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Kaiser oxime resin-derived palladacycle: A recoverable polymeric precatalyst in Suzuki–Miyaura reactions in aqueous media

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ABSTRACT

Representative cross-coupling reactions of aryl bromides with different types of aryl-, alkyl, trivinylboroxine–pyridine complex, and alkenylboronic acids are performed using a polymer-bonded palladacycle derived from Kaiser oxime resin as precatalyst and potassium carbonate as base under water reflux. These processes afford biphenyls, alkylbenzenes, styrenes, and stilbenes, respectively. The same boronic acids can be cross-coupled with representative allyl and benzyl chlorides using KOH as base in aqueous acetone at 50 °C providing allylbenzenes, diarylmethanes, and 1,4-pentadienes. The palladated polymer can be recovered by filtration and reused during 3–9 cycles with up to 5% of Pd leaching in each run. Very low Pd leaching levels in the crude product can be determined by ICP–OES analyses. The reaction does not work when Hg(0) is added. TEM analyses from the solution indicate the formation of Pd nanoparticles.

1. Introduction

Considerable efforts have been devoted to develop supported Pd–ligand complexes where the ligand is covalently bonded to an organic polymer or to an inorganic solid in order to facilitate ligand and specially Pd recovery in cross-coupling reactions [1]. In these processes and due to the high temperatures that must be used combined to the high tendency of Pd(II) to be reduced to Pd(0), the Pd leaching to the solution takes place easily by reactions with components present in the medium [1b,2]. The formed Pd(0), specially before aggregation to nanoparticles, is a very active catalyst able to work through a neutral mechanism [3]. The revival of palladacycles as catalysts or precatalysts in cross-coupling reactions occurred in the middle of the nineties when Herrmann et al. used cyclopalladated tri-*o*-tolylphosphine as catalyst in Heck reactions [4]. The stability and, at the same time, high ability of carbapalladacyles to slowly release Pd(0) suppress aggregation and give them a high efficiency as catalysts in a wide scope of reactions [5]. They can be easily prepared, show high stability under atmospheric conditions and can be anchored to different solid supports. The use of solid-supported palladacycles presents advantages compared to their unsupported counterparts: (a) they can present similar catalytic activity because decompose giving atomic Pd(0), (b) due to the slow decomposition rates, the supported complex can survive the cross-coupling process and therefore after filtration it would be possible to recover the unreacted palladacycle and reused it again, (c) a lower percentage of Pd in the supported palladacycle decreases the leaching in the final product, which is a very important problem in active pharmaceutical ingredients (APIs) [6] and finally, (d) the product can be easily separated from the polymer.

However, immobilized palladium salts or complexes are usually active in organic solvents and in some cases bearing small proportions of water. In our previous work, we have reported that dimeric oxime-derived carbapalladacycles **1** [7] and **2** [8] are excellent precatalysts in cross-coupling reactions under phosphine-free conditions such as, Heck, Stille, Suzuki, Ullmann, Sonogashira, Hiyama, and Glaser in organic and aqueous media, being even more efficient than Pd salts [9]. Cross-coupling processes such as Suzuki [8a,b,m] and Hiyama [8h,i,j] reactions could be performed using water as solvent even with hydrophobic substrates. The great importance of using water as a reaction solvent, specially in palladium-catalysed cross-coupling reactions has been highlighted in recent years [10]. However, cross-couplings using polystyrene-supported palladium complexes in water as solvent have seldom been studied. Recently, we have described that the palladated Kaiser oxime resin **3** is a very active precatalyst in Mizoroki–Heck reactions in organic and aqueous media [11]. This polymeric complex **3** [12] can be recovered by filtration and reused during several cycles with rather low leaching of palladium into the solution. In this paper, we present the catalytic activity and the corresponding studies about recycling of this polymer-supported palladacycle in different types of Suzuki–Miyaura cross-coupling reactions [13] of aryl bromides, allyl and benzyl chlorides with aryl, alkyl, and alkenylboronic acids in aqueous media.

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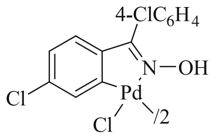

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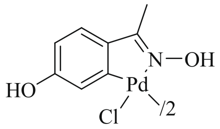

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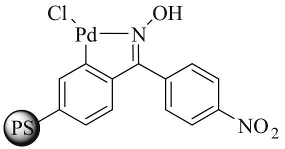

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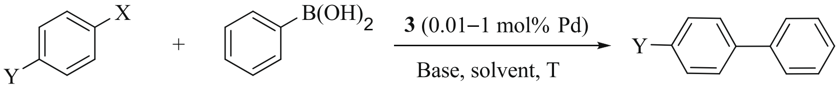
2. Results and discussion

