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# Palladium catalyzed cross- and homo-coupling reactions of 4-Halo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes with various organometallic reagents

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ABSTRACT

An investigation of palladium catalyzed Kumada type reactions between various Grignard reagents and mono-substituted octafluoroparacyclophane derivatives revealed that by varying the reaction temperature, and mode of addition of the Grignard reagent, it was possible to influence whether the major product was the cross-coupled, or the homo-coupled (reductive dimer) paracyclophane product. This provides an improved methodology to prepare aryl substituted paracyclophanes, and additionally an alternative route to the unusual and rare di-cyclophane skeleton. Analogous reactions with alkyl lithium reagents were also explored, resulting in the generation of some previously unreported octafluoroparacyclophane products.

## 1. Introduction

Molecules that have aromatic rings connected by multiple aliphatic bridges are broadly classified as Cyclophanes [1], and comprise a structurally diverse and well studied class of compounds. The paradigm of cyclophane chemistry is [2.2]paracyclophane (PCP) since it best exemplifies the numerous interesting and unusual characteristics of these highly strained systems with proximate aromatic rings [2,3]. Even now, there is renewed interest in this area due to recent advances in the use of the paracyclophane motif in material science applications, and also the utilization of such molecules as ligands, reagents and catalysts in enantioselective reactions [4].

Over the last two decades, the area of fluorinated paracyclophanes has continued to evolve. Initially this was driven by the industrial application of 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (OFP, **1**) [5] as the monomer for the Parylene VIP AF4 polymer, which combines high thermal and chemical stabilities, with low dielectric constant and moisture absorption [6,7] (Scheme 1). There are now viable large scale syntheses of bridge fluorinated **1** [8–10], and more recently the per-fluorinated paracyclophane (PFP) [11] available in the literature [12]. Such syntheses have permitted fundamental studies on the reactivity of both OFP [13,14] and PFP [15]. The majority of reports are concerned with OFP, and early OFP derivatives have since been used as building blocks in a wide spectrum of synthetic [16–21] and spectroscopic [22–26] endeavors.

Bi-aryl molecules are a family of compounds that are prevalent in nature, and are important as pharmaceuticals, agrochemicals and chiral ligands and catalysts [27]. The preparation of several OFP derivatives with one or more new aryl–aryl linkages have been reported, almost all of which have employed Palladium catalyzed reactions, such as reductive homo-couplings [20], and Suzuki [19], Kumada [13,14] and Negishi cross-coupling reactions [28].

## 2. Results and discussion

Based on experience, such reported Palladium catalyzed OFP reactions whilst being successful and always completely reproducible, are somewhat sensitive to the reaction conditions. Herein is an investigation into the optimization of some cross-coupling Kumada type reactions, where varying the reaction conditions (e.g. temperature, rate of addition) generated different, and in some cases, unexpected, products. As shown in Table 1, the initial focus was on the reaction of PhMgBr with OFP-Halides and $PdCl_2$ in THF. As anticipated, it was quickly established (entries 1–3) that OFP-I **2** was the preferred starting material for such reactions, always generating the highest yield. OFP-Cl **3** did not react under the

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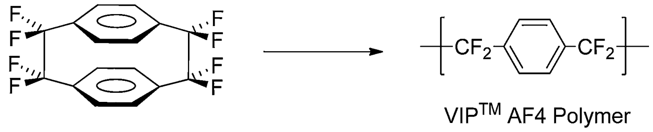
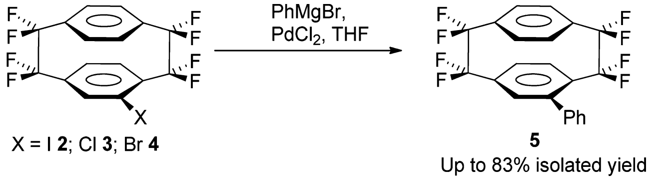


**1**, OFP

**Scheme 1.** Polymerization of OFP producing the VIP AF4 Polymer.



**Scheme 2.** Kumada aryl cross coupling reactions employing OFP-Halides.

typical reaction conditions, whereas OFP-Br **4** did react, but always with lower isolated yields of desired product, due to an increase in the amount of reduction product, and lower conversion (Scheme 2).

Next the reaction of PhMgBr with **2** was further explored. Running this reaction in the presence of $PdCl_2$, in refluxing THF lead to the desired OFP-Ph **5** cross-coupled product in 49% isolated yield, and as shown in entry 4, reaction in the absence of any $PdCl_2$ catalyst, only resulted in the generation of reduction product **1** in high yield. It was found that the yield was influenced by the speed of addition of the phenyl magnesium bromide. By adding the organometallic reagent slowly (via syringe pump) into the refluxing THF solution, the yield of the cross-coupled product was increased up to 83% (entry 5).

