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## LIGAND ASSESSMENT FOR THE SUZUKI-MIYAURA CROSS COUPLING REACTION OF ARYL AND HETEROARYL BROMIDES WITH *n*-BUTYLBORONIC ACID. THE ADVANTAGES OF BUCHWALD'S *S*-PHOS

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Dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday for his dynamic and memorable contributions to organic chemistry

**Abstract** – An investigation of biarylphosphine ligands for the Suzuki-Miyaura cross coupling reaction of aryl and heteroaryl bromides with *n*-butylboronic acid is presented. The results obtained on ligand modification and aryl as well as heteroaryl bromides variation represent a significant improvement in the state of the art of alkylboronic acid cross coupling methodology.

## INTRODUCTION

Transition metal catalyzed cross coupling reactions have forever changed the landscape of the C-C bond forming process, among which the Suzuki-Miyaura discovery provided, arguably, the major impact.<sup>1-3</sup> The discovery of the so-called B-alkyl Suzuki-Miyaura reaction<sup>4</sup> originally involved hydroboration to generate the trialkylborane derivatives among which 9-BBN became a widely used coupling partner.<sup>5</sup>

Practical applications associated with use of 9-BBN and other trialkylboranes are limited due to their sensitivity to air, as well as their pyrophoric nature and modest shelf life, leading to their normal use by *in situ* generation which limited their use in large-scale applications.<sup>6,7</sup> A derivative of 9-BBN has been investigated as an alternative in the B-alkyl Suzuki-Miyaura cross-coupling.<sup>8</sup> In recent years, the wider commercial availability of alkylboronic acids<sup>9</sup> constitutes evidence of the growing interest of  $sp^3$  boronic acid coupling reactions, in particular for the synthesis of linear and branched alkyl aromatics.<sup>10</sup> Significantly, medicinal chemistry research is adapting alkylboronic acids for the selective introduction of alkyl groups in compounds of biological interest.<sup>11</sup> In terms of availability, although alkyl aromatic compounds abound from petroleum distillates, and are obtained by fractionation and are, at least currently, inexpensive commercial commodities,<sup>12</sup> their synthesis is usually bypassed in lieu of acylation using the Friedel-Crafts reaction and reduction which is thereby bound by the  $S_EAr$  rules and controlled in regioselectivity by present substituents.<sup>13</sup>

Recent developments in cross couplings of alkylboronic acids with aryl halides have overcome the original use of toxicologically unacceptable metals (thallium or silver)<sup>2,5</sup> and by application, for example, of trifluoroalkylborates,<sup>14</sup> dialkyl pinacolborates,<sup>15</sup> as well as dialkyl pinacolborates as boronic acid partners in the presence of a ligand e.g. RuPhos<sup>16</sup> or under copper-catalysis conditions.<sup>17</sup> In further advances, effective ligands and palladacycles for the B-alkyl Suzuki-Miyaura cross-coupling have been developed which, however, comprise lengthy synthesis and/or greater instability of the used palladacycles.<sup>18,19</sup> Thus, to date the Suzuki-Miyaura reaction of aryl halides with alkylboronic acids has witnessed only a few reports and these show moderate yields of products and lack of generalization.<sup>20</sup>

## RESULTS AND DISCUSSION

Herein we present our study on the Suzuki-Miyaura reaction of aryl bromides with *n*-butylboronic acid under a variety of conditions (base, solvent, temperature variation) using pre-catalyst **1** and ligands **2-5** (Figure 1) which, to the best of our knowledge, are not thoroughly investigated ligands in Pd-catalyzed cross coupling reactions of alkylboronic acids and therefore may provide additional synthetic potential in the increasingly active field of alkyl-C bond forming reactions.<sup>21-23</sup>