2.1. Cross-coupling of aryl bromides with boronic acids

The evaluation of palladated Kaiser oxime resin **3**, prepared as previously described [11], as precatalyst in the Suzuki reaction of 4-bromoacetophenone and phenylboronic acid was performed under different reaction conditions using homeopathic loading (0.01 mol%) of Pd (Table 1). For room temperature conditions, KOH as base and different aqueous solvents such as, MeOH–H_2O (3:1), *N*,*N*-dimethylacetamide (DMAc)–H_2O (4:1), *n*-butanol–H_2O (3:1), acetone–H_2O (3:1) and THF–H_2O (3:1) were studied. In the first and last case, high yields (99% and 90%, respectively) were obtained, respectively, although in the first case the reaction time was too long (3 d). Aqueous THF was used for the recycling experiments at rt affording 90%, 81% and 75% crude yield after 3 cycles, the reaction time being increased from 14 to 70 h (Table 1, entries 13). Room temperature reactions with this Pd loading resulted too slow and therefore the polymer was degraded during these cross-couplings. The Pd leaching on the isolated 4-acetylbiphenyl crude product was between 19 and 27 ppm after filtration of the polymeric palladacycle **3** and the polymer contained 56% of Pd loading after the third run, (determined by ICP–OES, see Section 4).

In order to decrease the reaction time, the temperature was increased to 60 °C for the cross-coupling of 4-bromoacetophenone with phenylboronic acid in aqueous MeOH (1:3) using K_2CO_3 as

Table 1
Recycling experiments on the cross-coupling of aryl bromides and chlorides with phenylboronic acid using polymer **3**.[a]



Entry	Run	X	Y	Mol% Pd	Base	*T* (°C)	Solvent	Time	Yield (%)[b]	Pd leaching[c]
1	1	Br	Ac	0.01	KOH	25	THF/H_2O 3:1	14 h	90 (75)	23.8
2	2							48 h	81 (69)	26.6
3	3							70 h	75 (62)	18.9[d]
4	1	Br	Ac	0.01	K_2CO_3	60	MeOH/H_2O 3:1	1.5 h	99 (93)	1.8
5	2							1.8 h	95 (89)	1.2
6	3							2 h	92 (83)	1.5
7	4							2.5 h	94 (84)	1.1
8	5							3.5 h	96 (88)	1.0
9	6							4 h	90 (79)	1.7[e]
10	1	Br	Ac	0.01	K_2CO_3	60	*n*-BuOH/H_2O 3:1	2 h	96 (90)	16.3
11	2							3 h	91 (83)	10.7
12	3							3.5 h	92 (86)	21.1
13	4							4 h	89 (83)	18.5
14	5							5.5 h	90 (82)	16.6[f]
15	1	Br	Ac	0.01	K_2CO_3	100	H_2O	30 min	99 (92)	1.7
16	2							1.8 h	99 (95)	1.5
17	3							2 h	99 (91)	1.5
18	4							2.5 h	96 (90)	2.3
19	5							2.5 h	95 (88)	1.4
20	6							2.5 h	96 (91)	1.4
21	7							3 h	94 (90)	1.6[g]
22	1	Br	MeO	0.1	K_2CO_3	100	H_2O	2.5 h	94 (82)	16.5
23	2							2.5 h	92	17.6
24	3							3 h	88	20.2
25	4							5 h	89	–
26	5							6 h	83	14.4
27	6							14 h	87	–
28	7							24 h	89	–
29	8							24 h	61	–[h]
30	1	Cl	Ac	1[i]	K_2CO_3	100	H_2O	24 h	42	39.8
31	2							14 h	75	42.6
32	3							14 h	39	–
33	4							24 h	32	–[j]

[a] *Reaction conditions*: aryl halide (10 mmol), phenylboronic acid (1.82 g, 15 mmol), base (20 mmol), **3** (see column) and aqueous solvent (40 mL) or H_2O (20 mL).

[b] Isolated yield of the crude product (calculated from ^{1}H NMR, using *N*,*N*-dimethylformamide as internal standard). In parenthesis, yield after recrystallization from MeOH–H_2O.

[c] From ICP–OES analysis (mg Pd/kg product) of the crude product after filtration of the polymer **3**.

[d] The polymer **3** was isolated with a 56% Pd loading.

[e] The polymer **3** was isolated with a 72% Pd loading.

[f] The polymer **3** was isolated with a 45% Pd loading.

[g] The polymer **3** was isolated with a 81% Pd loading.

[h] The polymer **3** was isolated with a 76% Pd loading.

[i] In the presence of 0.5 equiv. of TBAB.

[j] The polymer **3** was isolated with a 59% Pd loading.

