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

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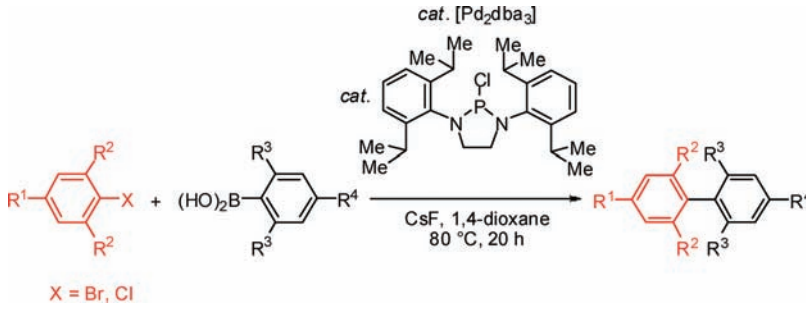
ABSTRACT



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(sp^2)−C(sp^2) 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-yielding[3] 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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(1) (a) Ackermann, L., Ed. *Modern Arylation Methods*; Wiley-VCH: Weinheim, Germany, 2009. (b) Beller, M., Bolm, C., Eds. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.

(2) Select reviews: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (b) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, 59–72. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101. (d) Littke, A. F. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009; pp 25−68.

(3) For a low-yielding early example, see: Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001–7002.

(4) (a) Demchuk, O. M.; Yoruk, B.; Blackburn, T.; Snieckus, V. *Synlett* **2006**, 2908–2913. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876. (d) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.

(5) A review: Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.

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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.

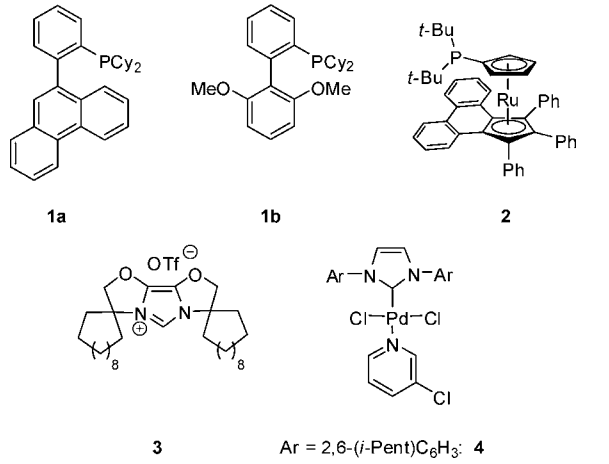


Figure 1. Ligands **1**−**3** and complex **4** for syntheses of tetra-*ortho*-substituted biaryls.

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

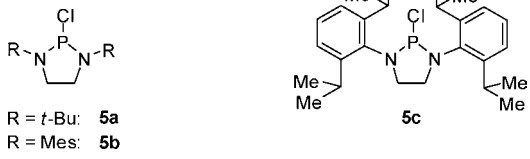
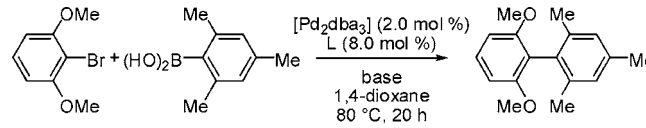


Figure 2. Diaminochlorophosphine ligands **5a**−**c**.

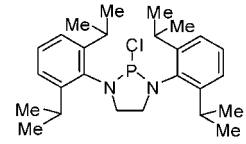
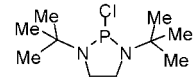
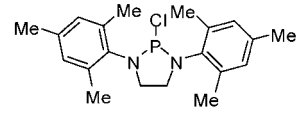
cross-coupling reactions of aryl halides.[8,9] While this catalytic system enabled the use of chloroarenes in Suzuki−Miyaura couplings, noteworthy limitations were represented by unsatisfactory low conversions with sterically hindered substrates, as well as the need for KO*t*-Bu as a strong base. Given 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 diamino-

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



6a **7a** **8aa**

entry	L	base	yield
1	---	CsF	---
2	 **5c**	KO*t*-Bu	---
3	**5c**	NaO*t*-Bu	---
4	**5c**	K_2CO_3	---
5	**5c**	K_3PO_4	---
6	**5c**	KO*t*-Bu	---
7	**5c**	CsOAc	---
8	**5c**	KF	5%
9	**5c**	Cs_2CO_3	35%
10	**5c**	CsF	99%[b]
11	 **5a**	CsF	5%
12	 **5b**	CsF	35%
13	*t*-Bu_2PCl **9**	CsF	---

