University of Groningen

Advancing selectivity control with highly reactive organometallic reagents

Giannerini, Massimo

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Giannerini, M. (2015). *Advancing selectivity control with highly reactive organometallic reagents*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 01-03-2024

Chapter 6

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

The use of hindered aryllithium reagents in cross-coupling is described. Taking advantage of the fast transmetallation of organolithium reagents, the coupling of ortho-substituted aryllithium reagents and arylhalides proceeds expeditious, allowing for the synthesis of sterically congested tri- and tetrasubstituted biaryls at ambient temperature in reaction times as short as one hour.

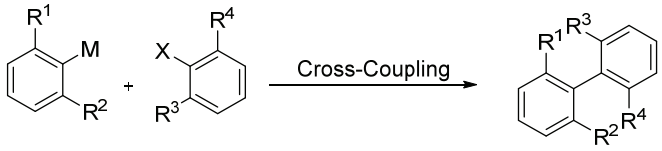
Part of this chapter has been published:

Giannerini, M.; Hornillos, V.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 13329.

1 Introduction

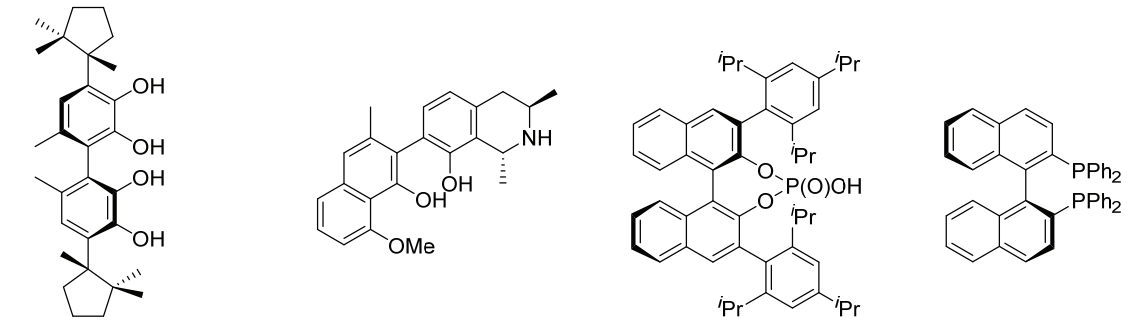
1.1 Hindered biaryls: recurring motifs in nature

At the early stage of Pd catalyzed cross-coupling, carbon sp^2-sp^2 bond formation has been the basis from which this methodology took its origin.[1] Starting from these pioneering studies, the Pd catalyzed formation of biaryl cores attracted interest and during subsequent years became the first alternative to the classic copper mediated protocols.[2] Although the synthesis of biaryls was successfully achieved already at the outset of the Pd-catalyzed cross-coupling methodology, the assembly of two hindered bis-*ortho*-substituted aryl units remained a challenging issue due to the high level of steric bulk that affects the rate of the oxidative addition and of the transmetallation step.[3]



Scheme 1. Cross-coupling of hindered biarylic compounds

Despite the difficulties in the construction of hindered *tri*- and *tetra*- substituted biaryls *via* cross-coupling, these structures are frequently present in many natural products and are the basic structures for the design of important classes of organocatalysts and ligands (figure 1).[4]



Mastigophorene A **Dioncophylline E** **TRIP** **BINAP**

Figure 1. Cross-coupling of hindered biarylic compounds

For many of the above mentioned compounds atropisomerism[4a] is a key stereochemical feature accounting for their biological activity[5] or, in the case of ligands[4b], bearing the chiral information in the asymmetric catalytic systems. This form of isomerism is possible when free rotation of the two aryl units (with $R^1 \neq R^2$ and $R^3 \neq R^4$) is locked, giving rise to two distinct isomers with P and M chirality (Figure 2). The bulk of the *ortho*-substituents is a determinant for the atropisomerism, as this is appreciable (in non-bridged structure) only when the free rotation of the two aryl units is impeded by the steric hindrance of the *ortho*-groups.

