E-Z Isomerization of Phosphine-olefin (PEWO-F_4) Ligands Revealed upon $PdCl_2$-Capture: Facts and Mechanism.

Marconi N. Peñas-Defrutos, Andrea Vélez, Estefanía Gioria, and Pablo Espinet*

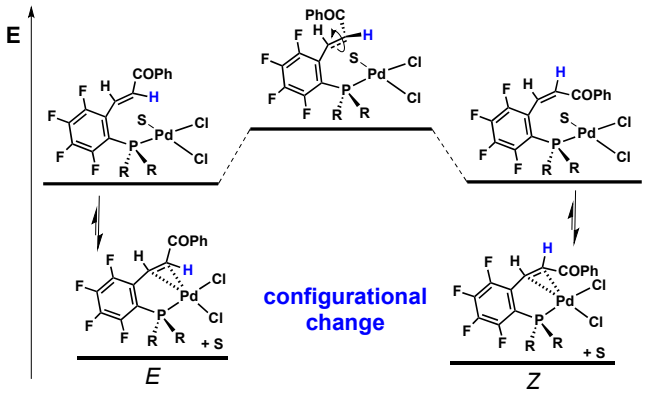
IU CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47071-Valladolid (Spain) Fax: (+)34 983 423013

E-mail: espinet@qi.uva.es

Keywords: phosphine-olefin ligand, hybrid phosphine, electron deficient olefin, palladium, chalcones, configurational change, mechanism.

Supporting Information Placeholder

ABSTRACT: The PEWO phosphines $R_2P(o\text{-}C_6H_4CH{=}CHC(O)Ph)$, $R_2P(o\text{-}C_6H_2F_2CH{=}CHC(O)Ph)$, and $R_2P(o\text{-}C_6F_4CH{=}CHC(O)Ph)$, as well as their P-monodentate complexes *trans*-$[PdCl_2(P\text{-monodentate})_2]$ show, in solution and (when available) in the X-ray diffraction structures, *E*-configuration of the double bond. In contrast, the structures of $[PdCl_2(P\text{-chelate})]$ display *E*- and Z-configuration. The *E/Z* isomerization of the later requires first decoordination on the double bond, which then allows for easy rotation about the electron-deficient double bond. Thus, the *E/Z* equilibria exist for the free and the P-monodentate complexes as well, but are not observed because they are extremely displaced towards the *E*-isomer. Their capture in the form of $[PdCl_2(P\text{-chelate})]$, with equilibrium constants in the order $K_{eq} \approx$ 1-3 allows the two configurations to be observed and isolated. Evaluation of their ability to couple Pf–Pf from *cis*-$[PdPf_2(THF)_2]$ (Pf = C_6F_5) affords values of their $\Delta G^{\ddagger}(Pf\text{–}Pf)_{Pd}$ parameters confirming that higher substitution of H by F produces lower coupling barriers, and a double bond more electron-deficient when free and more electron-withdrawing when coordinated.



INTRODUCTION

Since the recognition of Pd-catalyzed reactions with the Nobel award to Heck, Suzuki and Negishi in 2010, a main concern in organic and organometallic chemistry is the development and control of new challenging C–E (E = C, N, O) cross coupling reactions. Ligand design is a crucial tool to improve the performance of most catalytic transformations. For example, hemilabile chelating ligands were studied because of their useful versatility of create or occupy coordinative vacancies.[1] Later on, the extraordinary performance of bulky phosphines such as P^tBu_3 or PR_2(biaryl) phosphines has lead Pd catalytic cycles to previously unforeseen efficiency.[2]

It is well known that electron-withdrawing olefins (EWO) are able to dramatically diminish in Pd^{II} complexes the activation barrier to reductive elimination (RE), which in many catalytic transformations constitutes the rate-limiting step.[3] Combining a phosphine with an electron withdrawing olefin in the same molecule produces PEWO ligands that facilitate coordination of the EWO to Pd by the entropy favored chelate effect. The good results reported by group of Lei and others using the ligand PhPEWO-H_4, shown in Figure 1A,[4,5] for Negishi catalysis, led our group to explore fluorinated analogues RPEWO-F_4 (Figure 1B) because the presence of four F atoms should make the double bond more electron attractor and consequently should further lower the RE barrier compared to PhPEWO-H_4. The palladium complexes with PhPEWO-F_4 turned out to be also excellent catalysts in Neghisi type aryl–alkyl couplings. Moreover, the use of ^{19}F NMR spectroscopy facilitated mechanistic studies on the real origin of "reduction" product Ar–H instead of Ar–alkyl, which is not β-H elimination from the alkyl as previously believed.[6]