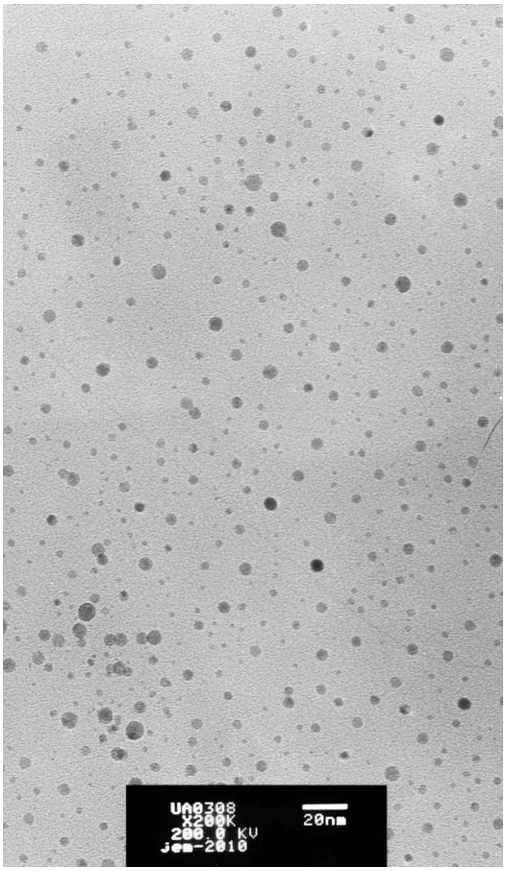


Fig. 1. TEM images of the reaction solution after Suzuki reaction of 4-bromoacetophenone and phenylboronic acid under water reflux.

base (Table 1, entries 4–9). Under these reaction conditions yields between 93% and 79% were achieved during 6 cycles, the reaction time being kept from 1.5 to 4 h. Similar results were obtained in aqueous *n*-butanol, the reaction time being slightly longer (Table 1, entries 10–14). From ICP–OES analyses can be established that MeOH is better solvent than *n*-butanol, affording much lower Pd leaching in the final product and higher Pd loading in the final recovered polymer **3**.

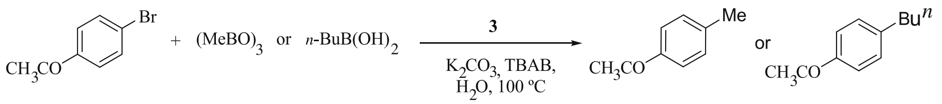
Recycling experiments were carried out using neat water under reflux and K_2CO_3 as base [8b]. The first run of the cross-coupling of 4-bromoacetophenone with phenylboronic acid took place in only 30 min in quantitative yield with only 0.01 mol% Pd loading. The same process performed in the presence of dimeric palladacycle **2** gave a 88% yield of 4-acetylbiphenyl after 15 min [8b], revealing that both palladacycles exhibit similar efficiency. High yields were obtained in the 7 following runs (9994%) increasing the reaction time until 3 h (Table 1, entries 15–21). It can be deduced that the polymer showed higher stability using K_2CO_3 instead of KOH and that water gave better results than MeOH and *n*-butanol. The Pd leaching in the crude product was very low (1.42.3 ppm) and the polymer was recovered still with 81% Pd contents. When the cross-coupling (Table 1, entry 15) was performed in the presence of 300 equiv. of Hg(0) by Pd equiv., the reaction did not take place after 8 h reaction time. TEM analyses of the solution performed after this reaction was performed with a 0.1 mol% Pd loading indicated the presence of 3–10 nm sized Pd nanoparticles (Fig. 1). The same results were observed in the Heck reaction using polymer **3** [11b,c] indicating that the polymer is a precatalyst acting as a source of Pd(0) [14].

Under the same reaction conditions, K_2CO_3 as base under water reflux, the deactivated 4-bromoanisole needed a larger Pd loading (0.1 mol%) affording good yields (94–89%) during 7 cycles, the reaction time being in the range of 2.5–24 h (Table 1, entries 22–29). Pd analyses of the crude 4-methoxybiphenyl indicated a 14.4–20.2 ppm of Pd leaching and the polymer was isolated in the last run with a 76% of Pd loading.

