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Tetrahedron
Tetrahedron 62 (2006) 11063–11072

Regioselectivity in alkenyl(aryl)-heteroaryl Suzuki cross-coupling reactions of 2,4-dibromopyridine. A synthetic and mechanistic study

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Received 3 August 2006; revised 5 September 2006; accepted 12 September 2006
Available online 6 October 2006

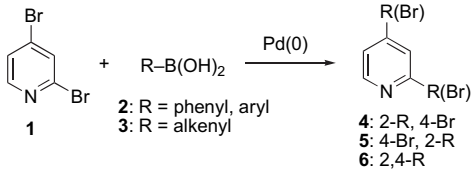
Abstract—2,4-Dibromopyridine undergoes a regioselective Suzuki cross-coupling reaction at position 2 with several alkenyl(aryl) boronic acids to render 4-bromo-2-carbon substituted pyridines, difficult to be prepared otherwise, in good yields under palladium catalysis, either $Pd(PPh_3)_4$/TlOH or $Pd_2dba_3/PCy_3/K_3PO_4$ at 25 °C. This behavior is explained on the basis of the electrophilic character of both C–Br bonds, being their relative reactivity in 2,4-dibromopyridine similar to that in the corresponding monobromopyridines. In addition, the dicoupled compound **6** is not formed through a double oxidative addition of 2,4-dibromopyridine to $Pd(PPh_3)$.

1. Introduction

As part of ongoing studies in our laboratories concerning complex pyridine-containing molecules, we have recently published an efficient and versatile stereoselective synthesis of the ocular pigment A2E, a pyridinium bisretinoid fluorophore.[1] The synthetic procedure that consisted in the substitution of both bromides in 2,4-dibromopyridine by means of two sequential selective palladium-catalyzed cross-coupling reactions, selectively introduced an organic substituent only at position 2 of the pyridine ring, followed by a second one at position 4.[2] This result prompted us to extend the applicability of this methodology and to study the scope of the processes. In addition, the 2,4-substituted pyridyl moiety is the structural motif in numerous pharmaceuticals and natural products.[3] While 4-alkenyl(aryl)-2-bromopyridines can be easily prepared from 4-bromopyridine followed by simple introduction of a bromo substituent at position 2, there is no straightforward method to 4-bromo-2-carbon substituted pyridines.

The coupling between an organic electrophile and an alkenyl-(aryl)boronic acid, known as Suzuki reaction, is amongst the most outstanding reactions in organic synthesis.[4] Several studies regarding selective palladium-catalyzed reactions of dihalopyridines, mainly 2,5-, 2,3-, 2,6-, and 3,5-disubstituted, have appeared in the literature during the last decade.[5] The observed selectivity was attributed either to the different electrophilicities of the carbon atoms or to the lower reactivity of the monosubstitution product, because of electronic or steric factors. However, the use of 2,4-dibromopyridine in regioselective cross-couplings is scarce and, to the best of our knowledge, there are only two examples, a Suzuki coupling with 3-bromophenylboronic acid that gave the 2-coupled compound in a moderate 24% yield[6a] and a palladium-catalyzed amination with a poor regioselectivity.[6b]

In this work we report a study on the regioselectivity of palladium-catalyzed cross-coupling reactions between aryl and alkenyl boronic acids (Suzuki reaction) and 2,4-dibromopyridine (Scheme 1). The ^{13}C NMR spectrum of 2,4-dibromopyridine shows that the chemical shifts of the carbon centers with bromine atoms attached (C^2 and C^4) differ slightly (142.5 and 133.9 ppm, respectively). Therefore, oxidative addition to Pd(0) could preferentially occur at one carbon center, presumably C^2, ensuring positional selective coupling reactions as could be expected for an S_N2-like process.



Scheme 1. Suzuki coupling of 2,4-dibromopyridine (**1**) and boronic acids **2** and **3**.

Keywords: 2,4-Dibromopyridine; Suzuki reaction; Regioselectivity; Palladium catalysis.
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doi:10.1016/j.tet.2006.09.040

2. Results and discussion

To investigate the regioselectivity and efficiency of different systems for the Suzuki cross-coupling reaction of 2,4-dibromopyridine (**1**)[7] and arylboronic acids (**2**)[8] to afford 2-aryl-4-bromopyridine, the reaction with phenylboronic acid (**2a**) was chosen as a model. The selectivity is given as the ratio among the three possible products, the monocoupled regioisomers, **4** and **5**, and the dicoupled product **6**.

We have used Pd(0) and Pd(II) species as catalysts, and polar and apolar solvents in aqueous or anhydrous conditions. The results are shown in Table 1 and the identification of the cross-coupling products was done either by comparison with published data[9] and/or by NMR experiments.

When $Pd(OAc)_2$ was utilized as pre-catalyst in the presence of bulky and electron rich phosphines, [(2-biphenylyl)di-*tert*-butylphosphine (2-BDBP)[10] and PCy_3[11]], known to accelerate the oxidative addition step, with different anhydrous bases (KF, K_2CO_3, Cs_2CO_3) we found out that the conversions at 25 °C or 50 °C were still low in the presence of 2.0 or 2.4 equiv of phenylboronic acid. The dicoupled compound **6a** was the major product even if the reaction was run with 1.0 equiv of phenylboronic acid (Table 1, entry 1). The proportion of **6a**, much higher than the statistical one, is difficult to explain solely on the basis of reactivity arguments.

If instead Pd_2dba_3 was the palladium source, the outcome was different depending upon the phosphine. While PCy_3 gave a very selective catalyst in spite of the presence of 2.5 equiv of **2a** (entry 3), 2-BDBP with 1.0 equiv of **2b** at 25 °C yielded the dicoupled compound **6b** as the major product (entry 5). It is also interesting to point out that the 4-coupled compound **5a** was obtained in higher ratio than the 2-coupled **4a** when 2-BDBP was used, either with $Pd(OAc)_2$ or with Pd_2dba_3 (Table 1, entries 5–7).[12]

When the reaction was carried out with $Pd(PPh_3)_4$ in combination with 3 M K_2CO_3 in toluene a selectivity of 6:1:0.5 was obtained (entry 8), but 2.0 equiv of boronic acid and temperatures up to 50 °C were necessary to achieve complete conversion which, on the other hand, caused a reduction of the selectivity (**4a/5a/6a**, 6:1:1.5) (entry 9). However, $Pd(PPh_3)_4$ in the presence of 10% aq TlOH in THF at 25 °C (entry 10) gave a very good selectivity, ratio **4a/5a/6a** 18:1:1, with total conversion after 12–24 h.[13]

In order to establish whether electronic effects of *p*-substituted arylboronic acids **2** (X=MeO, Me, F, CHO, CO_2Me) are important for this cross-coupling reaction, we run the reaction with 2,4-dibromopyridine in the presence of Pd(0) species [$Pd(PPh_3)_4$, aq TlOH, and THF, and Pd_2dba_3, PCy_3, K_3PO_4, and dioxane] at 25 °C. From the results shown in Table 1 it is possible to infer that either electron donating groups, such as MeO or Me, or fluoride (entries 11–13) on the boronic acid did not influence much the final result, while electron withdrawing groups, such as CHO or CO_2Me, prevented the cross-coupling to occur (entries 14 and 15).[14]

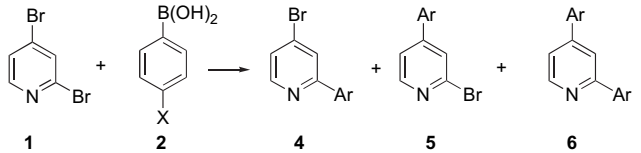
Thus, two catalytic systems, namely $Pd(PPh_3)_4$ in the presence of aqueous TlOH in THF and Pd_2dba_3/PCy_3 in anhydrous conditions (K_3PO_4 in dioxane), were found to be highly selective to obtain 4-bromo-2-arylpyridines through a Suzuki coupling of 2,4-dibromopyridine (**1**) and arylboronic acids (**2**) at 25 °C. On the other hand, if the aim is to prepare symmetrical 2,4-disubstituted pyridines, the reaction conditions will be Pd_2dba_3, (2-biphenylyl)di-*tert*-butylphosphine, $K_3PO_4 \cdot 1.5H_2O$ with an excess of boronic acid (Table 1, entries 6 and 7). Accordingly, two important ligands in luminescence devices,[15] 2,4-diphenylpyridine (**6a**) and 2,4-di(methoxyphenyl)pyridine (**6b**), were obtained in very good yields, 85 and 82%, respectively.