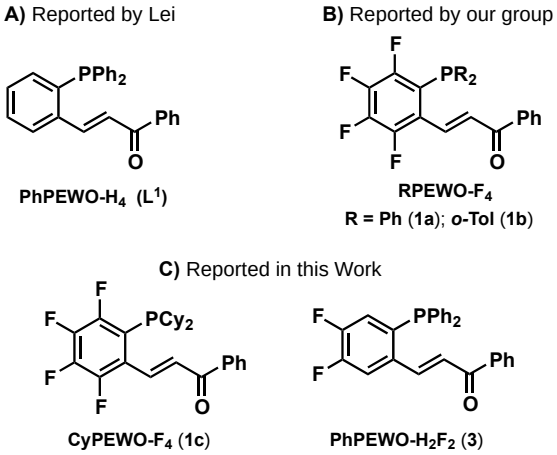


Figure 1. PEWO ligands

Ranking the relative ability of ligands to reduce the C–C coupling barrier on Pd^{II} can be made by measuring $\Delta G^{\ddagger}(Pf\text{–}Pf)_{Pd}$ upon addition of the quested ligand to *cis*-$[PdPf_2(THF)_2]$ (Pf = C_6F_5).[7] Tetrafluorinated RPEWO-F_4 ligands are able to promote the difficult homocoupling of two cis C_6F_5 moieties on Pd nearly as fast as the extremely bulky ligand P^tBu_3, or some of the most used biaryl phosphines, such as ^{t}BuXphos,[8] which are usually considered to behave as functionally three-

coordinate species.[9] PhPEWO-H_4 ligands do much worse than all the previously mentioned.

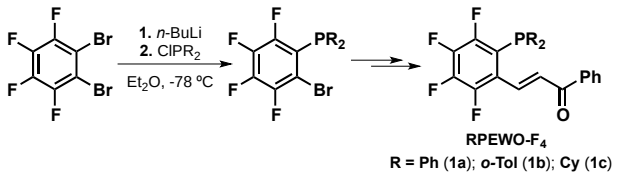
The weak point of these PEWO ligands (which has been explained in detail for related P-olefin hybrid ligands) is the deep stabilization of the Pd^0 species formed in the reductive elimination.[10] This increases the activation barrier of the subsequent oxidative addition. Making the phosphine PR_2 moiety a better donor, should lead to a Pd^0(RPEWO-F_4) center easier to oxidize, while the EWO-F_4 moiety will still keep on easing the reductive elimination. Alternatively, diminishing the electron acceptor power of the EWO moiety might provide a more convenient coupling/reoxidation trade off. In order to test these ideas, we decided to prepare two new fluorinated PEWO ligands CyPEWO-F_4 (**1c**) and PhPEWO-H_2F_2 (**3**) (shown in Figure 1C) for evaluation of their $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$ parameter.

The electron withdrawing olefins in Figure 1 are all drawn with *E* configuration, which is the one observed for the free PEWO phosphines of this work in chloroform or dichloromethane solution, and in their X-ray diffraction structures reported here, but this configuration may not necessarily be maintained in the different species along a catalytic cycle. In fact, very little is known about this circumstance and its effect on the energy of intermediates or transition states in the cicle. The study of their complexes with $PdCl_2$, which are in practice synthesized *in situ* as precatalysts, allows us to achieve some knowledge about *E* versus Z complexes.

