COMMUNICATION

Synthesis of fluorinated biaryls by [MCl$_2$(PEWO)] (M = Ni, Pd) catalysed Negishi homo-coupling or selective cross-coupling

Jaime Ponce-de-León[a] and Pablo Espinet.*[a]

Hetero-coupling to produce polyfluorinated assymmetric biaryls with high selectivity, as well as homo-coupling to yield symmetric fluorinated biaryls, is achieved with [MCl$_2$(PhPEWO-F)] catalysts (M = Ni, Pd; PhPEWO-F = 1-(PPh$_2$),2-(CH=CH-C(O)Ph)-C$_6$F$_4$ and Zn(C$_6$F$_5$)$_2$ as example of highly fluorinated nucleophile, at relatively low temperature (80 °C), short times, and with high selectivity.

The transition-metal catalysed aryl-aryl coupling reactions are very efficient for conventional aryls, less easy when polyfluorinated aryls (Ar^F) are involved, and difficult when the two aryls are polyfluorinated, particularly if they possess F$_{ortho}$ atoms. Consistently, the C$_6$F$_5$-C$_6$F$_5$ coupling is a most difficult case. In spite of this, or perhaps because of this, there are a number of catalytic procedures published, which work with variable success. Some representative reactions and examples are: a) Cu or Ni-catalysed decarboxylative cross-coupling processes. The polyfluorinated aryl is introduced as an alkaline carboxylate and requires very high temperature for decarboxylation;[1] b) Pd- or Ni-catalysed Suzuki-Miyaura processes, where the polyfluoroaryl for Ar–Ar^F coupling is in the nucleophile;[2] c) base-free Hiyama processes, where the polyfluoroaryl comes from a flouroarene that undergoes C–F, or C–H activation.[3] On the other hand, Pd-catalysed Ar^F–Ar^F homocoupling of Ar^F boronic acids or boronates, including C$_6$F$_5$–C$_6$F$_5$, can be achieved with Pd(0) as catalyst and stoichiometric Ag$_2$O as oxidant.[4] Some representative examples are given in the previous references.

Although palladium catalysed Suzuki-Miyaura is often the preferred cross-coupling process in the literature, the application of highly fluorinated arylboronate esters, especially pentafluorophenyl boronates, is sometimes inefficient at transmetalation to Pd because of their low nucleophilicity.[4a]

This is why these processes can require high temperatures and long reaction times. We hypothesized that this inconvenience might be mitigated using more nucleophilic Zn reagents.

In general, hetero-coupling reactions can further suffer from variable contamination by homocoupling products, due to the operation of undesired transmetalation processes,[5] which are facilitated by the slowness of reductive elimination when Ar^F groups are involved. In two recent studies on these problems, we have utilized cis-[M(C$_6$F$_5$)$_2$(THF)$_2$] (M = Ni, Pd) complexes to measure the ($\Delta G^{\ddagger}$(C$_6$F$_5$–C$_6$F$_5$)$_{Pd}$)[6] and ($\Delta G^{\ddagger}$(C$_6$F$_5$–C$_6$F$_5$)$_{Ni}$)[7] barriers to reductive elimination of C$_6$F$_5$–C$_6$F$_5$ upon addition of the ligand being tested as coupling promoter and hydrolysis protector. The study in Pd showed that the Buchwald phosphine ^{t}BuXPhos was very efficient for both functions (full conversion and 100% coupling in 2.6 h, at 0 °C), and was followed by PhPEWO-F (full conversion and (C$_6$F$_5$)$_2$:C$_6$F$_5$H = 93.7:6.3 mol% in 5.6 h, at 25 °C).[6] With Ni, PhPEWO-F (Fig. 1) was amazingly efficient (full conversion and (C$_6$F$_5$)$_2$:C$_6$F$_5$H = 95:5 mol% in < 5 min. at 25 °C; full conversion and (C$_6$F$_5$)$_2$:C$_6$F$_5$H = 100:0 in 8 h, at -50 °C!!), whereas ^{t}BuXPhos was very inefficient (83% conversion and (C$_6$F$_5$)$_2$:C$_6$F$_5$H = 23:77 mol% in 6 h, at 25 °C; CyXPhos (Fig. 1)was similarly inefficient: 47% conversion and (C$_6$F$_5$)$_2$:C$_6$F$_5$H = 29:71 mol% in 6 h, at 25 °C).[7]
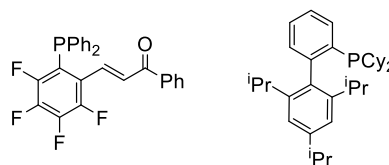
Figure 1. Chelating ligands PhPEWO-F (left) and CyXPhos (right).