An important goal would be to prepare 2-alkenyl-4-bromopyridines (**4**) in one step from 2,4-dibromopyridine (**1**). For that purpose, we used boronic acids **3g**, **3h**, and **3i**[16] under both catalytic systems [$Pd(PPh_3)_4$, aq TlOH, and THF, and Pd_2dba_3, PCy_3, K_3PO_4, and dioxane] at 25 °C and the results are shown in Table 2.

Interestingly, boronic acids **3g**, **3h**, and **3i** presented an almost total selectivity for position 2 when the coupling was run with $Pd(PPh_3)_4$ and TlOH in THF (Table 2, entries 1, 3, and 4).

However, when the reaction was performed with Pd_2dba_3/PCy_3 in the presence of 1.2 equiv of boronic acid **3g** the selectivity dropped to 5.5:1:1.5 (entry 2), lower than the one for arylboronic acids **2** (Table 1). This result indicates that there is a significant competition among 2,4-dibromopyridine and the monocoupled compounds for the boronic acid present in the reaction mixture.

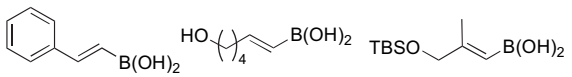
Table 1. Reaction of 2,4-dibromopyridine (**1**) with phenylboronic acid (**2a**)



Entry	**2** (equiv)	Reaction conditions[a]	*T* (°C)	**4**:**5**:**6**[b]	Yield[c] (Conv)[d]
1	**2a** (1.2)	$Pd(OAc)_2$, Cs_2CO_3, PCy_3, dioxane	25	2:1:7	— (35)
2	**2a** (1.0)	Pd_2dba_3, K_3PO_4,	25	11:0.3:1	43 (60)
3	**2a** (2.5)	PCy_3, dioxane	25	7:0:1	69 (>98)
4	**2b** (2.5)		25	7:0:1	72 (>98)
5	**2b** (1.0)	Pd_2dba_3, $K_3PO_4 \cdot 1.5H_20$,	25	1:1.2:15	— (46)
6	**2b** (2.5)	2-BDBP, toluene	40	1:1.2:26	82 (>98)
7	**2a** (2.5)		40	0:0:1	85 (>98)
8	**2a** (1.2)	$Pd(PPh_3)_4$, aq K_2CO_3,	50	6:1:0.5[e]	31 (75)
9	**2a** (2.0)	toluene	50	6:1:1.5[e]	40 (>98)
10	**2a** (1.2)	$Pd(PPh_3)_4$, aq TlOH,	25	18:1:1[e]	67 (>98)
11	**2b** (1.2)	THF	25	15:1:1[e]	64 (>98)
12	**2c** (1.2)		25	17:1:1[e]	60 (>98)
13	**2d** (1.2)		25	15:1:1.5[e]	68 (>98)
14	**2e** (1.2)		25	—	— (0)
15	**2f** (1.2)		25	—	— (0)

2-BDBP: (2-biphenylyl)di-*tert*-butylphosphine.
[a] $Pd(PPh_3)_4$, 8–15 mol %; $Pd(OAc)_2$, 1–5 mol %; Pd_2dba_3, 1.5–10 mol %.
[b] Calculated by ^1H NMR of the crude mixture.
[c] Yield of the pure major product.
[d] Conversion calculated by ^1H NMR of the crude mixture.
[e] 4,4′-Dibromo-2,2′-bipyridine was detected in variable amounts.

Table 2. Coupling of 2,4-dibromopyridine (**1**) and alkenylboronic acids **3g–i**



3g **3h** **3i**

Entry	**3** (equiv)	Reaction conditions	**4**:**5**:**6**[a]	Yield (%)[b]
1	**3g** (1.2)	$Pd(PPh_3)_4$, aq TlOH, THF	17:1:<1	71
2	**3g** (1.2)	Pd_2dba_3, K_3PO_4, PCy_3, dioxane	5.5:1:1.5	40[c]
3	**3h** (1.2)	$Pd(PPh_3)_4$, aq TlOH, THF	15:1:0	77
4	**3i**[d] (1.7)[e]	$Pd(PPh_3)_4$, aq TlOH, THF	16:1:0	75

[a] Calculated by ^{1}H NMR of the crude reaction mixture.
[b] Yield of the pure major product.
[c] Conversion (81%) calculated by ^{1}H NMR of the crude reaction mixture.
[d] Prepared in situ.
[e] Effective equivalents (1.2 equiv) considering boronic acid dimer and protodeboronation by ^{1}H NMR.

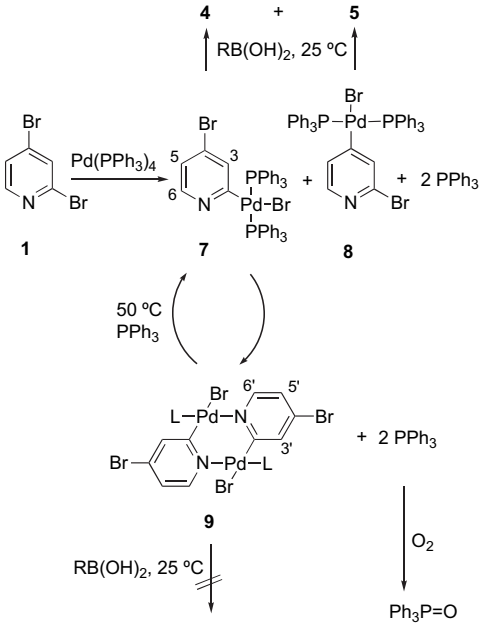
Due to the instability problems of compound **3i**, caused by the methyl group cis to the boronic acid moiety, an important protodeboronation process was detected and, hence, a bigger excess of **3i** was needed (entry 4).[17] Thus, when 1.7 equiv (1.2 effective, as determined by ^{1}H NMR) of **3i** were used, compound **4i**, key intermediate in the synthesis of A2E,[2] was obtained in good yield.

We demonstrated the selectivity of the coupling by means of two-dimensional NMR experiments (^{1}H and ^{13}C correlations, HSQC and HMBC) with compounds **3h** and **3i**. All the other compounds showed the same behavior, with (H^6, H^5, and H^3) pyridyl-proton shifts of the 4-coupled product **5** at higher field.

So, 2-alkenyl-4-bromopyridines were obtained in good yields (71–77%) when 2,4-dibromopyridine was treated with alkenyl boronic acids in the presence of $Pd(PPh_3)_4$/TlOH in THF at 25 °C by means of a highly regioselective cross-coupling process.

In order to get some insights into the mechanism of the process, we studied the reaction of 2,4-dibromopyridine and $Pd(PPh_3)_4$ in toluene by ^{1}H and ^{31}P NMR. Thus, treatment of 2,4-dibromopyridine with 1.0 equiv of $Pd(PPh_3)_4$ in toluene at 25 °C under oxygen-free conditions for 16 h lead to a mixture of both σ-palladium complexes **7** and **8** in 81% yield along with traces of a compound identified as the dimeric complex **9** (Scheme 2).

To the best of our knowledge, this is the first time that the formation of complex **7** has been observed by ^{1}H and ^{31}P NMR and MS. The ^{1}H NMR of σ-palladium complex **7** (Fig. 1b) shows the pyridine proton upfield shifted (7.40, 6.65, and 6.22 ppm for H^6, H^3, and H^5, respectively) compared to 2,4-dibromopyridine signals (Fig. 1a) due to an anisotropic shielding effect of the triphenylphosphine ligand as well as by back donation from palladium to the pyridine ring via the carbon atom. The oxidative addition of Pd-complex **7** undergoes a rapid conversion into the Pd-dinuclear-complex **9**, whose structure has unequivocally been established by X-ray crystallography, through an attack of the basic free pyridyl nitrogen on the neighboring metal, followed by elimination of one phosphine (Scheme 2). ^{1}H NMR of the dinuclear complex **9** shows H^3 and H^5 at 6.73 ppm, while the H^6 proton resonance appears as a multiplet at 8.32 ppm,



Scheme 2. Reaction of 2,4-dibromopyridine (**1**) with 1.0 equiv of $Pd(PPh_3)_4$.

