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Silia*Cat* Diphenylphosphine Palladium(II) Catalyzed Borylation of Aryl Halides

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We investigate the heterogeneously catalyzed direct synthesis of boronic acid pinacol esters using a wide range of aryl chlorides, bromides, and iodides, and bis(pinacolato)diboron as the borylating agent over the sol–gel entrapped Silia*Cat* diphenylphosphine palladium(II) catalyst. Optimization of the reaction conditions, scale-up of the optimized process, and analysis of palladium leaching enabled us to establish a new selective route for direct access to a diverse set of boronic acid pinacol esters.

Introduction

The Suzuki–Miyaura reaction[1] is perhaps the single most important cross-coupling synthetic methodology to prepare diverse biaryls and heterobiaryls, ubiquitous motifs in pharmaceuticals, natural products, and organic chemistry needed in many industrial sectors.[2] The palladium-catalyzed Suzuki–Miyaura cross-coupling involves a boron-containing nucleophile (a variety of aryl and heteroarylboronic acids, esters, Ar—BBN, trifluoroborates, as well as other boron species) and vinyl or aryl halides (the electrophilic species). Besides crucial high functional-group tolerance, its significant benefits include high efficiency, low toxicity, mild reaction conditions, as well the relative stability of boronic acid to heat, oxygen, and water, as well as ease of handling and separation of boron-containing byproducts.[2]

The typical preparation of arylboronic acids or esters used in the Suzuki–Miyaura coupling involves the reaction between an organoborate and alkyl- or aryllithium compounds or Grignard reagents.[3] However, the method is difficult to apply to aryl chlorides or to substrates bearing functional groups that are not compatible with organolithium reagents.[4] Also, some aryllithium intermediates are intrinsically unstable, as in the case of many aromatic heterocycles.[5]

The use of boronic esters in place of boronic acids in the Suzuki–Miyaura coupling is desirable if reactive functional groups are present in the electrophilic aryl halides. One effective methodology to prepare highly functionalized boronic esters makes use of the magnesiation of iodoaryl and iodoheteroaryl boronic esters with *i*PrMgCl·LiCl leading to mixed bimetallic compounds that are easily turned into boronic esters.[6]

In 1995, Miyaura pioneered the palladium-catalyzed borylation of aryl halides.[7] The report described the first synthesis of numerous aryl- and heteroaryl boron derivatives bearing sensitive functional groups through cross-coupling of bis(pinacolato)diboron (B_2Pin_2) with aryl halides or vinyl halides, without the use of toxic organometallic reagents. With easy and greater access to diverse borylated species, the use of the Suzuki–Miyaura reaction became routine both in industry and in research laboratories.[8] Borylated pinacol esters derived from B_2Pin_2, for example are suitable synthetic coupling partners in cross-coupling reactions because they survive the normal product work-up procedures including chromatographic purification, and are stable towards oxidation by oxygen in air.[9]

Since then, considerable attention has been devoted to catalytic borylation. Beyond Pd, new Cu,[10] Rh,[11] Ni,[12] and Ir[13] catalysts have been identified.

The most versatile catalyst systems reported to date employ (dicyclohexylphosphino) biphenyl-type ligands such as SPhos and XPhos.[14] The use of Pd^0 complexes coordinated to these ligands allows the borylation of sterically or electronically challenging aryl chlorides (2 mol% Pd/SPhos, room temperature, 86%) and 4-chloroanisole (0.1 mol% Pd/XPhos, 110 °C, 94%). Another efficient and selective catalyst suitable for the cross-coupling of pinacolborane with aryl bromides enabling the synthesis of *ortho-*, *meta-*, and *para*-substituted electron-rich and electron-deficient arylboronates results from the combination of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and bis(2-di-*tert*-butylphosphinophenyl)ether.[15]

All the above reactions are homogeneously performed in the presence of Pd species in solution. Intense research attempts are devoted to efficiently heterogenize the palladium catalytic species,[16] with the aim to obtain selective and reusable solid cross-coupling catalysts avoiding product contamination associated with the use of expensive and nonreusable ho-

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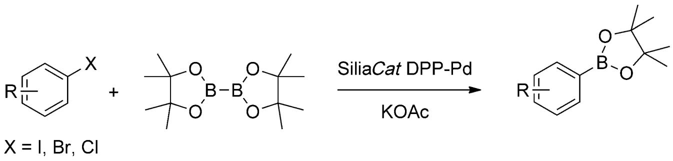
mogeneous Pd catalysts, and their undesired tendency to remain in the final products.

In this work, we report the successful heterogeneous palladium-catalyzed coupling reaction of B_2Pin_2 and aryl iodide, bromide, and chloride over Silia*Cat* diphenylphosphine palladium(II) (DPP–Pd) [Eq. (1)].



(1)

Silia*Cat* DPP–Pd (Figure 1) is an organosilica matrix functionalized with diphenylphosphine ligand bound to Pd^{2+} with a typical palladium loading of 0.2–0.3 mmol g−1, high surface area (300–650 $m^2 g^{-1}$), and large accessible mesoporosity.[17] Accordingly, this sol–gel catalyst is highly active in C–C coupling reactions.[18]

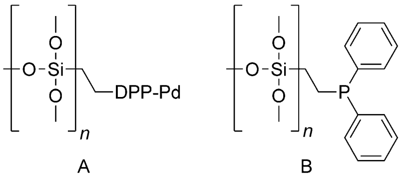


Figure 1. Chemical structure of A) commercially available Silia*Cat* DPP–Pd and B) the heterogenized diphenylphosphine ligand in Silia*Cat* DPP.

The reaction is heterogeneous in nature. There is no induction period, and no further conversion is observed in the reaction filtrate obtained after filtering the catalyst at 50% substrate conversion. We have recently discussed how to distinguish between homogeneous and heterogeneous palladium-catalyzed cross-coupling reactions,[16] almost concomitantly to Crabtree who published a similar study[19] of broader scope, addressing this central issue of modern research in catalysis, which is of great important in practical catalyst development and the object of the present study.

Following optimization of the reaction conditions, we investigate the scale-up of the process along with stability and reusability of the solid catalyst in several consecutive reaction runs. The catalyst is truly broad in scope and can be conveniently used in air without the need to exclude oxygen. The limited leaching in valued Pd and the excellent mechanical properties of organosilica make the case for practical application.

