Suzuki–Miyaura and Related Cross-Couplings in Aqueous Solvents Catalyzed by Di(2-pyridyl)methylamine-Palladium Dichloride Complexes

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Dedicated to Prof. Peter Stannety on occasion of his 60th anniversary

Abstract: Di(2-pyridyl)methylamine-based palladium dichloride complexes **4** are versatile catalysts for different types of cross-coupling reactions in water or aqueous solvents under aerobic conditions. The Suzuki–Miyaura reaction of arylboronic acids can be performed with bromoarenes under water reflux using K_2CO_3 as base or at room temperature or 60 °C in aqueous methanol using KOH as base. For aryl chlorides the corresponding cross-couplings with arylboronic acids can be carried out in refluxing water with K_2CO_3 as base and TBAB as additive to provide biaryls and heterobiaryls. Arylboronic acids react with benzylic chlorides and allylic substrates such as chlorides, acetates or carbonates also in refluxing water with K_2CO_3 as base or at room temperature in aqueous acetone and KOH as base, to give diarylmethanes and arylpropenes. Trimethylboroxine and alkylboronic acids are coupled with bromo- and chloroarenes under water at reflux with K_2CO_3 as base and TBAB as additive to furnish methyl- and butylarenes. These cross-couplings have also been performed in shorter times under microwave irradiation. Several important intermediates such as, 4′-methylbiphenyl-2-carbonitrile, 4-biphenylacetic acid, 3-(3-methylphenyl)benzoic acid, 4,5-diphenyl-2-methyl-3(2*H*)pyridazinone and 2-(4′-fluorobenzyl)thiophene have been prepared under aqueous and aerobic conditions in good yields.

Keywords: biaryls; boronic acids; cross-coupling reactions; N ligands; palladium

Introduction

The Suzuki–Miyaura reaction has became in the last 10 years the method of choice for biaryl and heterobiaryl synthesis.[1] These moieties are widely present in numerous classes of organic compounds, such as natural products, pharmaceuticals, agrochemicals and ligands for asymmetric synthesis and in new materials, such as liquid crystals.[2] The wide-ranging applications of the Suzuki–Miyaura reaction are based on the use of less toxic materials, boronic acids and esters, mild and operationally easy reaction conditions, the use of aqueous inorganic bases, tolerance to many functional groups and its suitability for sterically hindered substrates. Some of the challenges related to the industrial applications of this cross-coupling reaction are focused on the use of aryl chlorides as substrates, the recovery of the catalyst, to avoid toxic phosphanes and to perform the process in neat water.

Reactions in water have important economical and safety implications, specially for large-scale production.[3] Suzuki–Miyaura reactions have been carried out in neat water by using aqueous soluble substrates with $Pd(OAc)_2$[4] or Pd/C[5] as catalysts under phosphane-free conditions. A second strategy employs hydrophilic phosphanes as ligands.[6] For non-hydrophilic substrates the presence of high amounts of an ammonium salt as additive, e.g., tetra-*n*-butylammonium bromide (TBAB),[7] and $Pd(OAc)_2$ as catalyst accelerates the cross-coupling of bromoarenes[8] and chloroarenes[9] in water. Aqueous surfactants have proved to be good additives for Suzuki-Miyaura reactions in water.[10] We reported for the first time the coupling of aryl chlorides in water in the presence of substoichiometric amounts of TBAB by using an oxime-derived palladacycle **1** as catalyst.[11] This catalyst has been immobilized by covalent anchoring to silica, and employed as a reusable heterogeneous catalysts for Suzuki–Miyaura reactions in water.[12]

N,N-Type ligands have shown excellent properties for palladium complexation and also as catalysts for cross-coupling reactions compared to P,P-type ligands, due

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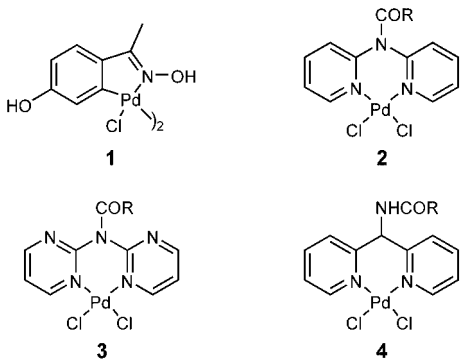


Figure 1.

to the stronger σ-donation which favors both oxidative addition and slow reductive-elimination steps in the catalytic cycle.[13] Polymer-bound di-2-pyridylamine-derived ligands have shown a high binding selectivity for mercury and palladium ions,[14] and the corresponding palladium(II) chloride complex **2** presents a high temperature and pH stability, palladium not being removed from the ligand within a pH range of 0–12.[15] Moreover, the catalytic activity of this complex **2** in Heck, Sonogashira, amination and polymerization reactions has been studied in organic solvents.[15] Suzuki–Miyaura reactions of aryl iodides and bromides have been studied with polymer-bound di-2-pyrimidylamine-based complexes **3** under THF reflux with moderate catalytic activity.[16] Very recently, as part of our studies to find robust and easily prepared systems to catalyze C–C bond forming reactions, we have communicated that di(2-pyridyl)methylamine-derived palladium(II) chloride complexes **4** with less electron-rich ligands are very active homogeneous catalysts for Heck, Suzuki and Sonogashira couplings in organic and aqueous solvents.[17] We report here the scope of this type of catalyst in homogeneous Suzuki–Miyaura reactions between bromo- or chloroarenes and arylboronic acids in water and aqueous solvents. In addition, related C(sp^3)–C(sp^2) bond formation reactions in water between alkylboronic acids and aryl halides and between arylboronic acids and benzylic chlorides and allylic substrates are also discussed.

Results and Discussion

Synthesis of Di(2-pyridyl)methylamine-derived Palladium Complexes

For the preparation of complexes **4**, the known di(2-pyridyl)methylamine (**5**),[18] prepared from di-2-pyridyl ketone, was acylated with acetic anhydride and cyclohexyl isocyanate affording the acetamide **6a** and urea **6b** in 88 and 84% yield, respectively. The corresponding palladium(II) chloride complexes **4a** and **4b** were obtained

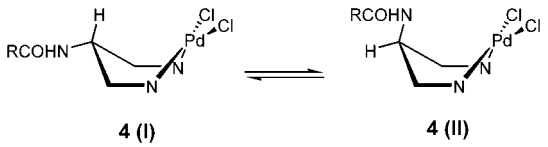
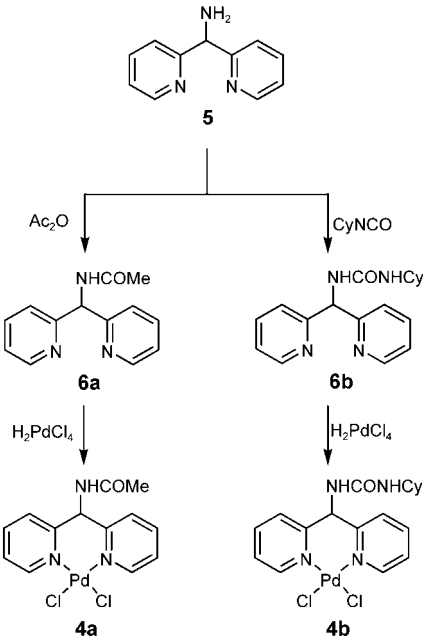


Figure 2.