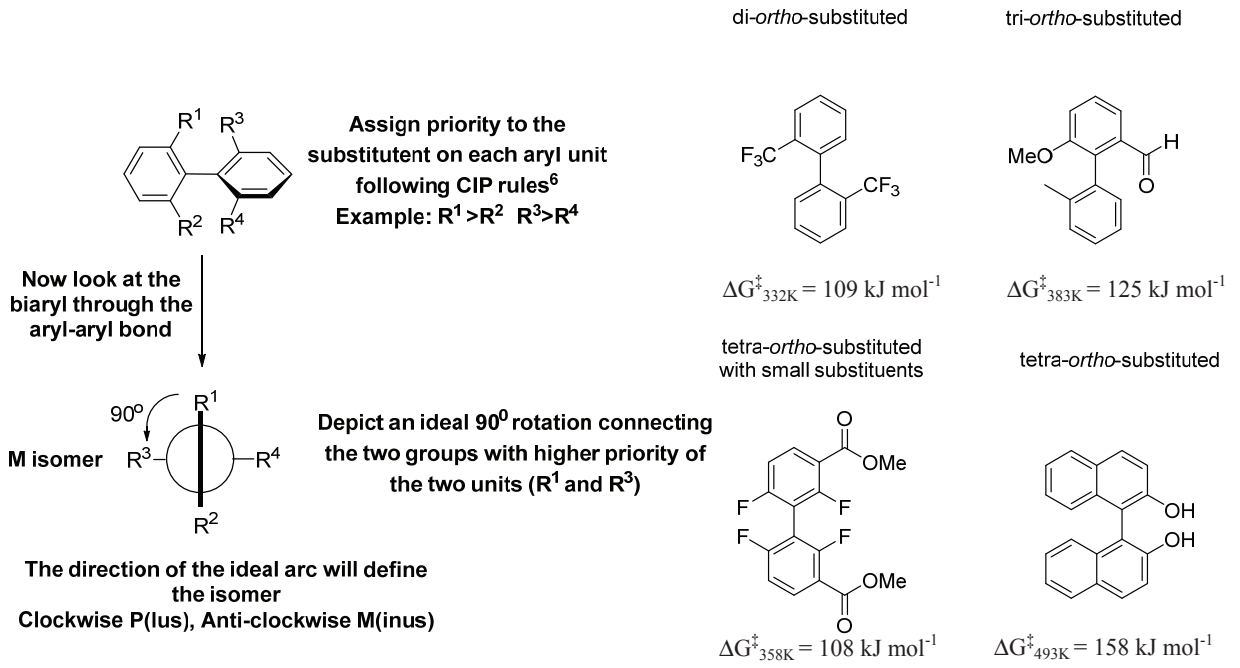


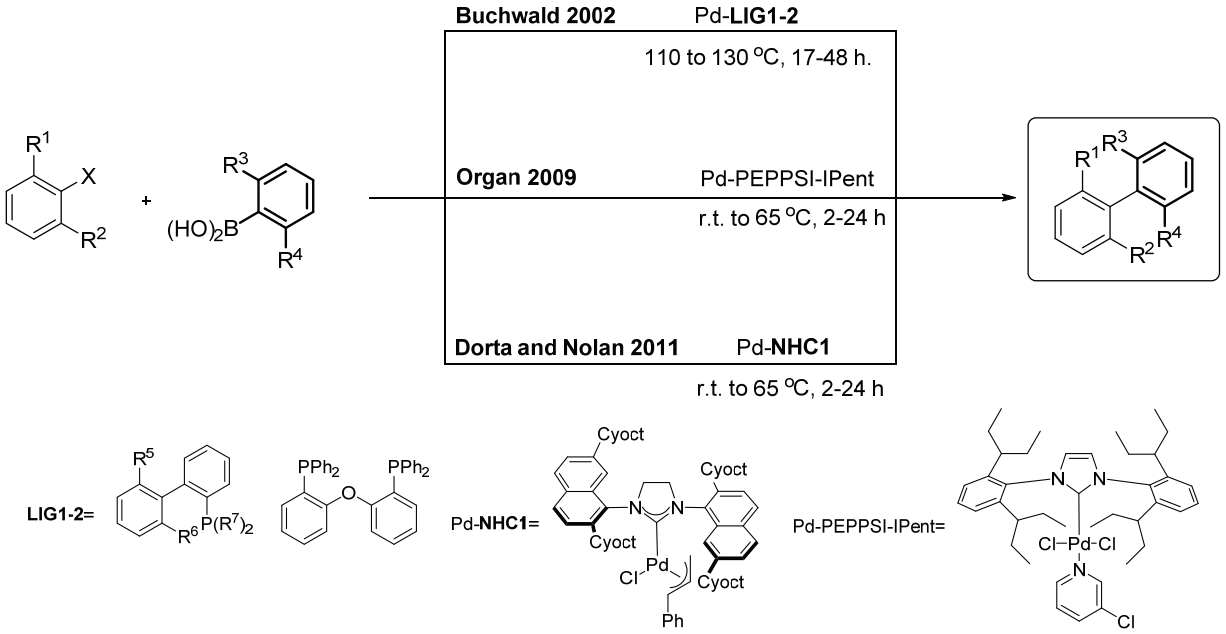
Figure 2. Atropoisomers absolute configuration and influence of the steric bulk on their configurational stability.[4,6]

The portfolio of Pd mediated cross-coupling reaction for the synthesis of hindered biaryls is still limitated, expecially when considering protocols proceeding at room temperature. A final aim of expanding such methodology is indeed the development of atroposelective Pd-catalyzed cross-couplings that currently have been only sporadically reported.[7] It would be desirable for this cross-coupling to proceed at mild temperatures especially when dealing with compounds that can undergo atropoisomerization at temperatures close to ambient conditions.

1.2 Hindered biaryls: Pd-catalyzed cross-coupling evolution toward protocol at room temperature

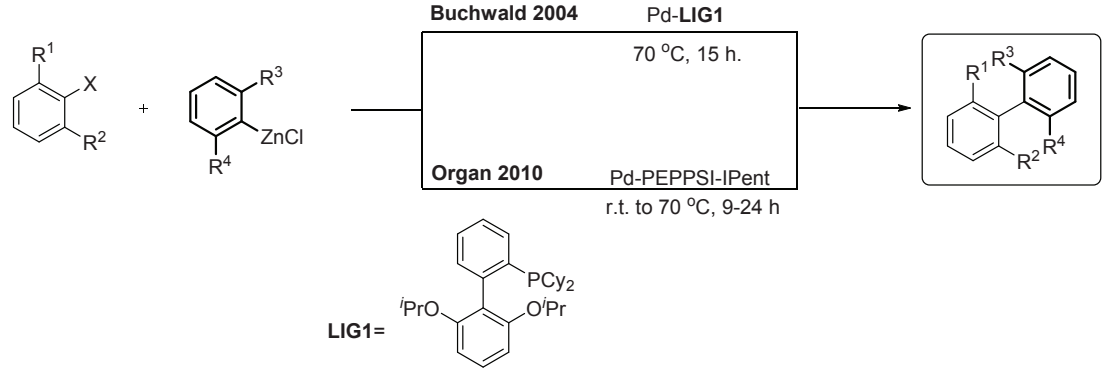
The development of increasingly efficient catalysts for the Pd catalyzed cross-coupling paved the way to reactions previously precluded.[3,8] Also the cross-coupling of hindered biaryls was addressed by tuning the ligand design, and Buchwald published in 2002 the first general protocol for the synthesis of tri- and tetra-substituted biaryls based on the use of biaryl-dialkyl-phosphine ligands and organoboron reagents (Suzuki coupling).[9] This transformation was characterized by the use of elevated temperature (110-130°C) and prolonged reaction time (Scheme 2). After this pioneering work many successful high yielding examples have been reported mostly with organoboron compounds.[10] While these reagents are characterized by a very benign functional group tolerance, the reaction conditions are generally harsh due to the high temperature and the long reaction time needed.[10] Only few example are available in which Suzuki coupling is performed at room temperature: mostly carbenes ligands were proven efficient to perform this task. The group of Organ reported in 2009 a general Suzuki-Miyaura cross-coupling based on the use of PEPPSI-IPent catalyst for the synthesis of tetra-*ortho* substituted biaryls at temperatures as low as 65 °C over 24 h.[11] Two years later using a tailored NHC carbene-Pd complex Dorta, Nolan and coworkers could perform for the first time this cross-coupling at room temperature.[12] Tang and coworkers recently disclosed a remarkable atroposelective coupling with organoboronic acids proceeding at room

temperature, but this methodology was limited to the synthesis of tri-*ortho*-substituted biaryls.[7o]



Scheme 2. Suzuki cross-coupling for the synthesis of hindered biaryls.

The use of Grignard and zinc reagents for the synthesis of hindered biaryls is more rare.[13] In 2008 Wolf disclosed the synthesis of tri-*ortho* substituted biaryls with Grignard reagents at room temperature using a reaction time of 24 h[14] but also in this case the protocol was not applied to the synthesis of tetra substituted biaryls. With respect to the use of zinc reagents significant progress has been made after the seminal report of sterically demanding cross-coupling at 70 °C over 15 h performed by the group of Buchwald.[15] Organ and co-workers extended the use of PEPPSI catalyst to the Negishi cross-coupling of hindered aryls. These coupling were performed successfully at temperatures varying from 23 to 70 °C and reaction times ranging from 9 to 24 hours (Scheme 3).[16]



Scheme 3. Negishi cross-coupling for the synthesis of hindered biaryls.

The brief survey of the state of the art regarding the coupling of hindered biaryls highlights a lack of concise methodologies capable to proceed at ambient condition and within short reaction times, whereas organolithium reagents have not been used so far.