Results and Discussion

The reaction conditions were optimized by using 4-bromobenzonitrile as a substrate. Stronger bases, such as K_3PO_4 or K_2CO_3, promoted further reactions of the arylboronic esters formed with the haloarenes resulting in contamination by a substantial amount of dimer (36–60% yield). Milder KOAc base was unexpectedly the best basic species. Best results in terms of conversion (the yield of the product) and selectivity were obtained by performing the reaction in alcohol (*i*PrOH, *n*BuOH, 2-BuOH) and alcohol mixtures such as *n*PrOH/MeOH.

For example, entry 1 in Table 1 demonstrates that with DMSO as the solvent, 88% conversion and 83% selectivity were obtained in 16 h by using 1.5 equivalents of B_2Pin_2 and 3 equivalents of KOAc. The conversion in *n*PrOH/MeOH (v/v = 3/1) was instead complete in 2 h reaction time in 80% selectivity (entry 2). Further attempts to increase selectivity in arylboronic esters and reducing formation of the dimer below 20% by varying different reaction parameters were unsuccessful (entries 3–9).

Table 1. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and 4-bromobenzonitrile in DMSO and in *n*PrOH/MeOH.[a]

Entry	B_2Pin_2 [equiv.]	Base [equiv.]	Solvent	*t* [h]	Conv. (Select.)[b] [%]
1	1.50	KOAc (3)	DMSO	16	88 (83)
2	1.50	KOAc (3)	*n*-PrOH/MeOH	2	100 (80)
3	1.25	KOAc (3)	*n*-PrOH/MeOH	0.5	81 (83)
				1	88 (83)
				2	93 (84)
4	1.10	KOAc (3)	*n*-PrOH/MeOH	0.5	88 (75)
				1	100 (71)
5	1.05	KOAc (3)	*n*-PrOH/MeOH	1	100 (78)
6	1.00	KOAc (3)	*n*-PrOH/MeOH	1	96.5 (72)
7	0.75	KOAc (3)	*n*-PrOH/MeOH	1	86 (45)
8	1.05	KOAc (2)	*n*-PrOH/MeOH	1	84 (72)
				2	90 (69)
9	1.00	KOAc (2)	*n*-PrOH/MeOH	1	78 (79)
				2	86 (78)

[a] Experimental conditions: Substrate (5 mmol, 1 equiv.), B_2Pin_2 (from 1.0 to 1.5 equiv.), KOAc (from 2 to 3 equiv.), *n*PrOH/MeOH HPLC grade (20 mL, 3/1 v/v), Silia*Cat* DPP–Pd (0.5 mol%, Pd loading 0.25 $mmol\,g^{-1}$), 80 °C. [b] Conversion/selectivity evaluated by GC–MS.

Results in Table 2, however, demonstrate that with the anhydrous *i*PrOH used as solvent, the selectivity increases to more than 90%. Complete conversions with 99% (entry 5) or 98% (entry 6) selectivity were obtained in 1 h over 1 mol% of the Silia*Cat* DPP–Pd catalyst by using 1 equivalent of B_2Pin_2 in the presence of 2 equivalents of KOAc in 0.5 M and 0.75 M solvent with respect to the reagents.

The amount of catalyst was then decreased from 1 to 0.25 mol%. If 0.5 mol% catalyst was used, the complete conversion required 2 h (entry 8), whereas over 0.25 mol% catalyst a maximum 85% conversion was obtained in 4 h (entry 9).

The solvent also plays an important role. The reaction is generally accelerated in polar solvents (DMSO $\geq$ DMF > dioxane > toluene). However, in the seminal 1995 report, Miyaura performed the borylation in dioxane (the exact solvent), and toluene is generally the best solvent for nickel-catalyzed borylation. In Table 3 it is shown that for different solvents (EtOH, *n*BuOH, 2-BuOH, DMF, DMSO), complete conversion was in

Table 2. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and 4-bromobenzonitrile in anhydrous *i*PrOH (method A).[a]

Entry	B_2Pin_2 [equiv.]	Catalyst [mol %]	Base [equiv.]	Solvent [M][b]	*t* [h]	Conv. (Select.)[c] [%]	Yield[c] [%]	Leaching [mg kg^{-1}][d] Pd	Si
1	1.25	1	KOAc (3)	*i*PrOH (0.56)	1	100 (90)	80	$<$0.50	1.40
2	1.1	1	KOAc (3)	*i*PrOH (0.52)	1	100 (94)	88	$<$0.50	0.96
3	1	1	KOAc (3)	*i*PrOH (0.50)	1	100 (95)	92	0.50	0.89
4	1	1	KOAc (2.5)	*i*PrOH (0.50)	1	100 (97)	94	$<$0.50	0.98
5	1	1	KOAc (2)	*i*PrOH (0.50)	1	100 (99)	97	1.57	1.12
6	1	1	KOAc (2)	*i*PrOH (0.75)	1	100 (98)	96	0.68	1.20
7	1	1	KOAc (2)	*i*PrOH (1.00)	1	100 (94)	93	$<$0.50	0.56
8	1	0.5	KOAc (2)	*i*PrOH (0.50)	1	94	–	$<$0.50	0.30
					2	100 (89)			
9	1	0.25	KOAc (2)	*i*PrOH (0.50)	1	59	–	2.50	1.46
					2	63			
					4	85 (96)			

[a] Experimental conditions: Substrate (5 mmol, 1 equiv.), B_2Pin_2 (from 1.25 to 1 equiv.), KOAc (from 3 to 2 equiv.), anhydrous *i*PrOH (from 0.5 to 1.0 M, molar concentration with respect to the reagents), Silia*Cat* DPP–Pd (from 0.25 to 1 mol %, Pd loading 0.25 mmol g^{-1}), 82 °C. [b] Molar concentration with respect to the reagents. [c] Conversion/selectivity evaluated by GC–MS. Isolated yield. [d] The leaching in Pd and Si was assessed by ICP–OES analysis of the isolated crude product in DMF solvent (concentration 100 mg mL^{-1}) and reported as mg kg^{-1} API. $LOD_{Pd} = 0.05$ ppm in solution (100 mg mL^{-1} concentration) or 0.50 mg kg^{-1} in the crude product; $LOD_{Si} = 0.02$ ppm in solution (100 mg mL^{-1} concentration) or 0.20 mg kg^{-1} in the crude product.