Scheme 1.

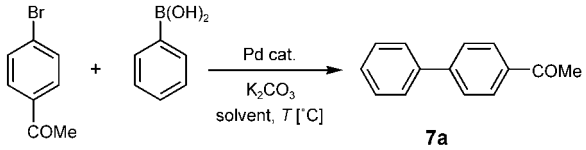
in 73 and 94% yield after reaction of ligands **6** with fresh prepared H_2PdCl_4 (Scheme 1).[17] These complexes **4a** and **4b** showed a low solubility in most organic solvents and their NMR spectra revealed a mixture of conformational isomers **I** and **II** (Figure 2) in 6:1 and 3:1 ratios, respectively. Both isomers interconverted when complex **4a** was heated to 56 °C in DMSO-d_6 in an NMR tube. Similar conformers have been observed for [di(2-pyridyl)methylphenylsilane]palladium(II) dichloride, used as a catalyst in the Stille reaction.[19] In the case of compound **4a**, isomer **I** could be isolated by recrystallization from the isomeric mixture and its structure determined by single-crystal X-ray analysis showing a six-membered chelate ring in a boat conformation with the acetamido substituent at the bowsprit position, with the CH and palladium ends being out of plane.[17] The coordination sphere about the palladium is square planar, which guaranteed a good stability and catalytic activity.[20] In the ^{1}H NMR spectrum (500 MHz), the hydrogen at the flagpole position in the isomer of the type **I** appears shifted to lower fields than in isomers of the type **II**. Complex **4b** was also prepared because the urea moiety is a more robust functional group than acetamido to work under aqueous basic conditions at high temperatures and long reaction times.

Suzuki–Miyaura Coupling of Aryl Halides with Arylboronic acids

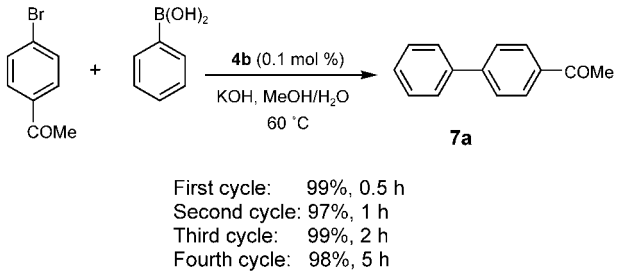
Initial studies about the reaction conditions for the cross-coupling of aryl bromides were performed with 4-bromoacetophenone and phenylboronic acid as reaction model in different solvents with complexes **4**, using K_2CO_3 as base in the absence of additives (Scheme 2 and Table 1). The process took place in shorter reaction times and with lower catalyst loadings in refluxing water than in toluene or in aqueous DMF (Table 1, entries 1–3). Experiments about the catalyst activity with the two complexes **4b**, **4a** or $Pd(OAc)_2$ under water reflux indicated that the former gave the best results, TON up to 10^5 and TOF 8×10^4 (Table 1, entries 3–5). For room temperature couplings, the reaction failed in water and was faster in toluene than in aqueous solvents such as DMF or MeOH, probably due to solubility reasons (Table 1, entries 6–8). When KOH was used instead of K_2CO_3 in aqueous MeOH, a higher TON was obtained (Table 1, compare entries 8 and 9). When the reaction in aqueous MeOH and KOH as base was carried out at 60 °C with **4b** as catalyst more higher TON (up to 9200) and TOF (up to 7369 h^{-1}) than at room temperature were obtained (Table 1, compare entries 8 and 9 with entries 10 and 11). These results can be compared to those described with palladacycle **1**[11] in aqueous solvents and are superior to Buchmeiser's complexes **2**[15] and **3**[16] in organic solvents.

The stability and reactivity of complex **4b** during the Suzuki–Miyaura cross-coupling reaction were studied for 4-bromoacetophenone and phenylboronic acid with KOH as base in aqueous NaOH at 60 °C (Scheme 3). After filtration, fresh reagents were added to the filtrate and almost quantitative conversions were obtained during 4 consecutive catalytic cycles, although an increase of the reaction time was observed, probably due to successive work-ups.

Cross-couplings of different bromoarenes with arylboronic acids to give biphenyls **7** were performed with catalyst **4b** in refluxing water with K_2CO_3 as base (Scheme 4 and Table 2). Good yields were obtained with bromoarenes bearing electron-withdrawing and -releasing groups as well as with *ortho*-substituted derivatives. It is worthy of note that 4-bromophenol gave high conversions under water reflux and at room temperature with KOH as base in aqueous methanol, probably due to its solubility in aqueous basic media (Table 2, entries 2 and 3). Biaryl **7c**, which is an intermediate in the preparation of modern angiotensin II receptor antagonists, such as the antihypertensive drugs losartan, valsar-



Scheme 2.



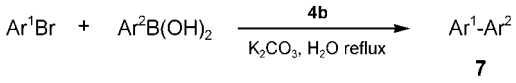
Scheme 3.

Table 1. Suzuki–Miyaura coupling of $PhB(OH)_2$ and 4-BrC_6H_4COMe: reaction conditions study.[a]

Entry	Cat. [mol % Pd]	Solvent	T [°C]	t [h]	Yield [%][b]	*TON*	*TOF* [h^{-1}]
1	**4b** (10^{-2})	toluene	110	9	97	9700	1078
2	**4b** (10^{-2})	DMF/H_2O[c]	110	3.5	87	8700	2486
3	**4b** (10^{-3})	H_2O	100	1.25	99	10^5	80000
4	**4a** (10^{-3})	H_2O	100	1.25	79	79000	63200
5	$Pd(OAc)_2$ (10^{-3})	H_2O	100	1.25	64	64000	51200
6	**4b** (10^{-1})	toluene	rt	1	85	850	850
7	**4b** (0.2)	DMF/H_2O[c]	rt	92	41	205	2
8	**4b** (0.2)	MeOH/H_2O[d]	rt	6	82	410	68
9	**4b** (10^{-1})	MeOH/H_2O[d, e]	rt	24	87 (82)	870	36
10	**4b** (10^{-1})	MeOH/H_2O[f, e]	60	0.5	100 (99)	1000	2000
11	**4b** (10^{-2})	MeOH/H_2O[f, e]	60	1.25	92	9200	7360

[a] Reaction conditions: 4-bromoacetophenone (1 mmol), $PhB(OH)_2$ (1.5 mmol), K_2CO_3 (2 mmol), solvent (2 mL).
[b] Of compound **7a**, determined by GLC, based on 4-bromoacetophenone using decane as internal standard. In parenthesis isolated yield after flash chromatography or recrystallization.
[c] Volume ratio 95/5.
[d] Volume ratio 2/3.
[e] KOH was used as base.
[f] Volume ratio 3/1.

