

# *In Situ* Generation of ArCu from CuF<sub>2</sub> Makes Coupling of Bulky Aryl Silanes Feasible and Highly Efficient

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**Abstract:** A bimetallic system Pd/CuF<sub>2</sub>, catalytic in Pd and stoichiometric in Cu, is very efficient and selective for the coupling of fairly hindered aryl silanes with aryl, anisyl, phenylaldehyde, or pyridyl iodides of conventional size. The reaction involves the activation of the silane by Cu<sup>I</sup> followed by disproportionation and transmetalation from the Cu<sup>I</sup>(aryl) to Pd<sup>II</sup>, on which coupling takes place. The Cu<sup>III</sup> formed in the disproportionation is reduced to Cu<sup>I</sup>(aryl) by the aryl silane in excess, so that the CuF<sub>2</sub> used is fully converted into Cu<sup>I</sup>(aryl) and used in the coupling. Moreover, no extra source of fluoride is needed. Interesting size selectivity towards coupling is found in competitive reactions of hindered aryl silanes. Easily accessible [PdCl<sub>2</sub>(IDM)(AsPh<sub>3</sub>)] is by far the best catalyst, and the isolated products are essentially free of As or Pd (< 1 ppm). The mechanistic aspects of the process are experimentally examined and discussed.

## Introduction

Compounds containing bulky aryls are interesting targets because they are found as components of many natural products.<sup>1</sup> They find use in medicinal chemistry since they improve the lipophilicity and metabolic stability of drugs.<sup>2</sup> Heterocoupling of bulky aryls can be achieved using lithium,<sup>3</sup> magnesium,<sup>4</sup> or zinc derivatives,<sup>5</sup> but these strongly basic reagents severely narrow the scope of application, as they are less compatible with many functional groups. Suzuki reactions have been occasionally used,<sup>6</sup> but voluminous boronic acids are very prone to protodeboronation and their manipulation is cumbersome.<sup>6,7</sup> As a matter of fact, Suzuki reactions involving transmetalation of bulky groups are extremely challenging: fine tuning of the reaction and optimization for every substrate is usually needed. As a matter of fact, all the reported examples rely on the use of bulky and electron-rich ligands, which can be expensive or not readily available. Simpler robust methodologies are still lacking.<sup>8</sup>

The Hiyama-Denmark reaction is a cross-coupling process very interesting because of the stability of the reagents, the high compatibility with functional groups, and the non-toxicity of the by-products.<sup>9</sup> Although the process can now be used for the synthesis of complicated molecules,<sup>10</sup> it is much less popular than the homologous Suzuki or Negishi reactions.<sup>11</sup> A serious

limitation is that it is inefficient to cope with bulky groups. To the best of our knowledge there are very few Hiyama coupling examples dealing with any hindered silane or arylalkoxysilane,<sup>12</sup> and there is no precedent of use of diorthosubstituted aryl silanes. This reactivity constraint is easy to understand: in the direct Si/Pd aryl transmetalation the Si-Ar-Pd transition state is a very congested high-energy structure.<sup>13</sup> It was our purpose in this paper to find an efficient methodology to circumvent this problem and open the procedure to bulky arylsilanes.

## Results and Discussion

### *Synthetic Studies*

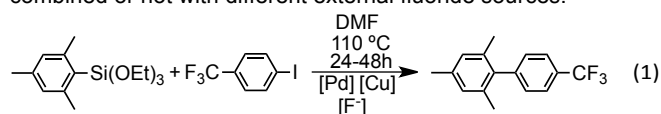
Recently we managed to achieve coupling of bulky and common aryls with the Stille reaction, by using Au<sup>I</sup> as a transmetalation cocatalyst. The use of linear gold complexes as "aryl carriers" leads to a sequential Sn/Au/Pd bulky-aryl double transmetalation, where any of the two steps is much less congested and has lower transmetalation barrier than the direct Sn/Pd transmetalation.<sup>14,15</sup> In that research we found that for the facilitation of the transmetalation to Pd<sup>II</sup> (whether Sn/Pd or Au/Pd) it was important that Pd should contain an ancillary ligand easy to be displaced; at the same time, for the stabilization of the Pd<sup>0</sup> intermediate good coordinating soft ligands should be available to coordinate to Pd. This led us to discover the excellent behaviour of [PdCl<sub>2</sub>(IDM)(AsPh<sub>3</sub>)], an asymmetric complex with one strong and one weak ligand that does not symmetrize to [PdCl<sub>2</sub>(IDM)<sub>2</sub>] and [PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub>] under the working conditions for that Au-cocatalyzed Stille process. Unfortunately our attempts, at the beginning of this work, at extending this Au<sup>I</sup> co-catalysis to the Hiyama reaction have been unsuccessful.

