Synthesis of 2-Diphenylphosphinoyl-2'-Halo Biphenyls *Via* Suzuki-Miyaura Coupling as Possible Route to Non-Symmetric Biphenyl Phosphines

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Abstract: The preparation of 2-diphenylphosphinoyl-2'-halogenated biphenyls led to gaining interesting insight into the Suzuki-Miyaura coupling of *ortho*-halogenated penylboronic acids. Advantages and limitations on the use of halogenated biphenyls for the synthesis of diphosphine ligands are presented.

Keywords: Suzuki-Miyaura coupling, biphenyl phosphines, palladium catalysis, ligand synthesis.

INTRODUCTION

Phosphines play a very important role in homogeneous catalysis, with the choice of ligand often being the crucial factor determining the success of a reaction [1,2]. In particular, those possessing novel electronic and steric properties and functional groups are of great interest, as they can have beneficial effects on metal catalysed reactions in a homogeneous or multiphasic solution. A class of ligands explored. Hayashi showed that BIPHEP is an excellent ligand for C–C and C–N bond formation [3,4]. In an interesting development by Mikami, the dynamic axial chirality of BIPHEP-type ligands has been successfully exploited in asymmetric transformations through asymmetric activation [5,6]. Several chiral derivatives of BIPHEP are known and have been used in a number of asymmetric reactions, including asymmetric hydrogenation [7].

Table 1. Suzuki-Miyaura Coupling of 1 with 2a

Entry[a]	Cat. (mol%)	T (°C)	Base	Ligand (equiv.)	Yield (%)
1	Pd(OAc)$_2$,3	101	K$_3$PO$_4$	PPh$_3$,2	5
2	Pd(OAc)$_2$,10	101	K$_3$PO$_4$	PPh$_3$, 2	15
3	Pd$_2$(dba)$_3$,10	101	KF	PPh$_3$,2	Trace
4	Pd$_2$(dba)$_3$,10	101	KF	PCy$_3$,2	Trace
5	Pd$_2$(dba)$_3$,10	101	KF	P^{t}Bu$_3$,2	-
6	Pd(OAc)$_2$,10	101	KF	PPh$_3$,4	15
7	Pd(OAc)$_2$,10	80	NaOCH$_3$	PPh$_3$,8	Trace
8[b]	Pd(OAc)$_2$,10	80	NaOCH$_3$	PPh$_3$,8	Trace
9	Pd$_2$(dba)$_3$,10	80	NaOCH$_3$	PPh$_3$,4	Trace
10[b]	Pd$_2$(dba)$_3$,10	80	NaOCH$_3$	PPh$_3$,4	Trace
11	Pd(OAc)$_2$,10	80	NaO^{t}Bu	PPh$_3$,8	Trace
12[b]	Pd(OAc)$_2$,10	80	NaO^{t}Bu	PPh$_3$,8	Trace
13	Pd$_2$(dba)$_3$,10	80	NaO^{t}Bu	PPh$_3$,4	Trace
14[b]	Pd$_2$(dba)$_3$,10	80	NaO^{t}Bu	PPh$_3$,4	Trace
15[c]	Pd(OAc)$_2$,10	101	K$_3$PO$_4$	PPh$_3$,2	30

[a] Reaction conditions: all reactions were performed in dioxane for 15 h, using 1 equiv. of **1** and 1.5 equiv. of boronic acid **2a**. [b] The reaction was performed in toluene. [c] The boronic acid was dissolved in 10 mL of dioxane and added dropwise (1 mL/h).

worthy of note is that containing *ortho*-substituted biphenyl backbones; among these 2,2'-bis(diphenylphosphino) biphenyl (BIPHEP) and its derivatives are probably the best known, although their chemistry has not been extensively

One of the oldest methods to access biphenyls is to generate benzyne in the presence of an aromatic lithium or magnesium compound. The addition of the organometallic species to benzyne can produce an *ortho*-metallated biphenyl, which can subsequently be quenched with an electrophile. This was the principal behind the synthesis of biphenyl-based ligands reported by Buchwald [8-10]. We recently reported an improved synthesis of 2,2'-disubstituted

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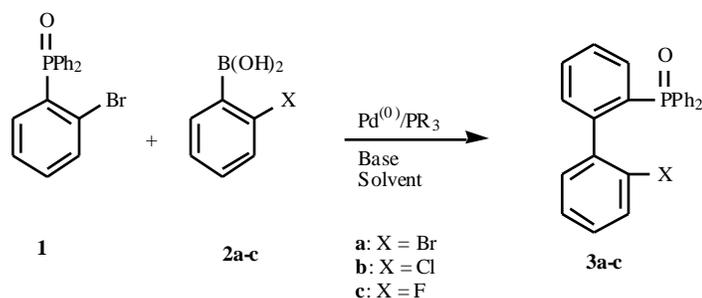
Scheme 1. Suzuki coupling for the synthesis of **3**.

