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ortho-(Dimesitylboryl)phenylphosphines: Positive Boryl Effect in the Palladium-Catalyzed Suzuki–Miyaura Coupling of 2-Chloropyridines

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Abstract: Catalytic systems combining *ortho*-(dimesitylboryl)phenylphosphines and palladium precursors have been evaluated in the Suzuki–Miyaura couplings of chloro-N-heterocycles, in particular 2-chloropyridines, with arylboronic acids. The Lewis basic character of the substrates does not interfere with the Lewis acidic site of the ligands, even for a substrate featuring free NH_2 groups. The influence of several reaction parameters has been studied and the *ortho*-dimesitylboryl moiety was actually found to substantially enhance the catalytic performance. The role of this group has been examined using preformed phosphine-borane/Pd complexes and the formation of an original phosphine/η^4-boratabutadiene complex has been identified as a possible deactivation pathway. Regioselective coupling of 2,6-dichloro-3-nitropyridine with phosphine-borane/Pd catalysts has also been explored, and sequential double cross-couplings were found to give a direct and efficient access to unsymmetrical 2,6-diarylpyridines.

Keywords: C–Cl bond activation; N-heterocycles; palladium; phosphine-boranes; regioselective coupling; Suzuki–Miyaura cross-couplings

Introduction

Ligand modulation keeps playing a central role in the development of organometallic catalysis in general and of Pd-catalyzed cross-coupling reactions in particular.[1] In that respect, phosphines are prominent scaffolds and subtle variations of the phosphorus environment (modulation of the electronic properties and steric shielding, incorporation of secondary coordination sites, etc.) have allowed significant progress to be achieved in terms of activity and selectivity.[2]

Phosphine-boranes are archetypes of ambiphilic ligands combining a phosphine and a Lewis acid moiety.[3] They have been very sporadically investigated in transition metal catalysis, although the additional borane group offers a true potential for catalytic enhancement. In the 1990s, Kagan and Landis investigated the possibility of the Lewis acid moiety to anchor incoming substrates (in Rh-catalyzed hydrogenation, hydrosilylation and hydroformylation).[4] Quite disappointingly, the incorporation of boronates or benzoxaborolidine fragments did not have a major impact, and essentially identical catalytic behaviour was observed between **A**/**B**, and the corresponding boron-free diphosphines (Figure 1). Over the last few years, phosphine-boranes have attracted a surge of interest, stimulated by their envisioned and now recognized ability to engage into unusual coordination modes (especially P→M→B bridging coordination).[5,6]

The availability of a broad range of phosphine-boranes and their versatile coordination properties have stimulated renewed interest for their applications in catalysis. We have started to explore the use of *ortho*-(dimesitylboryl)phenylphosphines in model Rh-catalyzed hydroformylation and Pd-catalyzed Suzuki–

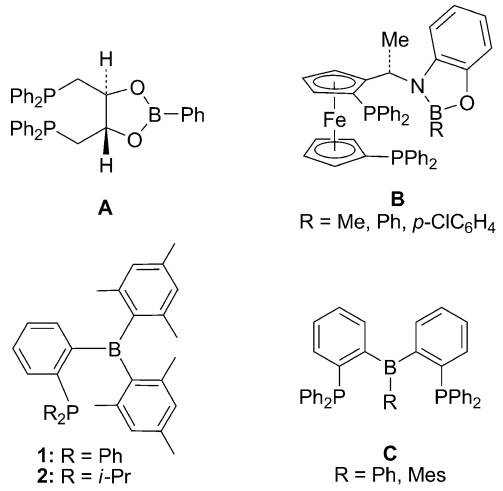


Figure 1. Phosphine-borane ligands evaluated in transition metal catalysis.

Miyaura cross-coupling reactions.[7] Thereby, unexpected analogies were disclosed between ligands **1** and **2** (Figure 1), and Buchwald-type biarylphosphines.[8] Complexes deriving from diphosphine-boranes of type **C** have also been recently evaluated in transition metal catalysis (Figure 1).[9] Peters showed the ability of an Ni complex to activate reversibly H_2 and promote the catalytic hydrogenation of olefins.[9a] In addition, some "boron enhancement effect" has been evidenced by Nakazawa with Rh (but not Ir) complexes in the transfer hydrogenation of ketones.[9b,10]

Here we report an advanced evaluation of phosphine-boranes **1** and **2** in Pd-catalyzed Suzuki–Miyaura reactions. Given the importance of this cross-coupling for the preparation of heterobiaryl derivatives,[11] the reaction of chloro-N-heterocycles, in particular 2-chloropyridines, has been investigated. The Lewis acid moiety of the ligand proved to be compatible with the Lewis basic character of the substrates, even those featuring free NH_2 groups, and the *ortho*-dimesitylboryl moiety was actually found to have a very positive effect on the catalytic performance. The influence of several reaction parameters has been examined. Catalytic experiments with preformed phosphine-borane/Pd complexes have provided some insight into the role of the $BMes_2$ group and C–H activation of one of the mesityl groups has been identified as a possible deactivation pathway. The possibility to achieve regioselective couplings from 2,6-dichloro-3-nitropyridine has also been explored, and sequential double cross-couplings gave a direct and efficient access to unsymmetrical 2,6-diarylpyridines.

Results and Discussion

Cross-Couplings of Chloro-N-heterocycles and Arylboronic Acids Catalyzed by Phosphine-Borane/Pd Systems

With the aim to apply palladium catalytic systems containing phosphine-boranes **1** and **2** in the synthesis of functionalized heterocycles, we first studied the cross-coupling of 2-chloropyridine with phenylboronic acid as model reaction. Gratifyingly, the basic nitrogen atom of the substrate did not interfere with the Lewis acidic site of the phosphine-borane ligand and the cross-coupling reaction proceeded efficiently. The catalytic species were generated *in situ* from the corresponding palladium precursor in the presence of the appropriate phosphine-borane ligand. Using **1** and [$PdCl_2$(cod)] as starting catalytic species, a good yield of the desired product 2-phenylpyridine was obtained (65%), higher in relation to that obtained from [Pd(ma)(nbd)] (ma = maleic anhydride; nbd = norbornadiene) (entries 1 and 2, Table 1). The catalytic system based on [Pd_2(dba)$_3$] was significantly less efficient (entry 3, Table 1). No important differences were observed between Pd/**2** and Pd/**1** (entry 4 *vs.* entry 1, Table 1). The yield increased when the $PhB(OH)_2$/substrate ratio was increased to 1.5/1 (entries 5 and 6, Table 1), giving up to 94% of 2-phenylpyridine.

Some other chloro-N-heterocycles were tested as substrates using the [$PdCl_2$(cod)]/**1** catalytic system (Table 2). Remarkably, no major difference was observed between 2-, 3- or 4-chloropyridine and isolated yields higher than 90% were systematically obtained after 20 h (entries 1 and 2). Pyrimidine, pyrazine, quinoline and quinazoline substrates were also efficiently coupled (as for 2-chloropyridine, yields reach 90–93% after 20 h) (entries 3–6).

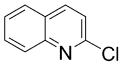
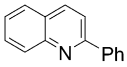
The ability of our **L**/Pd catalytic systems to cross-couple N-heterocycles and Ph-$B(OH)_2$ prompted us

Table 1. Suzuki–Miyaura cross-coupling reactions of 2-chloropyridine catalyzed by Pd/**L** systems (see Figure 1).[a]

Entry	Pd precursor	Ligand	Yield[b] [%]
1	[$PdCl_2$(cod)]	**1**	65 (46)
2	[Pd(ma)(nbd)]	**1**	49 (19)
3	[Pd_2(dba)$_3$]	**1**	24 (10)
4	[$PdCl_2$(cod)]	**2**	62 (44)
5[c]	[$PdCl_2$(cod)]	**1**	94 (77)
6[c]	[Pd_2(dba)$_3$]	**1**	69 (21)

[a] Results from duplicate experiments. *Reaction conditions:* 1 mmol of substrate; 2 mL of toluene; K_3PO_4/Ph-$B(OH)_2$/**I**/Pd = 2.1/1.1/1/0.01; **L**/Pd = 2; 100 °C; 20 h.
[b] Determined by ^{1}H NMR using 2-methoxynaphthalene as internal standard; in brackets, yields at 5 h.
[c] Ph-$B(OH)_2$/**I** = 1.5.