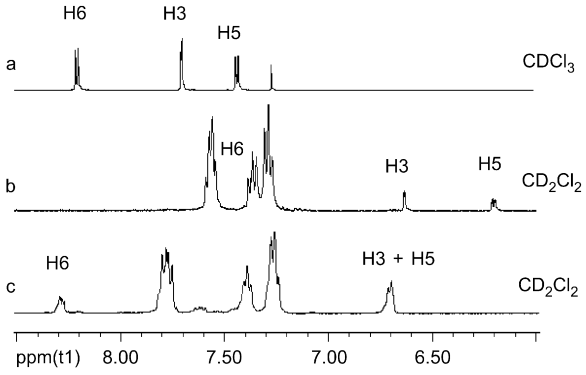


Figure 1. ^{1}H NMR spectra: (a) 2,4-dibromopyridine (**1**); (b) complex **7**; (c) dinuclear complex **9**.

upfield for a nitrogen coordinated to a metal atom indicating that the deshielding effect induced by the coordination is partially counteracted by the palladium back donation (Fig. 1c). Its ^{13}C NMR shows two characteristic resonances at 189.1 and 151.7 ppm for C^2–Pd and C^6, respectively. The tendency of the 2-carbon bonded pyridine to coordinate another metal center through the nitrogen atom is in accordance with its high basicity.[18]

The X-ray structure of complex **9** shows a boat conformation for the six-membered ring containing both Pd and N. Each palladium atom exhibits a square-planar geometry with bromide and phosphine trans to carbon and nitrogen, respectively (Fig. 2).

The ^{31}P NMR spectrum of the reaction of 2,4-dibromopyridine and $Pd(PPh_3)_4$ (Fig. 3) showed four signals. The signal at 22.65 ppm corresponds to the monomeric complex **7** and the presence of only one signal indicates that both phosphine ligands are equivalent. The resonance at downfield shift, 23.86 ppm (Fig. 3a) was assigned to the 2-bromopyrid-4-yl palladium complex **8**, not observed in ^{1}H NMR due to

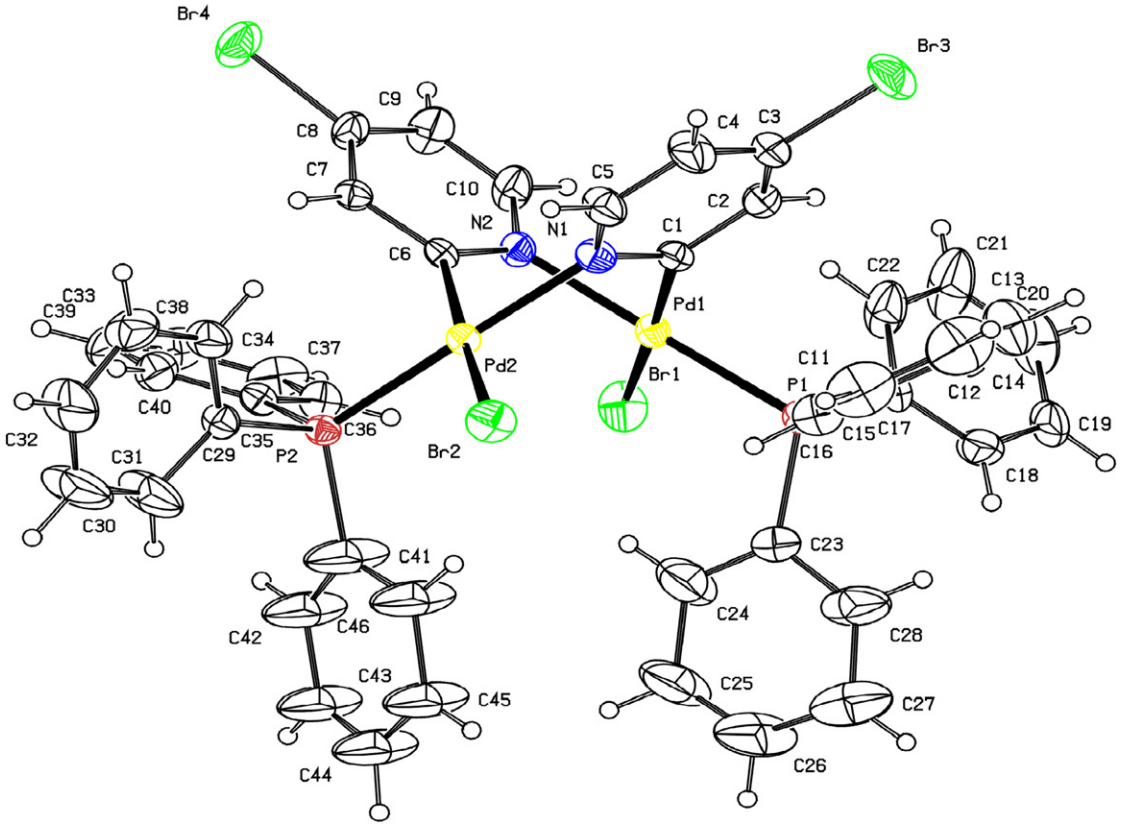


Figure 2. ORTEP representation of complex **9**.

either detection limits or signal-overlapping. The ratio between complex **7** and complex **8** in the oxidative addition determines the selectivity of the cross-coupling process. After 1 h, another signal started to appear at 30.45 ppm, much higher field than in the monomeric complex, and is due to the dimeric complex **9** (Fig. 3b).

The equilibrium between monomer complex **7** and dinuclear complex **9** in toluene shifts to the monomer upon addition of triphenylphosphine at 50 °C but no change is observed at 25 °C. Traces of air speed up the transformation of the mononuclear complex (22.21 ppm) into the dinuclear complex (30.45 ppm) (Scheme 2; Fig. 3b) due to the oxidation of PPh_3 (−4.85 ppm) to PPh_3O (24.70 ppm).[19]

Aiming to determine the formation pathway of the 2,4-disubstituted pyridine **6**, an equimolar mixture of both

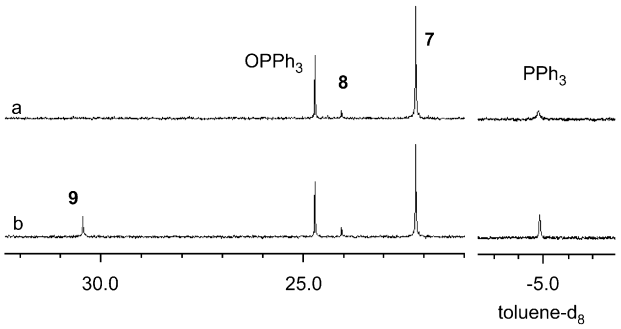


Figure 3. ^{31}P NMR spectra of the reaction of **1** with $Pd(PPh_3)_4$: (a) t=1 h; (b) t=11 h.

monobromopyridines, **4a** and **5a**, was treated with $Pd(PPh_3)_4$ (50 mol %), $PhB(OH)_2$ (100 mol %), and 3 M K_2CO_3 (100 mol %) in toluene for 15 h at 50 °C. The NMR analysis of the resulting reaction mixture showed that 2-bromo-4-phenylpyridine **5a** reacted seven fold faster than the corresponding 4-bromopyridine **4a**, in agreement with the obtained regioselectivity (Table 1, entry 8). The electrophilic character of the C–Br bond does not change much in the monobromo derivatives **4a** and **5a** compared to 2,4-dibromopyridine (**1**) as shown by their ^{13}C NMR shifts (Fig. 4). Therefore, their reactivity should be similar to that of **1** and, as expected, the selectivity dropped to 3.5:0:1 when the reaction was run in the presence of $Pd(PPh_3)_4$ and TlOH in THF with 1.2 equiv of boronic acid for longer periods.[20]

The presence of compound **5a**, even in those cases with excess of boronic acid, together with the reported observation that potentially bifunctional 2,6-dichloropyridine adds oxidatively only to one molecule of $Pd(PPh_3)_4$,[18a] could indicate that the dicoupled compound is formed mainly through the monocoupled derivatives and not by double oxidative addition on 2,4-dibromopyridine (**1**). When 2,4-dibromopyridine

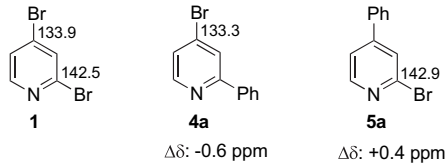


Figure 4. ^{13}C NMR chemical shifts for mono- and dibromopyridines.

was treated with 2.0 equiv of $Pd(PPh_3)_4$ at 25 °C, the corresponding 2,4-dimetallated pyridine was not detected but the signals corresponding to mono- and di-palladium complexes **7** and **9** (δ=22.21 and 30.44 ppm, respectively) along with triphenylphosphine oxide (δ=24.70 ppm), $Pd(PPh_3)_4$ (δ=24.39 ppm), and the lower field signal, 24.05 ppm, assigned to the 2-bromopyrid-4-yl palladium complex **8**.[21]

To summarize, we have carried out effective regioselective Suzuki cross-couplings between 2,4-dibromopyridine and several alkenyl(aryl) boronic acids that furnished 4-bromo-2-carbon substituted pyridines, difficult to be prepared otherwise, in good yields under palladium catalysis, either $Pd(PPh_3)_4$/TlOH or $Pd_2dba_3/PCy_3/K_3PO_4$ at 25 °C. Also, we have shown that the C–Br bond at position 2 of the pyridine ring is more reactive than at position 4 and the observed low TON could be due to the formation of a dinuclear palladium complex from the mononuclear σ-alkenyl palladium complex. In addition we have concluded that the dicoupled compound **6** is not formed through a double oxidative addition of 2,4-dibromopyridine to Pd(0) species.