RESULTS

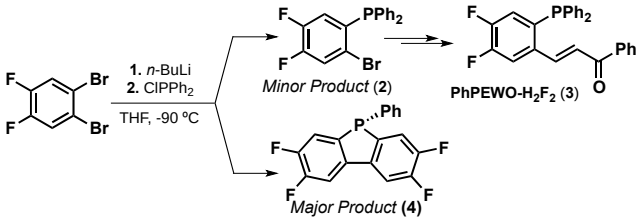
Synthesis of new PEWO ligands. Using the methodology previously developed in our group to obtain the tetrafluorinated ligands PhPEWO-F_4 (**1a**) and *o*-TolPEWO-F_4 (**1b**) from 1,2-$Br_2C_6F_4$ in three steps (Scheme 1, and SI for full details),[6] the homologous CyPEWO-F_4 (**1c**) was prepared in 50% overall yield (Scheme 1). In spite of the presence of two alkyl groups in **1c**, the wide C–P–C angles they force and the fluorination of the aryl substituent contribute to stabilize the phosphorus atom against oxidation, so that this phosphine, as **1a,b**, is perfectly stable to air and moisture for days.

Scheme 1. Synthesis of phosphines **1a-c**



Whereas the selective lithiation of one of the two C–Br bonds and subsequent reaction with the corresponding $ClPR_2$ is very efficient on *o*-$C_6Br_2F_4$, with 1,2-dibromo-4,5-difluorobenzene different reaction conditions are needed (THF at –90 ºC) in order to obtain the bromo-PPh_2 derivative **2** (Scheme 2). Even in these conditions, **2** is the minor product of the reaction and is isolated in about 20% yield. Luckily, the next two synthetic steps to produce PhPEWO-H_2F_2 (**3**) are high yield, and **3** was prepared with only modest further yield loss. The mayor product of the first reaction step with 1,2-dibromo-4,5-difluorobenzene is the fluorinated phosphine **4**, formed by an undesired C–C coupling. Phosphines **2** and **4** can be efficiently separated after the first reaction step using column chromatography. Both are unreported in the literature (the non-fluorinated homologous of **4** is commercial).[11] Phosphine **4** is not used in this work except for its evaluation towards Pf–Pf coupling induction in *cis*-[$PdPf_2(THF)_2$], but full details of its characterization and its X-Ray structure are given in the Supporting Information.

Scheme 2. Synthesis of phosphines **2**-**4**.



The two new PEWO ligands, **1c** and **3**, have *E* configuration for the C=C moiety in $CDCl_3$ solution, as supported by the value of the coupling constants observed in their ^{1}H NMR spectra ($^3J_{H\text{-}H} \approx 15$ Hz). Moreover, the two ligands display also *E* configuration in their X-Ray structures. In fact for all the four free PEWO ligands used in this work (**1a-c** and **3)** only *E* configuration is observed by ^{19}F and ^{1}H NMR. In our previous works and here, the *Z* configuration has never been detected when the olefin substituent is the group C(O)Ph. During our work with P-olefin ligands, only in one occasion (for the equivalent to **1a** but with Me instead of C(O)Ph), an *E*:*Z* mixture was obtained.[6a] In that case the two configurational isomers could be separated chromatographically and did not interconvert in solution at 25 °C, suggesting that their isomerization barrier as free olefins was reasonably high.

Determination of $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$ for the new ligands.

Ligands **1c**, **3**, and **4** were submitted to the reported protocol to determine their $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$ by measuring the rate of formation of Pf–Pf upon addition of the ligand (2 eqs.) to *cis*-[$PdPf_2(THF)_2$] in toluene (Figure 2).[7]

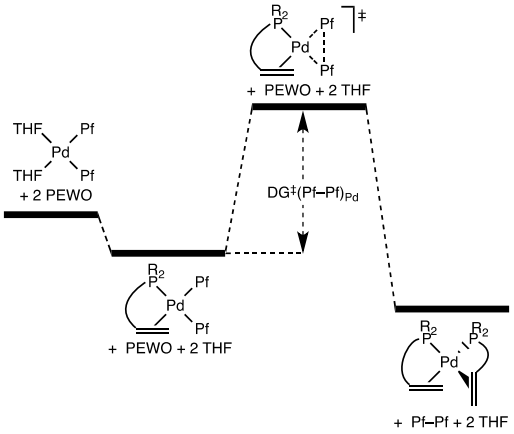


Figure 2. The procedure for measuring $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$, illustrated for the case of PEWO Ligands. For explanation of the PEWO acronyms in the text see reference 12.