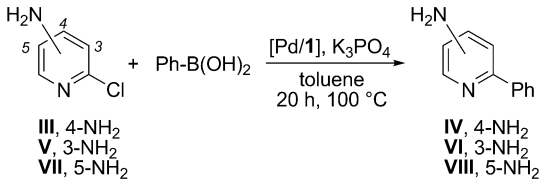
Table 2. Suzuki–Miyaura cross-couplings of chloro-N-heterocycles catalyzed by **1**/Pd system.[a]

Entry	Substrate	Product	Yield[b] [%]
1			93
2[c]			93
3			91
4			91
5			90
6			93

[a] Results from duplicate experiments. *Reaction conditions:* 1 mmol of substrate; 2 mL of toluene; K_3PO_4/Ph-B(OH)$_2$/substrate/Pd = 2.1/1.5/1/0.01; **1**/[$PdCl_2$(cod)] = 2; 100 °C; 20 h.
[b] Isolated yields.
[c] Substrate used as hydrochloride salt.

to study Suzuki–Miyaura reactions using polysubstituted pyridines and we turned our attention to aminochloropyridines. The introduction of electron-rich substituents such as amino groups at the pyridine ring makes the C–Cl bond activation more difficult. In addition, it increases the basicity of the pyridine nitrogen and thus favours N coordination over oxidative addition of the C–Cl bond. In this area, substrates featuring free NH_2 groups are most challenging. Protection/deprotection is usually necessary to achieve efficient cross-coupling[12] and to avoid Buchwald–Hartwig amination of chloroaminopyridine substrates.[13] So far, direct couplings of unprotected substrates remain rather scarce, although significant progress has been achieved recently in this area thanks to the fine tuning of the ligand structure and reaction conditions.[14,15] The ability of **1**/Pd systems to mediate the coupling of phenylboronic acid and aminochloropyridines **III**, **V** and **VII** was first evaluated with different Pd precursors (Table 3). For 4-amino-2-chloropyridine, the coupling product **IV** was obtained in high yields (up to 98%; entries 1–3), without significant formation of side-products (less than 5%). For 3- and 5-amino substrates **V** and **VII**, conversions and yields were much lower (entries 4–6 and 7, 8, respectively). This indicates that **1**/Pd systems are very sensitive to electronic and steric factors. When placed in the *ortho* or *para* position to chlorine, the NH_2 group disfavours the oxidative addition step (to an even greater extent in the 5-amino derivative **VII**), and

Table 3. Suzuki–Miyaura cross-coupling reactions of amino-2-chloropyridines catalyzed by **1**/Pd systems.[a]



III, 4-NH_2
V, 3-NH_2
VII, 5-NH_2

IV, 4-NH_2
VI, 3-NH_2
VIII, 5-NH_2

Entry	Pd precursor	Substrate	Conv.[b] [%]	Yield[b] [%]
1	[$PdCl_2$(cod)]	**III**	97	92
2	[Pd_2(dba)$_3$]	**III**	95	94
3	[Pd(ma)(nbd)]	**III**	100	98
4	[$PdCl_2$(cod)]	**V**	59	42
5	[Pd_2(dba)$_3$]	**V**	30	16
6	[Pd(ma)(nbd)]	**V**	14	0
7	[$PdCl_2$(cod)]	**VII**	32	21
8	[Pd(ma)(nbd)]	**VII**	27	21

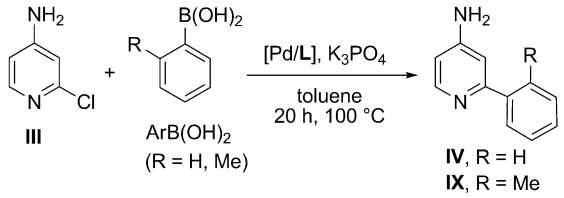
[a] Results from duplicate experiments. *Reaction conditions:* 1 mmol of substrate; 2 mL of toluene; K_3PO_4/Ph-B(OH)$_2$/substrate/Pd = 2.1/1.1/1/0.01; **1**/Pd = 2.
[b] Conversions and yields determined by ^{1}H NMR using 2-methoxynaphthalene as internal standard.

steric shielding is also likely to play a significant role for the 3-amino substrate **V**.

For the 4-amino substrate **III**, the catalytic influence of various parameters was then studied, including the metal precursor, the nature of the ligand, the boronic acid/chloropyridine ratio and the ligand/Pd ratio (Table 4). With the diphenylphosphine-dimesitylborane ligand **1**, the nature of the organometallic precursor, Pd(II) or Pd(0), had little influence and essentially identical results were obtained with [$PdCl_2$(cod)] and [Pd_2(dba)$_3$] (entries 1 and 2). The related di(isopropyl)phosphine-dimesitylborane ligand **2** behaved somewhat differently (entries 3 and 4). It is less efficient (conversions of *ca.* 44% were obtained with both Pd precursors), and in this case, the yield in coupling product **IV** was higher with [Pd_2(dba)$_3$] than using [$PdCl_2$(cod)] (41 *vs.* 26%, entries 3 and 4). Whereas sterically demanding alkyl substituents usually increase the activity of phosphines in cross-coupling reactions, such an effect is not observed here and the diphenylphosphine-borane **1** gives significantly better results.

The influence of the ratio between the phenylboronic acid and aminochloropyridine **III** was then evaluated with two catalytic systems, namely **1**/[$PdCl_2$(cod)] or **2**/[Pd_2(dba)$_3$]. In both cases, no catalytic improvement was noticed with 1.5 equiv. of phenylboronic acid (entries 6, 7 *vs.* 1, 4, respectively), probably due to the high chemoselectivity of these phosphine-borane/Pd systems for cross-coupling over undesirable processes (such as proto-deboronation, homo-coupling, etc.). The effect of the ligand to Pd ratio was also examined for the **1**/[Pd_2(dba)$_3$] system. Quite re-

Table 4. Suzuki–Miyaura cross-coupling reactions between 4-amino-2-chloropyridine and aryl boronic acids catalyzed by **L**/Pd systems.[a]



Entry	Pd precursor, **L** (**L**/Pd)	$ArB(OH)_2$/**III**[b]	Conv.[c] [%]	Yield[c] [%]
1	$[PdCl_2(cod)]$, **1** (2/1)	1.1 (R = H)	97 (96)	92 (90)
2	$[Pd_2(dba)_3]$, **1** (2/1)	1.1 (R = H)	95 (89)	94 (86)
3	$[PdCl_2(cod)]$, **2** (2/1)	1.1 (R = H)	42 (16)	26 (16)
4	$[Pd_2(dba)_3]$, **2** (2/1)	1.1 (R = H)	46 (45)	41 (41)
5	$[PdCl_2(cod)]$, PPh_3 (2/1)	1.1 (R = H)	24 (24)	11 (6)
6	$[PdCl_2(cod)]$, **1** (2/1)	1.5 (R = H)	97 (93)	95 (87)
7	$[Pd_2(dba)_3]$, **2** (2/1)	1.5 (R = H)	42 (43)	38 (15)
8	$[Pd_2(dba)_3]$, **1** (1/1)	1.1 (R = H)	94 (87)	92 (74)
9	$[Pd_2(dba)_3]$, **1** (5/1)	1.1 (R = H)	93	81
10	$[Pd_2(dba)_3]$, **3**[d] (1/1)	1.1 (R = H)	92 (92)	79 (64)
11	$[Pd_2(dba)_3]$, **1** (2/1)	1.1 (R = Me)	92 (89)	86 (80)
12	$[Pd_2(dba)_3]$, **2** (2/1)	1.1 (R = Me)	81 (79)	75 (73)
13[e]	$[Pd_2(dba)_3]$, **3**[d] (2/1)	1.1 (R = Me)	100	91
14[f]	**1-Pd**	1.5 (R = H)	96 (95)	92 (84)
15[f]	**1′-Pd**	1.5 (R = H)	40 (37)	33 (29)