3. Experimental section

3.1. General

Reagents and solvents were purchased as reagent-grade and used without further purification unless otherwise stated. Solvents were dried according to published methods[22] and distilled before use. All reactions were performed in oven-dried or flame-dried glassware under an inert atmosphere of Ar unless otherwise stated. NMR spectra were recorded in a Bruker AMX400 (400.13 MHz and 100.61 MHz for proton and carbon, respectively) spectrometer at 298 K with residual solvent peaks as internal reference and the chemical shifts are reported in δ (ppm), coupling constants J are given in (hertz) and expressed as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{13}C-multiplicities assigned with DEPT experiments and COSY, HMBC, and HSQC methods were used to establish atom connectivities. Electronic impact ionization (EI) and fast atom bombardment (FAB) mass spectra were recorded on a VG-Autospec M instrument. Infrared spectra (IR) were obtained on a JASCO FT/IR-4200 infrared spectrometer. Peaks are quoted in wave numbers (cm^{-1}) and their relative intensities are reported as follows: s=strong, m=medium, w=weak. Melting points (mp) were taken on a Stuart Scientific apparatus. Elemental analysis was performed using a Fisons EA-1108 analyzer.

3.2. General methods for Suzuki reactions

Method A: in a Schlenk flask, a solution of $Pd(PPh_3)_4$ (0.08 or 0.24 equiv) and aryl(vinyl)boronic acid (1.2–2.0 equiv) in THF (0.2 M) was thoroughly degassed. Then, a solution of 2,4-dibromopyridine (1.0 equiv) in THF (0.4 M) was added dropwise followed by a previously degassed 10% aq TlOH solution (3.8 equiv). The reaction mixture was stirred at 25 °C until no reaction progress was observed either by TLC or by ^{1}H NMR, 4–24 h. It was then diluted with CH_2Cl_2 and filtered through a plug of Celite®. The filtrate was washed with saturated $NaHCO_3$ aqueous solution, dried (Na_2SO_4), and concentrated to dryness.

Method B: in a Schlenk flask, a solution of $Pd(PPh_3)_4$ (0.15 equiv) and aryl(vinyl)boronic acid (2.0 equiv) in toluene (0.14 M) was degassed via three 'freeze–thaw' cycles. Then, a solution of 2,4-dibromopyridine (1.0 equiv) in toluene (0.35 M) was added dropwise followed by 3 M aq K_2CO_3 (2.0 equiv). The resulting mixture was heated at 50 °C, followed as in method A. After cooling down to 25 °C, water was added and the mixture was extracted with diethyl ether. The combined organic extracts were washed with water, dried (Na_2SO_4), and concentrated to dryness.

Method C: in a Schlenk flask, a mixture of Pd_2dba_3 (0.10 equiv), PCy_3 (0.20 equiv), and aryl (vinyl)boronic acid (1.0–2.4 equiv) in dioxane (0.2 M) was thoroughly degassed. Then, a solution of 2,4-dibromopyridine (1.0 equiv) in dioxane (0.2 M) was added dropwise, followed by K_3PO_4 (2.0 equiv). The reaction mixture was stirred at 25 °C for 26–72 h. It was then diluted with Et_2O and filtered through a plug of Celite®. The filtrate was dried (Na_2SO_4) and concentrated to dryness.

Method D: in a Schlenk flask, a mixture of Pd_2dba_3 (0.015 equiv), (2-biphenylyl)di-*tert*-butylphosphine (0.06 equiv), $K_3PO_4 \cdot 1.5H_2O$ (2.4 equiv), and aryl (vinyl)boronic acid (1.0–2.5 equiv) in toluene (0.3 M) was degassed via three 'freeze-thaw' cycles. Then, a solution of 2,4-dibromopyridine (1.0 equiv) in toluene (0.6 M) was added dropwise. The reaction mixture was stirred at 25–40 °C for 24–42 h. It was then diluted with Et_2O and filtered through a plug of Celite®. The filtrate was dried (Na_2SO_4) and concentrated to dryness.

3.2.1. 4-Bromo-2-phenylpyridine (4a). Following method A, 2,4-dibromopyridine (**1**) (50 mg, 0.21 mmol) with phenylboronic acid (**2a**) (31 mg, 0.25 mmol) in the presence of $Pd(PPh_3)_4$ (19 mg, 0.02 mmol) and 10% aq TlOH solution (1.8 mL, 0.80 mmol) in THF (1.5 mL), for 24 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 92:8 hexane/EtOAc), 33 mg (67%) of 4-bromo-2-phenylpyridine (**4a**)[9a] as a yellow oil, 2 mg (4%) of 2-bromo-4-phenylpyridine (**5a**) as a white solid (mp 64 °C, hexane/CH_2Cl_2, lit.[9c] 65–66 °C), and 2 mg (4%) of 2,4-diphenylpyridine (**6a**) as a yellow solid (mp 67–68 °C, hexane/CH_2Cl_2, lit.[9d] oil). Data of **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J=5.3 Hz, 1.7 Hz, 1H, H^5), 7.44–7.51 (m, 3H, $H^{3'}$ and $H^{4'}$), 7.90 (d, J=1.7 Hz, 1H, H^3), 7.96–7.98 (m, 2H, $H^{2'}$), 8.51 (d, J=5.3 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.8 (CH), 125.1 (CH), 126.9 (2CH), 128.7 (2CH), 129.5 (CH), 133.3 (C), 137.9 (C), 150.2 (CH), 158.8 (C) ppm. IR (NaCl) ν 3041 (d, C–H), 1566 (f), 1544 (f), 1497 (d), 1460 (m), 1443 (f), 1378 (f), 1094 (d), 1072 (d), 1053 (m), 873 (d), 823 (m), 772 (f), 729 (m), 692 (f), 633 (m), 590 (m). MS (EI$^+$) m/z (%) 236 ([M+1]$^+$ [^{81}Br], 12), 235 (M$^+$ [^{81}Br], 98), 234 ([M+1]$^+$ [^{79}Br], 21), 233 (M$^+$ [^{79}Br], 100), 155 (9), 154 (70), 153 (10). HRMS (EI$^+$) calcd for $C_{11}H_8N^{81}Br$, 234.9820 and $C_{11}H_8N^{79}Br$, 232.9840; found, 234.9828 and 232.9844. Data of **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.52 (m, 4H, H^5–$H^{3'}$–$H^{4'}$), 7.59–7.61 (m, 2H, $H^{2'}$), 7.70 (br s, 1H,

H^3), 8.40 (d, J=5.1 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.8 (CH), 125.8 (CH), 127.0 (2CH), 129.2 (2CH), 129.6 (CH), 136.7 (C), 142.9 (C), 150.4 (CH), 151.3 (C) ppm. IR (NaCl) ν 3057 (d, C–H), 1585 (f), 1529 (f), 1457 (m), 1369 (m), 1125 (d), 1078 (m), 844 (d), 786 (d), 760 (f), 699 (m), 612 (d). MS (EI^+) m/z (%) 236 ($[M+1]^+$ [^{81}Br], 6), 235 (M^+ [^{81}Br], 48), 234 ($[M+1]^+$ [^{79}Br], 6), 233 (M^+ [^{79}Br], 49), 155 (13), 154 (100), 153 (13). HRMS (EI^+) calcd for $C_{11}H_8{}^{81}BrN$, 234.9820 and $C_{11}H_8{}^{79}BrN$, 232.9840; found, 234.9821 and 232.9837. Data of **6a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J=5.1 Hz, 1.7 Hz, 1H, H^5), 7.44–7.55 (m, 6H, $2H^{3'}$–$2H^{3''}$–$H^{4'}$–$H^{4''}$), 7.68 (m, 2H, $2H^{2''}$), 7.94 (br s, 1H, H^3), 8.11 (m, 2H, $2H^{2'}$), 8.76 (d, J=5.1 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.5 (CH), 120.0 (CH), 126.9 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 138.2 (C), 139.2 (C), 149.0 (C), 149.9 (CH), 157.8 (C) ppm. IR (NaCl) ν 3059 (d, C–H), 1594 (f), 1542 (m), 1497 (d), 1470 (m), 1445 (d), 1391 (m), 1075 (d), 887 (d), 844 (d), 760 (f), 737 (m), 693 (f), 641 (d), 611 (d). MS m/z (%) 232 ($[M+1]^+$, 3), 231 (M^+, 100), 230 (82), 202 (5), 154 (4), 102 (3). HRMS calcd for $C_{17}H_{13}N$, 231.1048; found, 231.1043.