biphenyl ligands by the Suzuki-Miyaura cross coupling of various boronic acids [11,12]. However these reactions could only achieve monophosphine ligands. The synthesis of 2,2'-biphenyl phosphines has relied on the Ulmann coupling of *ortho*-iodobenzene derivatives with the limitation of being able to synthesize only symmetric phosphine ligands [6,13,14]. In this context, 2-diphenylphosphinoyl-2'-halogenated biphenyls could open a new route for the preparation of symmetric and non-symmetric 2,2'-biphenyl-based bisphosphines. Herein we report the preparation of 2-

RESULTS AND DISCUSSION

2-Diphenylphosphinoyl-2'-halobiphenyls **3** could be generated by the Suzuki-Miyaura coupling of 2-bromophenyl-diphenylphosphino oxide **1** with the 2-halogenated phenylboronic acids **2**, as shown in Scheme **1**. However, when 2-bromophenyl boronic acid **2a** was reacted with **1** in dioxane in the presence of Pd(OAc)$_2$ and PPh$_3$, only 5% yield of the expected product **3a** was isolated after 15 h reaction time.
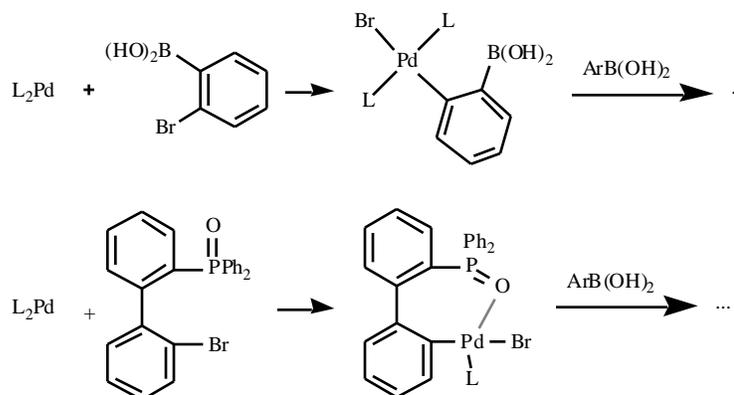
Scheme 2. Possible cause for the slow coupling of **1** with **2a**.

diphenylphosphinoyl-2'-halogenated biphenyls *via* Suzuki-Miyaura coupling of *ortho*-halogenated phenylboronic acids. Advantages and limitations on the use of halogenated biphenyls for the synthesis of bisphosphine ligands are also shown.

Various reaction conditions were screened in order to optimize the yield (Table **1**). No significant improvement was achieved from the third to the 14th entries. Only the use of K$_3$PO$_4$ or KF as base (entries 2 and 6) affordedreasonable amounts of product, and no improvement was observed
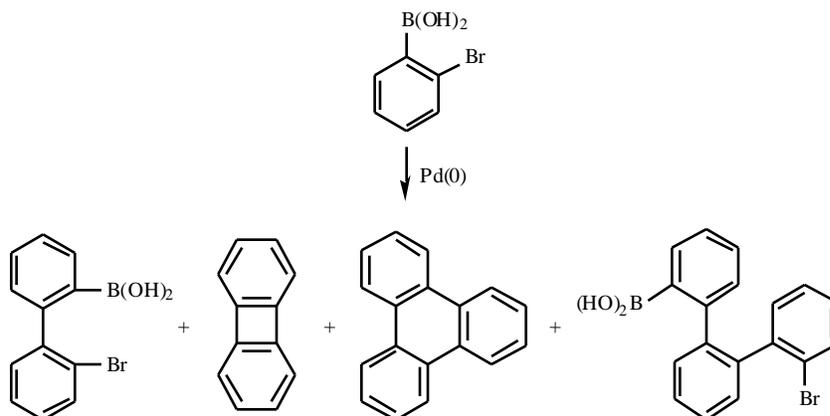
Scheme 3. Self-coupling reaction of **2a**.

either by lowering the temperature from 101 °C to 80 °C or by using different phosphine ligands. The best results were obtained using Pd(OAc)$_2$ (10 mol%), dioxane, PPh$_3$, K$_3$PO$_4$ or KF at 101 °C. The yield appears to be dependent on the percentage of catalyst used. Thus, when 3 mol% of Pd(OAc)$_2$ was used, the product was isolated in 5% yield, and increasing the catalyst loading to 10 mol% resulted in a 15% yield.