Aryl bromides are more reactive substrates than chlorides and they do not need the presence of TBAB as additive [8b]. However, for the coupling of 4-chloroacetophenone and phenylboronic acid TBAB, which can act as phase-transfer catalyst and also can stabilize palladium nanoparticles avoiding aggregation, has to be added

Table 2

Recycling experiments on the cross-coupling of 4-bromoacetophenone and TMB or *n*-butylboronic acid using polymer **3**.[a]



Entry	Run	Organoboron	Mol% Pd	Time (h)	Yield (%)[b]	Pd leaching[c]
1	1	TMB	1	7	91 (79)	177
2	2			14	83	144
3	3			24	34	16[d]1
4	1	TMB	5	4	95 (82)	1201
5	2			8	84	917
6	3			14	86	1133
7	4			24	71	877
8	5			24	42	–[e]
9	1	*n*-BuB(OH)$_2$	1	2	69 (51)[f]	385
10	2			3.1	65[f]	358
11	3			4	62[f]	269
12	4			8	60[f]	308
13	5			14	48[f]	507[g]

[a] *Reaction conditions*: 4-bromoacetophenone (99 mg, 0.5 mmol), trimethylboroxine or *n*-butylboronic acid (0.75 mmol), K_2CO_3 (138 mg, 1 mmol), TBAB (166 mg, 0.5 mmol), **3** (see column) in H_2O (2 mL), at 100 °C.

[b] Isolated yield of the crude product (calculated from ^1H NMR, using *N*,*N*-dimethylformamide as internal standard). In parenthesis, yield after flash chromatography (hexane-EtOAc).

[c] From ICP–OES analysis (mg Pd/kg product) of the crude product after filtration of the polymer **3**.

[d] The polymer **3** was isolated with a 59% Pd loading.

[e] The polymer **3** was isolated with a 68% Pd loading.

[f] 20–30% of 4,4′-bis(acetyl)biphenyl was obtained in the crude product.

[g] The polymer **3** was isolated with a 81% Pd loading.

[15]. In the first run 1 mol% Pd loading was used giving only 42% yield of 4-acetylbiphenyl under water reflux after 24 h reaction time (Table 1, entry 30). Surprisingly, in the second run a higher 75% conversion was obtained after 14 h (Table 1, entry 31), whereas in the following runs only 39% and 32% yield was observed after 14 and 24 h (Table 1, entries 32 and 33). It seems that in the second run an unusual higher leaching of Pd(0) to the solution was produced. From these results it can be concluded that dimeric 4-hydroxyacetophenone palladacycle **2** [8a,b] shows much better catalytic efficiency than the palladated polymer **3** for the cross-coupling with aryl chlorides.

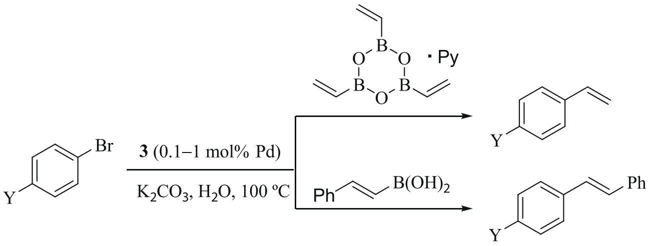
For the formation of aryl–alkyl bonds [16], the cross-coupling of aryl bromides with trimethylboroxine (TMB) and *n*-butylboronic acid was performed under the reaction conditions previously described using palladacycle **2** as precatalyst [8b]. The methylation of 4-bromoacetophenone with TMB was carried out using the polymeric palladacycle **3** (1 mol% Pd), K_2CO_3 as base, and TBAB as additive under water reflux (Table 2, entries 13). In the first run the reaction took place in high yield only in 7 h, whereas using the dimeric complex **2**, 10 mol% of Pd loading was used [8b].This apparently contradictory result can be explained by the formation of larger Pd colloids, which afford the formation of inactive palladium black [12c]. Unfortunately, in the third cycle only 34% conversion was obtained after 24 h reaction time. When the Pd loading was increased to 5 mol%, good conversions were observed during 4 cycles (95–71%) (Table 2, entries 4–8). However, the Pd leaching determined by ICP–OES analyses of crude products was higher when using 5 than 1 mol% of Pd loading.

In the case of the cross-coupling of 4-bromoacetophenone with *n*-butylboronic acid the alkylation proceeded in moderate yield due to concomitant homocoupling of 4-bromoacetophenone (Table 2, entries 9–13). However, the formation of 4-butylacetophenone was similar during 4 cycles (69–60% yield), the reaction time ranging from 2 to 8 h. During the fifth run the conversion decreased to 48% and the reaction time increased to 14 h. Similar results were observed in the first run using dimeric palladacycle **2** [8b] as precatalyst. The Pd contents in the polymer was analyzed also by ICP–OES analysis being 81% relative to the starting complex, which is higher than in the case of the coupling with trimethylboroxine (Table 2, footnotes d,e,g).