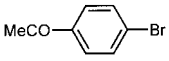
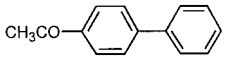
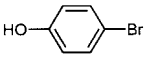
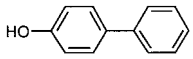
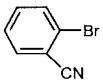
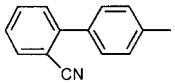
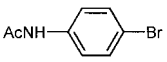
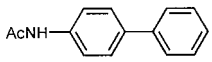
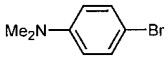
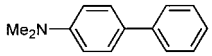
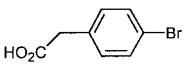
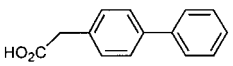
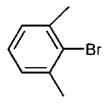
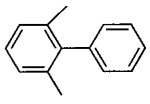
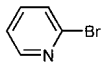
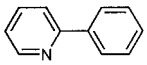
tan etc.,[21] was prepared quantitatively by reaction of *o*-bromobenzonitrile with *p*-tolylboronic acid (Table 2, entry 4). The anti-inflammatory 4-biphenylacetic acid **7f** was obtained in 91% yield by reaction of *p*-bromophenylacetic acid with phenylboronic acid (Table 2, entry 8).[22] Basic substrates such as *p*-bromo-*N*,*N*-dimethylaniline and 2-bromopyridine could be coupled with phenylboronic acid with a higher loading of catalyst (0.1 mol %) in moderate yields (Table 2, entries 6 and 10). The coupling of *p*-bromo-*N*,*N*-dimethylaniline with phenylboronic acid also was performed in aqueous DMF giving rise to a higher yield than in water but with a longer reaction time (Table 2, entries 6 and 7). In the case of the hindered 2,6-dimethyl-1-bromobenzene a rather fast coupling took place with phenylboronic acid by using 1 mol % of complex **4b** (Table 2, entry 9).



Scheme 4.

Reaction conditions for the cross-coupling between 4-chloroacetophenone and phenylboronic acid using complexes **4** or $Pd(OAc)_2$ as catalysts and K_2CO_3 as base in different solvents (Scheme 5 and Table 3) needed the presence of tetra-*n*-butylammonium bromide (TBAB, 0.5 equivs.), as was previously found out in our previous work with aryl chlorides and palladacycle **1** as catalyst.[11] When toluene was used as solvent, only 6% conversion after one day was observed. However, aqueous DMF[23] at 130 °C or water at reflux were adequate conditions to achieve a full conversion with 0.1 mol % of complex **4b** (Table 3, entries 1–3). The reaction time can be reduced at 5 min under microwave irradiation at 120 W in water as solvent at 120 °C (Table 3, entry 4). The efficiency of complexes **4a**, **4b** and $Pd(OAc)_2$ as catalysts were studied also in water at reflux with 0.01 mol % of palladium during 3 d; **4b** was the most active with a TON of up to 6,500 (Table 3, entries 5–7). This process can be performed with complex **4b** in high-

Table 2. Suzuki–Miyaura coupling of aryl bromides and arylboronic acids in water with complex **4b**.[a]

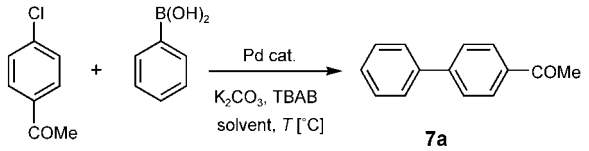
Entry	Ar–Br	Boronic Acid	Mol % Pd	*t*	No.	Product	Yield [%][b]	TON
1		$PhB(OH)_2$	10^{-3}	75 min	**7a**		100 (91)	100,000
2		$PhB(OH)_2$	7.6×10^{-4}	2 h	**7b**		95 (82)	125,000
3	”	”	0.1[c]	120 h	**7b**	”	75	750
4		$4\text{-}MeC_6H_4B(OH)_2$	0.1	1 h	**7c**		100 (99)	1000
5		$PhB(OH)_2$	0.1	2 h	**7d**		100 (97)	1000
6		$PhB(OH)_2$	1	5 h	**7e**		59	59
7	”	”	1[d]	48 h	**7e**	”	96 (84)	96
8		$PhB(OH)_2$	0.1	30 min	**7f**		100 (91)	1000
9		$PhB(OH)_2$	1	3 h	**7g**		83	83
10		$PhB(OH)_2$	0.1	22.5 h	**7h**		62	620

[a] Reaction conditions: aryl bromide (1 mmol), arylboronic acid (1.5 mmol), cat. **4b** (see column), K_2CO_3 (2 mmol), H_2O (2 mL), 100 °C.
[b] Determined by GLC, based on aryl bromide using decane as internal standard. In parenthesis isolated yield after flash chromatography or recrystallization.
[c] Reaction conditions: aryl bromide (1 mmol), arylboronic acid (1.5 mmol), KOH (2 mmol), $MeOH/H_2O$: 2/3 (2 mL), room temperature.
[d] The reaction was performed in DMF/H_2O at 110 °C.

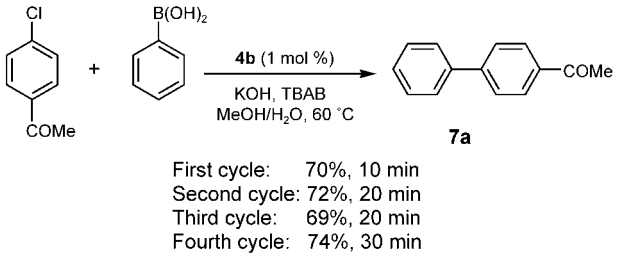
er yields than with $Pd(OAc)_2$ at lower temperatures, either 60 °C or room temperature, in aqueous MeOH with KOH as base (Table 3, entries 8 to 10).

Several reaction cycles were also performed between *p*-chloroacetophenone and phenylboronic acid in the presence of catalyst **4b** (1 mol %) in aqueous methanol at 60 °C and KOH as base in short periods of time, 10 to 30 min, giving around 70% isolated yield without loosing catalytic activity. This study was carried out by adding fresh reagents (*p*-chloroacetophenone, phenylboronic acid and KOH) to the obtained solution after filtration of the formed biphenyl **7a** (Scheme 6).

Different types of activated and deactivated aryl chlorides were coupled with arylboronic acids in refluxing water using catalyst **4b** (0.1 to 1 mol %), K_2CO_3 as base and TBAB as additive (Scheme 7 and Table 4). The synthesis of the biphenyl unit of antihypertensive drugs, 4′-methylbiphenyl-2-carbonitrile (**7c**),[21] was carried out in this case also in good yield with 2-chlorobenzonitrile using a higher catalyst loading and longer reaction time (compare Table 3, entry 4 and Table 4, entry 2). 3-(3-Methylphenyl)benzoic acid (**7l**), a precursor of non-peptide Ras CAAX mimetics which are farnesyltransferase inhibitors,[24] was prepared from 3-chlorobenzoic acid and *m*-tolylboronic acid (Table 4, entry 6). Heterocyclic chlorides, such as 3-chloropyridine and 4,5-dichloro-2-methyl-3(2*H*)pyridazinone were coupled with one and two equivs. of phenylboronic acid to afford products **7h** and **7m**,[25] respectively (Table 4, entries 7 and 8).



Scheme 5.



Scheme 6.

