (d, ³J(H,H)=7.0 Hz, 2H), 7.69 (d, ³J(H,H)=6.7 Hz, 2H), 8.05 (d, ³J(H,H)=6.7 Hz, 2H).

4.3.1.2. 1-(3-Biphenyl)ethanone (3b). Elution with AcOEt/Cyclohexane 5:95 afforded 100 mg (78% yield) of a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):^{11b} 2.67 (s, 3H), 7.31 (t, ³J(H,H)=7.6 Hz, 1H), 7.39 (t, ³J(H,H)=7.6 Hz, 2H), 7.46 (t, ³J(H,H)=7.4 Hz, 1H), 7.54 (d, ³J(H,H)=7.6 Hz, 2H), 7.70 (d, ³J(H,H)=7.4 Hz, 2H, 1H), 7.85 (d, ³J(H,H)=7.4 Hz, 1H), 8.1 (s, 1H).

4.3.1.3. 1-(2-Biphenyl)ethanone (3c). Elution with AcOEt/Cyclohexane 5:95 afforded 115 mg (90% yield) of a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):^{11b} 2.01 (s, 3H), 7.41 (m, 7H), 7.54 (m, 2H).

4.3.1.4. 4-Nitrobiphenyl (3d). Elution with AcOEt/Cyclohexane 1:99 afforded 111 mg (86% yield) of a yellowish solid. Mp 114–115 °C (lit. mp 113–115 °C).¹⁸ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.49 (m, 3H), 7.64 (d, ³J(H,H)=7.1 Hz, 2H), 7.75 (d, ³J(H,H)=7.1 Hz, 2H), 8.31 (d, ³J(H,H)=7.1 Hz, 2H).

4.3.1.5. Biphenyl (3e). Elution with AcOEt/Cyclohexane 1:99 afforded 98 mg (98% yield) of a white solid. Mp 71–72 °C (lit. mp 71 °C).¹⁹ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.41 (m, 6H), 7.61 (d, ³J(H,H)=7.3 Hz, 4H).

4.3.1.6. 4-Methylbiphenyl (3f). Elution with Et₂O/Cyclohexane 1:99 afforded 94 mg (86% yield) of a yellowish solid. Mp 47–48 °C (lit. mp 47.7 °C).²⁰ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.41 (s, 3H), 7.40 (m, 3H), 7.44 (t, ³J(H,H)=7.6 Hz, 2H), 7.50 (d, ³J(H,H)=8.4 Hz, 2H), 7.59 (d, ³J(H,H)=8.4 Hz, 2H).

4.3.1.7. 4-Methoxybiphenyl (3g). Elution with AcOEt/Cyclohexane 2:98 afforded 86 mg (72% yield) of a white solid. Mp 92–94 °C (lit. mp 91.1–92.3 °C).²¹ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.87 (s, 3H), 6.99 (d, ³J(H,H)=8.8 Hz, 2H), 7.31 (t, ³J(H,H)=7.3 Hz, 1H), 7.42 (m, 2H), 7.55 (m, 4H).

4.3.1.8. 4-Chlorobiphenyl (3h). Elution with cyclohexane afforded 81 mg (66% yield) of a white solid. Mp 78–79 °C (lit. mp 79–79.5 °C).²² ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.41 (m, 5H), 7.54 (m, 4H).

4.3.1.9. 3-Methylbiphenyl (3i). Elution with Et₂O/Cyclohexane 1:99 afforded 86 mg (79% yield) of an orange oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):^{11b} 2.46 (s, 3H), 7.20 (m, 1H), 7.39 (m, 6H), 7.62 (d, ³J(H,H)=7.3 Hz, 2H).

4.3.1.10. 2-Methylbiphenyl (3j). Elution with Et₂O/Cyclohexane 1:99 afforded 90 mg (82% yield) of a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):^{11b} 2.29 (s, 3H), 7.26 (m, 4H), 7.35 (m, 3H), 7.41 (m, 2H).

4.3.1.11. 2,6-Dimethylbiphenyl (3k). Elution with cyclohexane afforded 104 mg (88% yield) of a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):²³ 2.05 (s, 6H), 7.14 (m, 5H), 7.35 (m, 1H), 7.42 (m, 2H).

4.3.1.12. 2,6,2'-Trimethylbiphenyl (3l). Elution with cyclohexane afforded 78 mg (61% yield) of a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):²³ 1.96 (s, 6H), 1.98 (s, 3H), 7.17 (m, 7H).

4.3.1.13. 1-(4-(4'-Methoxy)biphenyl)ethanone (3m). Elution with AcOEt/Cyclohexane 10:90 afforded 137 mg (93% yield) of a yellowish solid. Mp 152–153 °C (lit. mp 153.5–155 °C).²⁴ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.64 (s, 3H), 3.88 (s, 3H), 7.01 (d, ³J(H,H)=8.8 Hz, 2H), 7.59 (d, ³J(H,H)=8.8 Hz, 2H), 7.65 (d, ³J(H,H)=8.3 Hz, 2H), 8.02 (d, ³J(H,H)=8.3 Hz, 2H).

4.3.1.14. 1-(4-(4'-Methyl)biphenyl)ethanone (3o). Elution with AcOEt/Cyclohexane 10:90 afforded 123 mg (90% yield) of a white solid. Mp 122–123 °C (lit. mp 121–121.4 °C).²⁵ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.42 (s, 3H), 2.65 (s, 3H), 7.29 (d, ³J(H,H)=8.1 Hz, 2H), 7.54 (d, ³J(H,H)=8.1 Hz, 2H), 7.68 (d, ³J(H,H)=8.3 Hz, 2H), 8.03 (d, ³J(H,H)=8.3 Hz, 2H).