Alkenylboronic derivatives such as, trivinylboroxine–pyridine complex [16] and styrylboronic acid were chosen as representative vinylating agents for the synthesis of styrene and stilbene derivatives by means of the Suzuki–Miyaura cross-coupling reaction

Table 3

Recycling experiments on the cross-coupling of aryl bromides with alkenylboronic acids using polymer **3**.[a]



Entry	Run	X	Y	Borane	Mol% Pd	TBAB (equiv.)	Time (h)	Yield (%)[b]	Pd leaching[c]
1	1	Br	Ac	$(CH_2{=}CHBO)_3 \cdot Py$	1	1	2.5	94 (88)	238
2	2					1	3	89	243
3	3					1	3.5	91	221
4	4					1	5	93	222
5	5					1	9	83	276
6	6					1	16	85	–
7	7					1	24	76	–[d]
8	1	Br	MeO	$(CH_2{=}CHBO)_3 \cdot Py$	1	1	6.5	91 (82)	279
9	2					1	14	93	245
10	3					1	14	83	247
11	4					1	24	61	363
12	5					1	24	48	–[e]
13	1	Br	Ac	(*E*)-$PhCH{=}CHB(OH)_2$	0.1	–	5	91 (84) [5][f]	12.6
14	2					–	5	85 [6][f]	11.6
15	3					–	8	81 [18][f]	11.5
16	4					–	14	76 [31][f]	16.4
17	5					–	24	79 [42][f]	13.2
18	6					–	24	76 [35][f]	16.8
19	7					–	24	49 [44][f]	17.6[g]
20	1	Br	MeO	(*E*)-$PhCH{=}CHB(OH)_2$	0.5	–	5	96 (89) [8][f]	61.8
21	2					–	6	89 [21][f]	88.4
22	3					–	10	77 [30][f]	87.8
23	4					–	15	62 [56][f]	98.9
24	5					–	24	55 [50][f]	131.5
25	6					–	24	23 [48][f]	93.5[h]

[a] Reaction conditions for trivinylboroxine: aryl bromide (0.25 mmol), trivinylboroxine (89 mg, 0.37 mmol), TBAB (83 mg, 0.25 mmol), K_2CO_3 (60 mg, 0.5 mmol), **3** (80 mg, 1 mmol) and H_2O (1.5 mL). Reaction conditions for (*E*)-styrylboronic acid: aryl bromide (0.5 mmol), (*E*)-styrylboronic acid (111 mg, 0.75 mmol), K_2CO_3 (276 mg, 2 mmol), **3** (see column) and H_2O (2 mL).

[b] Isolated yield of the crude product (calculated from ^1H NMR, using *N*,*N*-dimethylformamide as internal standard). In parenthesis, yield after flash chromatography (hexane-EtOAc).

[c] From ICP–OES analysis (mg Pd/kg product) of the crude product after filtration of the polymer **3**.

[d] The polymer **3** was isolated with a 63% Pd loading.

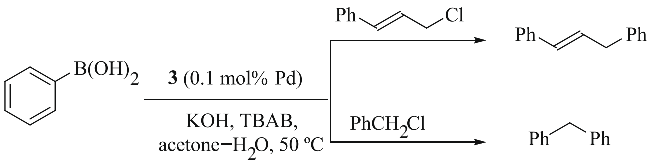
[e] The polymer **3** was isolated with a 44% Pd loading.

[f] Yield of styrene in the crude product.

[g] The polymer **3** was isolated with a 61% Pd loading.

[h] The polymer **3** was isolated with a 56% Pd loading.

Table 4
Recycling experiments on the cross-coupling of cinnamyl and benzyl chloride with phenylboronic acid using polymer **3**.[a]



Entry	Run	Organic chloride	Time (h)	Yield (%)[b]	Pd leaching[c]
1	1	Cinnamyl chloride	1	95 (86)	16.0
2	2		1.3	96	14.5
3	3		2	92	17.5
4	4		2.5	89	19.1
5	5		4	91	–
6	6		5	83	–
7	7		8	79	19.8
8	8		14	84	14.5
9	9		24	73	–[d]
10	1	Benzyl chloride	1	99 (86)	21.0
11	2		1.2	91	21.8
12	3		1.6	93	20.4
13	4		2	96	17.4
14	5		3.3	92	19.6
15	6		4	89	21.0[e]

[a] *Reaction conditions*: organic chloride (1 mmol), phenylboronic acid (182 mg, 1.5 mmol), KOH (112 mg, 2 mmol), TBAB (322 mg, 1 mmol), **3** (8 mg, 0.1 mol% Pd) in 3:2 acetone–H_2O (5 mL).

[b] Isolated yield of the crude product (^1H NMR). In parenthesis yield after flash chromatography (hexane–EtOAc).

[c] From ICP–OES analysis (mg Pd/kg product) of the crude product after filtration of the polymer **3**.

[d] The polymer **3** was isolated with a 71% Pd loading.

[e] The polymer **3** was isolated with a 69% Pd loading.