Copper is a very tempting alternative to gold.<sup>16</sup> Although there is no direct parallelism of gold and copper, due to the richer variety of accessible oxidation states and coordination geometries for the latter, copper has been successfully used as additive for the cross-coupling of indolylox (in the form of stoichiometric Cu<sup>I</sup>),<sup>17</sup> or for the transmetalation of the alkyl group from 2-(2-hydroxyprop-2-yl)phenyl alkylsilanes (remarkably in catalytic amount in the form of Cu(hfacac)<sub>2</sub>).<sup>18</sup> These reports did not address the transmetalation of bulky groups. There are also several studies of palladium-free systems where the transmetalation between organosilanes and copper takes place, always in the presence of fluoride salts.<sup>19,20,21</sup> The palladium-free Hiyama reaction catalysed by CuI, CsF, and P,N ligands has been reported.<sup>22</sup> However, chemical systems analogous to all those mentioned above were in our hands inefficient for the cross coupling of ortho-disubstituted arylsilanes.<sup>23</sup> Eventually, in a methodical testing of Pd/Cu systems with different copper additives and fluoride sources for the mesityl-aryl cross coupling

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(Equation 1 and Table 1), we found some interesting results. Several Cu sources in stoichiometric and sub-stoichiometric conditions relative to the mesityltris(ethoxy)silane were tested, combined or not with different external fluoride sources.



**Table 1.** Experiments with different Cu sources, using  $[\text{PdCl}_2(\text{AsPh}_3)_2]$  as catalyst.<sup>a</sup>

Entry	Cu source	Cu %	CsF	Yield % MesC <sub>6</sub> H <sub>4</sub> CF <sub>3</sub> -p
1	None	0	yes	<5
2	CuI	50	yes	4
3	Cu(O <sup>t</sup> Bu)	100	no	0
4	<b>CuF<sub>2</sub></b>	<b>100</b>	<b>no</b>	<b>88</b>
5	<b>CuF<sub>2</sub>·3H<sub>2</sub>O</b>	<b>100</b>	<b>no</b>	<b>81</b>
6	Cu(OH) <sub>2</sub>	100	no	0
7	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	25	yes	25
8	Cu(OTf) <sub>2</sub>	25	yes	25
9	CuF <sub>2</sub>	25	yes	17

[a] Reaction conditions: 1 equivalent IC<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>-p, 2 equivalents MesSi(OEt)<sub>3</sub> in DMF at 110 °C for 24-48 h; 2 mol% [Pd] =  $[\text{PdCl}_2(\text{AsPh}_3)_2]$ ; the specified amount of Cu promoter (mol% relative to IC<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>-p); 2 equivalents of CsF when specified. Termination of the reaction and yields were determined by <sup>19</sup>F NMR integration.

Copper(I) compounds CuI and Cu(O<sup>t</sup>Bu), hoped to form CuMes and transmetalate Mes to Pd, gave poor results or showed to be ineffective (entries 2-3). In contrast the reactions with CuF<sub>2</sub> in stoichiometric amount proceeded in good yield (entries 4, 5) without added CsF. A oxygenated source of Cu<sup>II</sup>, Cu(OH)<sub>2</sub>, which is in theory good for the transfer, failed to work in the absence of fluoride (entry 6). The addition of CsF activated the reaction of copper sources with labile anions (entries 7, 8) but could not make the process catalytic in copper. In all active conditions (entries 4,5,7-9) the amount of IC<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>-p converted to MesC<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>-p was stoichiometric relative to the amount of Cu<sup>II</sup> used, or fairly close to it.

Thus, although we failed to find conditions for a process catalytic in copper (it is catalytic in Pd) a very interesting atom economical transformation stoichiometric in CuF<sub>2</sub> was found (Table 1, entry 4). The need for a stoichiometric amount of CuF<sub>2</sub> might look a disadvantage but, much on the contrary, it has several advantages. As discussed later it provides stoichiometrically the exact amounts of Cu<sup>I</sup>Ar and fluoride needed for the reaction, sparing the need for any other source of fluoride used in typical Miyaura couplings (e.g. CsF or (NBu<sub>4</sub>)F). Moreover, CuF<sub>2</sub> is of similar cost or cheaper (per F atom) than other fluoride sources, and is easier to handle than, for instance, the very hygroscopic (NBu<sub>4</sub>)F.

Anhydrous CuF<sub>2</sub> is a moderately hygroscopic white solid leading to the green complex CuF<sub>2</sub>·3H<sub>2</sub>O when hydrated. Using the later as copper additive (Table 1, entry 5) also gave excellent cross-coupling yield, showing that the reaction is fairly

compatible with water, although it produced about 10% of the homocoupling biphenyl F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> (a byproduct not easy to separate), and a larger amount of MesH by hydrolysis of the silane. By contrast, in optimized conditions with the anhydrous CuF<sub>2</sub>, the cross-coupling product F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>Mes could be easily purified by extraction with ether and filtration through a short pad of silica.<sup>23</sup>

Other palladium precatalysts were checked (Table 2) in the model reaction 1, using CuF<sub>2</sub> as promoter, to optimize the reaction. The formation of F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> was eliminated (Table 2, entry 5) or highly diminished (Table 2, entry 8) with the most efficient catalysts.

A blank experiment without Pd catalyst confirmed that CuF<sub>2</sub> alone does not activate the cross coupling process. Remarkably, for catalysts bearing bulky ligands (Table 2, entries 1 and 2), very efficient in other instances, almost no reaction was observed, while other palladium precatalysts used were very efficient for the cross-coupling process (Table 2, entries 3-8).<sup>24</sup> Not surprisingly from our previous experience with stannanes,<sup>14</sup> the mixed complex  $[\text{PdCl}_2(\text{IDM})(\text{AsPh}_3)]$  showed excellent performance (Table 2, entry 5).

