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Palladium (II) Precursors for Clean In Situ Formation of Ad Hoc Cross-Coupling Catalysts. Their Application in One-Pot/Two-Step Catalyses with 2-Biaryl-Dialkylphosphine Ligands

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Abstract: Complexes *cis*-[Pd(Ar^F)$_2$(NCMe)$_2$] (**A**) and *cis*-[Pd(Ar^F)$_2$(THF)$_2$] (**B**) ($Ar^F = C_6F_3H_2$) are fast general precursors easy to prepare, store and handle, which allow *in situ* synthesis of tailor-made [Pd(Ar)(X)(L)] catalysts for chosen **Ar-Nu** couplings, provided that the L ligand (in this case PR_2(2-biaryl)) induces (Ar^F)$_2$ coupling. This fluorinated byproduct is inert in the reaction conditions, and no other byproduct is expected because the Ar and X groups are the same in the catalyst, the intermediates and the products. The application of **A** or **B** in catalysis (*e.g.* with 1% catalyst) consists of a first step (formation of 1% tailor-made catalyst) where 100 ArX + 1 **A** (or **B**) + 1 L in THF gives a solution with 99 ArX + 1 [Pd(Ar)(X)(L)] + (Ar^F)$_2$. The only other byproduct is THF or NCMe. In the second step, addition of the nucleophile, 100 Q(Nu), triggers and completes the catalytic cycle yielding 100 **Ar-Nu** + 100 Q(X) + 1 [Pd^0(L)]. The 100% yield is theoretical, but the tested catalysis (Ar-Me Negishi coupling, C_6F_5-alkynyl Stille coupling and Ar-naphthyl Suzuki coupling) using **A** as precursor, SPhos as ligand, and 1000:1 reagents:catalyst ratio, afford 95–99% yield. In contrast, aryl-amination requires 1000:5 ratio to give 96% yield (or 1000:50 for 99% yield) because $PhNH_2$ eventually displaces the SPhos from Pd and blocks the catalyst. As a bonus, the presence of F in the precursors facilitates stepwise ^{19}F NMR monitoring of the formation of [Pd(Ar)(X)(L)] with different phosphines, facilitating analysis of weaknesses or strengths of each of them to produce the catalyst, and helps in the choice of the most convenient one for the case. The *in situ* catalyst formation is ideal for serial two-step catalysis with different phosphines or different nucleophiles.

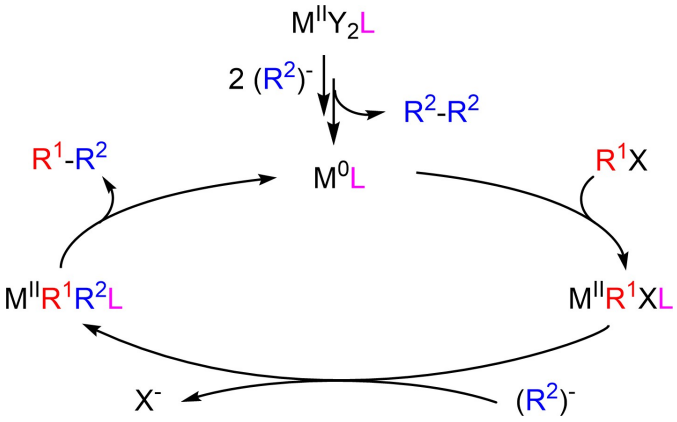
Keywords: Palladium; 2-biarylphosphines; tailor-made catalysts; *in-situ* catalysts; C–C cross-coupling; C–N cross-coupling

Introduction

The success of a metal-catalyzed process depends on the use of ligands able to carry out efficiently the different catalytic steps. We will deal here with Pd-catalyzed cross-couplings, where the M^0/M^{II} mechanism in Scheme 1 is absolutely dominant for Pd, and also operates in many cases for Ni. It is very frequent that the catalyst (any molecule in the cycle) is not available in the lab store or commercially and it has to be prepared *in situ* from some precursor.[1]

The choice of the ligand is critical for the catalytic success, but it is also important to avoid the production of non-inert byproducts formed or set free from the reagents in the conversion of the precursor to the catalyst, because these byproducts can alter or block the evolution of the catalysis in synthetic processes, or give rise to misleading information in mechanistic studies.

Often we find the use as precursors of dihalo-complexes, for instance **[$PdCl_2$(NCMe)$_2$]**, where the weak coordinating acetonitrile can be easily replaced



Scheme 1. Sketch of an M-catalyzed cross-coupling reaction using an out-of-cycle MY_2L precursor. L can be one chelate or two monodentate ligands.

by a ligand of choice. Entering the cycle from this pre-catalyst as [Pd^0(L)] will be at the cost of two molecules of $(R^2)^-$ nucleophile and will liberate not only two NCMe molecules, but also two Y^- halides that could eventually exchange with X^- of the electrophile if $Y \neq X$. Most probably both species will, at least, have a negative kinetic influence on the transmetalation rates (Scheme 1).

Accessible complexes of the type **[M(R^1)(X)L_n]** (*e.g.* [$Pd(C_6F_5)$(Cl)(weak ligand)$_2$]) can be an excellent choice if R^1 coincides with the group in the RX electrophilic reagent. In that case, a fast and simple ligand substitution will produce the *in cycle* species, setting free a weak ligand. Otherwise, these precursors will have to waste one molecule of nucleophile and produce one unwanted R^1-R^2 coupling molecule before the first productive turnover starts. Of this kind we can consider also other off-cycle precursors that need the addition of active reagents (*e.g.* a base) in order to trigger the reduction of Pd(II) to Pd(0), generating in solution some unwanted active species, such as indazole or carbazole, formed by addition of base to the precursor.[2] For instance, the commercial complexes L-Pd-G2, L-Pd-G3 and L-Pd-G4 pertain to this type.[3] Another disadvantage is that these commercial Pd^{II} pre-catalysts can be considerably more costly than the corresponding L ligands.

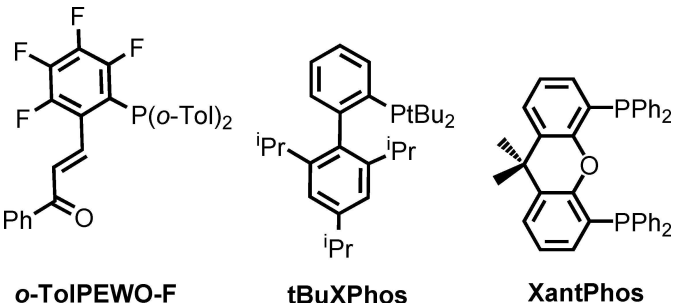
Precursors type [Pd^0(ligand)$_n$] can produce *in situ* the desired [Pd^0(L)] complex (from now on L will represent the ligand wanted for catalysis), but stable Pd(0) precursors such as $Pd(dba)_2$, $Pd_2(dba)_3$, Pd-(PPh_3)$_4$, or ^{DMP}DAB-Pd-MAH, frequently used, release in solution the fairly strong ligands dba or PPh_3 or, in the latter case, N,N′-diaryldiazabutadiene and maleic anhydride,[4] all able to interfere at the different steps of the catalysis.[5,6,7] Other approaches and precursors to enter the cycle as Pd(0) have been reviewed recently.[8,9]

Some weak ligands can stabilize Pd(II) organometallic complexes and our brief analysis so far suggests that an ideal precursor might be a stable **[$Pd(R)_2$(weak-ligand)]** complex. This precursor should satisfy some conditions: 1) be storable; 2) undergo easy and fast weak-ligand substitution by ligand L; 3) produce reduction to [Pd^0(L)] at mild temperature (*e.g.* ambient) or at higher temperatures compatible with the catalysis; 4) R-R should be inert, not interfering with the reagents or intermediates in the cycle. As early example of this class, in 1999 Pan and Young reported thermally unstable [PdR_2(COD)] complexes (R = CH_2SiMe_3, CH_2SiMe_2Ph).[10] Although quite unstable at room temperature, they were used by the group of Buchwald in 2013 as precursors of [Pd^0(L)].[11]

During our works on complexes with fluorinated aryls we had noted several times that PEWO ligands (see Figure 1)[12] were able to displace THF from [$Pd(C_6F_5)_2(THF)_2$] (**4a**) and induce the difficult C_6F_5-C_6F_5 coupling at room temperature. In 2016 we undertook quantitative experiments that included other ligands, 2-biaryldialkylphosphines among them,[13] observing different rates of C_6F_5-C_6F_5 formation as indicative of simultaneous formation of the unobservable [Pd^0(L)]. These rates should allow us to rank the ability of added ligands to promote a difficult coupling such as C_6F_5-C_6F_5.