Following method C, 2,4-dibromopyridine (**1**) (0.25 g, 1.05 mmol) with phenylboronic acid (**2a**) (0.31 g, 2.53 mmol) in the presence of Pd_2dba_3 (0.10 g, 0.10 mmol), PCy_3 (0.06 g, 0.21 mmol), and K_3PO_4 (0.45 g, 2.11 mmol) in dioxane (10.5 mL), for 36 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 92:8 hexane/EtOAc), 173 mg (72%) of **4a** and 25 mg (10%) of **6a**.

3.2.2. 2,4-Diphenylpyridine (6a). Following method D, 2,4-dibromopyridine (**1**) (75 mg, 0.32 mmol) with phenylboronic acid (**2a**) (96 mg, 0.79 mmol) in the presence of Pd_2dba_3 (4 mg, 5×10^{-3} mmol), (2-biphenylyl)di-*tert*-butylphosphine (6 mg, 0.02 mmol), and $K_3PO_4\cdot1.5H_2O$ (182 mg, 0.76 mmol) in toluene (1.5 mL), for 24 h at 40 °C, afforded, after purification by flash chromatography (SiO_2, 85:15 hexane/EtOAc), 63 mg (85%) of 2,4-diphenylpyridine (**6a**).

3.2.3. 4-Bromo-2-(*p*-methoxyphenyl)pyridine (4b). Following method A, 2,4-dibromopyridine (**1**) (100 mg, 0.42 mmol) with *p*-methoxyphenylboronic acid (**2b**) (76 mg, 0.50 mmol) in the presence of $Pd(PPh_3)_4$ (114 mg, 0.10 mmol) and 10% aq TlOH solution (3.6 mL, 1.60 mmol) in THF (3.0 mL), for 12 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 85:15 hexane/EtOAc), 71 mg (64%) of 4-bromo-2-(*p*-methoxyphenyl)pyridine (**4b**) as a white solid (mp 37–38 °C, hexane/CH_2Cl_2), 5 mg (4%) of 2-bromo-4-(*p*-methoxyphenyl)pyridine (**5b**) as a white solid (mp 57 °C, hexane/CH_2Cl_2, lit.[23] 54–55 °C), and 5 mg (4%) of 2,4-bis(*p*-methoxyphenyl)pyridine (**6b**) as a white solid (mp 158 °C, hexane/CH_2Cl_2, lit.[24] 152–153 °C). Data of **4b**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H, OMe), 6.97 (d, J=8.9 Hz, 2H, $H^{3'}$), 7.30 (dd, J=5.1 Hz, 1.6 Hz, 1H, H^5), 7.81 (br s, 1H, H^3), 7.92 (d, J=8.9 Hz, 2H, $H^{2'}$), 8.43 (d, J=5.1 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2 (CH_3), 114.1 (2CH), 122.8 (CH), 124.3 (CH), 128.2 (2CH), 130.4 (C), 133.2 (C), 150.1 (CH), 158.4 (C), 160.8 (C) ppm. IR (NaCl) ν 2957 (w, C–H), 2932 (w, C–H), 2836 (w, C–H). MS (EI^+) m/z (%) 266 ($[M+1]^+$ [^{81}Br], 12), 265 (M^+ [^{81}Br], 97), 264 ($[M+1]^+$ [^{79}Br], 14), 263 (M^+ [^{79}Br], 100), 250 ($[M-CH_3]^+$ [^{81}Br], 21), 248 ($[M-CH_3]^+$ [^{79}Br], 22). HRMS (EI^+) calcd for $C_{12}H_{10}{}^{81}BrNO$, 264.9925 and $C_{12}H_{10}{}^{79}BrNO$, 262.9946; found, 264.9926 and 262.9938. Anal. Calcd (%): C 54.57, H 3.82; N 5.30; found: C 54.98, H 3.83, N 5.37. Data of **5b**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H, OMe), 7.00 (d, J=8.7 Hz, 2H, $H^{3'}$), 7.41 (dd, J=5.1 Hz, 1.5 Hz, 1H, H^5), 7.56 (d, J=8.7 Hz, 2H, $H^{2'}$), 7.65 (br s, 1H, H^3), 8.35 (d, J=5.1 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4 (CH_3), 114.7 (CH), 120.2 (2CH), 125.1 (CH), 128.2 (2CH), 128.8 (C), 142.9 (C), 150.2 (CH), 150.7 (C), 161.0 (C) ppm. IR (NaCl) ν 2934 (w, C–H), 2837 (w, C–H), 1609 (m), 1584 (s), 1520 (s), 1459 (m), 1372 (m), 1293 (m), 1253 (s), 1182 (m), 1120 (m), 1081 (m), 1047 (m), 987 (w), 822 (s), 753 (w), 686 (w), 570 (w). MS (EI^+) m/z (%) 266 ($[M+1]^+$ [^{81}Br], 10), 265 (M^+ [^{81}Br], 87), 264 ($[M+1]^+$ [^{79}Br], 12), 263 (M^+ [^{79}Br], 92), 185 (13), 184 (100), 169 (37), 153 (10), 141 (29), 140 (27), 114 (16), 92 (28), 69 (55). HRMS (EI^+) calcd for $C_{12}H_{10}{}^{81}BrNO$, 264.9925 and $C_{12}H_{10}{}^{79}BrNO$, 262.9946; found, 264.9927 and 262.9946. Data of **6b**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 6H, 2×OMe), 7.02 (m, 4H, $H^{3'}$ and $H^{3''}$), 7.34 (dd, J=5.2 Hz, 1.4 Hz, 1H, H^5), 7.64 (d, J=8.7 Hz, 2H, $H^{2''}$), 7.83 (br s, 1H, H^3), 8.01 (d, J=8.9 Hz, 2H, $H^{2'}$), 8.65 (d, J=5.2 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3 ($2CH_3$), 114.1 (CH), 114.5 (CH), 117.3 (CH), 119.0 (CH), 128.1 (CH), 128.18 (CH), 128.23 (CH), 130.9 (C), 132.2 (C), 148.6 (C), 149.9 (CH), 157.6 (C), 160.4 (2C). IR (NaCl) ν 3023 (w, C–H), 2959 (w, C–H), 2839 (w, C–H), 1607 (m), 1541 (m), 1517 (s), 1466 (w), 1425 (w), 1382 (w), 1306 (m), 1284 (w), 1250 (s), 1183 (s), 1116 (m), 1043 (s), 1020 (s), 828 (s), 814 (s), 755 (m), 540 (w). MS (EI^+) m/z (%) 292 ($[M+1]^+$, 3), 291 (M^+, 100), 276 (10), 248 (4), 205 (4), 204 (4), 146 (4), 124 (3), 108 (2). HRMS (EI^+) calcd for $C_{19}H_{17}NO_2$, 291.1259; found, 291.1254. Anal. Calcd for $C_{19}H_{17}NO_2$: C 78.33, H 5.88, N 4.81; found: C 78.35, H 5.95, N 4.92.

Following method C, 2,4-dibromopyridine (**1**) (0.25 g, 1.05 mmol) with *p*-methoxyphenylboronic acid (**2b**) (0.38 g, 2.53 mmol) in the presence of Pd_2dba_3 (0.10 g, 0.10 mmol), PCy_3 (0.06 g, 0.21 mmol), and K_3PO_4 (0.45 g, 2.11 mmol) in dioxane (10.5 mL), for 26 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 85:15 hexane/EtOAc), 0.20 g (72%) of 4-bromo-2-(*p*-methoxyphenyl)pyridine (**4b**) and 31 mg (10%) of 2,4-bis(*p*-methoxyphenyl)pyridine (**6b**).

3.2.4. 2,4-Bis(*p*-methoxyphenyl)pyridine (6b). Following procedure D, 2,4-dibromopyridine (**1**) (0.25 g, 1.05 mmol) with *p*-methoxyphenylboronic acid (**2b**) (0.40 g, 2.62 mmol) in the presence of Pd_2dba_3 (14 mg, 0.2 mmol), (2-biphenylyl)di-*tert*-butylphosphine (19 mg, 0.06 mmol), and $K_3PO_4\cdot1.5H_2O$ (0.60 g, 2.53 mmol) in toluene (3.0 mL), for 42 h at 40 °C, afforded, after purification by flash chromatography (SiO_2, 75:25 hexane/EtOAc), 251 mg (82%) of **6b**.

