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Cross-coupling reactions with boronic acids in water catalysed by oxime-derived palladacycles

Luis Botella, Carmen Nájera *

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apartado 99, E-03080 Alicante, Spain

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This paper is dedicated to Professor Pascual Royo on occasion of his 65th birthday

Abstract

Palladacycles derived from phenone-oximes **1** are efficient precatalysts for the Suzuki–Miyaura coupling of arylboronic acids with aromatic and heteroaromatic bromides and chlorides under water reflux under aerobic conditions. Alternatively, the coupling can also be carried out at room temperature in methanol–water. Aryl bromides gave biaryls with TON up to 10^5 and TOF up to $7 \times 10^4\ h^{-1}$. Activated and deactivated aryl chlorides need the presence of TBAB for the couplings, showing slightly lower efficiency (TON up to 9000 and TOF up to 3850 h^{-1}). $C(sp^2)$–$C(sp^3)$ bonds can also be formed by cross-coupling reactions of trimethylboroxine and butylboronic acid with aromatic bromides and chlorides under water reflux and of benzylic and allylic chlorides or acetates with arylboronic acids in acetone–water at room temperature.

Keywords: Oxime derived palladacycles; Cross-coupling reactions; Boronic acids

1. Introduction

Organometallic catalysis in air and in water has become an important goal in green chemistry specially for the development of industrial processes under simple, economical, safe and environmentally favourable conditions [1]. Palladium mediated carbon–carbon bond forming reactions are specially powerful and versatile methodologies in synthesis [2–4]. Cross-coupling reactions of aryl halides with organoboron compounds, the well-known Suzuki–Miyaura reaction [5], has become a very potent and popular method for the synthesis of biaryls, important building blocks and pharmacophores [6]. This coupling is specially useful because of the broad tolerance to different functional groups, the ability to couple sterically demanding substrates, mild reaction conditions, non-toxic and easy to handle reagents. Recent progress in this field is focused to the use of the inexpensive and accessible aryl chlorides, but mainly based on the use of toxic phosphanes as co-catalysts or *N*-heterocyclic carbene (NHC) complexes in organic solvents under inert atmosphere [7]. On the other hand, this type of cross-coupling processes can be also applied with organoboranes or ate complexes to create $C(sp^2)$–$C(sp^3)$ [8–16] and $C(sp^3)$–$C(sp^3)$ [17,18] bonds. Alkylboronic acids have been used very recently for cross-coupling of sp^2-hybridized halides and triflates, but in the presence of a high excess of Ag(I) salts [19,20].

Concerning the use of organoaqueous media, arylboronic acids and sodium tetraphenylborate are appropriate reagents for cross-coupling reactions under inert atmosphere. A well-established strategy for the coupling of arylboronic acids with aryl bromides is the use of water soluble phosphanes such as sodium triphenylphosphino-3-trisulfonate (TPPTS) in combination with $Pd(OAc)_2$ in acetonitrile–water (3/1) at 80 °C. Under these conditions, deactivated aryl bromides afforded turnover numbers (TON) up to 6400 and turnover frequencies (TOF) up to 300 h^{-1} [21]. Higher activity was found with sterically demanding water-soluble alkylphosphanes even working at room temperature in

* Corresponding author. Tel.: +34-965-903728; fax: +34-965-903549; www.ua.es/dept.quimorg
E-mail address: cnajera@ua.es (C. Nájera).

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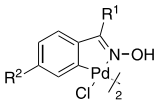
acetonitrile–water (1/1) with TON up to 734 000 and TOF 183 500 h^{-1} [22]. Triarylphosphane–palladium complexes bound to a poly(ethyleneglycol)–polystyrene graft copolymer (PEG–PS resin), were efficient catalyst in neat water for the coupling of arylboronic acids with aryl bromides and allylic acetates at room temperature in the presence of 2 mol% of Pd [23]. Phosphane-free couplings were carried out with 0.2 mol% of $Pd(AcO)_2$ in the presence of tetrabutylammonium bromide (TBAB) with aryl bromides at 70 °C [24]. Sodium tetraphenylborate and aryl chlorides derived from phenols and benzoic acids were coupled in water as well using 1–3 mol% of $PdCl_2$ or $Pd(OAc)_2$ as catalysts [25].

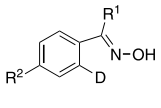
We have recently described that oxime-derived palladacycles **1** (Fig. 1) are robust and versatile precatalysts for a wide range of cross-coupling processes in organic solvents such as Heck, Suzuki, Stille, Sonogashira and Ullmann reactions under aerobic conditions [26,27]. These type of palladacycles were also active catalysts precursors for the Suzuki coupling of arylboronic acids and aryl chlorides in water [28]. In this account we report the scope of these compounds as catalysts for the formation of $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ bonds in neat water or in aqueous solvents, through the coupling of aryl and alkylboronic acids with different organic bromides and chlorides.

2. Results and discussion

2.1. Cross-coupling of aromatic and heteroaromatic bromides with arylboronic acids

New phenone oxime-derived palladacycles **1b** and **1c** with hydroxy groups at the aromatic ring were prepared by reaction of the corresponding oximes with Li_2PdCl_4 and NaOAc in methanol [26–29]. Its reduction with sodium cyanoborohydride led to the expected deuterated oximes **2b** and **2c** in 79 and 78% yield, respectively (Fig. 1). The evaluation in the Suzuki reaction of palladacycles **1** (Fig. 1) and other palladium salts was carried out by using phenylboronic acid and *p*-bromoacetophenone (Scheme 1 and Table 1). After several studies about aqueous solvents, temperature, bases and catalyst loading, the best conditions are summarized in Table 1. When the reaction was carried out in refluxing

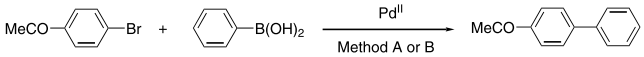




1a; R^1 = Me, R^2 = H (92%)
1b; R^1 = Me, R^2 = OH (92%)
1c; R^1 = *p*-HOC_6H_4, R^2 = OH (75%)

2b; R^1 = Me, R^2 = OH (79%)
2c; R^1 = *p*-HOC_6H_4, R^2 = OH (78%)

Fig. 1. Oxime-derived palladacycles and deuterated oximes.