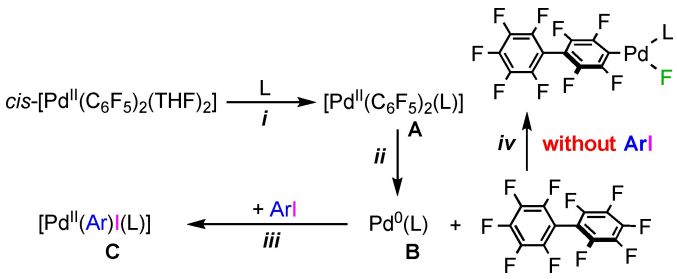
In one case, specifically the reaction using (L) = tBuXPhos, the fugacious [Pd^0(L)] intermediate was spontaneously oxidized by the decafluorobiphenyl (evolution ***iv*** in Scheme 2), so disturbing our method of rate measurement by ^{19}F NMR monitoring the decafluorobiphenyl formed. Addition to the solution of ArI = *p*-IC_6H_4F, a much faster oxidant than decafluorobiphenyl, solved this problem and led to formation, as the final products, of decafluorobiphenyl and the in-cycle molecule [$Pd^{II}(C_6H_4F)$(I)(L)] (**C** in Scheme 2), a typical cross-coupling catalyst. As a matter of fact, *cis*-[$Pd(C_6F_5)_2(THF)_2$] (**4a**) fulfills all the conditions mentioned above for an ideal catalyst precursor.

The addition of ArI was incorporated as preventive routine to all the experiments, which followed, with



***o*-TolPEWO-F** **tBuXPhos** **XantPhos**

Figure 1. Three phosphines that accelerate cross-couplings.



Scheme 2. Reactivity and reaction pathways of *cis*-[Pd-$(C_6F_5)_2(THF)_2$] (**4 a**) upon addition of L ligands and ArI (ArI = *p*-IC_6H_4F).

this incorporation, the three steps pathway from **4 a** to **C** shown in Scheme 2. This led eventually to two practical applications. First of all, this protocol allows to carry out the weak-ligand substitution at low temperatures, for determination of the initial rates of weak-ligand substitution to form **A** (step ***i*** in Scheme 2) and then bring it quickly to a higher temperature (e. g. room temperature) to produce the C_6F_5-C_6F_5 coupling and measure the rate of step ***ii*** for different L ligands. Compared to ***ii***, step ***iii*** is instantaneous. Consequently [Pd^0(L)] (**B**) is not observable. However, monitoring the rate of C_6F_5-C_6F_5 formation (virtually identical to that of **C**) we can experimentally obtain the coupling activation energy of step ***ii***, ($\Delta G^{\ddagger}(C_6F_5\text{-}C_6F_5)_{Pd}$), and rank the coupling efficiency of different L ligands using the challenging C_6F_5-C_6F_5 coupling as model.[14] We found that under similar reaction conditions: **1)** many ligands such as PPh_3 or dppe (1,2-bisdiphenylphosphinoetane) do not progress beyond the fast THF substitution step and yield complexes **A**; **2)** other ligands follow regular first order reactions of formation of C_6F_5-C_6F_5. Very fast couplings were found for tBuXPhos, P^tBu_3, or *o*-TolPEWO-F, whereas XantPhos was slower but regular, hence functional (Figure 1); **3)** tBuBrettPhos behaved irregularly, in this case because of competition between two coordination modes of this 2-biaryldialkylphosphine.[13,15]

The second utility is that, in the presence of efficient coupling-promoter L ligands and *p*-FC_6H_4I, a successful sequence ***i***→***ii***→***iii*** yields solutions containing only the corresponding [$Pd^{II}(C_6H_4F)(I)(L)$], THF, and decafluorobiphenyl, which is basically unreactive in the presence of ArI.[13] In other words, *cis*-[Pd-$(C_6F_5)_2(THF)_2$] is an excellent precursor for clean *in situ* synthesis of [$Pd^{II}(C_6H_4F)(I)(L)$] (L = tBuXPhos, P^tBu_3 and *o*-TolPEWO-F), three potential catalysts with different ligands (these ligands give the fastest conversions of *cis*-[$Pd(C_6F_5)_2(THF)_2$]).

At that time, this interesting practical aspect was not further developed in our group to the *in situ* synthesis of other similar [Pd^{II}(Ar)(X)(L)] molecules because we were very involved in studying the high catalytic activity of 2-chalcone phosphines (PEWO ligands, Figure 1) in Pd cross-coupling catalysis. It is worth noting in this context that the structure and catalytic activity of PEWO ligands reminds that of 2-biaryldialkylphosphines. A mechanistic report on PEWO ligands in Pd catalysis is now published.[16] When we extended our ligand-ranking protocol to Ni complexes we found that, on Ni centers, the 2-chalcone PEWO ligands display an astonishing coupling activity at low temperature, compared to the unexpectedly poor performance of 2-biaryl phosphines.[17]

Recently, in 2021, Buchwald's group reported the use of three Pd(II) organometallic complexes as precursors, namely [$Pd(CH_2TMS)_2(COD)$] (**P1**),[10] [$Pd(2,4,6\text{-}C_6F_3H_2)_2(COD)$] (**P2**),[18] and the neophyl complex [$Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)(COD)$] (**P3**),[19] to synthesize and isolate [Pd^{II}(Ar)(X)(L)] catalysts with L = 2-biarylphospines.[20] The **P1** and **P2** precursors had good reactivity, but the authors discarded **P1** because of low thermal stability and **P2** because of limited substrate scope (meaning less efficient results) found for several L ligands. Consequently they focused on precursor **P3** for the synthesis and isolation of [Pd^{II}(Ar)(X)(L)] catalysts. They studied ten 2-biaryl-phosphines, several ArX oxidants (usually ArBr, but also ArI and ArOTf in a couple of cases) and different solvents at 60 °C. The [Pd(Ar)(X)(L)] yields ranged from 99% to 54%, depending on the reagents and conditions used.

Based on our studies with *cis*-[$Pd(C_6F_5)_2(THF)_2$] (**4 a**),[13] and on the recent Buchwald results with the neophyl complex [$Pd(CH_2CMe_2\text{-}o\text{-}C_6H_4)(COD)$] (**P3**),[20] our purpose here is to examine and understand the influence of the 2-biarylphoshine, the Ar^F or the neophyl group, and the ancillary weak ligands in the precursors (THF, NCMe, or COD) on the rates of the different steps of catalyst formation (Scheme 2) in order to improve their efficiency. We aim to find a good precursor that has easy lab synthesis in large amount, is largely stable in the fridge or at room temperature, and can be comfortably handled. It should be highly efficacious to prepare tailor-made [Pd-(Ar)(X)(2-biaryldialkylphosphine)] solutions for *one-pot* two-*step* catalysis, saving the need of catalyst isolation. Obviously, the catalyst can also, if wanted, be isolated as solid from these solutions, but this is not our main target. The catalytic protocols reported here can be applied to other ligands able to promote [Pd^0(L)] formation.

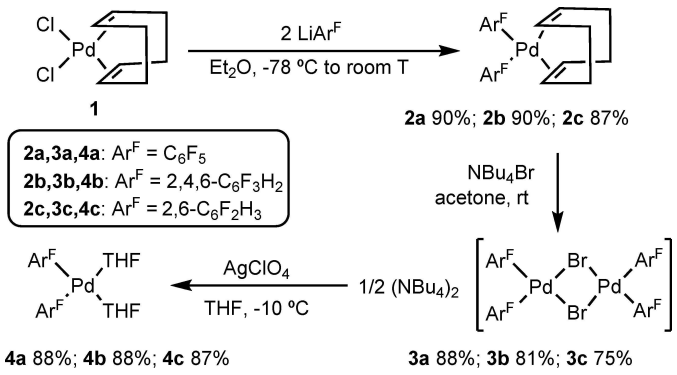
An advantage of *cis*-[$Pd(C_6F_5)_2(THF)_2$] and similar complexes with other fluorinated aryls Ar^F is that they allow for easy monitoring of the reactions by ^{19}F NMR, regardless of the possible high ^1H NMR complexity of the products.

