Synthetic Methods

DOI: 10.1002/ange.200906811

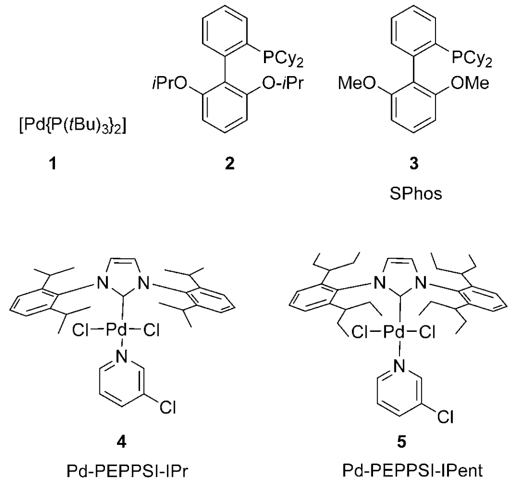
Pd-PEPPSI-IPent: Low-Temperature Negishi Cross-Coupling for the Preparation of Highly Functionalized, Tetra-*ortho*-Substituted Biaryls**

*Selçuk Çalimsiz, Mahmoud Sayah, Debasis Mallik, and Michael G. Organ**

Biaryls are important motifs seen in the structures of many biologically active compounds and organic materials. Thus, the development of efficient bond-forming procedures between sp^2-hybridized carbon atoms has been pursued intensively by both academic and industrial scientists.[1] The synthesis of biaryl compounds began with the century-old Ullmann reaction[2] and has evolved into a wide variety of Ni- and Pd-catalyzed cross-coupling procedures.[3] Organotin (Stille–Migita) and organoboron (Suzuki–Miyaura) reagents have been used most widely as the transmetalating partner in cross-coupling reactions; organozincs (Negishi coupling) are the most reactive partners, but have been employed to a lesser extent owing primarily to their increased basicity and moisture sensitivity.[4]

In 2001, Dai and Fu reported the first general protocol for Pd-catalyzed Negishi coupling between aryl zinc reagents and aryl/heteroaryl chlorides, and gave good yields using $[Pd\{P(tBu)_3\}_2]$ (**1**; Scheme 1) in THF/NMP at 100 °C.[5] In 2004, Milne and Buchwald prepared a variety of sterically bulky biaryls that contained heterocycles with many functional groups by coupling aryl/heteroaryl halides with aryl zinc reagents that were prepared in situ using the hindered biaryl ligand **2** in conjunction with $[Pd_2(dba)_3]$ at 70 °C.[6] In 2006, our research group developed a user-friendly Negishi protocol capable of cross-coupling aryl zinc halides with aryl bromides, chlorides, and triflates in excellent yields using Pd-PEPPSI-IPr (**4**) under mild conditions.[7] Similarly, in 2008, Knochel and co-workers reported a one-pot Negishi coupling protocol employing **4** to form biaryls and heterobiaryls from aryl/heteroaryl zinc reagents generated in situ and aryl bromides, chlorides, or triflates under mild conditions.[8] In a series of publications, Knochel and co-workers also reported Negishi protocols for coupling zinc reagents with aryl halides bearing relatively acidic hydrogen atoms using $Pd(OAc)_2$ in conjunction with Buchwald's SPhos ligand (**3**).[9]

Recently, we have shown Pd-PEPPSI-IPent (**5**) to be an excellent catalyst for the Suzuki–Miyaura cross-coupling of



Scheme 1. Previously employed catalysts in the Negishi cross-coupling reaction and Pd-PEPPSI-IPent. Cy = cyclohexyl, dba = *trans,trans*-dibenzylideneacetone.

sterically bulky aryl bromides/chlorides with aryl boronic acids at 65 °C employing KO*t*Bu/*t*BuOH.[10] Despite the widespread use of boronic acids for Suzuki–Miyaura coupling reactions, their tendency to form boroxines, frequent need for recrystallization of the aryl boronic acids prior to use, and competitive protodeboronation under coupling conditions remains problematic.[11] Conversely, Negishi reactions are an attractive alternative because they typically requires milder reaction conditions and, although organozincs are quite basic, they are highly tolerant of various functional groups.[12] Herein, we investigate the use of **5** in Negishi cross-coupling reactions for the synthesis of very challenging and structurally diverse biaryl compounds.