We have recently carried out a detailed experimental and computational study of the complete sequence (from the precatalyst to the cross-coupling product) of the Pd Negishi process with ligand PhPEWO-F, and have found that the chelating coordination of the electron withdrawing olefin (EWO) accelerates the transmetalation step and reduces the coupling barrier, which are positive contributions to achieve

fast cross-coupling and reduce undesired homo-couplings. The negative counterpart is that the EWO coordination increases the barrier of the oxidative addition step. In spite of this, we succeeded in a preliminary test of catalytic synthesis to produce C_6F_5–C_6F_5 working at 80 °C.[8]

Here we develop this initial test on Pd and explore the feasibility of nickel- and palladium-catalysed Ar-C_6F_5 Negishi couplings, employing commercial Zn(C_6F_5)$_2$ as nucleophile. It should be a good model of other polyfluorinated aryls.

The reaction conditions were chosen, to be shared in all the reactions, after some solvent and temperature trials on the highly challenging C_6F_5–C_6F_5 coupling (Eq. 1). The oxidative addition step did not operate at room temperature and required 80 °C. At this temperature, dioxane was an efficient solvent, whereas toluene or acetonitrile were not. C_6F_5 transmetalation was more efficient for the transfer of the first perfluoroaryl group, which determined the use of 1.5 mol of Zn(C_6F_5)$_2$ per mol of C_6F_5I. The experiments (Table 1) showed that with 5% Ni the use of PhPEWO-F (entry 3, >99% yield) makes a drastic difference with PPh$_3$ or CyXPhos (entries 1 and 2, 0% yield). We also found that the direct use of the isolable [PdCl$_2$(PhPEWO-F)] as precatalyst improved the results initially obtained by its in situ formation from [PdCl$_2$(NCMe)$_2$],[8] providing quantitative C_6F_5–C_6F_5 coupling with only 3% of this precatalyst.

$$\mathbf{Ar\!-\!I} + 1.5\ Zn(\mathbf{C_6F_5})_2 \xrightarrow[\text{Dioxane, N}_2,\ 80\ ^oC]{\text{([Ni]+L) or [Pd]}} \mathbf{Ar\!-\!C_6F_5} + \begin{array}{l}\mathbf{Ar\!-\!Ar}\\ \mathbf{Ar\!-\!H}\end{array} \quad (1)$$

Table 1. Preliminary tests of catalytic C_6F_5–C_6F_5 coupling efficiency of PhPEWO-F compared to other phosphines in Ni, and improved results in Pd. [Ni] = [NiCl$_2$(NCMe)$_2$]; **ArI** = **C_6F_5**I.

Entry/Catalyst	[M] %	Time (h)	Yield (%)
1/ [Ni] + 2 PPh$_3$	5	24	0
2/ [Ni] + 1 CyXPhos	5	24	0
3/ [Ni] + 1 PhPEWO-F	5	4	>99
4/ [PdCl$_2$(PhPEWO-F)]	3	2	>99

These reaction conditions where then applied to the preparation of the Ar-C_6F_5 biaryls collected in Scheme 1, changing the ArI reagent in order to cover a reasonable scope, from aryls presumably leading to easier coupling (*p*-tol or *p*-CN) to others with different F or CF$_3$ substitutions. In principle, couplings with less fluorinated Zn(Ar^F)$_2$ reagents should have similar or lower coupling barriers than for C_6F_5.

The reactions were monitored by ^{19}F NMR (with unreactive $C_6F_3Cl_3$ as internal standard reference) on successive small aliquots of the reaction solution, which provides excellent identification of the conversion efficiency, the F containing products, and the yields in each of them. The data in Scheme 1 reflect NMR yields (relative to 100% for initial ArI) in the biphenyl shown. Complete tables with all the products of catalysis and isolated yields are given as ESI (Tables ESI1 and ESI2). In all cases the out-of-cycle initial formation of LM^0 (L = PhPEWO-F) from the [MCl$_2$L] precatayst (3% for Pd, 5% for Ni) produces 3 mol% or, respectively, 5 mol% of C_6F_5–C_6F_5. Also, a

small amount of C_6F_5H is formed by reaction of Zn(C_6F_5)$_2$ with the last traces of water in the "dry" solvent.

