

Tetra-*ortho*-Substituted Biaryls through Palladium-Catalyzed Suzuki–Miyaura Couplings with a Diaminochlorophosphine Ligand

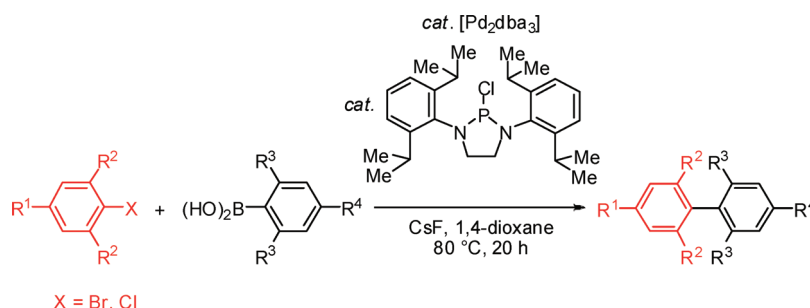
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ABSTRACT



A palladium complex derived from a sterically hindered diaminochlorophosphine allowed for Suzuki–Miyaura cross-couplings of chloroarenes with ample scope and provided access to tetra-*ortho*-substituted bi(hetero)aryls.

Transition-metal-catalyzed cross-coupling reactions are indispensable tools for regioselective C(sp²)–C(sp²) bond formations, which have found valuable applications in numerous research areas.¹ Particularly, Suzuki–Miyaura couplings have proven useful because of their remarkable tolerance of functional groups, along with the low toxicities and ready availability of organoboron nucleophiles.² While considerable progress in Suzuki–Miyaura coupling chemistry

has been accomplished in recent years through the development of stabilizing ligands,² syntheses of highly *ortho*-substituted biaryls continue to constitute a significant challenge. Thus, high-yielding³ preparations of tetra-*ortho*-substituted biaryls have thus far only been accomplished with palladium complexes derived from biphenyl monophosphines **1**,^{4,5} tertiary phosphine **2**,⁶ or N-heterocyclic carbenes (salt **3** or complex **4**)⁷ as sterically demanding, electron-rich

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stabilizing ligands (Figure 1). Contrarily, heteroatom-substituted phosphines were, to the best of our knowledge, as of yet not employed as ligands for these challenging transformations.

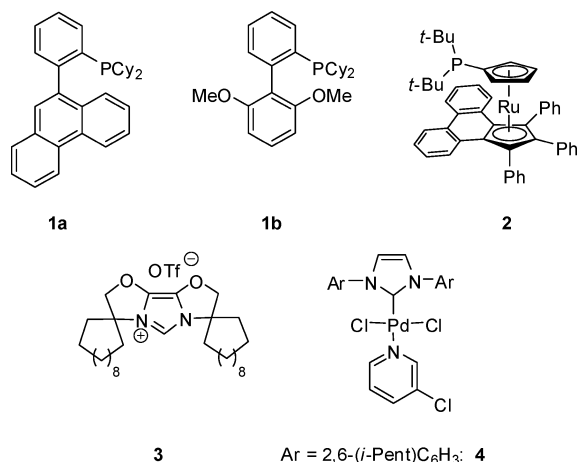


Figure 1. Ligands **1–3** and complex **4** for syntheses of tetra-*ortho*-substituted biaryls.

Previously, we reported on applications of diaminochlorophosphine **5a** (Figure 2) as a ligand for palladium-catalyzed

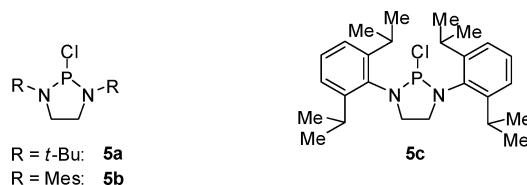


Figure 2. Diaminochlorophosphine ligands **5a–c**.

cross-coupling reactions of aryl halides.^{8,9} While this catalytic system enabled the use of chloroarenes in Suzuki–Miyaura

couplings, noteworthy limitations were represented by unsatisfactory low conversions with sterically hindered substrates, as well as the need for KO*t*-Bu as a strong base. Given that more effective arylations of amines or α -C–H acidic compounds could be achieved with sterically hindered ligand **5c**,¹⁰ we became interested in exploring its application to challenging Suzuki–Miyaura couplings with sterically congested substrates. Herein, we wish to report on these studies, which resulted in the development of a catalytic system for coupling reactions of aryl bromides as well as aryl or alkenyl chlorides with CsF as a milder base. Furthermore, these findings include the first use of a heteroatom-substituted phosphine as ligand for syntheses of tetra-*ortho*-substituted biaryls through Suzuki–Miyaura couplings.

