

Cross-Coupling Reactions

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Promoting Difficult Carbon–Carbon Couplings: Which Ligand Does Best?

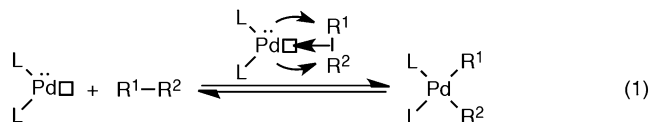
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Dedicated to Professor Juan Forniés

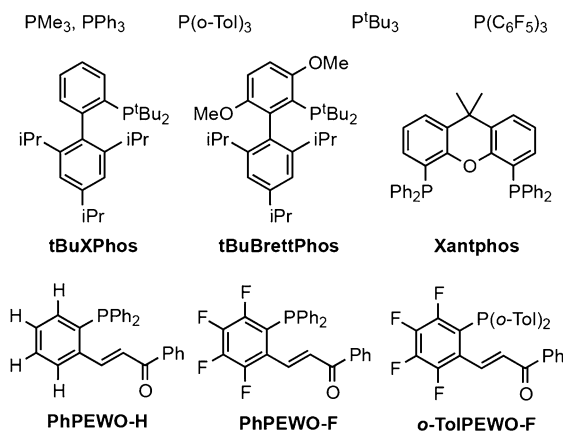
Abstract: A Pd complex, *cis*-[Pd(C₆F₅)₂(THF)₂] (**1**), is proposed as a useful touchstone for direct and simple experimental measurement of the relative ability of ancillary ligands to induce C–C coupling. Interestingly, **1** is also a good alternative to other precatalysts used to produce Pd⁰L. Complex **1** ranks the coupling ability of some popular ligands in the order P^tBu₃ > *o*-TolPEWO-F ≈ *t*BuXPhos > P(C₆F₅)₃ ≈ PhPEWO-F > P(*o*-Tol)₃ ≈ THF ≈ *t*BuBrettPhos ≫ Xantphos ≈ PhPEWO-H ≫ PPh₃ according to their initial coupling rates, whereas their efficiency, depending on competitive hydrolysis, is ranked *t*BuXPhos ≈ P^tBu₃ ≈ *o*-TolPEWO-F > PhPEWO-F > P(C₆F₅)₃ ≫ *t*BuBrettPhos > THF ≈ P(*o*-Tol)₃ > Xantphos > PhPEWO-H ≫ PPh₃. This “meter” also detects some other possible virtues or complications of ligands such as *t*BuXPhos or *t*BuBrettPhos.

Pd-catalyzed cross-coupling reactions involve several steps, but reductive elimination is most decisive because it is typically irreversible, and is the driving force pulling forward the whole catalytic cycle.^[1] When the reductive elimination is slow, competitive side-reactions from the [PdR¹R²L₂] intermediates formed in the course of the catalytic cycle, such as homocoupling, β-hydride elimination, hydrolysis, or others, can dramatically decrease the yield of the desired R¹–R² product. Examples of challenging reductive eliminations are those forming Ar–N,^[2] Ar–O,^[3] or Ar–F bonds.^[4] The often facile C–C couplings are also difficult when they involve perfluoroaryl^[5] or perfluoroalkyl compounds (e.g. CF₃).^[6,3c]

Along the oxidation step, two electrons of the Pd⁰ atom get involved in the formation of two Pd^{II}–R bonds [Equation (1)], which is favored for electron-rich Pd centers. In the opposite sense, along the reduction process the Pd center gains electron density. It immediately follows that (for the same R¹ and R² groups involved) L dissociation, or ancillary ligands able to withdraw electron density from Pd, should favor the reductive elimination by lowering the corresponding activation barrier [Eq. (1)].



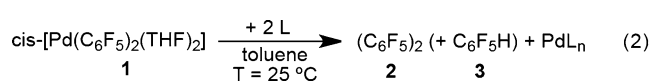
The collection of ligands in Scheme 1, available to us to check their relative ability to induce reductive elimination, model the following classes: i) weak ligands facilitating ligand dissociation to short-living tricoordinated Pd^{II} intermediates



Scheme 1. Phosphine ligands used in this work.

(THF, P(C₆F₅)₃); ii) bulky ligands providing low-energy access to tricoordinated complexes (P^tBu₃, P(*o*-Tol)₃, *t*BuXPhos, *t*BuBrettPhos, and the previously unreported *o*-TolPEWO-F); iii) ligands with electron-withdrawing potential (PhPEWO-F, *o*-TolPEWO-F, PhPEWO-H, P(C₆F₅)₃, *t*BuXPhos and *t*BuBrettPhos); and iv) large bite-angle ligands (e.g. Xantphos).