3.2.5. 4-Bromo-2-(*p*-methylphenyl)pyridine (4c). Following method A, 2,4-dibromopyridine (**1**) (75 mg, 0.32 mmol) with *p*-methylphenylboronic acid (**2c**) (52 mg, 0.38 mmol) in the presence of $Pd(PPh_3)_4$ (89 mg, 0.08 mmol) and 10% aq TlOH solution (2.7 mL, 1.22 mmol) in THF (2.3 mL), for 12 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 95:5 hexane/EtOAc), 48 mg

(60%) of 4-bromo-2-(*p*-methylphenyl)pyridine (**4c**) as a white solid (mp 61 °C, hexane/CH_2Cl_2), 3 mg (3%) of 2-bromo-4-(*p*-methylphenyl)pyridine[25] (**5c**) and 3 mg (3%) of 2,4-bis(*p*-methylphenyl)pyridine[26] (**6c**). Data of **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H, Me), 7.28 (d, J=7.8 Hz, 2H, H$^{2'}$), 7.36 (dd, J=5.1 Hz, 1.8 Hz, 1H, H^5), 7.86–7.88 (m, 3H, H^3 and 2H$^{3'}$), 8.48 (d, J=5.1 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 123.5 (CH), 124.9 (CH), 126.8 (CH), 129.6 (CH), 133.4 (C), 135.2 (C), 139.7 (C), 150.2 (CH), 158.8 (C) ppm. FTIR (neat) ν 3009 (w, C–H), 2939 (w, C–H), 2909 (w, C–H), 2851 (w, C–H). MS (EI$^+$) m/z (%) 250 ([M+1]$^+$ [^{81}Br], 13), 249 (M$^+$ [^{81}Br], 95), 248 ([M+1]$^+$ [^{79}Br], 39), 247 (M$^+$ [^{79}Br], 100). HRMS (EI$^+$) calcd for $C_{12}H_{10}N^{81}Br$, 248.9976 and $C_{12}H_{10}N^{79}Br$, 246.9997; found, 248.9978 and 246.9997. Anal. Calcd (%): C 58.09, H 4.06, N 5.65; found: C 58.11, H 4.03, N 5.69.

3.2.6. 4-Bromo-2-(*p*-fluorophenyl)pyridine (4d). Following method A, 2,4-dibromopyridine (**1**) (27 mg, 0.11 mmol) with *p*-fluorophenylboronic acid (**2d**) (18 mg, 0.13 mmol) in the presence of $Pd(PPh_3)_4$ (29 mg, 0.02 mmol) and 10% aq TlOH solution (0.9 mL, 0.40 mmol) in THF (1.5 mL), for 16 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 95:5 hexane/EtOAc), 19 mg (68%) of 4-bromo-2-(*p*-fluorophenyl)pyridine (**4d**) as an oil. Data of **4d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J=8.6 Hz, 2H, H$^{3'}$) 7.39 (dd, J=5.2 Hz, 1.6 Hz, 1H, H^5), 7.85 (d, J=1.6 Hz, 1H, H^3), 7.96 (dd, J=8.6 Hz, 5.4 Hz, 2H, H$^{2'}$), 8.48 (d, J=5.2 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.8 (d, J_{C-F}=21.6 Hz, 2CH), 123.5 (CH), 125.1 (CH), 128.9 (d, J_{C-F}=8.5 Hz, 2CH), 133.5 (C), 134.2 (d, J_{C-F}=3.3 Hz, C), 150.3 (CH), 157.8 (C), 163.8 (d, J_{C-F}=249.7 Hz, C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ 112.0 ppm. MS (EI$^+$) m/z (%) 254 ([M+1]$^+$ [^{81}Br], 9), 253 (M$^+$ [^{81}Br], 92), 252 ([M+1]$^+$ [^{79}Br], 13), 251 (M$^+$ [^{79}Br], 100). HRMS (EI$^+$) calcd for $C_{11}H_7{}^{81}BrFN$, 252.9725 and $C_{11}H_7{}^{79}BrFN$, 250.9746; found, 252.9730 and 250.9737.

3.2.7. 4-Bromo-2-[(1*E*)-2-phenylethenyl]pyridine (4g). Following method A, 2,4-dibromopyridine (**1**) (100 mg, 0.42 mmol) with (*E*)-2-phenylvinylboronic acid (**3g**) (0.15 g, 1.01 mmol) in the presence of $Pd(PPh_3)_4$ (38 mg, 0.03 mmol) and 10% aq TlOH solution (3.6 mL, 1.60 mmol) in THF (3.0 mL), for 21 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 90:10 hexane/EtOAc), 79 mg (72%) of 4-bromo-2-[(1*E*)-2-phenyleth-1-enyl]pyridine (**4g**) as a white solid (mp 51 °C, hexane/CH_2Cl_2) and traces of a compound identified as 2,4-bis[(1*E*)-2-phenyleth-1-enyl]pyridine (**6g**) (mp 174 °C, hexane/CH_2Cl_2, lit.[27] 175 °C). Data of **4g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J=16.1 Hz, 1H, H$^{1'}$ or H$^{2'}$), 7.29–7.40 (m, 4H, ArH), 7.54–7.58 (m, 3H, ArH), 7.65 (d, J=16.1 Hz, 1H, H$^{1'}$ or H$^{2'}$), 8.40 (d, J=5.2 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.9 (CH), 125.0 (CH), 126.4 (CH), 127.1 (CH), 128.6 (CH), 128.7 (CH), 133.0 (C), 134.2 (CH), 136.0 (C), 150.1 (CH), 156.9 (C) ppm. MS (EI$^+$) m/z (%) 261 ([M+1]$^+$ [^{81}Br], 20), 260 (M$^+$ [^{81}Br], 98), 259 ([M+1]$^+$ [^{79}Br], 21), 258 (M$^+$ [^{79}Br], 100). HRMS (EI$^+$) calcd for $C_{13}H_{10}N^{81}Br$, 259.9898 and $C_{13}H_{10}N^{79}Br$, 257.9918; found, 259.9894 and 257.9912. Data of **6g**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.09 (d, J=16.3 Hz, 1H, H$^{1''}$), 7.23 (d, J=16.1 Hz, 1H, H$^{1'}$), 7.29 (d, J=5.2 Hz, 1H, H^5), 7.3–7.4 (m, 7H, ArH and H$^{2''}$), 7.51 (s, 1H, H^3), 7.59 (d, J=7.5 Hz, 2H, Ar*H*), 7.62 (d, J=7.5 Hz, 2H, Ar*H*), 7.72 (d, J=16.1 Hz, 1H, H$^{2'}$), 8.54 (d, J=5.2 Hz, 1H, H^6) ppm. ^{13}C NMR (100.63 MHz, CD_2Cl_2) δ 119.7 (CH), 120.1 (CH), 126.6 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 128.9 (CH), 129.31 (CH), 129.34 (CH), 129.4 (CH), 133.3 (CH), 133.6 (CH), 136.9 (C), 137.3 (C), 145.9 (C), 150.4 (CH), 156.5 (C) ppm. FTIR (neat) ν 3025 (d, C–H). MS (EI$^+$) m/z (%) 284 ([M+1]$^+$, 6), 283 (M$^+$, 37), 282 ([M−1]$^+$, 100). HRMS calcd for $C_{21}H_{17}N$, 283.1361; found, 283.1348.