At the outset of our studies, we probed representative chlorophosphines in the palladium-catalyzed synthesis of tetra-*ortho*-substituted biaryl **8aa** through Suzuki–Miyaura coupling (Table 1). Preliminary experiments with diami-

Table 1. Chlorophosphines as Ligands in the Synthesis of Tetra-*ortho*-Substituted Biaryl **8aa**^a

entry	6a	7a	L	base	yield
1			---	CsF	---
2				KO <i>t</i> -Bu	---
3				NaO <i>t</i> -Bu	---
4				K ₂ CO ₃	---
5				K ₃ PO ₄	---
6				KO <i>t</i> -Bu	---
7				CsOAc	---
8				KF	5%
9				Cs ₂ CO ₃	35%
10				CsF	99% ^b
11				CsF	5%
12				CsF	35%
13				CsF	---

^a Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [Pd₂(dba)₃] (2.0 mol %), L (8.0 mol %), base (1.50 mmol), 1,4-dioxane (2.0 mL), 20 h, GC conversion. ^b Yield of isolated product.

nochlorophosphines **5** revealed 1,4-dioxane to be the solvent of choice. While a variety of bases provided unsatisfactory

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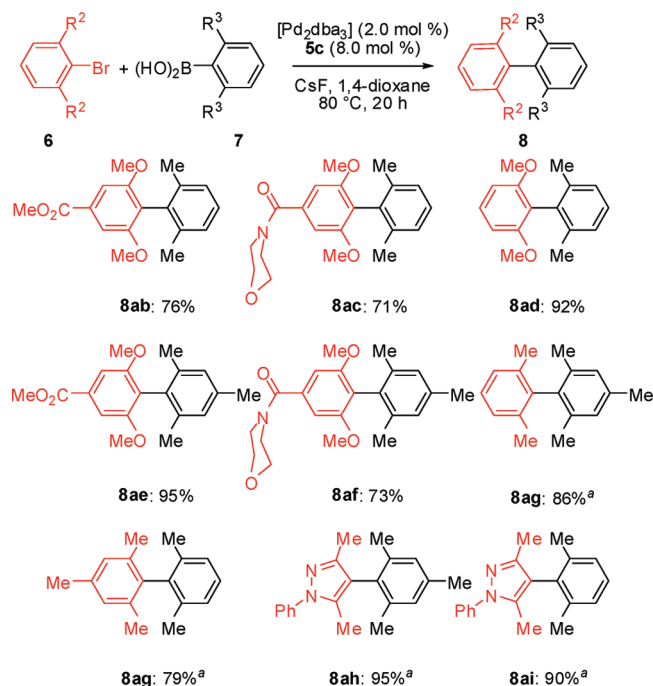
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results (entries 1–8), cesium salts were found to be more effective (entries 9 and 10), with CsF being optimal (entry 10). Unfortunately, diaminochlorophosphine **5a** or **5b** only gave rise to significantly less efficient catalysis (entries 11 and 12), as was also observed for alkyl-substituted phosphine chloride **9**¹¹ (entry 13).

With an optimized catalytic system in hand, we explored its scope for the preparation of various tetra-*ortho*-substituted biaryls **8** (Scheme 1).