[a] Results from duplicate experiments. *Reaction conditions:* 1 mmol of **III**; 2 mL of toluene; K_3PO_4/**III**/Pd = 2.1/1/0.01.
[b] In brackets the substituent on the arylboronic acid.
[c] Conversions and yields determined by ^1H NMR using 2-methoxynaphthalene as internal standard. In brackets, the results obtained after 5 h of reaction.
[d] **3** = (2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)-diphenylphosphine.
[e] After 5 h.
[f] Preformed complex as catalytic precursor (Scheme 1).

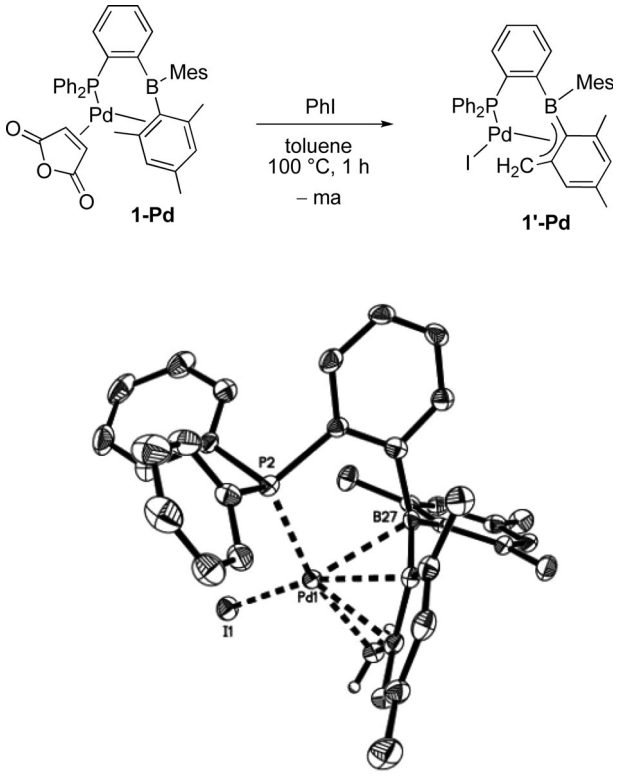
markably, essentially identical results (94% conversion, 92% yield) were obtained with only one equivalent of phosphine-borane **1** per metal center (entry 8 *vs.* entry 2). On the other hand, the use of an excess of phosphine-borane (5 equiv.) had a negative effect: the conversion was essentially the same, but the selectivity dropped and the yield in the coupling product **IV** was about 10% lower (entry 9 *vs.* entry 8).

A positive effect of the $BMes_2$ moiety on catalytic activity was supported by comparing the catalytic behaviour of Pd/**1** with that of related systems Pd/PPh_3 and Pd/**3**. The Pd/PPh_3 catalyst gave low activity in contrast to Pd/**1**: only 11% yield of **IV** *vs.* more than 92% (entry 5 *vs.* entries 1 and 2). The sterically demanding biarylphosphine **3** {(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)-diphenylphosphine} was chosen as a representative member of the very efficient Buchwald-type ligands. The two catalytic systems Pd/**1** and Pd/**3** gave similar conversions (~93%, entries 8 and 10), but a significantly higher yield was obtained with the phosphine-borane **1** (92 *vs.* 79%, entry 8 *vs* entry 10).

To assess the influence of steric effects, the coupling of 4-amino-2-chloropyridine **III** with substituted phenylboronic acids was then examined. With 2-methylphenylboronic acid, the coupling product **IX** was obtained in high yield (86%) and good chemoselectivity (side-products < 6%) using **1** and $[Pd_2(dba)_3]$ (entry 11).[16] Here also, the dialkylphosphine ligand **2** proved to be less efficient than **1** (81% conversion, 75% yield, entry 12), but the difference between the two phosphine-boranes is smaller than that observed with phenylboronic acid. In addition, the biarylphosphine **3** surpassed **1** in this case (100% conversion, 91% yield, entry 13), suggesting that the phosphine-borane ligands are more sensitive to the steric shielding of the substrates. Consistently, the 2,6-dimethylphenylboronic acid could not be efficiently coupled with either of the phosphine-borane **1** and **2**.[17]

Synthesis and Catalytic Evaluation of Preformed Phosphine-Borane Complexes: Towards a Better Understanding of the Boryl Effect

At this stage, the catalytic properties of preformed complexes deriving from the phosphine-borane ligand **1** were also evaluated to better assess the contribution



Scheme 1. Reaction of complex **1-Pd** with iodobenzene (ma = maleic anhydride); and molecular structure of the ensuing complex **1′-Pd** (ellipsoids drawn at 50% probability and hydrogen atoms omitted for clarity, except for H on CH_2).

of the $BMes_2$ group. We first used the previously described complex **1-Pd** featuring a weak π interaction between one of the Mes groups and Pd.[7b] Within the margin of error we obtained the same results as with the related *in situ* generated catalytic system (96% conversion, 92% yield of **IV** after 20 h, see entry 14, Table 4). This parallels what was observed with 4-bromoanisole as model substrate[7b] and further supported the contribution of weak π-arene coordination from $BMes_2$ to Pd, akin to that commonly envisioned with biarylphosphines.[18] With the aim of characterizing a more advanced catalytic intermediate, complex **1-Pd** was then treated with iodobenzene (1.25 equiv.).[19] The reaction proceeded only at high temperature and was complete in *ca.* 1 h at 100 °C (Scheme 1). Under these conditions, significant decomposition occurred (as apparent from the formation of black Pd and free ligand), but a new complex **1′-Pd** was formed. After standard work-up and purification by column chromatography on silica gel, complex **1′-Pd** was isolated in 26% yield as a yellow powder. Mass spectrometry and elemental analysis are not consistent with simple oxidative addition of iodobenzene at palladium, but clearly indicate the incorporation of iodine and release of maleic anhydride. According to NMR spectroscopy, one of the Mes group at boron underwent C–H activation and diagnostic signals for a CH_2 group are observed both in ^{1}H (AB system, $\delta = 4.63$ and 2.93 ppm, $J_{H,H} = 2$ Hz) and ^{13}C ($\delta = 62.49$ ppm, $J_{C,P} = 39$ Hz) NMR spectra. In addition, the ^{11}B NMR resonance signal for **1′-Pd** ($\delta =$ 52.8 ppm) is shifted upfield by about 10 ppm ($\delta =$ 69.4 ppm for **1-Pd**), suggesting the presence of some Pd→B interaction.[6] The precise structure of complex **1′-Pd** was figured out by X-ray diffraction analysis. Actually, one of the Mes groups at boron underwent an original C–H activation process. In addition to the phosphorus and iodine atoms, the metal center is bonded to a $BCCCH_2$ fragment whose geometry remains essentially planar. The Pd/C distances range from 2.15 to 2.33 Å, and the Pd/B distance is short [2.395(4) Å]. The overall structure of **1′-Pd** is very similar to that reported recently by Hoefelmeyer for the compound obtained upon reacting 8-($BMes_2$)quinoline with [$PdCl_2(PhCN)_2$].[20] Complexes featuring acyclic boron-containing π-ligands are relatively scarce,[21] and complex **1′-Pd** represents a rare example of a η^4-boratabutadiene complex.[22]

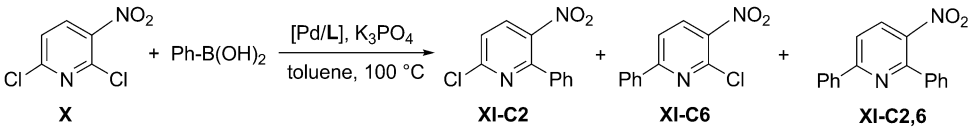
The exact mechanism for the transformation of **1-Pd** into **1′-Pd** remains unclear at this stage,[23] but there are a few precedents for such concomitant Ar–X and phosphine ligand C–H activation.[24] In addition, the reaction of **1-Pd** with *p*-nitroiodobenzene also gave **1′-Pd**, and the concomitant formation of *p*-nitrobenzene could be unequivocally identified by gas chromatography.