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [$Pd_2(dba)_3$] (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

(6) (a) Hoshi, T.; Saitoh, I.; Nakazawa, T.; Suzuki, T.; Sakai, J.-i.; Hagiwara, H. *J. Org. Chem.* **2009**, *74*, 4013–4016. (b) Hoshi, T.; Nakazawa, T.; Saitoh, I.; Mori, A.; Suzuki, T.; Sakai, J.-i.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 2063–2066.

(7) (a) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383–2387. (b) Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiang, W.; Andrus, M. B. *Tetrahedron* **2005**, *61*, 7438–7446. (c) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.

(8) (a) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444–2447. For reviews, see: (b) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214. (c) Ackermann, L. *Synthesis* **2006**, 1557–1571. (d) Ackermann, L. *Synlett* **2007**, 507–526. (e) Ackermann, L.; Althammer, A. *Chem. Unserer Zeit.* **2009**, *43*, 74–83.

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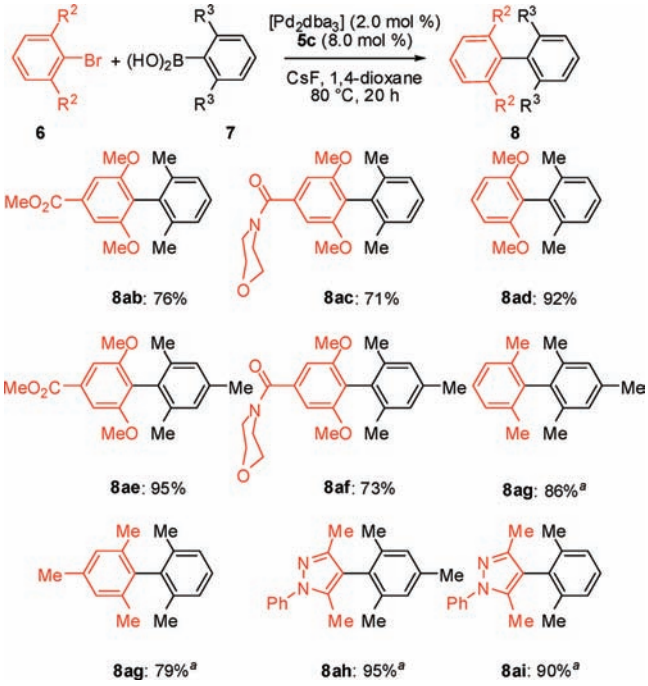
results (entries 1−8), cesium salts were found to be more effective (entries 9 and 10), with CsF being optimal (entry 10). Unfortunately, diaminochlorophosphine **5a** or **5b** only gave rise to significantly less efficient catalysis (entries 11 and 12), as was also observed for alkyl-substituted phosphine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



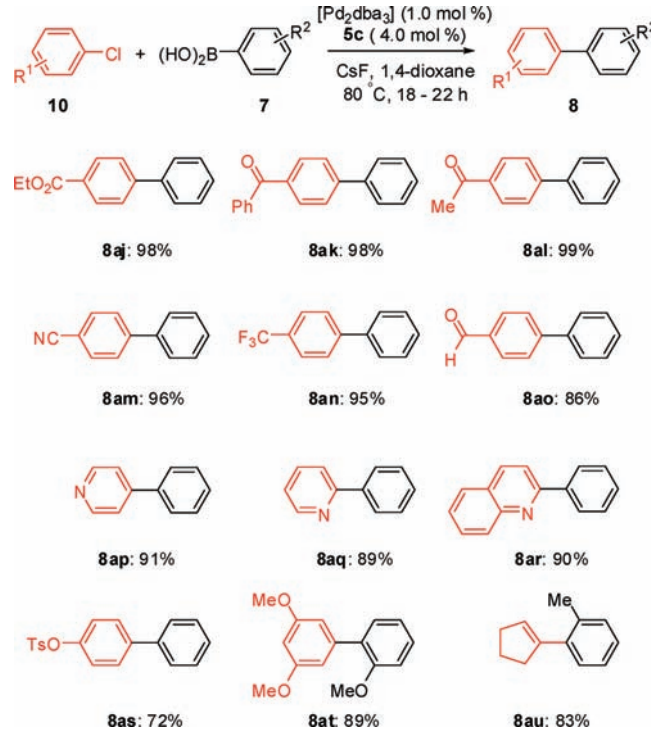
[a] [Pd] (8.0 mol %).