However more surprisingly, it was found that when the reaction was performed at room temperature (entries 6 and 7), in addition to the expected cross-coupled and reduction products, another product was generated. The new unexpected product was identified as bis(OFP) **6** (Scheme 3). Fortunately, the preparation of di-cyclophane **6** has been previously reported [20], including the crystal structures of both diastereomers (since the starting material **2** is planar chiral [29] and racemic), but most importantly also their remarkable $^{19}F$ NMR spectra, which at room temperature shows significant line broadening caused by restricted molecular rotation observable on the NMR time scale (see Supporting information). Therefore, this distinguishing $^{19}F$ NMR behaviour immediately prompted the product identification as **6**. As shown in entry 7, a yield of 44% for bis(OFP) **6** was obtained at room temperature, whereas no traces of this homo-coupled product were detected at the higher temperatures. The ratio of diastereomers of **6** produced in this reaction was determined by $^{19}F$ NMR and GC to be 1.9:1. (*meso*:*dl*). (The previous deliberate synthesis of **6** using OFP-I/Cu/$PdCl_2$.dppf/DMF/70 °C gave a yield of 74%, with a diastereomeric ratio of *meso*:*dl* of 3:2 [20]). In this room temperature reaction, it appears that the Grignard reagent is not acting as a nucleophile (necessary for transmetalation at the palladium), but rather acting as a reductant, thus promoting reductive homo-coupling rather than the intended cross-coupling.

Most commonly, homo-coupled products in these types of reaction arise from *oxidative* dimerization of the nucleophilic species [30–32]. In this case it is *reductive* dimerization of the paracyclophane halide. Usually such couplings are achieved using metals or other reductants [33]. It is possible that in these reactions it is the known single electron transfer (SET) character of the aryl Grignard reagent [34] coming into effect, promoting reductive homo-coupling of the OFP-I. Alternatively, PhMgBr rather than transmetalating the intermediate palladium species, is reacting with OFP-I to produce “OFP-MgBr”, which in turn transmetalates with the palladium species, ultimately leading to homo-coupled products.

Having established that in these reactions, the PhMgBr can act as a reductant, as well as a nucleophile, it was investigated whether the nucleophilic (transmetalation) behaviour of the Grignard could be minimized, in order to maximize the homo-coupling process. In this regard, the reaction of more sterically hindered aryl Grignard reagents was explored. As shown in entries 8 and 9, when mesityl magnesium bromide was used, no cross-coupled or homo-coupled products were observed. However, when PCP-MgBr [35] was used (prepared via PCP-Br/$^tBuLi/MgBr_2{\cdot}Et_2O$), it was observed that the homo-coupled product **6** was again generated, in 30% isolated yield (entry 10). Disappointingly, no evidence of the cross-coupled “mixed” di-cyclophane (OFP-PCP) was detected, nor was any di-PCP [36] observed.

Encouraged by these productive aryl Grignard reagent reactions, a brief investigation of alkyl organometallics was explored (entries 11–14). Addition of 0.4 equivalents of *tert*-Butyl Lithium to OFP-I **2** and $PdCl_2$ in THF only yielded reduction product **1**, whereas Methyl Lithium (complex with LiBr) gave successful products of cross-coupling, with higher yields being generated at lower temperatures (entries 12–14). The production of OFP-$CH_3$ **7** then permitted the subsequent facile generation of two more previously

**Table 1**
Organometallic reactions with OFP-Halides.

| Entry | OFP-X | R–M (3 equiv.) | Addn. | Temp. | Time | OFP **1** | OFP-R **5** or **7** | Bis(OFP) **6** |
|---|---|---|---|---|---|---|---|---|
| 1 | –I | PhMgBr | A | Reflux | 2 h | 44 | 49 | |
| 2 | –Br | PhMgBr | A | Reflux | 2 h | 50[a] | 19 | |
| 3 | –Cl | PhMgBr | A | Reflux | o/n | NR | | |
| 4 | –I | PhMgBr[b] | A | Reflux | 1 h | 98 | | |
| 5 | –I | PhMgBr | D | Reflux | o/n | 8 | 83 | |
| 6 | –I | PhMgBr | D | RT | 2 h | 20 | 35 | 40 |
| 7 | –I | PhMgBr | D | RT | o/n | 15 | 38 | 44 |
| 8 | –I | MesMgBr | D | RT | o/n | 93 | | |
| 9 | –I | MesMgBr | A | 0 °C | 1 h | NR | | |
| 10 | –I | PCPMgBr | D | RT | o/n | 60 | | 30 |
| 11 | –I | $^tBuLi$[c] | A | RT | 2 h | 30[d] | | |
| 12 | –I | $CH_3Li$ | D | Reflux | 2 h | 66 | 31 | |
| 13 | –I | $CH_3Li$ | D | RT | o/n | 40 | 55 | |
| 14 | –I | $CH_3Li$ | D | 0 °C | 5 h | 17 | 81 | |

D = slow addition (either dropwise or via syringe pump); A = added in a single aliquot.

[a] 20% starting material left.

[b] zero $PdCl_2$ added.

[c] 0.4 equivalents used.

[d] 65% starting material left.