The coupling of 2-mesitylzinc halide (**7**) with 2,6-dimethyl-1-bromobenzene (**8**) was thought to be a good substrate pairing to develop general coupling conditions. Although these substrates have no functionality, this pair led to the formation of a tetra-*ortho*-substituted biaryl that is still beyond the capability of most catalysts. In a direct comparison of catalysts **4** and **5** that was conducted at room temperature, **5** completed the reaction in about 4 hours, meanwhile **4** turned over continuously, but at a much slower rate (Figure 1).

To shed some light on the performance of **4**, and to compare the reactivity of **5** with different ligand systems that are known to be highly effective at cross-coupling (e.g. **2** and **3**),[13] we systematically modified the model reaction to expose the differences (Figure 2). Under the optimized reaction conditions in THF/NMP (2:1),[7] catalyst **5** displayed 80%

[*] Dr. S. Çalimsiz, M. Sayah, Dr. D. Mallik, Prof. M. G. Organ
Department of Chemistry, York University
4700 Keele Street, Toronto, ON, M3J 1P3 (Canada)
Fax: (+1) 416-736-5936
E-mail: organ@yorku.ca
Homepage: http://www.yorku.ca/organ/

[**] This work was supported by the NSERC (Canada) and the ORDCF (Ontario).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906811.

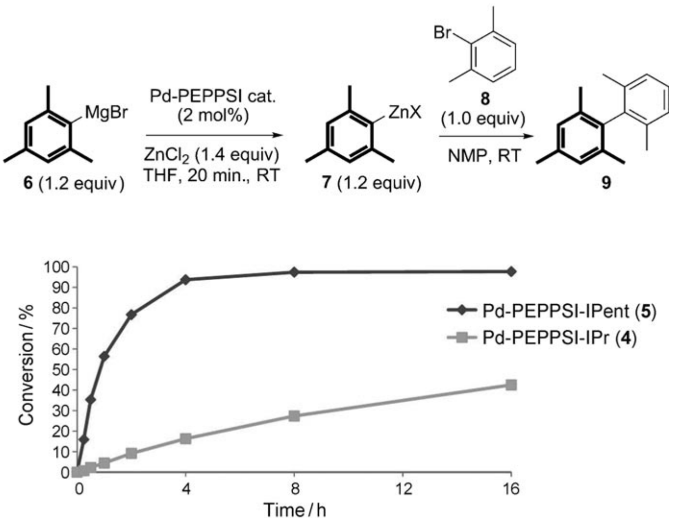


Figure 1. Effect of reaction time on the model Negishi reaction utilizing Pd-PEPPSI complexes **4** and **5**. Conversions were determined by GC/MS analysis against a calibrated internal standard (undecane). Reactions were performed in duplicate. NMP = *N*-methylpyrrolidine, THF = tetrahydrofuran.

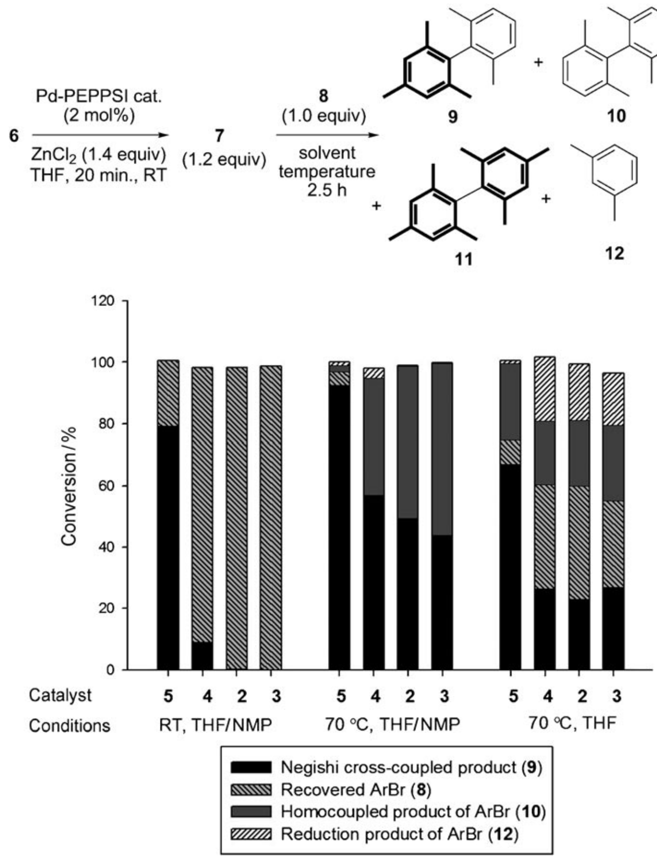


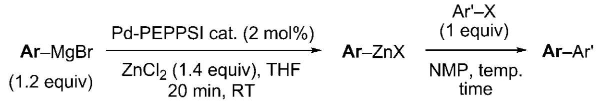
Figure 2. Catalyst, temperature, and solvent effects in the coupling of mesitylzinc bromide (**7**) and 1-bromo-2,6-dimethylbenzene (**8**). Percent conversion is based on **8** and determined by GC/MS analysis against a calibrated internal standard (undecane). Reactions were performed in duplicate.