Noteworthy, complex **1′-Pd** proved to be significantly less active than **1-Pd** in the cross-coupling of 4-amino-2-chloropyridine **III** with phenylboronic acid (37–40% conversion, compared with 95–96%; see entries 14 and 15, Table 4). The C–H activation process undergone by the phosphine-borane ligand from **1-Pd** to **1′-Pd** is thus detrimental to the catalytic efficiency and may represent in that regard a deactivation pathway.[25]

Double Suzuki–Miyaura Cross-Coupling, Synthesis of Unsymmetrical 2,6-Diarylpyridines

Polysubstituted pyridines are ubiquitous structural motifs. They have found applications in many areas ranging from biologically active compounds,[26] coordination complexes,[27] advanced functional materials,[28] etc. This widespread interest prompts chemists to develop efficient synthetic routes and recently, regioselective Pd-catalyzed coupling reactions have emerged as a valuable and promising approach.[29,30] In this context, selective functionalization of polyhalogenated heteroaromatic compounds is most attractive as it may afford a straightforward access to polysubstituted heterocycles.

Table 5. Suzuki–Miyaura cross-coupling reactions between 2,6-dichloro-3-nitropyridine and phenylboronic acid (relative ratio 1/2.2) catalyzed by **L**/Pd systems.[a]



Entry	Pd precursor, **L**	Time [h]	Yields[b] [%]		
			XI-C2	**XI-C6**	**XI-C2,6**
1	$[PdCl_2(cod)]$, **1**	5	35.0	<1	56.4
2	$[PdCl_2(cod)]$, **1**	20	30.0	<1	62.0
3	$[PdCl_2(cod)]$, **2**	5	9.7	<1	83.8
4	$[PdCl_2(cod)]$, **2**	20	5.7	0	92.8
5	$[Pd_2(dba)_3]$, **1**	5	17.8	<1	79.2
6	$[Pd_2(dba)_3]$, **1**	20	8.0	0	87.4
7	$[Pd_2(dba)_3]$, **2**	5	10.5	<1	84.0
8	$[Pd_2(dba)_3]$, **2**	20	0.7	0	95.4

[a] Results from duplicate experiments, quantitative conversions. *Reaction conditions:* 1 mmol of **X**; 2 mL of toluene; K_3PO_4/**X**/Ph-$B(OH)_2$/Pd = 2.1/1/2.2/0.01; **L**/Pd = 2.

[b] Determined by GC, based on calibration curves and using 2-methoxynaphthalene as internal standard. Less than 4% of biphenyl was observed in any case.

In this respect and as an extension of the results described above on Suzuki–Miyaura cross-coupling of 2-chloropyridines, we became interested in using our phosphine-borane/Pd catalytic systems for the regioselective preparation of polyarylated pyridines. Adjacent coordinating ester or amide groups have been shown to impart good selectivity in the coupling of 2,6-chloropyridines.[31] We were keen to see whether the high sensitivity of phosphine-borane/Pd systems towards substrate substitution may enable us to achieve selective couplings. For this purpose, we chose 2,6-dichloro-3-nitropyridine **X** as a model of an unsymmetrically substituted substrate and investigated its cross-coupling with arylboronic acids.

First, we evaluated the activity of **L**/Pd systems (**L** = **1** and **2**) for the coupling of **X** with phenylboronic acid [**X**/PhB$(OH)_2$ = 1/2.2] at 100 °C (Table 5). The reaction gave rise to three different coupling products: the two regioisomeric chlorophenylpyridines, referred to as **XI-C2** and **XI-C6**, and the diphenyl-substituted pyridine **XI-C2,6**. An X-ray diffraction study was performed on **XI-C6** in order to reliably assign the regioisomeric structures of the mono-coupled products (see Figure S1 in the Supporting Information).

With $[PdCl_2(cod)]$ as palladium precursor, the di(isopropyl)phosphine-borane ligand **2** afforded the double cross-coupled product **XI-C2,6** in very high yield (up to 93% yield based on **X**, see entries 3 and 4). Under the same conditions, the diphenylphosphine-borane ligand **1** was less selective, giving approximately 60% of **XI-C2,6** and 35% of the mono-cross-coupled product **XI-C2** (entries 1 and 2). Both systems preferentially activated the C-2–Cl bond of **X** (less than 1% of **XI-C6** was observed),[32] and the initially formed mono-cross-coupled product **XI-C2** evolves into **XI-C2,6** at longer times (entry 1 *vs.* entry 2 and entry 3 *vs.* entry 4). The catalytic trend observed using $[Pd_2(dba)_3]$ was quite similar to that observed with $[PdCl_2(cod)]$. The two organometallic precursors gave about the same results with the phosphine-borane **2**, while $[Pd_2(dba)_3]$ showed slightly higher activity than $[PdCl_2(cod)]$ with ligand **1**. Accordingly, higher yields of the diphenylpyridine **XI-C2,6** were obtained with $[Pd_2(dba)_3]$ (88%, entry 6) than with $[PdCl_2(cod)]$ (62%, entry 2). This suggests that the $[Pd_2(dba)_3]$/**1** catalytic system activates more readily the C-6–Cl bond than $[PdCl_2(cod)]$/**1** and in consequence displays lower selectivity between the C-2–Cl and C-6–Cl bonds of **X**.

With the aim to achieve selective activation of the most reactive C-2–Cl bond of **X**, coupling reactions were then carried out with only 1.1 equiv. of Ph-$B(OH)_2$ (Table 6). In agreement with previous observations, the **2**/$[PdCl_2(cod)]$ catalytic system (entry 2) was the most active (96% conversion). The chlorophenylpyridine **XI-C2** was obtained as major product (62.3% yield) along with small amounts of the regioisomeric mono-cross-coupled product **XI-C6** (11%) and double cross-coupled product **XI-C2,6** (10%).

Under the same conditions, the biarylphosphine **3**/Pd system (entry 3) proved to be less active (76% conversion) and less selective: in this case, the major product was the diphenylpyridine **XI-C2,6** (24.5% yield), and the mono-cross-coupled product **XI-C2** represents only *ca.* 23% yield.[33] In all cases, only biphenyl was observed as by-product (less than 4% for any of the three catalytic systems, Pd/**1**, Pd/**2** and Pd/

Table 6. Suzuki–Miyaura cross-coupling reactions between 2,6-dichloro-3-nitropyridine and phenylboronic acid catalyzed by Pd/**L** systems (see scheme of Table 5).[a]

Entry	**L**	Conv. [%][b]	Yields [%][b,c]		
			XI-C2	**XI-C6**	**XI-C2,6**
1	**1**	88	73.0	2.0	8.5
2	**2**	96	62.3	11.0	10.0
3[d]	**3**	76	23.4	2.2	24.5
4[e]	**1**	89	60.0	10.3	5.5
5[f]	**1**	76	55.5	6.5	3.3

[a] Results from duplicate experiments. *Reaction conditions:* 1 mmol of **X**; 2 mL of toluene; K_3PO_4/**X**/Ph-$B(OH)_2$/$[PdCl_2(cod)]$ = 2.1/1/1.1/0.01; **L**/Pd = 2; $[PdCl_2(cod)]$ as palladium precursor; reaction time: 20 h; 100 °C. See Table S1 in the Supporting Information for results at 5 h.