3.2.8. 4-Bromo-2-[(1*E*)-6-hydroxyhexenyl]pyridine (4h). Following method A, 2,4-dibromopyridine (**1**) (100 mg, 0.42 mmol) with (*E*)-6-hydroxyhex-1-en-1-ylboronic acid (**3h**) (73 mg, 0.51 mmol) in the presence of $Pd(PPh_3)_4$ (39 mg, 0.03 mmol) and 10% aq TlOH solution (3.6 mL, 1.60 mmol) in THF (3.0 mL), for 24 h at 25 °C, afforded, after purification by flash chromatography (SiO_2, 40:60 hexane/EtOAc), 83 mg (77%) of 4-bromo-2-[(1*E*)-6-hydroxyhex-1-enyl]pyridine (**4h**) as a yellow oil and 5 mg (5%) of 2-bromo-4-[(1*E*)-6-hydroxyhex-1-enyl]pyridine (**5h**) as an oil. Data of **4h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.62 (m, 4H, H$^{4'}$ and H$^{5'}$), 2.21 (br s, 1H, OH), 2.27 (c, J=7.0 Hz, 2H, H$^{3'}$), 3.64 (t, J=6.2 Hz, 2H, H$^{6'}$), 6.39 (dt, J=15.7 Hz, 1.4 Hz, 1H, H$^{1'}$), 6.72 (dt, J=15.7 Hz, 7.0 Hz, 1H, H$^{2'}$), 7.23 (dd, J=5.3 Hz, 1.8 Hz, 1H, H^5), 7.39 (d, J=1.8 Hz, 1H, H^3), 8.28 (d, J=5.3 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_2, C$^{4'}$), 32.1 (CH_2, C$^{5'}$), 32.4 (CH_2, C$^{3'}$), 62.4 (CH_2, C$^{6'}$), 124.1 (CH, C^3), 124.7 (CH, C^5), 128.9 (CH, C$^{1'}$), 133.1 (C, C^4), 137.4 (CH, C$^{2'}$), 149.9 (CH, C^6), 157.4 (C, C^2) ppm. FTIR (NaCl) ν 3500–3000 (br, O–H), 2932 (s, C–H), 2860 (m, C–H), 1652 (m), 1568 (s), 1542 (s), 1464 (m), 1385 (m), 1063 (w), 972 (m), 876 (w), 818 (w), 690 (m). MS (EI$^+$) m/z (%) 258 ([M+1]$^+$ [^{81}Br], 2), 257 (M$^+$ [^{81}Br], 14), 256 ([M+1]$^+$ [^{79}Br], 6), 255 (M$^+$ [^{79}Br], 12). HRMS (EI$^+$) calcd for $C_{11}H_{14}NO^{81}Br$, 257.0238 and $C_{11}H_{14}NO^{79}Br$, 255.0259; found, 257.0228 and 255.0257. Data of **5h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.65 (m, 4H, H$^{4'}$ and H$^{5'}$), 2.29 (m, 2H, H$^{3'}$), 3.69 (t, J=6.1 Hz, 2H, H$^{6'}$), 6.28 (d, J=15.8 Hz, 1H, H$^{1'}$), 6.49 (dt, J=15.8 Hz, 6.9 Hz, 1H, H$^{2'}$), 7.15 (dd, J=5.2 Hz, 1.4 Hz, 1H, H^5), 7.39 (br s, 1H, H^3), 8.24 (d, J=5.2 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0 (CH_2), 32.2 (CH_2), 32.7 (CH_2, C$^{3'}$), 62.6 (CH_2, C$^{6'}$), 119.7 (CH, C^5), 124.7 (CH, C^3), 126.8 (CH, C$^{1'}$), 137.6 (CH, C$^{2'}$), 142.8 (C, C^2), 148.0 (C, C^4), 150.1 (CH, C^6) ppm. MS (EI$^+$) m/z (%) 258 ([M+1]$^+$ [^{81}Br], 0.8), 257 (M$^+$ [^{81}Br], 6), 256 ([M+1]$^+$ [^{79}Br], 3). HRMS (EI$^+$) calcd for $C_{11}H_{14}NO^{81}Br$, 257.0238 and $C_{11}H_{14}NO^{79}Br$, 255.0259; found, 257.0230 and 255.0257.

3.2.9. 4-Bromo-2-[(1*E*)-3-*tert*-butyldimethylsilyloxy-2-methylpropenyl]pyridine (4i). To a cold (−78 °C) solution of (*E*)-*tert*-butyl(3-iodo-2-methylallyloxy)dimethylsilane[28] (0.45 g, 1.44 mmol) in THF (4.0 mL) in a Schlenk flask was added dropwise *t*BuLi (1.8 mL, 1.7 M in pentane, 3.03 mmol) and the mixture was stirred at −78 °C for 30 min. Then, $B(OiPr)_3$ (0.7 mL, 2.88 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h. At this time, following method A, $Pd(PPh_3)_4$ (78 mg, 0.07 mmol), a solution of 2,4-dibromopyridine (**1**) (0.19 g,

0.80 mmol) in THF (4.0 mL) and a 10% aq TlOH (7.0 mL, 3.2 mmol) solution were added sequentially and the mixture was stirred at 25 °C until complete disappearance of dibromopyridine **1** as observed by TLC and NMR (10 h). The crude mixture was diluted with Et_2O, filtered through a Celite® plug, and washed with an aqueous saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 (anhyd) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (96:4 hexane/EtOAc) affording 0.20 g (75%) of 4-bromo-2-[(1*E*)-3-*tert*-butyldimethylsilyloxy-2-methylprop-1-enyl]pyridine **4i** as a yellow oil and 13 mg (5%) of 2-bromo-4-[(1*E*)-3-*tert*-butyldimethylsilyloxy-2-methylprop-1-enyl]pyridine **5i** as a yellow oil. Data of **4i**: ^{1}H NMR (CD_2Cl_2) δ 0.12 (s, 6H, $Si(CH_3)_2$), 0.95 (s, 9H, *t*Bu), 2.05 (br s, 3H, CH_3), 4.19 (d, J=0.7 Hz, 2H, $H^{3'}$), 6.51 (m, 1H, $H^{1'}$), 7.26 (dd, J=5.3 Hz, 1.8 Hz, 1H, H^5), 7.39 (d, J=1.8 Hz, 1H, H^3), 8.38 (d, J=5.3 Hz, 1H, H^6) ppm. ^{13}C NMR (CD_2Cl_2) δ −5.1 (CH_3, $Si(CH_3)_2$), 15.8 (CH_3, CH_3–$C^{2'}$), 18.9 (C, C-*t*Bu), 26.3 (CH_3, *t*Bu), 68.5 (CH_2, $C^{3'}$), 121.7 (CH, $C^{1'}$), 124.3 (CH, C^5), 127.6 (CH, C^3), 132.9 (C, C^4), 145.1 (C, $C^{2'}$), 150.4 (CH, C^6), 159.2 (C, C^2) ppm. FTIR (neat) ν 2929 (w, C–H), 2855 (w, C–H). MS (EI$^+$) *m*/*z* (%) 343 (M$^+$ [^{81}Br], 21), 341 (M$^+$ [^{79}Br], 21), 286 ([M−*t*Bu]$^+$ [^{81}Br], 100), 284 ([M−*t*Bu]$^+$ [^{79}Br], 95). HRMS (EI$^+$) calcd for $C_{15}H_{24}NOSi^{81}Br$, 343.0790 and $C_{15}H_{24}NOSi^{79}Br$, 341.0810; found, 343.0794 and 341.0810. Data of **5i**: ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H, $Si(CH_3)_2$), 0.95 (s, 9H, *t*Bu), 1.83 (s, 3H, CH_3), 4.17 (s, 2H, $H^{3'}$), 6.44 (s, 1H, $H^{1'}$), 7.12 (dd, J=5.1 Hz, 1.2 Hz, 1H, H^5), 7.35 (br s, 1H, H^3), 8.28 (d, J=5.1 Hz, 1H, H^6) ppm. ^{13}C NMR ($CDCl_3$) δ −5.4 (CH_3, $Si(CH_3)_2$), 15.2 (CH_3, CH_3–$C^{2'}$), 18.4 (C, C–*t*Bu), 25.9 (CH_3, *t*Bu), 67.5 (CH_2, $C^{3'}$), 119.5 (CH, $C^{1'}$), 122.7 (CH, C^5), 127.5 (CH, C^3), 142.3 (C, C^2), 143.7 (C, $C^{2'}$), 148.7 (C, C^4), 149.7 (CH, C^6) ppm. FTIR (neat) ν 2951 (w, C–H), 2929 (w, C–H), 2855 (w, C–H), 1660 (w). MS (EI$^+$) *m*/*z* (%) 343 (M$^+$ [^{81}Br], 2), 342 ([M−1]$^+$ [^{81}Br], 11), 341 (M$^+$ [^{79}Br], 2), 340 ([M−1]$^+$ [^{79}Br], 11), 300 (100), 298 (98), 286 ([M−*t*Bu]$^+$ [^{81}Br], 25), 284 ([M−*t*Bu]$^+$ [^{79}Br], 25). HRMS (EI$^+$) calcd for $C_{15}H_{24}NOSi^{81}Br$, 343.0790 and $C_{15}H_{24}NOSi^{79}Br$, 341.0810; found, 343.0781 and 341.0801.