Results and Discussion

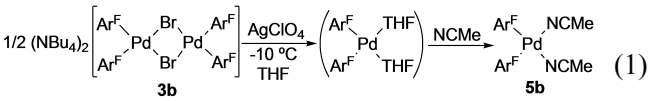
A) Synthesis of complexes [Pd(Ar^F)$_2$(COD)]: (Ar^F = C_6F_5 (2 a); 2,4,6-$C_6F_3H_2$ (2 b); 2,6-$C_6F_2H_3$ (2 c)); *cis*-[Pd(Ar^F)$_2$(THF)$_2$]: (Ar^F = C_6F_5 (4 a); 2,4,6-$C_6F_3H_2$ (4 b); 2,6-$C_6F_2H_3$ (4 c)); and *cis*-[Pd(2,4,6-$C_6F_3H_2$)$_2$(NCMe)$_2$] (5 b). The synthesis of these complexes was carried out using methodology previously developed in our group (Scheme 3).[21,22] Fluorinated aryl (Ar^F) complexes with progressively less fluorinated aryls were chosen, until they turned inconveniently unstable. Their syntheses start with arylation of [PdCl$_2$(COD)] (**1**) to colorless [Pd(Ar^F)$_2$(COD)] (**2 a–c**). Displacement of COD by bromide, adding (NBu$_4$)Br, gives pale yellow (NBu$_4$)$_2$[Pd$_2$(μ-Br)$_2$(Ar^F)$_4$] (**3 a–c**). Then, a soluble silver salt forces precipitation of AgBr in THF,[23] allowing for isolation of colorless *cis*-[Pd(Ar^F)$_2$(THF)$_2$] (**4 a–c**). It is well known that the presence of two F$_{ortho}$ atoms in the Ar^F groups enhances the thermal stability of the complexes. In fact, attempts at obtaining [Pd(Ar^F)$_2$(COD)] complexes with 2,4-$C_6F_2H_3$ or 3,4,5-$C_6F_3H_2$ produced quickly black Pd^0 and the corresponding biaryl. This impeded to prepare their corresponding THF complexes.

In the solid, the COD complexes **2 a–c** are indefinitely stable in the fridge and the ionic dimers **3 a–c** are indefinitely stable at room temperature. Finally, complexes **4 a–c**, prepared from **3 a–c** working in THF at −10 °C, are also easy to crystallize. After isolation, **4 a–c** are stored in the fridge at −30 °C. No sign of decomposition is observed by ^{19}F NMR after 4 months. At room temperature compound **4 a** is stable for weeks, and **4 b** is stable for days, meaning that both can be safely handled in air at room temperature. Compound **4 c** is less stable and should better be handled cool.

The dimers **3 a–c** are general precursors of *cis*-[Pd(Ar^F)$_2$(L′)$_n$] complexes with many other strong or weak ligands, and this is the method to prepare **5 b** using NCMe to displace THF (Eq. 1).



Scheme 3. Synthetic pathway of **2 a–c**, **3 a–c** and **4 a–c** complexes.



(1)

THF is significantly weaker ligand for Pd(II) than NCMe. It could be expected that the weak-ligand substitution step on **5 b** should be much slower than on **4 b**. However, in THF solution at room temperature or higher, **5 b** is in fast equilibrium (observable at −40 °C) with **4 b** and *cis*-Pd[(C$_6$F$_3$H$_2$)$_2$(NCMe)(THF)] (Figure 2). Consequently, in this or similar solvents (*e.g.* dioxane), the ligand substitution occurs, mostly or completely, on the fastest species in equilibrium, **4 b**. For this reason, the overall ligand substitution of **5 b** is only a bit slower than for **4 b**.

B) Experimental measurement of the Gibbs free energy of Ar^F-Ar^F coupling from *cis*-[Pd(Ar^F)$_2$(THF)$_2$] complexes 4 a–c and 5 b. A quantitative estimation of the relative thermal stability of these complexes, each measured at a convenient temperature is given in Table 1. These experimental values were transformed to ΔG$^{\neq}$ at 0 °C for direct comparison (column 4). They reflect a higher drop in stability from **4 a** to **4 b** than from **4 b** to **4 c**, and a very pronounced stabilization for NCMe as ancillary ligand (**5 b**) instead of THF (**4 b**). Thus **5 b**, which offers by far the highest stability as solid for storage and handling, yet reacts as fast as **4 b**, being probably the most convenient catalyst.

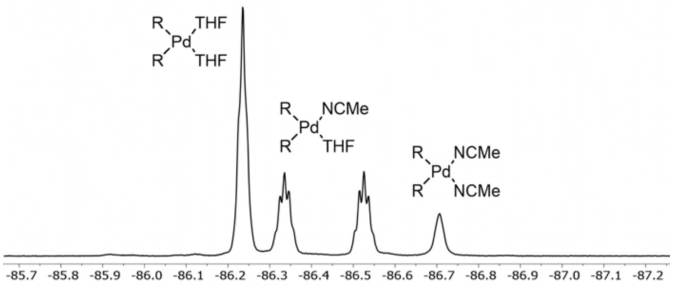


Figure 2. ^{19}F NMR spectrum (F$_{ortho}$ zone) of a 2.5×10^{-2} M solution of **5 b** in THF, at −40 °C.

Table 1. Experimental ΔG$^{\neq}$(Ar-Ar)$_{Pd}$ (kcal mol^{-1}) for reductive elimination of complexes **4 a–c** in toluene.[24]

Complex	Aryl	ΔG$^{\neq}$ at T °C	ΔG$^{\neq}$ at 0 °C
4 a[a,b]	C_6F_5	23.1 at 25 °C	22.8
4 b[b]	2,4,6-$C_6F_3H_2$	21.3 at 0 °C	21.3
4 c[b]	2,6-$C_6F_2H_3$	20.7 at 0 °C	20.7
5 b[c]	2,4,6-$C_6F_3H_2$	24.6 at 25 °C	24.4

[a] From Ref. [13];
[b] ancillary ligand = THF;
[c] ancillary ligand = NCMe.

C) Effects of the precursor (P3, 2b, 4b or 5b) and the entering 2-biaryl phosphine on the ligand substitution, the reduction, and the oxidative addition steps. For the studies that follow, Ar^F = 2,4,6-$C_6F_3H_2$ was chosen because of the simple ^{19}F NMR spectral pattern of their complexes. The same 2-biaryldialkylphosphines plus the less bulky SPhos, electrophile (*p*-$BrC_6H_4(CF_3)$), and reaction conditions of Ref. [20] are used here (Figure 3) in order to compare the results of our precursors **2b**, **4b** and **5b** with those reported for **P3**. This way we can compare neophyl *vs.* 2,4,6-$C_6F_3H_2$, and 1,5-COD *vs.* 2 THF or 2 NCMe effects.

The results in Table 2 and Table 3 collect the percentages of conversion of the different precursors to compound **A** (the ligand-substituted Pd(II) intermediate) and to compound **C** (the [Pd{$C_6H_4(CF_3)$-*p*}(Br)(L)] catalyst produced in 1 h at 25 °C or at 60 °C, respectively. This allows us to compare the progress of the steps ***i*** → ***ii*** → ***iii*** in Scheme 2, depending on the Pd precursor and the tested phosphine. The results are quite informative.

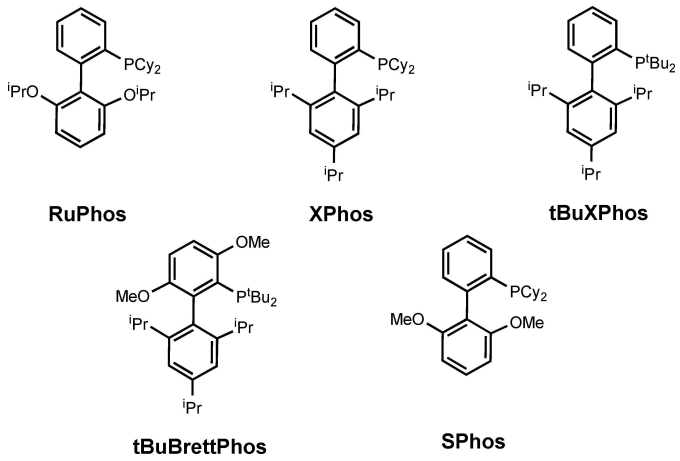


Figure 3. 2-biarylphosphines used in this work.

Table 2. Data for conversion, ligand substitution (**A**) and reduction + oxidative addition by *p*-$BrC_6H_4(CF_3)$ (**C**) steps on precursors **P3**, **2b**, **4b** and **5b**. At 25 °C, 60 min, in THF.

Entry	Precursor	entering L	conv.[a] %	A	C
1[b]	**P3**	RuPhos	99	99	0
2[b]	**P3**	XPhos	70	70	0
3[b]	**P3**	tBuXPhos	10	0	10
4[b]	**P3**	tBuBrettPhos	0	0	0
5	**2b**	RuPhos	74	70	4
6	**2b**	XPhos	32	26	6
7	**2b**	tBuXPhos	8	0	8
8	**2b**	tBuBrettPhos	0	0	0
9	**4b**	RuPhos	100	91	9
10	**4b**	XPhos	100	67	33
11	**4b**	tBuXPhos	100	8	92
12	**4b**	tBuBrettPhos	8	4	4
13	**4b**	SPhos	100	90	10
14	**5b**	tBuXPhos	91	0	91

[a] The difference to 100 is precursor.
[b] **P3** data taken from Table 1 of Ref. [20].

