*** CHAPTER 6 ***

‡ Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides and its Application in the Atropselective Total Synthesis of Mastigophorene A ‡

**ABSTRACT:** This chapter describes the investigation into new palladium-catalyzed homo-coupling methodology to construct symmetrical biaryl compounds. With the recent advent of Pd-catalyzed cross-coupling reactions of organolithium reagents, an efficient homo-coupling of in situ generated aryllithium reagents with a Pd-PEPPSI catalyst could be developed. Although the overall scope of Pd-catalyzed cross-coupling reactions with organolithium reagents is quite impressive, the methodology lacks application within the realms of natural product synthesis. Application of the newly developed methodology was found in the shortest atropselective construction of the naturally occurring, chiral biaryl compound, mastigophorene A.

This chapter has been published in part:

The synthetic efforts described in this chapter resulted from collaboration with the Feringa laboratory. Development of the Pd-catalyzed homo-coupling was performed by Dr. C. Vila, Dr. V. Hornillos and Dr. M. Giannerini. The substrate scope was investigated by Dr. C. Vila. Homo-coupling of test substrates for the mastigophorene A synthesis were performed by D. Heijnen.
6.1 Introduction

The synthesis of biaryl compounds has been studied for more than a century\textsuperscript{[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 biaryls play a crucial role in catalysis as a range of ligands possess this structural motif (Figure 1). Furthermore, natural products with a symmetric biaryl moiety, not necessarily enantiopure, show interesting biological activities.\textsuperscript{[2]}

![Figure 1. Representative ligands and natural products with a symmetric biaryl structure.](image-url)

In 1901, Ullmann reported the synthesis of biaryls from aryl halides using stoichiometric amounts of copper under harsh reaction conditions.\textsuperscript{[3,4]} Over the years, several coupling methodologies have been described using nickel, palladium or iron complexes as the catalyst, with different organic halides and organometallics such as Grignard, zinc, boron or tin reagents.\textsuperscript{[5]} These methods, however, are generally not employed in the synthesis of symmetric tetra-ortho-substituted biaryls, with the exception of the Suzuki-Miyaura coupling. Despite low catalyst loadings, an excellent scope and mostly good to excellent yields, the Suzuki-Miyaura coupling commonly requires two different, independently synthesized, reagents to be coupled, namely an aryl halide and an aryl boron reagent. This feature makes the synthesis of symmetrical biaryl compounds inherently less efficient, especially when considering natural product synthesis where step-count is an important issue.
Aryllithium reagents are readily prepared via halogen-lithium exchange or direct metalation,[6] and might provide a valuable alternative for the synthesis of symmetric biaryls. Moreover, as boron, tin or zinc reagents are frequently prepared from the corresponding lithium reagents,[7] the direct use of organolithium reagents could be beneficial as it eliminates additional transformations and purification processes. Important advances have been made in recent years although homo-coupling of organolithium reagents using Pd-catalysis has received only little attention. Spring and co-workers reported the homo-coupling of aryllithium reagents formed by directed lithiation, that underwent transmetalation with, stoichiometric, copper (I) and subsequent oxidation of the cuprate yielding the corresponding biaryls.[8] Yoshida and co-workers reported a FeCl$_2$-catalyzed oxidative homo-coupling of aryllithium reagents in a flow system.[9] The corresponding biaryls were obtained with good yields in very short reaction times at temperatures of -48 to +24 °C. Recently, Taillefer described methodology for the FeCl$_3$-catalyzed oxidative homo-coupling of arylobromides and iodides in the presence of $n$BuLi (1.6 eq) or $t$BuLi (2 eq), with a wide substrate scope.[10] In addition, Lu presented a vanadium tetrachloride (1 mol%) catalyzed oxidative homo-coupling of aryllithium reagents, prepared via lithium-halogen exchange with $n$BuLi, although only three different biaryls were reported and the reaction required 10-12 h to provide the corresponding products.[11] Homo-coupling of seven aryllithium compounds catalyzed by a [NiCl$_2$dpmp]-2,2-bipyridyl complex (0.7 mol%) was demonstrated by Carter and co-workers.[12] These reactions were carried out at room temperature and good yields ranging from 72% to 86% were obtained.

Most of these protocols require in situ preparation of the organolithium at low temperatures and the use of stoichiometric or super-stoichiometric amounts of a lithium reagent for the lithium-halogen exchange. Moreover, the methodologies reported so-far did not involve the construction of sterically congested tetra-ortho-substituted biaryls, except for three examples of Cu-mediated coupling reported by Spring and co-workers.[8] As far as we know, application of this type of coupling methodology in the synthesis of biaryl containing natural products has not been reported. Recent the Feringa laboratory published a series of papers reporting the palladium-catalyzed cross-coupling of alkyl- and aryllithium reagents with aryl halides/triflates.[13,14] Concurrent with our synthetic efforts to synthesize mastigophorenes A and B (Figure 1) the Feringa group was well on its way developing a palladium-catalyzed homo-coupling of aryllithium reagents. We strengthened our efforts by collaborating with the Feringa laboratory which resulted in the development of novel homo-coupling methodology with direct application in natural product synthesis. In this chapter we thus present a highly efficient and selective homo-coupling of aryl halides in the presence of $t$BuLi (0.7 eq), using 1 mol% of a palladium catalyst (PEPPSI-IPr or PEPPSI-IPent) featuring short reaction times (1 h) at rt. In addition, we were eager to apply this methodology in the construction of the naturally occurring symmetric, tetra-ortho-substituted, biaryl compounds mastigophorene A or B (Figure 1). The chiral biaryl axis was installed with surprisingly high diastereoselectivity via
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point-to-axial chirality transfer from a remote stereocenter induced by the Pd-PEPPSI-IPent catalyst.

6.2 Development of a Pd-catalyzed homo-coupling employing aryllithium reagents

We initially chose 2-bromoanisole as a model substrate (Table 1), in which the halogen-lithium exchange process is facilitated due to coordination and stabilization by the methoxy group at the ortho position. The alkyllithium reagent was added slowly to the 2-bromoanisole (1a) in toluene at room temperature using QPhos\textsuperscript{[15]}-Pd\textsubscript{2}dba\textsubscript{3} \textit{C1} (entries 1-3) or Pd-PEPPSI-IPent\textsuperscript{[16]} \textit{C2} (entries 4-6). These were the best catalysts selected from a short screening (see experimental section).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-cat (x mol%)</th>
<th>RLi (n eq)</th>
<th>2a (%)\textsuperscript{a}</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>3 (%)\textsuperscript{a}</th>
<th>4 (%)\textsuperscript{a}</th>
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<td>nBuLi (1 eq)</td>
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<td>sBuLi (1 eq)</td>
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<td>3</td>
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<td>sBuLi (1 eq)</td>
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<td>4</td>
<td>2</td>
<td></td>
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<tr>
<td>6</td>
<td>C2 (5%)</td>
<td>tBuLi (1 eq)</td>
<td>full\textsuperscript{d}</td>
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<td>trace</td>
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<td>tBuLi (0.7 eq)</td>
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<td>11\textsuperscript{c}</td>
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<tr>
<td>8</td>
<td>C2 (2.5%)</td>
<td>tBuLi (0.7 eq)</td>
<td>full\textsuperscript{e} (84)</td>
<td>trace</td>
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</tr>
<tr>
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<td>C2 (1%)</td>
<td>tBuLi (0.7 eq)</td>
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<td>trace</td>
<td>2\textsuperscript{e}</td>
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<td>10</td>
<td>C3 (1%)</td>
<td>tBuLi (0.7 eq)</td>
<td>full\textsuperscript{f} (91)</td>
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<td>trace</td>
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<tr>
<td>11</td>
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<td>tBuLi (1 eq)</td>
<td>-</td>
<td>full</td>
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</tbody>
</table>

Reaction conditions: 1a (0.3 mmol) and the palladium catalyst in 2 mL of toluene at 20 °C; RLi (n eq) diluted to 1 mL with toluene was added dropwise over 1 h. \textsuperscript{a} Conversions were determined by GC-MS analysis. \textsuperscript{b} Isolated yield, after column chromatography, in brackets. \textsuperscript{c} R = fBu. \textsuperscript{d} >99% conversion.

Table 1. Palladium-catalyzed dimerization of 2-bromoanisole.
We studied the homo-coupling reaction using the commercially available alkyl lithium reagents \( n\text{BuLi} \) (entries 1 and 4), \( s\text{BuLi} \) (entries 2 and 5) and \( t\text{BuLi} \) (entries 3 and 6) to generate the corresponding (2-methoxyphenyl)lithium \textit{in situ}. The highest selectivity for the formation of 2,2'-dimethoxy-1,1'-biphenyl 2a (entries 3 and 6) was obtained when \( t\text{BuLi} \) was used. Subsequently, we tried to reduce the catalyst loading to 2.5 mol\% (entries 7-8) and the amount of \( t\text{BuLi} \) to 0.7 eq. Full conversion to 2a (84\% isolated yield), was observed when Pd-PEPPSI-IPent was used as a catalyst, while QPhos-Pd\( \text{db}a\) C1 was less selective and some alkylated anisole was observed. The catalyst loading could be reduced to 1 mol\% (entry 9), without erosion in the yield and selectivity. Finally, Pd-PEPPSI-IPr\textsuperscript{[17]} C3, was also tested, and full conversion to the product 2a was achieved, with 91\% isolated yield (entry 10). Without Pd-catalyst no coupling reaction takes place (entry 11).

With the optimized conditions in hand (entries 9 and 10), we studied the scope and limitations of our new methodology (Scheme 1). With 2-chloroanisole, full conversion was not achieved and 2a was obtained in 69\% isolated yield using Pd-PEPPSI-IPent, while with 2-iodoanisole 2a was obtained in 95\% yield. These results are explained by a faster lithium-halogen exchange of the bromide or iodide, than that of the chloride and this favors the catalytic homo-coupling and the selective formation of the biaryl. Next, various aromatic bromides with a methoxy group at the \textit{ortho} position were studied. Biaryls 2b, 2c and 2d, with different electron-donating substituents at the aromatic ring, were obtained with excellent yields. Even 2,2',4,4'-tetramethoxy-6,6'-dimethyl-1,1'-biphenyl 2e, a tetra-\textit{ortho}-substituted biaryl, was successfully synthesized in 75\% yield in 1 h at room temperature. When 2-bromo-1,3-dimethoxybenzene was used, the reaction had to be performed at 50 °C, in order to obtain the corresponding tetra-\textit{ortho}-substituted biaryl 2f, in 85\% yield. Although a higher temperature was required, probably due to the steric hindrance of the two coupling partners, selectivity was not affected. 2,2'-Dimethoxy-1,1'-binaphthalene 2g and 2,2'-dimethoxy-1,1'-binaphthalene 2h were obtained in 90\% and 92\% yields, respectively.