2 Goal

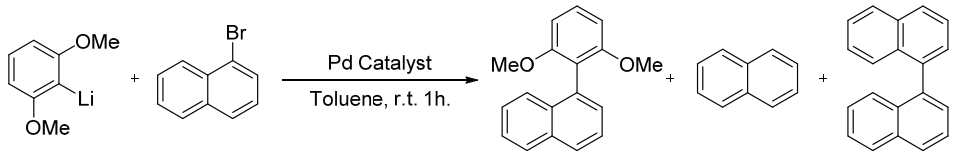
After describing the first Pd-catalyzed cross-coupling procedure with aryllithiums at room temperature,[17] we envisioned that the cross-coupling of hindered biaryls could represent an ideal case to prove the efficiency of this methodology. Two main reasons prompted us to undertake this research: 1) as highlighted in the introduction of this chapter, in the field of cross-coupling of hindered biaryls there is a severe lack of protocols in which the coupling proceeds rapidly at room temperature. The high reactivity demonstrated by the organolithium reagents in our earlier work[17] suggested that a fast transmetallation of the organolithium compounds could serve both to operate at room temperature and to achieve full conversion within short reaction times. 2) The synthesis of hindered biaryls implies the location of one or two *ortho*-funtionalities with respect to the lithiated position. This allows us to take full advantage of the *ortho*-lithiation techniques,[18] the most atom efficient and straightforward way to access aryllithium compounds. The presence of *ortho*-coordinating groups renders the lithiation faster and the formed organolithium reagents are usually more stable and easy to handle. The goal of the project was to combine these elements to provide a new procedure to couple hindered organolithium reagents at ambient conditions in short reaction times.

3 Results and discussion

3.1 Optimization of the cross-coupling reaction

Initially we applied our previously reported conditions[17a] 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 $P(^tBu)_3$[19] and slow addition of **1a** led to a selective reaction in which common side products derived from halogen/lithium exchange like dehalogenated product **4a** and homocoupled product **5a** were not observed (Table 1, entry 1). Unfortunately, despite its high selectivity this catalyst resulted in incomplete conversion (86%) the remaining being unreacted bromide. Buchwald's hindered biaryl-dialkylphosphines[20] were also screened. The use of SPhos resulted in lower selectivity while still full conversion was not reached (Table 1, entry 2). XPhos instead was proven as a highly competent ligand in both terms of selectivity and reactivity (Table 1, entry 3). We also examined Pd-NHC catalysts for this C-C bond formation. *N*-Heterocyclic carbene (NHC) ligands have emerged as attractive ligands in cross-coupling due to their specific steric features and strong σ-bond donor capabilities.[21] Recently, the group of Organ introduced highly effective Pd-PEPPSI precatalysts that are air stable and commercially available.[22] To our delight the use of Pd-PEPPSI-IPent, which is known for its efficiency in cross-coupling of hindered substrates with other organometallics,[10,16] afforded biaryl **3a** with full conversion and >99% selectivity in the cross-coupling of bis-orthomethoxy-phenyllithium **1a** and bromonaphthalene **2a** at room temperature in 1 h (Table 1, entry 4).

Table 1. Tri-*ortho*-substituted biaryls *via* organolithium cross-coupling: optimization.



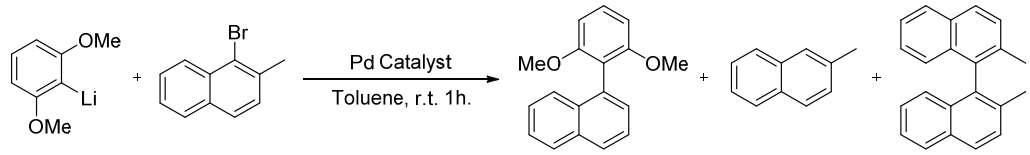
1a 1.5 equiv. **2a** **3a** **4a** **5a**

Entry[a]	Pd Catalyst	Conversion (%)[b]	3a/4a/5a[b]
1	$Pd_2(dba)_3$ 2.5 mol% / $P(^tBu)_3$ 7.5 mol%	86	99/1/-
2	$Pd_2(dba)_3$ 2.5 mol% / SPhos 10 mol%	90	83/7/10
3	$Pd_2(dba)_3$ 2.5 mol% / XPhos 10 mol%	full	95/1/4
4	Pd-PEPPSI-IPent 5 mol%	full	99/-/-

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

While the performance of Pd/XPhos was comparable with the one of Pd-PEPPSI in the synthesis of tri-*ortho*-substituted biaryls, the difference in reactivity became dramatic when the synthesis of a tetra-*ortho*-substituted was taken in account (Table 2).The conversion in the presence of XPhos was very low (Table 2, entry 2) while Pd-PEPPSI-IPent still afforded full conversion and selectivity. The choice between the two catalytic systems is obviously in favour of Pd-PEPPSI-IPent (Table 2, entry 3).

Table 2. Tetra-*ortho*-substituted biaryls *via* organolithium cross-coupling: optimization.



1a 1.5 equiv. **2b** **6a** **4b** **5b**

Entry[a]	Pd Catalyst	Conversion (%)[b]	6a/4b/5b[b]
1	$Pd_2(dba)_3$ 2.5 mol% / $P(^tBu)_3$ 7.5 mol%	50	96/2/2
2	$Pd_2(dba)_3$ 2.5 mol% / XPhos 10 mol%	20	-
3	Pd-PEPPSI-IPent 5 mol%	full	99/-/-

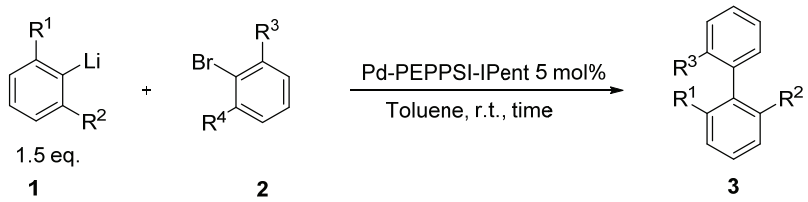
[a]Conditions: to a solution of **2b** (0.3 mmol) and Pd catalyst (5 mol%) in 2 mL of toluene a solution of aryllithium reagent **1a** (1.5 equiv) (see experimental section for details regarding the preparation of the solutions) was added over 1 h by syringe pump.
[b]GC analysis.