**Table 2.** Catalyst optimisation.<sup>a</sup> (R<sup>1</sup> = Mes; R<sup>2</sup> = p-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>).

	Pd precatalyst	Yield % R <sup>1</sup> -R <sup>2</sup>	Other % R <sup>2</sup> R <sup>2</sup> /R <sup>2</sup> H
1	$[\text{Pd}(\text{OAc})_2] + 2 \text{ eq. Xphos}$ (1)	12	66/0
2	$[\text{PdCl}_2(\text{Pr-carb.})(3\text{-Clpy})]$ (2)	< 5	70/0
3	$[\text{PdCl}_2(\text{AsPh}_3)_2]$ (3)	87	5/7
4	$[\text{PdCl}_2(\text{dppf})]$ (4)	88	5/5
5	<b><math>[\text{PdCl}_2(\text{IDM})(\text{AsPh}_3)]</math></b> (5)	<b>&gt; 98</b>	<b>0/0</b>
6	$[\text{PdCl}_2(\text{IDM})(3\text{-Clpy})]$ (6)	87	10/0
7	$[\text{PdCl}(\mu\text{-Cl})(\text{IDM})_2]$ (7)	81	9/0 <sup>b</sup>
8	<b><math>[\text{PdCl}_2(\text{PPh}_3)_2]</math></b> (8)	<b>96</b>	<b>2/0</b>

[a] Reaction conditions: 2 mol% of [Pd], 1 equivalent of CuF<sub>2</sub>, 1 p-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 2 equivalents MesSi(OEt)<sub>3</sub> in DMF at 110 °C for 24-48 h. [b] 11% unreacted ArI and some black Pd are observed.

It might seem that Pd complexes with any other weak ligand instead of AsPh<sub>3</sub> could be used if arsine is to be avoided, but this is not quite true: the use of 3-Clpy in place of AsPh<sub>3</sub> (Table 2, entry 6) affords worse results. Similarly,  $(\mu\text{-Cl})_2[\text{PdCl}(\text{IDM})_2]$ , which probably splits in DMF solution to give  $[\text{PdCl}_2(\text{IDM})(\text{DMF})]$ , gives worse results accompanied by catalyst decomposition that leaves 11% ArI unreacted (Table 2, entry 7). Thus, the ancillary weak ligand has some effect, which will be commented in the mechanistic considerations. For the moment we will concentrate on some steric effects with synthetic consequences that are obvious from the very direct comparison between the excellent performance of  $[\text{PdCl}_2(\text{IDM})(\text{AsPh}_3)]$  (5) and the fairly good of  $[\text{PdCl}_2(\text{IDM})(3\text{-Clpy})]$  (6) against the bad results of the electronically related PEPSI catalyst  $[\text{PdCl}_2(\text{Pr-}$

carbene)(3-Clpy)] (2). The three complexes have an easy leaving ligand and a heterocyclic carbene that remains strongly coordinated to Pd along the process, but the steric requirements of the IDM and <sup>i</sup>Pr-carbene are very different (Figure 1). The commonly accepted understanding of reductive elimination suggests that eventually the cross-coupling should take place via a palladium [PdMes(C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>)(carbene)] intermediate. The results in Table 2 show that, in our reaction involving a poor Cu<sup>I</sup> nucleophile,<sup>25</sup> acceding to form this tricoordinate intermediate and the subsequent transition state is very critically dependent on the steric factors of all the coordinated groups:<sup>26</sup> a smaller ancillary carbene ligand IDM is more compatible with the participation of the bulky aryl Mes than a bulkier carbene ligand <sup>i</sup>Pr-carbene (Table 2, entries 5,6 vs. 2). The same problem must be affecting the bulky Xphos in entry 4 compared to PPh<sub>3</sub> in entry 8. The steric compatibility or incompatibility of coupling groups and ligands of diverse sizes dominates the transmetalation rate and the feasibility of the subsequent coupling step.

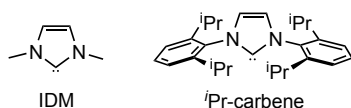


Figure 1. Carbene ligands in entries 5,6 (left) and 2 (right) of Table 2.

The requirement of steric compatibility is also clearly seen in the following case of stoichiometric syntheses: The stoichiometric reaction of PhSi(OEt)<sub>3</sub> with the isolated complex [Pd(C<sub>6</sub>H<sub>4</sub>CN-*p*)F(PPh<sub>3</sub>)<sub>2</sub>], has been reported to yield easily PhC<sub>6</sub>H<sub>4</sub>CN-*p* and FSi(OEt)<sub>3</sub>,<sup>27</sup> by direct exchange of Ph for F. In contrast, all our attempts to react the bulkier MesSi(OEt)<sub>3</sub> with the isolated complex [Pd(C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>-*p*)F(PPh<sub>3</sub>)<sub>2</sub>] failed (see experimental).

In our initial choice of possible catalysts we did not consider the common catalyst [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (8), driven by our previous experiences showing that: *i*) in the gold co-catalysed Stille reaction of bulky groups, [PdCl<sub>2</sub>(IDM)(AsPh<sub>3</sub>)] behaved very well but [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] performed extremely slow, as expected from the use of a strong ligand not easy to release during transmetalation;<sup>14</sup> and *ii*) we were aware that PPh<sub>3</sub> coordinates strongly to Cu<sup>I</sup> whereas AsPh<sub>3</sub> does not.<sup>28</sup> So we were concerned about possible detrimental interactions of copper and PPh<sub>3</sub>. However, when we tried it (last entry in Table 2) we were surprised and delighted to see that [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (8) performed almost as good as [PdCl<sub>2</sub>(IDM)(AsPh<sub>3</sub>)] (5).