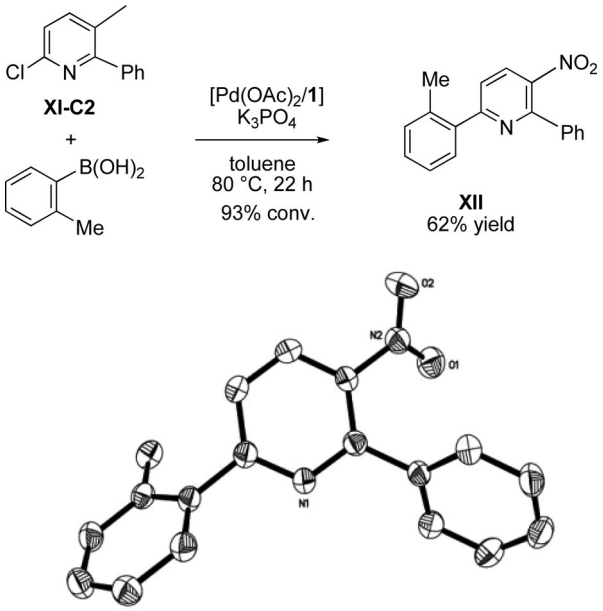
[b] Determined by GC, based on calibration curves and using 2-methoxynaphthalene as internal standard.

[c] Yields were calculated on the basis of **X**; given that only 1.1 equiv. of Ph-$B(OH)_2$ were employed, 50.5% is the highest yield achievable for **XI-C2,6**.

[d] **3** = (2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)-diphenylphosphine.

[e] $Pd(OAc)_2$ as palladium precursor.

[f] At 80 °C; data at 72 h.



Scheme 2. Synthesis of the unsymmetrical 2,6-diarylpyridine **XII** by cross-coupling of **XI-C2** with *ortho*-tolyl boronic acid; and crystal structure of **XII** (ellipsoids drawn at 50% probability and hydrogen atoms omitted for clarity).

3). The selectivity in mono-cross-coupled product **XI-C2** reached 73% yield with the diphenylphosphine-borane ligand **1**, with only 8.5% of double cross-coupled product **XI-C2,6** (entry 1). Lowering the reaction temperature from 100 to 80 °C (entry 5) triggered somewhat lower conversion and **XI-C2** was obtained in 55.5% yield (with 6.5 and 3.3% yields of **XI-C6** and **XI-C2,6** respectively). Replacing $[PdCl_2(cod)]$ for $Pd(OAc)_2$, the conversion remains unchanged, but the selectivity towards the formation of **XI-C2** slightly decreases (entry 1 *vs.* entry 4) (see Table S1 in the Supporting Information for catalytic experiments using $[Pd_2(dba)_3]$).

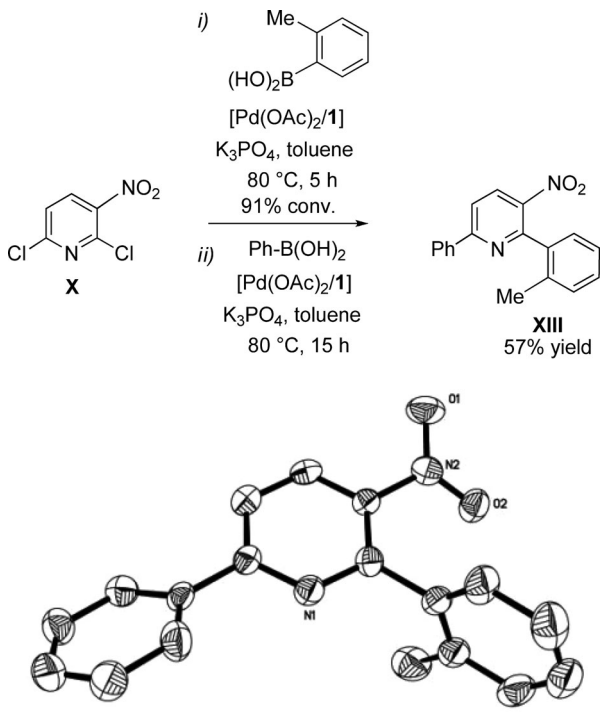
This study reveals that Pd catalysts deriving from the phosphine-boranes **1** and **2** are able to promote the cross-coupling of 2,6-dichloro-3-nitropyridine **X** with relatively high selectivity for the activation of the C-2–Cl bond. Comparatively, the biarylphosphine **3** does not enable us to discriminate efficiently the two C–Cl bonds and the formation of the symmetrical double cross-coupled product is favoured even with only one equivalent of phenylboronic acid.

Taking advantage of the regioselective coupling of **X** achieved by phosphine-borane/Pd catalysts, we then pursued the preparation of unsymmetrical 2,6-diarylpyridines. Pure chlorophenylpyridine **XI-C2** (obtained following entry 2 of Table 4 and isolated after purification by column chromatography) was reacted with *ortho*-tolylboronic acid in the presence of **1**/$Pd(OAc)_2$ (Scheme 2). The desired diarylpyridine **XII** was thereby obtained in 62% isolated yield and its molecular structure was secured by an X-ray diffraction study.

To further illustrate the synthetic interest of our approach, we then prepared the regioisomeric unsymmetrical 2,6-diarylpyridine **XIII**, simply by inverting the order of reaction of the two boronic acids (Scheme 3). Successive reactions of 2,6-dichloro substrate **X** with *ortho*-tolylboronic acid (1.1 equiv.) and phenylboronic acid (1.1 equiv.) afforded **XIII** with an overall isolated yield of 57% (without optimization). The molecular structure of **XIII** was unambiguously ascertained by an X-ray diffraction analysis.

Conclusions

Palladium catalysts derived from the phosphine-borane ligands **1** and **2** have been successfully applied in the cross-coupling of N-heterocycles, including substrates featuring unprotected NH_2 groups. The dimesitylboryl group of the ligand is compatible with the Lewis basic character of the substrates and, actually, it enhances significantly the catalytic performance. Experiments carried out with preformed phosphine-borane/Pd complexes further support the contribution of weak π-arene coordination to Pd (akin to those encountered with biarylphosphines). Upon reaction with iodobenzene, an original phosphine/η^4-boratabutadiene complex could be isolated, substantiating C–H activation of the mesityl groups at boron as a possible



Scheme 3. Synthesis of the unsymmetrical 2,6-diarylpyridine **XIII** by one-pot sequential double cross-coupling of 2,6-dichloro-3-nitropyridine **X**; and crystal structure of **XIII** (ellipsoids drawn at 50% probability and hydrogen atoms omitted for clarity).

deactivation pathway for these catalytic systems. The phosphine-borane ligands are more sensitive to substrate substitution than biarylphosphines but, in turn, they are able to achieve cross-couplings of 2,6-dichloro-3-nitropyridine with higher regioselectivities. Accordingly, sequential double Suzuki–Miyaura reactions provide a direct and efficient access to unsymmetrical 2,6-diarylpyridines.

Future studies will seek to exploit the availability and modularity of phosphine-boranes to tune and improve the catalytic activity and selectivity of the ensuing complexes.

Experimental Section

General

All preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. Toluene was distilled under argon from molten sodium. Unless stated otherwise, commercially compounds were used without further purification. Ligands **1**, **2**[34] and **3**[35] as well as precursor [Pd(ma)(nbd)][36] were prepared according to previously described procedures. NMR spectra were recorded on Bruker Avance 300 and 500 spectrometers at 293 K. GC analyses were carried out on an Agilent GC6890 with a flame ionization detector, using a SGE BPX5 column comprising 5% phenylmethylsiloxane.