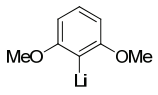
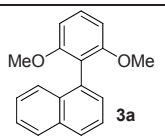
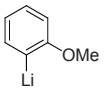
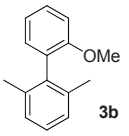
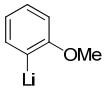
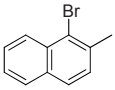
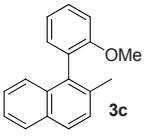
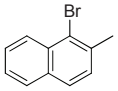
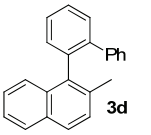
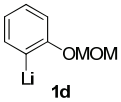
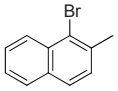
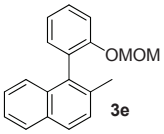
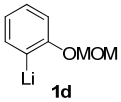
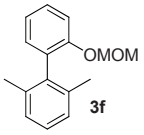
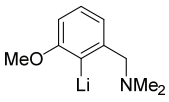
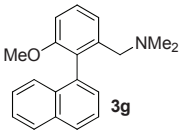
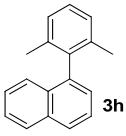
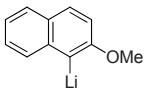
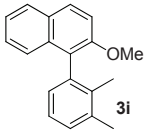
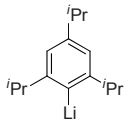
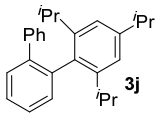
3.2 Scope

3.2.1 Tri-*ortho*-substituted hindered biaryls

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 arylbromides for the synthesis of tri-*ortho* substituted biaryls (Table 3). A variety of bulky organolithium reagents could be coupled with excellent yields and high selectivity at room temperature and in most cases within a reaction time of 1 h. The high selectivity (>98% for cross-coupling product) indicates that the transmetallation step takes place rapidly preventing side reactions to occur and excess of organolithium reagents to accumulate in the reaction medium. Mono-*ortho* (Table 3, entries 2-6) functionalized aryllithium compounds bearing methoxy (Table 3, entries 2 and 3) and phenyl (Table 3, entry 4) substituents were efficiently coupled with di-*ortho*-substituted arylbromides. Moreover a bulky MOM protecting group could be tolerated at the *ortho* position of the organolithium reagent allowing for an easy preparation via *ortho*-lithiation[18] of the corresponding MOM protected phenol (Table 3, entries 5 and 6). Taking advantage of the cooperative effect of two different *ortho*-directing groups, 3-methoxy-*N,N*-dimethylbenzylamine was selectively lithiated and subsequently coupled affording the functionalized product **3g** in excellent yields. Highly hindered di-*ortho*-substitued aryllithium reagents were coupled as well efficiently (Table 3, entries 1,7-10) at room temperature even when the extremely bulky 2,4,6-triisopropyl-phenyllithium[9g,13b,23] **1h** was used (Table 3, entry 10).

Table 3. Tri-*ortho*-substituted biaryls *via* organolithium cross-coupling: scope.



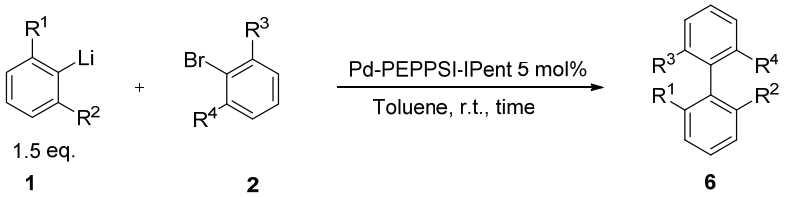
Entry[a,b]	Ar-Li	Ar[1]-Br	Product	Time (h)	Yield[c] (%)
1	 **1a**	 **2a**	 **3a**	1	49
2	 **1b**	 **2b**	 **3b**	1	82
3	 **1b**	 **2c**	 **3c**	1	85
4	 **1c**	 **2c**	 **3d**	1	89
5	 **1d**	 **2c**	 **3e**	1.5	96
6[d]	 **1d**	 **2b**	 **3f**	4	83
7	 **1e**	 **2a**	 **3g**	1.5	90
8	 **1f**	 **2a**	 **3h**	1	79
9	 **1g**	 **2d**	 **3i**	3	92
10[e]	 **1h**	 **2e**	 **3j**	1.5	69

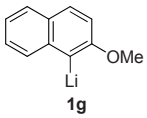
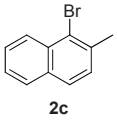
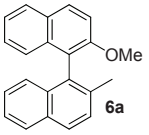
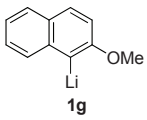
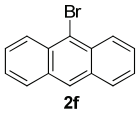
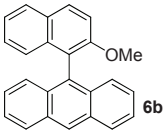
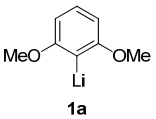
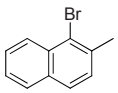
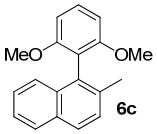
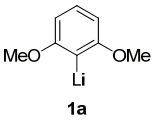
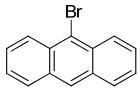
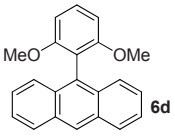
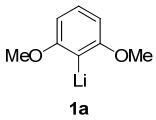
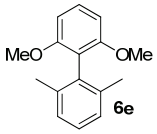
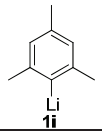
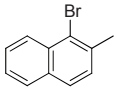
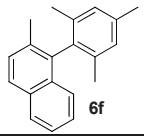
[a]Conditions: **2** (0.3 mmol) and Pd-PEPPSI-IPent (0.015 mmol) were dissolved in 2 mL of toluene. A solution of aryllithium reagent **1** (1.5 equiv) (see experimental section for details regarding the preparation of the solutions) was added over 1 h by syringe pump. [b]Selectivity >95% in all cases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

3.2.2 Tetra-*ortho*-substituted hindered biaryls

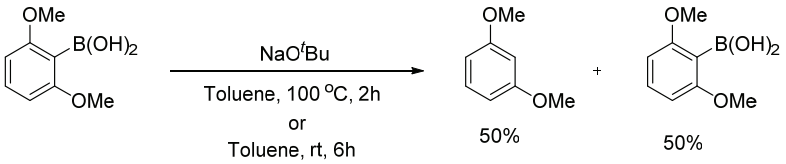
As observed for the synthesis of tri-*ortho*-substituted biaryls, a variety of organolithiums and arylbromides could be successfully employed for the synthesis of the tetra-*ortho*-substituted biaryl products. The methoxy-substituent was tolerated also in this case as demonstrated by using 2-methoxy-1-naphthyllithium **1g** which could be coupled efficiently at room temperature with 2-methyl-1-bromo-naphthalene **2c** and with 9-bromoanthracene **2f** (Table 4, entries 1 and 2). 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 via *ortho*-lithiation of inexpensive 1,3-dimethoxybenzene. This aryllithium reagent readily engaged in cross-coupling with di- *ortho*-substituted arylbromides with total selectivity affording the corresponding products with full conversion, high isolated yields and in short reaction time (3 h) (Table 4, entries 3-5). 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) in order to reach full conversion (Table 4, entries 4 and 5). The fact that 2,6-dimethoxy-phenyllithium 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 (see Scheme 4),[10g] while the corresponding zinc reagent has been scarcely used.[15] 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-bromo-naphthalene **2c** (Table 4, entry 6).