Table 3. Data for conversion, ligand substitution (**A**) and reduction + oxidative addition by *p*-$BrC_6H_4(CF_3)$ (**C**) steps on precursors **P3**, **2b**, **4b** and **5b**. At 60 °C, 60 min, in THF.

Ent.	Prec.	entering L	Conv. %[a]	A	C
15[b]	**P3**	RuPhos	100	41	59
16[b]	**P3**	XPhos	99	0	99
17[b]	**P3**	tBuXPhos	82	0	82
18[b]	**P3**	tBuBrettPhos	24	0	24
19	**2b**	RuPhos	100	6	94
20	**2b**	XPhos	91	0	91
21	**2b**	tBuXPhos	46	0	46
22	**2b**	tBuBrettPhos	6	0	6
23	**4b**	RuPhos	100	2	98
24	**4b**	XPhos	99	0	99
25	**4b**	tBuXPhos	100	2	98
26	**4b**	tBuBrettPhos	44	9	35
27	**4b**	SPhos	100	3	97
28	**5b**	tBuXPhos	100	0	100

[a] The difference to 100 is precursor.
[b] **P3** data taken from Table 1 of Ref. [20].

The conversion to **A** or **C** implies only ligand substitution and measures the rate of step ***i*** in Scheme 2. Comparing the results for identical phosphines it is clear that the rates depend on the precursor in the order **4b** > **P3** > **2b**. For **P3** and **2b** at this temperature we are likely in conditions for S_N^2 associative ligand substitution were the accessibility to the LUMO of Pd, lying perpendicular to the square coordination plane, is better in **P3** (with a less sterically demanding palladacycle) than in **2b** (with two aryls roughly orthogonal to the coordination plane hindering the trajectory of the entering ligand). In addition, the chelating effect in COD works against fast ligand substitution, and the trans influence, expectedly higher for the more σ-donor neophyl palladacycle than for the $C_6F_3H_2$ groups cooperates for a weaker COD coordination and easier COD substitution in **P3** than in **2b**. On the other hand, **P3** and **2b** are more hindered by COD than **4b** by THF or **5b** by NCMe, and THF or NCMe are easy to dissociate than COD. This combination of factors roughly explains the overall results observed that the ligand substitution is clearly faster for precursors **4b** and **5b**. As for the influence of the 2-biarylphosphines, the rate is faster for those having the P-donor site less hindered (PCy_2 faster than P^tBu_2). tBuBrettPhos seems to suffer a problem of overcrowding in the proximity of the P donor atom.

The formation of **C** from **A** (***ii***+***iii*** steps in Scheme 2) depends in practice on the reductive elimination step ***ii***, since step ***iii*** is, comparatively, instantaneous ([Pd^0(L)] is never observed). Looking for instance at entries 1 (**P3**), 5 (**2b**) and 9 (**4b**), all with RuPhos as L and having all formed high percentages of **A**, it is clear that the reduction from [Pd(neophyl)(L)] is slower than from **2b** or **4b**. The same conclusion is drawn from other entries. On the other hand, working with **4b** or **5b**, the high ratio of conversion to **C** in entries 11 and 14 supports tBuXPhos as the ligand better combining fast ligand substitution and fast reductive elimination at 25 °C. The smaller RuPhos and SPhos (entries 9 and 13) give fast ligand substitution but the reductive elimination is slow. Possibly the positive mesomeric effect of their alkoxy groups in *ortho* to the *ipso* carbon of the distal aryl strengthens the C_{ipso} donation to Pd and the chelating C_{ipso},P-coordination. This suggests that the reductive elimination occurs upon C_{ipso} decoordination.[25]

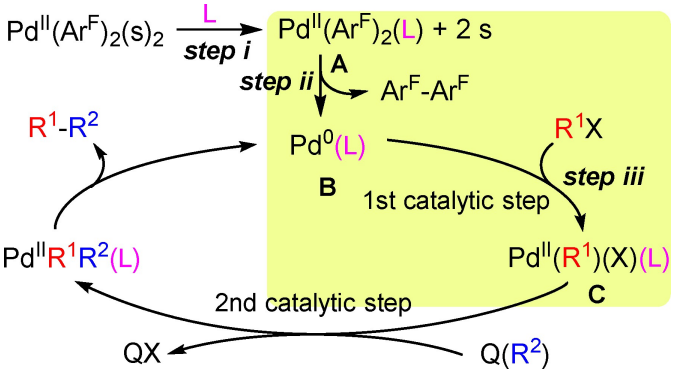
As a summary for reactions at 25 °C, **4b** and **5b** give by far the highest conversions and the combination of **4b** or **5b** with tBuXPhos is particularly efficient for in situ formation of catalyst [Pd{$C_6H_4(CF_3)$-*p*}(Br)(L)] at this low temperature. The rest of precursors suffer from slow reductive elimination step and, in the case of tBuBrettPhos, also from extremely slow ligand substitution at step **i**.

All rates of conversions to **A** or **C** increase substantially at 60 °C, as expected (Table 3). Even the reluctant tBuBrettPhos provides 44% conversion and 35% coupling in entry 26, which is anyhow very unsatisfactory. With **4b** (entries 23–27) all the entering ligands, except tBuBrettPhos, provide high conversion, and **C** yields in the range 94–99%. The entering ligand RuPhos, which afforded fast ligand substitution but slow reductive elimination at room temperature, still suffers in the conversion from **P3** at 60 °C and achieves only 59% conversion to **C** in entry 15, but it does better from **2b** (entry 19, 94%), and much better from **4b** (entry 23, 98%). The improvement is similarly good for the structurally related SPhos (entry 27, 97%). Ligands XPhos and tBuXPhos, now less retarded at the ligand substitution step, show powerful at the reductive elimination step ***ii***, maybe because the steric effect of the ^{i}Pr groups facilitates C_{ipso} decoordination.[25] The NCMe precursor **5b** reaches full conversion with tBuXPhos (entry 28).

Thus, although most of the cases with COD in the precursor (**P3** and **2b**) improve their conversions and **C** yields significantly in 1 h at 60 °C, clearly the **4b** and **5b** precursors still do as good or better because they are entropically favored in the first step (1 L displaces 2 THF or 2 NCMe) and the higher **A** concentration favors the rate of the subsequent coupling. The problem of slow reductive elimination of complex **A** observed for the entering ligand RuPhos at 25 °C is residual at 60 °C from **2b** and **4b** (**A** = *cis*-[$Pd(C_6F_3H_2)_2$(RuPhos)]) but still serious from **P3** (**A** = [Pd(neophyl)(RuPhos)], entry 15).

As overall conclusion of the results in Tables 2 and 3, it looks that most of the precursors **P3**, **2b** and **4b** might eventually evolve to high yield formation of [Pd(Ar)(Br)(L)] if an appropriate L is chosen and sufficient time at 60 °C or at higher temperature is given. The procedure should be potentially useful for different ArX electrophiles, provided that these are fast oxidants of [Pd^0(L)]. However, the highest activity and fastest evolution is achieved using **4b** or **5b**, which could be used also at room temperature, demonstrating that the choice of a weak monodentate ligand is a main condition for fast precursor conversion. Again, the best combination to produce catalyst **C** is precursors **4b** and **5b** with tBuXPhos and SPhos, but also XPhos and RuPhos could do fine. Ligand tBuBrettPhos has always poor conversion. At 25 °C precursor **4b** + tBuXPhos is excellent because tBuXPhos is very efficient promoter of step ***ii***. However, we will find some problems in the use of tBuXPhos in the next section, which has led us to pay more attention to SPhos. It seems not to be by chance that many example reactions in the Martin and Buchwald review on 2-biarylphosphines in Suzuki-Miyaura cross-coupling employ SPhos.[26]

D) Catalytic studies. Scheme 4 depicts the steps for formation of a chosen [$Pd(R^1)(X)(L)$] catalyst from a [PdR_2(weak ligand)] precursor (steps ***i***→***ii***→***iii*** in Scheme 2), and also the three main steps (oxidative addition, transmetalation and reductive elimination) of a cross coupling cycle $R^1X + Q(R^2) \rightarrow R^1\text{-}R^2$. In a clean reaction from a precursor, step ***i*** decides the ligand L of the catalyst and step ***iii*** (highlighted in yellow) coincides with the oxidative addition and decides the electrophilic reagent R^1X, whereas the transmetalation step decides the nucleophilic reagent $Q(R^2)$.



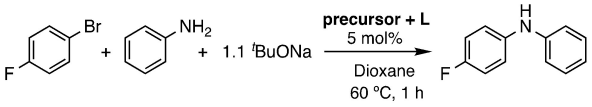
Scheme 4. *In situ* clean synthesis of a tailor-made [$Pd(R^1)(X)(L)$] catalyst using L, R^1 and R^2 groups, followed by cross-coupling catalysis.