Table 3. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and 4-bromobenzonitrile over 1 mol % Silia*Cat* DPP–Pd in different solvents (method A).[a]

Entry	Solvent	*t* [h]	Conv. (Select.)[b] [%]
1[b]	EtOH anh.	1	100 (82)
2	*n*-PrOH HPLC	1	97 (63)
3	anhydrous *n*-PrOH	1	99 (90)
4	*i*PrOH HPLC	1	100 (80)
5	anhydrous *i*PrOH	1	100 (99)
6	*n*BuOH HPLC	1	96 (62)
7	anhydrous 2-BuOH	1	100 (85)
8	anhydrous DMF	1	94
		2	100 (85)
9	anhydrous DMF/*i*PrOH	1	100 (84)
10	anhydrous DMSO	1	69
		2	71 (84)

[a] Experimental conditions: Substrate (5 mmol, 1 equiv.), B_2Pin_2 (1 equiv.), KOAc (2 equiv.), solvent (20 mL; 0.5 M, molar concentration with respect to the reagents), Silia*Cat* DPP–Pd (0.2 g, Pd loading 0.25 mmol g^{-1}), 1 h at 82 °C. [b] Conversion/selectivity evaluated by GC–MS.

general obtained in 1 h or 2 h. The best selectivity was nonetheless obtained in anhydrous *i*PrOH (99 %, Table 3, entry 5).

The conditions (method A) developed for 4-bromobenzonitrile borylation over 1 mol % Silia*Cat* DPP–Pd (Table 2, entry 5) were then applied to 4-bromoanisole, namely to a bromobenzene derivative functionalized with an electron-withdrawing group (Table 4, entry 1).

Now, only 66 % conversion could be obtained in 2 h. Conversion increased first to 75 % if the catalyst amount was doubled to 2 mol % (entry 2 in Table 4); and further increased to 80 % if the concentration of the reaction mixture was increased from 0.5 to 0.71 M (entry 3), or if 10 % higher amounts of B_2Pin_2 and KOAc were used (entry 4). Overall, entry 5 in Table 4 reveals that the complete conversion of 4-bromoanisole in 97 % selectivity (and 95 % isolated yield) was obtained (method B) if 1.1 equivalents of B_2Pin_2 were reacted with the substrate over 2 mol % catalyst in the presence of 2.2 equivalents of KOAc in 0.75 M *i*PrOH alcohol with respect to substrate and B_2Pin_2.

Further attempts to decrease the amount of the catalyst by using anhydrous *i*PrOH as solvent revealed that the conversion obtained in 3 h decreased to 96 % over 1.5 mol % (Table 4, entry 6) and to 93 % (entry 7) over 1 mol % Pd catalyst (with 0.75 M solvent). Conversion, however, rose again to 96 % by using a more concentrated 1 M solution (entry 8).

Heating should improve the conversion, so *i*PrOH was replaced by an alcohol solvent with a higher boiling point (2-BuOH) and the reaction mixture was heated from 82 °C to 92 °C. Under these harsher conditions, complete conversion over 1 mol % Pd catalyst was obtained in 3 h (Table 4, entry 9), and good 96 % conversion could also be reached in 5 h over 0.5 mol % Pd (entry 10). If the amount of the catalyst was further decreased to 0.25 mol %, the complete conversion required 16 h reaction time (entry 11).

Scale-up and stirring effects

In Table 5 the results of the borylation reaction of 4-bromoanisole over 2 mol % Silia*Cat* DPP–Pd are shown on scaling-up the reaction from 10 mmol to 200 mmol substrate. Leaching values in terms of mg kg^{-1} of both Si and Pd in the product [active pharmaceutical ingredients (APIs)] are included. In general, two methods (A and B) are used for the results in Tables 5–7. Method A (Table 2, entry 5) was used for substrates bearing electron-withdrawing groups ($-NO_2$ or $-CN$); whereas method B (Table 4, entry 5) was applied to the conversion of substrates containing electron-donating groups ($-OCH_3$, $-CH_3$, $-OH$ in *ortho*, *meta*, and *para* positions), and to the heteroatom substrates.

Early kinetic data (Table 5, entries 1–3) reveal that there is no induction period. More than 70 % of 4-bromoanisole was converted in the borylation product within the first 30 min of reaction and nearly all (98–99 %) substrate was converted in 90 min, except for the reaction with 10 mmol substrate in which the complete conversion required approximately 3 h (entry 1). Thus, the reaction rate increased by scaling up the conversion (Figure 2).

Table 4. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and 4-bromoanisole. Optimization of the reaction conditions.[a]

Entry	B_2Pin_2 [equiv.]	Catalyst [mol %]	KOAc [equiv.]	Solvents[b] [M]	*t* [h]	Conv. (Select)[c] [%]
1	1	1	2	*i*PrOH (0.50)	1	60
					2	66
					3	71 (92)
2	1	2	2	*i*PrOH (0.50)	1	75
					3	90 (94)
3	1	2	2	*i*PrOH (0.71)	1	80
					3	95 (96)
4	1.1	2	2.2	*i*PrOH (0.50)	1	85
					3	95 (99)
5	1.1	2	2.2	*i*PrOH (0.75)	1	84
					2	94
					3	100 (97)
6	1.1	1.5	2.2	*i*PrOH (0.75)	1	81
					3	96 (94)
7	1.1	1	2.2	*i*PrOH (0.75)	1	75
					3	93 (96)
8	1.1	1	2.2	*i*PrOH (1.00)	1	81
					3	96 (97)
9	1.1	1	2.2	2-BuOH (1.00)	1	85
					2	95
					3	100 (95)
10	1.1	0.5	2.2	2-BuOH (1.00)	1	75
					3	83
					5	96 (98)
11	1.1	0.25	2.2	2-BuOH (1.00)	1	54
					5	76
					16	100 (94)

[a] Experimental conditions: Substrate (from 5 to 10 mmol, 1 equiv.), B_2Pin_2 (from 1 to 1.1 equiv.), KOAc (from 2 to 2.2 equiv.), anhydrous 2-PrOH from 0.5 to 1.0 M, Silia*Cat* DPP–Pd (from 1 to 2 mol % Pd, Pd loading 0.25 mmol g^{-1}), at 82 °C. [b] Molar concentration with respect to the reagents. [c] Conversion/selectivity evaluated by GC–MS.