Table 4. Tetra-*ortho*-substituted biaryls *via* organolithium cross-coupling: scope.



Entry[a,b]	Ar-Li	Ar[1]-Br	Product	Time (h)	Yield[c] (%)
1	 1g	 2c	 6a	1.5	93
2	 1g	 2f	 6b	4	87
3	 1a	 2c	 6c	3	93
4[d]	 1a	 2f	 6d	3	83
5[d]	 1a	 2b	 6e	4	80
6	 1i	 2c	 6f	1.5	76

[a]Conditions: **2** (0.3 mmol) and Pd-PEPPSI-IPent (0.015 mmol) were dissolved in 2 mL of toluene. A solution of aryllithium reagent **1** (1.5 equiv) (see experimental section for details regarding the preparation of the solutions) was added over 1 h by syringe pump. [b]Selectivity >95% in all cases. [c]Isolated yields. [d]Reaction run at 40 °C.



Scheme 4. Instability of electron-rich arylboronic acids in strong basic medium.

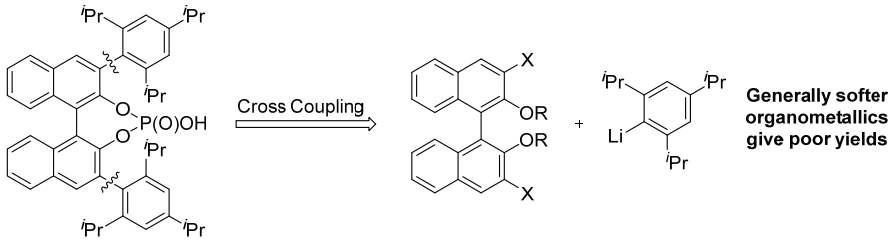
The scope of the cross-coupling demonstrated here confirms our hypothesis that the reactivity of organolithium reagents could serve as a powerful driving force to overcome the intrinsic difficulties in connecting two very hindered aryl units. Notably this is one of the very few reported protocols to generate hindered biaryls at room temperature and by far the fastest. It is also testimony of the potential of organolithium reagents to introduce unreported reaction profiles in terms of reactivity and performance. As a final remark, it should be noted that while the general assumption that organoboron reagents are highly functional group tolerant is valid, the harsh conditions often associates with the use of the highly hindered ones may be not compatible with labile moieties. Consequently it is not surprising that, comparing the scope

reported for organolithium reagents with the ones involving boron, magnesium and zinc derivatives, the differences in functional group tolerance is not so relevant in certain cases. Certain reports with hindered boronic acids present a functional groups tolerance comparable to the one reported for organolithium cross-coupling.[12] Moreover, focusing on the organometallic component, in many cases organolithiums presents a wider scope than zinc, magnesium and boron.[17]

4 Conclusions and future perspectives

Summarizing, 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 the necessity of purification. 2) The *ortho*-metallation procedure allows the direct formation of the organolithium for cross-coupling from simple aromatic compounds. 3) Functional groups that generally are less tolerated with organoboron reagents,[9g] such as *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 transmetallation step affording, as far as we know, the fastest protocol 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[24] which can also reach hindered biaryls using organolithium reagents but which is limited to the use of 1,2-dibromobenzenes at cryogenic temperatures and is usually associated with regioselectivity problems when dissymmetric substrates are used.[24c]

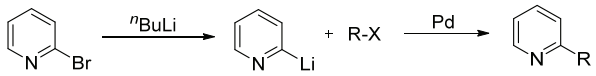
All this aspects clearly identify benefits of using lithium reagents. It is a fact that Pd catalyzed cross-coupling with softer organometallics is well established as a result of 40 years of tremendous efforts from the chemical community, although on the other hand applying challenging cross-coupling may be far from trivial. Often in synthesis, we observe a discrepancy between the high efficiency reported in methodologies and their actual performance in practical application. For example, despite the many successful reports for the cross-coupling of hindered biaryls, cross-coupling of sterically demanding units to the 3,3'-position of BINOL[4c] based core is generally challenging and with soft organometallics leads to the products in low yields. The use of highly reactive organolithium reagents could, in light of the results shown in this chapter, bring the opportunity to improve the outcome of such protocols.



Scheme 5. Application of hindered aryllithium cross-coupling to the synthesis of bulky ligands.

As we noted in this chapter, the stability of lithium reagents may follow an opposite trend if compared with organoboron reagents (see Table 4, entry 3-5). As not all the boronic acids are bench stable,[25] in these cases using the corresponding lithium reagents represent a viable alternative. Despite the great availability of organoboron reagents, for example many 2-

substituted heteroaromatic boronic acids suffer rapid protodeboronation. This fact, in combination with their lower reactivity often shown by these reagents (and so, longer exposition to high temperature and bases) account for erratic and unsatisfactory yields. The use of Sn reagents for heteroaromatic compounds is more appealing but involves formation of highly toxic waste.



Scheme 6. Use of organolithium reagents in place of unstable boronic acids.

Choosing carefully the condition may allow to produce 2-pyridyllithium[26] (see Scheme 6) and similar electron poor heteroaryllithium reagents solution stable at room temperature to be used successfully in cross-coupling protocols.

5 Experimental section

General Methods

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. THF and toluene were dried and distilled over sodium. Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Carbon assignments are based on APT ^{13}C-NMR experiments. Melting points were measured using a Büchi Melting Point B-545. $Pd_2(dba)_3$, $P(^{t}Bu)_3$ and Pd-PEPPSI-IPent were purchased from Aldrich and used without further purification. ^{n}BuLi (1.6 M solution in hexane) was purchased from Acros. ^{t}BuLi (1.7 M in pentane) and the compounds used as precursor for the preparation of lithium reagents, namely 1-bromo-2,6-dimethyl-benzene, 1,3-dimethoxybenzene, 1-bromo-2,6-dimethoxybenzene, 1-bromo-2,4,6-triisopropylbenzene, 1-bromo-2,4,6-trimethylbenzene, 2-bromoanisole and 2-bromo-1,1'-biphenyl were purchased from Aldrich. 1-Bromo-2-methoxynapthalene was purchased from TCI Europe. All the bromides were commercially available and were purchased from Aldrich. Organolithium reagents other than the aforementioned were prepared according to described procedures (see below).

General Procedures for the Cross-Coupling of Hindered Aryllithium Reagents

In a dry Schlenk flask PEPPSI-IPent (5 mol%, 0.015 mmol, 11.87 mg) and the substrate (0.3 mmol) were dissolved in 2 mL of dry toluene and the mixture was stirred at room temperature (unless otherwise stated: see experimental details). The corresponding lithium reagent (1.5 equiv) was slowly added over 1 h by syringe pump. When the addition was completed the reaction was stopped (or stirred for an additional 0.5-3 h: see experimental details) and a saturated aqueous solution of NH_4Cl was added whereupon the mixture was extracted with

ether (3 x 5mL). The organic phases were combined dried with anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product that was then purified by column chromatography.