Scheme 1. Synthesis of Tetra-*ortho*-Substituted Biaryls **8**



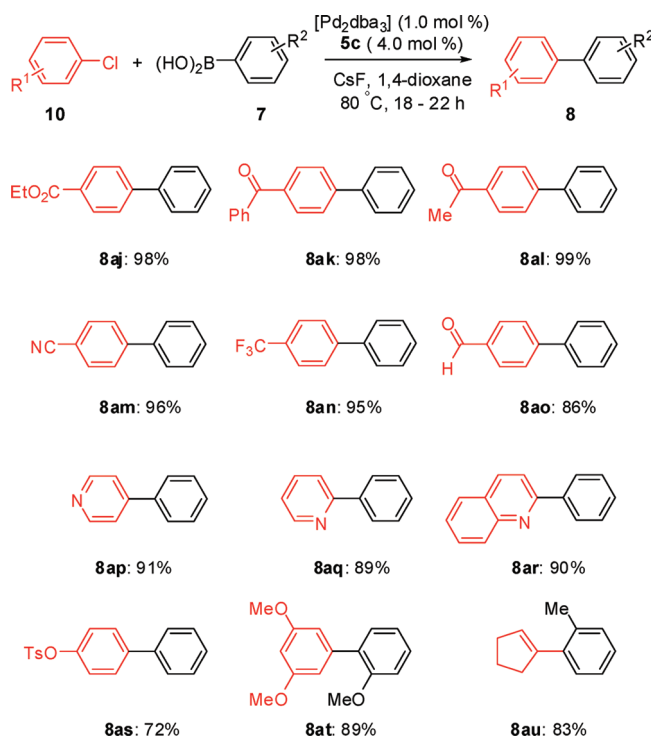
^a [Pd] (8.0 mol %).

Thus, diversely substituted products **8ab–8ai** with valuable functional groups, such as esters, amides, or heteroarenes, could be prepared in good yields.

Moreover, the optimized palladium complex generated from ligand **5c** was not limited to bromoarenes **6** as electrophiles but proved also applicable to the conversion of less expensive chloroarenes **10** (Scheme 2). Contrary to the previously reported catalytic system,^{8a} CsF could be employed as a mild base, thereby enabling the synthesis of biaryls **8aj–8ao** with various important functionalities. Additionally, *N*-heteroaryl chlorides served as viable substrates to yield biaryls **8ap–8ar**. An intramolecular competition experiment highlighted an excellent chemoselectivity, which resulted in the selective formation of biaryl **8as**. Further, *ortho*-substituted boronic acids also could be employed to provide access to arylated arene **8at** and alkene **8au**.

Importantly, *ortho*-substituted chloroarenes **10** were also efficiently converted (Scheme 3). Hence, di- and tri-*ortho*-

Scheme 2. Cross-Couplings with Chloroarenes **10**



substituted biaryls **8av–8ax** and **8ay–8az**, respectively, were obtained in high yields. Interestingly, the palladium catalyst derived from diaminochlorophosphine **5c** could be used for the challenging synthesis of tetra-*ortho*-substituted products **8ag–8bc**, as well.

We believe that the catalyst's high efficacy in the formation of tri- or tetra-*ortho*-substituted biaryls **8** is due to the considerable steric bulk exerted by the substituents on chlorophosphine **5c**. Thereby, highly active monophosphine-coordinated palladium species¹² are generated, a feature that is reflected by the selective formation of palladium(II) complex **11**,¹³ the molecular structure of

