Cross-Coupling

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Hindered Aryllithium Reagents as Partners in Palladium-Catalyzed Cross-Coupling: Synthesis of Tri- and Tetra-*ortho*-Substituted Biaryls under Ambient Conditions**

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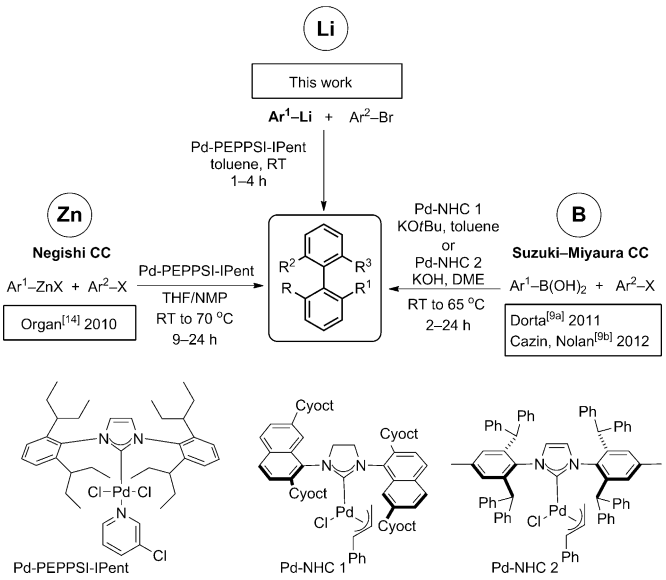
Palladium-catalyzed cross-coupling of arylmetal reagents and arylhalides to form biaryl compounds has played a pivotal role during the past decades in the assembly of $C(sp^2)$–$C(sp^2)$ bonds.[1] Biaryls are important structural motives in organic materials, chiral ligands, natural products, and pharmaceutical compounds.[2] Since the first reports in the 1970s[3] on the use of Pd to catalyze the formation of biaryls, major efforts have been focussed on tuning the ligand systems to improve efficiency and selectivity and to achieve cross-coupling under mild conditions.[4] Nevertheless, the synthesis of sterically congested tri- and tetra-*ortho*-substituted biaryls remains highly challenging.[5] High yields of biaryls have been reported with organoboron[6] compounds. Although these early methods include the use of boron derivatives that are functional-group tolerant, they featured usually high temperatures (80–110 °C) and long reaction times.[7] Since the first report of a highly efficient catalyst based on dialkyl biarylphosphines for this type of C–C bond formation by Buchwald and co-workers in 2002,[7a] in particular N-heterocyclic carbenes (NHCs) have been described as efficient ligands for the sterically demanding Suzuki–Miyaura cross-coupling under milder conditions. The research group of Organ reported in 2009 a general Suzuki–Miyaura cross-coupling at 65 °C (24 h) based on the PEPPSI-IPent catalyst for the synthesis of tetra-*ortho*-substituted biaryls and found that the rate-determining step is likely to be the transmetalation from the organoboron reagent to palladium.[8] More recently, the use of tailored NHC–Pd complexes has allowed the synthesis of tetra-*ortho*-substituted biaryls through cross-coupling using organoboron compounds at room temperature.[9] The use of Grignard and zinc reagents for this transformation has been scarcely reported.[10] In 2008 Wolf and Xu disclosed the synthesis of tri-*ortho*-substituted biaryls with Grignard reagents at room temperature (24 h)[11] but the application of this protocol to the synthesis of the tetrasubstituted analogues was not reported.[12] The first general report on sterically demanding cross-coupling reactions with organozinc reagents (70 °C, 15 h) was presented by Buchwald and Milne in 2004.[13] Organ and co-workers extended their use of the PEPPSI catalyst to the Negishi cross-coupling to form hindered biaryls at temperatures varying from 23 to 70 °C and reaction times ranging from 9 to 24 h (Scheme 1).[14]



Scheme 1. General procedures in Pd-catalyzed cross-coupling for the synthesis of tri- and tetra-*ortho*-substituted biaryls at room temperature. Cyoct = cyclooctyl.