Scheme 4 is useful to comment the different possibilities of actuation with an active precursor like **4b** or **5b**, namely: **1)** A solution of a specific *in situ* made *ad-hoc* catalyst can be prepared following Scheme 2.[13] Then, the solution can be used for catalysis, adding the corresponding electrophile and nucleophile, or the catalyst can be isolated and stored as solid, if preferred. **2)** For immediate use in catalytic tests, aliquots of the solution containing the catalyst can be used in serial trials. **3)** The selected catalyst can be prepared *in situ*, in the percentage required, controlled by the amount of precursor added, in a solvent containing dissolved the total amount of electrophile to be used in the catalysis. When the catalyst is formed, the catalysis can be triggered by simple addition of the nucleophile (*one-pot two-step catalysis*). **4)** A less-recommended protocol, because it does not guarantee the absence of undesired byproducts, is to put the precursor, L, R^1X and $Q(R^2)$ *all-in-pot* from the beginning. The catalyst synthesis and the catalysis itself will start competitively, producing probably some undesired products. Some interesting cases of the two later protocols are analysed now.

Please note that the catalysis reported below (Ar^F stands for $C_6F_3H_2$) are planned as tests of the protocols 3) and 4). Conditions such as temperature, time, and minimum precursor percentage required are not optimized. In the *all-in-pot* protocol we need a significant percentage of catalyst precursor (5 mol%) in order to be able to detect and identify the formation of undesired byproducts by ^{19}F NMR. Commercial reagents with simple structures are being used. Obviously, other molecules with complex structures might display problems not observed here, but this can happen the same using isolated catalysts.

D1.1 – Examples of "*All-In-Pot*" Catalysis

D1.1) Buchwald-Hartwig amination with precursors 2b, 4b, or 5b and L = tBuXPhos. Considering the wide use of 2-biarylphosphines in Buchwald-Hartwig amination, [27] a C–N coupling between *p*-BrC_6H_4F and aniline was examined (Eq. 2, 5% precursor = **2b**, **4b** or **5b**, 5% L = tBuXPhos).



(2)

The catalysis was run in dioxane at 60 °C. The solvent and all reagents were put in a flask, under N_2, before starting the heating. After 60 min at 60 °C, the amount of ArNHPh formed was very different for **2b**, and quite similar for **4b** and **5b** (Table 4).

For **2b**, only 3% of product was obtained and $(C_6F_3H_2)_2$ was not observed, whereas for **4b** and **5b** 91–95% of product was obtained, and 4.5 mol% of $(C_6F_3H_2)_2$ was observed, supporting high formation of catalyst [Pd(C_6H_4F-*p*)(Br)(tBuXPhos)]. This suggests that the catalyst formation from the precursor is being seriously interfered by other molecules in solution in the reaction from **2b**, but not from **4b** or **5b**. A reasonable kinetic hypothesis is that at the start of the reactions the COD displacement in **2b** by the small and abundant $PhNH_2$ is faster than by the bulkier tBuXPhos (see its slowness in Table 3, entry 21), blocking the precursor as a stable and catalytically inactive *cis*-[Pd($C_6F_3H_2$)$_2$($PhNH_2$)$_2$], which does not undergo easy reductive elimination.[28] In contrast, in line with the results obtained in Table 3, the sterically unhampered **4b** and **5b** precursors produce quickly *cis*-[Pd($C_6F_3H_2$)$_2$(tBuXPhos)] and then Ar^F-Ar^F plus the catalytically active [Pd(C_6H_4F-*p*)(Br)(tBuXPhos)], which remains active in the catalytic conditions (see Table 3, entries 25 and 28).

Table 4. Pd catalyzed aryl amination, at 60 °C. ArBr = *p*-FC_6H_4Br.[a]

Entry/precursor + L	ArBr	ArNHPh	$(C_6F_3H_2)_2$
1/**2b** + tBuXPhos	97	3	n. o.
2/**4b** + tBuXPhos	9	91	4.5
3/**5b** + tBuXPhos	5	95	4.5

[a] At 60 °C for 1 h. ArBr (0.10 mmol), $PhNH_2$ (0.10 mmol), **2b**, **4b** or **5b** + tBuXPhos (0.005 mmol), THF (1 mL). Yields (%) determined by ^{19}F NMR.

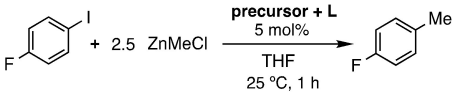
D1.2) Negishi Aryl-Me coupling with precursors 2b or 4b, L = tBuXPhos. Somehow in contrast with the previous results, the C–C Negishi coupling of *p*-IC_6H_4F with ZnMeCl (Eq. 3, 5 mol% precursor = **2b** or **4b**, 5 mol% L = tBuXPhos) shows that the two precursors **2b** and **4b** provide identical almost full conversion to *p*-FC_6H_4Me in 60 min at 25 °C. (Table 5, column 3, entries 1–4). This is obviously satisfactory from a synthetic point of view, but a bit mechanisti-

Table 5. Negishi *p*-IC_6H_4F + ZnMeCl catalysis.[a] Ar = *p*-C_6H_4F; $Ar^F = C_6F_3H_2$.

	% F in C_6H_4F			% F in Ar^F	
Ent./ precursor + L	ArH	ArMe	ArZnCl	$(Ar^F)_2$	(Ar^F)ZnCl
1/**2b** + tBuXPhos [b]	1	96	3	0	100
2/**4b** + tBuXPhos [b]	2	95	4	25	75
3/**2b** + tBuXPhos [c]	2	97	2	6	94
4/**4b** + tBuXPhos [c]	2	97	1	85	15

[a] ArI (0.10 mmol), ZnMeCl (0.25 mmol), **2b** or **4b** + tBuXPhos (0.005 mmol), THF (1 mL).
[b] All the reagents in the flask at the start of catalysis.
[c] Mixing of precursor, tBuXPhos and ArI for 1 h, prior to ZnMeCl addition. EtH (by ^1H NMR), and traces of Ar-Ar^F (by ^{19}F NMR) are observed. Yields (%) determined by ^{19}F NMR.

cally puzzling considering the large difference in catalyst formation, monitored by $(Ar^F)_2$ formation, found in 1 h at 25 °C: only 8% from **2 b** (entry 7), versus 92% from **4 b** (entry 11). Is it possible that both precursors are identically active?



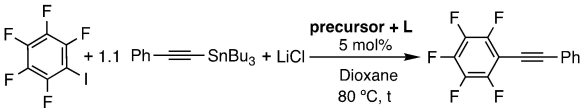
(3)

The experimental results in Table 5 uncover two competing pathways from the two precursors to the *in cycle* [Pd^0(tBuXPhos)] catalyst (Scheme 5). They are presented in this Scheme for **4 b** but operate the same for **2 b**. One follows the sequence in section **C**, via $C_6F_3H_2$-$C_6F_3H_2$ coupling. The other is faster and involves double $C_6F_3H_2$/Me transmetalation followed by fast Me-Me coupling. Entry 1 of Table 5, where $C_6F_3H_2$-$C_6F_3H_2$ is not observed, clearly supports that all the [Pd^0(tBuXPhos)] catalyst from the COD complex **2 b** is being formed *via* pathway **(b)**. Entry 3 remarks that even waiting 1 h before adding ZnMeCl, in order to allow for the slower pathway **(a)** to participate, only 6 mol% of the Pd catalyst proceeds from this much slower pathway, while 94 mol% comes *via* pathway (**b**).

The higher reactivity of the THF complex **4 b** is reflected in Table 5 entry 2, which shows that pathway **(a)**, although slow, is faster than **2 b** and reaches almost 1/3 of the conversion via pathway **(a)**. With this reasonably fast conversion of **4 b**, retarding one hour the addition of the Zn nucleophile makes most of the [Pd^0(tBuXPhos)] catalyst to be formed via pathway **(a)**, exactly 85% versus 15%. It is worth noting that the putative intermediate of a single $C_6F_3H_2$/Me transmetalation in pathway **(b)**, namely *cis*-[Pd($C_6F_3H_2$)(Me)(L)] (L = COD or 2 THF), must undergo the second Me transmetalation faster than $C_6F_3H_2$-Me coupling, since $C_6F_3H_2$-Me is not observed. This kind of R/R′ transmetalation involving fluorinated aryls has been thoroughly studied in our group.[29]