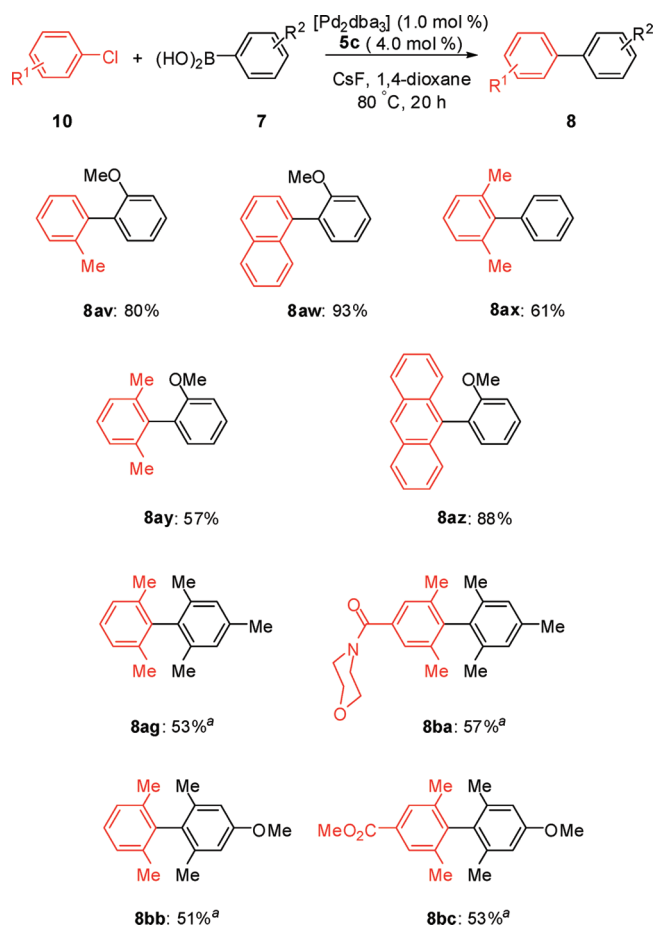
(11) For representative examples of alkyl-substituted secondary phosphine chlorides or oxides in transition-metal-catalyzed arylation reactions, see: (a) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276. (b) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381–384. (c) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638–7650. (d) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162–167. (e) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698. (f) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415–2419. (g) Lerebours, R.; Wolf, C. *Org. Lett.* **2007**, *9*, 2737–2740. (h) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052–13053. (i) Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601–8604. (j) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (k) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147–1150. (l) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650. (m) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516.

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(13) Palladium(II) complex **11** (1.0 mol %) provided biaryl **8an** in 93% with KO^tBu as base, under otherwise identical reaction conditions, as described in Scheme 2.

(14) CCDC-757573 contains the supplementary crystallographic data for complex **11**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223–336–033; or deposit@ccdc.cam.ac.uk).

Scheme 3. Cross-Couplings with *ortho*-Substituted Aryl Chlorides **10**

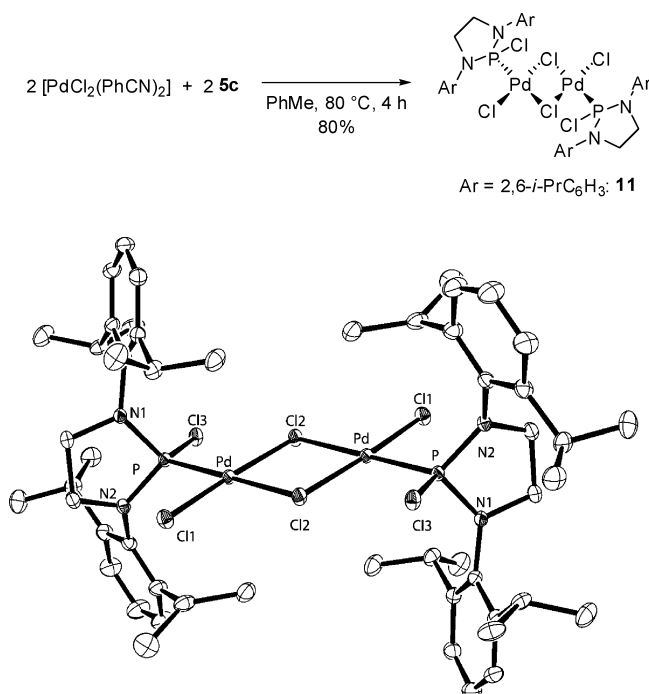


^a [Pd] (8.0 mol %), 110 °C, 24 h.

which was confirmed by X-ray crystal structure analysis (Scheme 4).¹⁴

In summary, we have reported on the use of a heteroatom-substituted phosphine for challenging Suzuki–Miyaura cross-

Scheme 4. Synthesis and Molecular Structure of Complex **11**



coupling reactions with sterically hindered substrates. Hence, a palladium complex derived from a diaminochlorophosphine enabled inter alia the synthesis of tetra-*ortho*-substituted biaryls.

Acknowledgment. Support by the DFG and the DAAD (fellowship to H.K.P.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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