Biaryl Synthesis

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Palladium-Catalyzed, *tert*-Butyllithium-Mediated Dimerization of Aryl Halides and Its Application in the Atropselective Total Synthesis of Mastigophorene A

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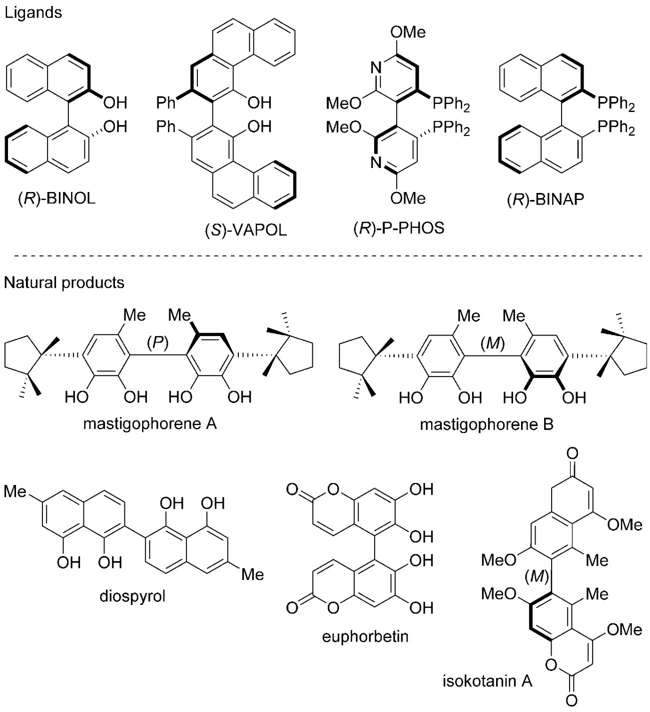
In memory of Richard F. Heck (1931–2015)

Abstract: *A palladium-catalyzed direct synthesis of symmetric biaryl compounds from aryl halides in the presence of tBuLi is described. In situ lithium–halogen exchange generates the corresponding aryl lithium reagent, which undergoes a homocoupling reaction with a second molecule of the aryl halide in the presence of the palladium catalyst (1 mol %). The reaction takes place at room temperature, is fast (1 h), and affords the corresponding biaryl compounds in good to excellent yields. The application of the method is demonstrated in an efficient asymmetric total synthesis of mastigophorene A. The chiral biaryl axis is constructed with an atropselectivity of 9:1 owing to catalyst-induced remote point-to-axial chirality transfer.*

The synthesis of biaryl compounds has been studied for more than a century[1] and is an important process in organic chemistry, as the biaryl structure is present in numerous natural products, bioactive compounds, agrochemicals, dyes, and ligands. Symmetric biaryl compounds play a crucial role in catalysis, as a range of ligands possess this structural motif (Scheme 1). Furthermore, natural products with a symmetric biaryl moiety, not necessarily enantiomerically pure, show interesting biological activities.[2]

Symmetric biaryl compounds can be synthesized in a wide variety of ways. A classic approach is the Ullmann coupling,[3,4] but also nickel-, palladium-, and iron-catalyzed coupling reactions between different organic halides and organometallic reagents, such as Grignard, zinc, boron, and tin reagents, are known.[5] These methods, however, are generally not employed in the synthesis of symmetric tetra-*ortho*-substituted biaryl compounds, with the exception of the Suzuki–Miyaura coupling. Despite its efficiency, the Suzuki–Miyaura coupling requires two independently synthesized reagents to be coupled, namely, an aryl halide and an aryl boron reagent. This feature makes the synthesis of symmetric biaryl compounds inherently less efficient, especially for natural product synthesis, for which step count is an important issue. However, this disadvantage can be circumvented by the homocoupling of aryl halides through the in situ generation of aryl lithium reagents by lithium–halogen exchange.[6,7] Such an approach might therefore provide a valuable alternative.



Scheme 1. Representative ligands and natural products with a symmetric biaryl structure.

Despite important recent advances, the homocoupling of organolithium reagents under Pd catalysis has received little attention.[8–12] The methodologies reported so far were rather limited in their scope and did not involve the construction of sterically congested tetra-*ortho*-substituted biaryl compounds, except for three examples of a copper-mediated coupling reported by Spring and co-workers.[8] Furthermore, the application of this type of coupling methodology in the synthesis of biaryl-containing natural products has not been reported.