Preparation of organolithium reagents:

A. 2-Methoxyphenyllithium, (1,1'biphenyl)-2-yllithium, 2,6-dimethylphenyllithium, 2,4,6-trimethyl-phenyllithium and 2,4,6-triisopropylphenyllithium.

In a dry Schlenk flask the corresponding bromide (1.8 mmol) was dissolved in dry THF (0.9 mL) and the solution was cooled down to -78 °C. ^{t}BuLi (2 equiv) was added slowly and the solution was stirred for 1 h. Then the solution was allowed to reach room temperature.

B. 2-Methoxyphenyllithium, (1,1'biphenyl)-2-yllithium, 2,6-dimethylphenyllithium, 2,4,6-trimethyl-phenyllithium and 2,4,6-triisopropylphenyllithium.

In a dry Schlenk flask (methoxymethoxy)benzene[27] (1.0 mmol, 138 mg) was dissolved in dry THF (3 mL) and the solution was cooled down to -78 °C. ^{t}BuLi (1 equiv) was added slowly and the solution was stirred for 1 h. Then the solution was allowed to reach room temperature.

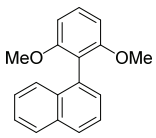
C. 2-Methoxy-1-naphthyllithium.

In a dry Schlenk flask 1-bromo-2-methoxynaphthalene (1.8 mmol, 427 mg) was dissolved in dry THF (0.9 mL) and added (addition rate: 8 mL/h) to a cold (-10 °C) solution (1.6 M in hexane) of ^{n}BuLi (1.05 equiv). Then the solution was stirred for 30 min and allowed to reach room temperature. The resulting solution of the lithium reagent was diluted with 1 mL of toluene.

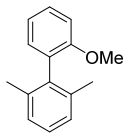
D. 2.6-Dimethoxyphenyllithium and 2-methoxy-6-dimethylaminomethyl-phenyllithium.

In a dry Schlenk flask 2,6-dimethoxybenzene or 3-methoxy-benzylamine (1.8 mmol) was dissolved in dry THF (0.9 mL) and the solution was cooled down to -10 °C. ^{n}BuLi (1.6 M in hexane, 1 equiv, 1.125 mL) was added slowly and the solution was stirred for 30 min. Then the solution was allowed to reach room temperature. The resulting solution of the lithium reagent was diluted with 1 mL of toluene.

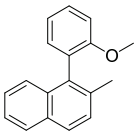
Spectral data of compounds 3a-3j and 6a-6f



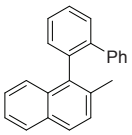
1-Butyl-4-methoxybenzene (3a): Reaction temperature: r.t. White solid obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 200:1), [94% yield]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 8.1 Hz, 1H),7.56 – 7.37 (m, 5H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.67 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 133.6, ù132.7, 132.6, 129.1, 128.2, 128.1, 127.5, 126.0, 125.51, 125.46, 125.39, 117.6, 104.2, 56.0. HRMS (ESI+, *m/z*): calculated for $C_{18}H_{17}O_2$ [M+H$^+$]: 265.1223; found: 265.1224.The physical data were identical in all respects to those previously reported.[28]



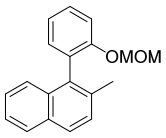
2'-Methoxy-2,6-dimethyl-1,1'-biphenyl (3b): Reaction temperature: r.t. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [82% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 1H), 7.21 (dd, *J* = 8.6, 6.2 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.10 – 6.99 (m, 3H), 3.77 (s, 3H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 138.3, 136.6, 130.7, 129.6, 128.4, 127.12, 127.08, 120.7, 110.9, 55.5, 20.5. The physical data were identical in all respects to those previously reported.[10h]



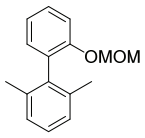
1-(2-Methoxyphenyl)-2-methylnaphthalene (3c): Reaction temperature: r.t. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [85% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H) 7.50 – 7.28 (m, 5H), 7.19 – 7.05 (m, 3H), 3.70 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 134.6, 133.9, 132.9, 132.00, 131.8, 128.8, 128.5, 128.2, 127.8, 127.2, 125.9, 125.7, 124.6, 120.7, 111.1, 55.6, 20.5. HRMS (ESI+, *m/z*): calculated for $C_{18}H_{17}O$ [M+H$^+$]: 249.1274; found: 249.1273. The physical data were identical in all respects to those previously reported.[29]



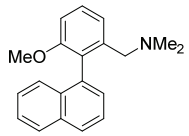
1-(2'-Biphenyl)-2-methylnaphthalene (3d): Reaction temperature: r.t. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/toluene 100:1), [89% yield]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.31 (m, 6H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.10 – 6.89 (m, 5H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.5, 138.1, 137.5, 133.7, 132.1, 131.7, 130.5, 129.5, 128.9, 128.7, 128.12, 128.07, 127.8, 127.5, 127.4, 126.8, 126.5, 126.2, 124.8, 20.9. The physical data were identical in all respects to those previously reported.[7h]



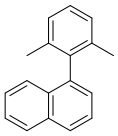
1-(2-(Methoxymethoxy)phenyl)-2-methylnaphthalene (3e): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for additional 0.5 h. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1.5), [96% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.36 (m, 4H), 7.35 – 7.28 (m, 2H), 7.18 – 7.15 (m, 2H), 4.99 (d, *J* = 6.8 Hz, 1H), 4.96 (d, *J* = 6.8 Hz, 1H), 3.17 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 134.7, 133.8, 132.9, 131.9, 129.4, 128.8, 128.5, 127.7, 127.2, 125.9, 125.7, 124.6, 122.1, 115.3, 94.4, 55.8, 20.5.



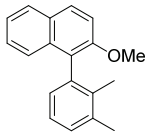
2'-(Methoxymethoxy)-2,6-dimethyl-1,1'-biphenyl (3f): Reaction temperature: 40 °C. After the addition of the lithium reagent was completed the reaction mixture was stirred for additional 3 h. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [83% yield]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (ddd, *J* = 8.5, 6.9, 2.2 Hz, 1H), 7.23 (dd, *J* = 8.2, 1H),7.18 (dd, *J* = 8.5, 6.3 Hz, 1H), 7.12 (dd, *J* = 7.2 Hz, 2H), 7.08 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.06 (dd, *J* = 7.5, 2.1 Hz, 1H), 5.06 (s, 2H), 3.31 (s, 3H), 2.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 138.3, 136.6, 130.8, 130.7, 128.4, 127.1, 127.0, 122.1, 115.2, 94.6, 55.8, 20.5. The physical data were identical in all respects to those previously reported.[30]



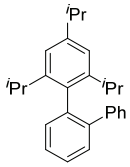
1-(3-methoxy-2-(naphthalen-1-yl)phenyl)-N,N-dimethylmethanamine (3g): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for additional 0.5 h. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 9:1 + NEt_3 1%), [90% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, *J* = 9.0 Hz, 2H), 7.55 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.39 – 7.28 (m, 4H), 6.94 (d, *J* = 8.1 Hz, 1H), 3.62 (s, 3H), 3.05 (d, *J* = 13.9 Hz, 2H), 2.95 (d, *J* = 13.9 Hz, 2H), 2.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 140.1, 135.14, 133.6, 132.8, 128.9, 128.7, 128.4, 127.8, 127.6, 126.0, 125.9, 125.7, 125.5, 121.3, 109.26, 60.9, 56.0, 45.7.