Suzuki–Miyaura Coupling of Benzylic Chlorides and Allylic Derivatives with Arylboronic Acids

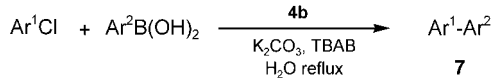
Palladium-catalyzed cross-coupling between benzylmetals and aryl halides or benzyl halides and arylmetals are two convenient strategies for the preparation of symmetrical and unsymmetrical diarylmethanes.[26] This type of unit is present in natural and biologically active products[27] and in supramolecular structures.[28] The extension of the Suzuki–Miyaura coupling to benzyl halides and arylboronic acids in organic[23,29] and aqueous[11] solvents has became an excellent methodology for the synthesis of these compounds. We have used the reaction conditions already set up for the coupling of benzylic chlorides with arylboronic acids catalyzed by the oxime-derived palladacycle **1**.[11] Thus, by using water under reflux and K_2CO_3 as base or aqueous acetone with KOH as base at room temperature, complex **4b** catalyzed the coupling of different benzylic chlorides and arylboronic acids in the presence of TBAB as additive to

Table 3. Suzuki–Miyaura coupling of $PhB(OH)_2$ and $4\text{-}ClC_6H_4COMe$: reaction conditions study.[a]

Entry	Cat. [mol % Pd]	Solvent	Base	T [°C]	t	Yield [%][b]	*TON*
1	**4b** (10^{-1})	toluene	K_2CO_3	110	22 h	6	60
2	**4b** (10^{-1})	DMF/H_2O[c]	K_2CO_3	130	1.5 h	95 (91)	950
3	**4b** (10^{-1})	H_2O	K_2CO_3	100	7.5 h	100 (97)	1000
4	**4b** (10^{-1})	H_2O	K_2CO_3	120[d]	5 min	88	880
5	**4b** (10^{-2})	H_2O	K_2CO_3	100	72 h	65	6500
6	**4a** (10^{-2})	H_2O	K_2CO_3	100	72 h	48	4800
7	$Pd(OAc)_2$ (10^{-2})	H_2O	K_2CO_3	100	72 h	29	2900
8	**4b** (1)	$MeOH/H_2O$[e]	KOH	60	10 min	76	76
9	**4b** (1)	$MeOH/H_2O$[e]	KOH	rt	64 h	42	42
10	$Pd(OAc)_2$ (1)	$MeOH/H_2O$[e]	KOH	rt	18 h	1.5	1.5

[a] Reaction conditions: 4-chloroacetophenone (1 mmol), $PhB(OH)_2$ (1.5 mmol), base (2 mmol), TBAB (0.5 mmol), solvent (2 mL).
[b] Of compound **7a**, determined by GLC, based on 4-chloroacetophenone using decane as internal standard. In parenthesis isolated yield after flash chromatography or recrystallization.
[c] Volume ratio 95/5.
[d] The reaction was performed under microwave irradiation conditions (120 W, 120 °C).
[e] Volume ratio 3/1.

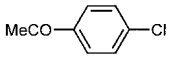
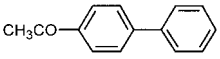
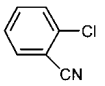
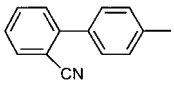
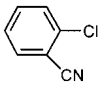
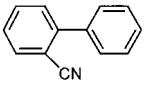
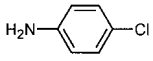
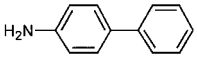
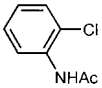
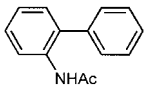
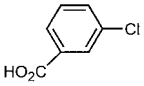
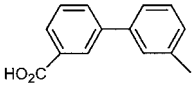
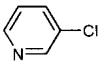
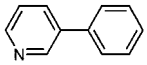
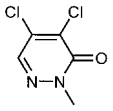
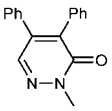
give diarylmethanes **8** (Scheme 8 and Table 5). The solvent at room temperature in these cases was acetone instead of methanol in order to avoid competitive nucleophilic substitution. The reaction of benzyl and 3-methoxybenzyl chlorides and phenylboronic acid in water was performed under reflux and under microwave irradiation with different loadings of catalyst **4b** to give good yields in short reaction times (Table 5, entries 1–3 and 5–7, respectively). For the room temperature couplings, higher complex loadings and longer reaction times were necessary for achieving high yields without deactivation of the catalyst (Table 5, entries 4 and 8). In the case of other benzylic chlorides, both reaction conditions were used (Table 5, entries 9–15). 2-(4′-Fluorobenzyl)thiophene (**8e**),[30] a key intermediate in the synthesis of the very potent 5-lipoxygenase inhibitor ABT-761,[31] has been prepared by coupling 4-fluorobenzyl chloride with 2-thiopheneboronic acid (Table 5, entries 12 and 13).



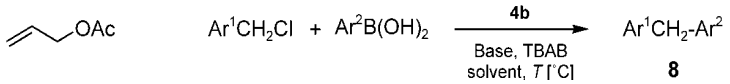
Scheme 7.

1,3-Diarylpropenes are interesting alkenes which have been recently used for the synthesis of the cyclolignans, dihydrodibenzo[*a, c*]cycloheptenes, by benzylation of phosphonium salts followed by Wittig olefination.[32] This type of olefins can be prepared in a very direct regio- and stereoselective manner by coupling of arylboronic acids with allylic substrates, although this cross-coupling has been less studied.[11,23,26,33] We have used the reaction conditions mentioned for benzylic chlorides in the coupling of different types of allylic substrates, such as chlorides, acetates and methyl carbonates, with arylboronic acids to provide compounds **9** in good yields (Scheme 9 and Table 6). Cinnamyl chloride was phenylated in aqueous DMF at 130 °C with low efficiency, achieving much better results in water at reflux (with TON up to 2000) or under microwave irradiation (with TOF up to 8400 h^{-1}) (Table 6, entries 1–3). Alter-

Table 4. Suzuki–Miyaura coupling of aryl chlorides and arylboronic acids in water with complex **4b**.[a]

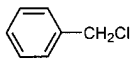
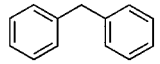
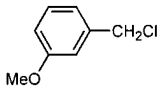
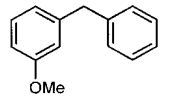
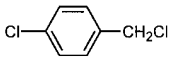
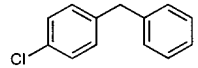
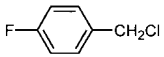
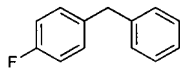
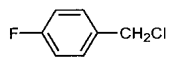
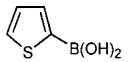
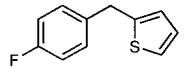
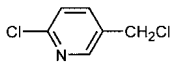
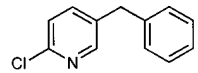
Entry	Ar–Cl	Boronic Acid	Mol % Pd	*t* [h]	No.	Product	Yield [%][b]
1		$PhB(OH)_2$	0.1	7.5	**7a**		100 (97)
2		$4\text{-}MeC_6H_4B(OH)_2$	1	7.5	**7c**		99 (92)
3		$PhB(OH)_2$	0.1	7.5	**7i**		99
4		$PhB(OH)_2$	1	7.5	**7j**		73 (52)
5		$PhB(OH)_2$	0.1	47	**7k**		40
6		$3\text{-}MeC_6H_4B(OH)_2$	1	21	**7l**		69 (51)
7		$PhB(OH)_2$	1	46	**7h**		100 (72)
8		$PhB(OH)_2$[c]	0.1	9	**7m**		99 (93)

[a] Reaction conditions: aryl chloride (1 mmol), arylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), TBAB (0.5 mmol), **4b** (see column), H_2O (2 mL), 100 °C.
[b] Determined by GLC, based on aryl chloride using decane as internal standard. In parenthesis isolated yield after flash chromatography or recrystallization.
[c] 3 mmol of $PhB(OH)_2$ were used.

