COMMUNICATION

Pd/Cu bimetallic catalysis to access highly fluorinated biaryls from aryl halides and fluorinated arenes

Jaime Ponce-de-León,[#] Guillermo Marcos-Ayuso,[#] Juan A. Casares* and Pablo Espinet*
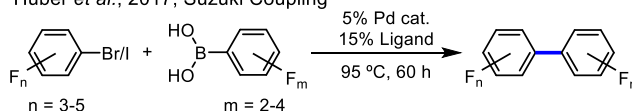
An efficient Pd/Cu bimetallic cross-coupling catalysis of fluoroaryl halides and fluoroarenes is reported. *In situ* generation of the Cu nucleophile by rate determining C–H activation of highly fluorinated aryls (≥ 4 F atoms) leads to high cross-coupling selectivity with little formation of homocoupling products.

Fluorinated biaryls are of wide interest in different areas, such as materials science,[1] pharmaceutical,[2] and ligand design.[3] There are several methods in the literature for the synthesis of biaryls with only one fluorinated aryl moiety,[4] but just in few cases both biaryls are highly fluorinated (Scheme 1). Because of the difficult reductive elimination of polyfluoroaryl of groups, undesired Ar/Ar' transmetalations can give rise also to undesired homocoupling products.
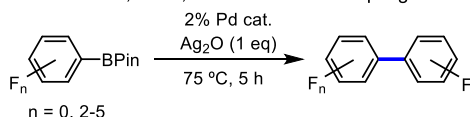
The Suzuki coupling (Huber *et al.*, 2017) requires high temperatures and long reaction times (60 h, 95 °C) and provides low yields, particularly when both aryls have two fluorine atoms in ortho position.[5,6] The Pd-catalyzed homocoupling of highly fluorinated arylboronates (Marder *et al.*, 2020) takes place under milder conditions (5 h, 75 °C), but stoichiometric Ag_2O is needed and its scope is limited to the synthesis of symmetrical biaryls.[7] Recently (our group, 2021), we have reported the efficient Negishi coupling between $Zn(C_6F_5)_2$ and fluorinated or non-fluorinated aryl iodides, in a method in which the use of the chelating ligand PhPEWO-F (1-(PPh_2),2-(CH=CH–C(O)Ph)–C_6F_4) helps to minimize undesired aryl homocouplings by inducing very fast reductive elimination from $[PdAr^1Ar^2]$.[8] All these processes require the previous synthesis and purification of the nucleophile ($Ar^F B(OR)_2$, $Ar^F BPin$, $ZnAr^F_2$).

IU CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47071-Valladolid (Spain).
E-mail: espinet@qi.uva.es; juanangel.casares@uva.es
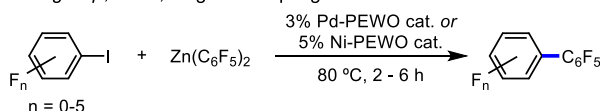[#] These authors have contributed equally to the paper.

Previous work

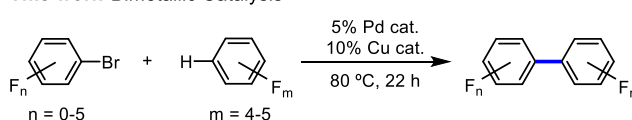Huber *et al.*, 2017, Suzuki Coupling

Marder *et al.*, 2020, Oxidative Homocoupling

Our group, 2021, Negishi Coupling

This work Bimetallic Catalysis

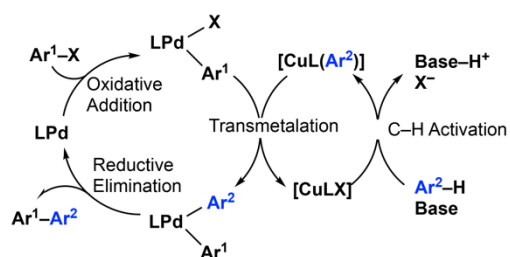Scheme 1. Literature syntheses of polyfluorinated biaryls.