Table 5. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and 4-Bromoanisole in *i*PrOH (method B). Scale-up to 200 mmol starting product.[a]

Entry	Substrate [mmol]/[equiv.]	*t* [h]	Conv. (Select.)[d] [%]	Yield[d] [%]	Leaching[e] [mg kg^{-1} API] Pd	Si
1[b]	10/1	0.5	77	95	5.45	2.65
		2	92			
		3	100 (97)			
2[b]	20/1	0.5	77	97	8.12	5.78
		1.5	98			
		2	100 (98)			
3[b]	40/1	0.5	77	97.2	8.84	5.25
		1.5	99			
		2	100 (98)			
4[c]	40/1	0.5	78	97.5	8.17	5.84
		1.5	98			
		2	100 (98)			
5[c]	200/1	0.5	79	97	8.22	4.89
		1.5	99			
		2	100 (98)			

[a] Experimental conditions: Method B: Substrate (from 10 to 200 mmol, 1 equiv.), B_2Pin_2 (1.1 equiv.), KOAc (2.2 equiv.), *i*PrOH (0.75 M, molar concentration with respect to substrate and to B_2Pin_2, over Silia*Cat* DPP–Pd (2 mol %), 82 °C. [b] Magnetic stirring (700 rpm). [c] Mechanical stirring (550–600 rpm). [d] Conversion/selectivity evaluated by GC–MS. Isolated yield. [e] The leaching in Pd and Si was assessed by ICP–OES analysis of the isolated crude product in DMF solvent (concentration 100 mg mL^{-1}) and reported as mg kg^{-1} API.

In Figure 3 the kinetics of the reaction on 40 mmol substrate scale is shown if magnetic stirring (700 rpm) was replaced by mechanical stirring either with a normal stirrer (blade PTFE 19 mm/76 mm, width/length, for 10 mm shafts in a 500 mL three-necks flask) or with an oval stirrer (blades in PTFE 19 mm/60 mm, width/length, for 10 mm shafts). Only 89 % and 95 % conversion degrees, respectively, were achieved in 3 h.

The plot in Figure 3 also reveal that complete conversion in 90 min requires the use of a perforated banana-type stirrer (blades in PTFE 21 mm/87 mm, width/length, for 10 mm shafts). Stirring at 600 rpm rate was enough to ensure complete conversion of the entire substrate in 1.5 h.

The efficiency of the latter perforated banana-type stirrer is further shown in Figure 4. Under 40 mmol scale, complete conversion in 98 % selectivity in 90 min requires either 700 rpm magnetic stirring (Table 5, entry 3) or 600 rpm mechanical stirring (entry 4). The use of perforated banana-type stirrer in the scaled-up conversion of 200 mmol substrate in a 1000 mL three-necks flask (50 g borylation product synthesis) enables full conversion at 550 rpm (entry 5).

The results in Table 5 show that the values of palladium leached in the isolated crude product were <10 mg kg^{-1}, and that the values of leached Si were <10 mg kg^{-1} even after the conversion of 200 mmol starting product.

Scope of the heterogeneous reaction

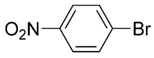
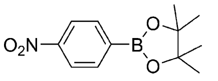
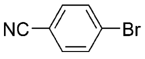
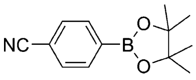
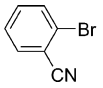
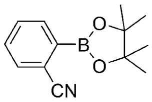
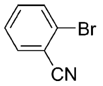
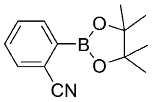
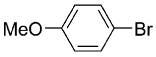
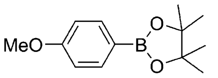
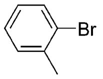
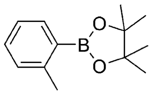
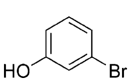
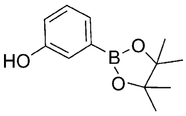
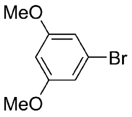
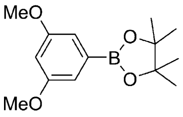
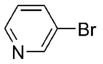
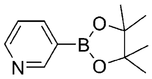
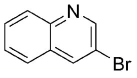
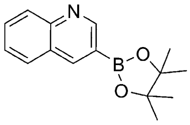
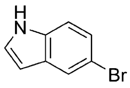
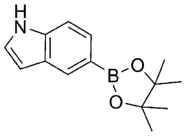
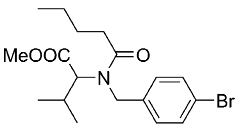
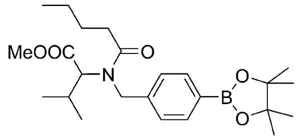
To explore the scope of the Silia*Cat* DPP–Pd heterogeneously catalyzed reaction we extended its application to various aryl bromides, chlorides, and iodides carrying electron-withdrawing or electron-donating groups, and to heteroatom substrates such as pyridine, indole, and quinoline.

The results obtained with bromide substrates by using method A (for substrates bearing electron-withdrawing groups) or method B (for substrates containing electron-donating groups and heteroatoms) are listed in Table 6. In general, borylation proceeded in good to excellent yields, achieving the desired boronic ester in 3 h. Only the indole derivative (entry 11) required 20 h to afford maximum 80 % conversion (with 81 % selectivity).

The results in Table 7 reveal that different aryl chloride substrates bearing electron-withdrawing groups or electron-donating groups can be coupled with B_2Pin_2 to selectively form boronate esters in the presence of Silia*Cat* DPP–Pd under the conditions of method B (Table 4, entry 5).