Scheme 1. Scope of Ar–C_6F_5 synthesis comparing Ni (a) and Pd (b) catalysis and different Ar groups.

a: 99 (6h) b: 99 (5h)	a: 99 (6h) b: 99 (5h)

It is interesting to note that no intermediates were observed during the catalytic reactions, and the consumption of ArI and formation of Ar–C_6F_5 and other products were simultaneous. This means that all the steps in the catalytic cycle subsequent to the oxidative addition (OA), namely transmetalations (TM), undesired transmetalations (UTM), and reductive eliminations (RE), are faster than OA. Yet, they have their own different rates for each case of aryl group and are consequently determinant of the products composition when more than one product is observed. On the other hand, the very similar catalytic behaviour observed for Ni and Pd supports a M^0/M^{II} cycle for both (Figure 2).

Figure 2. Desired (left, in black) and undesired (right, in red) cycles competing in the Ar–C_6F_5 cross-coupling Negishi process. For simplicity, only productive transmetalations are shown. In addition, ArH and C_6F_5H are generated from Ar–**{Zn}** species after hydrolysis.

Some significant observations can be made on the results in Scheme 1. For the biphenyls in the first row of Scheme 1 the cross-coupling yields are essentially quantitative. Neither Ar-Ar nor C_6F_5–C_6F_5 (except the 3 or 5% formed in precatalyst activation) are observed (Tables ESI1 and ESI2, entries 1-4). The cross-coupling reaction induced by PhPEWO-F is so much faster than undesired transmetalations that these have no chance to compete and the cross-couplings are fully selective. The times required for 3% [Pd] catalyst (determined by the oxidative addition step) are very similar to those with 5% [Ni]+L catalyst. Therefore, both catalysis work very well for the expectedly easier couplings of C_6F_5 to no- or little-fluorinated aryl partners. However, in the other rows of Scheme 1 the polarization of the electron density of the aryls, away from C_{ipso}, makes the coupling rates from $[M(C_6F_5)(Ar)L]$ progressively slower. This slowness allows for rate competence of the undesired processes in red in Figure 2, *via* retro-transmetalation to $[M(C_6F_5)IL]$, and of other exchanges non specified in Figure 2 (e.g. C_6F_5/Ar) that lead eventually to the same undesired coupling products.[i][Error! Marcador no definido.] Consequently, other products of the reaction (Ar–Ar, C_6F_5–C_6F_5 in higher percentage than 5 or 3%, and Ar–**{Zn}** detected as ArH after hydrolysis) are formed (Table 2). Moreover, this detrimental effect is higher with the Ni catalyst; the Pd catalyst starts to do noticeably better than Ni in all cases, showing higher selectivity to the cross-coupling and shorter reaction times, although the results with Ni are still very satisfactory.

Table 2. Products observed for reactions (Eq. 1) at the times indicated in Scheme 1, given in mol%.

Ar	Cat.	ArI	ArC$_6$F$_5$	Ar$_2$[a]	ArH[b]	(C$_6$F$_5$)$_2$[a]
3,4-C$_6$H$_3$F$_2$	[Ni]+L	9	89	0	2	6
2,4-C$_6$H$_3$F$_2$	[Ni]+L	1	88	8	3	9
3,5-C$_6$H$_3$F$_2$	[Ni]+L	0	92	6	2	8
3,5-C$_6$H$_3$(CF$_3$)$_2$	[Ni]+L	0	79	16	5	12
3,4-C$_6$H$_3$F$_2$	[Pd]	5	95	0	0	4
2,4-C$_6$H$_3$F$_2$	[Pd]	4	95	0	1	3
3,5-C$_6$H$_3$F$_2$	[Pd]	0	>99	0	0	3
3,5-C$_6$H$_3$(CF$_3$)$_2$	[Pd]	0	>99	0	0	3

[a] For Ar and C_6F_5 groups balance to 100 these molar number have to be multiplied by 2. [b] ArH comes from the Ar groups trapped as Ar–**{Zn}** at the end of the reaction and is obtained and measured after hydrolysis.

As for the two cross-coupling products of the third row, involving compounds with two F atoms in the 2,6 positions, the cross-coupling selectivity lowers more significantly, although it is still very high for Pd (87% and 69% respectively) compared to Ni (48% and 41%). The complete set of products for these two more difficult reactions is gathered in Table 3, and is given with the rest in Tables ESI1 and ESI2, entries 9-10. As expected, the presence of F in 2,6 produces the highest polarization of the C_{ipso} electron density and the slowest coupling rates and, consequently, the highest incidence of undesired transmetalations and couplings. The significant formation of C_6F_5–C_6F_5 and Ar–Ar in the mixtures confirms this effect.

Table 3. Products observed for reactions (Eq. 1) at the times indicated in Scheme 1, given in mol%.