In order to check the scope of the process in Eq. 2, the reactivity of other differently substituted bulky arylalkoxysilanes as nucleophiles was studied, with the best catalyst 5 and, for some reactions, with 8. The cross-coupling results are gathered in Table 3. At that point, the excellent performance of 5 towards bulky groups was found to be quite general, whereas 8 turned out to be less efficient or very little efficient in other couplings (see entries 2,3,6,11 in Table 3). As a matter of fact, [PdCl<sub>2</sub>(IDM)(AsPh<sub>3</sub>)] (5) is extremely efficient and quite general, as discussed below. It might appear that its molecular

composition were announcing a contaminant and not easily accessible catalyst, but in fact it is very easy to make in two steps from simple precursors,<sup>14b</sup> and the isolated cross-coupling reaction products analysed by the ICP-MS show that the palladium or arsenic concentrations in the product are < 1 μg/g (see SI for details).

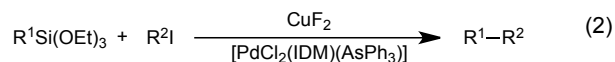


Table 3. CuF<sub>2</sub>-promoted Hiyama coupling of substituted aryls.<sup>a</sup>

Entry	Product R <sup>1</sup> -R <sup>2</sup>	Yield	Other products <sup>f</sup>
1a		73 70 <sup>h</sup>	R <sup>2</sup> -R <sup>2</sup> : 14%; also R <sup>1</sup> -R <sup>1</sup>
1b		80 <sup>b</sup>	
2		71 35 <sup>h</sup>	R <sup>2</sup> -R <sup>2</sup> : 21%; also R <sup>1</sup> -R <sup>1</sup>
3		95	
4		> 98	
5		> 98 > 95 <sup>d</sup> 54 <sup>d,e</sup>	
6		78 71 <sup>h</sup>	
7		> 95 <sup>d</sup> 90 <sup>c</sup>	
8		> 95 <sup>d</sup> 87 <sup>c</sup>	
9		> 95 <sup>d</sup> 88 <sup>b</sup>	
10		> 95 <sup>d</sup> 90 <sup>c</sup>	
11		> 95 <sup>d</sup> 88 <sup>e,c</sup> 25 <sup>h</sup>	

[a] Reaction conditions: 2 mol% of **5**; CuF<sub>2</sub>:R<sup>2</sup>: R<sup>1</sup>Si(OEt)<sub>3</sub> = 1:1:2, in DMF at 110 °C for 24-48h. [b] CuF<sub>2</sub> was substituted by 2 equivalents of CsF. [c] Isolated yield. [d] Yield (% from R<sup>2</sup>I) determined by <sup>19</sup>F NMR. [e] R<sup>2</sup>Br was used instead of R<sup>2</sup>I. [f] Byproducts for 1a. [g] GC-MS yield, using biphenyl as internal standard. [h] [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] was used instead of [PdCl<sub>2</sub>(IDM)(AsPh<sub>3</sub>)].

As shown in Table 3, the reactions with **5** as catalyst afford excellent yields for the coupling of mesityl and naphthyl

derivatives (entries 3-5), which do not work under the normal Hiyama protocols. The good result obtained for 2,4,6-trisopropyltris(ethoxy)silane (Table 3, entry 6) is noteworthy considering the extreme bulkiness of this substrate. Suzuki couplings using the much more reactive boronic counterpart usually fail for similarly bulky aryls.<sup>29</sup> It is also worth commenting that the procedure with  $\text{CuF}_2$  tolerates equally well electron-withdrawing (Table 3, entries 5, 6, 9) and electron-donating (Table 3, entries 7-8) substituents. Sensitive groups difficult to access otherwise, such as aldehydes (Table 3, entry 9), and pyridyl (Table 3, entry 11) can be effectively coupled.

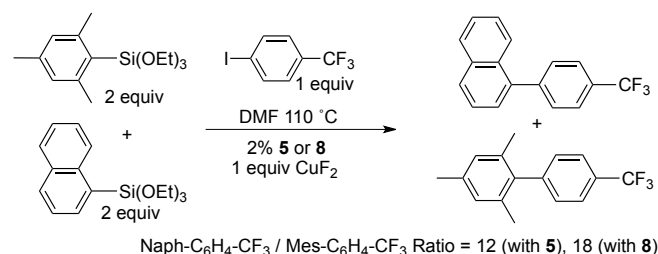
While the yield of desired cross coupling product  $\text{R}^1\text{-R}^2$  is very good for the bulky arylalkoxysilanes, as found initially for  $\text{MesSi}(\text{OEt})_3$  (virtually quantitative yield by NMR, Table 3, entries 3-11), it is noticeably lower for aryls of conventional size (Table 3, entries 1-2). This apparently surprising behaviour makes sense when examination of the products reveals (Table 3, entries 1-2) that this lower yield is mostly due to a loss of coupling selectivity producing a significant percentage of  $\text{R}^1\text{-R}^1$  and  $\text{R}^2\text{-R}^2$  homocoupling products. In fact using  $\text{CsF}$  instead  $\text{CuF}_2$  in Table 3, entry 1b improved the yield of  $\text{PhC}_6\text{H}_4\text{CF}_3$ . This confirms that  $\text{CsF}$  succeeds to produce cross-coupling with arylalkoxysilanes of conventional bulk, while  $\text{CsF}$  fails and  $\text{CuF}_2$  is required when the coupling involves a bulky arylalkoxysilane.