The reaction of CyPEWO-F_4 (**1c**) with *cis*-[$PdPf_2(THF)_2$] in toluene is not simple. As in the case of **1a-b**,[7] **1c** also produces

a fast reaction at room temperature, which is better monitored at 0 °C. In addition to the expected Pf–Pf (which is formed in 30% yield) and PfH (in 3% yield), other products are formed. Formation of Pf–Pf, which can be cleanly monitored in the ^{19}F NMR spectra to measure the initial rate of formation, is accompanied by appearance of an unidentified product at higher rate, and by other less defined and less abundant products. The fact that the starting *cis*-[$PdPf_2(THF)_2$] is being competitively consumed by other processes, affects negatively the rate of formation of Pf–Pf, so that the k_{obs} is not a true rate constant. Since the other processes are consuming competitively about 2/3 of the *cis*-[$PdPf_2(THF)_2$], the real rate constant of the coupling induced by **1c** is in fact higher by a factor of almost 3 (see Figure S3 and comments in SI). All this considered, a reasonable estimation for **1c** would be $\Delta G^{\ddagger}(Pf–Pf)_{Pd} \leq 21.5$ kcal.mol^{-1}.

The reaction with **4** at 25 °C did not induce coupling and produced a *cis*- *trans*-[$PdPf_2$(**4**)$_2$] mixture, as expected. In contrast ligand **3** induced efficient coupling (with only 3% hydrolysis) at a slower rate than previously reported for **1a-b**, according to its higher $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$ = 23.7 kcal.mol^{-1} at 25 °C. The Pd^0 complex [Pd(**3-chel**)$_2$] (**5**), resulting from Pf–Pf coupling, was isolated and fully identified. Its X-ray structure is shown in Figure 3. The two ligands are coordinated as P-olefin chelate and the coordinated olefin displays clearly *E* configuration.

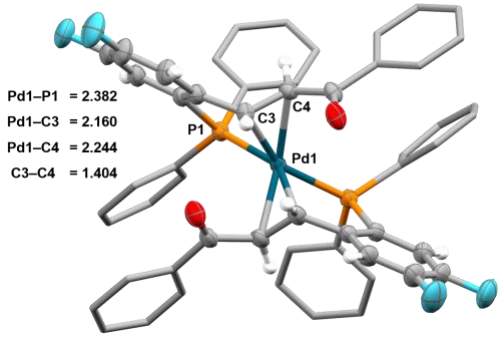


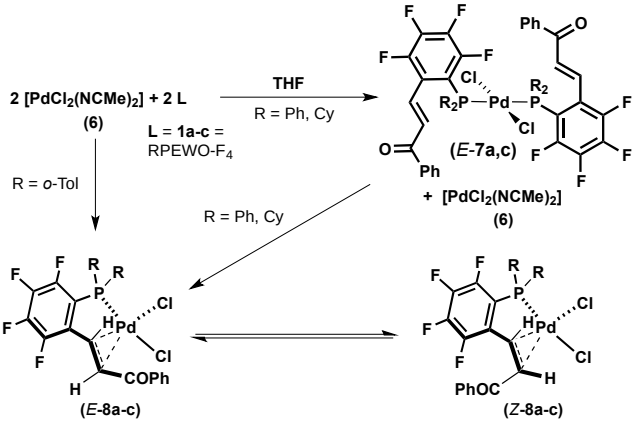
Figure 3. X-Ray structure of [Pd^0(*E*-**3-chel**)$_2$] (**5**). Bond distances in Å.

Comparing the $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$ values for PEWO ligands available so far, they decrease in the order PhPEWO-H_4 > PhPEWO-H_2F_2 > any PhPEWO-F_4 confirming that the ligand ability to accept back-donation towards the π* empty orbital of the coordinated olefin, when the back-donation from Pd increases as Pd evolves from Pd^{II} to Pd^0, is critical to facilitate a more accessible coupling barrier. In this respect the high degree of fluorination of the aryl bearing the P atom, and the presence of the CO substituent at the other side of the olefin, play an important role to make the olefin strongly electron withdrawing.