Organolithium compounds are among the most reactive, readily accessible and commonly used reagents in synthesis. Moreover, in spite of the recent development of direct access to various arylmetal species,[15] aryllithiums are still often employed as precursors for other organometallic compounds (B, Sn, Zn) frequently used in cross-coupling processes.[16] Pioneering studies by Murahashi and co-workers[17] on the use of organolithium reagents in catalytic cross-coupling reactions showed the limitations associated to their high reactivity. In alternative approaches, Yoshida and co-workers achieved the cross-coupling of aryllithium reagents using a flow micro-

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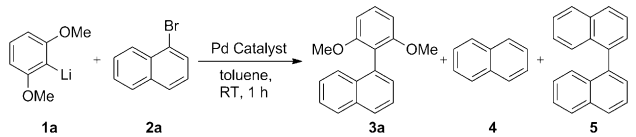
reactor,[18] while the group of Smith III has developed a method based on a stoichiometric silicon-based transfer agent.[19] However, to our knowledge, none of these methods has been applied to the synthesis of hindered biaryls. Recently we developed a methodology to perform Pd-catalyzed direct cross-coupling reactions of organolithium reagents with (hetero)aryl- and alkenylbromides at room temperature in short times.[20] Despite the important advances achieved in the cross-coupling of hindered biaryls,[7–14] these protocols usually require long reaction times. The control over the high reactivity of organolithium reagents might be advantageous in facilitating the transmetalation with Pd. In addition, the easy accessibility of *ortho*-functionalized organolithium reagents through direct *ortho* lithiation[21] could make them particularly useful for the synthesis of *ortho*-functionalized hindered biaryls. A notable advantage is the great stability that *ortho* substituents, such as alkoxy or amino groups, give to the lithium reagent in contrast to the corresponding zinc, and especially organoboron reagents,[7k] which suffer from instability and, as far as we know, these *ortho*-functionalized organometallics have not been coupled before at room temperature. We envisioned that highly hindered aryllithium reagents might be successfully applied to the synthesis of tri- and tetra-*ortho*-substituted biaryls at low temperature and within short reaction times (Scheme 1). Herein we describe the successful realization of this fast and mild biaryl formation.

Initially we applied our reported conditions[20] for the coupling of hindered 2,6-dimethoxy-phenyllithium (**1a**) with 1-bromonaphthalene (**2a**). The use of the in situ generated complex from $[Pd_2(dba)_3]$ and $P(tBu)_3$,[22] and slow addition of **1a** led to a selective reaction in which common side products derived from halogen/lithium exchange like dehalogenated product **4** and homocoupled product **5** were not observed (Scheme 2). Unfortunately, despite its high selectivity this catalyst resulted in incomplete conversion (86%). To enhance reactivity we examined Pd–NHC catalysts for this C–C bond formation. NHC ligands have emerged as attractive ligands in cross-coupling owing to their specific steric features and strong σ-bond donor capabilities.[23] Recently, the group of Organ introduced highly effective Pd-PEPPSI precatalysts that are air stable and commercially available.[24] The use of Pd-PEPPSI-IPent (Scheme 1), which is known for its efficiency in cross-coupling of hindered substrates with other organometallics,[8,14] afforded biaryl **3a** with full conversion and >99% selectivity in the cross-coupling of bis-*ortho*-methoxy-phenyllithium (**1a**) and 1-bromonaphthalene (**2a**) at room temperature in 1 h (Scheme 2).



Pd Catalyst	Conversion[a]	3a/4/5[a]
$[Pd_2(dba)_3]$ (2.5 mol%) $P(tBu)_3$ (7.5 mol%)	86%	99 : 1 : –
Pd-PEPPSI-IPent (5 mol%)	full	>99 : – : –

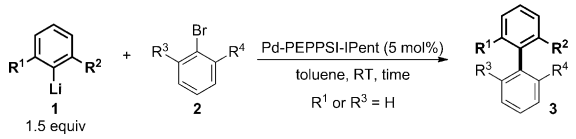
Scheme 2. Optimization of the reaction between **1a** and **2a**. Conditions: to a solution of **2a** (0.3 mmol) and Pd catalyst (5 mol%) in toluene (2 mL) a solution of aryllithium reagent **1a** (1.5 equiv; see the Supporting Information for details regarding the preparation of the solutions) was added over 1 h by using a syringe pump. [a] GC analysis.