The formation of homocoupling products with arylalkoxysilanes of conventional bulk is easily explained assuming that the bimetallic Cu-mediated Hiyama process facilitates also undesired transmetalations that eventually can generate homocoupling products.<sup>30</sup> Thus, when the arylalkoxysilane has a conventional size all  $[\text{PdR}^1\text{R}^2(\text{L})]$ ,  $[\text{PdR}^2\text{R}^2(\text{L})]$ , and  $[\text{PdR}^1\text{R}^1(\text{L})]$  transition states are kinetically accessible and can generate  $\text{R}^1\text{-R}^2$ ,  $\text{R}^2\text{-R}^2$ , and  $\text{R}^1\text{-R}^1$ , respectively.<sup>31</sup> However, when  $\text{R}^1$  is bulky the formation of  $[\text{PdR}^1\text{R}^1(\text{L})]$  is made inaccessible at some point of the process (as discussed later) and the rate of formation of  $\text{R}^1\text{-R}^1$  drops to zero. The positive consequence of this is that the reaction becomes very selective in favour of the heterocoupling product.

In principle a fine combination of  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{L}$  groups should allow for tuning of selectivity of the reactions as controlled by the kinetic accessibility of the corresponding  $[\text{PdR}^1\text{R}^2(\text{L})]$  intermediate. For instance, a smaller ligand might allow for further improvement of the reaction in Table 3 entry 6. Similarly, competitive reactions coupling differently sized arylalkoxysilanes should show selectivity of the bulky alkoxysilane towards the less encumbered intermediate. As a proof of principle, the competitive reaction in Scheme 1 afforded highly selective coupling (12:1 ratio) of the less hindered arylalkoxysilane (1-naphthyl) using complex **5**. With complex **8** the reaction was somewhat slower and correspondingly more selective (18:1 ratio). This shows how much the size influence on the nucleophilicity of these Si reagents (and their corresponding  $\text{Cu}^I$  intermediates), is determinant for processes when it has to proceed through critically crowded species.

The stringent reaction conditions used in the reactions (DMF at 110 °C for 24-48 h) are responsible for some side reactions from the arylalkoxysilane. As a proof of this, if  $\text{CuF}_2$  and  $\text{MesSi}(\text{OEt})_3$  are heated in DMF at 110 °C for 48 h in the

absence of any Pd catalyst or aryl-iodide, full consumption of the silane is observed, along with formation of  $\text{Mes-H}$ ,  $\text{MesOEt}$  and  $\text{Mes-Mes}$  (only traces). These products likely come from hydrolysis of a copper organometallic intermediate (in the case of  $\text{Mes-H}$ ), or reductive elimination from  $\text{Cu}^{\text{III}}$  (see text later) in the case of  $\text{MesOEt}$ . These side products are not specified in Table 3, and are the reason for the need to use some excess of the arylalkoxysilane.



**Scheme 1.** Selectivity of naphthyl vs. mesityl coupling with **5** or **8** as catalyst.

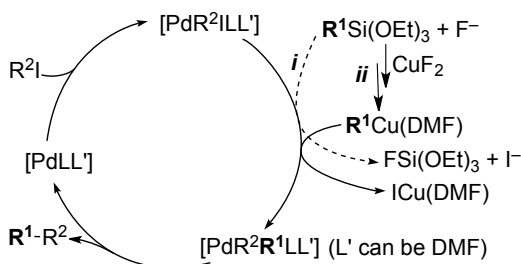
Up to now we have shown that the so far inaccessible coupling of bulky silyl derivatives using the Hiyama-Denmark protocols can be made accessible in a bimetallic catalysis using  $[\text{PdCl}_2(\text{IDM})(\text{AsPh}_3)]$  (or, occasionally  $[\text{PdCl}_2(\text{PPh}_3)_2]$ ) and stoichiometric  $\text{CuF}_2$  instead of other fluoride sources (different steric conditions might require other ligand optimizations). The process is not convenient for small aryls, where the classical Hiyama-Denmark conditions are much better. Now we will consider some mechanistic aspects of this bimetallic process that explain the performance observed.