The protocol to measure $\Delta G^{\ddagger}(Pf–Pf)_{Pd}$, not only is able to identify ligands efficient to produce fast coupling. Additionally, as in the case of **1c**, it is able to detect undesired complications. Obviously, the use in catalysis of ligands misbehaving at the coupling step should be taken with caution.

*Reaction of PEWO ligands with [$PdCl_2(NCMe)_2$] (**6**). Effect of coordination of RPEWO-F_n **1a-c** (n = 4) and **3** (n = 2) to $PdCl_2$.*[12] Our catalytic studies using PhPEWO-F_4 (**1a**) suggest that, since the final reductive elimination occurs from a [PdR^1R^2(PEWO-chel)] chelate complex, a Pd:L = 1:1 ratio is convenient.[6] This ratio can be achieved preparing, independently or *in situ*, the [$PdCl_2$(PEWO-chel)] precatalyst from PEWO and [$PdCl_2(NCMe)_2$] (**6**) in 1:1 ratio. In the case of **1a** we had already reported the formation of the complex *via* a trans-[$PdCl_2${*E*-(PhPEWO-F_4)}$_2$] (**7a**) intermediate where the ligand is acting as P-monodentate (Scheme 3),[6a] and the crystal structure of [$PdCl_2${*Z*-(PhPEWO-F_4-chel)}] (*Z*-**8a**) was solved.

Scheme 3. Synthesis of PEWO chelating $PdCl_2$ complexes.



The reaction of **1a** was revisited at 243K for this paper at (Figure 4), and we could detect additionally intermediate *E*-**8a** (not reported in our original paper) and confirm the sequence **7a**/*E*-**8a**/*Z*-**8a** shown in Scheme 3.

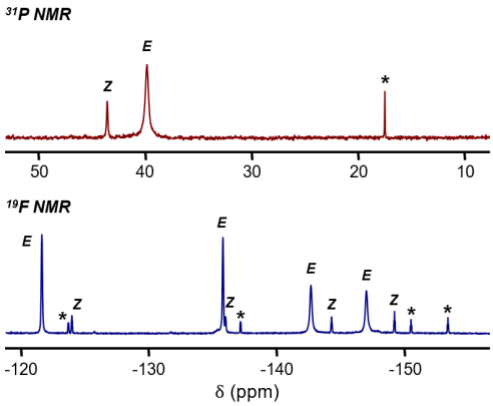


Figure 4. ^{19}F and ^{31}P spectra of a mixture in evolution from *E*-**7a**/*E*-**8a** to *Z*-**8a** at 243 K in CD_2Cl_2 (asterisk is **7a**).

For *o*-TolPEWO-F_4 (**1b**), the corresponding intermediate **7b** could not be observed. Maybe it is not formed because of the bulkiness of the *o*-Tol group compared to Ph in the neighborhood of the coordination plane.[13] The reaction lead to a mixture of the *Z*-**8b** and *E*-**8b** products at 298 K. Working at lower temperature in a more controlled manner (details in SI) the kinetic product [$PdCl_2${*E*-(*o*-TolPEWO-F_4)}] (*E*-**8b**) was first formed. Complex *E*-**8b** evolves in chloroform or

dichloromethane solution to reach equilibrium of the two isomers. The two configurational isomers could be crystallized for X-Ray diffraction studies, and Figure 5 collects their molecular structures. Both structures display a square-planar geometry around the Pd^{II} atom, with the olefin bond located roughly perpendicular to the coordination plane. The Pd–$C_{olefinic}$ bond distances lay in a very short range 2.184–2.217 Å. Note that the C3–C4 distances are almost identical for the two configurations.