General Procedure for Catalytic Suzuki–Miyaura C–C Cross-Coupling

Palladium precursor {0.01 mmol, for $Pd(OAc)_2$: 2.25 mg; for $[PdCl_2(cod)]$: 2.9 mg; for $[Pd_2(dba)_3]$: 9.1 mg} and the appropriate ligand (0.02 mmol, for **1**: 10.2 mg; for **2**: 6.5 mg; for **3**: 6.7 mg; for PPh_3: 5.2 mg) were transferred in a Schlenck tube in the glove box. Toluene (2 mL), phenylboronic acid (135 mg, 1.1 mmol), K_3PO_4 (445 mg, 2.1 mmol), 2-methoxynaphthalene as internal standard (30 mg, 0.19 mmol) and 1 mmol of substrate (for **I**, 113.5 mg; for **III**, **V** and **VII**, 128.6 mg; for **X**, 193 mg) were then successively added under argon. The catalytic mixture was stirred at the desired temperature (80 or 100 °C) for some hours (from 2 to 72 h). The mixture was then diluted with toluene (*ca.* 2 mL), filtered and analyzed by GC to determine conversion, selectivity and yield.

Synthesis and Characterization of the Pd(II) Complex 1′-Pd

207 mg (0.29 mmol) of the Pd complex [*ortho*-Ph_2P-$(C_6H_4)BMes_2$]Pd(ma) **1-Pd** were dissolved in toluene (10 mL) under argon. Then 40 μL (0.36 mmol) of iodobenzene were added and the solution was stirred at 100 °C for 1 h. The black palladium formed upon heating was removed by filtration. The orange filtrate contains free ligand **1** along with the new complex **1′-Pd** (1:1 according to ^{31}P NMR). The volatiles were removed under vacuum. The brown solid residue was washed with pentane (5 mL) and diethyl ether (2.5 mL). Complex **1′-Pd** was purified by column chromatography (dichloromethane/pentane 1/1) and isolated as a yellow powder; yield: 55 mg (26%); mp 248–251 °C. Crystals suitable for XRD analysis were obtained by slow evaporation from a toluene solution. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$ (m, 2H, H_{arom}), 7.40 (m, 5H, H_{arom}), 7.27 (m, 5H, H_{arom}), 7.53 (m, 2H, H_{arom}), 6.81 (bs, 1H, mMes), 6.75 (bs, 1H, mMes), 6.70 (bs, 1H, mMes), 6.55 (bs, 1H, mMes), 4.63 (dd, 1H, CH_2-Pd, $J_{H,H} = 2$ Hz, $J_{H,P} = 8$ Hz), 2.93 (dd, 1H, CH_2-Pd, $J_{H,H} = 2$ Hz, $J_{H,P} = 13$ Hz), 2.45 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{11}B NMR (160.5 MHz, $CDCl_3$): $\delta = 52.8$; ^{31}P NMR (202.5 MHz, $CDCl_3$): $\delta = 39.8$; $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): $\delta = 161.78$ (d, $J_{C,P} = 43$ Hz, C_{ipso}-P), 145.83 (d, $J_{C,P} = 2$ Hz, C_{quat}), 144.41 (d, $J_{C,P} = 2$ Hz, C_{quat}), 142.40 (s, C_{quat}), 141.60 (s, C_{quat}), 138.51 (s, C_{quat}), 134.79 (d, $J_{C,P} = 43$ Hz, C_{ipso}-P), 133.88 (d, $J_{C,P} = 14$ Hz, CH_{arom}), 133.62 (d, $J_{C,P} = 20$ Hz, CH_{arom}), 133.24 (d, $J_{C,P} = 10$ Hz, CH_{arom}), 133.08 (d, $J_{C,P} = 3$ Hz, CH_{arom}), 133.00 (d, $J_{C,P} = 44$ Hz, C_{ipso}-P), 132.59 (bs, CH_{arom}), 131.19 (d, $J_{C,P} = 3$ Hz, CH_{arom}), 130.81 (d, $J_{C,P} = 2$ Hz, CH_{arom}), 130.43 (d, $J_{C,P} = 6$ Hz, CH_{arom}), 129.96 (d, $J_{C,P} = 2$ Hz, CH_{arom}), 129.04 (s, CH_{arom}), 128.99 (d, $J_{C,P} = 37$ Hz, C_{ipso}-B), 128.26 (d, $J_{C,P} = 11$ Hz, CH_{arom}), 128.12 (d, $J_{C,P} = 10$ Hz, CH_{arom}), 127.98 (s, CH_{arom}), 126.18 (d, $J_{C,P} = 3$ Hz, C_{quat}), 123.81 (d, $J_{C,P} = 3$ Hz, CH_{arom}), 107.90 (bs, C_{ipso}-B), 62.49 (d, $J_{C,P} = 39$ Hz, CH_2-Pd), 25.81 (s, CH_3), 25.67 (s, CH_3), 23.33 (s, CH_3), 21.45 (s, CH_3), 21.18 (s, CH_3), (one of the C_{ipso}-B is not seen); MS (FAB): $m/z = 742.526$, calculated

for $C_{36}H_{35}PBIPd$: 742.772; elemental analysis: calculated: C 58.16%, H 4.71%; found: C 57.95%, H 4.55%.

Synthesis of 2-Phenyl-3-nitro-6-chloropyridine, XI-C2

0.01 mmol of $[PdCl(cod)_2]$ (3.1 mg) and 0.02 mmol of ligand **2** (8.8 mg) were transferred in a Schlenck tube in the glove box. Toluene (2 mL), phenylboronic acid (135 mg, 1.1 mmol), K_3PO_4 (445 mg, 2.1 mmol), 2-methoxynaphthalene as internal standard (30 mg, 0.19 mmol) and 1 mmol of **X** (193 mg) were then successively added under argon. The mixture was stirred at 100 °C for 20 h. Toluene (*ca.* 2 mL) was then added and the reaction mixture was filtered on celite. After solvent evaporation, the crude was purified by column chromatography (silica, using pentane/diethyl ether = 95/5 as eluent). The product **XI-C2** was isolated as a colourless oil after two consecutive purifications by column chromatography; yield: 52 mg (26%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (d, 1H, $^3J_{H,H} = 8.4$ Hz, H-5-pyridine ring), 7.51 (m, 2H, phenyl group), 7.43 (m, 3H, phenyl group), 7.38 (d, 1H, $^3J_{H,H} = 8.4$ Hz, H-4-pyridine ring).

Its regioisomer, 2-chloro-3-nitro-6-phenylpyridine **XI-C6,**[37] was isolated from one of the separated fractions during the purification of **XI-C2**. It was crystallized from a diethyl ether/pentane solution and its structure was determined by X-ray diffraction analysis.

Synthesis of 2-Phenyl-3-nitro-6-(2′-methylphenyl)-pyridine, XII

0.01 mmol of $Pd(OAc)_2$ (2.25 mg) and 0.02 mmol of ligand **1** (10.2 mg) were transferred in a Schlenck tube in the glove box. Toluene (2 mL), *ortho*-tolylboronic acid (150 mg, 1.1 mmol), K_3PO_4 (445 mg, 2.1 mmol), 2-methoxynaphthalene as internal standard (30 mg, 0.19 mmol) and 1 mmol of **XI-C2** (222 mg) were then successively added under argon. The mixture was stirred at 80 °C for 22 h. Toluene (*ca.* 2 mL) was then added and the reaction mixture was filtered on celite. After solvent evaporation, the crude was purified by column chromatography (silica, using pentane/diethyl ether = 95/5 as eluent). The product **XII** was isolated as white powder; yield: 180 mg (62%). Single crystals suitable for X-ray diffraction analysis were obtained at 0 °C from a diethyl ether solution. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.14 (d, $^3J_{H,H} = 8.4$ Hz, H^5-pyridine ring), 7.55 (m, 2H), 7.47 (d, $^3J_{H,H} = 8.4$ Hz, H^4-pyridine ring), 7.40 (m, 4H), 7.27 (m, 3H), 2.40 (s, CH_3).