Importantly, heterocycles are also efficient coupling partners, as is illustrated by the smooth dimerization of 3-bromo-2-methoxypyridine, and the corresponding bipyridine 2i was isolated in 85\% yield. Other aryl bromides with electron-donating groups at the \textit{ortho} position to the bromide such as thiomethyl or \( N,N\)-dimethylamino were also tested, providing the corresponding biaryls 2k and 2l. Subsequently, we performed the reaction with aryl bromides bearing electron-withdrawing groups such as \textit{ortho}-bromotrifluoromethylbenzene and \textit{meta}-bromotrifluoromethylbenzene, affording the corresponding fluorinated biaryls 2m and 2n with good yields. The use of 1-bromonaphthalene, 2-bromonaphthalene and \textit{para}-chlorobromobenzene, led to a lower selectivity and the products (2o-q) were obtained with moderate yields. However, 4-bromodibenzofuran reacted efficiently and afforded biaryl 2r in 88\% yield. To demonstrate the synthetic utility of the present methodology, 2a was prepared on a gram scale (1.12 g, 6 mmol) using 0.5 mol\% of Pd-PEPPSI-IPr in 98\% yield in 2 h.
The proposed catalytic cycle for the reaction is depicted in scheme 2, and is believed to follow “classic” Pd cross-coupling mechanism. Oxidative addition of the Pd\(^{0}\)-catalyst into the aryl bromide takes place, generating the Ar-Pd\(^{II}\)-Br species. This is followed by transmetalation of the aryllithium reagent, formed \textit{in situ} by lithium-halogen exchange, forming Ar-Pd\(^{II}\)-Ar, which undergoes reductive elimination to afford the desired symmetric biaryl product and regenerating the Pd\(^{0}\) catalyst.
6.3 Application in the asymmetric total synthesis of mastigophorene A

Although the recently developed palladium-catalyzed cross-coupling reactions using organolithium reagents display a broad scope, no application has been reported so far within the realms of natural product synthesis. The efficiency of the homo-coupling procedure described here prompted us to explore the method in a total synthesis leading to the dimeric sesquiterpenes mastigophorene A and B (Figure 1). Isolated from the liverwort *Mastigophora diclados*[^18a^], mastigophorene A and B showed neurotrophic (nerve growth stimulating) activity[^18b^], and have therefore been regarded as leads for therapeutic agents for neurodegenerative diseases[^19^]. Additionally, it was found that mastigophorenes A and B exhibit neuroprotective properties at concentrations as low as 0.1-1 μM[^18c^]. 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, three total syntheses of mastigophorene A and B have been reported, two of which are atropselective (Scheme 3). Meyers and Degnan installed the biaryl axis atropselectively using a chiral auxiliary-assisted asymmetric Ullmann coupling[^20^], whereas Bringmann’s strategy relied on installation of the chiral biaryl axis using a dynamic kinetic resolution[^21^].

In the latest endeavor, Fukuyama constructed enantiopure herbertenediol which was subsequently dimerized to the mastigophorenes A and B employing a horseradish peroxidase-catalyzed oxidative coupling, giving a mixture of the atropisomers (64 : 36, 28% combined yield) in favor of mastigophorene B[^18c^]. This ratio matches that obtained from the natural isolate and therefore it is questionable whether the enzyme directly participates in the formation of the bond[^18a,b^]. The Fukuyama synthesis comprises 17 synthetic transformations whereas the Meyers and Bringmann approaches, in large part due to the atropselective nature of their syntheses, consisted of over 20 steps. Evident from the reported syntheses is that stereoselective introduction of the benzylic quaternary stereocenter, and biaryl axis required elaborate synthetic strategies (Scheme 3).
Recently, we reported an asymmetric Pd-catalyzed conjugate addition of ortho-substituted arylboronic acids to cyclic enones, with application in the asymmetric total synthesis of (−)-herbertenediol (the mastigophorene A and B monomer), in just six steps (see Chapter 5). This synthetic sequence in combination with the previously developed Pd-catalyzed homo-coupling was envisioned to give straightforward access to enantioenriched mastigophorenes A and B. The hindered biaryl axis in the mastigophorenes presented us with the challenge to construct this stereochemical element in a diastereoselective manner.

Our synthetic approach thus relied on the construction of enantiopure bromo-dimethoxyherbertenediol 11 (Scheme 4), following our previously reported route to herbertenediol (see Chapter 5). This compound was synthesized starting with the Pd-catalyzed asymmetric conjugate addition of ortho-substituted arylboronic acid 6 to 3-methylcyclopent-2-enone 5. The benzylic quaternary stereocenter was installed in 46% yield with 92% ee. Dehydrogenation of 7, following a modified procedure reported by the Stahl laboratory, provided enone 8 in 72% yield. Geminal dimethylation and subsequent removal of the enone functionality (thioenone formation and RaNi reduction) gave rise to dimethoxyherbertenediol 10 in 56% over the three steps. Subsequently, 10 was brominated with either Br₂ or pyridinium tribromide furnishing aryl bromide 11, setting the stage for the pivotal homo-coupling.

Scheme 3. Meyers and Bringmann’s atropselective total syntheses of mastigophorene A.
Initial attempts, employing the optimized conditions of the reported method for homo-coupling (*vide supra* and Table 2), barely afforded the desired dimeric product (~5% isolated yield) since the reaction suffered from significant dehalogenation of 11, and incomplete conversion. GC-MS analysis however revealed an intriguing feature of the reaction, namely that formation of dimerized product, although in small amounts, was accompanied by a high diastereoselectivity of 9:1. This result indicated that there is a substantial influence of the *para*-substituent on the homo-coupling outcome, suggesting a steric interaction between the catalyst/ligand system and the *para*-benzylic stereocenter, transferring its stereochemical information. This result is of significant importance since catalyst-induced point-to-axial chirality transfer in biaryl containing natural products is rarely reported.

Several accounts of point-to-axial chirality transfer, in which remote chiral centers are used to influence atropselectivity, are known within the literature. These reports however mainly focus on natural products bearing a chiral binaphthyl axis in combination with relatively proximal stereocenters. Other reports involve molecules in which the global structure, due to conformational constrains, rather than the stereochemical relationships proximal to the biaryl axis, dictates the atropselectivity. Concurrent with our work a case of catalyst-induced point-to-axial chirality transfer in the asymmetric total synthesis of chiral biaryl containing rugulotrosin A was communicated. In a systematic study by the Porco Jr. laboratory it was found that depending on the ligand used, the chiral biaryl axis could be introduced in good to excellent diastereomeric ratios using a Suzuki-Miyaura reaction. Dimerization of 12 was most efficiently achieved using chiral Pd-catalyst C5, providing protected ent-rugulotrosin 13 in 44% yield with a diastereoselectivity of 95:5 (Scheme 5).
Motivated by the obtained diastereoselectivity in the homo-coupling of bromide 11, we were eager to improve the conversion towards the desired dimeric product. In the second attempt (Table 2, entry 2) the reaction was performed at elevated temperature (40 °C) and with 1 eq. of iBuLi, albeit with no significant improvement compared to entry 1. We suspected that the t-butyl bromide, formed in the lithium-halogen exchange, was prone to elimination and/or oxidative addition of the catalyst (vide infra), thereby forming a competing pathway with the catalytic cycle. Switching the lithium source to MeLi (MeBr cannot eliminate) however did not lead to improvement as no conversion was obtained (entry 3). Another way to circumvent the in situ formation of t-butyl bromide is by pre-formation of the aryllithium species, by reaction of bromide 11 with two equivalents of iBuLi. Addition of the pre-formed aryllithium to a solution of 11 and Pd-PEPPSI-IPent catalyst (entry 4), did not provide dimer 14 at all. Heating of the reaction to 40 °C and 70 °C (entry 5 and 6) did show some improvement, forming homo-coupled product 14, but still no satisfying result was obtained.

Further optimization for homo-coupling of 11 was delayed at this point since all synthetic material was consumed. Because enantiopure bromide 11 was deemed precious and a more rigorous optimization procedure was necessary, we decided to switch to a model system. It was reasoned that the crowded cyclopentyl scaffold in 11, although apparently remote from the coupling site, impeded successful homo-coupling by slowing down the reaction. This led us to investigate the influence of steric bulk of the para-substituent on the Pd-catalyzed homo-coupling. As model substrates, analogues of 11 with a methyl or a t-butyl[27] substituent were prepared (Scheme 6).
Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (Mol%)</th>
<th>RLi (eq)</th>
<th>Temp. (°C)</th>
<th>14 (%) (^a,b)</th>
<th>11 (%) (^a)</th>
<th>10 (%) (^a)</th>
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<tr>
<td>1</td>
<td>2</td>
<td>tBuLi (0.7)</td>
<td>20</td>
<td>17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>tBuLi (1.0)</td>
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<td>-</td>
<td>&gt;99</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>MeLi (0.55)</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>ArLi (0.5) (^c)</td>
<td>40</td>
<td>-</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>ArLi (0.5) (^c)</td>
<td>70</td>
<td>21</td>
<td>50</td>
<td>29</td>
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</table>

Reaction conditions: 11 (0.2 mmol) and the palladium catalyst in 1.6 mL of toluene at 20 °C; RLi (n eq) diluted to 0.6 mL with toluene was added dropwise over 1 h. \(^a\) Relative ratios were determined by GC-MS analysis. \(^b\) dr = 9:1. \(^c\) ArLi = lithium-halogen exchange product of 11 was used. Lithium-halogen exchange was performed by addition of tBuLi (2 eq) to 11 in -20 °C dry THF.

Table 2. Attempts to construct tetramethoxymastigophorene 14.