#### Mechanistic studies and considerations

With the evidence provided so far, two pathways are possible for the Hiyama coupling, depending on how the nucleophilic moiety  $\text{R}^1$  reaches the Pd cycle (Scheme 2): (i) directly from the Si reagent in the conventional process (which requires a ionized source of  $\text{F}^-$ ); or (ii) as proposed in Scheme 2, via  $\text{CuR}^1$ , formed stoichiometrically *in situ* in the  $\text{CuF}_2$  mediated non-catalytic steps of the process. The conversion of  $\text{CuF}_2$  into  $\text{CuR}^1$  requires a change in oxidation state of copper. Sufficiently bulky  $\text{R}^1$  groups will have essentially zero rate via *i*, and consequently will need  $\text{CuF}_2$  as reagent to follow pathway *ii*. In this case other fluoride sources can be spared. Pathway *ii* is slow (therefore high temperature and long time are required), but efficient for the heterocoupling on Pd. In the case of conventional  $\text{R}^1$  groups, which hetero-couple well via pathway *i* using sources of ionic fluoride, the presence of undesired homocoupling products when  $\text{CuF}_2$  is used suggests that  $\text{CuF}_2$  is not a good source of ionized  $\text{F}^-$  and it is unable to make path *i* efficient; this also supports that in pathway *ii* there is some reversibility of the  $\text{Cu}^I/\text{Pd}^{\text{II}}$  transmetalation, giving rise to undesired transmetalations as the source of  $\text{R}^2\text{-R}^2$  and, at least in part,  $\text{R}^1\text{-R}^1$ .<sup>30</sup> From now on we will centre our attention on pathway *ii*.

The Pd catalysed cycle that closes the coupling process can be read in a rather conventional way, and we have already discussed above how the coupling rates depend on the size of

the groups to be coupled, as well as on the coordinating strength and size of the ancillary ligands. The ancillary ligands can influence every step of this cycle. For instance, phosphines can slow down the transmetalation, as compared to  $\text{AsPh}_3$ ; the stability of the  $\text{Pd}^0$  intermediate, which is critical for the protection of the catalyst working under harsh conditions depends on these ligands, as it happens also with the barrier to oxidative addition. Consequently it is not surprising that the nature of the ligands (also the weak ones) has a direct effect on the efficiency of the reaction.

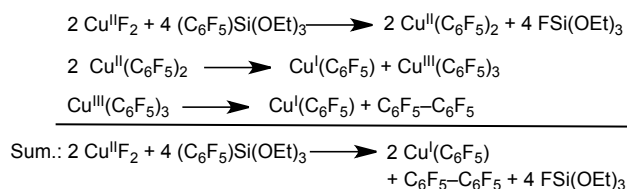


**Scheme 2.** Simplified picture of direct Hiyama-Denmark (i) and Cu-mediated (ii) catalyses. Ligand exchanges (L/L'/DMF) are possible.

Can we propose a reaction scheme for the non-catalytic part of the process and a plausible mode of reaction of  $\text{CuF}_2$  consistent with all the products and byproducts observed? Fortunately, studies available from literature and experiments discussed below allow us to get a convincing picture of this non-catalytic part of the reaction. In this respect there are reports in the literature where  $\text{Cu}^{\text{II}}$  fluorides react with organosilicon compounds. For instance, Lam *et al.* have reported the use of  $\text{Cu}(\text{OAc})_2 + \text{NBu}_4\text{F}$  to promote the coupling of amines with arylsilanes.<sup>20</sup> Several other results in the literature strongly suggest that the disproportionation of  $\text{Cu}^{\text{II}}$  organometallic compounds is fast and is the usual fate of these complexes under anaerobic conditions.<sup>32</sup> There are also examples that show that the reductive elimination from  $\text{Cu}^{\text{III}}$  is usually easy and fast.<sup>33</sup> Very recently, Nebra and Grushin have studied the reaction of  $[\text{CuF}_2(\text{bipy})(\text{H}_2\text{O})] \cdot 2\text{H}_2\text{O}$  with  $\text{CF}_3\text{SiMe}_3$ ,<sup>21</sup> and have concluded very convincingly that the transmetalation of  $\text{CF}_3$  to copper is followed by disproportionation of  $\text{Cu}^{\text{II}}$ , leading to a reversible equilibrium between  $\text{Cu}^{\text{I}}$  +  $\text{Cu}^{\text{III}}$  and  $\text{Cu}^{\text{II}}$  species that can be observed because the  $\text{CF}_3\text{-CF}_3$  coupling is not feasible.

We have obtained further mechanistic hints of this disproportionation from experiments using  $\text{CuF}_2$  and pentafluorophenyltris(ethoxy)silane.<sup>34</sup> Thus, a suspension of  $\text{CuF}_2$  was stirred in the absence of Pd catalyst with 3 equivalents of  $(\text{C}_6\text{F}_5)\text{Si}(\text{OEt})_3$  in DMF for 24 hours at RT. After this time, the  $^{19}\text{F}$  NMR spectrum of the reaction mixture (Figure S1) showed signals corresponding to the  $\text{Cu}^{\text{I}}$  complex  $[\text{Cu}(\text{C}_6\text{F}_5)(\text{DMF})_n]$ ,<sup>35</sup> along with decafluorobiphenyl and  $\text{C}_6\text{F}_5\text{H}$  (originated by hydrolysis). The presence of decafluorobiphenyl suggests that two non-bulky  $\text{C}_6\text{F}_5$  groups are preferentially transferred to  $\text{Cu}^{\text{II}}$  (Scheme 3), which, by disproportionation,<sup>36</sup> leads to complex  $[\text{Cu}(\text{C}_6\text{F}_5)(\text{DMF})_n]$ , the nucleophile conveying  $\text{R}^1$  to the Pd cycle in Scheme 2. The possible alternative product of oxidation,  $\text{C}_6\text{F}_5\text{OEt}$ , is not observed, which is consistent with easier

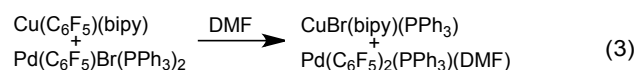
transmetalation of two fluoroaryl groups to copper and subsequent fast coupling.  $[\text{Cu}(\text{C}_6\text{F}_5)(\text{DMF})_n]$  is additionally formed in the reduction of  $[\text{Cu}(\text{C}_6\text{F}_5)_3]$  that produces the observed decafluorobiphenyl, an homocoupling product, so that in theory all  $\text{CuF}_2$  is stoichiometrically transformed into  $\text{Cu}^{\text{I}}$ , at the expense of consuming 50% of  $\text{R}^1\text{Si}(\text{OEt})_3$  to give  $\text{C}_{12}\text{F}_{10}$ , as in Scheme 3.