Two hypothetic situations that could explain the low yield obtained are shown in Scheme 2. In the first scenario, the boronic acid **2** could, as with **1**, undergo oxidative addition setting itself up for self-coupling reactions. In the second situation the product **3a** could undergo oxidative addition opening the possibility of further Suzuki-Miyaura coupling in the reaction media. However the second case seems less likely, since only two phosphorus peaks (one belonging to the starting material and the other to the desired product) were observed in the ^{31}P-NMR of the crude reaction mixture.

To investigate the possibility of self coupling of the 2-bromophenylboronic acid **2a**, an experiment was performed using the same reaction conditions as shown in Table 1 (entry 2) but in the absence of the starting bromide **1**. After 15 h at 101 °C, the crude mixture showed compounds that could be associated with a self-coupling process (Scheme **3**), as evidence by spectroscopic data.

To minimize this self coupling problem, **2a** was dissolved in dioxane, divided into ten portions and added dropwise (each portion in 1 h time). Using this procedure we were able to increase the isolated yield to 30% (entry 15, Table 1). Although there was an improvement, however, most of the starting material still remained unreacted. This prompted us to look into the possibility of palladium being trapped by **3a**. As aforementioned, further coupling of **3a** with **2a** to give new phosphorus species was not occurring. As indicated in Scheme 2, however, **3a** could undergo oxidative addition on the palladium catalyst to form a stable chelated Pd(II) complex and thereby inhibit the desired Suzuki coupling. To gain evidence for this, the palladium catalyst was added to a reaction tube together with PPh$_3$ and 20 mol% of **3a**. After addition of dioxane the mixture was stirred at 90 °C for 1 h. The solution was then added to a mixture of **1** and 2-chlorophenylboronic acid **2b** in dioxane, and the reaction was carried out under the same conditions as those employed for the coupling of **1** and **2b** (see below). After 15 h, only traces of coupling product could be detected by ^{31}P-NMR, confirming the inhibiting role played by **3a** under these conditions (Scheme **4**).
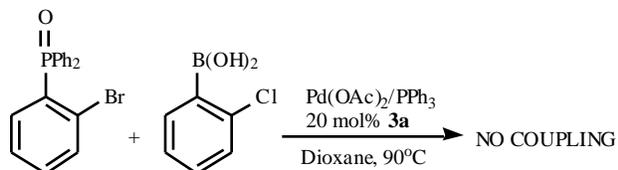
Scheme 4. Inhibiting effect of **3a** on the Suzuki-Miyaura coupling of **1** and **2b**.

In contrast to **2a**, the chloro and fluoro analogues **2b** and **2c** underwent smooth coupling with **1** to give **3b** and **3c** in excellent yields under the same reaction conditions (Scheme **5**). This is not unexpected, as the stronger C-Cl or C-F bond would inhibit an oxidative addition reaction from occurring.

With the three halogenated biphenyls (**3a**, **3b**, **3c**) in hand, the next step was to introduce a second phosphorus atom in the 2' position. This would afford symmetric and asymmetric biphenyl diphosphines. One approach we adopted for the synthesis of such ligands relied on a study published by Williams and coworkers [15,16] and later embraced by Helmchen for the synthesis of phosphorus-containing aryloxazolines [17]. In these studies, it was shown that aryl fluorides can undergo nucleophilic aromatic substitutions with potassium or lithium diphenylphosphide. For this reaction, fluorides are the most reactive of the halides and the reaction is normally complete within minutes for substrates containing electron-withdrawing groups.

3b (X = Cl), 87%
3c (X = F), 88%
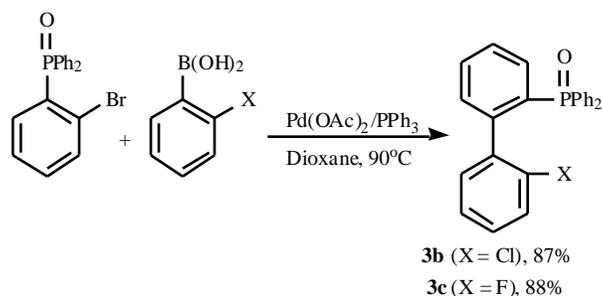
Scheme 5. Suzuki-Miyaura coupling of **2b,c** with **1**.