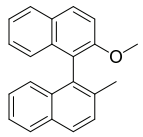
1-(2,6-Dimethylphenyl)naphthalene (3h): Reaction temperature: r.t. White solid obtained after column chromatography (SiO_2, *n*-pentane/toluene 100:0.5), [79% yield]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.57 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.37 (dd, *J* = 4.6, 0.8 Hz, 2H), 7.29 (dd, *J* = 10.9, 4.6 Hz, 2H), 7.21 (d, *J* = 7.7 Hz, 2H), 1.94 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 138.8, 137.0, 133.7, 131.7, 128.3, 127.3, 127.27, 127.2, 126.4, 126.1, 125.8, 125.7, 125.4, 20.4. The physical data were identical in all respects to those previously reported.[31]



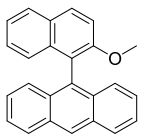
1-(2,3-Dimethylphenyl)-2-methoxynaphthalene (3i): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for additional 2 h. White solid (mp 102-103 °C) obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [92% yield]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.0 Hz, 1H), 7.85 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.40 (d, *J* = 9.0 HZ, 1H), 7.38 – 7.20 (m, 5H), 7.06 (dd, *J* = 6.9, 1.6 Hz, 1H), 3.86 (s, 3H), 2.41 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 136.7, 136.1, 136.0, 133.6, 129.1, 129.0, 128.8, 128.6, 127.8, 126.2, 125.3, 125.22, 125.17, 123.4, 113.6, 56.6, 20.7, 16.3.



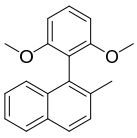
2,4,6-Triisopropyl[1,1';2',1'']terphenyl (3j): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for additional 0.5 h. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane/toluene 100:1), [69% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.45 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.38 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.25 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.17 – 7.06 (m, 5H), 6.93 (s, 2H), 2.89 (septet, *J* = 7.0 Hz, 1H), 2.57 (septet, *J* = 6.8 Hz, 2H), 1.27 (d, *J* = 7.0 HZ, 6H), 1.04 (d, *J* = 6.8 Hz, 6H), 0.87 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.2, 141.1, 138.8, 135.5, 131.3, 129.6, 129.4, 127.4, 127.2, 126.7, 126.3, 120.5, 34.1, 30.4, 25.5, 24.1, 22.7. The physical data were identical in all respects to those previously reported.[10f]



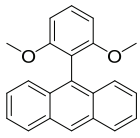
2-Methoxy-2'-methyl-1,1'-binaphthalene (6a): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for an additional 0.5 h. White solid obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [93% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 1H), 7.94 – 7.87 (m, 3H), 7.56 (d, *J* = 9.4 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.27 – 7.20 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 3.78 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 135.0, 133.7, 133.2, 132.4, 132.1, 129.4, 129.2, 128.7, 127.95, 127.93, 127.5, 126.6, 125.85, 125.84, 125.1, 124.7, 123.6, 122.0, 113.8, 56.6, 20.3. The physical data were identical in all respects to those previously reported.[32]



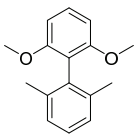
9-(2-Methoxynaphthalen-1-yl)anthracene (6b): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for an additional 3 h. Yellow solid (degrades at 219-220 °C) obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 200:1), [87% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.11 (m, 3H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 9.1 Hz, 1H), 7.51 – 7.38 (m, 4H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.13 (dt, *J* = 7.3, 1.0 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 3.69 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 134.5, 131.6, 131.5, 131.0, 129.9, 129.1, 128.6, 127.9, 126.8, 126.65, 126.61, 125.6, 125.4, 125.1, 123.7, 121.0, 113.9, 56.7. HRMS (APCI+, *m/z*): calculated for $C_{25}H_{19}O$ [M+H$^+$]: 335.1430; found: 335.1440.



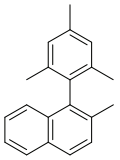
1-Butyl-4-methoxybenzene (6c): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for an additional 2 h. White solid (mp 120-122 °C) obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 200:1), [93% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H) 7.48 – 7.31 (m, 4H), 6.78 (d, *J* = 8.4 Hz, 2H), 3.68 (s, 6H), 2.27 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 134.5, 132.9, 132.0, 130.9, 129.1, 128.6, 127.9, 127.2, 125.6, 125.5, 124.4, 116.4, 104.2, 55.9, 20.4. HRMS (ESI+, *m/z*): calculated for $C_{19}H_{19}O_2$ [M+H$^+$]: 279.1380; found: 279.1381. The physical data were identical in all respects to those previously reported.[33]



9-(2,6-Dimethoxyphenyl)anthracene (6d): Reaction temperature: 40 °C. After the addition of the lithium reagent was completed the reaction mixture was stirred for an additional 2 h. Yellow solid obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [83% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.51 (t, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 3.56 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 131.6, 130.5, 130.3, 129.6, 128.5, 126.5, 126.4, 125.0, 124.9, 115.5, 104.3, 56.0. HRMS (ESI+, *m/z*): calculated for $C_{22}H_{19}O_2$ [M+H$^+$]: 315.1380; found: 335.1382. The physical data were identical in all respects to those previously reported.[9]



2,6-Dimethoxy-2',6'-dimethyl-1,1'-biphenyl (6e): Reaction temperature: 40 °C. After the addition of the lithium reagent was completed the reaction mixture was stirred for an additional 2 h. White solid obtained after column chromatography (SiO_2, *n*-pentane/Et_2O 100:1), [80% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, *J* = 8.3 Hz, 1H), 7.24 – 7.10 (m, 3H), 6.69 (d, *J* = 8.3 Hz, 2H), 3.74 (s, 6H), 2.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 137.1, 134.1, 128.6, 127.1, 126.8, 117.7, 104.00, 55.8, 20.1. The physical data were identical in all respects to those previously reported.[10h]



1-Mesityl-2-methylnaphthalene (6f): Reaction temperature: r.t. After the addition of the lithium reagent was completed the reaction mixture was stirred for an additional 0.5 h. Transparent oil obtained after column chromatography (SiO_2, *n*-pentane), [76% yield].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H)7.50 – 7.37 (m, 2H), 7.35 – 7.24 (m, 2H), 7.06 (s, 2H), 2.44 (s, 3H), 2.17 (s, 3H), 1.84 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.7, 135.7, 133.3, 132.4, 132.4, 128.9, 128.4, 128.1, 127.1, 126.2, 125.3, 125.0, 21.4, 20.1, 20.0. The physical data were identical in all respects to those previously reported.