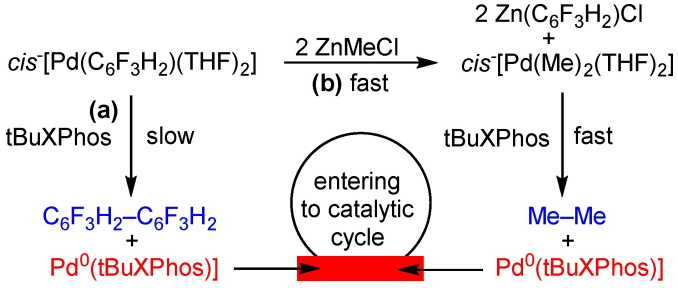
D1.3) Stille Pentafluorophenyl-Alkynyl coupling with precursors 2 b or 4 b, L = tBuXPhos, XPhos or SPhos. A Stille coupling involving pentafluorophenyl iodide (C_6F_5I) and a phenylalkynylstannane ($PhC{\equiv}CSnBu_3$) has been chosen as example of a weak and bulky nucleophile. We have recently reported solutions for Stille fluoroaryl-alkynyl couplings under different conditions.[30] Although the best synthesis, needing less additives, is achieved with $ClC{\equiv}CPh$ and $C_6F_5SnBu_3$, we found that the $C_6F_5C{\equiv}CPh$ coupling from C_6F_5I and $PhC{\equiv}CSnBu_3$ was also feasible, with reasonable yield, using either 5 mol% [$PdCl_2$(Ph-PEWO-F)] or 10 mol% {[$PdCl_2(NCMe)_2$] + tBuX-Phos} as catalyst, 24 h, 80 °C in 1,4-dioxane, and stoichiometric LiCl as additive (85% yield was achieved in both cases).[31]

Applying the reaction conditions in Eq. 4 (**2 b** or **4 b** as precursors and Sn:C_6F_5I = 1.1:1 ratio) to the reactions with L = tBuXPhos, afforded identical (±1%) catalytic results for both precursors. Hence only the results with **4 b** are collected in Table 6 (entries 1–3). In addition to the coupling product, small but not negligible percentages of hydrolysis (Ar-H) and transmetalation (Ar-Sn) products are formed. It is clear that at 80 °C the catalyst formation has been sufficient.



(4)

The reactions in entries 1–3 of Table 6 proceed very slowly, but the yield of catalysis with tBuXPhos as ligand improve by increasing the Sn:C_6F_5I ratio to 2:1. Hence it is the slowness of the catalytic cycle that is determining the rate of formation and the catalytic yield of the coupling product. The results in entries 4–6 afford up to 85% of C_6F_5-Alkynyl yield in 24 h.



Scheme 5. The two *in situ* competing pathways to formation of the [Pd^0(L)] catalyst.

Table 6. Ar-Alk Stille catalysis with **4 b** as catalyst precursor. Ar = C_6F_5; Alk = C≡CPh.[a]

Entry	L/Sn:C_6F_5I ratio	t (h)	Ar-I	Ar-Alk	Ar-H	Ar-Sn
1	tBuXPhos/1.1:1	1	60	32	5	3
2		5	41	49	6	4
3		24	20	57	18	5
4	tBuXPhos/2.0:1	1	48	39	8	5
5		5.5	12	72	9	7
6		24	0	85	8	7
7	XPhos/1.1:1	1	14	79	5	2
8		5	10	83	5	2
9		24	7	86	5	2
10	SPhos/1.1:1	1	5	92	3	0
11		5	3	94	3	0
12		24	0	94	6	0

[a] Entries 1–3 and 7–12: ArI (0.20 mmol), $AlkSnBu_3$ (0.22 mmol), LiCl (0.20 mmol), **4 b** + L (0.01 mmol), dioxane (2 mL). Entries 4–6: $AlkSnBu_3$ (0.40 mmol). Alk = Alkynyl. Yields (%) determined by ^{19}F NMR.

From our previous experience in Stille coupling of bulky aryls, we know that steric conflicts between the bulkiness of the groups on Pd and the stannane produce slow reactions.[32,33] Consistent with this, the yield improves to 86% in 24 h with the somewhat smaller XPhos (Table 6 entries 7–9), and the smallest SPhos affords the best results in the desired coupling product (Table 6 entries 10–12) with 92% in just 1 h, and 94% in probably little more time (5 h indicates only the next time we tested the catalysis). SPhos also produces less contamination by undesired Ar-H and Ar-Sn (Table 6, columns 6 and 7). This remarkable result is very interesting because it shows that the bulkier 2-biaryl phosphines are not necessarily more efficient than the smaller ones. On the contrary, they can find serious steric hindrance along the catalytic cycle (probably at the transmetalation or coupling transition states) if they have to face bulky partners as, in this case, the stannane.

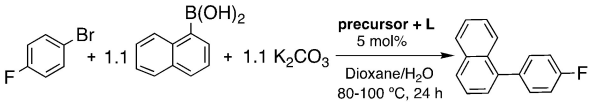
In an *all-in-pot* protocol there is a competition of rates of several processes. The formation of Ar-Alk requires the previous formation of cis-[Pd(Ar)(Alk)(L)] along the catalysis. Similarly, undesired formation of Ar-Sn uncovers Pd-Ar/Sn-Alk transmetalations contaminating the process. Table 7 highlights that the Ar^F groups originally contained in the precursor do not appear only as Ar^F-Ar^F from coupling in *cis*-[Pd-$(Ar^F)_2$(L)] but also as Ar^F-Alk, proving the previous formation of *cis*-[Pd(Ar^F)(Alk)(L)] (Equation 5). Ar^F-Sn is the counterpart of this transmetalation.

$$\begin{matrix} cis\text{-}[Pd(C_6F_3H_2)_2(L)] \\ + \\ (Alkynyl)SnBu_3 \end{matrix} \rightleftharpoons \begin{matrix} cis\text{-}[Pd(C_6F_3H_2)(Alkynyl)(L)] \\ + \\ (C_6F_3H_2)SnBu_3 \end{matrix} \quad (5)$$

Double transmetalations should probably occur also, giving *cis*-[Pd(Alk)(Alk)$(THF)_2$], and Alk-Alk couplings, undetectable in the ^{19}F NMR spectrum.

The species in Eq. 5 can give rise also to $C_6F_3H_3$ by hydrolysis. An inconvenience of all this complexity is that in these conditions the formation Ar^F-Ar^F is not reporting the amount of catalyst [Pd^0(L)] formed.

D1.4) Suzuki coupling with precursor 5b and L = tBuXPhos, or SPhos. The *all-in-pot* Suzuki *p*-F C_6H_4-naphthyl coupling in Eq. 6 affords the expected coupling product in column 4 and the biphenyl $(C_6F_3H_2)_2$ in column 5 of Table 8, but also other ^{19}F-containing undesired products, namely: significant amounts of the hydrolysis product Ar^FH in column 8; the wrong coupling $C_6F_3H_2$-naphthyl product in column 6; and, finally, traces of the mixed biaryl *p*-F C_6H_4-$C_6F_3H_2$ in column 7, which requires a double transmetalation.



(6)

This case is similar to the previous Stille one although it differs in the larger percentage of hydrolysis here, due to the different nucleophilic reagent and the explicit presence of water. We find again the results of a speed race in different directions of all the interdependent reagents, leading to group exchanges as in Eq. 7.

$$\begin{matrix} cis\text{-}[Pd(C_6F_3H_2)_2(L)] \\ + \\ B(naph)(OH)_2 \end{matrix} \rightleftharpoons \begin{matrix} cis\text{-}[Pd(C_6F_3H_2)(naph)(L)] \\ + \\ B(C_6F_3H_2)(OH)_2 \end{matrix} \quad (7)$$

The final result of these exchanges is difficult to predict even if some reaction rates for isolated conditions (section C) are known. For instance, two ligands (tBuXPhos and SPhos) that are similarly efficient in catalyst formation at 60 °C (Table 3), have very different ability to form the desired coupling product Ar-naphthyl in *all-in-pot* conditions at 100 °C (Table 8, entry 1 *vs* 2). Consistent with the results of the Stille catalysis in Table 6, in the Suzuki process in Table 8 the smaller SPhos is again much more efficient than tBuXPhos (95% *vs* 50%). The steric conflict here is caused by the bulky naphthyl group.[33]

D2. – Examples of *"one-pot two-step"* catalysis. Protocol. The four Ar-R^2 couplings have been checked with reagent:catalyst ratios in the range 1000:50 (5 mol% catalyst) to 1000:1 (0.1 mol% catalyst). This is an example of the protocol for 5 mol% of [Pd-(Ar)(X)(SPhos)] catalyst prepared *in situ:* 5 mol% of precursor **5b**, and 100 mol% of ArX dissolved in the

Table 7. Percentage of Ar^F found as different species at the end of the process. ΣAr^F groups correspond to 5 mol% of precursor.

Ent	L; Sn: C_6F_5I ratio	Ar^F-Ar^F	Ar^F-Alk	Ar^F-Sn	Ar^F-H
3	tBuXPhos; 1.1:1	28	25	42	5
6	tBuXPhos; 2.0:1	0	41	55	4
9	XPhos; 1.1:1	11	37	45	7
12	SPhos; 1.1:1	52	22	24	2

[a] Percentage of Ar^F groups originally in the precursors that are eventually involved in couplings to [Pd(L)] from other complexes formed by exchanges.