3.2.10. *trans*-Bromo(4-bromopyrid-2-yl-κ*C*^{2})bis(triphenylphosphane)palladium(II) (7) and di-μ-(4-bromopyrid-2-yl)-κ*N*:κ*C*^{2}-bis[bromotriphenylphosphanepalladium(II)] (9). To a thoroughly degassed solution of $Pd(PPh_3)_4$ (0.36 g, 0.32 mmol) in toluene (0.5 mL), a solution of 2,4-dibromopyridine (**1**) (75 mg, 0.32 mmol) in toluene (0.5 mL) was added dropwise. The reaction mixture was stirred at 25 °C for 16 h. Then, the solvent was removed under reduced pressure; the residue was titrated with ether yielding 225 mg (81%) of complex **7** along with complex **8**. After crystallization from CH_2Cl_2/hexane, complex **9** was obtained as a crystalline solid (mp>190 °C, decomp.). Data of mononuclear complex **7**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.22 (dd, J=5.3 Hz, 1.9 Hz, 1H, H^5), 6.65 (d, J=1.9 Hz, 1H, H^3), 7.29–7.35 (m, 12H, PPh_3), 7.37–7.41 (m, 6H, PPh_3), 7.40 (d, J=5.3 Hz, 1H, H^6), 7.57–7.61 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, CD_2Cl_2) δ 22.6 ppm. MS (FAB$^+$) *m*/*z* (%) 870 (8), 868 (9), 788 (54), 632 (64), 630 (82). HRMS (FAB$^+$) calcd for $C_{41}H_{34}NP_2{}^{79}Br_2{}^{106}Pd$, 865.9568; found, 865.9576. Data of mononuclear complex **8**: ^{31}P NMR (162 MHz, CD_2Cl_2) δ 23.86 ppm. Data of dinuclear complex **9**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.74 (m, 4H, 2×H^5 and 2×H^3), 7.27–7.33 (m, 12H, PPh_3), 7.41–7.44 (m, 12H, PPh_3), 7.78–7.85 (m, 12H, PPh_3), 8.31 (d, J=5.9 Hz, 1H, Ar*H*), 8.32 (d, J=5.4 Hz, 1H, Ar*H*) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2) δ 123.1 (d, $^3J_{C-P}$=3.0 Hz, CH), 129.0 (d, $^3J_{C-P}$=10.9 Hz, CH), 131.2 (d, $^4J_{C-P}$=2.0 Hz, CH), 131.2 (d, $^1J_{C-P}$=52.3 Hz, C), 135.6 (d, $^2J_{C-P}$=11.6 Hz, CH), 151.7 (CH), 189.1 (C) ppm. ^{31}P NMR (162 MHz, CD_2Cl_2) δ 30.2 ppm. MS (FAB$^+$) *m*/*z* (%) 1211 (0.6), 1131 (1), 788 (64), 630 (89).

3.3. Crystal data and structure refinement for 9

Crystallographic data were collected on a Bruker Smart 1000 CCD diffractometer at 20 °C using graphite monochromated Mo Kα radiation (λ=0.71073 Å), and were corrected for Lorentz and polarization effects. The frames were integrated with the Bruker SAINT[29] software package and the data were corrected for absorption using the program SADABS.[30] The structures were solved by direct methods using the program SHELXS97.[31] All non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least-squares calculations on F^2 using the program SHELXL97. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters. Drawings were produced with PLATON.[32] Empirical formula: $C_{46}H_{36}Br_4N_2P_2Pd_2$; formula weight: 1211.15; temperature: 293(2) K; crystal system: triclinic (*P*-1); unit cell dimensions: a=11.1679(9) Å, b=13.0847(10) Å, c=18.1885(14) Å; α=71.522(2)°, β=81.415(2)°, γ=73.8510(10)°; volume: 2415.9(3) Å^3; Z=2; density (calculated): 1.665 Mg/m^3; absorption coefficient=4.150 mm^{-1}. F(000)=1176; crystal size=0.40×0.12×0.06 mm^3; independent reflections 10085 [R(int)=0.0349]; data/restraints/parameters=10085/0/475; final R [I>2σ(I)]: R_1=0.0579, wR_2=0.1599; R indices (all data): R_1=0.1004, wR_2=0.1731.[33]

Acknowledgements

We thank MEC, Spain (SAF2004-07131) and Xunta de Galicia for financial support. C.S. and J.-L.A.-G. are recipients of F.P.U. and F.P.I fellowships, respectively. We thank also Professor Lugtenburg for his help in finishing this manuscript.

Supplementary data

^{31}P NMR of **1** with 2.0 equiv of $Pd(PPh_3)_4$. Copy of ^{1}H and ^{13}C NMR spectra of all new compounds. HMBC for **4h**, **5h**, **4i**, and **5i**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.040.

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12. Since mechanistic studies on the Suzuki coupling reaction of 2,4-dibromopyridine and phenylboronic acid in the presence of $Pd(PPh_3)_4$ showed that the selectivity follows the pattern for the oxidative addition step, a cautiously tentative interpretation for this finding could be that, unexpectedly, this phosphine reversed the oxidative addition selectivity between 2- and 4-C–Br bonds. The same behavior was observed in pentafluoropyridine with $[Pd(PCy_3)_2]$, see: Jasim, N. A.; Perutz, R. N.; Whitwood, A. C.; Braun, T.; Izundu, J.; Neumann, B.; Rothfeld, S.; Stammler, H.-G. *Organometallics* **2004**, *23*, 6140–6149.
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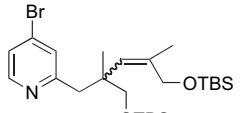
17. The protodeboronation product is easily detected by the ^1H NMR resonances of the methylene protons at δ=4.98 and 4.80 ppm. See: Burgess, K.; van der Donk, W. A.; Westcott, S. A.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 9350–9359. In fact, a side product (**10**) was obtained through a double fold Heck reaction of 2,4-dibromopyridine and 2-methyl-3-*tert*-butyldimethylsilyloxyprop-1-ene. Data: ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H, $Si(CH_3)_2$), 0.06 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, *t*Bu), 0.92 (s, 9H, *t*Bu), 1.13 (s, 3H, CH_3–$C^{2'}$), 1.58 (d, J=0.9 Hz, 3H, CH_3–$C^{4'}$), 2.89 (d, J=12.7 Hz, 1H, $H^{1'}$), 2.93 (d, J=12.7 Hz, 1H, $H^{1'}$), 3.35 (d, J=9.6 Hz, 1H, $H^{1''}$), 3.42 (d, J=9.6 Hz, 1H, $H^{1''}$), 3.93 (d, J=0.7 Hz, 2H, $H^{5'}$), 5.45 (br s, 1H, $H^{3'}$), 7.26 (dd, J=5.3 Hz, 1.8 Hz, 1H, H^5), 7.39 (d, J=1.8 Hz, 1H, H^3), 8.31 (d, J=5.3 Hz, 1H, H^6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5 (CH_3, $Si(CH_3)_2$), −5.2 (CH_3, $Si(CH_3)_2$), 15.0 (CH_3, CH_3–$C^{4'}$), 18.3 (C, $SiC(CH_3)_3$), 18.4 (C, $SiC(CH_3)_3$), 22.2 (CH_3, CH_3–$C^{2'}$), 26.0 (CH3, 2×$SiC(CH_3)_3$), 41.9 (C, $C^{2'}$), 45.3 (CH_2, $C^{1'}$), 69.7 (CH_2, $C^{1''}$), 69.8 (CH_2, $C^{5'}$), 124.2 (CH, C^5), 128.2 (CH, C^3), 128.3 (CH, $C^{3'}$), 132.2 (C, C^4), 135.5 (C, $C^{4'}$), 149.3 (CH, C^6), 161.5 (C, C^2) ppm. MS (EI^+) *m/z* (%) 529 (M^+ [^{81}Br], 2), 527 (M^+ [^{79}Br], 2). HRMS (EI^+) calcd for $C_{25}H_{46}{}^{81}BrNO_2Si_2$, 529.2230 and $C_{25}H_{46}{}^{79}BrNO_2Si_2$, 527.2250; found, 529.2274 and 527.2277.



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19. A similar dimer complex was recently reported as a precatalyst for the Suzuki reaction between 2-bromopyridine and phenyl boronic acid, but the reaction has to be performed at 80 °C, see: Beeby, A.; Bettington, S.; Fairlamb, I. J. S.; Goeta, A. E.; Kapdi, A. R.; Niemelä, E. H.; Thompson, A. L. *New J. Chem.* **2004**, *28*, 600–605. In our case the dimer was not active since, in order to attain high regioselectivity, we had to run the reaction at 25 °C.
20. This result contrasts with what was found in other dihalopyridines, in which the monosubstitution product presents a reduced reactivity. (a) Woods, C. R.; Benaglia, M.; Toyota, S.; Hardcastle, K.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2001**, *67*, 238–241; (b) Puglisi, A.; Benaglia, M.; Roncan, G. *Eur. J. Org. Chem.* **2003**, 1552–1558.
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33. Crystallographic data (excluding structure factors) for complex **8** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 603585. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).