Some copper complexes are able to activate C–H bonds in fluorinated aryls,[9] and allow *in situ* generation of the corresponding copper nucleophile in low concentration. Since the Cu/Pd transmetalation of fluorinated aryls is fast,[10] a bimetallic Pd/Cu catalytic system,[11] with fluorinated aryl halides as electrophiles and fluoroaryl copper complexes as nucleophiles (Scheme 2), might be made feasible. The low Cu concentration should help to minimize the problem of the undesired transmetalations and subsequent homocoupling.

As a matter of fact, Cazin group has shown the feasibility of this process for several aryl halides by using Pd and Cu complexes with NHC ligands on both metals, and they have proposed the mechanism shown in Scheme 2.[12] Their ligand selection prevented ligand exchange between the metals, which could complicate the evolution of the bimetallic system.[13]

Scheme 2. Bimetallic mechanism for cross coupling between arenes containing an acidic proton and aryl halides.

Initially we essayed a system similar to the one used by Lesieur *et al.*,[12] using [Pd(allyl)Cl(IPr)] and [Cu(IPr)Cl] as co-catalysts for the cross-coupling of 1-Br-2,6-$C_6H_3F_2$ (**1a**) as fluorinated aryl electrophile and C_6F_5H (**2n**) as precursor of the Cu nucleophile. However, no cross-coupling biaryl was formed and only C_6F_5–allyl was detected. This frustrating result suggests that the C–H activation and the Cu-to-Pd transmetalation steps are working but the ligand on Pd is not efficient to generate the palladium cycle. Therefore, we carried out a systematic study of the reaction looking for ligands or Pd precatalysts that could favor a productive cycle in palladium, and copper precatalysts and bases compatible with them. The reaction conditions were optimized for the catalysis between 1-Br-2,6-$C_6H_3F_2$ (**1a**) and C_6F_5H (**2n**). The precatalysts XPhos-Pd-G3 (5 %) and [Cu(IPr)Cl] (10 %) combined with Cs_2CO_3 as base, at 80 °C, gave the best yield (74 %) of the cross-coupling product **3an** (Scheme 3).[14] Along with the desired cross-coupling product **3an**, very small amounts of the hydrolysis product 1,3-difluorobenzene (**4a**) and the homocoupling biaryls of both aryls (**3aa** and **3nn**) were identified by ^{19}F NMR (see ESI for optimization checks with other ligands, solvents, bases, and concentration of reagents and catalysts, in Tables ESI1-ESI8).
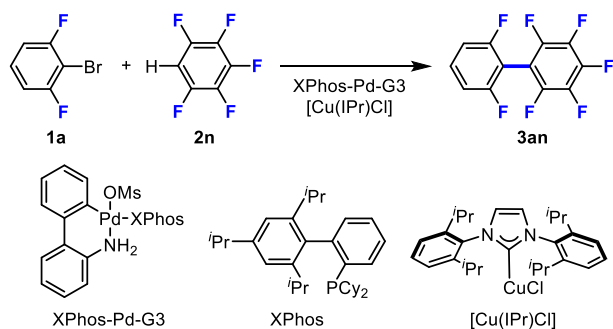
Scheme 3. Preliminary experiments for precatalysts choice.

The use of bulkier ligands at Pd (*t*BuXPhos-Pd-G3 or P*t*Bu₃-Pd-G3) afforded **3an** in only 27 or 10 % yield respectively, probably because the transmetalation becomes more difficult when the bulkiness of the ligands in Pd and in Cu increases. Aryl chlorides are only a bit less efficient than aryl bromides, whereas aryl iodides cannot be used because they can interfere with the Cu complexes.[15]