4.3.1.15. 1-(4-(2'-Methyl)biphenyl)ethanone (3p). Elution with AcOEt/Cyclohexane 10:90 afforded 118 mg (86% yield) of a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):^{11b} 2.28 (s, 3H), 2.66 (s, 3H), 7.28 (m, 4H), 7.44 (d, ³J(H,H)=8.5 Hz, 2H), 8.02 (d, ³J(H,H)=8.5 Hz, 2H).

4.3.1.16. 4-(3-Thienyl)acetophenone (3r). Elution with AcOEt/Cyclohexane 10:90 afforded 84 mg (64% yield) of a white solid. Mp 150–151 °C (lit. mp 149–150).²⁶ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.64 (s, 3H), 7.45 (m, 2H), 7.59 (m, 1H), 7.70 (d, ³J(H,H)=8.5 Hz, 2H), 8.00 (d, ³J(H,H)=8.5 Hz, 2H).

4.3.1.17. 2-Phenylpyridine (3s). Elution with AcOEt/Cyclohexane 2:98 afforded 89 mg (88% yield) of a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm):²⁷ 7.25 (m, 1H), 7.43 (m, 3H), 7.75 (m, 2H), 8.00 (d, ³J(H,H)=8.6 Hz, 2H), 8.71 (d, ³J(H,H)=4.8 Hz, 1H).

4.3.2. General procedure for the syntheses of biaryls (3n) and (3q). Catalyst **2'a** (277 mg, 4 mequiv of Pd) was added to a solution of aryl chloride (0.65 mmol, 1.0 equiv), arylboronic acid (0.91 mmol, 1.4 equiv), CsF (149 mg, 0.98 mmol, 1.5 equiv) in a mixture of toluene (3.5 mL), EtOH (0.25 mL), and H₂O (10 μ L). The reaction mixture was degassed with argon and heated at reflux for 20 h. After cooling to rt, **2'a** was filtered under vacuum on a 0.2 μ m membrane. The catalyst was washed with AcOEt (3 \times 10 mL). The organic phase was washed with H₂O (20 mL), dried over MgSO₄, filtered and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel to afford pure biaryls after drying under vacuum.

4.3.2.1. (1-(3'-Amino)biphenyl)ethanone (3n). Elution with AcOEt/Cyclohexane 10:90 afforded 95 mg (69% yield) of an orange solid. Mp 162–163 °C (lit. mp 160–161 °C).²⁷ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.97 (s, 3H), 4.13 (br s, 2H), 7.06 (d, ³J(H,H)=8.1 Hz, 1H), 7.35 (d, ³J(H,H)=7.6 Hz, 1H), 7.60 (m, 2H), 7.99 (d, ³J(H,H)=7.9 Hz, 2H), 8.34 (d, ³J(H,H)=7.9 Hz, 2H).^{11b}

4.3.2.2. (1-(3'-Nitro)biphenyl)ethanone (3q). Elution with AcOEt/Cyclohexane 10:90 afforded 122 mg (78% yield) of a yellowish solid. Mp 110–111 °C (lit. mp 110.5–111 °C).²⁸ ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.68 (s, 3H), 7.67 (t, ³J(H,H)=8.0 Hz, 1H), 7.74 (d, ³J(H,H)=8.2 Hz, 2H), 7.96 (d, ³J(H,H)=8.0 Hz, 1H), 8.09 (d, ³J(H,H)=8.2 Hz, 2H), 8.27 (d, ³J(H,H)=8.0 Hz, 1H), 8.50 (s, 1H).

4.4. General procedure for hot filtration and determination of the Pd leached in the reaction medium during the Suzuki reaction

The reaction mixture was filtered at reaction temperature on a 0.2 μ m membrane and the catalyst washed with AcOEt (3 \times 10 mL). For Pd determinations, the filtrates were combined and evaporated under reduced pressure. A mixture of concentrated H₂SO₄ (3 mL) and fuming HNO₃ (2 mL) was added to the residue. This mixture was heated in a fume hood until disappearance of nitric fumes, complete evaporation of HNO₃ and beginning of the reflux of the remaining H₂SO₄. After cooling to 100 °C, fuming HNO₃ (2 mL) was then added, the mixture was heated until evaporation of HNO₃ and this process was repeated three times, the heating of the sample in acids during, as a whole, 25 min. Most of the H₂SO₄ was then boiled off and after cooling a mixture of concentrated HCl (2 mL) and concentrated HNO₃ (2 mL) was added and heated until evaporation of the acids. The residue was then dissolved in H₂O (25 mL) and the amount of Pd present in this mixture was then determined by complexation following a procedure described in the lit.²⁹ or by ICP-MS.

4.5. General procedure for the determination of the Pd content of the catalyst

The same procedure as above was used using a 20 mg sample of catalyst instead of the reaction residue. Three independent experiments were performed and the average value retained.

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- Noteworthy when *sec*- or *n*-butyllithium was reacted with dichlorophenylphosphine by using the same reaction conditions than for the preparation of **1a**, only complex mixtures were obtained. Several attempts were then carried out in order to prepare *sec*- or *n*-butylchlorophenylphosphine by changing the nature of the solvent (Et₂O, THF), the temperature of the reaction (–78 °C in Et₂O or THF), replacing the alkyllithium reagents with the corresponding Grignard reagents, but all were unsuccessful.

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