Scheme 1. Cross-coupling studies of *p*-bromoacetophenone and phenylboronic acid.

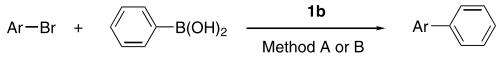
water with K_2CO_3 as base (method A) in the presence of complexes **1** with 10^{-2} mol% of Pd during 15 min, the process took place with ca. 10^4 TON and 4×10^4 h^{-1} TOF (Table 1, entries 1–3). Slightly lower yields were obtained when $Pd(OAc)_2$ or Li_2PdCl_4 were used as catalysts. Decreasing the loading of **1b** to 10^{-3} mol% of Pd gave 92% conversion in 100 min (Table 1, entry 6). For room temperature couplings, a mixture of MeOH–H_2O 3/1 and KOH as base gave the highest conversions with complexes derived from *p*-hydroxyacetophenone and benzophenone **1b** and **1c** in 5 h with 10^4 TON. Acetophenone derivative **1a** needed 4 days to afford similar TON (Table 1, entries 7–9). Pd salts such as $Pd(OAc)_2$ or Li_2PdCl_4 were not so efficient catalysts under these reaction conditions and the reaction stopped after 23 and 8 h with ca. 50% conversion (Table 1, entries 10 and 11). When the reaction in MeOH–H_2O and complex **1b** was carried out at 60 °C (method C) a higher efficiency was achieved after 2 h with 10^5 TON (Table 1, entry 12). Catalyst **1b** showed high stability in five subsequent 2 h catalytic cycles with 10^{-3} mol% of Pd under method C conditions (Table 1, entry 12) giving in all cases more than 95% isolated yield of *p*-phenylacetophenone.

The scope of the Suzuki reaction with different aromatic and heteroaromatic bromides was studied with complex **1b** and using methods A and B (Scheme 2 and Table 2). In general both methods afforded similar TONs (ca. 10^4) with activated and deactivated aryl bromides. However, reaction times were shorter when using method A. In some cases, method C was used instead of method B in order to decrease reaction times (Table 2, entries 8, 10 and 13). This methodology was applied to the synthesis of the anti-inflammatory 4-biphenylacetic acid (felbinac) and the analgesic 4-phenylmandelic acid employing method A but at room temperature with 0.05 mol% of complex **1b** (Table 2, entries 16 and 17). *p*-Bromophenylacetic acid was coupled in only 2 h to give biphenylacetic acid in 79% isolated yield. This result is very interesting as this coupling has been previously reported under very harsh reaction conditions, longer reaction times and higher catalyst loadings (refluxing isopropanol–water during 4 h in the presence of 5 mol% of Pd–C) [30]. In the case of *p*-bromomandelic acid, full conversion was also achieved in 2 h. Previously reported conditions for this substrate involved the use of higher catalyst loadings (Pd–C 2 mol%) and 62 °C affording the product in a 75% yield [31].

Table 1
Reaction conditions and catalyst studies on the Suzuki coupling of *p*-bromoacetophenone and phenylboronic acid [a]

Entry	Catalyst (mol% Pd)	Method	Time	Yield (%) [b]	TON	TOF (h^{-1})
1	**1a** (10^{-2})	A	15 min	93	9300	37200
2	**1b** (10^{-2})	A	15 min	88	8800	35200
3	**1c** (9×10^{-3})	A	15 min	73	8111	32444
4	$Pd(OAc)_2$ (1.1×10^{-2})	A	15 min	86	7818	31272
5	Li_2PdCl_4 (10^{-2})	A	15 min	57	5700	22800
6	**1b** (10^{-3})	A	100 min	92	92000	52600
7	**1a** (10^{-2})	B	4 days	100	10000	104
8	**1b** (10^{-2})	B	5 h	100 (98) [c]	10000	2000
9	**1c** (10^{-2})	B	5 h	94	9400	1880
10	$Pd(OAc)_2$ (10^{-2})	B	23 h	50	5000	217
11	Li_2PdCl_4 (10^{-2})	B	8 h	48	4800	600
12	**1b** (10^{-3})	C	2 h	100 (98) [c]	100000	50000

[a] Method A: *p*-bromoacetophenone (2 mmol), $PhB(OH)_2$ (3 mmol), K_2CO_3 (4 mmol), H_2O (7 ml), reflux. Method B: *p*-bromoacetophenone (2 mmol), $PhB(OH)_2$ (3 mmol), KOH (4 mmol), MeOH–H_2O: 3/1 (8 ml), r.t. Method C: method B but at 60 °C (bath temperature).
[b] GC yield.
[c] Isolated yield.



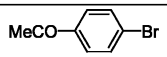
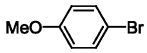
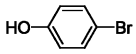
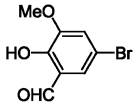
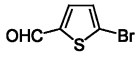
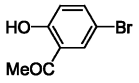
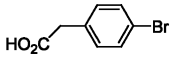
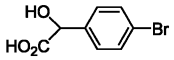
Scheme 2. Cross-coupling of aromatic bromides and phenylboronic acid.