Table 8. Pd-catalyzed Suzuki coupling. Ar = *p*-C_6H_4F. Ar^F = $C_6F_3H_2$. R = naphthyl. Ar^F to make ΣAr^F groups 100%, as in Table 7. ΣAr^F corresponds to 5 mol% of precursor.

Ent	Prec + L	ArBr	ArR	$(Ar^F)_2$	Ar^FR	Ar^FAr	Ar^FH
1[a]	**5b** + tBuXPhos	46	50	3	31	4	62
2[a]	**5b** + SPhos	0	95	10	43	4	43
3[b]	**5b** + SPhos	0	96	25	34	3	38

[a] ArBr (0.50 mmol), Naphthyl-$B(OH)_2$ (0.55 mmol), K_2CO_3 (0.55 mmol), **5b** + L (0.025 mmol), dioxane (2 mL), H_2O (0.5 mL). t = 24 h. T = 100 °C. [b] T = 80 °C. Yields (%) determined by ^{19}F NMR.

chosen solvent (THF for T = 25 °C, dioxane for T ≥ 60 °C) are put in a flask under N_2. After the time required for conversion (we use 1.5 h at 60 °C), which can be checked for catalyst formation by ^{19}F NMR monitoring of the $(C_6F_3H_2)_2$ formed, or guessed from Tables 2 and 3 here, the solution is expected to contain 5 mol% [Pd(Ar)(X)(SPhos)], 95 mol% ArX and 5 mol% of the inert fluorinated biphenyl $(C_6F_3H_2)_2$.[[i]] This stable solution is ready to complete the catalysis upon addition of 100 mol% of the chosen nucleophile Q(R^2); it can be consumed in one catalysis, but also be split in aliquots for serial tests of reactivity with different nucleophiles. In a 100% hypothetical yield, reagents + catalyst should be totally consumed to produce 100% of product.

The times and temperatures in the Tables of this section refer to the second step (the time of the catalytic process). The catalyst has been formed previously in the first step (1.5 h at 60 °C). Considering that for the same amount of reagents the increase of the reagent:catalyst ratios diminishes seriously the rates of the second step (proportional to a lower percentage of catalyst) the concentrations of all the reagents in the 1000:1 catalysis tests (0.1 mol% of [Pd(Ar)(X)(SPhos)]) are increased (5x) in order to accelerate the catalysis rate and allow for completion in a reasonable time.

D2.1) Buchwald-Hartwig amination (Eq. 2) with precursor 5 b and L = SPhos. The reaction shown in Eq. 2, using 5% of **5 b** + 5% of SPhos, and 100% of *p*-BrC_6H_4F in 2 mL of dioxane (1.5 h at 60 °C in the first step, and adding 100% of $PhNH_2$ (no excess of amine) in the second one (24 h, 60 °C)), afforded quantitative yield (Table 9, entry 1). Lowering the percentage to 0.5% of precursor + 0.5% of SPhos (entry 2) the time needs to be increased but still it yields 96% in the 24 h checking.

The problems reported by Buchwald when the catalysis was run at room temperature (they use 40% excess of the amine),[27] are also found here. In effect, the yield lowers significantly (entry 3) if the second step of the catalysis is carried out at 25 °C, but still reaches 82% in 24 h (entry 3). At that point, a ^{31}P NMR spectrum of the solution showed that SPhos is not coordinated to Pd anymore, as expected from the published study. Reheating the solution to 60 °C for 8 h only produced a negligible increase in yield.

Reducing the percentages of **5 b** and SPhos to 0.1% (reagents:catalyst = 1000:1) and working at 80 °C (entry 4) lowers the yield to 29% in 24 h. It is obvious that the higher proportion of amine blocks more quickly the catalyst, likely via SPhos substitution by amine. Probably this blockage has happened at the beginning and does not need 24 h. In fact, against the catalytic acceleration expected upon increasing the concentration of all the reagents, a faster blockage occurs. Comparing entries 5 and 6 (yield 4% in both), it is complete in 1 h. The blockage rate increase with concentration and temperature faster than the catalysis.

D2.2) Negishi Aryl-Me coupling (Eq. 3) with precursor 5 b and L = SPhos. We apply pre-formation of the catalyst for 1.5 h at 60 °C and then cool down to 25 °C for the second step, previous to addition of ZnMeCl. The results (Table 10) are similar to those obtained with tBuXPhos as ligand in section **D1.2** (Table 5) except for the fact that the amount of $(C_6F_3H_2)_2$ increases to 100%, as expected, and $(C_6F_3H_2)$ZnCl is not observed. This further supports the mechanistic interpretation given in section **D1.2.**

The yield is almost quantitative in 1 h with 0.5% catalyst but lowers to 28% in 1 h with 0.1% (entries 1 and 2). Probably entry 2 had not been completed in 1 h because of the negative rate influence of a lower

Table 9. Pd catalysed aryl amination in dioxane, with **5 b** and SPhos as catalysts precursors. Ar = *p*-C_6H_4F. L = SPhos. T and t are for the second step.

Ent	**5 b** %	T °C	T + t	ArBr	ArNHPh	$(C_6F_3H_2)_2$
1[a]	5	60	1 h	0%	99%	5
2[b]	0.5	60	24 h	3%	96%	0.5
3[c]	5	25	24 h	15%	82%	4.9
4[d]	0.1	80	24 h	71%	29%	0.1
5[e]	0.1	60	1 h	96%	4%	0.1
6[e]	0.1	60	24 h	96%	4%	0.1

[a] ArBr (0.50 mmol), $PhNH_2$ (0.50 mmol), ^{t}BuONa (0.55 mmol), **5 b** + SPhos (0.025 mmol), dioxane (2 mL).
[b] **5 b** + SPhos (0.0025 mmol).
[c] Step one is carried out at 60 °C to make the catalyst and step 2 is continued at 25 °C.
[d] **5 b** + SPhos (0.0005 mmol).
[e] ArBr (2.5 mmol), $PhNH_2$ (2.5 mmol), ^{t}BuONa (2.75 mmol), **5 b** + SPhos (0.0025 mmol), dioxane (1.5 mL). Yields (%) determined by ^{19}F NMR; ± 1 differences are not significant.

Table 10. Negishi *p*-IC_6H_4F + ZnMeCl catalysis in THF, with **5 b** and SPhos as catalysts precursors. Ar = *p*-C_6H_4F; Ar^F = $C_6F_3H_2$. T and t are for the second step.

Entry	**5 b** %	ArI	ArH	ArMe	ArZnCl	$(C_6F_3H_2)_2$
1[a]	**0.5**	1	0	98	1	0.5
2[b]	**0.1**	71	0	28	1	0.1
3[c]	**0.1**	9.5	0	90	0.5	0.1
4[d]	**0.1**	2	0	97.5	0.5	0.1

[a] ArI (0.20 mmol), ZnMeCl (0.50 mmol, 0.25 mL of 2 M solution in THF), **5 b** + SPhos (0.001 mmol), THF (1.75 mL), t = 1 h.
[b] **5 b** + SPhos (0.0002 mmol), t = 1 h.
[c] ArI (1 mmol), ZnMeCl (2.5 mmol, 1.25 mL of 2 M solution in THF), **5 b** + SPhos (0.001 mmol), THF (0.75 mL), t = 1 h.
[d] Same as [c], t = 4 h. Yields (%) determined by ^{19}F NMR; ± 1 differences are not significant.

catalyst concentration. In effect, the yield increased to 90% in 1 h (for the second step) by increasing the amount of reagents in the same volume of solvent (entry 3) and to 97.5 in the next checking at 4 h.

D2.3) Stille perfluoroaryl-alkynyl coupling (Eq. 4) with precursor 5b and L = SPhos. The catalytic tests afford the results in Table 11. The second step of the catalysis is practically complete in 60 min at 80 °C (entry 1, 95% yield). In fact, looking at entries 10–12 of Table 6 we can see that the second step of the *one-pot two-step* reaction is somewhat faster than the *all-in-pot* alternative (all the catalyst is pre-formed), but both protocols are amazingly efficient, considering the mentioned difficulty of this C_6F_5-C≡CPh coupling.[30] The results here not only improve those achieved in section **D1.3**, but also those previously reported in reference [30].

After the step of catalyst formation with **5b** and the small SPhos, the Stille reactions are almost quantitative in 1 h in dioxane at 80 °C (entries 1 and 2). Lowering the catalyst proportion to reagents: catalyst = 1000:1 (0.1%) with the same amount of solvent shows the negative rate lowering (entry 3), which can be partially remediated with longer reaction time (entry 4) and/or temperature (entry 5, 95% yield in 20 h). Very effective is to increase all the concentrations keeping the 1000:1 ratio, which brings the catalysis to yields in the range 90–94% in only 2–4 h (entries 6–10).