As part of our research program on the use of organolithium compounds in palladium-catalyzed cross-coupling reactions,[13,14] we are interested in the synthesis of symmetric

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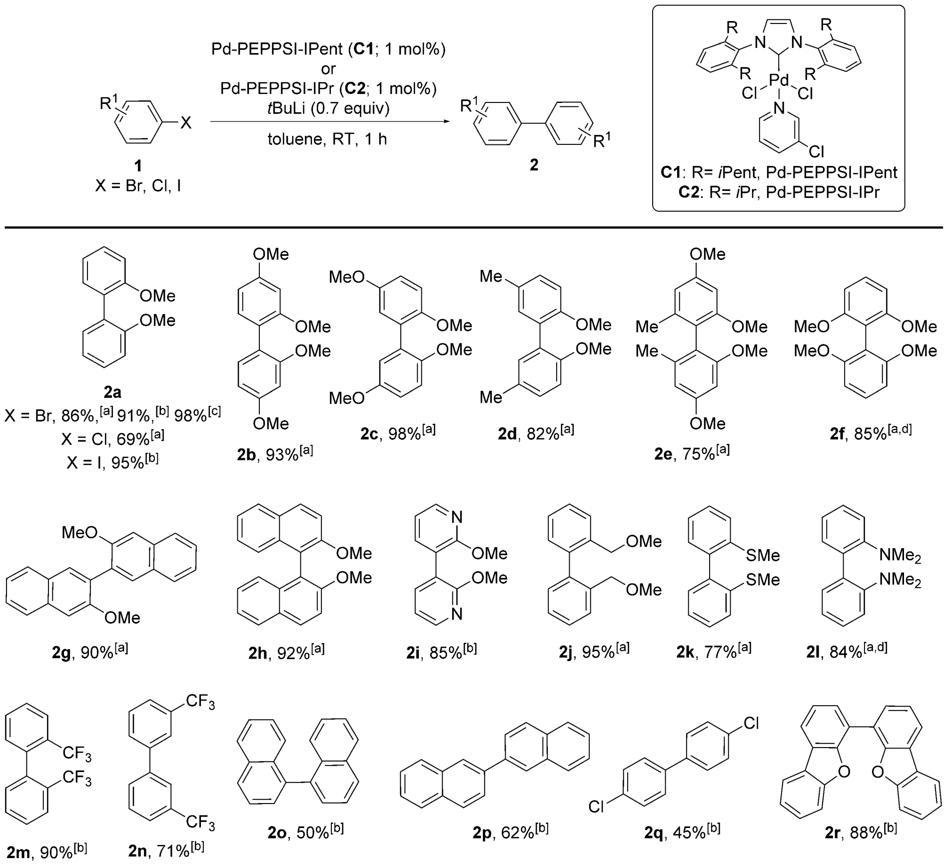
biaryl compounds with these highly reactive reagents. We present herein a highly efficient and selective homocoupling of aryl halides. We also applied this methodology in the construction of the naturally occurring symmetric, tetra-*ortho*-substituted biaryl compound mastigophorene A (Scheme 1).

As a starting point for developing the homocoupling reaction, we initially chose 2-bromoanisole (**1a**) as a model substrate. In search for the optimal reaction conditions (see the Supporting Information) we eventually arrived at Pd-PEPPSI-IPent[15] (**C1**; 1 mol%) and *t*BuLi (0.7 equiv) as the catalyst and lithiating reagent, respectively. Full conversion was observed, and the desired product **2a** was isolated in 86% yield. Pd-PEPPSI-IPr[16] (**C2**) proved to be an equally efficient catalyst. The use of 0.7 equivalents of *t*BuLi in the reaction is intriguing. Generally in Li–X exchange reactions with *t*BuLi, 2 equivalents of the reagent are used to compensate for the elimination of *t*BuBr, which is formed in situ.[17] We postulate that the solvent (toluene), the slow addition of *t*BuLi, and the reaction rate contributed to the suppression of the elimination of *t*BuBr. In toluene, *t*BuLi forms a tetrameric aggregate[18] and thus exhibits lower reactivity than that of monomeric *t*BuLi in THF, a solvent generally used in Li–X exchange reactions.[6b]



Scheme 2. Scope of the palladium-catalyzed homocoupling of aryl bromides in the presence of *t*BuLi (see product **2a** for coupling with an aryl iodide and an aryl chloride). [a] **C1** (1 mol%) was used. [b] **C2** (1 mol%) was used. [c] The reaction was carried out on a 6 mmol scale with **C2** (0.5 mol%) for 2 h. [d] The reaction was performed at 50°C.