Synthesis of 2-(2′-Methylphenyl)-3-nitro-6-phenyl-pyridine, XIII

0.02 mmol of $Pd(OAc)_2$ (4.5 mg) and 0.04 mmol of ligand **1** (20.4 mg) were transferred in a Schlenck tube in the glove box. Toluene (4 mL), *ortho*-tolylboronic acid (405 mg, 3 mmol), 2-methoxynaphthalene as internal standard (60 mg, 0.38 mmol) and 2 mmol of **X** (386 mg) were then successively added under argon. The mixture was stirred at 80 °C for 5 h (91% conversion, as determined by GC). Phenylboronic acid (2.4 mmol, 280 mg), K_3PO_4 (890 mg, 4.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg) and ligand **1** (0.04 mmol, 20.4 mg) were then added and the mixture stirred at 80 °C for 15 h (selectivity of 63% in **XIII** according to GC). Toluene (*ca.* 2 mL) was then added and the reaction mixture was filtered on celite. After solvent evaporation, the crude was purified by column chromatography (silica, using pentane/diethyl ether = 95/5 as eluent). The product **XIII** was isolated as white powder after two consecutive purifications by column chromatography; yield: 331 mg (57%). Single crystals suitable for X-ray diffraction analysis were obtained from a diethyl ether solution. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.31$ (d, $^3J_{H,H} = 8.8$ Hz, H^5-pyridine ring), 8.06 (m, 2H), 7.84 (d, $^3J_{H,H} = 8.8$ Hz, H^4-pyridine ring), 7.43 (m, 4H), 7.22 (m, 3H), 2.70 (s, CH_3).

CCDC 915133, CCDC 915134, CCDC 915135, and CCDC 915136, contain the supplementary crystallographic data for compounds **1′-Pd**, **XI-C6**, **XII**, and **XIII**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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References

[1] a) I. J. S. Fairlamb, *Org. Biomol. Chem.* **2008**, *6*, 3645–3656; b) M.-N. Birkholz, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2009**, *38*, 1099–1118; c) I. Moreno, R. SanMartin, B. Ines, M. T. Herrero, E. Dominguez, *Curr. Org. Chem.* **2009**, *13*, 878–895; d) C. M. So, W. K. Chow, P. Y. Choy, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 7996–8001; e) C. Valenty, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* **2012**, *124*, 3370–3388; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314–3332; f) R. J. Lundgren, M. Stradiotto, *Chem. Eur. J.* **2012**, *18*, 9758–9769; g) H. Li, C. C. C. Johansson Seechurn, T. J. Colacot, *ACS Catal.* **2012**, *2*, 1147–1164.

[2] a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461–1473; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50.

[3] G. Bouhadir, A. Amgoune, D. Bourissou, *Adv. Organomet. Chem.* **2010**, *58*, 1–107.

[4] a) A. Boerner, J. Ward, K. Kortus, H. Kagan, *Tetrahedron: Asymmetry* **1993**, *4*, 2219–2228; b) B. F. M. Kimmich, C. R. Landis, D. R. Powell, *Organometallics* **1996**, *15*, 4141–4146.

[5] For reviews dealing with the coordination of ambiphilic phosphine-boranes ligands and related systems, see: a) I. Kuzu, I. Krummenacher, J. Meyer, F. Armbruster, F. Breher, *Dalton Trans.* **2008**, 5836–5865; b) F.-G. Fontaine, J. Boudreau, M.-H. Thibault, *Eur. J. Inorg. Chem.* **2008**, 5439–5454.

[6] For reviews dealing with borane complexes and the coordination of related σ-acceptor Z-type ligands, see:

a) H. Braunschweig, R. D. Dewhurst, A. Schneider, *Chem. Rev.* **2010**, *110*, 3924–3957; b) A. Amgoune, D. Bourissou, *Chem. Commun.* **2011**, *47*, 859–871; c) H. Braunschweig, R. D. Dewhurst, *Dalton Trans.* **2011**, *40*, 549–558.

[7] a) M. W. P. Bebbington, S. Bontemps, G. Bouhadir, M. J. Hanton, R. P. Tooze, H. van Rensburg, D. Bourissou, *New J. Chem.* **2010**, *34*, 1556–1559; b) R. Malacea, N. Saffon, M. Gómez, D. Bourissou, *Chem. Commun.* **2011**, *47*, 8163–8165.

[8] As biarylphosphines, *ortho*-(dimesitylboryl)phenylphosphines are inert to air oxidation: a) S. Porcel, N. Saffon, G. Bouhadir, L. Maron, D. Bourissou, *Angew. Chem.* **2010**, *122*, 6322–6325; *Angew. Chem. Int. Ed.* **2010**, *49*, 6186–6189; b) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

[9] a) W. H. Harman, J. C. Peters, *J. Am. Chem. Soc.* **2012**, *134*, 5080–5082; b) H. Kameo, H. Nakazawa, *Organometallics* **2012**, *31*, 7476–7484.

[10] For a general discussion on the ability of boranes to participate in ligand cooperation for hydrogen storage and related perspectives in catalysis, see: a) N. Tsoureas, G. R. Owen, A. Hamilton, A. G. Orpen, *Dalton Trans.* **2008**, 6039–6044; b) G. R. Owen, *Chem. Soc. Rev.* **2012**, *41*, 3535–3546.

[11] For selected contributions, see: a) N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1304–1306; *Angew. Chem. Int. Ed.* **2006**, *45*, 1282–1284; b) C. A. Fleckenstein, H. Plenio, *Green Chem.* **2007**, *9*, 1287–1291; c) K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366; d) C. Liu, W. Yang, *Chem. Commun* **2009**, 6267–6269; e) V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellogg, *Org. Proc. Res. Dev.* **2010**, *14*, 30–47; f) M. R. Kumar, K. Park, S. Lee, *Adv. Synth. Catal.* **2010**, *352*, 3255–3266; g) D. Zhao, J. You, C. Hu *Chem. Eur. J.* **2011**, *17*, 5466–5492.

[12] a) S. Caron, S. S. Massett, D. E. Bogle, M. J. Castaldi, T. F. Braish, *Org. Proc. Res. Dev.* **2001**, *5*, 254–256; b) C. A. Fleckenstein, H. Plenio, *Chem. Eur. J.* **2008**, *14*, 4267–4279; see also the contributions cited in ref.[14]

[13] For selected reviews, see: a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; b) D. S. Surry, S. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.

[14] For recent examples, see: a) T. Itoh, K. Sato, T. Mase, *Adv. Synth. Catal.* **2004**, *346*, 1859–1867; b) T. Itoh, T. Mase, *Tetrahedron Lett.* **2005**, *46*, 3573–3577; c) K. L. Billingsley, K. W. Anderson, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 3564–3568; *Angew. Chem. Int. Ed.* **2006**, *45*, 3484–3488; d) A. S. Guram, A. O. King, J. G. Allen, X. Wang, L. B. Schenkel, J. Chan, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, P. J. Reider, *Org. Lett.* **2006**, *8*, 1787–1789; e) A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, *J. Org. Chem.* **2007**, *72*, 5104–5112.

[15] For rare examples dealing with more reactive bromopyridines, see: a) M. Feuerstsein, H. Doucet, M. Santelli, *J. Organomet. Chem.* **2003**, *687*, 327–336; b) C. Liu, N. Han, X. Song, J. Qiu, *Eur. J. Org. Chem.* **2010**, 5548–5551; c) J. Zhang, Y. Wu, Z. Zhu, G. Ren, T. C. Mak, M. Song, *Appl. Organomet. Chem.* **2007**, *21*, 935–940.