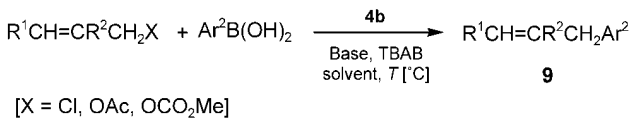


Scheme 8.

Table 5. Suzuki–Miyaura coupling of benzyl chlorides and arylboronic acids in aqueous solvents with complex **4b**.[a]

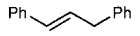
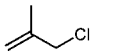
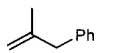
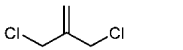
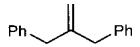
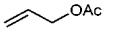
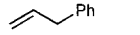
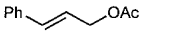
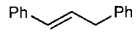
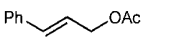
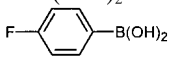
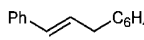
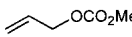
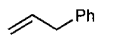
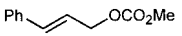
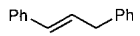
Entry	$ArCH_2$–Hal	Boronic Acid	Mol % Pd	Base	Solvent	T [°C]	t	No.	Product	Yield [%][b]	TON
1		$PhB(OH)_2$	1	K_2CO_3	H_2O	100	3 h	**8a**		100	100
2	”	”	0.1	K_2CO_3	H_2O	100	2 h	**8a**	”	57	570
3	”	”	0.1	K_2CO_3	H_2O	120[c]	5 min	**8a**	”	73	730
4	”	”	1	KOH	Acetone/ H_2O[d]	rt	87 h	**8a**	”	80 (70)	80
5		$PhB(OH)_2$	1	K_2CO_3	H_2O	100	2.5 h	**8b**		100 (75)	100
6	”	”	0.1	K_2CO_3	H_2O	100	4.5 h	**8b**	”	75	750
7	”	”	0.1	K_2CO_3	H_2O	120 [c]	5 min	**8b**	”	100	1000
8	”	”	1	KOH	Acetone/ H_2O[d]	rt	65 h	**8b**	”	93 (91)	93
9		$PhB(OH)_2$	0.1	K_2CO_3	H_2O	100	2 h	**8c**		100 (79)	1000
10		$PhB(OH)_2$	0.1	K_2CO_3	H_2O	100	1.5 h	**8d**		78 (71)	780
11	”	”	1	KOH	Acetone/ H_2O[d]	rt	56 h	**8d**	”	77	77
12			1	K_2CO_3	H_2O	100	75 min	**8e**		68 (57)	68
13	”	”	1	KOH	Acetone/ H_2O[d]	rt	168 h	**8e**	”	46	46
14		$PhB(OH)_2$	0.1	K_2CO_3	H_2O	100	2 h	**8f**		100	1000
15	”	$PhB(OH)_2$	1	KOH	Acetone/ H_2O[d]	rt	73 h	**8f**	”	100 (75)	100

[a] Reaction conditions: benzyl chloride (1 mmol), arylboronic acid (1.5 mmol), base (2 mmol), TBAB (1 mmol), **4b** (see column), solvent (2 mL).
[b] Determined by GLC, based on benzyl chloride using decane as internal standard. In parenthesis isolated yield after flash chromatography.
[c] The reaction was performed under microwave irradiation conditions (120 W, 120 °C).
[d] Volume ratio 3/2.



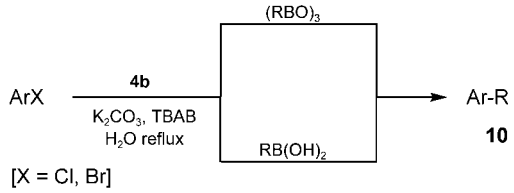
Scheme 9.

Table 6. Suzuki–Miyaura coupling of allyl chlorides, acetates and carbonates with arylboronic acids in aqueous solvents with complex **4b**.[a]

Entry	Allyl–X	Boronic Acid	Mol % Pd	Base	Solvent	T [°C]	t	No.	Product	Yield [%][b]	TON
1		$PhB(OH)_2$	0.05	K_2CO_3	H_2O	100	3 h	**9a**		100	2000
2	”	$PhB(OH)_2$	5	K_2CO_3	DMF/ H_2O[c]	130	30 min	**9a**	”	100	20
3	”	$PhB(OH)_2$	0.05	K_2CO_3	H_2O	120[d]	10 min	**9a**	”	70	1400
4	”	$PhB(OH)_2$	0.1	KOH	Acetone/H_2O[e]	20	8 h	**9a**	”	95 (83)	950
5		$PhB(OH)_2$	0.05	K_2CO_3	H_2O	100	24 h	**9b**		76	1520
6	”	$PhB(OH)_2$	1	KOH	Acetone/H_2O[e]	20	9.5 h	**9b**	”	80	80
7		$PhB(OH)_2$[f]	0.5	K_2CO_3	H_2O	100	1.5 h	**9c**		100 (86)	200
8	”	$PhB(OH)_2$[f]	1	KOH	Acetone/H_2O[e]	20	14.5 h	**9c**	”	87	87
9		$PhB(OH)_2$	0.5	K_2CO_3	H_2O	100	8 h	**9d**		82	164
10		$PhB(OH)_2$	0.1	K_2CO_3	H_2O	100	2 h	**9a**		100 (83)	1000
11	”	$PhB(OH)_2$	0.5	KOH	Acetone/H_2O[e]	20	25 h	**9a**	”	70 (61)	140
12			0.1	K_2CO_3	H_2O	100	2.5 h	**9e**		100 (89)	1000
13		$PhB(OH)_2$	0.5	K_2CO_3[g]	H_2O	100	2 h	**9d**		51	102
14		$PhB(OH)_2$	1	K_2CO_3[g]	H_2O	100	1 h	**9a**		100 (97)	100
15	”	$PhB(OH)_2$	0.5	K_2CO_3	H_2O	100	15 min	**9a**	”	100 (85)	200
16	”	$PhB(OH)_2$	0.05	K_2CO_3	H_2O	100	45 min	**9a**	”	100	2000
17	”	$PhB(OH)_2$	1	KOH	Acetone/H_2O[e]	20	62 h	**9a**	”	85	85

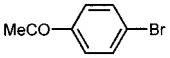
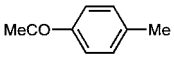
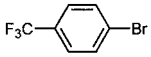
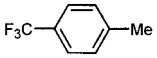
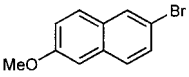
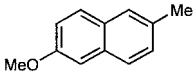
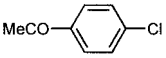
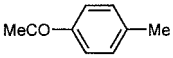
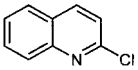
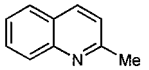
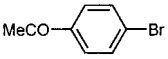
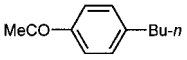
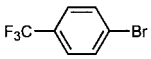
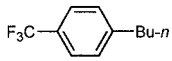
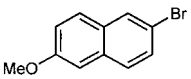
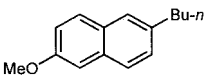
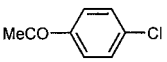
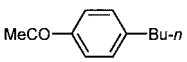
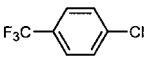
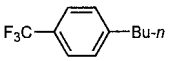
[a] Reaction conditions: allylX (1 mmol), arylboronic acid (1.5 mmol), base (2 mmol), TBAB (1 mmol), **4b** (see column), solvent (2 mL).
[b] Determined by GLC, based on allylic substrate using decane as internal standard. In parenthesis isolated yield after flash chromatography.
[c] Volume ratio 95/5.
[d] The reaction was performed under microwave irradiation conditions (120 W, 120 °C).
[e] Volume ratio 3/2.
[f] 3 mmol were used.
[g] 0.5 mmol of K_2CO_3 were used.