2.2. Cross-coupling of aromatic and heteroaromatic chlorides with arylboronic acids

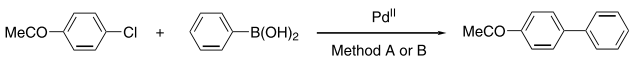
Preliminary studies about the appropriate reaction conditions for the Suzuki coupling of *p*-chloroacetophenone with phenylboronic acid using the previously mentioned methods A and B, showed that the presence of TBAB was crucial to obtain good conversions (Scheme 3 and Table 3), presumably due to the rapid formation of Bu_4N^+ $PhB(OH)_3^-$ [24]. Under water reflux conditions (method A), 0.5 equivalent of TBAB gave good conversions after 2 h with 5×10^{-3} mol% of complexes **1** (Table 3, entries 2 and 3). For room temperature conditions (method B), higher catalyst loadings (0.5 mol% of **1**) and one equivalent of TBAB had to be used when reagents were allowed to react for 18 h. As expected being the coupling more sluggish than in the case of aryl bromides. Palladium(II) salts were ineffective under both reaction conditions. The thermal stability of these palladacycles was also studied following method A conditions with 0.05 mol% of compound **1b** in 1 h intervals. After the first and second cycle 99% conversion was obtained. The conversion decrease in the third and fourth cycle to 75 and 46%, respectively.

The reactivity of different aromatic and heteroaromatic chlorides with different arylboronic acids was studied using precatalyst **1b** under method A conditions (Scheme 4 and Table 4). The amounts of complex **1b** and TBAB were optimized in each example. In the case of *o*-chlorobenzaldehyde, a better result was obtained when using method B (Table 4, entries 3 and 4). This aldehyde was also coupled with *p*-(trifluoromethyl)phenylboronic acid under water reflux (Table 4, entry 5) to give in 76% yield 4′-(trifluoromethyl)-2-biphenylcarbaldehyde a precursor of the xenalipin acid, a compound which reduces cholesterol and trigliceride levels in plasma [21]. This product was prepared in a 73% yield by Genêt et al. by using 5 mol% of $Pd(OAc)_2$ in the presence of TPPTS but starting from *o*-bromobenzaldehyde [21]. This methodology has been also applied to the synthesis of 4′-methylbiphenyl-2-carbonitrile, an intermediate in the preparation of modern angiotensin II receptor antagonists such as the antihypertensive drugs, losartan, valsartan, irbesartan, and tasosartan [32]. This compound was obtained in a 70% yield after coupling *o*-chlorobenzonitrile with *p*-methylphenylboronic acid either with 0.05 and 0.5 mol% of complex **1b** in 2 days and 2 h, respectively (Table 4, entries 6 and 7). Less reactive chlorides such as *p*-chloroanisol and *p*-chlorophenol were coupled in moderate yields (Table 4, entries 9 and 10). Moreover, *p*-chloroaniline suffered efficient coupling in 6 h with 0.5 mol% of palladacycle **1b** (Table 4, entry 11). As in the case of the corresponding bromides, biarylacetic acid and *p*-phenylmandelic acid were prepared from the corresponding chlorides in moderate yields after 2.5 h with 0.5 mol% of complex **1b** (Table 4, entries 12 and 13). Different chloro-substituted pyridines and 1-chloroisoquinoline were coupled with phenylboronic acid in good yields in short times ranging from 3 to 4 h (Table 4, entries 14–18). In the case of 2,4,6-trichloropyrimidine, an excess of phenylboronic acid was used affording after 2.5 h and in the presence of 0.35 mol% of complex **1b** the corresponding triphenyl substituted pyrimidine (Table 4, entry 19). This 2,4,6-triphenylpyrimidine has been recently prepared in under glyme reflux conditions during 24 h and using $Pd(OAc)_2$ (2.5 mol%) and PPh_3 (5 mol%) in 93% yield [33]. Finally,

Table 2
Suzuki coupling of aryl bromides and phenylboronic acid[a]

Entry	ArBr	mol % Pd	Method	Time	Yield (%)[b]	TON	TOF (h^{-1})
1		10^{-3}	A	100 min	92 (80)[c]	92000	52600
2		10^{-2}	B	5 h	100	10000	2000
3		$8x10^{-3}$	A	45 min	70	8750	11667
4		10^{-2}	B	2 h	78 (57)[c]	7800	3900
5		$5x10^{-3}$	A	15 min	88 (55)[c]	17600	70400
6		10^{-2}	B	7 h	70	7000	1000
7		$9x10^{-3}$	A	45 min	97	10777	14370
8		10^{-2}	C	22 h	98 (83)[d]	9800	445
9		10^{-2}	A	3 h	71 (40)[d]	7100	2366
10		10^{-2}	C	22 h	56	5600	254
11		10^{-2}	B	6 d	84 (54)[d]	8400	58
12		$8x10^{-3}$	A	30 min	82 (71)[c]	10250	20500
13		$9x10^{-3}$	C	3 h	90	10000	3333
14		10^{-2}	A	100 min	100 (72)[d]	10000	6000
15		10^{-2}	B	5 h	73	7300	1460
16		10^{-1}	A[e]	2 h	87 (79)[c]	870	435
17		10^{-1}	A[e]	2 h	100[f] (87)[c]	1000	500

[a] See footnote a in Table 1.
[b] GC yield.
[c] Isolated yield after recrystallization.
[d] Isolated yield after column chromatography.
[e] The reaction was performed at r.t.
[f] HPLC yield.



Scheme 3. Cross-coupling studies of *p*-chloroacetophenone and phenylboronic acid.

this methodology was applied to the synthesis of 4,5-diarylpyrazinones, a family of compounds, which present important agrochemical and pharmaceutical activities [34]. Thus, diarylation of the 4,5-dichloro-2-methyl-3(2*H*)pyridazinone took place after 4 h with 0.05 mol% of precatalyst **1b**. Previously described synthesis was carried out under nitrogen atmosphere with 3 mol% of $Pd(PPh_3)_4$ in refluxing toluene [34].