Complete conversions in high yield were obtained for 4-chloracetophenone in 0.5 h (Table 7, entry 2) and for 4-chlorotoluene in 2 h (entry 3). Coupling of

Table 6. SiliaCat DPP–Pd catalyzed coupling reaction of B_2Pin_2 and different aryl bromide substrates.[a]

Entry	Substrate	Method	Product	*t* [h]	Conv. (Select.)[b] [%]	Yield[c] [%]
1		A		1	100 (97)	93.5
2		A		1	100 (99)	94
3		A		1 2	51 74 (81)	–
4		B		1 2	77 99 (87)	86[d]
5		B		1 2 3	84 94 100 (97)	95
6		B		2 3	90 100 (99)	98
7		B		1	100 (98)	96
8		B		1 2	95 100 (98)	96
9		B		2 3	89 100 (98)	96
10		B		1 2	95 100 (88)	85[d]
11		B		1 2 20	48 58 89 (81)	72[d]
12		B		3	100 (97)	87

[a] Experimental conditions: Method A: Substrate (5 mmol, 1 equiv.), B_2Pin_2 (1 equiv.), KOAc (2 equiv.), anhydrous 2-PrOH (20 mL, 0.5 м, molar concentration with respect to aryl bromide and to B_2Pin_2) over SiliaCat DPP–Pd (1 mol%), 82 °C; Method B: Substrate (10 mmol, 1 equiv.), B_2Pin_2 (1.1 equiv.), KOAc (2.2 equiv.), anhydrous 2-PrOH (28 mL, 0.75 м, molar concentration with respect to aryl bromide and to B_2Pin_2) over SiliaCat DPP–Pd (2 mol%), 82 °C. [b] Conversion/selectivity evaluated by GC–MS. [c] Isolated yield. [d] Yield evaluated by GC–MS.

3-chloropyridine (90% isolated yield) occurred with 98% conversion in 3 h. Complete conversion of 4-chloroaniline and 2-chloroquinoline was obtained in 2 h, but with lesser selectivity (yields less than 80%, entries 5 and 6).

Under homogeneous conditions, the coupling of halide substrates with the C–I bond is faster than with the C–Br or C–Cl bonds. The heterogeneous reaction over Silia*Cat* DPP–Pd, however, revealed the opposite: namely 4-iodoanisole was less reactive than 4-bromoanisole and 4-chloroanisole (Table 8). In detail, the 4-iodoanisole borylation catalyzed by Silia*Cat* DPP–Pd, according to both method A and method B afforded 47% (Table 8, entry 1) and 74% (entry 2) conversion, respectively, in 3 h reaction time. This finding is in contrast to what is normally obtained in the Suzuki–Miyaura conversion of aryl halides, and points to a likely hindering effect of the matrix mesoporosity in the presence of the larger I containing substrates.

To increase the conversion to more than 80%, 1.5 equivalents of B_2Pin_2 and 3 equivalents of KOAc were needed (Table 8, entry 3, method C), with excellent conversion and selectivity obtained also for 3-iodoanisole (entry 4).

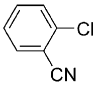
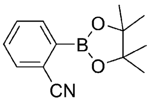
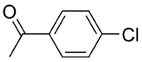
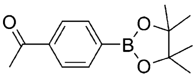
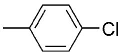
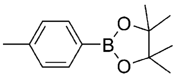
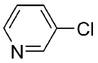
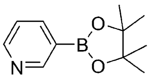
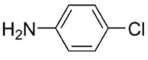
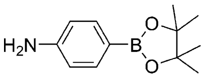
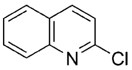
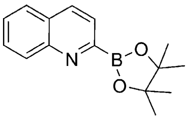
Leaching and catalyst stability

To investigate leaching of both Pd and Si from the Silia*Cat* DPP–Pd catalyst during catalysis, we analyzed the crude solid products by inductively coupled plasma optically emission spectroscopy (ICP–OES, Table 9). In general, values of leached Pd and Si in isolated crude product were <5 ppm, except for the 3-bromopyridine (entry 9), 3-bromoquinoline (entry 10), 3-chloropyridine (entry 13), and 2-chloroquinoline (entry 14) substrates. This clearly points to coordination of the nitrogen atoms in these aryl halides with the organosilica-tethered Pd.

The catalyst employed in the 72 mmol (12.5 g) substrate conversion in the 1st run was filtered after reaction completion, washed extensively (×2 with EtOAc, ×3 with $EtOH/H_2O$ v/v = 1/1, ×2 with EtOH), dried at room temperature, and reused in a subsequent run. Overall, six consecutive runs were performed with recovering and washing the catalyst each time as described above (Table 10).

In the 1st and 2nd run complete conversion could be obtained in 2 h. Then, a rapid decrease in activity was observed,

Table 7. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and different aryl chloride substrates.[a]

Entry	Substrate	Product	*t* [h]	Conv. (Select.)[b] [%]	Yield[c] [%]
1			1 24	21 (98) 48 (66)	31[d]
2			0.5	100 (98)	95
3			1 2	95 100 (97)	94
4			1 2 3	75 90 98 (96)	90
5			2	100 (75)	75[d]
6			2	100 (70)	70[d]

[a] Experimental conditions: Method B: Substrate (10 mmol, 1 equiv.), B_2Pin_2 (1.1 equiv.), KOAc (2.2 equiv.), anhydrous 2-PrOH (28 mL, 0.75 M, molar concentration with respect to aryl bromide and to B_2Pin_2) over Silia*Cat* DPP–Pd (2 mol%), 82 °C. [b] Conversion/selectivity evaluated by GC–MS. [c] Isolated yield. [d] Yield evaluated by GC–MS.

offset by increasing the reaction time. Hence, in 3rd run, complete conversion in 92% isolated yield required 4 h; whereas complete conversion in the 4th and 5th runs required 20 h, that is, ten times the original reaction time. Clearly, the tethered catalyst decomposes upon reuse, even if in general four catalytic cycles can be performed with the same catalyst affording the desired product in almost quantitative yield.

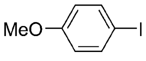
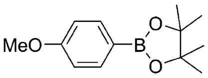
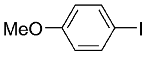
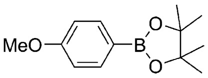
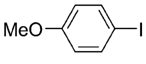
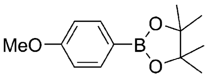
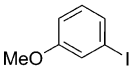
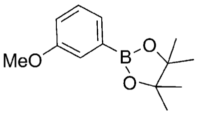
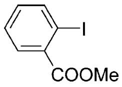
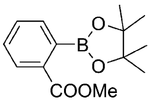
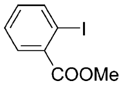
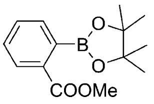
Conclusions

The heterogeneously catalyzed direct synthesis of boronic acid pinacol esters can now be performed with a wide range of aryl chlorides, bromides, and iodides, and bis(pinacolato)diboron as the borylating agent over the sol–gel entrapped Silia*Cat* diphenylphosphine palladium(II) catalyst. The use of anhydrous nontoxic *i*PrOH as a reaction solvent avoids homocoupling and increases the selectivity.