A ranking of the relative ability of ligands to induce reductive elimination should be of help for a more rational ligand choice in catalysis but it is difficult to measure this ability in the context of a running catalysis. Here we propose the use of *cis*-[PdPf₂(THF)₂] (Pf = C₆F₅) (**1**),^[7] as a “meter” on which the rates and activation energies for the process in Equation (2) can be measured directly for different ligands.



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Complex **1** is convenient for a number of reasons: i) the two Pf groups to be coupled are already in a *cis* arrangement sparing the kinetic interference of an isomerization process; ii) THF is a very weak ligand for Pd, which is displaced fast by even fairly weak ligands,^[7,8] so THF substitution by ligand in Scheme 1 can be considered instantaneous compared to reductive elimination. These two conditions are major requirements for a valid determination of the coupling rate; we tried first [PdPf₂(COD)] and found that the coupling rate was often determined by the COD displacement step and not by the coupling step itself; iii) complex **1** is conveniently easy to make, handle and store; iv) the coupling reaction is easily monitored by ¹⁹F NMR in protic toluene, where the F_o and F_p signals of **1** and **2** (also **3**) can be precisely integrated; and v) the Pf-Pf coupling rate is slow compared to conventional aryls, which facilitates kinetic studies for efficient ligands at room or not very low temperature. Higher temperature might be used if interested in ranking less efficient ligands. The reductive elimination from **1**, either spontaneous (for complex **1**) or induced by addition of the ligands in Scheme 1, was studied monitoring the rate of formation of decafluorobiphenyl (Pf-Pf, **2**). In several cases C₆F₅H (**3**) was also detected [Equation (2)]. It is formed by slow Pd-Pf hydrolysis by adventitious water in the anhydrous toluene solvent.^[9] This was confirmed using toluene saturated with D₂O for the spontaneous decomposition of **1**, which afforded a mixture of C₆F₅H and C₆F₅D (see the Supporting Information for details).

Adding PPh₃ or PMe₃ to **1** produces immediately *cis*-[PdPf₂(PR₃)₂] (R = Ph, Me),^[10] which are indefinitely stable in solution, indicating a too high coupling activation energy for measuring it at room temperature.^[11] For the rest of the ligands the results are shown in Table 1, where ΔG[‡](Pf-Pf)

Table 1: Experimental activation barriers ΔG[‡](Pf-Pf) for the reductive elimination of *cis*-[PdPf₂(THF)₂] promoted by different ligands in Scheme 1, at T = 25 °C (except for entries 1–3, at T = 0 °C), and products obtained.

Entry	Ligand	ΔG [‡] (Pf-Pf) [kcal mol ⁻¹]	Products ^[c] Pf-Pf%:Pf-H%	Time [h] ^[d]
1	PtBu ₃	20.7 ^[a]	98.0:2.0	4
2	<i>o</i> -TolPEWO-F	21.6 ^[a]	97.7:2.3	1.4
3	<i>t</i> BuXPhos	21.8 ^[a] [b]	100:0	2.6
4	P(C ₆ F ₅) ₃	22.3	95.5:4.5	8
5	PhPEWO-F	22.3	93.7:6.3	5.6
6	P(<i>o</i> -Tol) ₃	23.0	41.6:2.1	6
7	THF	23.1	48.0:7.2	8
8	<i>t</i> BuBrettPhos	23.3 ^[b]	49.0:0	8
9	Xantphos	24.2	19.1:0	8
10	PhPEWO-H	24.6	15.3:0.8	8

[a] Measurement of initial rates was performed at T = 0 °C for higher precision. [b] 3 equiv of *p*-FC₆H₄I were added. [c] In toluene, at T = 25 °C. Yields obtained by ¹⁹F NMR integration using PhCF₃ as internal standard. [d] After 8 h or times indicated when the reaction is practically finished.

values, as measured from initial reaction rates, are given. The effect of the comparatively slow competitive formation of C₆F₅H on the measurement of ΔG[‡](Pf-Pf) values is small (except perhaps for entry 7) because it hardly affects the

initial concentrations. The spontaneous coupling and hydrolysis of *cis*-[PdPf₂(THF)₂] (**1**), just discussed, serves as reference for the different ligands.