[17–19] with aryl bromides in water (Table 3). The vinylation of 4-bromoacetophenone and 4-bromoanisole with trivinylboroxine was carried out using 0.1 mol% Pd loading of dimeric palladacycle **2**, K_2CO_3 as base and in the presence of TBAB under water reflux affording 4-acetyl and 4-methoxystyrene in 83% and 76% yield after 5 and 18 h reaction time, respectively. The same reactions needed a higher 1 mol% Pd loading of palladated polymer **3** to give the corresponding 4-acetyl and 4-methoxystyrene in 88% and 82% yield after 2.5 and 6 h reaction time, respectively (Table 3, entries 1 and 8). These are the first cross-coupling reactions of trivinylboroxine with aryl bromides in water. Recycling experiments in the first case took place in 94–76% yield during 7 cycles and during 2.5–24 h (Table 3, entries 1–7), the polymer being recovered with 63% Pd loading. In the case of the deactivated 4-bromoanisole moderate yields were obtained in the cycles 4 and 5 (Table 3, entries 8–12) and the polymer **3** was isolated with 44% Pd loading after 5 runs. In both cases, similar Pd leachings was observed in the crude product (221–363 ppm Pd).

Styrylboronic acid reacted with representative 4-bromoacetophenone and anisole using 0.1 mol% Pd loading of palladacycle **2** with K_2CO_3 as base under water reflux and in the absence of TBAB to afford 4-acetyl and 4-methoxystilbene in 88% and 79% yield and in 5 and 8 h, respectively. When 0.1 and 0.5 mol% Pd loading of polymer **3** was used 84% and 89% yield of these stilbenes were obtained after 5 h reaction time, respectively (Table 3, entries 13 and 20). Recycling experiments were carried out during 7 and 6 runs under these reaction conditions (Table 3, entries 13–25). Thus, 4-acetyl and 4-methoxystilbene were obtained in good yields with higher than 97:3 α/β regioisomer ratio. However, styrene was formed under these reaction conditions, these protonolysis being increased in up to 50% yield during the recycling experiments, affording lower yield of stilbenes after each consecutive run.

2.2. Cross-coupling of allyl and benzyl chlorides with boronic acids

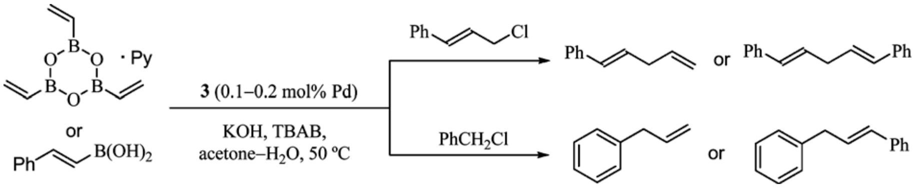
For the formation of allyl–aryl bonds the cross-coupling of allyl halides with arylboronic acids is the most convenient strategy. The allylation of arylboronic acids took place easily using palladacycle **2** as precatalyst at rt using KOH as base, TBAB as additive and a 3:2 mixture of acetone-water [8b]. The evaluation of palladated Kaiser oxime resin **3** as recoverable Pd polymeric complex was performed with cinnamyl chloride and phenylboronic acid under the above mentioned reaction conditions at 50 °C (Table 4, entries 1–9). During 9 runs the yield was kept between 95% and 73% and the reaction time increased from 1 to 24 h. The Pd leaching analyzed in the crude product ranged between 14.5 and 20 ppm and the polymer was isolated with a 71% Pd content after 9 cycles. When this cross-coupling reaction (Table 4, entry 1) was performed in the presence of 200 equiv. of Hg by Pd equiv. during 8 h, the reaction failed. Again, it can be concluded that the polymer is acting as source of Pd(0) [14].

The formation of benzyl–aryl bonds was examined using the cross-coupling of benzyl halides with arylboronic acids. This type of transformation allows the synthesis of symmetrical and unsymmetrical diarylmethanes, which are present in supramolecular structures [20] and biologically active compounds [21]. The reaction between benzyl chloride and phenylboronic acid was performed under the same reaction conditions than cinnamyl chloride (Table 4, entries 10–15). During 6 cycles the reaction took place in 1–4 h and 99–89% yield. Similar Pd leaching was observed in the crude product than in the former cinnamyl chloride. Recovered palladacycle **3** was isolated with 69% Pd loading after 6 runs.