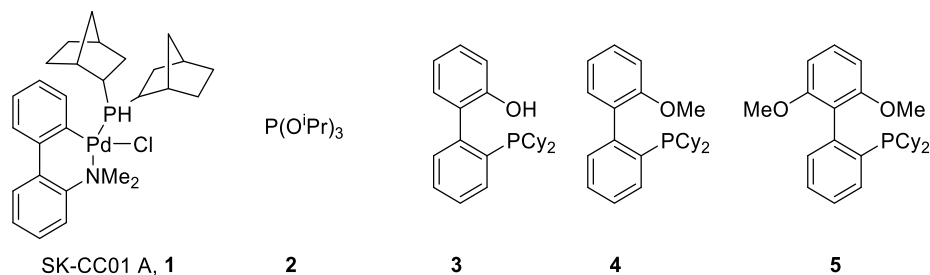
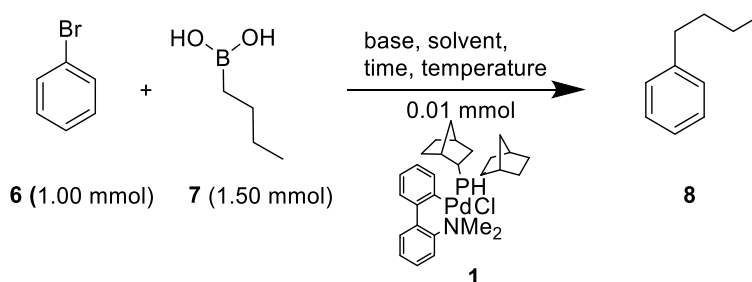


Figure 1. Ligands used in this work for the Suzuki-Miyaura cross coupling reaction of *n*-butylboronic acids

Table 1. Optimization of the Suzuki-Miyaura reaction of bromobenzene **6** with *n*-butylboronic acid **7** using pre-catalyst **1**

Entry	base, equiv	solvent	conversion [a/a %] 60 °C, 19 h <sup>a</sup>	conversion [a/a %] 105 °C, 24 h <sup>a</sup>
1	K <sub>3</sub> PO <sub>4</sub> , 3	THF	14	quant
2	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	THF	18	80
3	K <sub>3</sub> PO <sub>4</sub> , 3	dioxane	27	97
4	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	dioxane	13	97
5	3N NaOH, 3	dioxane	35	quant
6	K <sub>3</sub> PO <sub>4</sub> , 3	DMAc	< 5	quant
7	K <sub>3</sub> PO <sub>4</sub> , 3	toluene	56	quant
8	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	toluene	66	quant
9	3N NaOH, 3	toluene	6	quant
10	K <sub>3</sub> PO <sub>4</sub> , 3	THF	n.a.	65 <sup>b</sup>

<sup>a</sup> Conversion based on GC-MS analysis without product isolation and purification, [a/a%: ratio of product peak area / total area]; <sup>b</sup> Only 1.10 mmol of *n*-butylboronic acid was used in the reaction.

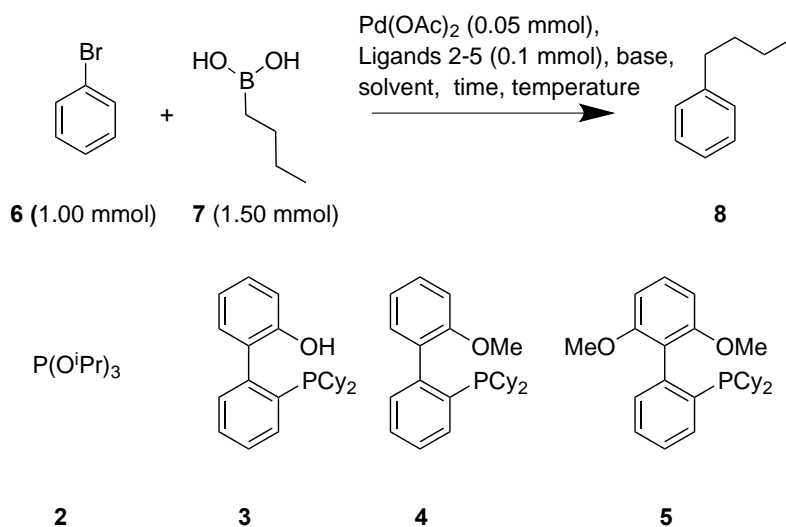
To initiate our study, the commercially available pre-catalyst ligand system **1** was screened in the reaction of bromobenzene (**6**) with *n*-butylboronic acid (**7**) to form *n*-butylbenzene (**8**) (Table 1) as a function of base and solvent (Table 1).<sup>24</sup> High conversions were achieved using THF (entries 1-2), dioxane (entries 3-5) and toluene (entries 7-9) as solvents. Extending the reaction time generally improved the yields but not of product purity. Using 3 equiv of K<sub>3</sub>PO<sub>4</sub> proved to be effective in four different solvents (entries 1, 3, 6 and 7) and, interestingly, use of this base in DMAc (see SI) was the only effective combination (entry 6). Two other bases (3 equiv of K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> (10:1 ratio) and 3N NaOH gave good observed conversion rates (entries 2, 4, 5, 8 and 9). Interestingly, using the combination 3 equiv of K<sub>3</sub>PO<sub>4</sub> as base and THF as solvent, the reaction showed good conversion using only 1.10 mmol of *n*-butylboronic acid (entry 10).