Methyl substituted analogue 17 was obtained starting with a directed ortho-lithiation of commercially available 15. With two lithiation sites present, the bulky tBuLi was chosen to achieve at least some selectivity for deprotonation. After careful flash chromatographic separation and GC-MS analysis of all fractions, collecting those fractions exhibiting ~90% purity, desired product 16 was obtained in 54% yield. Bromination with pyridium tribromide smoothly afforded bromide 17 in 90%, with an overall purity of ~90% which was considered sufficient for studying the homo-coupling reaction. The synthesis of tert-butyl substrate 22 was initiated by Friedel-Crafts alkylation of catechol 18 with isobutene.\(^{[28]}\) The obtained 29% yield for 19 did not reflect the yield obtained in the literature (72%), as the reaction was carried out under non-ideal conditions. Ideally an atmosphere of isobutene is used, applying a balloon on the reaction vessel, but practical constrains forced us to bubble isobutene (obtained from dehydration of t-butanol) through the reaction mixture. Tert-butyl catechol 19 was then subjected to NaOH and Me\(_2\)SO\(_4\) to construct 21, however, due to reasons unknown only mono-methylation occurred to produce phenol 20. Work-up of the reaction mixture and subjecting the crude to NaH and MeI then furnished the desired dimethylated product 21, in 78% over the two steps. Bromination with elemental bromine produced bromide 17b in 88% yield. Although this sequence seems redundant, direct tert-butylation of 3,4-dimethoxytoluene 15 provided a regioisomeric product (see experimental section)!
Para-methyl model substrate 17a

Para-tert-butyl model substrate 17b


With the desired model substrates in hand the dimerization reaction could be studied (Table 3). Homo-coupling of methyl substrate 17a under slightly modified conditions, using 5 mol% Pd-PEPPSI-IPent and 1.2 eq. tBuLi, gave 68% isolated yield of the corresponding biaryl product (Table 3, entry 1). However, upon application of these conditions on t-butyl substituted 17b, a poor selectivity for homo-coupling over debromination was observed, and consequently the isolated yield dropped significantly. Optimization of the reaction conditions, for methyl substrate 17a, by increasing catalyst loading or temperature did not lead to increased selectivity (entry 2 and 3). We also tried to improve our result from entry 1 by changing the concentration of either the lithiating reagent or the substrate, unfortunately leading to increased amounts of dehalogenation (entry 4 and 5). Failure was also met with a more gradual addition of tBuLi by direct contact of the tip of the needle with the reaction surface, providing dehalogenation exclusively, a result that remained unexplained (entry 6).

Also other catalysts (Pd-PEPPSI-IPr, Pd$_2$dba$_3$/XPHOS and Pd(P$_t$Bu$_3$)$_2$) were investigated to achieve efficient coupling. Despite our efforts using these catalysts, no homo-coupling could be achieved for the methyl substrate 17a. Notably, the failure of Pd-PEPPSI-IPr to achieve homo-coupling seems surprising, however congruent results were obtained by Organ and co-workers, who showed that formation of sterically hindered tetra-ortho-substituted biaryls using aryl/boron reagents, was facilitated by Pd-PEPPSI-IPent, whereas Pd-PEPPSI-IPr showed poor or no catalytic activity at all.$^{[16a,c]}$

It was postulated that the steric topology around the palladium nucleus is crucial, and that reactivity of the catalyst was facilitated by “flexible steric bulk” in the ligand.$^{[30]}$
Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat (mol%)</th>
<th>SM</th>
<th>23 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>22 (%)&lt;sup&gt;b&lt;/sup&gt; Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>17a</td>
<td>25</td>
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<td>40 °C</td>
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<td>4</td>
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<td>55</td>
<td>Diluted tBuLi&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>6</td>
<td>5</td>
<td>17a</td>
<td>&gt;98</td>
<td>-</td>
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<td>5</td>
<td>17a</td>
<td>15</td>
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<td>5</td>
<td>17a</td>
<td>15</td>
<td>85</td>
<td>Aliq. Add.&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>5</td>
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<td>50</td>
<td>80</td>
<td>0 °C</td>
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<tr>
<td>10</td>
<td>5</td>
<td>17b</td>
<td>20</td>
<td>80 (75%)</td>
<td>See entry 7 and 8&lt;sup&gt;d&lt;/sup&gt;</td>
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</table>

Reaction conditions: 17 (0.3 mmol) and the palladium catalyst in 2 mL of toluene at 20 °C; tBuLi (1.2 eq) diluted to 1 mL with toluene was added dropwise over 1 h, unless otherwise noted. <sup>a</sup> Conversions were determined by GC-MS analysis. <sup>b</sup> Isolated yield, after column chromatography, in brackets. <sup>c</sup> Incomplete conversion. <sup>d</sup> tBuLi added at 2 drops per 5 min interval.

Table 3. Optimization of the homo-coupling for sterically congested substrates.

With the above mentioned optimization attempts for methyl substrate 17a being fruitless, we decided to apply a lower reaction temperature (0 °C) and aliquoted addition (two drops per five minutes) of the tBuLi (entry 7 and 8 respectively). Both conditions led to significant improvement of the selectivity, as 85% conversion to the desired product 22a, compared to 75% in entry 1, was observed. Isolation provided the desired homo-coupled product 23a in a satisfying 79% yield. Lowering the reaction temperature was also used in the dimerization of 17b, providing only a modest selectivity for the formation of 22a (entry 9). When we subjected 17b to the low temperature combined with the slow addition conditions from entry 8 and 9, we were pleased to see that this reaction smoothly provided the homo-coupled product 22b in an excellent 75% isolated yield (entry 10).

Throughout the optimization process (Table 2 and 3), dehalogenation of the aryl bromides was the only side product, raising the question where the proton originates from. Upon quenching the reaction mixture with methyl iodide instead of methanol, the corresponding methylated product was detected only in trace amounts. This suggests...
that the majority of protonation occurs during reaction and not upon quenching. One possibility, namely deprotonation of the generated t-butyl bromide by the in situ formed aryllithium species 24, was examined. Formation of the latter at -40 °C (in the absence of Pd-PEPPSI-IPent), addition of t-butyl bromide, and consecutive (immediate!) quenching with methyl iodide showed no methyl incorporation, and full conversion towards the dehalogenated product 16 was observed (Scheme 7).

**Scheme 7. Quenching of the in situ generated aryllithium species.**

Reasoning that the electron rich aryllithium reagent is indeed rather basic, the deprotonation of t-butyl bromide, performed at -40 °C, strongly supports the hypothesis that protonation originates from elimination of t-butyl bromide. This side reaction is most likely promoted by the slower homo-coupling reaction due to the large substituents present in 11. Fortunately, the competition between Pd-catalyzed homo-coupling and dehalogenation could be shifted towards homo-coupling by lowering the temperature to 0 °C and slow addition of tBuLi, keeping the concentration of t-butyl bromide low (Table 3, entry 10).

The experiment mentioned above does not rule out a mechanism in which the palladium catalyst is involved (Scheme 8). The catalyst can perform an oxidative insertion into t-butyl bromide 25, followed by β-hydride elimination, forming a Br-Pd(II)-H species and isobutene. Transmetalation with ArLi in this species leads to Ar-Pd(II)-H, and subsequent reductive elimination could also lead to debrominated product 16, and regeneration of the Pd0 catalyst.

**Scheme 8. Proposed Pd-catalyzed dehalogenation via a Pd-hydride species.**
Following the optimization, the anticipated homo-coupling of enantiopure mastigophorene building block 11 was performed (Scheme 9). Gratifyingly, applying the optimized conditions we obtained tetramethoxymastigophorene 14, although inseparable at this stage (vide infra) from the debrominated starting material, dimethoxyherbertenediol 10 (Scheme 4). Upon investigation of the homo-coupling product mixture, exhibiting a diastereomeric ratio of 9:1, by $^1$H-NMR, an intense resonance at $\delta$ 1.95 (s, 6H) was observed which is characteristic of ($P$)-helicity in mastigophorene analogue 14.$^{[20]}$ This obtained diastereoselectivity approaches the 97 : 3 diastereoselectivity obtained in Bringmann’s atropselective total synthesis.$^{[21]}$ and matches with the 88 : 12 diastereomeric ratio obtained in atropselective total synthesis by the Meyers laboratory (Scheme 3).$^{[20]}$

Scheme 9. End-game of the atropselective mastigophorene A total synthesis.

As previously stated, the observed diastereoselectivity strongly suggests a catalyst-induced point-to-axial chirality transfer, involving a steric interaction between the catalyst and the para-benzylic quaternary stereocenter. This hypothesis is substantiated by the fact that an oxidative coupling (no imposed steric hindrance of the added reagent) using di-tert-butyl peroxide of the herbertenediol monomethyl ether, provided the mastigophorones A and B analogues with very low asymmetric induction ($dr$ = 40 : 60) in favor of mastigophorene B.$^{[21]}$ The same ratio was obtained from the natural isolate, clearly indicating a chiral bias towards ($M$)-helicity exerted by the crowded cyclopentyl moiety alone.$^{[18a,b]}$ It is therefore even more noticeable that the point-to-axial chirality transfer in the homo-coupling to ($P$)-14 overcomes this intrinsic stereochemical bias towards ($M$)-helicity.

Tetramethoxymastigophorene A (14) was thus obtained together with the dehalogenated compound dimethoxyherbertenediol 10 which we were not able to separate by flash column chromatography (Scheme 9). We therefore decided to subject the mixture to $\text{BBr}_3$ (90% yield), cleaving the methyl ethers. In this stage the side products from the previous step were separated using flash column chromatography affording pure mastigophorene A in 27% yield over two steps. Unfortunately, and despite our homo-coupling optimization efforts (vide supra), we obtained only a modest yield (~30%) accompanied with significant dehalogenation. This result reflects the degree of steric hindrance exerted by the cyclopentyl scaffold on the outcome of the reaction, compared to tert-butyl model substrate 17b.
The synthetic natural product was identified by means of NMR analysis and optical rotation to indeed accord with mastigophorene A (observed rotation = −67.9 (c = 0.4, CHCl₃); literature [18b] = −65.3 (c = 0.4, CHCl₃)). Conclusive evidence of the axial configuration was obtained by X-ray crystallography, clearly showing (P)-helicity (Figure 2).

Figure 2. X-ray Structure of Mastigophorene A.

6.4 Conclusion

In summary, we have developed a new and efficient catalytic system for the synthesis of symmetric biaryls from aryl halides in the presence of tBuLi (0.7 eq) using only 1 mol% of palladium catalyst. The reaction takes place at ambient temperatures and generally provides good to excellent yields. A wide scope of symmetric biaryl compounds was shown, even allowing the construction of tetra-ortho-substituted symmetric biaryls in high yields. Additionally, we successfully implemented the newly developed methodology in the shortest atropselective total synthesis of mastigophorene A in just eight steps. Although considerable optimization of the reaction conditions was required to effect successful homo-coupling, we did manage to obtain the biaryl linkage with a diastereoselectivity of 9:1 due to catalyst-induced point-to-axial chirality transfer. Compared to the previous stereoselective syntheses (>20 steps) this is a major improvement and a consequence of the straightforward enantioselective installation of the benzylic quaternary stereocenter in 92% ee and the highly diastereoselective homo-coupling.