The method tolerates a wide range of functional groups and allows easy, direct access to a diverse set of boronic acid pinacol esters. Excellent yields and selectivities are achieved with very low (<5 ppm) leaching of valued Pd during catalysis.

All the reagents utilized are stable in air. Hence, the process does not require the use of a glovebox or inert conditions, with relevant practical advantages over existing methods that often require the exclusion of air and humidity from the reaction system.

Table 8. Silia*Cat* DPP–Pd catalyzed coupling reaction of B_2Pin_2 and different aryl iodides.[a]

Entry	Substrates	Method	Solvent [M][b]	Products	*t* [h]	Conv. (select.)[c] [%]	Yield[d] [%]
1		A	*i*PrOH (0.50)		3 20	47 57 (100)	74
2		B	*i*PrOH (0.75)		1 3	31 74 (100)	57
3		C	*i*PrOH (1.25)		1 3	71 82 (98)	81
4		C	*i*PrOH (1.25)		3	100 (98)	94[e]
5		B	*i*PrOH (0.75)		3 20	45 68 (70)	48
6		C	*i*PrOH (1.25)		3 5	65 82 (92)	75

[a] Experimental conditions: Method A: See the experimental conditions in Table 6; Method B: See the experimental conditions in Table 6; Method C: Substrate (10 mmol, 1 equiv.), B_2Pin_2 (1.5 equiv.), KOAc (3 equiv.), anhydrous 2-PrOH (20 mL, 1.25 M, molar concentration), 2 mol% Silia*Cat* DPP–Pd, 82 °C. [b] Molar concentration with respect to substrate and to B_2Pin_2. [c] Conversion/selectivity evaluated by GC–MS. [d] Yield evaluated by GC–MS. [e] Isolated yield.

The method could by easily scaled up from 10 to 200 mmol of starting product with noticeable increase in reaction rate and consistent low leaching upon scale-up, a clearly beneficial feature for practical applications of this commercial catalytic material in synthetic organic and medicinal chemistry. Further studies using this sol–gel catalyst under flow and in consecutive reactions performed in one pot are in course.

Experimental Section

Materials and analyses

All reactions were run in oven-dried flasks using anhydrous solvents. Inert conditions were not required. Unless otherwise noted, reagents were commercially available and used without purification. The substrate used in Table 5, entry 12, was synthesized by following the literature procedure.[20]

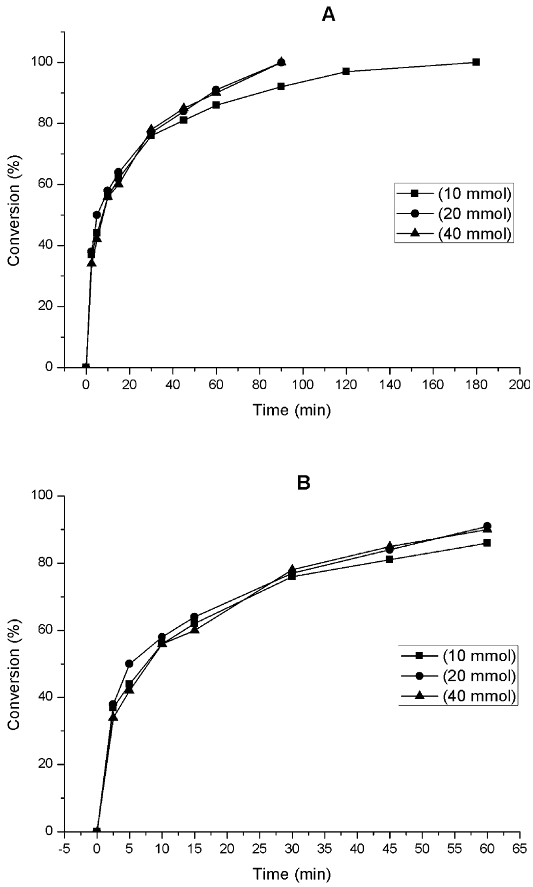


Figure 2. A) Performance of the Silia*Cat* DPP–Pd in the scale-up borylation reaction from 10 to 40 mmol starting product. B) Zoom from 0 to 65 min.

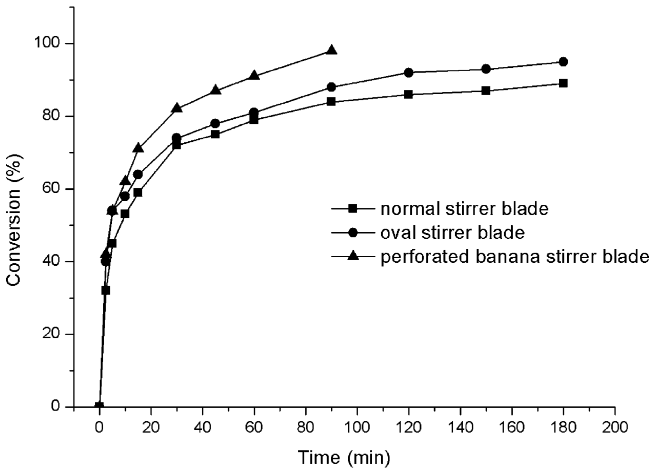


Figure 3. Performance of the Silia*Cat* DPP–Pd in the 40 mmol scale-up 4-bromoanisole borylation reaction under mechanical stirring. Influence of the stirrer blade type on the reaction.

GC–MS was used to assess conversion and selectivity. The yields were also measured by isolating the reaction products. The leaching in Pd and Si was assessed by ICP–OES analysis of the isolated crude product in DMF solvent (concentration 100 mg mL^{-1}). Leaching values are given in mg kg^{-1} API. Limit of detection: $LOD_{Pd}=$ 0.05 ppm in solution (100 mg mL^{-1} concentration) or 0.50 mg kg^{-1} in the crude product; $LOD_{Si}=0.02$ ppm in solution (100 mg mL^{-1} concentration) or 0.20 mg kg^{-1} in the crude product.