Based on the above results, optimized conditions (K<sub>3</sub>PO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> (ratio 10:1) and 3N NaOH in THF, dioxane, DMAc or toluene at 120 °C) were applied for the investigation of the prototype cross

coupling reactions of bromobenzene (**6**) with *n*-butylboronic acid (**7**) using ligands **2** - **5** and Pd(OAc)<sub>2</sub> as catalyst.

The results on the scope of the reaction, summarized in Table 2, merit brief commentary. The non-aryl-phosphine ligand P(*Oi*-Pr)<sub>3</sub> (**2**) was found to be effective for cross coupling reactions using the K<sub>3</sub>PO<sub>4</sub>/THF (entry 4), dioxane (entry 1), 3N NaOH/THF-5% H<sub>2</sub>O (entry 3), and 3N NaOH/*i*-PrOH (entry 2) combinations although, once more, solvent is critical (compare entries 4 and 5) and several systems produced low or moderate yielding results (see SI). The 2'-(dicyclohexylphosphino)[1,1'-biphenyl]-2-ol (**3**)<sup>25</sup> showed excellent conversion to *n*-butylbenzene (**8**) under K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub>/THF (entry 8), K<sub>3</sub>PO<sub>4</sub>/toluene (entry 7), and Na<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> (ratio 10:1)/toluene (entry 6) base-solvent combinations although extended reaction times (> 19 h) and higher (> 60 °C) were required. Surprisingly using dioxane, DMAc and THF as solvents and K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> (ratio 10:1) as bases gave disparately different results for ligand **3** compared with the pre-catalyst (**1**) (compare SI Table 2, entries 7-9 with Table 1, entries 2, 6, and SI Table 1, entry 10). A shift from the K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> to the Na<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> (ratio 10:1) combinations led to the result of quantitative conversion after 45 h at 105 °C (compare entries 6 and 8). On the other hand, the Na<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> in toluene conditions were a less effective combination for ligand **1** while being reasonably successful for ligand **3** (SI, Table 1, entries 11 and Table 2, entry 6). Ligand 2-(dicyclohexylphosphino)-2'-methoxy-1,1'-biphenyl (**4**)<sup>26</sup> the corresponding methyl ether of **3**, gave synthetically useful results for a number of base-solvent combinations as shown in Table 2, entries 9-16. Thus, reaction of K<sub>3</sub>PO<sub>4</sub> in THF (entry 12), toluene (entry 10), and dioxane (entry 11) were complete after 45 h/105 °C conditions with the latter two reactions proceeding at lower temperatures (60 °C) and shorter reaction times (entries 10 and 11). A change to 3N NaOH in *i*-PrOH gave quantitative conversion after 35 h at 105 °C (entry 9). A major impact of solvent effects on the Suzuki-Miyaura coupling reaction is evident in our studies since, as observed in another comparison, very different results were observed for ligands **2-5** and **1** in reactions using 3N NaOH/dioxane combination (compare SI, Table 2, entries 5, 10, 11, 13, and Table 1, entry 5).