2.3. Cross-coupling of aromatic and heteroaromatic bromides and chlorides with alkylboronic acids

The formation of $C(sp^2)$–$C(sp^3)$ bonds was studied with aromatic and heteroaromatic bromides and chlorides employing trimethylboroxine (TMB) and butyl-

Table 3
Reaction conditions and catalyst studies on the Suzuki coupling of *p*-chloroacetophenone and phenylboronic acid [a]

Entry	Catalyst (mol% Pd)	Method	Time (h)	Yield (%) [b]	TON	TOF (h^{-1})
1	**1a** (10^{-2})	A	2	69	6900	3450
2	**1b** (10^{-2})	A	2	77	7700	3850
3	**1b** (10^{-2})	A [c]	4	10	1000	250
4	**1c** (10^{-2})	A	2	69	6900	3450
5	$Pd(OAc)_2$ (10^{-2})	A	2	5	500	250
6	Li_2PdCl_4 (10^{-2})	A	2	–	–	–
7	**1a** (1)	B	18	43	43	2.4
8	**1b** (1)	B	18	50	50	2.8
9	**1c** (1)	B	18	42	42	2.3
10	$Pd(OAc)_2$ (1)	B	18	1.5	1.5	–

[a] Method A: *p*-chloroacetophenone (2 mmol), $PhB(OH)_2$ (3 mmol), K_2CO_3 (4 mmol), TBAB (1 mmol), H_2O (7 ml), reflux. Method B: *p*-chloroacetophenone (2 mmol), $PhB(OH)_2$ (3 mmol), KOH (4 mmol), TBAB (2 mmol), MeOH–H_2O 3/1 (8 ml), r.t.
[b] GC yield.
[c] 0.4 mmol of TBAB were used.

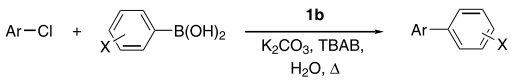
boronic acid. The methylation of aryl bromides and activated aryl chlorides has been recently performed with TMB in the presence 10 mol% of $Pd(PPh_3)_4$ in refluxing aqueous dioxane for 1 day under nitrogen [10]. We have found that the methylation of *p*-bromo and *p*-chloroacetophenone can be carried out under water reflux in the presence of K_2CO_3 as base (method A) with 5 mol% of palladacycle **1b** giving *p*-methylacetophenone in high yields after 80 min and 4 h, respectively (Scheme 5 and Table 5). All essayed aryl chlorides were methylated in the presence of TBAB. In the case of 4,5-dichloro-2-methyl-3(2*H*)pyridazinone mono and dimethylation was observed in ca. 1/1 ratio by ^{1}H-NMR (Table 5, entry 4). Both products were easily separated by flash chromatography yielding 2,4,5-trimethyl-3(2*H*)pyridazinone and 4-chloro-2,5-dimethyl-3(2*H*)-pyridazinone in 20 and 35% yields, respectively.

The alkylation with *n*-butylboronic acid was also carried out under method A (water reflux) adding one equivalent of TBAB in the case of aryl chlorides (Table 5, entries 5–10). For this cross-coupling reaction only 1 mol% of Pd was used and the presence of Ag(I) salts [19,20] was not necessary. In all the cases symmetrical biaryls were obtained in variable amounts as by-products due to the Ullmann-type coupling processes of the aryl halides.

2.4. Cross-coupling of benzylic and allylic chlorides or acetates with arylboronic acids

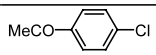
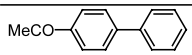
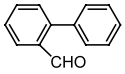
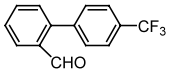
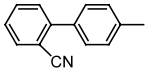
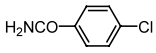
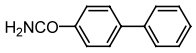
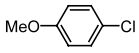
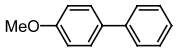
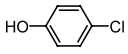
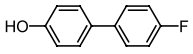
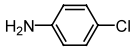
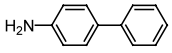
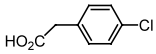
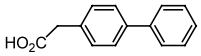
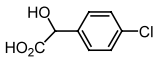
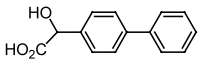
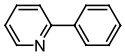
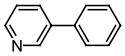
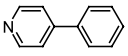
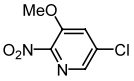
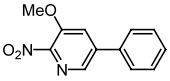
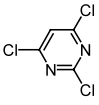
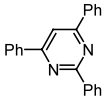
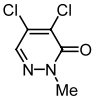
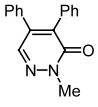
The extension of the Suzuki reaction to the coupling of benzylic bromides and iodides [8], allylic bromides [35] and allylic acetates [23] with arylboronic acids, has increased considerably the scope of this methodology. We have found that oxime-derived palladacycles catalyse the cross-coupling of benzylic and allylic chlorides as well as allylic acetates under very smooth reactions conditions. The reaction of benzylic chlorides with arylboronic acids was performed at room temperature with 0.05 mol% of complex **1b** in acetone–water (3/2), KOH as base and TBAB as additive (similar to method B) to afford in good yields the corresponding bis(aryl)methanes (Scheme 6 and Table 6). The presence of TBAB decreased the reaction time (Table 6, compare entries 1 and 2). These reaction conditions are more convenient than the previoulsy described for the coupling of benzyl bromides with 3 mol% of $Pd(PPh_3)_4$ as catalyst, which should to be heated at reflux of dimethoxyethane for 18 h under argon [8]. When the reaction was carried out in refluxing water and K_2CO_3 as base (method A) the corresponding benzylic alcohols were mainly formed and the use of aqueous MeOH (method B) gave considerable amounts of benzylic methyl ethers.