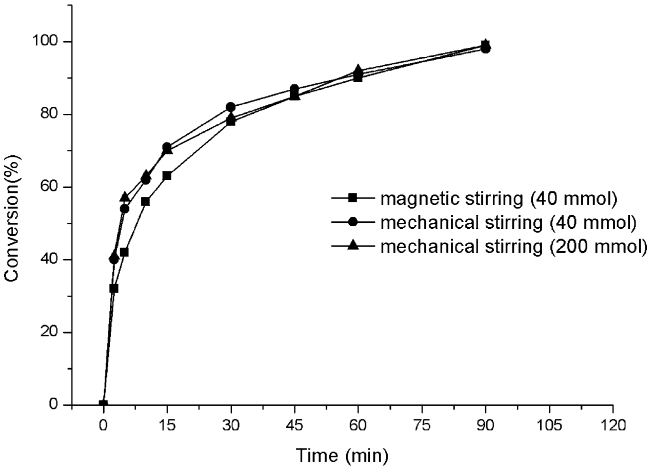


Figure 4. Performance of the Silia*Cat* DPP–Pd in the scale-up borylation reaction under magnetic stirring (700 rpm) and mechanical stirring (550–600 rpm).

Synthetic method A

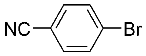
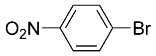
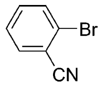
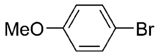
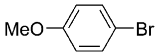
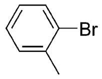
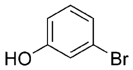
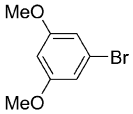
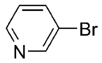
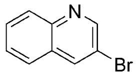
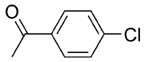
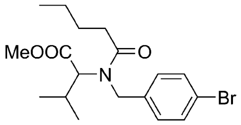
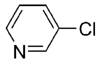
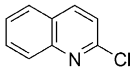
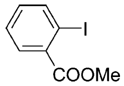
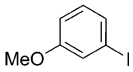
A 100 mL two-necked flask containing a magnetic stir bar and a condenser was charged with KOAc (10 mmol, 2 equiv.), pinacol B_2Pin_2 (5 mmol, 1 equiv.), anhydrous *i*PrOH (20 mL, 0.5 M, molar concentration with respect to the reagents). After 5 min stirring, the substrate (5 mmol, 1 equiv.) was added to the resulting mixture. Then the reaction mixture was heated at 80 °C and Silia*Cat* DPP–Pd (1 mol %, Pd loading 0.25 mmol g^{-1}) was added. The reaction was monitored by GC–MS. After completion of the reaction, the reaction mixture was cooled to RT and ethyl acetate (50 mL) was added. The mixture was filtered by using a 70 mL Büchner funnel equipped with paper glass (microfiber filter 961). The heterogeneous catalyst was collected and rinsed with ethyl acetate (3×50 mL).

The filtrate was evaporated under vacuum. The solid residue was dissolved in EtOAc (50 mL), washed with brine (3×50 mL), and dried over magnesium sulfate. After filtration, the solvent was removed to obtain a crude product, purified by flash chromatography if needed. The catalyst recovered by filtration was washed again with $EtOH/H_2O$ (1:1, v/v, 3×25 mL), EtOH (2×25 mL), and THF (2×25 mL), and dried at RT by simply letting the solvent to evaporate under ambient conditions. The catalyst stored in an open vessel was then reused in a subsequent reaction run as described above.

Synthetic method B

A 100 mL two-necked flask containing a magnetic stir bar and a condenser was charged with KOAc (22 mmol, 2.2 equiv.), pinacol B_2Pin_2 (11 mmol, 1.1 equiv.), and anhydrous *i*PrO (28 mL, 0.75 M, molar concentration with respect to the reagents). After 5 min stirring, the substrate (10 mmol, 1 equiv.) was added to the resulting mixture. Then the reaction mixture was heated to reflux (82 °C) and Silia*Cat* DPP–Pd (2 mol %, Pd loading 0.25 mmol g^{-1}) was added. The reaction was monitored by GC–MS. After completion of the reaction, the reaction mixture was cooled to RT and ethyl ace-

Table 9. SiliaCat DPP–Pd catalyzed coupling reaction of B$_2$Pin$_2$ and different aryl halides. Leaching test.

Entry	Substrate	B$_2$Pin$_2$ [equiv.]	Catalyst [mol %]	KOAc [equiv.]	Solvent [M][d]	*t* [h]	Conv. (select.)[e] [%]	Yield[e] [%]	Leaching[f] [mg kg^{-1} API] Pd	Si
1[a]		1	1	2	*i*PrOH (0.50)	1	100 (99)	94	1.57	1.12
2[a]		1	1	2	*i*PrOH (0.50)	1	100 (97)	94.5	1.16	0.82
3[a]		1.1	2	2.2	*i*PrOH (0.75)	2	99 (82)	–	4.60	3.07
4		1.1	1.5	2.2	*i*PrOH (0.75)	3	96 (94)	–	1.93	2.07
5[a]		1.1	2	2.2	*i*PrOH (0.75)	3	100 (97)	95	5.45	2.65
6[a]		1.1	2	2.2	*i*PrOH (0.75)	3	100 (99)	98	0.56	3.05
7[a]		1.1	2	2.2	*i*PrOH (0.75)	1	100 (98)	96	5.76	2.70
8[a]		1.1	2	2.2	*i*PrOH (0.75)	2	100 (98)	96	3.93	4.09
9[a]		1.1	2	2.2	*i*PrOH (0.75)	3	100 (98)	96	14.5	3.85
10[a]		1.1	2	2.2	*i*PrOH (0.75)	2	100 (88)	85	11.77	3.80
11[b]		1.1	2	2.2	*i*PrOH (0.75)	0.5	100 (98)	95	< 0.50	4.28
12[b]		1.1	2	2.2	*i*PrOH (0.75)	2	100 (97)	94	3.16	5.56
13[b]		1.1	2	2.2	*i*PrOH (0.75)	3	98 (96)	90	13.87	2.61
14[b]		1.1	2	2.2	*i*PrOH (0.75)	2	100	70	18.81	1.53
15[c]		1.5	2	3	*i*PrOH (1.25)	5	82 (92)	75	1.38	2.77
16[c]		1.5	2	3	*i*PrOH (1.25)	3	100 (98)	92	1.25	6.06

For experimental conditions, see [a] Table 5, [b] Table 6, [c] Table 7. [d] Molar concentration with respect to the reagents. [e] Conversion/selectivity evaluated by GC–MS. Isolated yield. [f] The leaching in Pd and Si was assessed by ICP–OES analysis of the isolated crude product in DMF solvent (concentration 100 mg mL^{-1}) and reported as mg kg^{-1} API. LOD$_{Pd}$ = 0.05 ppm in solution (concentration 100 mg mL^{-1}) or 0.50 mg kg^{-1} in the crude product; LOD$_{Si}$ = 0.02 ppm in solution (concentration 100 mg mL^{-1}) or 0.20 mg kg^{-1} in the crude product.

tate (50 mL) was added. The mixture was filtered by using a 70 mL Büchner funnel equipped with paper glass (microfiber filter 961).