natively, the allylation can be performed at room temperature (with TON up to 950) in aqueous acetone and KOH as base (Table 6, entry 4). For the coupling of other allylic chlorides with phenylboronic acid (Table 6, entries 5–8) and for allylic acetates (Table 6, entries 9–12) and methyl carbonates (Table 6, entries 13–17) two different conditions, water at reflux and aqueous acetone at room temperature, were used. Under these reaction conditions the TOF (h^{-1}) numbers follow the order carbonate > chloride > acetate for reactions under water reflux (Table 6, compare entries 1, 10 and 16) and chloride > acetate > carbonate for reactions at room temperature (Table 6, compare entries 4, 11 and 17). Allylic carbonates have been coupled for the first time with phenylboronic acid, the amount of base being reduced to 0.5 equivs. (Table 6, entry 14).



Scheme 10.

Table 7. Suzuki–Miyaura coupling of aryl bromides or chlorides and trimethylboroxine or alkylboronic acids in water with complex **4b**.[a]

Entry	Ar–Hal	Boronic acid	Mol % Pd	*t*	No.	Product	Yield [%][b]
1		$(MeBO)_3$	5	7.5 h	**10a**		100 (87)
2	”	$MeB(OH)_2$	5	24 h	**10a**	”	64
3		$(MeBO)_3$	5	48 h[c]	**10b**		100
4		$(MeBO)_3$	5	9.5 h	**10c**		35
5		$(MeBO)_3$	5	56 h	**10a**		41
6		$(MeBO)_3$	10	25 h	**10d**		59
7		*n*-$BuB(OH)_2$	1	72 h	**10e**		63
8	”	*n*-$BuB(OH)_2$	1	10 min[d]	**10e**	”	80[e]
9		*n*-$BuB(OH)_2$	1	72 h	**10f**		89 (63)
10		*n*-$BuB(OH)_2$[f]	1	23 h	**10g**		100 (89)
11		*n*-$BuB(OH)_2$	1	72 h	**10e**		89 (63)
12		*n*-$BuB(OH)_2$	1	70 h	**10f**		70

[a] Reaction conditions: aryl halide (1 mmol), TMB or alkylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), TBAB (0.5 mmol) in the case of aryl chlorides, **4b** (see column), H_2O (2 mL), 100 °C.
[b] Determined by GLC, based on aryl halide using decane as internal standard. In parenthesis isolated yield after flash chromatography.
[c] The reaction was performed in a pressure tube.
[d] The reaction was performed under microwave irradiation conditions (120 W, 120 °C).
[e] 20% of 4,4′-diacetylbiphenyl was also obtained.
[f] 3 equivs. of *n*-$BuB(OH)_2$ were used.

Suzuki–Miyaura Coupling of Aryl Bromides and Chlorides with Alkylboronic Acids

Alkylboronic acids are less prone to react with aryl halides than arylboronic acids. The methylation of bromo- and chloroarenes has been performed with trimethylboroxine with $Pd(PPh_3)_4$ (10 mol %) in refluxing aqueous dioxane for 1 d[34] and with palladacyle **1** (10 mol %) in refluxing water.[11b] We have used the last reaction conditions with aryl bromides and chlorides and trimethylboroxine or methylboronic acid using complex **4b** (5 to 10 mol %) as catalyst, K_2CO_3 as base and TBAB as additive for the preparation of methylarenes **10** (Scheme 10 and Table 7, entries 1–6). Trimethylboroxine gave better results than methylboronic acid as methylating agent (Table 7, compare entries 1 and 2). As expected, activated aryl bromides gave better yields and faster conversions than unactivated or chlorides. However, a very low yield (8%) was obtained when 4-trifluoromethylbromobenzene was allowed to react with trimethylboroxine under microwave irradiation at 120 °C (120 W) during 5 min.

The alkylation with *n*-butylboronic acid of aryl halides was also carried out under the aqueous conditions described with palladacyle **1**[11b] avoiding the use of silver salts.[35] For these couplings between *n*-butylboronic acid and aryl bromides and chlorides, complex **4b** (1 mol %) as catalyst, K_2CO_3 as base and TBAB as additive were employed. Lower catalyst loading was used but long reaction times (*ca.* 3 d) were necessary to achieve good yields of butylarenes **10** (Scheme 10 and Table 7, entries 7–12). For this type of coupling, thermal and microwave irradiation gave similar conversions but microwave conditions needed shorter times (Table 7, compare entries 7 and 8). For deactivated 6-methoxy-2-bromonaphthalene, a 56% yield was obtained after 33 h with 1.5 equivs. of butylboronic acid, but faster and higher conversion was observed when 3 equivs. were used (Table 7, entry 10).

Conclusion

In conclusion, di(2-pyridyl)methylamine-derived palladium(II) chloride complexes **4** are thermally stable catalysts not sensitive to air or moisture and can be synthesized from readily available starting materials using a straightforward procedure. Their high efficiency in different Suzuki–Miyaura processes contrasts with the low activity shown by related di-2-pyridylamine-derived Buchmeiser's complexes **2**. Several types of cross-couplings between sp^2 and sp^3 hybridized bromides, chlorides and boronic acids can be carried out in organic solvents and even better in water or in aqueous solvents. This general catalytic activity makes these complexes very promising catalysts, and studies focused to support these complexes in order to recover and further reuse the catalyst are underway.

Experimental Section

General

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin layer chromatography was performed on Polygram® SIL G/UV_{254} plates. Melting points were determined on a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on a HP-6890 instrument equipped with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophometer (ν, cm^{-1}). ^1H NMR spectra were recorded on a Bruker AC-300 (300 MHz) and when specified on a Bruker Advance-DRX-500 (500 MHz). Chemical shifts are reported in ppm using either tetramethylsilane (TMS, 0.00 ppm) or DMSO as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ or DMSO-d_6 as the internal reference. EI-MS were measured on a Mass Selective Detector G2579A from Agilent Technologies 5973N in *m/z* (rel. intensity in % of base peak). HRMS were performed on a Finningan MAT95S apparatus. Elemental analyses were carried out in a Carlo Erba EA 1108 (CHNS-O) by the corresponding services at the University of Alicante. The catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with a precision of 1 μg. The reactions were set up in parallel with the aid of an RR98030 12 place Carousel Reaction Station™ equipped with gas-tight threaded caps with valve, cooling reflux head system and digital temperature controller from Radleys Discovery Technologies. Microwave reactions were performed with a CEM Discover Synthesis Unit in glass vessels (10 mL) sealed with a septum under magnetic stirring.