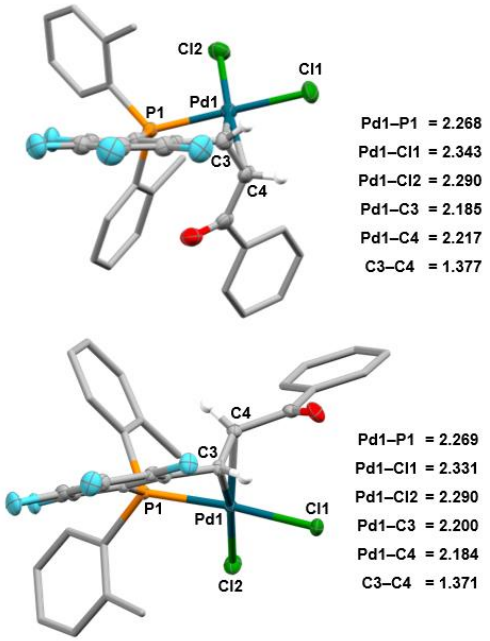


Figure 5. X-Ray structures of *Z*-**8b** (above) and *E*-**8b** (below) respectively, with selected distances in Å. *o*-Tol and Ph groups are in capped sticks. Crystallization solvent molecules and hydrogen atoms (except olefin ones) omitted for clarity.

The evolution of the reaction of $[PdCl_2(NCMe)_2]$ (**6**) and CyPEWO-F_4 (**1c**) seems to follow essentially the same steps as **1a**, but with a faster rate. ^{19}F and ^{31}P NMR monitoring reveals the presence of mixtures containing predominantly $[PdCl_2\{E\text{-}(CyPEWO\text{-}F_4)\}]$ (*E*-**8c**) and the formation of $[PdCl_2\{Z\text{-}(CyPEWO\text{-}F_4)\}]$ (*Z*-**8c**), which in turn evolves very quickly in THF solution to unidentified products. Total consumption of **8c** was observed in 30 minutes at room temperature, which prevented isolation for X-ray characterization of any of these two observed configurational isomers.

PhPEWO-H_2F_2 (**3**) shows interesting differences with the tetrafluorinated analogues. The presence of *trans*-$[PdCl_2(\mathbf{3})_2]$ as intermediate could be confirmed by ^1H, ^{19}F, and ^{31}P NMR monitoring of the reaction. Attempts at obtaining and purifying the putative complex $[PdCl_2\{E\text{-}(PhPEWO\text{-}H_2F_2)\}]$ (*E*-**9**) were unsuccessful. The coordinated olefin shows a dissociation equilibrium towards formation of a less soluble dimer $(\mu\text{-}Cl)_2[PdCl(E\text{-}PhPEWO\text{-}H_2F_2)]_2$ (*E*-**10**). In fact, crystallization for X-ray diffraction by slow evaporation of a $CHCl_3$ solution of the reaction solution produced a mixture of yellow *Z*-**9** and orange *E*-**10** crystals in approximately 1:2 ratio.

Figure 6 displays the X-Ray structures of complexes Z-**9** and *E*-**10**. The configuration of the olefin and the length of the (C3–C4) bond differ in the two isomers. For the chelated *Z*-**9**, the structure and relevant distances, including C3–C4, are very similar to *Z*-**8b**, but in the P-monodentate *E*-**10** dimer the C3–C4 is considerably shorter (1.304 Å) than in *Z*-**9** (1.381 Å) and almost identical to the value observed in the structure of the free ligand **3** (Scheme 2). This was expected, as olefin coordination is known to weaken the C–C bond.

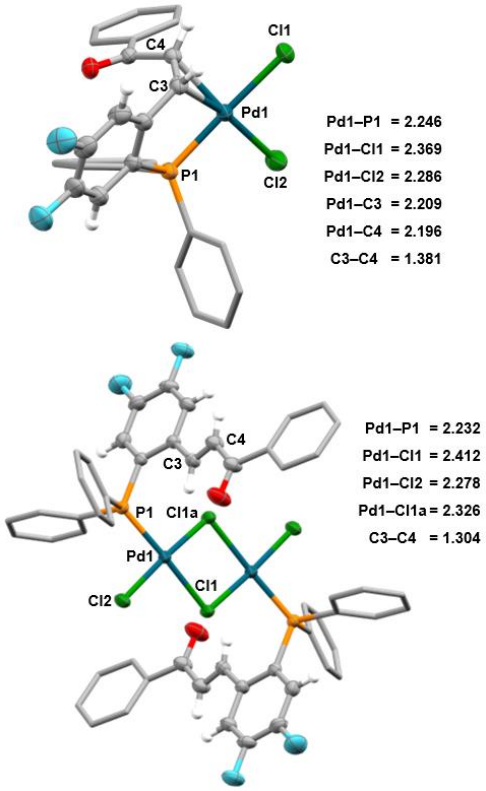


Figure 6. Molecular structures of *Z*-**9** (above) and *E*-**10** (below), Bond distances in Å. For *E*-**10**, only one of the two slightly different molecules making part of the asymmetric unit is shown. Ph groups are in capped sticks and crystal solvent molecules have been omitted for clarity.