For the cross-coupling of allylic chlorides or less costly acetates with arylboronic acids we used the same reaction conditions as for benzylic chlorides (acetone–water at room temperature) (Scheme 7 and Table 7). In the presence of 0.5 equivalent of TBAB the loading of the catalyst and the reaction time could be decreased to give full conversion to the corresponding products in less than 7 h at room temperature (TON up to 10^4) (Table 7, entries 1–3). In the case of cinnamyl chloride and acetate 3,3-diaryl-1-propenes were obtained as the minor regioisomers in 3–24% (Table 7, entries 1–4 and 7).

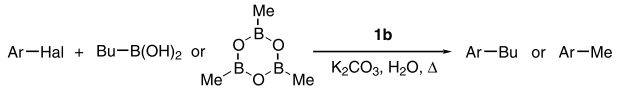


Scheme 4. Cross-coupling of aromatic chlorides and arylboronic acids.

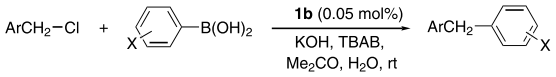
Table 4
Suzuki coupling of aryl chlorides and arylboronic acids [a]

Entry	ArCl	mol % Pd	TBAB (equiv)	Time	Product	Yield (%)[b,c]
1		10^{-2}	0.5	2.5 h		91
2		10^{-1}	0.5	1 h		100 (98)
3		1	1	2 h		41
4		1[d]	1	32 h		57 (52)
5		1	1	9 h		76 (34)
6		10^{-1}	0.5	2 d		69
7		1	1	2 h		70
8		1	1	2.5 h		40
9		1	1	6 h		40
10		1	1	2 d		41 (33)
11		1	1	6 h		83
12		1	1	2.5 h		50[e]
13		1	1	2.5 h		42[e]
14		1	0.5	3.5 h		66
15		1	0.5	3 h		92 (48)
16		1	0.5	3.5 h		100 (56)
17		1	1	4 h		76 (43)
18		1	1	3 h		61 (42)
19		0.7	1	2.5 h		100 (56)
20		10^{-1}	1	1 h		100 (92)

[a] Method A was used (see footnote a in Table 3).
[b] GC yield.
[c] In parenthesis isolated yield.
[d] Method B was used (see footnote a in Table 3).
[e] Determined by ^{1}H-NMR.



Scheme 5. Cross-coupling of aromatic bromides and chlorides with alkylboronic acids.

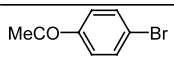
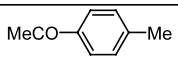
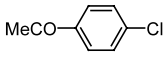
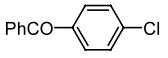
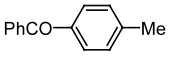
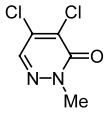
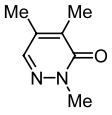
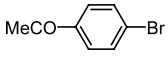
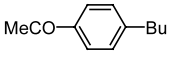
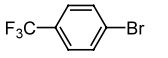
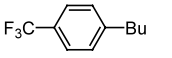
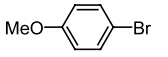
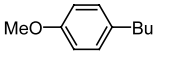
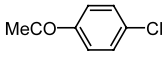
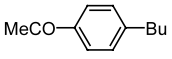
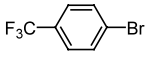
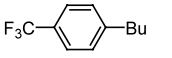
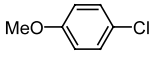
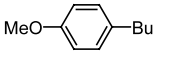


Scheme 6. Cross-coupling of benzylic chlorides and arylboronic acids.

3. Conclusions

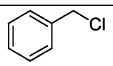
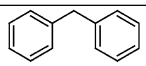
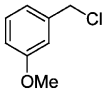
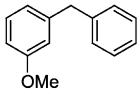
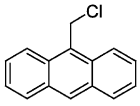
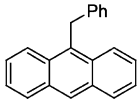
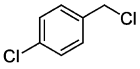
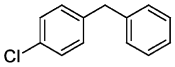
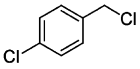
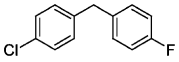
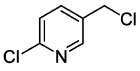
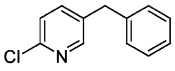
We can conclude that oxime-derived palladacycles are very versatile precatalysts for the cross-coupling under very simple and environmentally friendly conditions, of arylboronic acids with aromatic and heteroaromatic bromides and chlorides in refluxing water, or in aqueous methanol at room temperature under aerobic conditions. Aliphatic boronic acids can also be coupled efficiently in refluxing water with aromatic bromides and chlorides, whereas benzylic and allylic chlorides can be coupled with aromatic boronic acids in aqueous acetone at room temperature.

Table 5
Alkylation of aromatic bromides and chlorides with boronic acids [a]

Entry	ArHal	Boronic acid	mol % Pd	Time	Product	Yield (%)[b,c]
1		TMB	10	1.5 h		100
2		TMB[d]	10	4 h		81
3		TMB[d]	10	4 h		62
4		TMB[d]	10	20 h		48 (20)[e]
5		$BuB(OH)_2$	1	2 h		60 (41)[f]
6		$BuB(OH)_2$	1	5 h		60[g]
7		$BuB(OH)_2$	1	21 h		53[h]
8		$BuB(OH)_2$[d]	1	1 d		79[i]
9		$BuB(OH)_2$[d]	1	1 d		37[j]
10		$BuB(OH)_2$[d]	1	2 d		8[k]

[a] Method A: aryl bromide (0.5 mmol), TMB (0.5 mmol) or *n*-$BuB(OH)_2$ (1.5 mmol), K_2CO_3 (1.5 mmol), H_2O (4 ml), reflux.
[b] In parenthesis isolated yield.
[c] GC yield.
[d] TBAB (one equivalent) was also added.
[e] A 52% of 4-chloro-2,5-dimethyl-3(2*H*)pyridazinone was also obtained.
[f] 4,4′-Bis(acetyl)biphenyl (20%) was also isolated.
[g] 4,4′-Bis(trifluoromethyl)biphenyl (14%) was also obtained.
[h] 4,4′-Bis(methoxy)biphenyl (12%) was also obtained.
[i] 4,4′-Bis(acetyl)biphenyl (13%) was also obtained.
[j] 4,4′-Bis(trifluoromethyl)biphenyl (55%) was also obtained.
[k] 4,4′-Bis(methoxy)biphenyl (11%) was also obtained.