Ar	Cat.	ArI	ArC$_6$F$_5$	Ar$_2$[a]	ArH[b]	(C$_6$F$_5$)$_2$[a]
2,6-C$_6$H$_3$F$_2$	[Ni]+L	7	48	13	19	24
2,4,6-C$_6$Cl$_2$F$_3$	[Ni]+L	0	41	10	39	28
2,6-C$_6$H$_3$F$_2$	[Pd]	8	87	0.5	4	5
2,4,6-C$_6$Cl$_2$F$_3$	[Pd]	0	69	8	16	20
C$_6$F$_5$	[Ni]+L	0	–	–	–[c]	>99[d]
C$_6$F$_5$	[Pd]	0	–	–	–[c]	>99[e]

[a] For Ar and C_6F_5 groups balance to 100 these molar number have to be multiplied by 2. [b] ArH comes from the Ar groups trapped as Ar–**{Zn}** at the end of the reaction and is obtained and measured after hydrolysis. [c] Cannot be measured because all the hydrolysis product of Ar–**{Zn}** is C_6F_5H in this case. [d] A total of 105 mol% could be produced. [e] A total of 103 mol% could be produced.

It is well known that, on occasions, the addition of small amounts of weak ligands contributes to diminish the participation of undesired transmetalations as source of homocoupling. However, in these catalysis the addition of subcatalytic amounts of AsPh$_3$ did not increase the reaction yield. On the contrary, it lowered the reaction rate and more unreacted aryl iodide was observed for similar reaction times.

Due to the reversibility of all the transmetalations, the aryl groups have the opportunity to re-enter the catalytic cycle from Ar–**{Zn}**, but not from irreversible undesired Ar–Ar homocoupling products. This can eventually affect seriously its concentration and its activity as nucleophile, to the point that full conversion of ArI is not achieved, as in the two reactions with Ar = 2,6-C$_6$H$_3$F$_2$ in Table 2.

In catalysis oriented to Ar–Ar homocouplings, the desired and undesired transmetalations in the cycle of Figure 2 (which presumably are operative although they are undetectable), as well as the precatalyst activation, lead all to the same product, Ar–Ar. The irreversible formation of C_6F_5–C_6F_5 is, in the cross-couplings studied here, a sterile source of consumption of $Zn(C_6F_5)_2$ but, in catalytic reactions oriented to C_6F_5–C_6F_5 homocoupling (last two entries of Table 3), C_6F_5–C_6F_5 is the wanted product and Ni recovers full conversion, although still at longer reaction times than Pd (4 h for Ni, 2 h for Pd). Thus, Negishi homocoupling with PhPEWO-F as coupling promoter ligand is able to produce quantitative conversion to C_6F_5–C_6F_5 in short times. From the reactions studied, only 2,6-C$_6$H$_3$F$_2$–2,6-C$_6$H$_3$F$_2$ and C$_6$Cl$_2$F$_3$–C$_6$Cl$_2$F$_3$ couplings look comparable in difficulty to C_6F_5–C_6F_5, and any other Ar–Ar homocouplings should be faster.. Consequently, catalytic Ar^F–Ar^F Negishi homocouplings (exemplified by C_6F_5–C_6F_5 in this study) are a very reasonable alternative to the use of boronic acids or boronates + Pd(0) as catalyst + stoichiometric Ag$_2$O as oxidant.[4] Obviously, the method requires the synthesis of the corresponding $Zn(Ar^F)_2$ organozinc in each occasion, as the reported procedure requires that of the boronic acids or the boronates, but it avoids the handling of Pd(0) catalysts and spares the use of stoichiometric Ag$_2$O.

Finally, with the percentages of catalyst tested, we observe (mainly for Ni), some cases of uncomplete conversion of ArI (9% at most). These are due to catalyst decomposition, and the

easily observed formation of a red product supports the formation of the highly unreactive Ni⁰(PhPEWO-F)₂, which was independently synthesized and fully characterized (see ESI for details), including its X-ray diffraction structure (Fig. 3). A similar product Pd⁰(PhPEWO-F)₂ has been reported for Pd.[8]
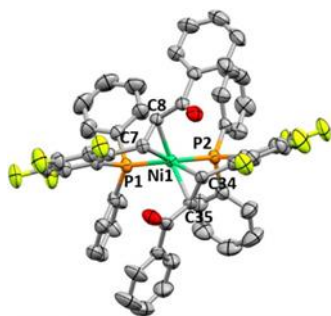
Figure 3. X-ray molecular structure of Ni⁰(PhPEWO-F)₂.