6.5 Discussion and future prospects

6.5.1 Reflection on the Pd-catalyzed homo-coupling

The current chapter was recently published. In the referee reports, interesting points were raised regarding the stoichiometry and mechanism of the reaction. These points are addressed in this paragraph as they are not substantiated by thorough experimentation, but rather on what is known in the literature.

It is well known that lithium-halogen exchange reactions using tBuLi are generally performed with two equivalents of tBuLi.[32] This is necessary as the lithium-halogen
exchange produces t-butyl bromide which in turn undergoes a fast elimination reaction with a second molecule of tBuLi. Performing these reaction with less than two equivalents of tBuLi therefore results in incomplete lithiation. This was pointed out by one of the referees as in our homo-coupling method we use just 0.7 equivalents of tBuLi (which corresponds to 1.4 eq for the Li-Br exchange) and achieve yields up to 98%, indicating complete lithiation. We reason that elimination of t-butyl bromide is suppressed by a right combination of solvent, addition time of the tBuLi, and a high catalyst turn-over frequency.

Using toluene as the solvent is postulated to be effective in taming the reactivity of tBuLi. The reagent forms tetramers in this solvent that are less reactive than the monomer present in THF,[33] the solvent commonly used for lithium-halogen exchange reactions. Support for this argument comes from the observation that in the Pd-catalyzed hetero-coupling of aryllithium reagents with aryl bromides, Et₂O as the solvent had a detrimental effect on the reaction outcome.[14] This is attributed as well to the lower aggregation state of the, therefore more reactive, tBuLi. Also the slow addition of tBuLi to the reaction mixture is assumed to be important as it keeps the concentration of the reagent low. These two factors in combination with a high turn-over frequency of the catalyst are thought to suppress the elimination of t-butyl bromide.

Another issue addressed in the referee reports was the mechanism of the reaction. The referee considered an ionic mechanism debatable as toluene is a non-polar solvent, and therefore a radical mechanism proposed by the referee. We however refute this argument as radical reactions in toluene are prone to produce significant amounts of side products arising from formation of benzylic radicals. Since no such side products, even not in trace amounts, were observed in GC-MS analysis we do have strong evidence to exclude a radical type mechanism.

The observed diastereoselectivity in the mastigophorene A synthesis provides an additional argument against an ionic mechanism. A ratio of 9:1 in favor of the product with (P)-helicity was obtained (Scheme 9). In contrast, the biosynthesis of mastigophorene A and B via radical oxidative coupling of herbertenediol (the mastigophorene monomer), results in a diastereomeric ratio of 6:4 in favor of mastigophorene B, containing (M)-helicity.[18a,b] This result was confirmed by Bringmann and co-worker who reported a biomimetic synthesis of the mastigophorenes A and B, involving a radical oxidative coupling.[31] In case our reaction would predominantly proceed via a radical mechanism, the coupling of the aryl radical species without the aid of a catalyst is expected to give a more “biomimetic”, that is hardly any stereoselectivity, outcome. A more thorough investigation is needed to address this issue, and it is intriguing that recently a stereoselective enzymatic biaryl coupling has been reported as well.[34]
6.5.2 Other natural product targets for the point-to-axial chirality transfer using the Pd-catalyzed homo-coupling of aryllithium reagents

A most intriguing result in the presented total synthesis of mastigophorene A is the catalyst-induced point-to-axial chirality transfer from an apparently remote stereocenter. As previously discussed, reports on this phenomenon are scarce in the literature. Therefore the catalyst-induced point-to-axial chirality transfer can be seen as an opportunity in stereoselective natural product synthesis. In scheme 10 a set of intricate chiral biaryl containing natural products is presented that can potentially be made with the homo-coupling methodology reported in this chapter, and using the recently communicated hetero-biaryl coupling using aryllithium reagents. In order to gain information about the scope and limitations, research should (authors opinion) focus on natural isolates with even more remote point-chiral stereocenters (e.g. ancistrocladisine and rugulotrosin A) and sterically less demanding point-chiral moieties (e.g. phlegmacin B1 and dioncophylline E).

The synthesis of a chiral biaryl axis, and to a lesser extent a chiral binaphthyl axis, is intrinsically difficult when the used methodology requires high temperatures, especially when the inversion barrier is low. We were therefore pleased to find that the homo-coupling in the mastigophorene A synthesis was successfully performed at 0 °C minimizing the risk of inversion (pseudo-racemization). Therefore, although a configurationally stable tetra-ortho-substituted biaryl axis was crafted in the current study, the method is suitable as well for more labile chiral tri- or even disubstituted...
biaryl axes. The low temperature used in the homo-coupling of aryllithium reagents is therefore advantageous compared to the widely used Suzuki coupling, which in the majority of cases requires heating.\[39\] To substantiate this assertion, the total synthesis of tri-ortho-substituted dioncophylline E is envisioned. It is known that the molecule is unstable at room temperature and therefore a low temperature construction of the chiral biaryl axis is essential to obtain stereochemically pure material. To push the boundaries of the methodology even further, one can aim at the total synthesis of the intricate michellamine A.\[40\] This molecule contains three chiral biaryl axes of which the outer two are configurationally stable, and the middle one prone to isomerization! A synthetically pleasing prospect is the potential of a point-to-axial chirality transfer in the construction of the outer biaryl axes, and an axial-to-axial chirality transfer to construct the central bis-substituted biaryl axis.

A final example of a natural product, potentially accessible using the Pd-catalyzed coupling of aryllithium reagents, is deoxyschizandrin.\[41\] This molecule is a member of so-called dibenzocyclooctadiene lignans and this class of natural products exhibits interesting biological activity.\[42\] A proposal for a short asymmetric total synthesis is outlined in scheme 11.

Starting from dimethylthiophene 27, dibromothiophene 28 is readily obtained.\[43\] Performing the Pd-catalyzed hetero-coupling of aryllithium reagents on bromothiophene 28 and aryl bromide 29 can then lead to biaryl thiophene 30. From a step-count perspective accessing 30 in one step is preferable, although such reaction has not been reported yet using the lithium cross-coupling chemistry. If troublesome, it is envisioned that 30 should be readily obtained via a two-step sequence. It is known from the literature that thiophene 30 can be completely reduced with Raney nickel, although a mixture of diastereomers was obtained.\[44\] This is however not problematic as bromination of 31 provides bromo compound 32, of which the diastereomers could be separated by recrystallization.\[45\] This molecule just has to undergo the biaryl coupling reaction to provide deoxyschizandrin. We hypothesize that this coupling can be accomplished using the methodology described within this chapter, together with point-to-axial chirality transfer from the syn-1,2-dimethyl group. Since 32 is a meso-compound the intriguing possibility arises to desymmetrize 32 by using a chiral version of the Pd-PEPPSI-IPENT catalyst.
A final aspect of the catalyst-induced point-to-axial chirality transfer that needs to be addressed is the issue of catalyst-control. Whereas in this chapter the diastereoselectivity was as such unexpected, it is hailed as an important result. Critical assessment however, touches upon the fact that only mastigophorene A was constructed, so what if one requires mastigophorene B? The most obvious is to perform a catalyst/ligand screening, however this is not deemed the most promising approach as only a very limited set of catalysts was shown to perform the coupling of aryllithium reagents in general. In the total synthesis of rugulotrosin A by Porco Jr. and co-workers (Scheme 5), for example, a whole range of different catalyst was screened to accomplish the dimerization.\[26\] Even with both enantiomers of the chiral catalysts, good to excellent diastereoselectivities were reported exclusively in favor of \((M)\)-helicity. The answer might therefore not lie in the use of the same methodology to access both atropisomers, which poses a significant limitation of the method. Even the use of similar chemistry with mechanistic resemblance (e.g. switching from a Suzuki to a Negishi coupling) might be a dead end. Therefore the use of a different biaryl coupling methodology, with different mechanistic characteristics should be evaluated as well. The answer is not trivial and only experimentation (in combination with deep thinking) can provide one.

\[\text{Scheme 11. A proposed asymmetric total synthesis of deoxyschizandrin.} \]

A final aspect of the catalyst-induced point-to-axial chirality transfer that needs to be addressed is the issue of catalyst-control. Whereas in this chapter the diastereoselectivity was as such unexpected, it is hailed as an important result. Critical assessment however, touches upon the fact that only mastigophorene A was constructed, so what if one requires mastigophorene B? The most obvious is to perform a catalyst/ligand screening, however this is not deemed the most promising approach as only a very limited set of catalysts was shown to perform the coupling of aryllithium reagents in general. In the total synthesis of rugulotrosin A by Porco Jr. and co-workers (Scheme 5), for example, a whole range of different catalyst was screened to accomplish the dimerization.\[26\] Even with both enantiomers of the chiral catalysts, good to excellent diastereoselectivities were reported exclusively in favor of \((M)\)-helicity. The answer might therefore not lie in the use of the same methodology to access both atropisomers, which poses a significant limitation of the method. Even the use of similar chemistry with mechanistic resemblance (e.g. switching from a Suzuki to a Negishi coupling) might be a dead end. Therefore the use of a different biaryl coupling methodology, with different mechanistic characteristics should be evaluated as well. The answer is not trivial and only experimentation (in combination with deep thinking) can provide one.
6.6 Experimental section

General methods:
All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. Reaction temperature refers to the temperature of the oil bath. The dry solvents were taken from an MBraun solvent purification system (SPS-800). Pd(II)(dba)$_3$, SPhos, XPhos, DavePhos, CPhos, QPhos, PCy$_3$, Pd-PEPPSI-IPr and Pd-PEPPSI-IPent were purchased from Aldrich, and P(tBu)$_3$ was obtained from Strem chemicals, and used without further purification. nBuLi (1.6 M solution in hexane) was purchased from Acros. tBuLi (1.7 M in pentane), secBuLi (1.4 M in cyclohexane), iPrLi (0.7 M in pentane) were purchased from Aldrich. All the aromatic halides were commercially available and were purchased from Aldrich, with the exception of 3-bromo-2-methoxypyridine, 2-bromo-3-methoxynaphthalene and 1-bromo-2-methoxynaphthalene (TCI Europe).

TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach’s stain (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H$_2$O (500 mL) and H$_2$SO$_4$ (25 mL), a KMnO$_4$ stain (K$_2$CO$_3$ (40 g), KMnO$_4$ (6 g), water (600 mL) and 10% NaOH (5 mL)), or elemental iodine. Flash chromatography was performed using SiliCycle silica gel type SiliaFlash P60 (230 – 400 mesh) as obtained from Screening Devices or with automated column chromatography using a Reveleris flash purification system purchased from Grace Davison Discovery Sciences. Reveleris pre-fabricated silica cartridges were purchased and used, for automated column chromatography, containing 40 μm silica.

GC-MS measurements were performed with an HP 6890 series gas chromatography system with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA), equipped with an HP 5973 mass sensitive detector.

High resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL. (ESI+, ESI- and APCI). $^1$H-, $^{13}$C- and $^{19}$F-NMR spectra were recorded on a Varian AMX400 (400, 101 and 376 MHz, respectively) using CDCl$_3$ as solvent unless stated otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CDCl$_3$: δ 7.26 for $^1$H, δ 77.16 for $^{13}$C). Data are reported as follows: chemical shifts (δ in ppm), multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, td = triple doublet, t = triplet, q = quartet, b = broad, m = multiplet), coupling constants $J$ (Hz), and integration.

Enantiomeric excesses were determined by chiral HPLC analysis using a Shimadzu LC-10ADVP HPLC instrument equipped with a Shimadzu SPD-M10AVP diode-array detector. Integration at three different wavelengths (254, 225, 190 nm) was performed and the reported enantiomeric excess is an average of the three integrations.

Optical rotations were measured on a Schimdt+Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/mL) at ambient temperature (±20 °C).
CHAPTER 6

General procedure for the palladium catalyzed homo-coupling of aryl halides in the presence of tBuLi:

In a dry Schlenk flask, Pd-PEPPSI-IPr or Pd-PEPPSI-IPent (1 mol%) and aromatic halide (0.3 mmol) were dissolved in 2 mL of dry toluene and the solution was stirred at room temperature. tBuLi (0.7 eq., 0.21 mmol, 0.12 mL of 1.7 M commercial solution) was diluted with toluene to reach the concentration of 0.21 M; this solution was slowly added (flow rate=1 mL/h) by the use of a syringe pump. After the addition was completed, the reaction was quenched with methanol, and the solvent was evaporated under reduced pressure to afford the crude product, which was then purified by column chromatography.

Gram scale reaction:

In a dry Schlenk flask Pd-PEPPSI-IPr (0.5 mol%, 0.003 mmol, 22.5 mg) and 2-bromoanisole (6 mmol, 1.12 g, 0.75 mL) were dissolved in 30 mL of dry toluene. A solution of tBuLi (0.7 eq., 4.2 mmol, 2.5 mL of 1.7 M commercial solution) was slowly added over 2h by the use of a syringe pump. After the addition was completed, the reaction was quenched with methanol, and the solvent was evaporated under reduced pressure to afford the crude mixture. The product 2a was then purified by column chromatography (SiO₂, pentane : Et₂O 95:5) affording 2a as an oily substance (637 mg, 2.97 mmol, 98% yield).

Optimization homo-coupling of 2-bromoanisole in the presence of organolithium reagent:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (x mol%)</th>
<th>Ligand (x mol%)</th>
<th>RLi (1.1 eq)</th>
<th>Conv (%)</th>
<th>2a (%)</th>
<th>3 (%)</th>
<th>4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PtBu₃)₂</td>
<td>-</td>
<td>iPrLi</td>
<td>Full</td>
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<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd₂dba₃  (2.5 mol%)</td>
<td>XPhos</td>
<td>iPrLi</td>
<td>Full</td>
<td>32</td>
<td>68</td>
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</tr>
<tr>
<td>3</td>
<td>Pd₂dba₃</td>
<td>JohnPhos</td>
<td>iPrLi</td>
<td>Full</td>
<td>9</td>
<td>91</td>
<td>0</td>
</tr>
</tbody>
</table>
Spectral data of compounds 2a-2q:

**2,2'-dimethoxy-1,1'-biphenyl (2a):**
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 29 mg, 91% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.33 (m, 2H), 7.28 (dd, $J = 7.4, 1.5$ Hz, 2H), 7.07-6.98 (m, 4H), 3.80 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 157.0, 131.5, 128.6, 127.8, 120.3, 111.1, 55.7.

HRMS (ESI+): [M+H]$^+$ calculated for C$_{16}$H$_{19}$O$_4$ $^+$ = 275.12779; found: 275.12807.

**2,2',4,4'-tetramethoxy-1,1'-biphenyl (2b):**
Yellow solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 38 mg, 93% yield, m.p. = 92-94 °C.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.16 (d, $J = 8.6$ Hz, 2H), 6.58-6.53 (m, 4H), 3.85 (s, 3H), 3.77 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 160.0, 158.1, 131.9, 120.1, 104.1, 98.9, 55.7, 55.3.

HRMS (ESI+): [M+H]$^+$ calculated for C$_{16}$H$_{19}$O$_4$ $^+$ = 275.12779; found: 275.12807.

<table>
<thead>
<tr>
<th></th>
<th>(2.5 mol%)</th>
<th>(10 mol%)</th>
<th>iPrLi</th>
<th>Full</th>
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<th>70</th>
<th>0</th>
</tr>
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<tr>
<td>4</td>
<td>Pd$_2$dba$_3$ (2.5 mol%)</td>
<td>DavePhos (10 mol%)</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>5</td>
<td>Pd$_2$dba$_3$ (2.5 mol%)</td>
<td>QPhos (10 mol%)</td>
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<td></td>
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<tr>
<td>6</td>
<td>Pd-PEPPSI-IPent (5 mol%)</td>
<td>-</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conversions were determined with GC-MS analysis.
2,2',5,5'-tetramethoxy-1,1'-biphenyl (2c):
Yellow solid obtained after column chromatography (SiO₂, pentane : ether 95:5), 40 mg, 98% yield.

\[ \text{H-NMR (400 MHz, CDCl}_3 \text{)} \delta 6.92 (d, J = 8.6 \text{ Hz}, 2H), 6.89-6.84 (m, 4H), 3.79 (s, 6H), \\
3.74 (s, 6H). \]

\[ \text{C-NMR (101 MHz, CDCl}_3 \text{)} \delta 153.3, 151.3, 128.6, 117.1, 113.4, 112.4, 56.5, 55.7. \]

2,2'-dimethoxy-5,5'-dimethyl-1,1'-biphenyl (2d):
White solid obtained after column chromatography (SiO₂, pentane : ether 95:5), 30 mg, 82% yield, m.p. = 58-60 °C.

\[ \text{H-NMR (400 MHz, CDCl}_3 \text{)} 7.13 (dd, J = 8.3, 1.8 \text{ Hz}, 2H), 7.05 (d, J = 2.2 \text{ Hz}, 2H), \\
6.88 (d, J = 8.3 \text{ Hz}, 0H), 3.76 (s, 6H), 2.33 (s, 6H). \]

\[ \text{C-NMR (101 MHz, CDCl}_3 \text{)} \delta 155.0, 132.0, 129.5, 128.9, 127.8, 111.1, 55.9, 20.5. \]


2,2',4,4'-tetramethoxy-6,6'-dimethyl-1,1'-biphenyl (2e):
White solid obtained after column chromatography (SiO₂, pentane : ether 95:5), 34 mg, 75% yield.

\[ \text{H-NMR (400 MHz, CDCl}_3 \text{)} 6.45 (d, J = 2.1 \text{ Hz}, 2H), 6.41 (d, J = 2.3 \text{ Hz}, 2H), 3.84 (s, \\
6H), 3.69 (s, 6H), 1.94 (s, 6H). \]
Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 159.4, 158.2, 139.2, 118.4, 106.1, 96.2, 55.8, 55.1, 20.0.

2,2',6,6'-tetramethoxy-1,1'-biphenyl (2f):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 35 mg, 85% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (t, $J = 8.3$ Hz, 2H), 6.67 (d, $J = 8.3$ Hz, 4H), 3.74 (s, 12H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 158.4, 128.7, 104.5, 56.2.

3,3'-dimethoxy-2,2'-binaphthalene (2g):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 42 mg, 90% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 (d, $J = 8.7$ Hz, 4H), 7.80 (s, 2H), 7.49 (d, $J = 7.6$ Hz, 2H), 7.38 (d, $J = 7.6$ Hz, 2H), 7.26 (s, 2H), 3.90 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 156.3, 134.4, 130.3, 129.9, 128.7, 127.7, 126.5, 126.3, 123.7, 105.4, 55.7.

2,2'-dimethoxy-1,1'-binaphthalene (2h):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 43 mg, 92% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.98 (d, $J = 9.0$ Hz, 2H), 7.87 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 9.0$ Hz, 2H), 7.34-7.30 (m, 2H), 7.22 (t, $J = 7.3$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 3.77 (s, 6H).

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$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 155.0, 134.0, 129.4, 129.2, 127.9, 126.3, 125.2, 123.5, 119.6, 114.2, 56.9.

![Structure of 2,2'-dimethoxy-3,3'-bipyridine (2i)]

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 161.2, 146.2, 139.6, 119.9, 116.5, 53.5.

2,2'-dimethoxy-3,3'-bipyridine (2i):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 29 mg, 91% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.18 (dd, $J = 5.0$, 1.9 Hz, 2H), 7.59 (dd, $J = 7.3$, 1.9 Hz, 2H), 6.95 (dd, $J = 7.3$, 5.0 Hz, 2H), 3.92 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 139.6, 136.2, 129.6, 128.0, 127.6, 127.1, 72.2, 58.3.

HRMS (ESI+): [M+Na]$^+$ calculated for C$_{16}$H$_{18}$O$_2$Na$^+$ = 265.11990; found: 265.12013.

![Structure of 2,2'-bis(methoxymethyl)-1,1'-biphenyl (2j)]

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 139.5, 136.2, 129.6, 128.0, 127.6, 127.1, 72.2, 58.3.

2,2'-bis(methoxymethyl)-1,1'-biphenyl (2j):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 35 mg, 95% yield, m.p. = 71-73 °C.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.54 (d, $J = 7.6$ Hz, 2H), 7.39 (td, $J = 7.5$, 1.4 Hz, 2H), 7.32 (td, $J = 7.5$, 1.3 Hz, 2H), 7.16 (dd, $J = 7.5$, 1.1 Hz, 2H), 4.15 (s, 4H), 3.24 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 139.5, 136.2, 129.6, 128.0, 127.6, 127.1, 72.2, 58.3.

HRMS (ESI+): [M+Na]$^+$ calculated for C$_{16}$H$_{18}$O$_2$Na$^+$ = 265.11990; found: 265.12013.