Cross-coupling reactions of allyl chlorides have only been studied with potassium alkenyltrifluoroborates for the synthesis of 1,4-pentadienes [22]. We have now studied representative examples of the cross-coupling reactions of cinnamyl chloride with trivinylboroxine and styrylboronic acid under the same reaction conditions previously described for phenylboronic acid (Table 5). The vinylation of cinnamyl chloride took place with trivinylboroxine using a low 0.1 mol% Pd loading of complex **2**, KOH as base, TBAB as additive in aqueous acetone at 50 °C giving 1-phenylpenta-1,4-diene in 81% yield after 1.5 h. When 0.2 mol% Pd loading of polymer **3** was used, a similar 80% yield of 1-phenylpenta-1,4-diene was obtained in 2.5 h (Table 5, entry 1). In the case of styrylboronic acid (1*E*,4*E*)-1,4-diphenylpenta-1,4-diene was obtained in 83% yield using 0.1 mol% Pd loading [22,23] of both complexes **2** and **3** after 1 h reaction time (Table 5, entry 9). Recycling experiments for both reactions have been performed during 8 cycles (Table 5, entries 1–16). The efficiency of the polymer **3** as precatalysts started to decreased in the cycle 7 and was recovered with a 79% and 61% Pd loading, respectively. In the case of (*E*)-styrylboronic acid 5–16% of styrene was formed due to a deborylation process. A higher leaching was observed in the case of trivinylboroxine from ICP–OES analyses of the crude products.

Benzyl chloride was cross-coupled with trivinylboroxine using 0.1 and 0.2 mol% Pd loading of complex **2** and **3**, respectively. Thus, allylbenzene was obtained in 70% and 66% yield, respectively, after 8 h reaction time. Recycling experiments using **3** gave allylbenzene in 68–82% crude yields during 4 runs (Table 5, entries 17–21). The reaction of benzyl chloride with styrylboronic acid has been performed, for the first time, using both complexes **2** and **3** (0.1 mol% Pd loading). Thus, (*E*)-1,3-diphenylprop-1-ene was obtained in 78% and 79% yield and after 3 and 3.5 h reaction time, respectively (Table 5, entry 22). This Suzuki–Miyaura reaction can be considered an alternative strategy to the cross-coupling of allyl chlorides with arylboronic acids for the synthesis of allylbenzenes (see Table 4, entries 10–15). However, lower yields and low recycling results were observed in this type of $C(sp^3)C(sp^2)$ couplings due to deborylation reactions of alkenylboronic derivatives,

Table 5
Recycling experiments on the cross-coupling of cinnamyl and benzyl chloride with alkenylboronic acids using polymer **3**.[a]



Entry	Run	Organic chloride	Borane	Mol% Pd	Time (h)	Yield (%)[b]	Styrene (%)	Pd leaching[c]
1	1	Cinnamyl chloride	$(CH_2{=}CHBO)_3 \cdot Py$	0.2	2.5	96 (80)		34.0
2	2				3	96		29.1
3	3				3	92		34.8
4	4				5	89		47.9
5	5				8	91		–
6	6				14	83		–
7	7				24	79		–
8	8				24	84		–[d]
9	1	Cinnamyl chloride	(*E*)-PhCH=CHB(OH)$_2$	0.1	1	96 (83)	–	8.5
10	2				3	94	–	11.6
11	3				4.5	88	–	11.6
12	4				5	89	–	11.8
13	5				8	92	5	10.1
14	6				14	88	11	11.2
15	7				24	75	12	14.6
16	8				24	61	16	17.7[e]
17	1	Benzyl chloride	$(CH_2{=}CHBO)_3 \cdot Py$	0.2	8	82 (66)		71.9
18	2				14	79		62.9
19	3				16	68		82.5
20	4				24	71		101.6
21	5				24	36		109.1[f]
22	1	Benzyl chloride	(*E*)-PhCH=CHB(OH)$_2$	0.1	3.5	92 (79)	–	14.7
23	2				5	86	–	16.2
24	3				10	76	5	18.6
25	4				14	78	8	14.9
26	5				24	72	12	21.1
27	6				24	37	21	19.2[g]

[a] Reaction conditions for trivinylboroxine: organic chloride (0.5 mmol), trivinylboroxine (180 mg, 0.75 mmol), TBAB (166 mg, 0.5 mmol), KOH (56 mg, 1 mmol), **3** (10 mg, 0.2 mmol Pd) in 3:2 acetoneH_2O (2.5 mL). Reaction conditions for (*E*)-styrylboronic acid: organic chloride (1 mmol), (*E*)-styrylboronic acid (222 mg, 1.5 mmol), KOH (112 mg, 2 mmol), TBAB (322 mg, 1 mmol), **3** (8 mg, 0.1 mmol Pd) in 3:2 acetone–H_2O (5 mL).

[b] Isolated yield of the crude product (^1H NMR). In parenthesis yield alter flash chromatography (hexane–EtOAc).

[c] From ICP–OES analysis (mg Pd/kg product) of the crude product after filtration of the polymer **3**.

[d] The polymer **3** was isolated with a 79% Pd loading.

[e] The polymer **3** was isolated with a 61% Pd loading.

[f] The polymer **3** was isolated with a 58% Pd loading.