Comparing the cases of PhPEWO-F_4 (**1a**), PhPEWO-H_2F_2 (**3**), and PhPEWO-H_4 (**L**^{1}), the strength of the olefin-Pd interaction is progressively weaker the lower the number of F atoms in the 1.2-substituted aryl: PhPEWO-F_4 (**1a**) produces only the chelated complex with $PdCl_2$, PhPEWO-H_4 (**L**^{1}) only the P-monodentate dimer, and PhPEWO-H_2F_2 (**3**) a mixture of the two isomers in equilibrium.

DISCUSSION

The data discussed above show that all the free PEWO olefins display *E*-configuration. They initially P-coordinate to $PdCl_2$ giving complexes also with *E*-configuration. Finally, we find *E- and Z*-configurations in the chelate complexes of Pd^{II}, and *E*-configuration in the Pd^0 complex. The *E* configuration is expected to be the most stable one for the free olefins, as found for instance for the closely related structures of chalcone derivatives, and in most 1,2-substituted olefins.[14] It is

indeed the only one observed in solution. The P-bonded Pd^{II} complexes with the olefin non-coordinated (**7a,c**), also display *E*-configurations supporting that this is their more stable configuration. However, the non-observation of the Z-configuration in these compounds does not mean anything about their existence in very unequal equilibria, or their possible isomerization barrier.

It is only when the PEWO phosphines get coordinated to Pd as chelate ligands, that both *E*- and/or Z-configurations are observed unambiguously. Since *E*-**8b** is available as isolated product, the evolution of one or the other in $CDCl_3$ or CD_2Cl_2 solution could be monitored. Starting from *E*-**8b** the equilibrium with *Z*-**8b** in $CDCl_3$ at 298 K is reached in much less than 24 h. This is shown in Figure 7, which displays the progressive appearance of the signals of the two non-equivalent Me groups of the two *o*-Tol groups in *Z*-**8b**, at the expense of the Me groups in *E*-**8b**. A similar behavior is observed in CD_2Cl_2, obviously with a different equilibrium constant. Note that the observation of isomerization with the NMR tube under monitoring in the probe (that is in the dark) excludes photo-mediation as the isomerization mechanism.

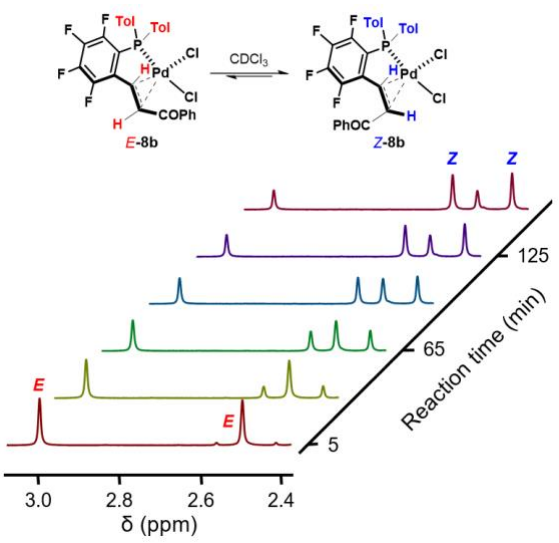


Figure 7. ^{1}H RMN monitoring of the isomerization of ***E*-8b** to ***Z*-8b**, in $CDCl_3$ at 298 K.