The scope of the reaction was explored first (Scheme 4) for different bromoaryls (**1a**-**1o**) versus C_6F_5H (**2n**). The protocol is very efficient for mono-, di- and trifluorinated aryl bromides, affording yields in the range 75–90 % (**3an**, **3mn**), and almost 70 % yield for the C_6F_5-C_6F_5 coupling (**3nn**,). The higher yields obtained for the less fluorinated aryl bromides are presumably due to a lower reductive elimination barrier compared to that for C_6F_5-C_6F_5. Alkyl or fluoroalkyl substituents at the bromoaryl ring, such as Me (**3kn**) and CF_3 (**3gn** and **3jn**), are compatible with this synthetic protocol. In contrast, the presence of a nitrile moiety blocks the reaction and no coupling product is observed (**3on**). This quenching is probably due to coordination of the nitrile to some metal intermediates.
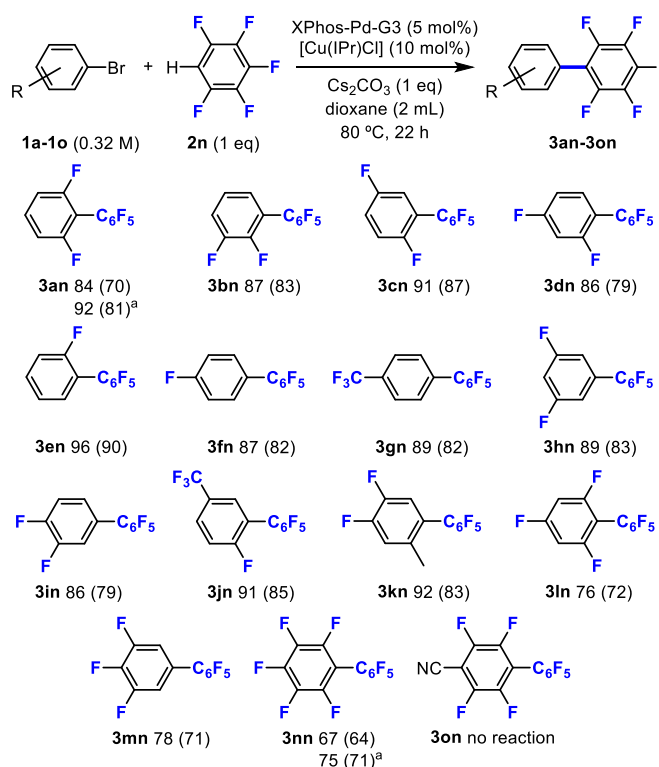

Scheme 4. Fluoroaryl bromide scope. Yield determined by ^{19}F NMR (Isolated yield in parenthesis). [a] 1.5 eq of C_6F_5H (**2n**). The X-ray structures of **3bn, 3fn** and **3gn** are given in the ESI.

The efficient formation of the $CuAr^F$ precursors in the presence of base requires the acidity provided by highly fluorinated the fluoroarene Ar^FH. The catalytic reactions were studied for two electrophiles 2,6-$C_6H_3F_2Br$ (**1a**) and 3,4,5-$C_6H_2F_3Br$ (**1m**), in order to increase the number of combinations tested with the commercially accessible 2,3,5,6-tetrafluoroarenes (Scheme 5). Thus, the 2,3,5,6-C_6HF_4-R systems (**2p**, R = OMe) undergoes efficient C–H activation to yield cross-coupling products with either **1a** or **1m** to give **3ap** or **3mp**, respectively. The heteroarene 2,3,5,6-tetrafluoropyridine (**2q**) also undergoes efficient C–H activation and yields the coupling products **3aq** or **3mq**. In contrast, 2,3,5,6-tetrafluoroaniline (**2r**) did not afford the coupling products **3ar** or **3mr**. These three examples show that the C–H activation process is quite sensitive to the

coordinative influence of the substituents: OMe leads clearly to lower yields due to weak O-coordination ability and perhaps some electronic deactivation; NH_2 quenches the reaction due to stronger N-coordination ability (as argued above for the nitrile group); finally, 2,3,5,6-tetrafluoropyridine gives the highest yields of these three because the coordinating ability of this pyridine is close to nil.
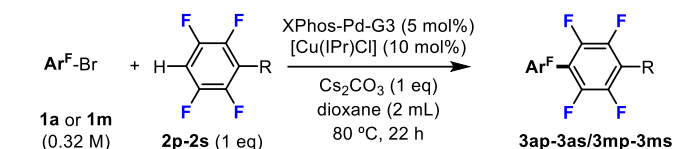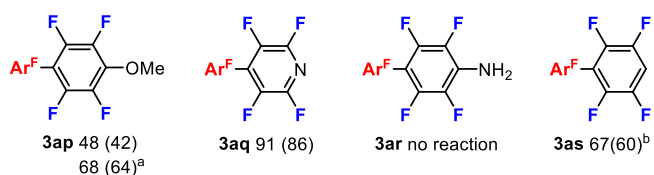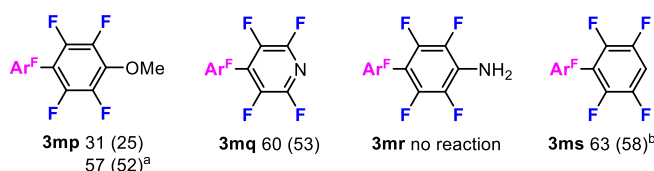
Scheme 5. Fluoroarenes scope. Yield determined by ^{19}F NMR (Isolated yield in parenthesis). [a] 1.5 eq of **2p** were used. [b] 3.0 eq of **2s** were used.