The fluoro-biphenyl **3c** seemed to fit in with the description and was therefore reacted with a phosphide (Scheme **6**). The compound was placed in a Schlenk tube, dissolved in THF and refluxed under inert atmosphere. LiPPh$_2$ was then added to the boiling mixture and allowed to react for 30 minutes. After cooling down, ^{31}P-NMR of the crude reaction showed no starting material and upon workup and purification, **4** was isolated in 87% yield. However, attempted extension of the reaction to alkyl phosphides met with failure, probably due to these phosphides acting as bases instead of nucleophiles.

4

R = Ar = Ph, 87%
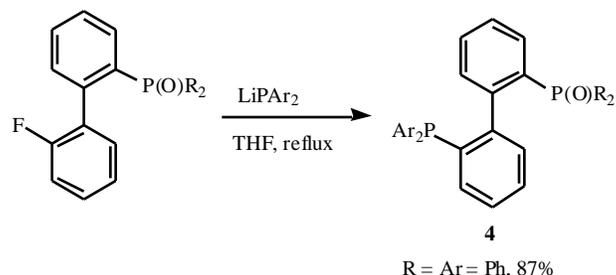
Scheme 6. Nucleophilic aromatic substitution on **3c**.

For the chloro and bromo analogies **3b** and **3a**, we attempted to use a metal-halogen exchange followed by reaction with a chlorinated phosphine. Thus, 2'-bromo- and 2'-chloro-2-(diphenylphosphinoyl)biphenyl were reacted under various conditions separately with different phosphorus-bearing electrophiles, but none of the reactions was successful. In all the cases where the 2'-chloro **3b** was employed, only starting material was recovered. The chloro compound seemed to be inert to all the lithium reagents at room temperature or in refluxing THF. In the case of the more reactive bromo **3a**, a cyclic phosphine oxide was isolated as the major product of the reaction (Scheme **7**). The result could be explained by a carbon-by-carbon concerted

substitution at the phosphorus. This behaviour was previously observed in related reactions by Schlosser and coworkers [14].
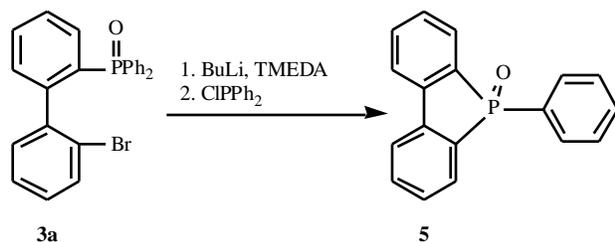
Scheme 7. Formation of cyclic phosphine Oxide **5**.

CONCLUSIONS

In conclusion, an interesting insight was gained on the Suzuki-Miyaura coupling of halogenated boronic acids for the formation of halobiphenyl phosphine oxides and on the reaction of the corresponding biphenyls with organometallic compounds. The chemistry led to successful synthesis of 2'-halogenated biphenyl phosphine compounds that may find use in the synthesis of other interesting ligands. In this context, an alternative synthesis of a BIPHEP precursor was shown, demonstrating that nucleophilic substitution of a fluorinated biphenyl is possible if appropriate nucleophiles are used.

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REFERENCES

[1] Cornils, B.; Herrmann, W. A., Eds. *Applied Homogeneous Catalysis with Organometallics Compounds*, VCH: Weinheim, Germany, **1996**.
[2] Ojima, I. *Catalytic Asymmetric Synthesis*, Wiley-VCH: New York, **2000**.
[3] Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, *19*, 1567.
[4] Ogasawara, M.; Ikeda, H.; Ohtsuki, H.; Hayashi, T. *Chem. Lett.* **2000**, *7*, 776.
[5] Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1999**, *38*, 495.
[6] Mikami, K.; Aikawa, K.; Korenaga, T. *Org. Lett.* **2001**, *3*, 243.
[7] Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Ben Hassine, B.; Genet, J. P. *Adv. Synth. Catal.* **2003**, *345*, 261.
[8] Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.
[9] Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498.
[10] Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789.
[11] Baillie, C.; Chen, W. P.; Xiao, J. L. *Tetrahedron Lett.* **2001**, *42*, 9085.
[12] Baillie, C.; Xiao, J. L. *Tetrahedron* **2004**, *60*, 4159.
[13] Gray, M.; Chapell, J. B.; Felding, J.; Taylor, J. N.; Snieckus, V. *Synlett* **1998**, 422.
[14] Desponds, O.; Schlosser, M. *J. Organomet. Chem.* **1996**, *507*, 257
[15] Allen, J. V.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron* **1994**, *50*, 799.
[16] Coote, S. J.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Synlett* **1993**, 509.
[17] Peer, M.; De Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547.