Synthesis of Di(2-pyridyl)methylamine (5)

Hydroxylamine hydrochloride (750.5 mg, 10.8 mmol) and NaOAc (886 mg, 10.8 mmol) were heated at 60 °C in H_2O (10 mL) for one hour. Di(2-pyridyl) ketone (1 g, 5.43 mmol) in MeOH (2 mL) was then added. The resulting mixture was stirred at 60 °C overnight. The oxime solidified upon cooling the reaction mixture to room temperature. The product was cooled on ice and then collected by filtration. The oxime was washed with a little cold H_2O and dried under vacuum. The crude oxime, a pink solid, was used in the next step without further purification.

Oxime (1 g, 5 mmol), NH_4OAc (655 mg, 8.5 mmol), NH_3 (25% aqueous, 15 mL), EtOH (20 mL) and H_2O (10 mL) were mixed and heated at 80 °C. Zn dust (1.47 g, 22.5 mmol) was added in small portions over 30 min. The resulting mixture was refluxed for 3 h and then stirred at room temperature overnight. The mixture was filtered to remove the solids, which were washed with MeOH and H_2O. The filtrate was concentrated to yield an aqueous solution that was made strongly alkaline with aqueous 10 M NaOH. The amine was extracted with CH_2Cl_2 and the organic phase was then washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford **5** as a pale yellow oil; yield: 780 mg (78%). Spectral data were in accordance with those previously reported.[18]

Synthesis of *N*-Di(2-pyridyl)methylacetamide (6a)

Compound **5** (92 mg, 0.5 mmol) and Et_3N (76 mg, 0.75 mmol) were mixed in dry CH_2Cl_2 (2 mL) under an argon atmosphere. Ac_2O (77 mg, 0.75 mmol) was added dropwise *via* a syringe and the resulting mixture was stirred at room temperature for 4 h. CH_2Cl_2 (15 mL) and H_2O (5 mL) were added and the phases separated. The organic phase was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography with EtOAc:MeOH (80:20) as eluent furnished **6a** as a white solid; yield: 104 mg (88%). ^{1}H NMR (DMSO-d_6): $\delta = 8.82$ (d, 1H, $J = 8.6$ Hz), 8.47 (d, 2H, $J = 4.9$ Hz), 7.76 (m, 2H), 7.46 (d, 2H, $J = 7.3$ Hz), 7.25 (m, 2H), 6.21 (d, 1H, $J = 8.6$ Hz), 1.98 (s, 3H); ^{13}C NMR (DMSO-d_6): $\delta = 168.9$, 160.1, 148.8, 136.8, 122.3, 121.9, 59.5, 22.6.

Synthesis of *N*-Cyclohexyl-*N'*-di(2-pyridyl)methylurea (6b)

The amine **5** (185 mg, 1 mmol) and cyclohexyl isocyanate (138 mg, 1.1 mmol) were mixed in CH_2Cl_2 (5 mL) and stirred for 1 h. Then, CH_2Cl_2 (10 mL) was added and the mixture was washed with H_2O. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford **6b** as a white solid; yield: 260 mg (84%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 8.51 (d, 2H, $J = 4.8$ Hz), 7.63 (m, 2H), 7.42 (d, 2H, $J = 7.9$ Hz), 7.15 (m, 2H), 6.90 (d, 1H, $J = 6.7$ Hz), 6.08 (d, 1H, $J = 6.1$ Hz), 4.86 (d, 1H, $J = 7.3$ Hz), 3.55 (m, 1H), 2.0–1.0 (m, 10H); ^{13}C NMR ($CDCl_3$): $\delta = 159.8$, 156.8, 148.8, 137.0, 122.4, 122.3, 60.1, 49.0, 33.7, 25.5, 24.8.

Synthesis of *N,N*-Di(2-pyridyl)methylamine-Derived Palladium Chloride Complexes (4)

$PdCl_2$ (33 mg, 0.186 mmol) was dissolved in concentrated HCl (1 mL). The resulting mixture was stirred until the $PdCl_2$ was completely dissolved (*ca.* 10 min.). A few drops of aqueous 15% NaOH were added until a pale precipitate of $Pd(OH)_2$ just began to form. The ligand **6** (0.22 mmol) was dissolved in methanol (2.5 mL) and the resulting solution was added to the solution of H_2PdCl_4. The initially dark solution gradually became paler and a yellow precipitate was formed. Stirring was continued for 2–3 hours after which the precipitate was collected by filtration and washed with H_2O and MeOH. The yellow powder obtained was dried under vacuum to afford **4a** (73%) or **4b** (94%). Compound **4a** is insoluble in H_2O, MeOH, CH_2Cl_2, $CHCl_3$ and EtOAc, sparingly soluble in MeCN and soluble in DMSO and DMF. Crystals suitable for X-ray analysis were grown from a concentrated solution of **4a** in DMSO; mp 295 °C (dec.). ^{1}H NMR (500 MHz, DMSO-d_6): major isomer (*ca.* 84%) $\delta = 9.84$ (d, 1H, $J = 9.9$ Hz), 8.87 (d, 2H, $J = 5.6$ Hz), 8.19 (t, 2H, $J = 6.7$ Hz), 7.91 (d, 2H, $J =$ 7.8 Hz), 7.59 (t, 2H, $J = 6.5$ Hz), 7.35 (d, 1H, $J = 9.8$ Hz), 2.26 (s, 3H); minor isomer (*ca*. 14%) δ 9.69 (1H), 8.89 (2H), 8.09 (2H), 7.91 (2H), 7.55 (2H), 6.30 (1H), 2.03 (3H). ^{13}C NMR (DMSO-d_6): both isomers $\delta = 170.1$, 154.3, 153.6, 141.1, 125.1, 121.6, 58.5, 22.7; IR (KBr): $\nu = 3320$, 3074, 3113, 1692, 1604, 1519, 1477, 1466, 1441, 1363, 1282, 1252, 1211, 1161, 1097, 1038, 766, 658, 640, 543 cm^{-1}; elemental analysis: calcd. for $C_{13}H_{12}Cl_2N_3OPd$: C 38.69, H 3.00, N 10.41; found: C 38.54, H 3.18, N 10.04.

Compound **4b** is insoluble in DMF, H_2O, MeOH and sparingly soluble in DMSO; mp 240–245 °C (dec.). The NMR spectrum of **4b** shows the presence of two isomers in an approximate ratio 3:1; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.95$ (d, 2H, $J = 6.1$ Hz, minor), 8.86 (d, 2H, $J = 4.9$ Hz, major), 8.19 (m, 2H, major), 8.10 (m, 2H, minor), 7.91 (m, 1H), 7.68 (d, 2H, $J = 7.3$ Hz), 7.57 (t, 2H, $J = 6.1$ Hz), 7.14 (d, 1H, $J =$ 11.0 Hz, major), 6.80 (d, 1H, $J = 7.3$ Hz, minor), 6.43 (d, 1H, $J = 7.3$ Hz), 3.51 (m, 1H), 1.90–1.00 (m, 10H); ^{13}C NMR (DMSO-d_6 of both isomers): $\delta = 156.4$, 156.0, 155.4, 154.0, 153.6, 153.4, 141.1, 140.8, 127.0, 125.2, 124.9, 121.4, 61.3, 59.9, 48.3, 32.3, 25.2, 24.3; IR (KBr): $\nu = 3372$, 3347, 3112, 3077, 3041, 2928, 2871, 2850, 1674, 1605, 1548, 1468, 1440, 1337, 1282, 1236, 1220, 1147, 1165, 1037, 985, 778, 633, 550 cm^{-1}; elemental analysis: calcd. for $C_{18}H_{22}Cl_2N_4OPd$: C 44.33, H 4.55, N 11.49; found: C 44.35, H 4.52, N 11.13.