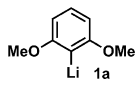
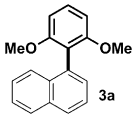
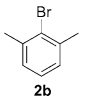
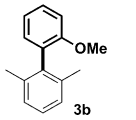
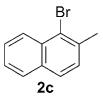
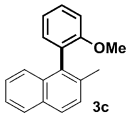
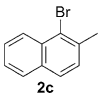
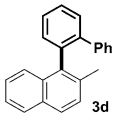
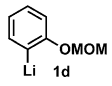
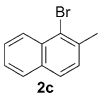
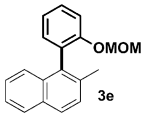
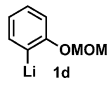
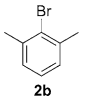
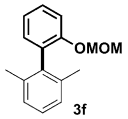
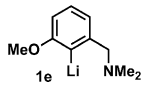
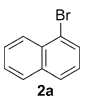
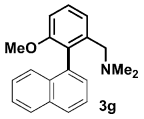
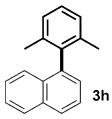
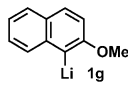
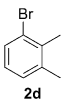
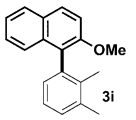
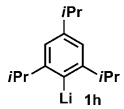
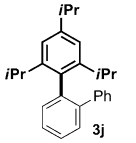
After having established Pd-PEPPSI-IPent as a highly efficient catalyst for the cross-coupling of **1a** and **2a**, we studied the scope of the cross-coupling between hindered aryllithium reagents and aryl bromides for the synthesis of tri-*ortho*-substituted biaryls (Table 1). A variety of bulky organolithium reagents could be coupled with excellent yield and high selectivity at room temperature in most cases within a reaction time of 1 h. The high selectivity (>98% for cross-coupling product) indicates that the transmetalation step takes place rapidly, thus facilitating a fast coupling process. Mono-*ortho*-functionalized aryllithium compounds bearing methoxy (Table 1, entries 2 and 3) and phenyl (Table 1, entry 4) substituents were efficiently coupled with di-*ortho*-substituted arylbromides. Moreover, a bulky methoxymethyl (MOM) protecting group could be tolerated at the *ortho* position of the organolithium reagent, thus allowing for an easy preparation through *ortho* lithiation[21] of the corresponding MOM-protected phenol (Table 1, entries 5 and 6). Taking advantage of the cooperative effect of two different *ortho*-directing groups, *N*,*N*-dimethyl-3-methoxy-benzylamine was selectively *ortho*-lithiated and successfully coupled with **2a** affording difunctionalized product **3g**, which bears two distinct functional groups, in excellent yield (Table 1, entry 7). Highly hindered di-*ortho*-substituted aryllithium reagents were coupled as well efficiently (Table 1, entries 1,8–10) at room temperature even when the extremely bulky 2,4,6-triisopropyl-phenyllithium[25] (**1h**) was used.

Having shown the excellent performance of hindered organolithium reagents in cross-coupling reactions we further explored this system for the synthesis of sterically demanding tetra-*ortho*-substituted biaryls. The difference in performance between $[Pd_2(dba)_3]/P(tBu)_3$ and PEPPSI-IPent was even higher in the synthesis of the tetra-*ortho*-substituted biaryl **6a** than that observed for the synthesis of the tri-*ortho*-substituted biaryl **3a.** In this case, full conversion was achieved with Pd-PEPPSI-IPent at room temperature in 1.5 h with complete selectivity and binaphthyl **6a** was isolated in 93% yield. $[Pd_2(dba)_3]/P(tBu)_3$ instead led to reduced conversion (50%) under the same conditions (Table 2, entries 1 and 2).

As observed for the synthesis of tri-*ortho*-substituted biaryls, a variety of organolithium and aryl bromides could be successfully employed for the synthesis of the tetra-*ortho*-substituted biaryl products. The more cumbersome methoxy substituent was tolerated also in this case, as demonstrated by using 2-methoxy-1-naphthyllithium (**1g**), which could be coupled efficiently at room temperature with 2-methyl-1-bromo-naphthalene (**2c**) and with 9-bromoanthracene (**2f**; Table 2, entries 1 and 3). Exploring the limits of this cross-coupling further, we used 2,6-dimethoxy-phenyllithium (**1a**). The presence of the two methoxy groups allowed for a mild synthesis of this reagent through *ortho* lithiation of inexpensive 1,3-dimethoxybenzene. This aryllithium reagent readily engaged in cross-coupling with di-*ortho*-substituted aryl bromides with total selectivity, thereby affording the corre-