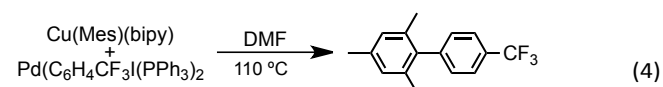
**Scheme 3.** Products formed in the reactions of  $\text{CuF}_2$  with  $(\text{C}_6\text{F}_5)\text{Si}(\text{OEt})_3$  as a model of regular size arylalkoxysilane (the reactions are stoichiometrically adjusted; the proportions used in the experiments can be different). *DMF acting as probable ligand for some species is omitted for simplification.*

Before we consider the singularities in the case of bulky arylsilanes it is interesting to comment on some other experiments (given in the supplementary information) that support some of the group exchanges proposed in the Cu/Si reactivity schemes:

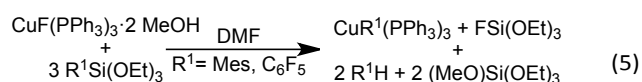
1) A reaction of  $\text{CuF}_2(\text{bipy}) \cdot 3\text{H}_2\text{O}$  in DMF,<sup>21</sup> with excess  $(\text{C}_6\text{F}_5)\text{Si}(\text{OEt})_3$  produces quantitatively  $\text{Cu}(\text{C}_6\text{F}_5)(\text{bipy})$  plus decafluorobiphenyl and some  $\text{C}_6\text{F}_5\text{H}$  (Figure S2). It was also confirmed that this  $\text{Cu}(\text{C}_6\text{F}_5)(\text{bipy})$  complex does work as efficient nucleophile (as proposed in Scheme 2, path **B**) in the model cross-coupling reaction shown in Equation 3.



2) Similarly,  $\text{Cu}(\text{Mes})(\text{bipy})$  can be generated in situ by treating  $\text{CuF}_2(\text{bipy}) \cdot 3\text{H}_2\text{O}$  with an excess of  $(\text{Mes})\text{Si}(\text{OEt})_3$ . When a preformed solution of this organometallic in DMF is transferred to a flask containing  $[\text{Pd}(\text{C}_6\text{H}_4\text{CF}_3)(\text{PPh}_3)_2]$  and heated to 110 °C for an hour, quantitative formation of  $\text{Mes-C}_6\text{H}_4\text{CF}_3$  is observed. This experiment confirms that a  $\text{Cu}^{\text{I}}$  organometallics transmetalate effectively the bulky aryl to the palladium catalyst.

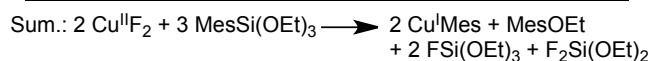
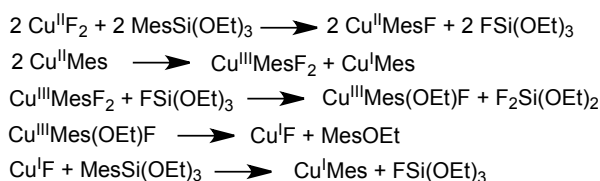


3) We could also verify that complexes of  $\text{Cu}^{\text{I}}\text{F}$  are easily arylated by arylalkoxysilanes, whether bulky or small, in DMF at room temperature, as for instance in equation 5.<sup>37</sup> The corresponding  $\text{Cu}^{\text{I}}(\text{PPh}_3)_3$  complexes generated in situ transmetalate effectively  $\text{C}_6\text{F}_5$  or Mes to the palladium catalysts  $[\text{Pd}(\text{C}_6\text{F}_5)\text{Br}(\text{PPh}_3)_2]$  and  $[\text{Pd}(\text{C}_6\text{H}_4\text{CF}_3)\text{I}(\text{PPh}_3)_2]$ , respectively (Figure S3).



Coming back to the analysis of Scheme 3, half of the  $R^1Si(OEt)_3$  reagent is consumed as the reducing agent, which means that in practice the amount  $R^1Si(OEt)_3$  acting as nucleophile is in only 1:1 ratio to the electrophile, not 2:1 as apparently suggest the reaction conditions. Since in the reaction conditions some  $R^1Si(OEt)_3$  is unavoidably hydrolysed, in practice the arylalkoxysilane can easily become the limiting reagent in the reaction, and this explains the appreciable amount of homocoupling products in entries 1,2 in Table 3. In fact, monitoring of the reaction by  $^{19}F$  NMR reveals that these side products start to be formed when  $R^1Si(OEt)_3$  is already scarce or has been totally consumed. Since this problem only happens when  $R^1$  has a conventional size (see below the analysis for the case of bulky aryls), the classic Hiyama reaction should be utilized for these aryls.