Typical Experimental Procedure for Suzuki–Miyaura Coupling of Aromatic and Heteroaromatic Bromides and Chlorides with Arylboronic Acids in Water

A mixture of aryl halide (1 mmol), arylboronic acid (1.5 mmol), potassium carbonate (2 mmol, 276 mg), tetra-*n*-butylammonium bromide (0.5 to 1 mmol, only with aryl chlorides) complex **4** (see Tables 1–4) and water (2.5 mL) was stirred under reflux in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with ethyl acetate (3×10 mL). The organic phases were dried and evaporated (15 mm Hg). The subsequent residue was purified by recrystallization or by flash chromatography on silica gel to give pure products **7**.

Typical Experimental Procedure for Suzuki–Miyaura Coupling of Aromatic and Heteroaromatic Bromides and Chlorides with Arylboronic Acids in Aqueous Methanol

A mixture of aryl halide (1 mmol), arylboronic acid (1.5 mmol), potassium hydroxide (2 mmol, 112 mg), tetra-*n*-butylammonium bromide (0.5 to 1 mmol, only with aryl chlorides), complex **4** (see Tables 1–4) and methanol/water: 3/1 (2.5 mL). The mixture was stirred at room temperature or at 60 °C (see Tables 1–4) and the reaction progress was analyzed 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 methanol/water: 3/1 and purified by recrystallization. When both aryl halide and biaryl were soluble, the reaction mixture was poured into an excess of water and extracted with ethyl acetate (3×10 mL). The organic phases were dried, evaporated (15 mm Hg) and the crude product **7** purified by recrystallization or flash chromatography on silica gel.

The compounds *4-phenylacetophenone*, *4-phenylphenol*, *2-phenylbenzonitrile*, *4'-methylbiphenyl-2-carbonitrile*, *biphenylacetic acid*, *3-(3-methylphenyl)benzoic acid*, *(4-phenyl)acetanilide*, *4-phenylaniline*, *2-phenylacetanilide*, *2-phenylpyridine* and *3-phenylpyridine* are commercially available. The compounds *4,5-diphenyl-2-methyl-3(2H)pyridazinone*,[34] *N,N-dimethyl(4-phenyl)aniline*,[36] *2,6-dimethylbiphenyl*,[37] have been previously reported.

Typical Experimental Procedure for Suzuki Coupling of Benzylic Chlorides and Allylic Chlorides, Acetates or Methyl Carbonates with Arylboronic Acids in Water

A mixture of benzylic or allylic substrate (1 mmol), arylboronic acid (1.5 mmol), potassium carbonate (2 mmol, 276 mg), tetra-*n*-butylammonium bromide (0.5 to 1 mmol), decane (1 mmol, 194 μL), complex **4b** (see Tables 5 and 6) and water (2.5 mL) was stirred under reflux in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with ethyl acetate (3×10 mL). The organic phases were dried and evaporated (15 mm Hg). The subsequent residue was purified by recrystallization or by flash chromatography on silica gel to give pure products **8** or **9**.

Typical Experimental Procedure for Suzuki Coupling of Benzylic Chlorides and Allylic Chlorides, Acetates or Methyl Carbonates with Arylboronic Acids in Aqueous Acetone

A solution of the benzylic chloride or allylic substrate (1 mmol), arylboronic acid (1.5 mmol), potassium hydroxide (2 mmol, 112 mg), tetra-*n*-butylammonium bromide (0.5 to 1 mmol), decane (1 mmol, 194 μL), complex **4b** (see, Tables 5 and 6) and acetone/water: 3/2 (3 mL). The mixture was stirred at room temperature in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the reaction mixture was extracted with ethyl acetate (3×10 mL). The organic phases were dried and evaporated (15 mm Hg). The subsequent residue was purified by distillation or by column chromatography on silica gel to provide products **8** or **9**.

The compounds *diphenylmethane*, *1-benzyl-4-chlorobenzene*, *1-benzyl-4-fluorobenzene*, *2-methyl-3-phenylpropene* and *3-phenylpropene* are commercially available and *3-benzylanisole*,[38] *2-(4′-fluorobenzyl)thiophene*,[39] *5-benzyl-2-chloropyridine*,[11] *1-phenyl-2-(phenylmethyl)propene*,[40] *(*E*)-1,3-diphenylpropene*,[41] and *(*E*)-3-(4-fluorophenyl)-1-phenylpropene* [42] have been previously reported.

Typical Experimental Procedure for Suzuki Coupling of Aromatic and Heteroaromatic Bromides and Chlorides with Trimethylboroxine

A solution of aryl halide (1 mmol), trimethylboroxine (1 mmol, 140 μL), potassium carbonate (3 mmol, 415 mg), tetra-*n*-butylammonium bromide (1 mmol, 322 mg, only with aryl chlorides), complex **4b** (5 to 10 mol % Pd) and water (3 mL) was stirred under reflux in air and the reaction progress was analyzed by GC (see Table 7). After the reaction was completed or stopped, the reaction mixture was extracted with ethyl acetate (3×10 mL). The organic phases were dried and evaporated (15 mm Hg). The subsequent residue was purified by flash chromatography on silica gel to afford products **10**.

The compounds *4-methylacetophenone*, *4-trifluoromethyltoluene* and *2-methylquinoline*, are commercially available and *2-methoxy-6-methylnaphthalene*[43] has been previously reported.

Typical Experimental Procedure for Suzuki Coupling of Aromatic Bromides and Chlorides with *n*-Butylboronic Acid

A solution of aryl halide (1 mmol), *n*-butylboronic acid (1.5 mmol, 153 mg), potassium carbonate (2 mmol, 276 mg), tetra-*n*-butylammonium bromide (1 mmol, 322 mg, only with aryl chlorides), complex **4b** (0.01 mmol, 4.88 mg, 1 mol % Pd) and water (3 mL) was stirred under reflux in air and the reaction progress was analyzed by GC (Table 7). After the reaction was completed or stopped, the reaction mixture was extracted with ethyl acetate (3×10 mL). The organic phases were dried and evaporated (15 mm Hg). The subsequent residue was purified by flash chromatography on silica gel to give products **10**.

The compound *4-butylacetophenone* is commercially available and the compound *butyl-4-trifluoromethylbenzene*[44] has been previously reported.

***2-Butyl-6-methoxynaphthalene* (10g):** mp 55–56 °C (hexane). ^{1}H NMR ($CDCl_3$): $\delta = 7.64$ (m, 2H), 7.52 (br s, 1H), 7.27 (m, 1H), 7.11 (m, 1H), 7.08 (br s, 1H), 3.87 (s, 3H), 2.72 (t, 2H, $J = 7.6$ Hz), 1.65 (m, 2H), 1.37 (m, 2H), 0.93 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 157.0$, 138.0, 132.8, 129.1, 128.8, 127.9, 126.6, 126.1, 123.5, 118.5, 105.6, 55.2, 35.6, 33.6, 22.4, 14.0; MS: $m/z = 214$ (24, M^+), 172 (16), 171 (100), 128 (21); HRMS: $m/z = 214.1356$ (calcd.: 214.1358).

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