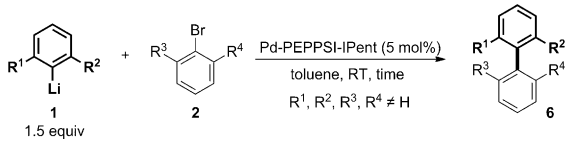
Table 1: Scope of the cross-coupling of hindered aryllithium reagents and arylbromides: synthesis of tri-*ortho*-substituted biaryls.[a,b]

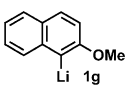
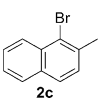
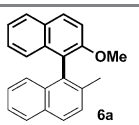
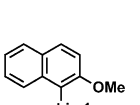
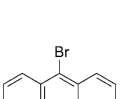
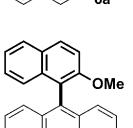
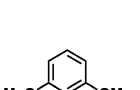
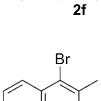


Entry	Ar–Li **1**	Ar′–Br **2**	Biaryl **3**	*t* [h]	Yield [%][c]
1				1	94
2				1	82
3				1	85
4				1	89
5				1.5	96
6[d]				4	83
7				1.5	90
8				1	79
9				3	92
10[e]				1.5	69

[a] Conditions: **2** (0.3 mmol) and Pd-PEPPSI-IPent (0.015 mmol) were dissolved in toluene (2 mL). A solution of aryllithium reagent **1** (1.5 equiv; see the Supporting Information for details regarding the preparation of the solutions) was added over 1 h by using a syringe pump. [b] Selectivity > 95% in all cases unless otherwise indicated. [c] Yields of isolated products. [d] Reaction run at 40°C. [e] 10% of homocoupling derived from bromide **2e**.

Table 2: Scope of the cross-coupling of hindered aryllithium reagents and arylbromides: synthesis of tetra-*ortho*-substituted biaryls.[a,b]



Entry	Ar–Li **1**	Ar′–Br **2**	Biaryl **6**	*t* [h]	Yield [%][c]
1				1.5	93
2[d]				1.5	(50)[f]
3				4	87
4				3	93
5[e]				3	83
6				4	(94)[f]
7[e]				3	80
8				1.5	76

[a] Conditions: **2** (0.3 mmol) and Pd-PEPPSI-IPent (0.015 mmol) were dissolved in toluene (2 mL). A solution of aryllithium reagent **1** (1.5 equiv; see the Supporting Information for details regarding the preparation of the solutions) was added over 1 h by using a syringe pump. [b] Selectivity > 95% in all cases. Full conversion achieved unless otherwise noted. [c] Yields of isolated products. [d] $[Pd_2(dba)_3]$ (2.5 mol%), $P(tBu)_3$ (7.5 mol%) used instead of Pd-PEPPSI-IPent, 2% of dehalogenation and 2% of homocoupling of bromide **2c** were observed. [e] Reaction run at 40°C. [f] Conversion.

sponding products with full conversion, high yields, and in short reaction time (3 h; Table 2, entries 4–7). The reactions proceeded at room temperature with excellent selectivity, although, in some particular cases, it was necessary to use a slightly elevated temperature (40°C) to reach full conversion (Table 2, entries 5–7). The fact that 2,6-dimethoxyphenyllithium can be used as an efficient coupling partner is a remarkable finding in light of the fact that the corresponding boronic acid suffers rapid proto-deboronation in the presence of strong bases at the high temperature generally required for these couplings,[7k] while the corresponding zinc reagent has been scarcely used.[13] Moreover, as far as we know, the use of *ortho*-alkoxy-substituted organometallic reagents has not been described before for the synthesis of hindered biaryls at room temperature. Also alkyl substituents in the organolithium reagents are well tolerated as is

illustrated in the coupling of 2-mesityllithium (**1i**) with 2-methyl-1-bromonaphthalene (**2c**; Table 2, entry 8).