All the curves of formation of **2** are regular except for *t*BuXPhos where **2** is first formed, and then consumed during the process because the *para* C–F bond of **2** oxidatively adds to the Pd⁰(*t*BuXPhos) formed (Figure 1; see the Supporting

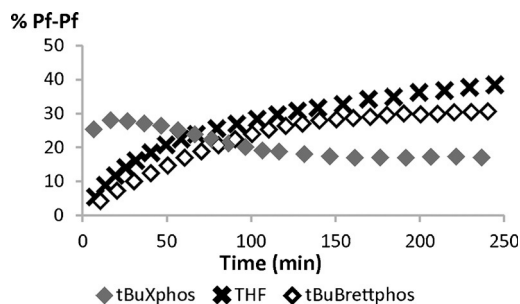


Figure 1. Percentages of Pf-Pf not adding ArI promoted by some ligands in Scheme 1. The line for THF is kept as shown in Figure 2 for reference.

Information for details). This complicates the measurement of coupling rate. Addition of *p*-FC₆H₄I prevents this effect by quickly oxidizing Pd⁰(*t*BuXPhos) to non-interfering [Pd^{II}-(C₆H₄F)I(*t*BuXPhos)], thus this additive was incorporated when required.

The evolution of formation of **2** upon addition of each of the ligands, in the conditions specified in Table 1, is regular for all of them (Figure 2). From these experiments the ligands coupling ability was quantitatively ranked by their ΔG[‡] values: P^tBu₃ > *o*-TolPEWO-F ≈ *t*BuXPhos > P(C₆F₅)₃ ≈ PhPEWO-F > P(*o*-Tol)₃ ≈ THF ≈ *t*BuBrettPhos ≫ Xantphos ≈ PhPEWO-H ≫ PPh₃.^[12]

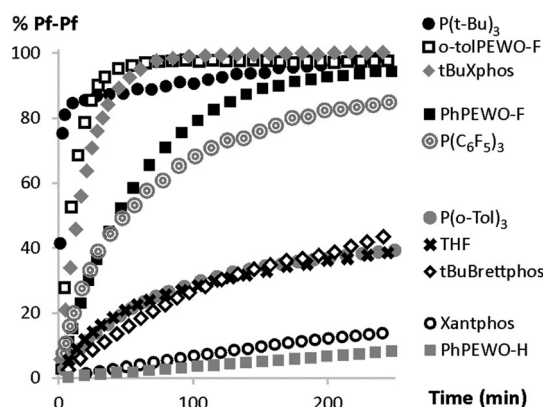
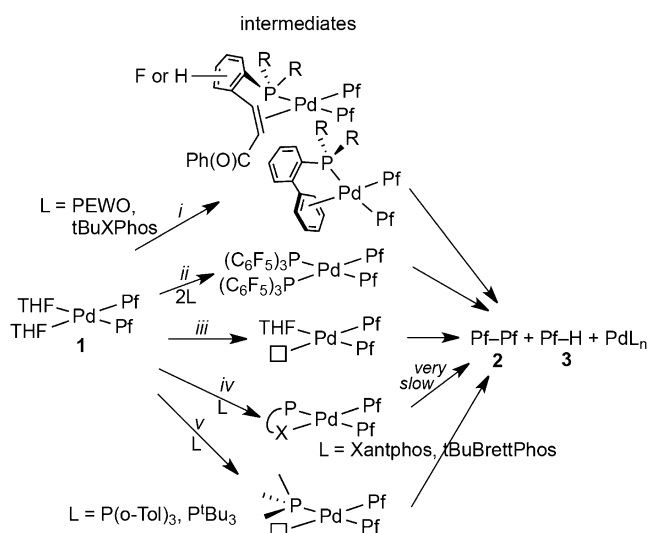


Figure 2. Percentages of Pf (relative to the starting material **1**) obtained as Pf-Pf promoted by ligands in Scheme 1. All at 25 °C, in toluene. L:1 = 2:1.

In addition to ranking their coupling ability, the results of Equation (2) uncover other interesting aspects of the behavior of the ligands. These are discussed with the help of Scheme 2, which summarizes the pathways observed to operate in the reactions **1** + 2L used to build Table 1.



Scheme 2. Reaction Pd^{II} intermediates and final products formed by reaction of **1** with the different ligands in Table 1.