For 1,2,4,5-tetrafluorobenzene (**2s**), with two C–H bonds, there was competition of mono- and diarylated products. An excess of the arene **2s** (3 eq) was necessary to diminish the formation of the diarylated product, and monoarylated product (**3as** or **3ms**) was obtained in only 67 % molar yield. Yet, full conversion of the aryl bromide was observed and the diarylated product was still formed in 33 % yield. Thus, in the absence of coordinating groups the cross-coupling process is very efficient. In order to understand the relevance of the different catalytic steps of the system, some stoichiometric experiments were carried out. The C–H activation of C_6F_5H by [Cu(IPr)Cl] and Cs_2CO_3 yields [Cu(IPr)(C_6F_5)] (**7**) in almost quantitative yield in two hours (eq. 1). The 1:1 addition of XPhos to *cis*-[Pd(C_6F_5)$_2$(THF)$_2$] (**8**) at room temperature in 1,4-dioxane affords [Pd(C_6F_5)$_2$(XPhos)] (**9**) (eq. 2) as a moderately stable compound, in contrast to its ^{t}BuXPhos analogue.[14] The X-ray structure of **9** can be found in the ESI.
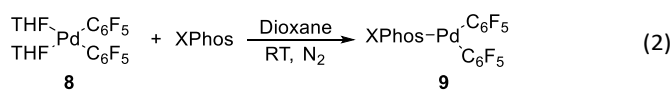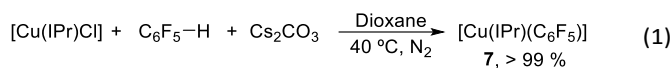

When a solution of **9** in dioxane was heated at 80 °C in the presence of C_6F_5–Br, reductive elimination of C_6F_5–C_6F_5

followed by instantaneous oxidative addition to the *in situ* generated [Pd^0(XPhos)] complex (the Pd^0 complex was never observed) was complete in 180 min, generating [PdBr(C_6F_5)(XPhos)] (**10**) (eq. 3).[16] At room temperature, **10** shows an equilibrium in solution between monomers and halogen bridged dimers [Pd(μ-Br)(C_6F_5)(XPhos)]$_2$, giving rise to broadening of its ^{19}F and ^{31}P NMR signals (See ESI for details).
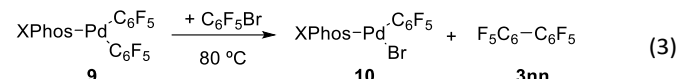

Interestingly, a close inspection of the ^{19}F NMR monitoring of the catalytic experiments, using C_6F_5–Br (**1n**) and C_6F_5H (**2n**) as reagents, led to the identification of the NMR signals of [Cu(IPr)(C_6F_5)] (**7**) and [Pd(C_6F_5)$_2$(XPhos)] (**9**) in the reaction mixture. This suggests that, for **1n** and **2n** as reagents, the reductive elimination is the slowest transformation in the catalytic cycle. The transmetalation/reductive elimination sequence was also evaluated for C_6F_5–C_6F_5 (**3nn**) and *p*-C_6H_4F–C_6F_5 (**3fn**) couplings, by following the reactivity of [Cu(IPr)(C_6F_5)] (**7**) with either [PdBr(C_6F_5)(Xphos)](**10**) or [PdBr(*p*-C_6H_4F)(Xphos)] (**11**) in dioxane at room temperature (Scheme 6). The reaction of **10** with **7** at room temperature did not produce the biaryl product (**3nn**), but full conversion to Pd biaryl complex **9** in four hours. Obviously, the reductive elimination is much slower than the transmetalation for these highly fluorinated reagents. In contrast, when **7** and **11** were mixed at room temperature the reaction took place in two hours, and only the coupling product (**3fn**) was detected along the reaction, showing that in this case, with one little fluorinated aryl, the reductive elimination is faster than the transmetalation.
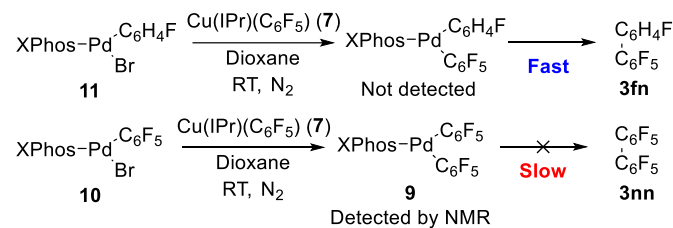
Scheme 6. Transmetalation studies.