[g] The polymer **3** was isolated with a 78% Pd loading.

although in less extension (5–21%) than in the cross-coupling with aryl bromides (Table 3). In the case of trivinylboroxine, the yield decreased to 36% in the run 5 and for styrylboronic acid in the cycle 6 (Table 5, entries 17–27).

3. Conclusions

We can conclude that the Kaiser oxime-based palladacycle is a very stable and efficient precatalyst for the Suzuki–Miyaura reaction of aryl bromides with aryl boronic acids using homeopathic Pd loading and K_2CO_3 as base under water reflux better than in aqueous alcohols. Under these reaction conditions alkylboronic acids such as, trimethylboroxine and *n*-butylboronic acid needed the presence of TBAB and higher Pd loading. Better recycling results have been observed for aryl than alkylboronic acids. Under the same reaction conditions alkenylation reactions of aryl bromides can be performed with trivinylboroxine–pyridine complex and with styrylboronic acid affording the corresponding styrenes and stilbenes. Styrylboronic acid suffers deborylation to styrene during the recycling experiments. In the case of allyl and benzyl chlorides the cross-coupling reactions either with phenylboronic acid or with alkenylboronic acids derivatives, needed a low 0.1–0.2% Pd loading, KOH as base, TBAB as additive in aqueous acetone at 50 °C, giving high and fast conversions with high yields during 6 cycles. In general, the immobilized palladacycle was more efficient than the unsupported counterparts except for the cross-coupling of aryl chlorides with arylboronic acids. In addition, can be recovered from the reaction medium and reused for several cycles. With respect to its efficiency, a better performance for fast runs was observed, the activity being lost when the cross-coupling became slow. In general, ICP–OES analyses showed low Pd contents in the final crude products and the polymer suffer up to 5% Pd leaching in each recycling run.

4. Experimental

4.1. General

Unless otherwise noted all commercials reagents and dry solvents were used without further purification. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 P-FT. ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were obtained on a Bruker AC-300 and Bruker AC-400, respectively, using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on an Agilent 5973 Network. Analytical TLC was performed on Merck aluminium sheets with silica gel 60 F_{254}. Silica gel 60, (0.04–0.06 mm) was employed for flash chromatography. Gas chromatographic analyses were performed on an Agilent 6890N instrument equipped with a WCOT HP-1 fused silica capillary column. The catalyst was weighed up in a electronic microscale balance Sartorius, XM1000P with precision of 1 μg. ICP–OES analyses were performed in a Perkin–Elmer Optima 4300 spectrometer. The reaction was filtered off and the solution was concentrated and treated with 65% aqueous HNO_3 (1 mL) overnight. The sample was diluted with water until 50 mL total volume and filtered through a HPLC filter. TEM analyses were performed in a JEOL JEM-2010 coupled to a micro analyzer system Oxford INCA Energy TEM100.

Kaiser resin is commercially available and can be prepared from polystyrene cross-linked with 1% divinylbenzene [24]. Palladacycles **2** [8b] and **3** [11b] were prepared as previously described.

4.2. Typical procedure for the cross-coupling reactions in water

A 2 M solution of K_2CO_3 (10 mL) was added to a suspension of aryl halide (10 mmol), boroxine (5 mmol) or boronic acid (15 mmol), TBAB (see tables), palladacycle **3** (see tables), in water (20 mL). The mixture was stirred under reflux and the reaction was monitored by GC until completion. Then the reaction was cooled down to room temperature and diluted with EtOAc (40 mL), filtered off (G3) and the polymer was washed with EtOAc (3 × 10 mL), EtOAc–MeOH (1:1) (3 × 10 mL) and MeOH (3 × 10 mL), dried under vacuum and reused in a new experiment. The filtrate was concentrated under vacuum and a small sample was analyzed by ICP–OES. The rest of the crude product was poured into EtOAc (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by flash chromatography or by recrystallization.

4.3. Typical procedure for the cross-coupling reactions in aqueous acetone

A 1 M solution of KOH (2 mL) was added to a solution of cinnamyl or benzyl chloride (1 mmol), TBAB (see Tables), boroxine (0.5 mmol) or boronic acid (1.5 mmol) and the polymer **3** (see tables) in acetone (3 mL) and the reaction mixture was heated at 50 °C. The reaction was monitored by GC until completion and worked-up as above.

The compounds 4-acetylbiphenyl, 4-methoxybiphenyl, diphenylmethane, 4-butylacetophenone, 4-methylacetophenone, 4-vinylacetophenone, 4-vinylanisole, 1-phenylpenta-1,4-diene, allylbenzene, (*E*)-4-acetylstilbene, (*E*)-4-methoxystilbene are commercially available. The following compounds (*E*)-1,3-diphenylpropene [25] and (1*E*,4*E*)-1,5-diphenyl-1,4-pentadiene [26] have been previously described.

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