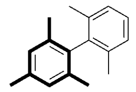
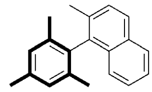
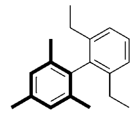
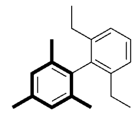
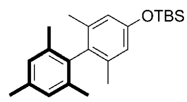
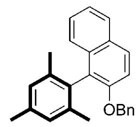
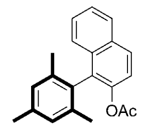
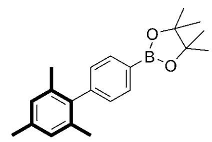
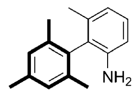
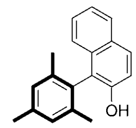
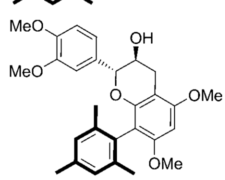
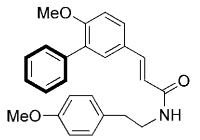
conversion into the cross-coupled product **9** after 2.5 hours. Conversely, when **4** was employed approximately 10% of **9** was observed, while ligand **2** or **3** (used in conjunction with $[Pd_2(dba)_3]$)[13b] produced only a trace amount of product. Notably, unreacted aryl bromide **8** accounted for the entire balance of the reaction mixture for all catalysts. Ligands **2** or **3** have been well engineered for highly effective reductive elimination, but phosphines are not as electron-rich as N-heterocyclic carbene (NHC) ligands; taken together, this suggests that oxidative addition is rate limiting with **2** and **3**. This suggestion is supported by the observation that heating to 70 °C, and with all else held constant, leads to complete consumption of **8** with ligands **2** and **3**. Interestingly, heating also led to significant homocoupling of **8** (i.e. **10**) with all catalysts except **5**, which still converted 95% of **8** into **9**. Also, based on the aryl zinc compound (i.e. **7**), catalysts **2**, **3**, and **4** all provided approximately 40% of the homocoupled organozinc product **11** (based on the consumption of **7**, i.e. 2 equiv of **7** to make 1 equiv of **11**), which is not accounted for on Figure 2. Formation of the expected product **9** and significant amounts of **11**, suggests that a second transmetalation step may be operative that competes with reductive elimination leading to the homocoupled products, as was suggested recently by Lei and co-workers.[14] Moreover, in the absence of NMP, reactions performed at 70 °C were less effective with all catalysts. Notably, significant disproportionation of **8**, which led to the formation of **10**, was observed for the first time using **5**, as was the reduction of **8** (to provide **12**) with catalysts **2**, **3**, and **4**. Even though there was again a significant amount of **11** formed (ca. 40%) with **2**, **3**, and **4**, there was not enough of it formed to account for the lack of consumption of the oxidative addition partner **8**.

Following the promising initial results with Pd-PEPPSI-IPent, **4** and **5** were evaluated in the Negishi coupling of aryl zinc reagents (prepared in situ) with oxidative additions partners bearing considerable steric bulk and/or various reactive functional groups (Table 1). Under standard reaction conditions using **5**, aryl bromides/chlorides containing phenols protected with alkyl, alkoxy, pinacol boronic ester, TBS, acetyl, and benzyl groups were coupled efficiently at room temperature or under mild heating. Acidic moieties including anilines (**19**), phenols (**20**), alcohols (**21**), and amides (**22**) were well tolerated. With a few exceptions, catalyst **4** provided considerably lower yields of cross-coupled products. Remarkably, catalyst **5** was able to generate 90% of **9** and 80% of **13** when the reaction was run at 0 °C and allowed to slowly warm to 6 °C.