6 References

1) a) Yamamura, M.; Moritani, I.; Murahashi, S. *J. Organomet. Chem.* **1975**, *91*, C39; b) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821; c) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc.,Chem. Commun.* **1977**, 683; d) Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1976**, *117*, C55; e) Kosugi, M.; Simizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423; f) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992; g) Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408; h) Miyaura, N.; Suzuki, A. *J. Chem. Soc.,Chem. Commun.* **1979**, 866.
2) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
3) Stradiotto, M.; Lundgren, R. J.; *Chem. Eur. J.* **2012**, *18*, 9758.
4) a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; b) Chen, Y.; Yekta, S.; Yudin, A. *Chem. Rev.* **2003**, *103*, 3155; c) Parmer, D,; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.
5) LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005.
6) Prelog, V; Helmchen, G. *Angew. Chem. Int. Ed.* **1982**, *21*, 567.
7) a) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101; b) Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593; c) Genov, M.; Almorin, A.; Espinet, P. *Tetrahedron: Asymmetry* **2007**, *18*, 625; d) Yin, J. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2000**, *122*, 12051; e) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc*. **2010**, *132*, 11278; f) Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun*. **2000**, 1723; g) Cammidge, A. N.; Crepy, K. V. L. *Tetrahedron* **2004**, *60*, 4377; h) Bermejo, A.; Ros, A.; Fernandez, R.; Lassaletta, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 15798; i) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed*. **2009**, *48*, 2708; j) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. *Angew. Chem., Int. Ed*. **2008**, *47*, 6917; k) Zhang, S.; Wang, Z. Q.; Xu, M.; Lin, G. *Org. Lett*. **2010**, *12*, 5546; l) Genov, M.; Almorin, A.; Espinet, P. *Chem. Eur. J*. **2006**, *12*, 9346; m) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. *Angew. Chem., Int. Ed*. **2011**, *50*, 8844; n) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L. *Org. Lett*. **2012**, *14*, 1966; o) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. *J. Am. Chem. Soc.* **2014**, *136*, 570.
8) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.
9) Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2002**, *124*, 1162.
10) a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195; b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2004**, *43*, 1871; c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc*. **2005**, *127*, 4685; d) Demchuk, O. M.; Yoruk, B.; Blackburn, T.; Snieckus, V.; *Synlett* **2006**, 2908; e) Hoshi, T.; Nakazawa, T.; Saitoh, I.; Mori, A.; Suzuki, T.; Sakai, J.; Hagiwara, H. *Org. Lett*. **2008**, *10*, 2063; f) Tang, W. *et al*. *Angew. Chem. Int. Ed*. **2010**, *49*, 5879; g) So, C. M.; Chow, W. K.; Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *Chem. Eur. J.* **2010**, *16*, 7996; h) Ackermann, L.; Potukuchi, H. K.; Althammer, A.; Born, R.; Mayer, P.; *Org. Lett*. **2010**, *12*, 1004; i) Zhao, Q.; Li, C.; Senanayake, C. H.; Tang, W. *Chem. Eur. J.* **2013**, *19*, 2261; k) for an example of such reaction performed at 50 °C see Lee, D.; Jin, M.; *Org. Lett.* **2011**, *13*, 252.

11) Organ, M. G.; Çalimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2383.
12) a) Wu, L.; Drinkel, E.; Gaggia, F.; Capolicchio, S.; Linden, A.; Falivene, L.; Cavallo, L.; Dorta, R. *Chem. Eur. J.* **2011**, *17*, 12886; b) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P.; *Chem. Eur. J.* **2012**, *18*, 4517.
13) a) Dai, C.; Fu, G. *J. Am. Chem. Soc*. **2001**, *123*, 2719; b) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J*. **2006**, *12*, 4749; c) Hartmann, C. E.; Nolan, S. P.; Cazin, S. J. C. *Organometallics* **2009**, *28*, 2915; d) Lesieur, M.; Slawin, A. M.; Cazin, S. J. C. *Org. Biomol. Chem*. **2014**, *12*, 5586.
14) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162.
15) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
16) Çalimsiz, S.; Sayah, M.; Mallik, D.; Organ, M. G. *Angew. Chem. Int. Ed*. **2010**, *49*, 2014.
17) a) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Nat Chem.* **2013**, *5*, 667-672; b) Hornillos, V.; Giannerini, M.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. *Org. Lett.* **2013**, *15*, 5114.
18) a) Snieckus, V.; *Chem. Rev.* **1990**, *90*, 879; b) Anctil, E. J.; Snieckus, V. in *Metal Catalyzed Cross-Coupling Reactions, Vol 1* (Eds A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp 761-813; c) Board, J.; Cosman, J. L.; Rantanen, T.; Singh, S. P.; Snieckus, V. *Platinum Metals Rev.* **2013**, *4*, 234.
19) Fu, G. C.; *Acc. Chem. Res.* **2008**, *41*, 1555.
20) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.
21) a) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768; b) Díez-González, S.; Nolan, S. P.; *Top. Organomet Chem.* **2007**, *21*, 47.
22) a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743; b) For a review on the applications of Pd-PEPPSI ligands see: Valente, C; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G.; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314.
23) O'Brien, C. J.; Organ, M. G.; Kantchev, A. B.; *Can. Pat. Appl.* **2007**, CA 2556850, A1 20070224.
24) a) Leroux, F.; Schlosser, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4272; b) Leroux, F. R.; Bonnafoux, L.; Heiss, C.; Colobert, F.; Lanfranchi, D. A. *Adv. Synth. Catal.* **2007**, *349*, 2705; c) Diemer, V.; Begaud, M.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem.* **2011**, 341.
25) Knapp, D. M., Gillis, E. P., Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.
26) a) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104,* 2667; b) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1788.
27) Vo, C. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082.
28) Becht, J. M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.
29) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Huges, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A, J. *Org. Lett.* **2006**, *8*, 4071.
30) Kurahashi, T.; Oda, K.; Sugimoto, M.; Ogura, T.; Fujii, H. *Inorg. Chem.* **2006**, *45*, 7709.
31) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333.
32) Clayden, J.; Kubinski, P. M.; Sammiceli, F.; Diorazio, L.; *Tetrahedron,* **2004**, *60*, 4387.
33) Glass, A. C.; Morris, B. B.; Zakharov, L. N.; Liu, S. Y. *Org. Lett.* **2008**, *10*, 4855.
34) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004,** *126,* 16433.