The results obtained in the synthesis of tetra-*ortho*-substituted biaryls highlight some of the main advantages related to the use of lithium reagents: 1) a variety of lithium reagents can be prepared simply starting from the corresponding bromide and be used in subsequent cross-coupling with short reaction times and without necessity of purification. 2) The *ortho* metalation procedure allows the direct formation of the organolithium for cross-coupling from simple aromatic compounds. 3) Functional groups that generally are less tolerated in other organometallic reagents (*o*-OMe) can stabilize the corresponding lithium reagents with the advantage of easy preparation, handling and still high efficiency in the coupling. 4) In virtue of their high reactivity, the organolithium compounds seem to facilitate the transmetalation step affording, as far as we know, the fastest protocol so far for the synthesis of highly hindered *ortho*-substituted biaryls. 5) The present method is more versatile and can give rise to a wider scope of products than the aryne coupling,[26] which can also reach hindered biaryls using organolithium reagents but is limited to the use of 1,2-dibromobenzenes at cryogenic temperatures and is usually associated with regioselectivity problems when dissymmetric substrates are used.[26c]

In conclusion we have demonstrated that the high reactivity of organolithium reagents is beneficial in cross-coupling reactions to obtain fast coupling of highly hindered mono- and di-*ortho*-substituted aryllithium reagents at room temperature. The Pd-PEPPSI-IPent complex was shown to be an extremely efficient catalyst for this C–C bond formation. In combination with *ortho*-substituted bromides, a series of tri- and tetra-*ortho*-substituted biaryls could be selectively obtained in high yields at ambient temperatures and in short reaction time. This methodology is to be considered the fastest protocol to access tetra-*ortho*-substituted biaryls at room temperature to date. Detailed mechanistic studies to elucidate the key parameters determining this fast and mild cross-coupling are ongoing.

Experimental Section

Representative example for the synthesis of **3a**: in a dry Schlenk flask PEPPSI-IPent (5 mol%, 0.015 mmol, 11.87 mg) and 1-bromonaphthalene (**2a**; 0.3 mmol, 62.1 mg) were dissolved in dry toluene (2 mL) and the mixture was stirred at room temperature. A solution of 2,6-dimethoxy-phenyllithium (**1a**; 0.75 mL, 0.6 M in pentane/THF 2:1, 1.5 equiv) was slowly added over 1 h by using a syringe pump. When the addition was completed the reaction was stopped, a saturated aqueous solution of NH_4Cl was added, and the mixture was extracted (3× 5 mL) with ether. The organic phases were combined and the solvent evaporation under reduced pressure afforded the crude product. Purification by column chromatography (pent/EtOAc 200:1) afforded product **3a** as a white solid in 94% yield.

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[1] a) E. Negishi, *Angew. Chem.* **2011**, *123*, 6870 – 6897; *Angew. Chem. Int. Ed.* **2011**, *50*, 6738 – 6764; b) *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 1* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[2] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516 – 4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442 – 4489; b) J. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651 – 2710; c) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518 – 5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427.

[3] a) M. Yamamura, I. Moritani, S. Murahashi, *J. Organomet. Chem.* **1975**, *91*, C39 – C42; b) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821 – 1823; c) E. Negishi, A. O. King, N. Okukado, *J. Chem. Soc. Chem. Commun.* **1977**, 683 – 684; d) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437 – 3440.

[4] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem.* **2012**, *124*, 5150 – 5174; *Angew. Chem. Int. Ed.* **2012**, *51*, 5062 – 5085.

[5] R. J. Lundgren, M. Stradiotto, *Chem. Eur. J.* **2012**, *18*, 9758 – 9769.

[6] A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854 – 6869; *Angew. Chem. Int. Ed.* **2011**, *50*, 6722 – 6737.

[7] a) J. Yin, M. P. Rainka, X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162 – 1163; b) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195 – 15201; c) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907 – 1912; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871 – 1876; d) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696; e) O. M. Demchuk, B. Yoruk, T. Blackburn, V. Snieckus, *Synlett* **2006**, 2908 – 2913; f) T. Hoshi, T. Nakazawa, I. Saitoh, A. Mori, T. Suzuki, J. Sakai, H. Hagiwara, *Org. Lett.* **2008**, *10*, 2063 – 2066; g) W. Tang, A. G. Capacci, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez, B. Qu, N. Haddad, B. Z. Lu, D. Krishnamurthy, N. K. Yee, C. H. Senanayake, *Angew. Chem.* **2010**, *122*, 6015 – 6019; *Angew. Chem. Int. Ed.* **2010**, *49*, 5879 – 5883; h) C. M. So, W. K. Chow, P. Y. Choy, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 7996 – 8001; i) L. Ackermann, H. K. Potukuchi, A. Althammer, R. Born, P. Mayer, *Org. Lett.* **2010**, *12*, 1004 – 1007; j) Q. Zhao, C. Li, C. H. Senanayake, W. Tang, *Chem. Eur. J.* **2013**, *19*, 2261 – 2265; k) for an example of such reaction performed at 50 °C see D. Lee, M. Jin, *Org. Lett.* **2011**, *13*, 252 – 255.