First of all, the meter complex $\text{cis-}[\text{PdPf}_2(\text{THF})_2]$ (**1**), which can be easily prepared and handled in THF, decomposes slowly but spontaneously when dissolved in non-coordinating solvents: THF is poorly coordinated to Pd^{II} , and dissociates easily in the absence of external THF, probably facilitating coupling from a tricoordinated $\text{cis-}[\text{PdPf}_2(\text{THF})]$ (Scheme 2, pathway iii).^[1] Concomitant hydrolysis from adventitious $\text{cis-}[\text{PdPf}_2(\text{THF})(\text{OH}_2)]$ molecules compete with Pf-Pf coupling, more favorably in this case than in any of the others according to Table 1. Since the reductive elimination has a moderate rate and the presence of molecules with coordinated water (more acidic) is more abundant than in the other entries of Table 1 because water competes with THF, spontaneous decomposition of **1** affords the highest PfH proportion (Pf-Pf: Pf-H = 48:7.2).

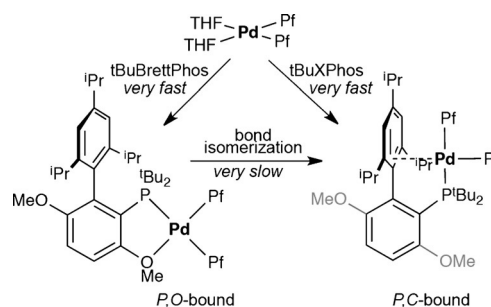
For Xantphos the coupling rate is one of the slowest, but no PfH is detected. The immediately formed $\text{cis-}[\text{PdPf}_2(\text{Xantphos})]$ (Scheme 2, path iv), which gives reductive elimination only very slowly, also prevents thermodynamically coordination of any OH_2 , thus blocking formation of PfH. Although the facilitation of reductive elimination processes by Xantphos at 80 °C is well established,^[6a,b] this ligand cannot deal with the Pf-Pf coupling at room temperature, showing that our coupling-meter complex is a very demanding one for the ligands.^[13]

Very interestingly, the two phosphines P^tBu_3 and $\text{P}(\text{C}_6\text{F}_5)_3$ are quite efficient for coupling (Scheme 2, paths v and ii), in spite of being electronically very different, although slower coupling and higher percentage of PfH is observed for the latter. They represent the two possible and apparently contradictory models that favor coupling by reducing the activation energy: a) bulky and strongly σ donor ligands that make tricoordinated structures accessible by rising the ground state energy for four-coordination;^[14] and b) poorly σ -donor but strongly π -acceptor ligands that stabilize the TS by minimizing electronic repulsions in the evolution towards Pd^0 .^[1] In contrast to the good donor P^tBu_3 , $\text{P}(\text{C}_6\text{F}_5)_3$ is a poor

σ -donor ligand (hence a weak ligand for Pd^{II} , although strong π^* -acceptor from Pd^0 at the σ^* P-C orbitals), so that $\text{cis-}[\text{PdPf}_2(\text{PR}_3)_2]$ ($\text{R} = \text{C}_6\text{F}_5$) easily dissociates phosphine. Assuming that PhH is formed in both cases from $\text{cis-}[\text{PdPf}_2(\text{PR}_3)(\text{OH}_2)]$ complexes (entries 1 and 4), the acidity of the coordinated OH_2 in the complex, as well as the percentage of these molecules in solution, should be higher and more efficient towards hydrolysis for $\text{P}(\text{C}_6\text{F}_5)_3$. $\text{P}(\text{o-Tol})_3$ (Scheme 2, path v), less donor and less bulky than P^tBu_3 , and also much less acceptor than $\text{P}(\text{C}_6\text{F}_5)_3$, affords slower coupling rate than the other two, and more hydrolysis than P^tBu_3 .

Overall the formation of PfH is clearly more efficient in complexes with a strongly withdrawing olefin (*o*-TolPEWO-F, 2.3 % PfH in 1.4 h; PhPEWO-F 6.3 % PfH in 5.6 h; Table 1, entries 2 and 5), than in PhPEWO-H with a less π -acceptor olefin fragment (entry 10, 0.8 % PfH in 8 h). However, this inconvenience is compensated by their higher coupling rates, which lead to better Pf-Pf/PfH ratios in the order *o*-TolPEWO-F > PhPEWO-F > PhPEWO-H. Interestingly PhPEWO-F and PhPEWO-H have practically identical size and their remarkably different behavior highlights the enormous effect of the fluorinated aryl ring on the π -acceptor effect of the PEWO-F olefinic fragment. On the other hand, *o*-TolPEWO-F and PhPEWO-F (Scheme 2, path i) share an identical π -acceptor moiety but have PR_2 fragments of very different size. Consistently, the one with larger substituents (*o*-TolPEWO-F) shows a remarkably faster coupling rate.