This analysis of the transmetalation/reductive elimination in stoichiometric conditions and at room temperature does not have direct translation to the catalytic conditions at 80 °C because the catalytic concentrations of the Pd and Cu species are not defined and because in both cases the cross-coupling product is formed. We know from the stoichiometric results that the transmetalations are fast for both reactions at room temperature, so they must be very fast at 80 °C. Moreover, for Pd, the transformation of [Pd^0(XPhos)] to [PdBr(aryl)(XPhos)] can be considered complete and instantaneous. For Cu, however, the [Cu(IPr)(C_6F_5)] concentration depends of a deprotonation equilibrium of aryl–H, which is influencing the Cu availability at the transmetalation and, consequently, the rate of this step. Information about the influence of the arene

deprotonation step in the transmetalation/reductive elimination process could be obtained from KIE experiments with C_6F_5–H/D. To this end, we conducted KIE experiments (see ESI for details) on the reactions between **7** and **10**, or **7** and **11** in standard catalytic conditions (Scheme 7).
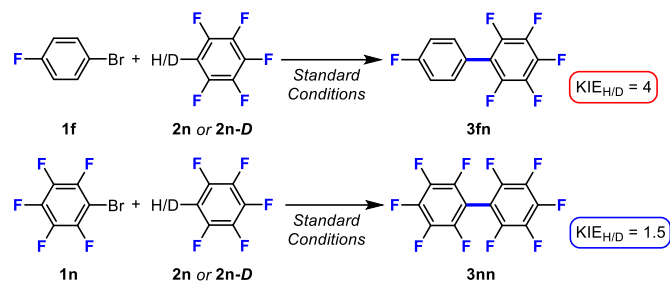
Scheme 7. KIE experiments.

With *p*-bromofluorobencene (**1f**) a KIE value of ≈ 4 was obtained. This value indicates that the C–H activation has a large contribution to the overall reaction rate. In contrast, with bromopentafluorobencene (**1n**) the KIE value is ≈ 1.5, which, along with the detection by NMR of the intermediate Pd biaryl complex **9** in this experiment, supports that reductive elimination is the slowest step in this case. Although the latter result is an extreme case of difficult cross-coupling and the KIE result could be spared, the compared KIE results show that the kinetic rate of the transmetalation/reductive elimination sequential process can be complex, and KIE experiments are useful for the determination of its Cu dependence in specific cases. Also, these results are consistent with the mechanism outlined in Figure 1 in which the oxidative addition is a fast step while the relative rates between reductive elimination and C–H activation can render one or the other step as rate limiting.

In conclusion, we have developed an efficient system to access highly fluorinated biaryls in good to excellent yields employing commercially available reagents, avoiding a previous step of nucleophile preparation. The choice of ligands for the Pd and Cu is crucial for a good outcome of the reaction. The experiments described above show that in the catalytic process there is a complex balance between the steps of C–H activation, transmetalation and reductive elimination. Using XPhos-Pd-G3 and [Cu(IPr)Cl] as precatalysts any of these steps can limit the overall reaction rate. In any case, the high efficiency of this catalytic system to avoid homocoupling side-reactions that usually appear as a consequence of unwanted transmetalations is remarkably useful and gives access to different precursors.

Conflicts of interest

There are no conflicts of interest to declare.

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16 [Pd(C_6F_5)(Br)(XPhos)] (**10**) was independently synthesized by an alternative method. See ESI for details.