[16] $PdCl_2(cod)$]/**1** catalyst led to a lower yield in **IX** than that obtained for the analogous catalytic system based on $[Pd_2(dba)_3]$ (33% *vs.* 86%, respectively), in contrast to the similar performance observed with phenylboronic acid (entries 1 and 2, Table 4).

[17] Less than 10% yield in the expected cross-coupling product was obtained under the conditions described for entries 11 and 12 in Table 4, using Pd/**1** and Pd/**2** catalytic systems.

[18] a) J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163; b) S. M. Reid, R. C. Boyle, J. T. Mague, M. J. Fink, *J. Am. Chem. Soc.* **2003**, *125*, 7816–7817; c) W. J. Marshall, V. V. Grushin, *Organometallics* **2003**, *22*, 555–562; d) U. Christmann, R. Vilar, A. J. P. White, D. J. Williams, *Chem. Commun.* **2004**, 1294–1295; e) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907–1912; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876; f) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; g) T. E. Barder, M. R. Biscoe, S. L. Buchwald, *Organometallics* **2007**, *26*, 2183–2192; h) S. Kozuch, J. M. L. Martin, *Chem. Commun.* **2011**, *47*, 4935–4937.

[19] Sluggish reactions were observed with 2-chloropyridine and 4-amino-2-chloropyridine.

[20] J.-H. Son, M. A. Pudenz, J. D. Hoefelmeyer, *Dalton Trans.* **2010**, *39*, 11081–11090.

[21] D. J. H. Emslie, B. E. Cowie, K. B. Kolpin, *Dalton Trans.* **2012**, *41*, 1101–1117.

[22] a) For 2-borataallyl Zr and Pd complexes, see: F. Jiang, P. J. Shapiro, F. Fahs, B. Twamley, *Angew. Chem.* **2003**, *115*, 2755–2757; *Angew. Chem. Int. Ed.* **2003**, *42*, 2651–2653; b) for 1-borataallyl Pt and Ni complexes, see: K. B. Koplin, D. J. H. Emslie *Angew. Chem.* **2010**, *122*, 2776–2779; *Angew. Chem. Int. Ed.* **2010**, *49*, 2716–2719; c) for borataalkene Ta complexes, see: K. S. Cook, W. E. Piers, R. McDonald, *Organometallics* **1999**, *18*, 1575–1577; K. S. Cook, W. E. Piers, R. McDonald, *Organometallics* **2001**, *20*, 3927–3937; d) for 1-bora-alkene and 1-bora-butadiene Fe and Co complexes, see: S. Helm, H. Nöth, *Angew. Chem.* **1988**, *100*, 1378–1384; *Angew. Chem. Int. Ed.* **1988**, *27*, 1331–1337; S. Channareddy, G. Linti, H. Nöth, *Angew. Chem.* **1990**, *102*, 222–224; *Angew. Chem. Int. Ed.* **1990**, *29*, 199–201; G. Gabbert, W. Weinmann, H. Pritzkow, W. Siebert, *Angew. Chem.* **1992**, *104*, 1670–1672; *Angew. Chem. Int. Ed.* **1992**, *31*, 1603–1605.

[23] The following limiting pathways can be envisioned: (i) oxidative addition of PhI at Pd followed by σ-metathesis between Ph at Pd and one of the Mes at B, (ii) C–H activation of a Mes ring at Pd followed by σ-metathesis with PhI and (iii) oxidative addition of PhI and C–H activation at Pd followed by reductive elimination of benzene.

[24] N. S. Towsend, A. B. Chaplin, M. A. Naser, A. L. Thompson, N. H. Rees, S. A. Macgregor, A. S. Weller, *Chem. Eur. J.* **2010**, *16*, 8376–8389.

[25] Cyclometallation involving geometrically available C–H bonds of P ligands has already been proposed to account for the decomposition of Pd catalysts. See, for example: a) U. Christmann, D. A. Pantazis, J. Benet-Buchholz, J. E. McGrady, F. Maseras, R. Vilar, *J. Am.*

Chem. Soc. **2005**, *128*, 6376–6390; b) C. Jimeno, U. Christmann, E. C. Escudero-Adán, R. Vilar, M. A. Pericàs, *Chem. Eur. J.* **2012**, *18*, 16510–16516.
[26] For selected contributions, see: a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; b) Y. Fernández Sainz, S. A. Raw, R. J. K. Taylor, *J. Org. Chem.* **2005**, *70*, 10086–10095, and references cited therein.
[27] For selected contributions, see: a) H.-L. Knong, H-L. Yeung, C.-T. Yeung, W-S. Lee, C-S. Lee, W-L. Wong, *Coord. Chem. Rev.* **2007**, 2188–2222; b) Y. You, S. Y. Park, *Dalton Trans.* **2009**, 1267–1282.
[28] For some selected recent reviews, see: a) Z. Ning, H. Tian, *Chem. Commun.* **2009**, 5483–5495; b) R. Lygaitis, V. Getaufis, J. V. Grazulevicius, *Chem. Soc. Rev.* **2008**, 770–788.
[29] For reviews, see: a) I. J. S. Fairlamb, *Chem. Soc. Rev.* **2007**, *36*, 1036–1045; b) S. Schröter, C. Stock, T. Bach, *Tetrahedron* **2005**, *61*, 2245–2267.
[30] For selected contributions, see: a) D. Conreaux, E. Bossharth, N. Monteiro, P. Desbordes, J.-P. Vors, G. Balme, *Org. Lett.* **2007**, *9*, 271–274; b) A. Tikad, S. Routier, M. Akssira, J.-M. Leger, C. Jarry, G. Guillaumet, *Org. Lett.* **2007**, *9*, 4673–4676; c) S. T. Handy, T. Wilson, A. Muth, *J. Org. Chem.* **2007**, *72*, 8496–8500; d) D. T. Tung, D. T. Tuan, N. Rasool, A. Villinger, H. Reinke, C. Fischer, P. Langer, *Adv. Synth. Cat.* **2009**, *351*, 1595–1609; e) F. Beaumard, P. Dauban, R. H. Dodd, *Org. Lett.* **2009**, *11*, 1801–1804; f) L. M. Daykin, J. S. Siddle, A. L. Ankers, A. S. Batsanov, M. R. Bryce, *Tetrahedron* **2010**, *66*, 668–675; g) J. L. Gustafson, D. Lim, K. T. Barrett, S. J. Miller, *Angew. Chem.* **2011**, *123*, 5231–5235; *Angew. Chem. Int. Ed.* **2011**, *50*, 5125–5129.
[31] W. Yang, Y. Wang, J. R. Corte, *Org. Lett.* **2003**, *5*, 3131–3134.
[32] For rationalization/prediction of the most reactive C–X bonds in polyhalogenated substrates, see: a) S. T. Handy, Y. Zhang, *Chem. Commun.* **2006**, 299–301; b) C. Y. Legault, Y. Garcia, C. A. Merlic, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 12664–12665.
[33] Catalysts based on the biarylphosphine **3** were in general less selective towards the formation of **XI-C2** (see Table S1 in the Supporting Information).
[34] T. W. Hudnall, Y.-M. Kim, M. W. P. Bebbington, D. Bourissou, F. P. Gabbaï, *J. Am. Chem. Soc.* **2008**, *130*, 10890–10891.
[35] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
[36] K. Itoh, F. Ueda, K. Hirai, Y. Ishii, *Chem. Lett.* **1977**, *6*, 877–880.
[37] R. Troschuetz, A. Karger, *J. Heterocyclic Chem.* **1996**, *33*, 1815–1821.