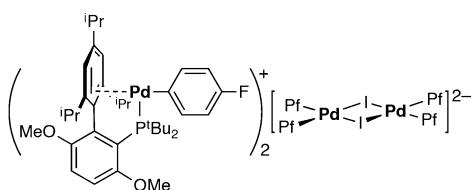
Quite unexpectedly, considering its structural similarity with *t*BuXPhos, *t*BuBrettPhos proved to be inefficient for coupling. At variance with *t*BuXPhos, the course of formation of **2** with *t*BuBrettphos in Figure 1 is quite regular but slow, and using *p*-FCH₃I the profile changes only slightly at later stages of the reaction (Figure 2). This points clearly to a different cause of the problem, which can be traced to the existence of two possible bond isomers for *t*BuBrettphos: P,O-bound and P,C-bound (Scheme 3). In fact a very similar P,O-



Scheme 3. Different coordination behavior of *t*BuXPhos and *t*BuBrettPhos.

bound complex was found by X-ray diffraction for $[\text{Pd}(\text{C}_6\text{H}_4\text{-CO}_2\text{Me-}p)(\text{CF}_3)(\text{CyBrettPhos})]$, having (determined by DFT calculations) an activation energy towards reductive elimination of $\text{F}_3\text{C-C}_6\text{H}_4\text{CO}_2\text{Me-}p$ about 5 kcal mol⁻¹ higher than its putative P,C-bound isomer.^[6c]

The NMR spectra of the PdPf_2 complexes are intrinsically very complex, providing limited structural information, but the kinetic behavior observed strongly suggests that: i) the highly efficient $t\text{BuXPhos}$ complex (lacking O atoms) must be P,C-bound; ii) the isomer formed with $t\text{BuBrettPhos}$ in Scheme 3 is the P,O-bound isomer, from which reductive elimination is occurring slowly; iii) P,O-bound to P,C-bound isomerization does not occur after long time at room temperature, or it would provoke a sharp increase in coupling rate that is not observed; iv) the $\text{Pd}^0(t\text{BuBrettPhos})$ complex formed upon reduction at room temperature probably remains P,O-bound since, in contrast with $\text{Pd}^0(t\text{BuXPhos})$, it is not able to activate C–F oxidation of the decafluorobiphenyl; and v) P,O-bound to P,C-bound isomerization occurs only upon oxidation with $p\text{-IC}_6\text{H}_4\text{F}$, as supported by the cation X-ray structure of $[\text{Pd}(\text{C}_6\text{H}_4\text{F})(t\text{BuBrettPhos})]_2[(\mu\text{-I})_2(\text{PdPf}_2)_2]$ (**4**; see Scheme 4 and Figure S2 in the Supporting



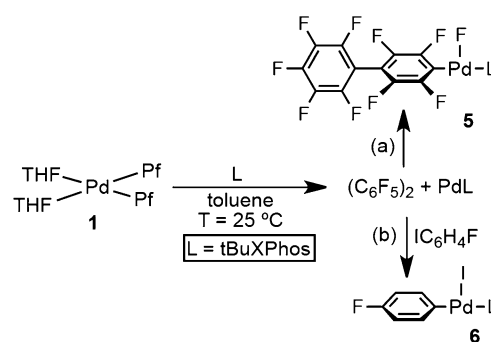
Scheme 4. Cation and anion structures of the ionic complex $[\text{Pd}(\text{C}_6\text{H}_4\text{F})(t\text{BuBrettPhos})]_2[(\mu\text{-I})_2(\text{PdPf}_2)_2]$ (**4**). See X-ray diffraction structure in the Supporting Information.

Information), which was crystallized from the mother liquors of the reaction in entry 8 of Figure 1. Formation of the anion of **4** from **1** and the bulky iodide, which does not fit on the crowded cation, consumes half of the initial meter reagent **1**, frustrating further coupling.

Concerning the absence of PfH in reactions with the ligands $t\text{BuXPhos}$ and $t\text{BuBrettPhos}$, this result suggests that the former prevents coordination of water to the P,C-bound species more efficiently than any of the other ligands helped by steric hindrance and aryl coordination, while the later, acting as P,O-chelate, does not offer an available coordination position to water (a case similar to the P,P-chelate Xantphos).