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 species[12] are generated, a feature that is reflected by the selective formation of palladium(II) complex **11**,[13] the molecular structure of

(10) Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7627–7630.

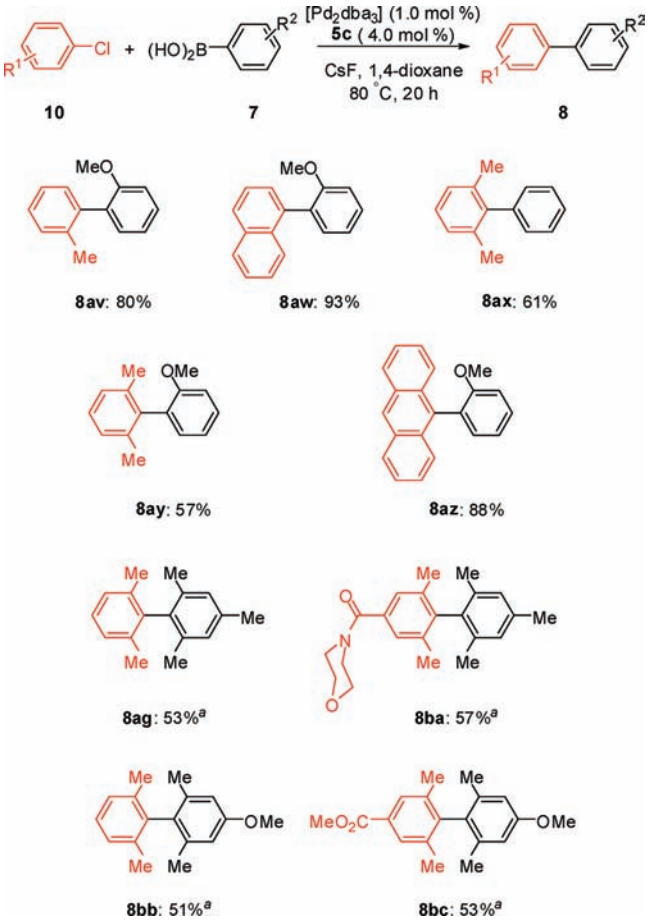
(11) For representative examples of alkyl-substituted secondary phosphine chlorides or oxides in transition-metal-catalyzed arylation reactions, see: (a) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276. (b) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, 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.

(12) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374.

(13) Palladium(II) complex **11** (1.0 mol %) provided biaryl **8an** in 93% with KO*t*-Bu 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**

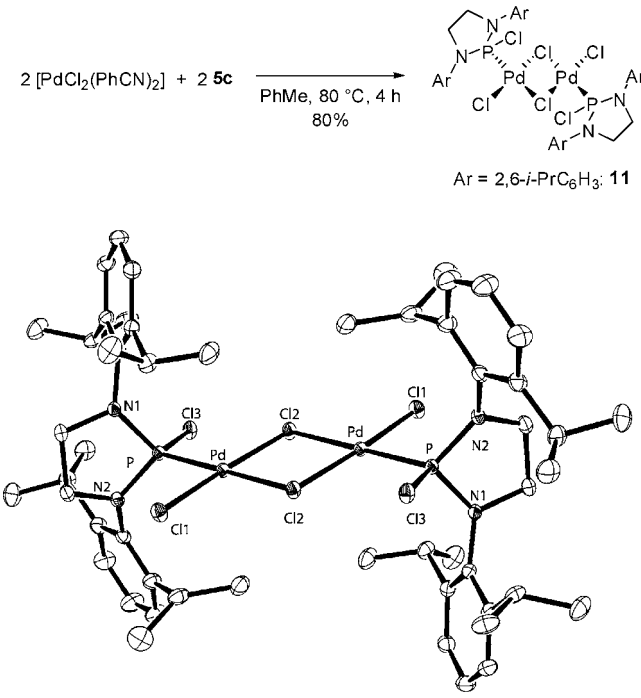


[a] [Pd] (8.0 mol %), 110 °C, 24 h.

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

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



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

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