The heterogeneous catalyst was collected and rinsed with ethyl acetate (3×50 mL). The organic solvent was evaporated under vacuum. The solid residue was dissolved in 100 mL EtOAc, washed with brine (3×100 mL), and dried over magnesium sulfate. After filtration, the solvent was removed to obtain a crude product, purified by flash chromatography when needed. If a heteroatom aryl substrate was converted, the ethyl acetate was replaced by THF. The catalyst recovered by filtration was washed again with EtOH/H$_2$O (1:1, v/v, 3×25 mL), EtOH (2×25 mL), and THF (2×25 mL), and dried at RT by simply letting the solvent to evaporate under ambient conditions. The catalyst stored in an open vessel was then reused in a subsequent reaction run as described above.

Method C

A 100 mL two-necked flask containing a magnetic stir bar and a condenser was charged with KOAc (30 mmol, 3 equiv.), pinacol B$_2$Pin$_2$ (15 mmol, 1.5 equiv.), anhydrous *i*PrOH (20 mL, 1.25 M, molar concentration with respect to the reagents). After 5 min stirring, the substrate (10 mmol, 1 equiv.) was added to the resulting mixture. Then the reaction mixture was heated to reflux (82 °C) and heterogeneous SiliaCat DPP–Pd (2 mol %, Pd loading 0.25 mmol g^{-1}) was added. The reaction was monitored by GC–MS. After completion of the reaction, the reaction mixture was cooled to RT, and ethyl acetate (100 mL) was added. The mixture was filtrated by using a 70 mL Büchner funnel equipped with paper glass microfiber filter 961. The heterogeneous catalyst was collected and rinsed with ethyl acetate (3×50 mL). The organic solvent was evaporated under vacuum. The solid residue was dissolved in EtOAc (100 mL), washed with brine (3×100 mL), and dried over magnesium sulfate. After filtration, the solvent was removed to obtain a crude product, purified by flash chromatography when needed. The catalyst recovered by filtration was washed again with EtOH/H$_2$O (1:1, v/v, 3×25 mL), EtOH (2×25 mL), and THF (2×25 mL), and dried at RT by simply letting the solvent to evaporate under ambient conditions. The catalyst stored in an open vessel was then reused in a subsequent reaction run as described above.

Table 10. Reusability of the Silia*Cat* DPP–Pd catalyst in the borylation of 4-bromobenzonitrile with B_2Pin_2.[a]

	t	Conv. (Select.)[b]	Yield[b]	Leaching[c] [$\mathrm{mg\,kg^{-1}}$ API]	
	[h]	[%]	[%]	Pd	Si
Run 1	1	96.5	94	4.93	1.99
	2	100 (95)			
Run 2	1	87	95	1.37	1.65
	2	100 (96)			
Run 3	2	90	92	4.28	2.20
	3	95			
	4	99 (97)			
Run 4	2	72	93	4.10	2.14
	4	83			
	20	100 (95)			
Run 5	2	67	95.5	9.57	6.56
	4	82			
	20	100 (98)			
Run 6	2	35	83	14.40	12.14
	4	51			
	20	88 (91)			

[a] Experimental conditions: 4-Bromobenzonitrile (12.5 g, 72 mmol, 1 equiv.), B_2Pin_2 (1 equiv.), KOAc (2 equiv.), anhydrous 2-PrOH (0.5 м, molar concentration with respect to the reagents), Silia*Cat* DPP–Pd (1 mol %, Pd loading 0.25 $\mathrm{mmol\,g^{-1}}$). [b] Conversion/selectivity evaluated by GC–MS. Isolated yield. [c] The leaching in Pd and Si was assessed by ICP–OES analysis of the isolated crude product in DMF solvent (concentration 100 $\mathrm{mg\,mL^{-1}}$) and reported as $\mathrm{mg\,kg^{-1}}$ API.

Scale-up of 200 mmol 4-bromoanisole conversion

A 1000 mL three-necked flask (center neck 45/50, side necks 24/40) containing a perforated banana-type stirrer blade PTFE (21 mm/87 mm, width/length, for 10 mm shafts) and a condenser was charged KOAc (43.19 g, 440 mmol, 2.2 equiv.), B_2Pin_2 (55.87 g, 220 mmol, 1.1 equiv.), 560 mL HPLC grade *i*PrOH (0.75 м, molar concentration with respect to reagents). After 5 min mechanical stirring, the 4-bromoanisole (37.41 g, 25.05 mL, 200 mmol, 1 equiv.) was added to the resulting mixture. Then, the reaction mixture was heated to reflux (82 °C) under 300 rpm mechanical stirring and Silia*Cat* DPP–Pd (2 mol %, Pd loading 0.25 $\mathrm{mmol\,g^{-1}}$) was added. The mechanical stirring was increased to 550 rpm. The reaction was monitored by GC–MS. When reaction was complete, the reaction mixture was cooled to RT, and distilled water (200 mL) was added, followed by diethyl ether (100 mL). The mixture was filtered by using a 200 mL Büchner funnel equipped with paper glass microfiber filter 961. The heterogeneous catalyst was collected and rinsed with diethyl ether (3×100 mL) and with distilled water (2×100 mL). The two layers were separated. The aqueous layer was extracted again with diethyl ether (200 mL).

The two organic layers were combined, dried over $MgSO_4$ and the organic solvent evaporated under vacuum. The crude product was obtained as a lemon-like yellow oil (46.2 g, 97 % yield). The catalyst recovered by filtration was washed again with $EtOH/H_2O$ (1/1, v/v, 3×50 mL), EtOH (2×50 mL), and THF (2×50 mL), dried at RT by simply letting the solvents evaporate in normal conditions, and stored prior to reuse.

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Keywords: boron · halides · heterogeneous catalysis · palladium · sol–gel processes

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