Table 2. Pd(OAc)<sub>2</sub>-Catalyzed Suzuki-Miyaura reaction of bromobenzene **6** with *n*-butylboronic acid **7** using ligands **2-5**. Variation of conditions.



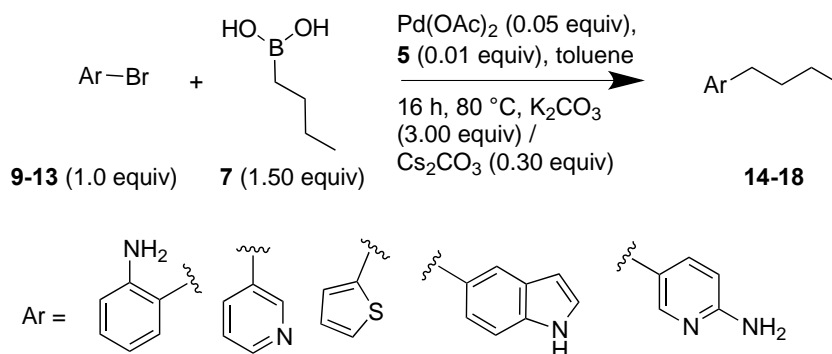
Entry	Ligand	base, equiv	solvent	conversion, [a/a%] 60 °C, 19 h <sup>a</sup>	conversion, [a/a%] 105 °C, 24 h <sup>a</sup>
1	<b>2</b>	K <sub>3</sub> PO <sub>4</sub> , 3	dioxane	quant	quant
2	<b>2</b>	3N NaOH, 3	<i>i</i> -PrOH	1	quant
3	<b>2</b>	3N NaOH, 3	THF / 5% H <sub>2</sub> O	10	97
4	<b>2</b>	K <sub>3</sub> PO <sub>4</sub> , 3	THF	---	92
5	<b>2</b>	K <sub>3</sub> PO <sub>4</sub> , 3	toluene	---	68
6	<b>3</b>	Na <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	toluene	---	quant
7	<b>3</b>	K <sub>3</sub> PO <sub>4</sub> , 3	toluene	---	90
8	<b>3</b>	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	THF	---	82
9	<b>4</b>	3N NaOH, 3	<i>i</i> -PrOH	16	quant
10	<b>4</b>	K <sub>3</sub> PO <sub>4</sub> , 3	toluene	98	98
11	<b>4</b>	K <sub>3</sub> PO <sub>4</sub> , 3	dioxane	92	96
12	<b>4</b>	K <sub>3</sub> PO <sub>4</sub> , 3	THF	74	96
13	<b>4</b>	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	dioxane	53	95
14	<b>4</b>	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	toluene	75	94
15	<b>4</b>	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	THF	28	82
16	<b>4</b>	3N NaOH, 3	toluene	11	74
17	<b>5</b>	K <sub>3</sub> PO <sub>4</sub> , 3	THF	quant	quant
18	<b>5</b>	K <sub>3</sub> PO <sub>4</sub> , 3	toluene	quant	quant
19	<b>5</b>	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	THF	65	quant
20	<b>5</b>	3N NaOH, 3	toluene	39	quant
21	<b>5</b>	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	toluene	quant	quant (73 %) <sup>b</sup>

22	5	3N NaOH, 3	<i>i</i> -PrOH	4	quant
23	5	K <sub>3</sub> PO <sub>4</sub> , 3	THF / 5% H <sub>2</sub> O	quant	quant
24	5	3N NaOH, 3	THF / 5% H <sub>2</sub> O	22	quant
25	5	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	THF / 5% H <sub>2</sub> O	48	quant
26	5	K <sub>3</sub> PO <sub>4</sub> , 3	dioxane	98	98
27	5	Na <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	dioxane	78	96
28	5	K <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	dioxane	35	85
29	5	Na <sub>2</sub> CO <sub>3</sub> , 3 + Cs <sub>2</sub> CO <sub>3</sub> , 0.3	toluene	63	81

<sup>a</sup> Conversion based on GC-MS analysis without product isolation and purification, [a/a%: ratio of product peak area / total area]; <sup>b</sup> Yield of isolated product.