We studied the scope and limitations of our new methodology under the optimized conditions (Scheme 2). With 2-chloroanisole, full conversion was not observed, and **2a** was obtained in 69% yield by the use of **C1**, whereas with 2-iodoanisole, **2a** was obtained in 95% yield. Next, various aromatic bromides with a methoxy group at the *ortho* position were studied. Biaryl compounds **2b**, **2c**, and **2d**, with different electron-donating substituents on the aromatic rings, were obtained in excellent yield. Even **2e**, a tetra-*ortho*-substituted biaryl compound, was successfully synthesized in 75% yield in 1 h at room temperature. To construct **2f**, the reaction had to be performed at 50°C. These conditions provided **2f** in 85% yield, without affecting the selectivity. Binaphthyl derivatives **2g** and **2h** were obtained in 90 and 92% yield, respectively.

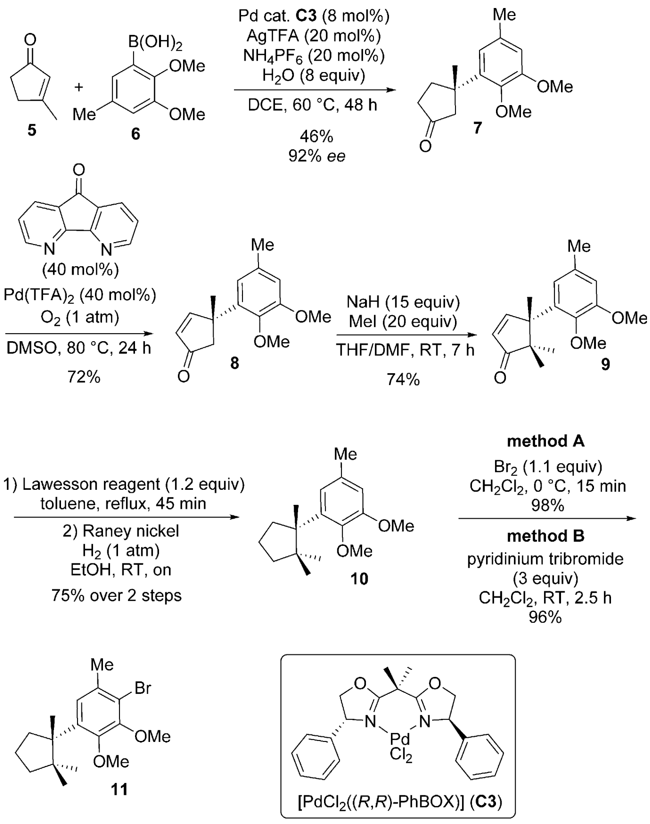
Heterocycles are also efficient coupling partners, as shown by the smooth dimerization of 3-bromo-2-methoxypyridine to afford the corresponding bipyridine **2i** in 85% yield. Aryl bromides with an electron-donating thiomethyl or *N*,*N*-dimethylamino group at the *ortho* position also provided the corresponding biaryls **2k** and **2l**. Subsequently, we performed the reaction with aryl bromides bearing electron-withdrawing groups: *ortho*- and *meta*-bromotrifluoromethylbenzene were converted into the corresponding fluorinated biaryl compounds **2m** and **2n** in good yields. Lower selectivity was observed in the synthesis of compounds **2o**–**q**, which were consequently obtained in only moderate yields. However, 4-bromodibenzofuran reacted efficiently to afford biaryl **2r** in 88% yield. To demonstrate the synthetic utility of the presented methodology, **2a** was prepared on a gram scale (1.12 g, 6 mmol) with Pd-PEPPSI-IPr (0.5 mol%) in 98% yield in 2 h.

Although the recently developed palladium-catalyzed cross-coupling reactions with lithium reagents display a broad scope,[14] no application has been reported so far within the realms of natural product synthesis. The efficiency of the homocoupling procedure described herein prompted us to explore the method in a total synthesis leading to the dimeric sesquiterpene mastigophorene A (Scheme 1).

Isolated from the liverwort *Mastigophora diclados*,[19a] mastigophorene A and B (Scheme 1) showed neurotrophic (nerve-growth-stimulating) activity,[19b] and have therefore been regarded as potential therapeutic agents for neurodegenerative diseases.[20] Additionally, it was found that mastigophorene A and B exhibit neuroprotective properties at concentrations as low as 0.1–1 μM.[19c] But foremost it is their molecular architecture, a highly sterically congested benzylic quaternary stereocenter together with a chiral biaryl axis, which sparked our interest.