A plausible mechanistic interpretation of the catalytic differences observed for Ni and Pd is that the worse performance of Ni at 80 °C, in contrast with it being more efficient than Pd at very low temperatures, is due to the higher lability of Ni^{II}–olefin bonds, which can induce a higher percentage of olefin decoordination at 80 °C than for Pd. Since coupling promotion requires chelating coordination of PhPEWO-F (remember the inefficiency of PPh₃ in Table 1, entry 1) the Ni^{II}–olefin lability explains the much lower performance of PhPEWO-F as coupling promoter in Ni at high temperature, and also higher catalyst decomposition in P-monodentate intermediates (Eq. 2).
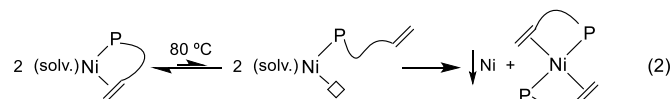
Since the oxidative addition step determines the reaction rates but not the selectivity of the process, their detailed understanding is somehow less necessary here, but the results deserve perhaps some comment. It is clear from the data shown in Scheme 1 that the oxidative additions are slower for Ni and Pd (5-6 h) for the more electron rich aryl iodides. They become faster for Pd with aryl iodides with more electron attractor substituents (2-3 h), but a less regular rate behaviour is observed for Ni. The variation is particularly irregular for 2,6-C₆F₂H₃I, for which completion of the reactions takes a very long time and some unreacted percentage of the iodide is observed with both catalysts (Table 3, entries 1 and 3). Although comparison of rates of some ArI pairs having identical F$_{ortho}$ substituents and the same [M] catalyst can be found as a function of Hammett parameters, a comprehensive explanation is not possible with the evidence available. It seems more reasonable to take into account that the oxidative addition step of aryl halides can follow different mechanisms, influenced by the aryl substituents and the metal.[9] So, upon moving from electron donor to strongly acceptor substituents, and from Ni to Pd, the apparently identical oxidative addition might be

changing mechanism or take place competitively via more than one mechanism.

In conclusion, the synthesis of symmetric and asymmetric biaryls fluorinated at one or the two aryls, including highly fluorinated species such as C₆F₅–C₆F₅ or C₆F₃Cl₂–C₆F₅, is made easily accessible to Ni- or Pd-catalysed Negishi processes using the chelating ligand PhPEWO-F in M:L = 1:1 ratio. This ligand facilitates fast and selective coupling even for difficult highly fluorinated aryls, and allows for milder conditions, shorter reaction times and higher selectivity than other processes in the literature.

The authors have contributed equally to the paper.

There are no conflicts of interest to declare.

References

1   Q. Chen, A. Wu, S. Qin, M. Zeng, Z. Le, Z. Yan and H. Zhang, *Adv. Synth. Catal.*, 2018, **360**, 3239.
2   L. Chen, H. Francis and B. P. Carrow, *ACS Catal.*, 2018, **8**, 2989.
3   (a) H. Saijo, H. Sakaguchi, M. Ohashi and S. Ogoshi, *Organometallics*, 2014, **33**, 3669–3672; (b) T. Schaub, P. Fischer, A. Steffen, T. Braun, U. Radius and A. Mix, *J. Am. Chem. Soc.*, 2008, **130**, 9304. (c) W. A. Golding and R. J. Phipps, *Chem. Sci.*, 2020, **11**, 3022.
4   (a) T. Korenaga, T. Kosaki, R. Fukumura, T. Ema and T. Sakai, *Org. Lett.*, 2005, **7**, 4915. (b) Y. P. Budiman, A. Jayaraman, A. Friedrich, F. Kerner, U. Radius and T. B. Marder, *J. Am. Chem. Soc.*, 2020, **142**, 6036.
5   For a thorough study of undesired transmetalations see: J. del Pozo, G. Salas, R. Álvarez, J. A. Casares and P. Espinet, *Organometallics*, 2016, **35**, 3604.
6   E. Gioria, J. del Pozo, J. M. Martínez-Ilarduya and P. Espinet, *Angew. Chem., Int. Ed.*, 2016, **55**, 13276.
7   J. Ponce-de-León, E. Gioria, J. M. Martínez-Ilarduya and P. Espinet, *Inorg. Chem*. 2020, **59**, 18287.
8   E. Gioria, J. del Pozo, A. Lledós and P. Espinet, *Organometallics,* 2021*,* **40**, 2272.
9   Mechanisms for oxidative addition to Ni(0): M. E. Greaves, E. L. B. Johnson Humphrey and D. J. Nelson, *Catal. Sci. Technol.*, 2021, **11**, 2980. For Pd, the mechanisms involving homolitic rupture of Ar–X have been only rarely invoked.