In light of the importance of heterocyclic compounds,[15] we examined the coupling between heteroaryl halides and hindered aryl zinc reagents (Table 2). Varieties of heterocyclic chlorides/bromides were coupled in excellent yields; these included pyrazine (**26**), quinoline (**29**, **31**), sterically bulky isoxazole (**23**) and pyrazole (**24**), as well as substituted pyrimidine (**28**), pyridazine (**25**), and pyridines (**27**, **30**, **32**). We then focused on the coupling of heteroaryl zinc reagents with aryl bromides/chlorides as well as heteroaryl bromides/chlorides (Table 3). Catalyst **5** effectively coupled 2-pyridyl (**33–36**), 4-isoquinolinyl (**37**, **38**), 2-thiophenyl (**39**), 2-thiazolyl (**40**), and 5-ethoxycarbonyl-2-furyl (**41–43**) zinc reagents with a variety of aryl- and heteroaryl halides at room temperature or under mild heating.[16]

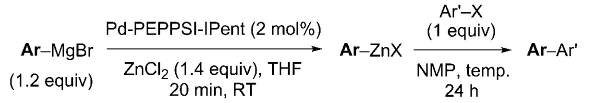
Table 1: Negishi cross-couplings of aryl zinc reagents with aryl halides.

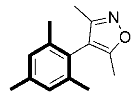
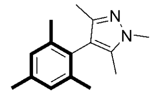
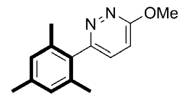
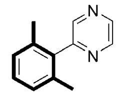
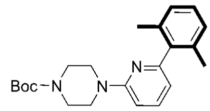
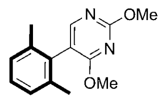
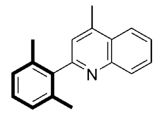
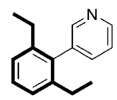
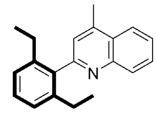
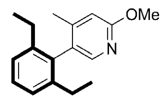


No.	X	*T* [°C]	*t* [h]		Product	Yield [%] with **4**[a]	Yield [%] with **5**[a]
1	Cl	23	8	**9**		3	quant. (90)[b]
2	Cl	23	8	**13**		11	96 (80)[b]
3	Br	40	24	**14**		1	73
4	Cl	50	24	**14**		1	71
5	Br	23	16	**15**		14	97
6	Br	23	4	**16**		63	87
7	Br	23	16	**17**		30	80
8	Cl	45	24	**18**		90	90
9	Br	50	24	**19**		1[c]	57[c]
10	Br	50	24	**20**		18[d]	95[d]
11	Br	50	24	**21**		14[c]	82[c]
12	Br	40	24	**22**		60[d]	69[d]

[a] Yields of isolated products are the average of two runs. [b] Reaction was performed at 0–6 °C with 1.6 equivalents of $ZnCl_2$. [c] ArMgBr (2.6 equiv), $ZnCl_2$ (3 equiv). [d] NaH (1.0 equiv). Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

Table 2: Negishi cross-coupling reactions of aryl zinc reagents with heteroaryl halides.



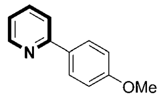
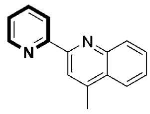
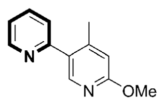
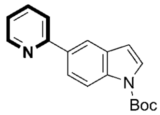
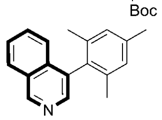
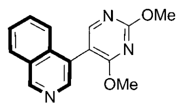
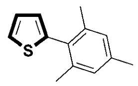
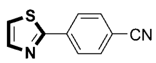
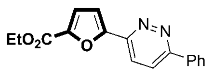
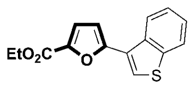
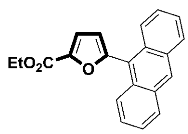
Entry	X	*T* [°C]		Product	Yield [%][a]
1	Br	23	**23**		82
2	Br	23	**24**		quant.
3	Cl	23	**25**		quant.
4	Cl	23	**26**		quant.
5	Br	23	**27**		85
6	Br	23	**28**		89
7	Cl	23	**29**		96
8	Br	60	**30**		98
9	Cl	60	**31**		95
10	Cl	60	**32**		91

[a] Yields of isolated products are the average of two runs. Boc = *tert*-butoxycarbonyl.