D2.4) Suzuki coupling (Eq. 5) with precursor 5b and L = tBuXPhos or L = SPhos. Finally, Table 12 collects the results of the *one-pot two-step* naphthyl-C_6H_4F-*p* Suzuki coupling, which shows the superiority of the catalyst with SPhos over the one with tBuXPhos (both with 5% catalyst). With tBuXPhos the yield in 24 h is only 40% at 80 °C (entry 1) and 90% at 100 °C (entry 2), whereas with SPhos the yields in 24 h are practically quantitative (97% at 100 or 80 °C, entries 3 and 4).[[ii]] The difference is to be attributed, as for the Stille catalysis, to a significantly higher steric hindrance between the catalyst and the naphthyl group when the ligand is tBuXPhos than when it is SPhos. This slows down the transmetalation rates in entries 1 and 2, compared to 3 and 4.

The higher rates with SPhos allow to reduce the percentage of catalyst. An experiment at 80 °C with less catalyst (0.5%) affords quantitative yield in 24 h (entry 5). Increasing the reagents:catalyst ratio to 1000:1 the yield is still quantitative in 10 h (0.1% catalyst, entry 6), while when increasing the concentration of the reagents (5x in the same volume of solvent) 99% yield is reached in less than 6 h (entry 7).

Table 11. Ar-Alk Stille catalysis in dioxane with **5b** and SPhos as catalysts precursors. Ar = C_6F_5; Alk = C≡CPh.[a] T and t are for the second step.

Entry	5b %	t(h)	T (°C)	ArI	ArAlk	ArH
1[a]	5	1	80	2%	95%	3%
2[a]	5	2	80	1%	96%	3%
3[b]	0.1	3	80	60%	39%	1%
4[b]	0.1	24	80	13%	84%	3%
5[b]	0.1	20	100	0%	95%	5%
6[c]	0.1	2	80	8%	90%	2%
7[c]	0.1	4	80	6%	92%	2%
8[c]	0.1	2	100	5%	92%	3%
9[c]	0.1	4	100	4%	93%	4%
10[c]	0.1	6	100	1%	94%	5%

[a] ArI (0.20 mmol), $AlkSnBu_3$ (0.22 mmol), LiCl (0.20 mmol), **5b** + SPhos (0.01 mmol), dioxane (2 mL).
[b] **5b** + SPhos (0.0002 mmol).
[c] ArI (1 mmol), $AlkSnBu_3$ (1.1 mmol), LiCl (1 mmol), **5b** + SPhos (0.001 mmol), dioxane (2 mL). Yields (%) determined by ^{19}F NMR; ±1 differences are not significant.

Table 12. Pd-catalysed Suzuki coupling in dioxane. Ar = *p*-C_6H_4F; $Ar^F = C_6F_3H_2$. T and t are for the second step.

Ent	precursor	T °C	ArBr	ArNaph	$(C_6F_3H_2)_2$
1[a]	**5b** + tBuXPhos	80	58%	40%	5 mol%
2[a]	**5b** + tBuXPhos	100	8%	90%	5 mol%
3[a]	**5b** + SPhos	100	0%	97%	5 mol%
4[a]	**5b** + SPhos	80	0%	97%	5 mol%
5[b]	**5b** + SPhos	80	0%	99%	0.5 mol%
6[c]	**5b** + SPhos	80	0%	99%	0.1 mol%
7[d]	**5b** + SPhos	80	0%	99%	0.1 mol%

[a] ArBr (0.50 mmol), Naphthyl-$B(OH)_2$ (0.55 mmol), K_2CO_3 (0.55 mmol), **5b** + L (0.025 mmol), dioxane (2 mL), H_2O (0.5 mL), t = 24 h.
[b] **5b** + SPhos (0.0025 mmol), t = 24 h.
[c] **5b** + SPhos (0.0005 mmol), t = 10 h.
[d] ArBr (2.5 mmol), Naphthyl-$B(OH)_2$ (2.75 mmol), K_2CO_3 (2.75 mmol), **5b** + SPhos (0.0025 mmol), dioxane (2 mL), H_2O (0.5 mL), t = 6 h. Yields (%) determined by ^{19}F NMR; ±1 differences are not significant.

Conclusions

The complexes $[Pd(C_6F_3H_2)_2(s)_2]$ (s = NCMe, THF) reported here, easy to make and store, are almost perfect precursors for *in situ* formation of tailor-made [Pd(Ar)(X)(L)] catalysts in about 1.5 h at 60 °C.[36] The considerable facility and rapidity of the ligand substitution step, compared to having COD in the precursor makes a crucial difference in the scope of 2-biaryldialkyl phosphines that can lead efficiently to the desired Pd(II) catalyst. The advantageous behavior of 2 $C_6F_3H_2$ groups on Pd instead of one neophyl palladacycle also contributes to lower reductive-elimination barrier and, consequently, to higher versatility in formation of the desired catalyst. In few words, the lower activation barriers of these two precursors in the conversion pathway from precursor to catalyst leads to

a larger scope of *in situ* catalyst formation with different L ligands.

The *in situ* approach to tailor-made [Pd(Ar)(X)(L)] catalysts with the same Ar and X groups provided by the electrophile is very easy and does not require a collection of Pd catalysts. It can be used at the level of 1–3 mL solutions and monitored by NMR, which means significantly less cost, less time, more chemical information, and more atom economy compared to trial and error blind catalysis. In the *one pot two step* protocol these precursors provide clean solutions containing the *tailor-made* Pd(II) catalyst by choice of L and ArX. The only "contamination" is the inert (in the reaction conditions) biphenyl $(C_6F_3H_2)_2$. This gives a convenient access to *in situ* prepared Pd(II) catalysts from the panoply of 2-biaryl phosphines commercially available nowadays. Furthermore, the access to these solutions allows to schedule serial catalytic experiments, either with different types of nucleophile or with different specific molecules of the same type of nucleophile, using aliquots.

The precursor *cis*-$[Pd(C_6F_3H_2)_2(NCMe)_2]$ (**5b**) is remarkable because its high thermal stability does not imply slower conversions: in THF or dioxane as solvents, it is converted, at basically no rate cost, to *cis*-$[Pd(C_6F_3H_2)_2(solvent)_2]$ (Figure 2). From the experiments reported here it looks possible to carry out most of the conventional Suzuki, Stille, and Negishi catalysis in almost quantitative yield with reagents: precursor 1000:1 ratios, using only precursor **5b** and the very efficient SPhos ligand. In contrast the Buchwald-Hartwig amination requires at least 1000:5 ratio or, perhaps, a different phosphine, because the catalyst with SPhos is eventually blocked in the presence of large $PhNH_2$ concentration.

Experimental Section

General procedure for Ligand Substitution, Reductive Elimination and Oxidation Studies with Dialkylbiaryl Phosphines. The corresponding $Pd(C_6F_3H_2)_2$ complex (**2b** or **4b**, 12.5 μmol) and ligand (13.75 μmol, 1.1 eq.) were added to a flame-dried NMR tube. *p*-$BrC_6H_4(CF_3)$ (2.6 μL, 18.7 μmol, 1.5 eq.) and 0.50 mL of dry THF were added at room temperature and the NMR tube was vigorously shaken until complete dissolution of solids. For experiments at 60 °C, the NMR tube was placed in an oil bath at that temperature. After 60 min, the reaction was checked by ^{19}F NMR. Catalyst product formation was determined *vs.* α,α,α-trifluorotoluene as internal standard.

Model procedure for *in situ* formation of tailor-made [Pd(Ar)(X)(L)] catalysts. The [Pd] precursor **4b** or **5b** (e.g. 5 mol%), the chosen ligand L (e.g. 5 mol%), and a magnetic stirrer are put into a flame-dried screwed-capped Schlenk flask under N_2 atmosphere. A solution of the wanted aryl halide (100%) is added to the flask under stirring and the solution is brought to the desired temperature in a preheated oil bath. The mixture is allowed to react at the chosen temperature for sufficient time to complete the catalyst formation (approximate reaction times and temperatures can be guessed from the data in the text, and full formation of $C_6F_3H_2$-$C_6F_3H_2$ can be confirmed from an aliquot by ^{19}F NMR). Examples are given in SI. Then, the chosen nucleophile (≥ 100%) can be added to continue the catalysis.

A full experimental report, including synthesis of the products, spectroscopic characterization of the reactions and kinetic Gibbs free energy determinations, is given in the Supporting Information.

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RESEARCH ARTICLE

Palladium (II) Precursors for Clean In Situ Formation of Ad Hoc Cross-Coupling Catalysts. Their Application in One-Pot/ Two-Step Catalyses with 2-Biaryl-Dialkylphosphine Ligands

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