It is fortunate that the  $CuF_2$  promoted reaction has a great bonus with  $MesSi(OEt)_3$  and similar bulky aryl arylalkoxysilanes: These cannot work to reduce  $CuF_2$  via the mechanism in Scheme 3 for the simple reason that putative  $Cu^{II}$  or  $Cu^{III}$  intermediates with two Mes groups are severely hindered. In fact, GC-MS analysis of the reaction products of the reactions in entries 7-11 of Table 3 reveal in all cases the formation of a main byproduct MesOEt, which suggests that at some time of the reaction coupling must take place from an intermediate containing a  $CuMes(OEt)$  moiety.<sup>38</sup> As already mentioned, the elimination of aryl ethers from  $Cu^{III}$  is a well-known process (Chan-Lahm-Evans reaction),<sup>39</sup> and this alternative for  $Cu^{III}$  reduction is proposed in Scheme 4, which shows a plausible set of equations leading to the products observed.



**Scheme 4.** Products formed in the reactions of  $CuF_2$  with  $MesSi(OEt)_3$  as a model of bulky arylalkoxysilanes (the reactions are stoichiometrically adjusted; the proportions used in the experiments can be different). *DMF acting as probable ligand for some species is omitted for simplification.*

Obviously the exact nature of the fluorosilane participating in each occasion is not defined (it could even be changing along the reaction as the F/OEt proportion changes) but the need of a disproportionation of  $Cu^{II}$  and a reductive coupling from  $Cu^{III}$  are solidly supported by the observation of MesOEt and by the stoichiometry of the reactions, which fully transform each initial mol of  $Cu^{II}$  into one mol of  $CuMes$ .

Note that, at variance with Scheme 3, as the reduction of  $Cu^{III}$  produces Mes-OEt instead of Mes-Mes, only 25% of the initial  $MesSi(OEt)_3$  plays the role of reducing agent, keeping the electrophile:nucleophile stoichiometry for the reaction 1:1.5. This lower consumption of  $MesSi(OEt)_3$  maintains a higher concentration of it up to the end of the process, in spite of some

hydrolysis, and prevents the competition of homocoupling processes.

The formation of the second molecule of  $CuMes$  finds also a different origin in Scheme 4 than in Scheme 3, consisting of the direct arylation of a  $CuF$  intermediate. This is supported by a parallel experiment in which, reacting  $[CuF(PPh_3)_3] \cdot 2MeOH$  in place of  $CuF_2$  for the experiment defined in Table 3 entry 5, gives  $MesC_6H_4CF_3$  in 83% yield, not producing Mes-OEt. This suggests that  $Cu^IF$  is able to undergo direct  $Cu^I/Si$  transmetalation to give  $R^1Cu$ . It also reveals that the Mes-OEt formed as byproduct in equation 2 and Table 3 is produced on a different oxidation state of Cu, as discussed.

## Conclusions

In summary, a bimetallic synthetic procedure involving Si/Cu/Pd aryl transfers has been developed that makes the Hiyama reaction useful for the coupling of bulky arylalkoxysilanes. It uses stoichiometric  $CuF_2$  in an atom-economical way, as the only source of the two important reagents required for the two aryl transmetalation steps in the reaction, namely: i) fluoride, for the initial Si-to-Cu transmetalation step; and ii)  $Cu^I$ , for the transmetalation from  $Cu(aryl)$  to Pd. The quantitative reduction of  $Cu^{II}$  to  $Cu^I$  occurs by a disproportionation of  $Cu^{II}$  to  $Cu^I + Cu^{III}$  and subsequent reduction of  $Cu^{III}$  to  $Cu^I$ . Very interestingly, using Pd catalysts very simple to prepare from readily-available materials, the reaction affords excellent yields, and has a wide scope of application. The reaction is compatible with active functional groups such as aldehydes or pyridine that, for hindered substrates, often fail with other cross coupling alternatives. Moreover, it shows size selectivity and offers the possibility of tuning for selective size competing couplings.

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**Keywords:** keyword 1 • keyword 2 • keyword 3 • keyword 4 • keyword 5

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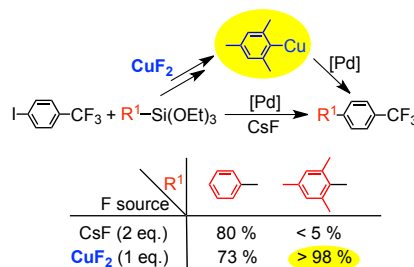
## Entry for the Table of Contents (Please choose one layout)

Layout 1:

## FULL PAPER

Text for Table of Contents

**Dual role of  $\text{CuF}_2$ :** In this Cu-promoted Hiyama process  $\text{CuF}_2$  plays the role of two reagents, providing the fluoride and the copper required to transform *in situ*, with full conversion, the bulky trialkoxysilane into a  $\text{CuAr}$  nucleophile that immediately transmetalates to Pd, which makes the otherwise inaccessible Pd-catalyzed coupling of bulky-aryl silanes feasible and highly efficient.



Juan delPozo, Juan A. Casares,\*  
Pablo Espinet\*

Page No. – Page No.

***In Situ* Generation of  $\text{ArCu}$  from  $\text{CuF}_2$  Makes Coupling of Bulky Aryl Silanes Feasible and Highly Efficient**