To date, two atropselective total syntheses of mastigophorene A and B have been reported, both of which consisted of more than 20 steps.[21,22] Recently, some of us reported an asymmetric palladium-catalyzed conjugate addition of *ortho*-substituted aryl boronic acids to cyclic enones, with application in the asymmetric total synthesis of (−)-herbertenediol (the mastigophorene A and B monomer), in just six steps.[23] This synthetic sequence in combination with the palladium-catalyzed homocoupling described herein was envisioned to give straightforward access to enantiomerically pure mastigophorenes A and B. The hindered biaryl axis in the mastigophorenes presented us with the formidable challenge of constructing this stereochemical element in a diastereoselective manner.

Our synthetic approach thus relied on the construction of enantiomerically pure **11** (Scheme 3) by following our previously reported route to herbertenediol.[23] This compound was synthesized by starting with the palladium-catalyzed asymmetric conjugate addition of aryl boronic acid **6** to pentenone **5** to give compound **7** (46% yield, 92% *ee*).[23] Dehydrogenation of **7** provided enone **8** in 72% yield.[24]

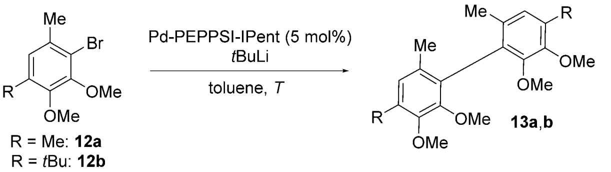


Scheme 3. Asymmetric synthesis of bromodimethylherbertenediol (**11**). DCE = dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, TFA = trifluoroacetate.

Geminal dimethylation and subsequent removal of the enone functionality (thioenone formation and reduction with Raney Ni)[21] gave rise to dimethylherbertenediol (**10**) in 56% over the three steps. Subsequently, **10** was brominated to furnish **11**, thus setting the stage for the pivotal homocoupling.

Initial attempts under the optimized conditions for homocoupling barely afforded the desired homocoupling product (< 5% yield), since significant dehalogenation of **11** occurred, and incomplete conversion. We reasoned that the crowded cyclopentyl scaffold in **11**, although apparently remote from the coupling site, impeded successful homocoupling. This hypothesis led us to investigate the influence of steric bulk of the *para* substituent in the homocoupling reaction. As model substrates, analogues of **11** with a methyl or a *t*Bu substituent were prepared (see the Supporting Information for their synthesis). Homocoupling of methyl substrate **12a** under slightly modified conditions, with 5 mol% of **C1** and 1.2 equivalents of *t*BuLi, gave the corresponding biaryl product in 68% yield (Table 1, entry 1). However, upon the application of these conditions with *t*Bu-substituted **12b**, poor selectivity for homocoupling over debromination was observed, and consequently the product yield dropped significantly. This result indicates that there is indeed an influence of the *para* substituent on the homocoupling, thus suggesting either an interaction between the catalyst/ligand system and the *para* substituent or simply an electronic effect. Although steric interactions are potentially detrimental for the formation of the homocoupled product, stereochemical information in the *para* substituent might be transferred in this way.

Table 1: Optimization of the homocoupling for sterically congested substrates.

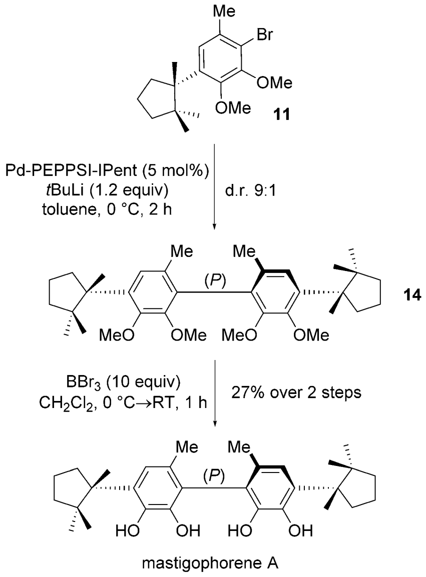


Entry[a]	Substrate	Conditions	Dehalogenation [%][b]	Homocoupling [%][b] (Yield [%][c])
1	**12a**	RT	25	75 (68)
2	**12b**	RT	80	20 (15)
3	**12a**	0°C	15	85 (79)
4	**12a**	RT, slow addition[d]	15	85
5	**12b**	0°C, slow addition[d]	20	80 (75)

[a] Reactions were carried out with 5 mol% of the catalyst. [b] Conversion and selectivity were determined by GC/MS analysis. [c] Yield of the isolated product after column chromatography. [d] *t*BuLi was added at a rate of 2 drops every 5 min.