As a final ligand, the extensively used 2-(dicyclohexylphosphino)-2'-methoxy-1,1'-biphenyl (*S*-Phos) ligand (**5**) was investigated.<sup>27</sup> A selection of the results is displayed in Table 2 (entries 19-27; for additional data, see SI). Thus, K<sub>3</sub>PO<sub>4</sub> as base in combination with a variety of solvents (THF, toluene, dioxane and THF/5% H<sub>2</sub>O, entries 17, 18, 23, and 26 respectively) successful led to nearly quantitative conversion even at lower temperatures (60 °C) and shorter reaction times (19 h). Reactions using K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub> (10:1), in THF (entry 19) toluene (entry 21), THF/5% H<sub>2</sub>O) (entry 25) and dioxane (entry 28) and 3N NaOH solution in toluene (entry 20), in *i*-PrOH (entry 22), and in THF/5% H<sub>2</sub>O (entry 24) showed good conversion rates at lower temperatures (60 °C) but these reactions went to completion at 105 °C after 45 h reflux with the exception of the reaction in dioxane (entry 28). The difference in conversion rates may be gleaned from comparison of the conditions of 3N NaOH/*i*-PrOH: full conversion at 105 °C after 45 h (entry 22) vs only 4% conversion after 19 h at 60 °C. These results may be compared to those of ligand **4** using the same parameters.

With the establishment of compounds **3-5** and, in particular, ligand **5** (*S*-Phos) as robust and practical ligands for the cross coupling reaction of bromobenzene (**6**) with *n*-butylboronic acid (**7**), we ventured to test the cross coupling of *n*-butylboronic acid with a selected group of substituted aryl and heteroaryl bromides using the favorable ligand **5** (*S*-Phos) (Scheme 1 and entries of Table 3) after some minor variation of the reaction conditions to achieve more practical usage.

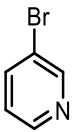
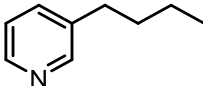
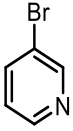
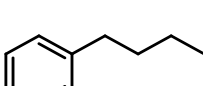
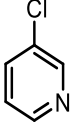
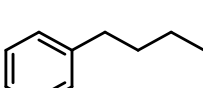

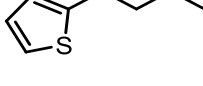

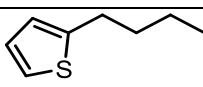
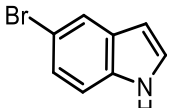
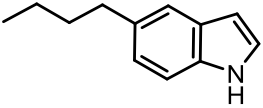
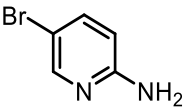
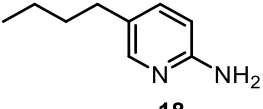


Scheme 1. Suzuki-Miyaura reaction of aryl and heteroaryl bromides with *n*-butylboronic acid **7** using ligand **5**

Thus, 2-bromoaniline (**9**) and 3-bromopyridine (**10**) undergo coupling with *n*-butylboronic acid **7** to give products **14** and **15** respectively (Table 3). Of interest is the lack of significant interference of the primary amine substituent in the coupling process.<sup>28</sup> Likewise, 2-bromothiophene (**11**) provides the corresponding 2-butylthiophene **16**, albeit in very low yield presumably due to the known competitive protodeboronation.<sup>2d,5d</sup> 5-Bromoindole (**12**) and 2-amino-5-bromopyridine (**13**) failed to furnish the cross coupling product **17** and **18** respectively. The potential action of 2-amino-5-bromopyridine (**13**) as a bidentate ligand for the palladium catalyst may be in part responsible for its failure to undergo cross coupling. A cursory examination of other methods of preparation shows comparable yields for compounds **14**, **15**, and **16** by classical and Corriu-Kumada methods (compare entries 1 and 2, entries 3, 4 and 5 as well as entries 6 and 7).