![Structure of 2,2'-bis(methylthio)-1,1'-biphenyl (2k)]

2,2'-bis(methylthio)-1,1'-biphenyl (2k):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 99:1), 29 mg, 77% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.39 (t, $J = 7.5$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 7.23 (d, $J = 7.4$ Hz, 2H), 7.19 (t, $J = 7.7$ Hz, 2H), 2.39 (s, 6H).
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$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 138.8, 138.1, 130.0, 128.5, 125.0, 124.5, 15.7.

![Chemical structure](image)

$N_2N_2N_2^{'},N_2^{'-}$-tetramethyl-$[1,1'-$biphenyl$]-2,2'$-diamine (2l):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 95:5), 30 mg, 84% yield, m.p. = 69-71 °C.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.37 (dd, $J = 7.6$, 1.5 Hz, 2H), 7.27 (t, $J = 7.6$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 6.99 (t, $J = 7.4$ Hz, 2H), 2.61 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 150.3, 133.3, 131.5, 127.6, 120.9, 118.0, 42.9.

HRMS (ESI+): [M+H]$^+$ calculated for C$_{16}$H$_{21}$N$_2$ = 241.16993; found: 241.17014.

$2,2'$-bis(trifluoromethyl)-1,1'-biphenyl (2m):
Oil obtained after column chromatography (SiO$_2$, pentane), 39 mg, 90% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) 7.75 (dd, $J = 7.6$, 1.2 Hz, 2H), 7.59-7.47 (m, 4H), 7.30 (d, $J = 7.4$ Hz, 1H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 137.4, 131.5, 130.6, 128.1, 125.9, 123.9 (q, $J_{C-F} = 274.0$ Hz).

$^{19}$F-NMR (376 MHz, CDCl$_3$) δ -58.2.

$3,3'$-bis(trifluoromethyl)-1,1'-biphenyl (2n):
Colorless oil obtained after column chromatography (SiO$_2$, pentane), 31 mg, 71% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.84 (s, 2H), 7.78 (d, $J = 7.7$ Hz, 2H), 7.67 (d, $J = 7.8$ Hz, 2H), 7.60 (t, $J = 7.7$ Hz, 2H).
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$^{13}\text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 140.5, 130.5, 129.5, 124.7 (q, J = 7.5 \text{ Hz}), 124.0 (q, J_{\text{C-F}} = 272.3 \text{ Hz}), 124.0 (q, J_{\text{C-F}} = 3.8 \text{ Hz}).$

$^{19}\text{F-NMR (376 MHz, CDCl}_3\text{)} \delta -62.5.$

1,1'-binaphthalene (2o):
White solid obtained after column chromatography (SiO$_2$, pentane), 19 mg, 50% yield.

$^1\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 7.97 (d, J = 8.2 \text{ Hz}, 2\text{H}), 7.96 (d, J = 8.2 \text{ Hz}, 2\text{H}), 7.61 (t, J = 7.5 \text{ Hz}, 2\text{H}), 7.53-7.46 (m, 4\text{H}), 7.41 (d, J = 8.4 \text{ Hz}, 2\text{H}), 7.30 (ddd, J = 8.3, 6.8, 1.1, 2\text{H}).$

$^{13}\text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 138.4, 133.5, 132.8, 128.1, 127.9, 127.8, 126.6, 126.0, 125.8, 125.4.$

2,2'-binaphthalene (2p):
White solid obtained after column chromatography (SiO$_2$, pentane), 24 mg, 62% yield.

$^1\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 8.19 (s, 2\text{H}), 7.96 (t, J = 9.1 \text{ Hz}, 4\text{H}), 7.90 (dd, J = 8.4, 1.7 \text{ Hz}, 2\text{H}), 7.57-7.48 (m, 4\text{H}).$

$^{13}\text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 138.4, 133.7, 132.7, 128.5, 128.2, 127.7, 126.4, 126.1, 126.0, 125.7.$

4,4'-dichloro-1,1'-biphenyl (2q):
White solid obtained after column chromatography (SiO$_2$, pentane), 15 mg, 45% yield.

$^1\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 7.48 (d, J = 8.7 \text{ Hz}, 4\text{H}), 7.41 (d, J = 8.7 \text{ Hz}, 4\text{H}).$

$^{13}\text{C-NMR (101 MHz, CDCl}_3\text{)} 138.4, 133.7, 129.0, 128.2.$
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4,4'-bidibenzo[b,d]furan (2r):
White solid obtained after column chromatography (SiO$_2$, pentane : ether 98:2), 44 mg, 50% yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.08-8.03 (m, 4H), 8.02 (dd, $J = 7.6$, 1.2 Hz, 2H), 7.62-7.53 (m, 4H), 7.51-7.46 (m, 2H), 7.40 (td, $J = 7.5$, 1.0 Hz, 2H)

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 156.2, 153.7, 128.6, 127.2, 124.9, 124.3, 122.9, 122.8, 121.0, 120.7, 120.3, 111.9.

Experimental section and data for the Mastigophorene total synthesis:
For the synthesis of dimethoxyherbertenediol 10 (92% ee) see chapter 5 and/or J. Buter, R. Moezelaar, A.J. Minnaard, Org. Biomol. Chem. 2014, 12, 5883 - Supporting Information.

(S)-2-bromo-3,4-dimethoxy-1-methyl-5-(1,2,2-trimethylcyclopentyl)benzene (11) (Method A):
To a solution of (S)-1,2-dimethoxy-5-methyl-3-(1,2,2-trimethylcyclopentyl)benzene 10 (230 mg, 0.877 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added pyridinium tribromide (841 mg, 2.63 mmol, 3 eq) in four portions over 1 h (not all solids dissolved!). The reaction was monitored by TLC analysis (2% ether in pentane) and GC-MS analysis which both showed complete conversion after 2.5 h.

To the reaction mixture was added aqueous saturated NaHCO$_3$ (10 mL). The phases were separated and the organic layer was washed twice with water (2x10 mL). The combined aqueous layers were back-extracted once with CH$_2$Cl$_2$ (10 mL). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography using 2% ether in pentane as the eluent afforded pure (S)-2-bromo-3,4-dimethoxy-1-methyl-5-(1,2,2-
trimethylcyclopentyl)benzene 11 (287 mg, 0.842 mmol, 96% yield) as a slight yellow oil.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.98 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.63 – 2.46 (m, 1H), 2.35 (s, 3H), 1.84 – 1.55 (m, 5H), 1.35 (s, 3H), 1.13 (s, 3H), 0.69 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 151.90, 150.86, 139.83, 132.11, 125.74, 117.68, 60.40, 59.88, 51.62, 44.92, 41.07, 39.19, 26.98, 25.37, 24.08, 23.14, 20.52.

(S)-2-bromo-3,4-dimethoxy-1-methyl-5-(1,2,2-trimethylcyclopentyl)benzene (11) (Method B):
To a cooled (0 °C) solution of (S)-1,2-dimethoxy-5-methyl-3-(1,2,2-trimethylcyclopentyl)benzene 10 (110 mg, 0.42 mmol) in dry CH$_2$Cl$_2$ (4 mL) was added dibromine (23 μl, 3.90 mmol, 1.1 eq). After addition the reaction mixture was stirred for 15 min. after which GC-MS and TLC analysis indicated complete conversion of the starting material. The reaction mixture was then quenched with an aqueous saturated NaHCO$_3$ solution. The phases were separated and the aqueous phase was extracted twice with CH$_2$Cl$_2$. The organic phase was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residual oil was subjected to flash column chromatography employing pentane as the eluent afforded pure (S)-2-bromo-3,4-dimethoxy-1-methyl-5-(1,2,2-trimethylcyclopentyl)benzene 11 (140 mg, 0.410 mmol, 98% yield) as a slight yellow oil.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.98 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.63 – 2.46 (m, 1H), 2.35 (s, 3H), 1.84 – 1.55 (m, 5H), 1.35 (s, 3H), 1.13 (s, 3H), 0.69 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 151.90, 150.86, 139.83, 132.11, 125.74, 117.68, 60.40, 59.88, 51.62, 44.92, 41.07, 39.19, 26.98, 25.37, 24.08, 23.14, 20.52.
Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides

2,2',3,3'-tetramethoxy-6,6'-dimethyl-4,4'-bis((S)-1,2,2-trimethylcyclopentyl)-1,1'-biphenyl (tetramethoxymastigophorene A) (14):
In a dry Schlenk flask, Pd-PEPPSI-IPent (12 mg, 19 μmol, 5 mol%) and (S)-2-bromo-3,4-dimethoxy-1-methyl-5-(1,2,2-trimethylcyclopentyl)benzene 11 (125 mg, 0.37 mmol) were dissolved in dry toluene (1.5 ml) and the solution was cooled to 0 °C with an ice bath. tBuLi (265 μL, 1.7 M in hexanes, 0.44 mmol, 1.2 eq) was slowly added (per 2 drops with 5 min intervals, total addition time = 40 min) by the aid of a syringe pump. After the addition was completed the reaction mixture was stirred for one additional hour after which the reaction was quenched with methanol. Celite was added, and the solvent evaporated under reduced pressure. The residue was directly loaded onto a prepared flash column, and eluted using pentane as the eluent, affording a mixture of the two diastereoisomers in a diastereomeric ratio of 9:1 (detected by GC-MS), mixed with dimethoxyherbertenediol 10. 1H-NMR analysis showed a major resonance at δ 1.95 which corresponds to (P)-helicity as found in mastigophorene A.

(S)-6,6'-dimethyl-4,4'-bis((S)-1,2,2-trimethylcyclopentyl)-[1,1'-biphenyl]-2,2',3,3'-tetraol (Mastigophorene A):
To a solution of 2,2',3,3'-tetramethoxy-6,6'-dimethyl-4,4'-bis((S)-1,2,2-trimethylcyclopentyl)-1,1'-biphenyl 14 (contaminated with dimethoxyherbertenediol 10) (62 mg, 0.119 mmol) in dry CH2Cl2 cooled to 0 °C was added dropwise BBr3 (1.2 mL, 1 M in CH2Cl2, 1.2 mmol, 10 eq). The ice-bath was removed and the reaction mixture was allowed to warm to rt and stirred for 1 h. TLC indicated complete conversion of the starting material after which the reaction mixture was poured onto 5% aqueous NaHCO3 (4 mL). The phases were separated and the aqueous phase was extracted twice with CH2Cl2. The combined organic phases were dried over Na2SO4, filtered and loaded on Celite. This concentrated sample was loaded on a silica cartridge where after automated flash column chromatography was performed employing a pentane : ether (9 : 1 to 8 : 2)
gradient as the eluent, to give pure mastigophorene A (23 mg, 27% over 2 steps, 0.05 mmol) which crystallized upon standing at rt.