Pd-PEPPSI-IPent (**5**) has proven to be an excellent catalyst for the Negishi cross-coupling procedure, and was used to prepare an impressive array of biaryl and heterobiaryl compounds bearing various functional groups and/or congested steric bulk in excellent yields under the mildest conditions yet reported for such difficult substrates. These results, in addition to our earlier report about the performance of **5** in Suzuki–Miyaura cross-couplings, reinforce the notion that conformationally flexible steric bulk is intricately linked to the performance of NHC-based palladium catalysts in cross-coupling reactions.[10,17] We are currently studying the origin of these effects. Further, the coupling that leads to the

Table 3: Negishi cross-couplings of heteroaryl zinc reagents with aryl halides and heteroaryl halides.

$$\underset{(1.5\ \text{equiv})}{\mathbf{Ar}\text{–ZnX}} \xrightarrow[\text{ZnCl}_2\ (1\ \text{equiv}),\ \text{THF, Ar'–X, 24 h}]{\text{Pd-PEPPSI-IPent (2 mol\%)}} \mathbf{Ar}\text{–Ar'}$$

Entry	X	*T* [°C]		Product	Yield [%][a]
1	Br	23	**33**		85
2	Cl	23	**34**		98
3	Br	60	**35**		64
4	Br	23	**36**		61
5	Br	70	**37**		77
6	Br	70	**38**		70
7	Br	23	**39**		quant.[b]
8	Cl	60	**40**		91[c]
9	Cl	23	**41**		79
10	Br	23	**42**		quant.
11	Br	23	**43**		91

[a] Yields of isolated products are the average of two runs. [b] Solvent system: THF/NMP (2:1); [c] $ZnCl_2$ (4.5 equiv).

formation of **9** and **13** at temperatures close to 0 °C indicates that even milder reaction conditions are possible when using **5** to prepare complex biaryl motifs.

Received: December 3, 2009
Revised: January 16, 2010
Published online: February 16, 2010

Keywords: biaryls · cross-coupling · heteroaryls · Negishi reaction · palladium

[1] a) C. Ivica in *Synthesis of Biaryls*, Elsevier, Oxford, **2004**; b) G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler in *Progress in Chemistry of Organic Natural Products*, *Vol. 82* (Eds.: W. Herz, H. Falk, G. W. Kirby, R. E. Moore), Springer, Vienna, **2001**; c) J. P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651 – 2710.

[2] a) F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359 – 1469.

[3] A. de Meijere, F. Diederich in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**.

[4] *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. I. Negishi), Wiley-Interscience, New York, **2002**.

[5] C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719 – 2724.

[6] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028 – 13032.

[7] M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749 – 4755.

[8] S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380 – 7382.

[9] a) G. Manolikakes, C. M. Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422 – 8436; b) G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765 – 2768; c) G. Manolikakes, J. Li, P. Knochel, *Synlett* **2009**, 681 – 686.

[10] M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem.* **2009**, *121*, 2419 – 2423; *Angew. Chem. Int. Ed.* **2009**, *48*, 2383 – 2387.

[11] a) M. Genov, A. Almorín, P. Espinet, *Chem. Eur. J.* **2006**, *12*, 9346 – 9352; b) S. T. Handy, Y. Zhang, H. Bregman, *J. Org. Chem.* **2004**, *69*, 2362 – 2366; c) H. Chaumeil, S. Signorella, C. Le Drian, *Tetrahedron* **2000**, *56*, 9655 – 9662; d) T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* **1992**, 207 – 210.

[12] a) E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC Press, Boston, **1996**; b) *Organozinc Reagents*, *A Practical Approach*, (Eds.: P. Knochel, P. Jones), Oxford, New York, **1999**.

[13] a) To the best of our knowledge **2** is the most reactive, commercially available ligand in the Buchwald family of sterically crowded ligands for Negishi cross-coupling; b) To ensure the formation of the active Pd complex formation when **2** or **3** were used in conjunction with $[Pd_2(dba)_3]$, the reaction was stirred in THF for 10 minutes before the addition of the Grignard reagent; colour changes from purple to dark orange signified formation of the complex. Reactions with **4** and **5** were conducted under the same conditions.

[14] Q. Liu, Y. Lan, J. Liu, G. Li, Y. D. Wu, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 10201 – 10210.

[15] Symposium abstract "Heterocyclic Chemistry: Synthesis Chemical Biology and Drug Discovery" for the 42nd IUPAC Congress August **2009**, Glasgow, UK.

[16] When heteroaryl zinc reagents were used, the addition of 1.0 equivalent of $ZnCl_2$ was beneficial. On the other hand, when NMP was employed as the cosolvent, significant decreases in the reaction rates were observed.

[17] G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem.* **2003**, *115*, 3818 – 3821; *Angew. Chem. Int. Ed.* **2003**, *42*, 3690 – 3693.