Table 3. Suzuki-Miyaura reaction of aryl and heteroaryl bromides with *n*-butylboronic acid **7** using ligand **5**

Entry	aryl bromide	product	yield <sup>a</sup> (%)
1			64
2			1. <i>n</i> -PrMgBr, Et <sub>2</sub> O 2. KOH, N <sub>2</sub> H <sub>4</sub> , triethylene glycol (73) <sup>b</sup>

3	 10a	 15	67
4	 10a	 15	<i>n</i> -BuMgBr, NiCl <sub>2</sub> *(dppp), THF, rt (47) <sup>c</sup>
5	 10b	 15	<i>n</i> -BuMgCl, MnCl <sub>2</sub> *THF, THF, rt (47) <sup>d</sup>
6	 11	 16	11
7	 11	 16	NiCl <sub>2</sub> *(dppp), THF, rt (8) <sup>e</sup>
8	 12	 17	no reaction
9	 13	 18	no reaction

<sup>a</sup> Yield of isolated product; <sup>b</sup> crude product;<sup>29</sup> <sup>c</sup> isolated product;<sup>30a</sup> <sup>d</sup> based on <sup>1</sup>H NMR (mesitylene internal standard);<sup>30b</sup> <sup>e</sup> isolated product.<sup>30a</sup>

## CONCLUSIONS

In conclusion, through a comprehensive investigation, we have demonstrated favorable ligands and base/solvent combinations for effective conditions for the cross coupling reaction of bromobenzene with *n*-butylboronic acid to yield 1-*n*-butylbenzene (**8**), representing a prototype Pd-catalyzed Suzuki-Miyaura reaction of sp<sup>3</sup>-alkylboronic acids. Our study, involving ligands **1-5** and broad variations of base/ligand combinations, has positioned ligand **5** (*S*-Phos) as a very conditions-forgiving system for a number of base/solvent combinations to give high or quantitative yields of product. The commercial availability of

ligands **3** and **4** on multigram scale by simple synthesis<sup>25,26</sup> and the convenient, robust and non-chromatography dependent processing of the coupling reaction bodes well for the broader utility of our established protocol. In view of the increasing utility of sp<sup>3</sup>-C bond forming reactions using alkylboronic acids<sup>1-5</sup> as well as their commercial availability, potential further implementation of the reported cross coupling regimens may be anticipated.

## ACKNOWLEDGEMENTS

We are grateful to NSERC Canada for partial support through the Discovery Grant (DG) Program. Thomas Jagusch thanks Clariant AG for a postdoctoral fellowship.

## EXPERIMENTAL

All reactions were performed in flame- or oven-dried glassware under argon, using syringe-septum cap techniques. All ligands were obtained from commercial sources and were used without further purification. Palladium(II) acetate was obtained from Aldrich and used without further purification. Preparative flash column chromatography was performed on Silica-P Flash Silica Gel from Silicycle Chemical Division silica gel. TLC was carried out on aluminium sheets 40-63  $\mu\text{m}$ , 500 m<sup>2</sup>/g F<sub>254</sub> purchased from Merck KGaA, NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer. Mass spectra were recorded on a Micromass 70-250S double focusing mass spectrometer (EI) or Waters ZQ Single Quad mass spectrometer (ESI). The conversion of the cross coupling reactions was determined on an HP 6890 Gas Chromatography apparatus using a 20% permethylated/ $\beta$ -cyclodextrin column via a/a% determination: ratio of product peak area / total area\*100%.

### General procedure using ligand **1**

A mixture of bromobenzene (1.00 mmol), *n*-butylboronic acid (1.50 mmol), base(s), solvent(s) (5 mL) and [bis(bicyclo[2.2.1]hept-2-yl)phosphine]chloro[2'-(dimethylamino- $\kappa$ N)[1,1'-biphenyl]-2-yl- $\kappa$ C]palladium (**1**) (0.01 mmol) was heated to 60 °C for 19 h and the progress of the reaction was analyzed by GC-MS. The reaction temperature was increased to 105 °C and maintained for 24 h and the progress of the reaction was analyzed by GC-MS.