Table 6
Arylation of benzylic chlorides with arylboronic acids [a]

Entry	$ArCH_2Cl$	Boronic acid	Time	Product	Yield (%)[b,c]	TON
1		$PhB(OH)_2$	4 d		53[d]	530
2			3 d		66	660
3		$PhB(OH)_2$	19 h		75 (71)	750
4		$PhB(OH)_2$	5 h		100	1000
5		$PhB(OH)_2$	28 h		76	760
6		$4\text{-F-}C_6H_4B(OH)_2$	4 d		88	880
7		$PhB(OH)_2$	1 d		63 (40)	630

[a] Method B: benzylic chloride (2 mmol), $ArB(OH)_2$ (3 mmol), **1b** (0.05 mol%), TBAB (1 mmol), KOH (4 mmol), acetone–water 3/2 (8 ml), r.t.
[b] GC yield.
[c] In parenthesis isolated yield.
[d] Without TBAB.

4. Experimental

4.1. General

Gas chromatographic analyses were performed on a HP-5890 instrument equipped with a WCOT HP-1 fused silica capillary column. M.p.s were determined with a Reichert Thermovar hot plate apparatus. IR were recorded on a Nicolet 400D FT. NMR spectra were performed on a Bruker AC-300 using $CDCl_3$ as solvent and Me_4Si as internal standard unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000. High resolution mass spectra (EI) were recorded with a Finnigan MAT 95S. Microanalyses were performed by the Microanalysis Service of the University of Alicante. Analytical TLC was performed on Schleicher and Schuell F1400/LS silica gel plates and the spots visualized with UV light at 254 nm. For flash chromatography Merck silica gel 60 (0.040–0.063 mm) was employed. All reagents and solvents were obtained from commercial sources and generally used without further purification.

4.2. Synthesis of palladacycles

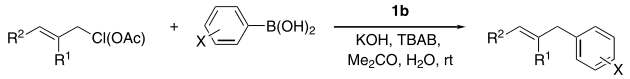
To a solution of Li_2PdCl_4 (2.62 g, 10 mmol) in MeOH (20 ml), a methanolic solution (10 ml) of the corresponding oxime (10 mmol) and AcONa (0.82 g, 10 mmol) was added. Then, the solution was stirred for 2–3 days at room temperature (r.t.). After adding water (10 ml), the corresponding cyclopalladated complexes precipitated and were filtered off. The different catalysts **1** were obtained with yields between 75 and 92%.

4.2.1. Complex *1b*

Yield: 92%; m.p. >250 °C; ν_{max} (KBr) 3425 (OH), 1622 (C=N) cm^{-1}; δ_H (300 MHz, DMF-d_7) 9.96 (2H, brs, $2\times$OH), 9.71 (2H, brs, $2\times$OH), 7.20 (2H, brs, ArH), 7.07 (2H, d, $J=8.5$ Hz, ArH), 6.50 (2H, dd, $J=$ 7.9 and 2.4 Hz, ArH), 2.24 (6H, s, $2\times CH_3$); δ_C (75 MHz, DMF-d_7) 167.3, 157.4, 152.7, 134.2, 127.2, 123.4, 111.3, 11,1; Anal. Found: C, 31.82; H, 2.94; N, 4.79. Calc. for $C_{16}H_{16}Cl_2N_2O_4Pd_2$: C, 32.90; H, 2.76; N, 4.80%.

4.2.2. Complex *1c*

Yield: 75%; m.p. >250 °C; ν_{max} (KBr) 3405 (OH), 1612 (C=N) cm^{-1}; δ_H (300 MHz, DMF-d_7) 10.50–9.40



Scheme 7. Cross-coupling of allylic chlorides and acetates with arylboronic acids.

(6H, brs, 6 × OH), 7.41 (4H, d, $J = 8.5$ Hz, ArH), 7.26 (2H, brs, ArH), 7.02 (4H, d, $J = 8.5$ Hz, ArH), 6.69 (2H, d, $J = 8.5$ Hz, ArH), 6.48 (2H, dd, $J = 7.9$ and 2.7 Hz, ArH); δ_C (75 MHz, DMF-d_7) 167.8, 160.0, 157.5, 152.9, 134.3, 131.5, 129.4, 123.7, 121.0, 115.8, 111.5; Anal. Found: C, 41.62; H, 2.71; N, 3.69. Calc. for $C_{26}H_{20}Cl_2N_2O_6Pd_2$: C, 42.19; H, 2.72; N, 3.78%.

4.3. Reduction of palladacycles with sodium cyanoborodeuteride

To a mixture of the complex to be reduced (0.125 mmol) in THF (2.5 ml) and MeOH (1.25 ml), sodium cyanoborodeuteride (0.25 mmol, 17 mg) was added portion wise at 0 °C and the mixture was stirred for 1 h allowing to warm to r.t. The black precipitate was filtered off, the solvents were evaporated (15 mmHg) and the residue hydrolysed with water and extracted with AcOEt. The organic layer was dried ($MgSO_4$) and evaporated (15 mmHg) and the product was purified by flash chromatography on silica gel.