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.87 (s, 2H), 5.58 (s, 2H), 4.73 (s, 2H), 2.73 – 2.65 (m, 2H), 1.94 (s, 6H), 1.83 – 1.53 (m, 10H), 1.46 (s, 6H), 1.21 (s, 6H), 0.80 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 141.72, 140.65, 134.02, 126.81, 122.88, 117.09, 51.49, 45.13, 41.31, 39.05, 27.35, 25.69, 22.98, 20.59, 19.37.

$[\alpha]_D^{20} = -67.9$ (CHCl$_3$, c = 0.4) for a 92% ee sample; literature value: $[\alpha]_D^{19} = -65.3$ (CHCl$_3$, c = 0.4).$^{[18b]}$

\[
\begin{align*}
\text{1,2-dimethoxy-3,5-dimethylbenzene (16):} \\
\text{To a solution of 1,2-dimethoxy-4-methylbenzene 15 (5 ml, 34.8 mmol) in dry THF (75 mL), cooled to -78 °C, was added dropwise tBuLi (22.5 mL, 1.7 M in hexanes, 1.1 eq) by syringe pump (22.5 mL/h). A bright yellow solution formed upon addition. After addition the reaction mixture was allowed to warm-up to 0 °C, whereupon a suspension formed. The reaction mixture was then cooled to -78 °C and iodomethane (2.60 ml, 41.8 mmol, 1.2 eq) was added dropwise. The reaction mixture was allowed to warm-up to rt and was stirred an additional hour at this temperature. The reaction mixture was quenched using an aqueous saturated NH$_4$Cl solution (100 mL). After phase separation, the aqueous layer was washed three times with ether. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. Flash column chromatography was performed employing pentane : ether = 9 : 1. The individual fractions were analyzed with GC-MS and the fractions of >85% purity (the desired compound elutes first!) were combined affording 1,2-dimethoxy-3,5-dimethyl benzene 16 (3.1 g, 18.7 mmol, 54% yield) with ~85% purity based on $^1$H-NMR analysis.}
\end{align*}
\]

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.58 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 152.42, 145.18, 133.39, 131.54, 123.30, 110.92, 60.20, 55.72, 21.29, 15.78.

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Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides

HRMS (ESI+): Calculated mass [M+H]^+ C_{10}H_{15}O_2 = 167.1067; found: 167.1066.

2-bromo-3,4-dimethoxy-1,5-dimethylbenzene (17a):
To a solution of 1,2-dimethoxy-3,5-dimethylbenzene 16 (3.0 g, 18 mmol) in dry CH_2Cl_2 (150 mL) was added pyridinium tribromide (11.5, 36.1 mmol, 2 eq) portionwise over 1 h. The wall of the Schlenk flask was rinsed with dry CH_2Cl_2 after each addition. The reaction was followed by TLC analysis (2% ether in pentane) and showed complete conversion after 5 h. To the reaction mixture was added an aqueous saturated NaHCO_3 solution (10 mL). The phases were separated and the organic layer was washed twice with water (2x10 mL). The combined aqueous layers were back-extracted once with CH_2Cl_2 (10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography using 2% ether in pentane as the eluent afforded 2-bromo-3,4-dimethoxy-1,5-dimethylbenzene 17a (4.0 g, 16.3 mmol, 90% yield) as a slight yellow oil with ~90% purity based on ^1H-NMR analysis.

^1H-NMR (400 MHz, CDCl_3) δ 6.69 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H).

^13C-NMR (101 MHz, CDCl_3) δ 151.55, 145.86, 133.63, 132.39, 118.50, 111.97, 60.66, 55.97, 24.05, 16.79.

HRMS (ESI+ and APCI) analysis could not be performed due to ion-suppression. GC-MS analysis gave the following mass fragmentation: Calculated mass [M]^+ C_{10}H_{13}O_2Br = 244.01; found: 246 (M^+ isotope), 244 (M^+), 231 (M-CH_3 isotope)^+, 229 (M-CH_3)\(^+\), 216 (M-(CH_3)_2 iso)\(^+\), 214 (M-(CH_3)_2)^+.
3-(tert-butyl)-5-methylbenzene-1,2-diol (19):
To a suspension of 4-methylbenzene-1,2-diol \(^{18}\) (2.6 g, 20.94 mmol) in benzene (50 mL) was added sulfuric acid (110 \(\mu\)L, 2.1 mmol, 10 mol%). The mixture was cooled with an ice/salt bath (-10 to -5 °C) and isobutene* was bubbled through the solution for 2 h. The Schlenk vessel was then closed and the reaction was heated to 60°C and stirred for 3 h. Full conversion was not obtained but it was decided to quench the reaction with a saturated aqueous NaHCO\(_3\) solution where after the phases were separated. The organic layer was washed with water, dried using MgSO\(_4\), filtered and concentrated under reduced pressure. The isolated oil was purified using flash column chromatography employing pentane : ether (3:2) affording 3-(tert-butyl)-5-methylbenzene-1,2-diol \(^{19}\) as a yellowish oil (1.1 g, 6.10 mmol, 29% yield).

* The isobutene was generated by slow addition of solid tert-butanol to concentrated sulfuric acid. The isobutene formed was led through a cannula (double tipped needle), into the flask containing 4-methylbenzene-1,2-diol and sulfuric acid.

The analytical data was in agreement with those reported in the literature.\[^{[28]}\]

1-(tert-butyl)-2,3-dimethoxy-5-methylbenzene (21):
To a cooled (0 °C) solution of 3-(tert-butyl)-5-methylbenzene-1,2-diol \(^{19}\) (1.1 g, 6.10 mmol) in CH\(_2\)Cl\(_2\) (8 mL) and water (4 mL) were added sodium hydroxide (976 mg, 24.4 mmol, 4 eq) and dimethyl sulfate (1.73 ml, 18.3 mmol, 3 eq). The reaction mixture was allowed to stir for 90 min after which GC-MS analysis showed complete conversion to the monomethylated compound. No significant change was observed upon subsequent stirring overnight.

The reaction mixture was carefully quenched using conc. aqueous NH\(_3\) and the organic phase was removed by evaporation. The aqueous layer was extracted twice with pentane. The combined organic phases were dried over MgSO\(_4\), filtered and concentrated under reduced pressure. NMR analysis and GC-MS analysis indicated ~95% monomethylated compound \(^{20}\) with ~5% of the desired dimethylated product \(^{21}\). The crude product was used in the next step.
Pd-Catalyzed, tBuLi-mediated dimerization of Aryl Halides

To a suspension of NaH (732 mg, 60% dispersion in oil, 3 eq) in dry THF (8 mL), cooled to 0 °C, was slowly added a solution of the monomethylated product in dry THF (7 mL). After addition, iodomethane (1.52 ml, 24.4 mmol, 4 eq) was added dropwise after which the reaction mixture was allowed to warm to rt. GC-MS analysis after 1h indicated complete conversion. The reaction mixture was cooled to 0 °C, diluted with ether, and carefully quenched by the dropwise addition of water. After quenching the phases were separated and the aqueous phase was extracted twice with ether. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure affording 1-(tert-butyl)-2,3-dimethoxy-5-methylbenzene 21 (992 mg, 4.76 mmol, 78% yield over 2 steps).

Analytical data of the monomethylated compound 20:

\[
^1H-\text{NMR (400 MHz, CDCl}_3\text{)} \delta 6.69 (s, 1H), 6.60 (s, 1H), 5.82 (s, 1H), 3.87 (s, 3H), 2.29 (s, 3H), 1.40 (s, 9H).
\]

\[
^{13}C-\text{NMR (101 MHz, CDCl}_3\text{)} \delta 146.56, 142.02, 135.25, 127.92, 119.45, 109.44, 56.17, 34.68, 29.57, 21.53.
\]

Analytical data of the bismethylated compound 21:

\[
^1H-\text{NMR (400 MHz, CDCl}_3\text{)} \delta 6.74 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.33 (s, 3H), 1.41 (s, 9H).
\]

\[
^{13}C-\text{NMR (101 MHz, CDCl}_3\text{)} \delta 153.08, 146.36, 142.95, 132.39, 119.36, 111.57, 60.47, 55.77, 35.07, 30.72, 21.71.
\]

![Diagram](image)

2-bromo-5-(tert-butyl)-3,4-dimethoxy-1-methylbenzene (17b):

To a cooled (0 °C) solution of 1-(tert-butyl)-2,3-dimethoxy-5-methylbenzene 21 (625 mg, 3.00 mmol) in dry CH₂Cl₂ (10 mL) was added a solution of dibromine (201 μl, 3.90 mmol, 1.05 eq) in dry CH₂Cl₂ (1.5 mL). After addition the reaction mixture was allowed to warm to rt and stirred for 1h. GC-MS and TLC analysis indicated complete conversion of the starting material. The reaction mixture was then quenched with an aqueous saturated Na₂S₂O₃ solution. The phases were separated and the organic phase was washed with brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residual oil was subjected to flash column chromatography employing pentane : ether (99 : 1) as the eluent, affording 2-bromo-5-(tert-butyl)-3,4-dimethoxy-1-methylbenzene 17b (756 mg, 2.63 mmol, 88% yield) as a slightly yellow oil.

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$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.95 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 2.37 (s, 3H), 1.37 (s, 9H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 151.44, 150.76, 142.47, 132.72, 123.50, 118.04, 60.40, 59.97, 35.05, 30.53, 23.07.

General procedure for the optimized Pd-catalyzed homo-coupling of the sterically hindered substrates 17a and 17b:
In a dry Schlenk flask, Pd-PEPPSI-iPent (5 mol%, 1 $\mu$mol) and the substrate (0.2 mmol) were dissolved in dry toluene (0.7 ml) and the solution was cooled to 0 °C with an ice bath. tBuLi (141 $\mu$L, 1.7 M in hexanes, 0.24 mmol, 1.2 eq) was slowly added (per 2 drops with 5 min intervals, total addition time = 40 min) by the aid of a syringe pump. After the addition was completed the reaction mixture was stirred for one additional hour after which the reaction was quenched with methanol. Celite was added, and the solvent evaporated under reduced pressure. The residue was directly loaded onto a prepared flash column, and eluted using pentane : ether as the eluent affording the homo-coupling product as an oil.