### General procedure using ligands **2-5**

A mixture of bromobenzene (1.00 mmol), *n*-butylboronic acid (1.50 mmol), base(s), solvent(s) (5 mL), palladium acetate (0.05 mmol) and ligand (**2-5**) (0.10 mmol) was heated to 60 °C for 19 h, unless otherwise indicated, and the progress of the reaction was analyzed by GC-MS. The reaction temperature was increased to 105 °C and maintained for 24 h and progress of the reaction was analyzed by GC-MS.

***n*-Butylbenzene (8)**

*n*-Butylboronic acid (3.75 g, 36.8 mmol), K<sub>2</sub>CO<sub>3</sub> (10.4 g, 75.2 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (2.50 g, 7.67 mmol) were suspended in toluene (125 mL) and degassed. Under an argon atmosphere, bromobenzene (2.57 mL, 24.5 mmol), *S*-Phos (105 mg, 0.25 mmol) and palladium acetate (280 mg, 1.25 mmol) were added. The orange, quickly darkening, suspension was heated to 80 °C for 16 h. The reaction flask was opened to the atmosphere and water (50 mL) was added. Stirring was continued for 1 h, during which a dark emulsion formed. The phases were separated and the aqueous layer (and the dark emulsion) were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL) and the emulsion was removed at the last extraction step. The combined extracts were successively washed with saturated NaHCO<sub>3</sub> (50 mL) solution and brine. The organic layer was treated with activated charcoal and dried over Na<sub>2</sub>SO<sub>4</sub>. The product solution was concentrated on a rotary evaporator, and the residue was subjected to micro-scale distillation under vacuo (3 mbar) yielding 2.42 g (73%) of *n*-butylbenzene, bp 35–36 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 0.86 (t, *J* = 7.0 Hz, 3H), 1.23–1.36 (m, 2H), 1.49–1.59 (m, 2H), 2.53–2.59 (m, 2H), 7.16–7.29 (m, 5H) ppm. <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 13.70, 21.71, 33.16, 34.82, 125.49, 128.12, 128.17, 142.21 ppm; IR (neat): ν 3026 (w), 2956 (m), 2928 (m), 2858 (w), 1496 (m), 1453 (m), 741 (s), 695 (s), 569 (w), 507 (w), 494 (w), cm<sup>-1</sup>. The NMR data were in agreement with that reported.<sup>31</sup>

***2-n*-Butylaniline (14)**

*n*-Butylboronic acid (382 mg, 3.75 mmol), K<sub>2</sub>CO<sub>3</sub> (1.04 g, 7.5 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (245 mg, 0.75 mmol) were suspended in toluene (12 mL) in a Schlenk tube and subjected to four freeze-pump-thaw cycles. Under an argon atmosphere, 2-bromoaniline (283 μL, 2.5 mmol), *S*-Phos (11 mg, 0.03 mmol) and palladium acetate (28 mg, 0.13 mmol) were sequentially added. The orange, quickly darkening suspension was heated to 80 °C for 16 h. The reaction mixture was cooled to room temperature and opened to the atmosphere. Water (20 mL) and NaOH (1 mL, 5 M) were added. Stirring was continued for 1 h, during which time a dark emulsion formed. The phases were separated, the aqueous layer (and the dark emulsion) were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL) and the emulsion was removed during the phase separation in the last extraction step. The combined extracts were washed with 50 mL of 1 M NaOH. The organic layer was treated with activated charcoal, dried over Na<sub>2</sub>SO<sub>4</sub> and after filtration the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrolether 1:9 → EtOAc:petrolether:triethylamine 20:80:1) yielded 239 mg of a slightly orange liquid (64%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.27–1.39 (m, 2H), 1.43–1.53 (m, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 4.73 (br s, 2H), 6.44–6.49 (m, 1H), 6.57–6.59 (m, 1H), 6.83–6.89 (m, 2H) ppm. <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 13.89, 22.14, 30.32, 30.58, 114.55, 116.17, 125.38, 126.21, 128.82, 145.85 ppm. The NMR data were in agreement with that reported.<sup>29</sup>