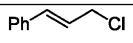
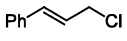
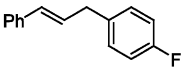
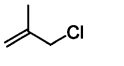
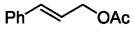
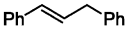
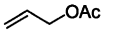
4.3.1. Deuterated oxime **2b**

Yield: 79%; m.p. 141 °C; R_f (C_6H_{14}–EtOAc, 1/1) 0.44; ν_{max} (KBr) 3330 (OH), 1642 (C=N) cm^{-1}; δ_H (300 MHz, Me_2SO-d_6) 10.85 (1H, s, OH), 9.63 (1H, s, OH), 7.46 (1H, d, $J = 8.5$ Hz, ArH), 6.76–6.74 (2H, m, ArH), 2.08 (3H, s, CH_3); δ_C (75 MHz, Me_2SO-d_6) 158.0, 152.6, 127.9, 126.9, 115.12, 115.07, 115.0, 11.5; *m/z* (EI) 152 (100, [M^+]), 151 (83, [$M^+ - 1$]), 136 (40), 135 (62), 134 (32), 121 (73), 120 (88), 119 (34), 95 (47), 94 (70), 93 (32), 92 (16), 91 (15), 67 (16), 66 (55), 65 (58), 64 (23), 63 (21).

4.3.2. Deuterated oxime **2c**

Yield: 78%; m.p. 264 °C; R_f (C_6H_{14}–EtOAc, 1/1) 0.30; ν_{max} (KBr) 3347 (OH), 1603 (C=N) cm^{-1}; δ_H (300 MHz, Me_2SO-d_6) 10.82 (1H, s, OH), 9.66 (2H, s, 2 × OH), 7.19 (1H, d, $J = 9.7$ Hz, ArH), 7.11 (2H, d, $J = 8.5$ Hz, ArH), 6.79 (2H, d, $J = 8.5$ Hz, ArH), 6.73-6.71 (2H, m, ArH); δ_C (75 MHz, Me_2SO-d_6) 158.1, 157.4, 154.9, 130.7, 128.8, 128.4, 128.3, 124.2, 115.0, 114.9, 114.7; *m/z* (EI) 230 (19, [M^+]), 122 (61), 121 (100), 110 (39), 109 (65), 93 (20), 65 (21).

Table 7
Arylation of allylic chlorides and acetates with arylboronic acids [a]

Entry	AllylCl or allylOAc	Boronic acid	mol % Pd	Time	Product	Yield (%)[b,c]	TON
1		$PhB(OH)_2$	10^{-1}[d]	5 h		100[e]	10^3
2			10^{-1}	1.5 h		100[f] (63)	10^3
3			10^{-2}	7 h		100[g]	10^4
4		4-F-$C_6H_4B(OH)_2$	10^{-2}	5.5 h		100[h]	10^4
5		$PhB(OH)_2$	10^{-2}	2 h		96 (69)	9600
6		$PhB(OH)_2$	10^{-2}	7 h		88	8800
7		$PhB(OH)_2$	10^{-1}	3 h		100[i]	10^3
8		$PhB(OH)_2$	1	7 h		63	63

[a] Method B: allylic chloride or acetate (2 mmol), $ArB(OH)_2$ (3 mmol), **1b**, TBAB (1 mmol), KOH (4 mmol), acetone–water 3/2 (8 ml), r.t.
[b] GC yield using decane as internal standard.
[c] In parenthesis isolated yield of the major regioisomer.
[d] Without TBAB.
[e] 4% of the other regioisomer.
[f] 6% of the other regioisomer.
[g] 10% of the other regioisomer.
[h] 24% of the other regioisomer.
[i] 3% of the other regioisomer.

4.4. Typical experimental procedure for Suzuki coupling of aromatic and heteroaromatic bromides and chlorides with arylboronic acids

4.4.1. Method A

A 25 ml round bottom flask was charged with aryl halide (2 mmol), arylboronic acid (3 mmol), K_2CO_3 (4 mmol, 553 mg), TBAB (1–2 mmol, only with aryl chlorides) palladacycle **1b** (see Tables 1–4) and water (7 ml). The mixture was stirred under reflux in air and the reaction progress was analysed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with EtOAc (3×15 ml). The organic phases were dried and evaporated (15 mmHg). The subsequent residue was purified by recrystallization or by flash chromatography on silica gel.

4.4.2. Method B

A 25 ml round bottom flask was charged with aryl halide (2 mmol), arylboronic acid (3 mmol), KOH (4 mmol, 224 mg), TBAB (1–2 mmol, only with aryl chlorides), palladacycle **1b** (see Tables 1–4) and MeOH–water 3/1 (8 ml). The mixture was stirred at r.t. and the reaction progress was analysed by GC. Normally, the product was not soluble in the solvent mixture. In those cases, when the reaction was completed or stopped, the mixture was filtered and the solid obtained was washed with MeOH–water 3/1 and purified by recrystallization. When both aryl halide and biaryl were soluble, the reaction mixture was poured into excess of water and extracted with EtOAc (3×15 ml). The organic phases were dried, evaporated (15 mmHg) and the crude product purified by recrystallization or flash chromatography on silica gel.

The compounds 4-*phenylacetophenone*, 4-*phenylanisole*, 4-*phenylphenol*, 2-*phenylbenzonitrile*, 5-*phenylpyrimidine*, 5-*phenyl*-2-*thiophenecarbaldehyde*, *biphenylacetic acid*, 2-*phenylbenzaldehyde*, 4′-*metilbiphenyl*-2-*carbonitrile*, 4-*phenylbenzamide*, 4′-*fluoro*-4-*hydroxybiphenyl*, 4-*phenylaniline*, 2-*phenylpyridine*, 3-*phenylpyridine*, 4-*phenylpyridine* and 1-*phenylisoquinoline* are commercially available. The compounds 5-*phenyl*-2-*hydroxyacetophenone* [36], 4-*phenylmandelic acid* [31], 4′-*trifluoromethylbiphenyl*-2-*carbaldehyde* [37], 5-*phenyl*-3-*methoxy*-2-*nitropyridine* [38], 2,4,6-*triphenylpyrimidine* [33] and 4,5-*diphenyl*-2-*methyl*-3(2H)-*pyridazinone* [34] have been previously reported. Physical, analytical and spectroscopic data of the other synthesized compounds follow.