2,2',3,3'-tetramethoxy-4,4',6,6'-tetramethyl-1,1'-biphenyl (22a):
Prepared according to the general procedure of the Pd-catalyzed homo-coupling in 79% isolated yield.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.58 (s, 2H), 3.84 (s, 6H), 3.77 (s, 6H), 2.28 (s, 6H), 2.23 (s, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 151.16, 145.51, 132.90, 131.55, 130.16, 111.25, 60.41, 55.63, 19.99, 12.86.

HRMS (ESI+): Calculated mass [M+H]$^+$ $C_{20}H_{27}O_4^+$ = 331.1904; found: 331.1902.
4,4’-di-tert-butyl-2,2’,3,3’-tetramethoxy-6,6’-dimethyl-1,1’-biphenyl (22b):
Prepared according to the general procedure of the Pd-catalyzed homo-coupling in 75% isolated yield as a waxy solid.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.93 (s, 2H), 3.86 (s, 6H), 3.64 (s, 6H), 1.95 (s, 6H), 1.42 (s, 18H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 151.10, 150.55, 142.05, 130.82, 130.03, 122.83, 59.93, 59.68, 35.04, 30.81, 19.88.

HRMS (ESI+): Calculated mass [M+H]$^+$ $C_{24}H_{39}O_4^+$ = 415.2843; found: 415.2839.

Attempted synthesis of isopropyl analogue 22c:
For our investigation of the influence of the para-substituent on the outcome of the Pd-catalyzed homo-coupling, we also tried to construct isopropyl test substrate 22c (Scheme 12, see below). Although initially considered to be 22c, the product turned out to be F. The synthesis started from 3,4-dimethoxytoluene that was brominated with dibromine to provide C. Interestingly, C was also obtained in a different, peculiar, way. In our preparation of tert-butyl substrate 22b we initially tried to tert-butylate 3,4-dimethoxytoluene A, but this provided us with the undesired regioisomer B. Surprisingly we found that bromination of B with pyridinium tribromide led to successful bromination, albeit that the tert-butyl group was removed simultaneously. The product’s analytical data were consistent with aryl bromide C, which indicated ipso-bromination. We therefore must assume that ipso-intermediate B1 was formed which eliminates isobutylene from the molecule, as indicated.

At first sight this sequence seems useless, however giving it some thought the reaction might have a useful application. To the best of our knowledge, bromine-tert-butyl exchange via ipso-bromination is extremely rare.$^{[40]}$ We postulate that this sequence might be useful if the tert-butyl functionality could act as a as a kind of protecting group, in the sense that it acts as a masked bromo substituent. The advantage is that the tert-butyl moiety is robust and tolerant to a wide variety of reaction conditions (lithiation, palladation!). Although we present here only one example, removal of the tert-butyl group was high yielding and easy to perform. A bromine atom was installed selectively which allows further functionalization, for instance using lithium cross-coupling chemistry. We are well aware that this reaction probably only applies to special cases, but its scope can be established by performing a systematic study into its potential.
Scheme 12. Attempted synthesis of isopropyl substrate 22c.

1-(tert-butyl)-4,5-dimethoxy-2-methylbenzene (B): To a mixture of 1,2-dimethoxy-4-methylbenzene A (5.2 g, 34 mmol), silica (17 g) and sodium bicarbonate (25.8 g, 308 mmol) in dichloroethane (120 mL) was added 2-bromo-2-methylpropane (34.5 ml, 308 mmol) and the mixture was stirred at 70 °C overnight. The reaction mixture turned blue/purple to green over time. The green color dissipated slowly, and when completely vanished the reaction did not progress any further (based on GC-MS analysis after 48 h). The reaction mixture was filtered, and concentrated under reduced pressure. Flash column chromatography employing pentane : ether (95 : 5) afforded the product, however, due to similar $R_f$ values of the starting material and the product, the individual column fractions had to be analyzed by GC-MS. All fractions with >95% purity were isolated yielding virtually pure 1-(tert-butyl)-4,5-dimethoxy-2-methylbenzene B (1.78 g, 8.55 mmol, 25% yield).

\[
\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 6.93 (s, 1H), 6.64 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H), 1.40 (s, 9H) \]

\[
\text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 146.44, 146.10, 140.14, 128.39, 116.11, 110.89, 56.12, 55.78, 35.45, 31.01, 22.64
\]

HRMS (ESI+): Calculated mass [M+H]$^+$ $C_{13}H_{20}O_2^+$ = 209.1536; found: 209.1536
‡ The obtained $^1$H-NMR spectrum differed slightly from previous reported data; A. P. Morgenstern, C. Schuit, W. Nauta, *J. Chem. Soc. C.* 1972, 3706. It is important to note that the $^1$H-NMR spectrum within this report was obtained on a 60 MHz spectrometer at 38 °C.

**1-bromo-4,5-dimethoxy-2-methylbenzene (B) (Method A):**
To a solution of 1-(tert-butyl)-4,5-dimethoxy-2-methylbenzene B (1.78 g, 8.55 mmol) in dry CH$_2$Cl$_2$ (100 mL) was added pyridinium tribromide (10.9 g, 34.2 mmol, 4 eq) portion wise over 1 h. The wall of the Schlenk flask was rinsed with dry CH$_2$Cl$_2$ after each addition. The reaction was stirred overnight at rt after which GC-MS and TLC analysis indicated complete conversion. The suspension was filtered and to the filtrate was added an aqueous saturated NaHCO$_3$ solution. The phases were separated and the organic layer was washed twice with water. The organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography using 3% ether in pentane as the eluent afforded pure 1-bromo-2,3-dimethoxy-5-methylbenzene C (1.8 g, 7.79 mmol, 91% yield) as a yellow oil.

**1-bromo-2,3-dimethoxy-5-methylbenzene (C) (Method B):**
To a solution of 1,2-dimethoxy-4-methylbenzene A (943 μL, 6.57 mmol) in dry CH$_2$Cl$_2$ (20 mL), cooled to 0 °C, was added slowly a solution of dibromine (338 μL, 6.57 mmol, 1 eq) in dry CH$_2$Cl$_2$ (4 mL). The reaction mixture was allowed to warm-up to rt at which it was stirred for 1.5 h. GC-MS analysis indicated selective formation of the desired product. The reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$. The phases were separated and the aqueous layer was extracted once using CH$_2$Cl$_2$. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography employing 3% ether in pentane afforded pure 1-bromo-2,3-dimethoxy-5-methylbenzene C (1.30 g, 5.63 mmol, 94% yield).
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$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.00 (s, 1H), 6.73 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.33 (s, 3H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 148.12, 147.60, 129.52, 115.25, 114.37, 113.51, 56.10, 55.94, 22.28.

HRMS (ESI+ and APCI) analysis could not be performed due to ion-suppression. GC-MS analysis gave the following mass fragmentation: Calculated mass [M]$^+$ C$_{9}$H$_{11}$O$_2$Br$^+$ = 229.99; found: 232 (M$^+$ isotope), 230 (M$^+$), 217 (M-CH$_3$ isotope)$^+$, 215 (M-CH$_3$)$^+$, 108 (M-(CH$_3$)$_2$Br)$^+$.

The analytical data are in accordance with the previously reported analytical data. See: J. L. Charlton, K. Koh, G. Plourde, Can. J. Chem. 1990, 68, 2028.

1-isopropyl-4,5-dimethoxy-2-methylbenzene (E):
A solution of 1-bromo-4,5-dimethoxy-2-methylbenzene C (1.0 g, 4.3 mmol) in dry THF (20 mL) was cooled to -78 °C. To the solution was slowly added nBuLi (1.9 mL, 2.5 M in hexanes, 4.7 mmol, 1.1 eq). The mixture was allowed to stir for 30 min. Acetone (2 mL) was added dropwise and the mixture was allowed to reach rt and stirred overnight. The reaction mixture was quenched with MeOH (5 mL) where after the reaction mixture was concentrated under reduced pressure. The crude reaction mixture was used in the next step.

A solution of alcohol D (1.0 g, 4.76 mmol) in dry CH$_2$Cl$_2$ (40 mL) was cooled to 0 °C. 2,2,2-trifluoroacetic acid (1.65 ml, 21.6 mmol, 5 eq) and triethylsilane (2.07 ml, 13 mmol, 3 eq) were added and the reaction was stirred at 0 °C for 1h. The reaction was complete after this time and the reaction mixture was allowed to warm to rt. The reaction was concentrated under reduced pressure. Flash column chromatography employing pentane : ether (95 : 5) as the eluent afforded 1-isopropyl-4,5-dimethoxy-2-methylbenzene E (643 mg, 3.31 mmol, 76% yield over 2 steps)

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.79 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.10 (p, J = 6.9 Hz, 1H), 2.29 (s, 3H), 1.23 (d, J = 6.9 Hz, 6H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) δ 147.22, 146.49, 138.85, 126.91, 113.72, 108.78, 56.11, 55.89, 29.12, 23.41, 18.73.

HRMS (ESI+): Calculated mass [M+H]$^+$ C$_{12}$H$_{19}$O$_2^+$ = 195.1380; found: 195.1380.
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3-bromo-1-isopropyl-4,5-dimethoxy-2-methylbenzene (F):
To a solution of 1-isopropyl-4,5-dimethoxy-2-methylbenzene E (590 mg, 3.04 mmol) in dry CH₂Cl₂ (10 mL) was added slowly a solution of dibromine (156 μl, 3.04 mmol, 1 eq) in dry CH₂Cl₂ (6 mL). After addition the reaction was stirred at rt for 60 min after which GC-MS indicated full conversion. The reaction mixture was quenched by the addition of saturated aqueous Na₂S₂O₃ (8 mL). The phases were separated and the organic phase was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash column chromatography using pentane : ether (98 : 2) afforded 3-bromo-1-isopropyl-4,5-dimethoxy-2-methylbenzene F (672 mg, 2.46 mmol, 81% yield) as a yellowish oil.

³¹H-NMR (400 MHz, CDCl₃) δ 6.79 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.18 (p, J = 6.8 Hz, 1H), 2.38 (s, 3H), 1.22 (d, J = 6.9 Hz, 6H).

³¹C-NMR (101 MHz, CDCl₃) δ 151.32, 144.33, 143.42, 127.59, 121.62, 108.79, 60.32, 56.25, 30.56, 23.37, 18.39.


6.7 References


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[34] L. S. Mazzaferro, W. Hüttel, A. Fries, M. Müller, J. Am. Chem. Soc. 2015, 137, 12289.