### 3-*n*-Butylpyridine (15)

*n*-Butylboronic acid (764 mg, 7.5 mmol), K<sub>2</sub>CO<sub>3</sub> (2.08 g, 15 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (490 mg, 1.5 mmol) were suspended in toluene (20 mL) in a Schlenk tube and subjected to four freeze-pump-thaw cycles. Under an argon atmosphere, 3-bromopyridine (480 μL, 5 mmol), *S*-Phos (21 mg, 0.05 mmol) and palladium acetate (56 mg, 0.25 mmol) were added. The orange, quickly darkening suspension, was heated to 80 °C for 16 h. The reaction flask was cooled to room temperature and opened to the atmosphere. Water (20 mL) and NaOH (1 mL, 5 M) were added. Stirring was continued for 1 h, during which a dark emulsion formed. The phases were separated and the aqueous layer (and the dark emulsion) were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL) and the emulsion was removed during the phase separation in the last extraction step. The combined extracts were washed with 50 mL of 1 M NaOH. The organic layer was treated with activated charcoal, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrolether 1:9 → EtOAc:petrolether:triethylamine 20:80:1) yielded 450 mg of a slightly yellow liquid (67%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.23–1.35 (m, 2H), 1.50–1.60 (m, 2H), 2.58 (t, *J* = 6.5 Hz, 2H), 7.26–7.31 (m, 1H), 7.59–7.62 (m, 1H), 8.37–8.42 (m, 2H) ppm; <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 13.46, 21.60, 31.78, 32.75, 123.13, 135.40, 137.35, 146.89, 149.45 ppm; IR (neat): ν 2927 (m), 2856 (m), 1718 (m), 1587 (m), 1467 (m), 1425 (m), 1267 (s), 1248 (s), 1102 (s), 1023 (s), 796 (s), 730 (s), 712 (s), 623 (s), 538 (s) cm<sup>-1</sup>. The NMR data were in agreement with that reported.<sup>30</sup>

### 2-*n*-Butylthiophene (16)

*n*-Butylboronic acid (764 mg, 7.50 mmol), K<sub>2</sub>CO<sub>3</sub> (2.08 g, 15.0 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (490 mg, 1.50 mmol) were suspended in toluene (20.0 mL) in a Schlenk tube and subjected to four freeze-pump-thaw cycles. Under an argon atmosphere, 2-bromothiophene (480 μL, 5.00 mmol), *S*-Phos (21.0 mg, 0.05 mmol) and palladium acetate (56.0 mg, 0.25 mmol) were added. The initially orange, quickly darkening suspension was heated to 80 °C for 16 h, cooled to room temperature and opened to the atmosphere. Water (20 mL) was added and the whole was stirred for 1 h, during which time a dark emulsion formed. The phases were separated and the aqueous layer including the dark emulsion were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The emulsion was removed during the phase separation in the last extraction step. The combined extracts were washed with saturated aqueous NaHCO<sub>3</sub> (50 mL). The organic layer was treated with activated charcoal, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (petrolether → EtOAc:petrolether 1:19) yielded 80 mg of a slightly yellow liquid (11%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.20–1.45 (m, 2H), 1.49–1.60 (m, 2H), 2.75 (m, *J* = 7.0 Hz, 2H), 6.75 (dd, *J* = 6.9/2.2 Hz, 1H), 6.90 (t, *J* = 6.9 Hz, 1H), 7.05 (dd, *J* = 6.9/2.2, 1H,) ppm; <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 13.62, 21.55, 29.77, 33.46, 123.98, 125.29, 126.80, 128.26 ppm; IR

(neat):  $\nu$  3422 (b), 2923 (m), 2853 (m), 1718 (m), 1416 (w), 1267 (s), 1206 (s), 1102 (s), 1023 (s), 1004 (s), 826 (s), 730 (s), 688 (s),  $\text{cm}^{-1}$ . The NMR data were in agreement with that reported.<sup>30a, 32</sup>

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