4.4.3. 5-Phenyl-2-hydroxy-3-methoxybenzaldehyde

M.p. 82 °C; R_f (C_6H_{14}–EtOAc, 7/1) 0.22; ν_{max} (KBr) 3168 (OH), 1666 (CHO), 1268, 1076 (C–O) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.09 (1H, s, OH), 9.97 (1H, s, CHO), 7.57–7.32 (7H, m, ArH), 3.98 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 196.7, 151.0, 148.5, 139.7, 133.2, 128.9, 127.5, 126.7, 122.6, 120.7, 116.9, 56.4; *m*/*z* (EI) 228 (100, [M^+]), 182 (15), 129 (27), 128 (28); HRMS (EI) [M^+], Found: 228.0756. $C_{14}H_{12}O_3$ requires 228.0786.

4.5. Typical experimental procedure for Suzuki coupling of aromatic and heteroaromatic bromides and chlorides with TMB

A 10 ml round bottom flask was charged with aryl halide (0.5 mmol), TMB (0.5 mmol, 70 μl), K_2CO_3 (1.5 mmol, 207 mg), TBAB (0.5 mmol, 161 mg, only with aryl chlorides), palladacycle **1b** (0.025 mmol, 14.6 mg, 10 mol% Pd) and water (4 ml). The mixture was stirred under reflux in air and the reaction progress was analysed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with EtOAc (3×10 ml). The organic phases were dried and evaporated (15 mmHg). The subsequent residue was purified by flash chromatography on silica gel.

The compounds 4-*methylacetophenone* and 4-*methylbenzophenone* are commercially available. Physical, analytical and spectroscopic data of the other synthesized compounds follow.

4.5.1. 2,4,5-Trimethyl-3(2H)-pyridazinone

R_f (C_6H_{14}–EtOAc, 1/1) 0.41; ν_{max} (liquid film) 1641 (C=O), 1596 (ArC) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.50 (s, 1H, ArH), 3.73 (s, 3H, CH_3N), 2.13 (s, 3H, CH_3C), 2.12 (s, 3H, CH_3C); δ_C (75 MHz, $CDCl_3$) 161.4, 138.6, 137.8, 136.1, 40.2, 16.3, 12.3; *m*/*z* (EI) 138 (52, [M^+]), 109 (16), 67 (34); HRMS (EI) [M^+], Found: 138.0813. $C_7H_{10}N_2O$ requires 138.0793.

4.5.2. 4-Chloro-2-5-dimethyl-3(2H)-pyridazinone

M.p. 128 °C; R_f (C_6H_{14}–EtOAc, 1/1) 0.22; ν_{max} (KBr) 1645 (C=O) 1600 (ArC) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.59 (1H, s, ArH), 3.79 (3H, s, CH_3N), 2.28 (3H, s, CH_3C); δ_C (75 MHz, $CDCl_3$) 157.5, 139.2, 137.4, 134.4, 40.9, 17.0; *m*/*z* (EI) 160 (10, [$M^+ + 2$]), 158 (34, [M^+]), 142 (19), 130 (22), 87 (33); HRMS (EI) [M^+], Found: 158.0227. $C_6H_7ClN_2O$ requires 158.0247.

4.6. Typical experimental procedure for Suzuki coupling of aromatic bromides and chlorides with butylboronic acid

A 25 ml round bottom flask was charged with aryl halide (2 mmol), butylboronic acid (6 mmol, 611 mg), K_2CO_3 (6 mmol, 829 mg), TBAB (2 mmol, 644 mg, only with aryl chlorides), palladacycle **1b** (0.01 mmol, 5.84 mg, 1 mol% Pd) and water (7 ml). The mixture was stirred under reflux in air and the reaction progress was analysed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with EtOAc (3×15 ml). The organic phases were dried and evapo-

rated (15 mmHg). The subsequent residue was purified by flash chromatography on silica gel.

The compound 4-*butylacetophenone* is commercially available and the compounds 1-*butyl*-4-*trifluoromethylbenzene* [39] and 4-*butylanisole* [40] have been previously reported.

4.7. Typical experimental procedure for Suzuki coupling of benzylic and allylic chlorides or acetates with arylboronic acids

A 25 ml round bottom flask was charged with benzylic or allylic chloride or acetate (2 mmol), aryl boronic acid (3 mmol), KOH (4 mmol, 224 mg), TBAB (1 mmol, 322mg), decane (2 mmol, 389 μl), palladacycle **1b** (see Tables 6 and 7) and C_3H_6O–water 3/2 (8 ml). The mixture was stirred at r.t. in air and the reaction progress was analysed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with EtOAc (3×15 ml). The organic phases were dried and evaporated (15 mmHg). The subsequent residue was purified by distillation or by column chromatography on silica gel.

The compounds *diphenylmethane*, 9-*benzylanthracene*, 1-*benzyl*-4-*chlorobenzene*, 2-*methyl*-3-*phenypropene* and 3-*phenylpropene* are commercially available and the compounds [3-benzylanisole] [41], 4-*chlorophenyl*(4-*fluorophenyl*)*methane* [42], 5-*benzyl*-2-*chloropyridine* [43], (*E*)-1,3-*diphenylpropene* [44] and (*E*)-3-(4-*fluorophenyl*)-1-*phenylpropene* [45] have been previously reported.

Acknowledgements

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