Overall, particularly considering the undesired competing hydrolysis, the efficiency for coupling may be ranked $t\text{BuXPhos} \approx \text{P}^t\text{Bu}_3 \approx o\text{-TolPEWO-F} > \text{PhPEWO-F} > \text{P}(\text{C}_6\text{F}_5)_3 \gg t\text{BuBrettPhos} > \text{THF} \approx \text{P}(o\text{-Tol})_3 > \text{Xantphos} > \text{PhPEWO-H} \gg \text{PPh}_3$. Obviously this preference should not be generalized to the whole catalytic cycle because other steps can be rate determining or fail; to mention just an obvious case, THF would not keep the catalyst alive through the Pd^0 stage.

The behavior of complex **1** as precursor of PdL_n deserves further comment. Complex **1** reacts with one molar equivalent of $\text{L} = t\text{BuXPhos}$ leading to PdL , decafluorobiphenyl and THF. As shown in Scheme 5, the reactivity of the Pd^0 complex is such that it is oxidized by the decafluorobiphenyl (usually fairly inert) to give complex **5** (pathway a). This reaction is prevented in the presence of a better oxidant ArX ($\text{IC}_6\text{H}_4\text{F}$) to give **6** (pathway b). The latter reaction shows that



Scheme 5. Synthetic potential of complex **1** as a precursor of the Pd^0L catalyst.

complex **1** offers an interesting alternative to commercial Buchwald's precatalysts to form PdL , avoiding the use of base and formation of indazole or carbazole byproducts,^[15,16] and to $\text{Pd}_2(\text{dba})_3$, or $\text{Pd}(\text{CH}_2\text{TMS})_2(\text{COD})$,⁴ avoiding the presence of dibenzilidenacetone (dba), or 1,5-cyclooctadiene (COD) in the PdL solution. As a matter of fact, **1** can be a general precursor of PdL with other ligands (as far as they promote coupling of **1**), and we are exploring this reactivity.

In conclusion, complex $\text{cis-}[\text{PdPf}_2(\text{THF})_2]$ (**1**) is a convenient touchstone that only requires the time of monitoring the formation of the coupling product Pf-Pf (**2**) to have quick information on old or newly synthesized ligands. Our protocol is useful to measure and rank experimentally the ability of ligands to promote electronically difficult couplings, isolated from other processes or steps. Moreover, the hydrolysis product **3** informs of the rate of this competitive unwanted process. In addition, our system happens to detect some side reactions with useful meaning: In the case of $t\text{BuXPhos}$, the consumption of **2** reports on the extremely good performance of this ligand in the oxidative addition step. On the other hand, the initially deceptive data of $t\text{BuBrettPhos}$ suggest to use it on a Pd^0 and not on a Pd^{II} catalyst precursor, in order to get the more active P,C-isomer from the beginning. This preference is shown in the coupling reaction experiment in the presence of $p\text{-F}(\text{C}_6\text{H}_4\text{I})$, which yields the P,C-bound isomer of **4** from $[\text{Pd}^0(t\text{BuBrettPhos})]$.

The scale of relative $\Delta G^\ddagger(\text{Pf-Pf})$ values, to which other ligands may be incorporated in the future, can help for a more precise understanding of the phenomena associated to difficult couplings. It is not unreasonable that the ligand trend observed with this meter could approximately stand for other kinds of difficult coupling rates, or for easier homo- or hetero-couplings not measurable because they are too fast.

The new ligands $o\text{-TolPEWO-F}$ and PhPEWO-F , which do not suffer easy air oxidation, are much faster than PhPEWO-H , and the former is as fast for the coupling step as the excellent $t\text{BuXPhos}$ or the pyrophoric P^tBu_3 . Other members of the PEWO-F family are being developed. However, it is $t\text{BuXPhos}$ the one that combines best a fast coupling performance with an extraordinary capability to give reoxidative addition with difficult ArX electrophiles.

Crystallographic data for CCDC 1495038 (complex **4**) can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgements

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Keywords: cross-coupling mechanisms · homogeneous catalysis · palladium catalysis · phosphines · reductive elimination

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- [11] *cis*-[PdPf₂(PPh₃)₂] gives rise to a *cis/trans* equilibrium but does not produce reductive elimination at room temperature.
- [12] Note that $\Delta G^\ddagger(\text{Pd-Pf})$ for the first three ligands in the list was determined at 0 °C and for the others at 25 °C.
- [13] The C₆F₅ group is quite electronegative and produces strong Pd–C₆F₅ bonds, increasing a barrier already high for chelating ligands. See: S.-L. Zhang, L. Huang, L.-J. Sun, *Dalton Trans.* **2015**, 44, 4613–4622.
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