[8] 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.

[9] a) L. Wu, E. Drinkel, F. Gaggia, S. Capolicchio, A. Linden, L. Falivene, L. Cavallo, R. Dorta, *Chem. Eur. J.* **2011**, *17*, 12886 – 12890; b) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C. S. J. Cazin, S. P. Nolan, *Chem. Eur. J.* **2012**, *18*, 4517 – 4521.

[10] a) C. Dai, G. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719 – 2724; b) 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; c) C. E. Hartmann, S. P. Nolan, C. S. J. Cazin, *Organometallics* **2009**, *28*, 2915.

[11] C. Wolf, H. Xu, *J. Org. Chem.* **2008**, *73*, 162 – 167.

[12] For an example of a tetra-*ortho*-substituted biaryl synthesized at room temperature with the use of Grignard reagents see: M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150 – 157.

[13] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028 – 13032.
[14] S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem.* **2010**, *122*, 2058 – 2061; *Angew. Chem. Int. Ed.* **2010**, *49*, 2014 – 2017.
[15] a) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem.* **2007**, *119*, 3876 – 3899; *Angew. Chem. Int. Ed.* **2007**, *46*, 3802 – 3824; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem.* **2011**, *123*, 9968 – 9999; *Angew. Chem. Int. Ed.* **2011**, *50*, 9794 – 9824.
[16] E. J. Anctil, V. Snieckus in *Metal Catalyzed Cross-Coupling Reactions*, *Vol. 1* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 761 – 813.
[17] S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, K. Kondo, *J. Org. Chem.* **1979**, *44*, 2408 – 2417.
[18] A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem.* **2010**, *122*, 7705 – 7709; *Angew. Chem. Int. Ed.* **2010**, *49*, 7543 – 7547.
[19] a) A. B. Smith III, A. T. Hoye, D. Martinez-Solorio, W.-S. Kim, R. Tong, *J. Am. Chem. Soc.* **2012**, *134*, 4533 – 4536; b) M. H. Nguyen, A. B. Smith III, *Org. Lett.* **2013**, *15*, 4258 – 4261.
[20] M. Giannerini, M. Fañanás-Mastral, B. L. Feringa, *Nat. Chem.* **2013**, *5*, 667 – 672.
[21] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879 – 933.
[22] G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555 – 1564.
[23] a) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824 – 2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768 – 2813; b) S. Díez-González, S. P. Nolan, *Org. Lett.* **2007**, *21*, 47 – 82.
[24] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743 – 4748; b) for a review on the applications of Pd-PEPPSI ligands see: C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* **2012**, *124*, 3370 – 3388; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314 – 3332.
[25] As far as we know, this highly hindered structural moiety has not been cross-coupled at room temperature by using any other organometallic reagent. For the use of 2,4,6-triisopropylphenylboronic acid for the synthesis of tri-*ortho*-substituted biaryls at 100 °C see Ref. [7h]. For the use of 2,4,6-triisopropyl-phenyl-zinc chloride for the synthesis of tri-*ortho*-substituted biaryls at 70 and 60 °C see Ref. [10b] and C. J. O'Brien, M. G. Organ, A. B. Kantchev, Can. Pat. Appl. CA 2556850, A1 20070224, **2007**, respectively.
[26] a) F. Leroux, M. Schlosser, *Angew. Chem.* **2002**, *114*, 4447 – 4450; *Angew. Chem. Int. Ed.* **2002**, *41*, 4272 – 4274; b) F. R. Leroux, L. Bonnafoux, C. Heiss, F. Colobert, D. A. Lanfranchi, *Adv. Synth. Catal.* **2007**, *349*, 2705 – 2713; c) V. Diemer, M. Begaud, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem.* **2011**, 341 – 354.