During further optimization (see the Supporting Information), for methyl substrate **12a**, it was found that a lower reaction temperature (0°C) and the aliquoted addition of the *t*BuLi (2 drops every 5 min; Table 1, entry 3 and 4, respectively) did lead to significant improvement of the selectivity for product **13a**. When applying a combination of these conditions to the homocoupling of the sterically demanding *t*Bu substrate **12b**, we were pleased to see that this reaction smoothly provided the homocoupled product, which was isolated in in excellent yield (75 %; Table 1, entry 5).

Following this optimization study, we carried out the anticipated homocoupling of the enantiomerically pure mastigophorene building block **11** (Scheme 4). Gratifyingly, we obtained **14**, although inseparable at this stage (see below) from the debrominated product, dimethylherbertenediol (**10**; Scheme 3). Investigation of the homocoupling product mixture by ^{1}H NMR and GC/MS analysis indicated that the homocoupling reaction afforded a surprising diastereomeric ratio of 9:1 in favor of *P* helicity of the biaryl axis. This result is close to the 98:2 and comparable to the 88:12 diastereoselectivity observed in the atropselective total syntheses reported by Bringmann et al.[22] and Degnan and Meyers,[21] respectively. The exact mechanism for stereoinduction is unknown, but it is most likely a consequence of the steric clash between the apparently remote benzylic quaternary stereocenter in **11** and the aromatic residues of the **C1** catalyst.



Scheme 4. Endgame of the mastigophorene A synthesis.

The observed diastereoselectivity strongly suggests a catalyst-induced point-to-axial chirality transfer involving a steric interaction between the catalyst and the benzylic quaternary stereocenter at the *para* position. This hypothesis is substantiated by the fact that an oxidative coupling of the herbertenediol monomethyl ether (no imposed steric hindrance of the added reagent) with di-*tert*-butyl peroxide provided analogues of mastigophorenes A and B with very low asymmetric induction (d.r. 40:60) in favor of the mastigophorene B analogue.[25] The same ratio was observed for the natural isolate, thus clearly indicating a chiral bias towards *M* helicity exerted by the crowded cyclopentyl moiety alone.[17a,b] It is therefore even more noticeable that the catalyst-induced point-to-axial chirality transfer[26] in the homocoupling to give (*P*)-**14** overcame this intrinsic stereochemical bias towards *M* helicity.

The high diastereoselectivity also indicates that the reaction proceeds through an ionic (polar) mechanism rather than a radical (oxidative-coupling) mechanism. This hypothesis is further supported by the fact that we did not observe side products arising from H$^\bullet$ abstraction from the solvent toluene at all.

Compound **14** was thus obtained together with the dehalogenated compound **10**. Since we were not able to separate these products by flash column chromatography, we treated the mixture with BBr$_3$ to cleave the methoxy groups (90 % yield). The side products from the previous step were removed by flash column chromatography, thus providing us with pure mastigophorene A (observed rotation: −67.9 (c = 0.4, CHCl$_3$); literature value:[19b] −65.3 (c = 0.4, CHCl$_3$)) in 27 % yield over two steps. Conclusive evidence for the axial configuration was obtained by X-ray crystallography, which clearly showed *P* helicity (Figure 1).

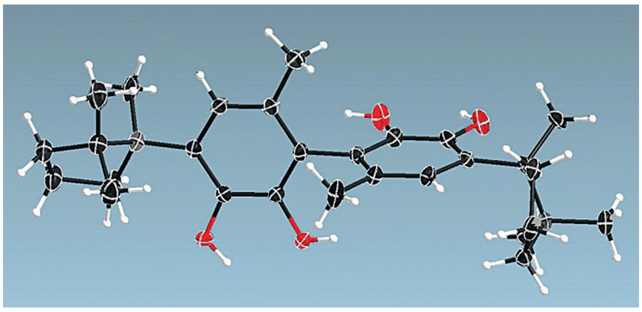


Figure 1. X-ray crystal structure of mastigophorene A.

In summary, we have developed a new catalytic system for the synthesis of symmetric biaryl compounds from aryl halides in the presence of *t*BuLi (0.7 equiv) and only 1 mol % of **C1**. The reaction takes place at ambient temperatures. Moreover, this methodology enables the synthesis of tetra-*ortho*-substituted symmetric biaryl compounds in high yields. We successfully implemented the newly developed methodology in the shortest atropselective total synthesis of mastigophorene A (eight steps). The major improvement over previous stereoselective syntheses (> 20 steps) is a consequence of the straightforward enantioselective installation of the benzylic quaternary stereocenter and the highly diastereoselective homocoupling reaction.

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Keywords: aryl lithium compounds · homocoupling · palladium · symmetric biaryls · total synthesis

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