The NMR observation of the two sides of an established equilibrium is only possible when the energy difference of the species at the two sides (ΔG) is small enough. The equilibrium constant in $CDCl_3$, $K_{E\text{-}to\text{-}Z}$ = 3.35 corresponds to ΔG = 0.72 kcal.mol^{-1}, isomer *Z* being more stable. In the somewhat more polar CD_2Cl_2, $K_{E\text{-}to\text{-}Z}$ = 1.22 corresponds to ΔG = 0.12 kcal.mol^{-1}, isomer *Z* being again more stable (Table 1).[15] These data were not determined for the other PEWO ligands, but their experimental observations and the crystallization of the two configurational isomers in more cases strongly suggest that, although influenced by the R substituents of each RPEWO and by the solvent, the energy difference between *E* and *Z* configurations in their chelated Pd-complexes is small.

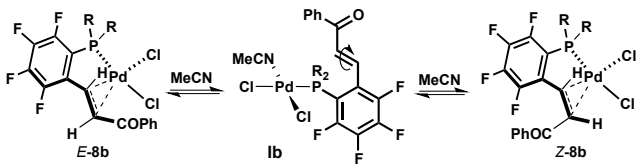
Table 1: Equilibrium concentrations and rate constants for isomerization of *E*-**8b** to *Z*-**8b**. Polarity $E_T(30)$: 39.1 for $CHCl_3$; 40.7 for CH_2Cl_2. [16]

Solvent[a]	Additive	*E*:*Z*	K_{eq}	ΔG[b]	k_{obs}[c]
$CDCl_3$	-	23:77	3.35	–0.72	8.0×10^{-5}
$CDCl_3$	MeCN				2.2×10^{-4}
CD_2Cl_2	-	45:55	1.22	–0.12	3.5×10^{-5}
CD_2Cl_2	MeCN				2.2×10^{-4}

[a] Details in SI. [b] In kcal·mol^{-1}. [c] In s^{-1}.

Examination of the X-ray diffraction structures supports that the *E*/*Z* isomerization of the double bond cannot take place unless previous decoordination of the double bond occurs, which means that it takes place on an unobserved [$PdCl_2$(P-monodentate)(S)] complex.[17] All this is consistent with the fact that kinetically the isomerization rate is order one in Pd concentration (Figure S7), hence the evolution to the isomerization transition states starts on a monomer. Moreover, addition of a large overstoichiometric amount of MeCN accelerates very significantly the isomerization rate (compare k_{obs} values in Table 1), which now should be taking place at an unobservable [$PdCl_2$(P-monodentate)(NCMe)] (**Ib**) species, also in undetectable concentration. These observations support the configurational isomerization mechanism shown in Scheme 4 for the case of acetonitrile as additive, which requires decoordination or (more likely) ligand substitution of the coordinated double bond, followed by rotation around it.

Scheme 4. MeCN catalyzed *E*/*Z* isomerization mechanism in complexes **8b**.



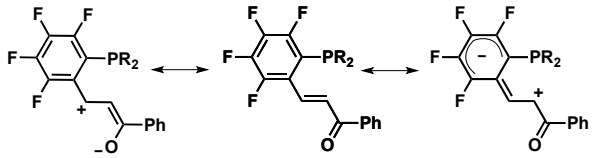
What we are proposing is that when this double bond is non-coordinated, in a P-monocoordinate PEWO-F_4 ligand, the isomerization by rotation is feasible. We do not observe *E* and *Z* isomers of **7a-c** simply because the *E* isomer is much more stable than Z, and the small concentration of the later in a very uneven equilibrium is unobservable. It is only upon double bond coordination that the two chelate complexes happen to have similar stability for the two configurations and a more balanced equilibrium is reached. Of course, if this happens to **7a-c** there is little argument not to accept that the same mechanism is operating also in the free ligands.

The experimental $\Delta G^{\ddagger}_{(E\text{-}to\text{-}Z\ isom.)}$ values at 298 K, in the absence of MeCN, are 23.5 kcal.mol^{-1} in CD_2Cl_2, and 23.0 kcal.mol^{-1} in $CDCl_3$. The catalytic acceleration by addition of MeCN requires a large MeCN:Pd ratio for the acceleration reported as k_{obs} in Table 1. This supports that the electron-withdrawing olefin is not such a weak ligand when involved in chelation; at least it is not easily displaced by acetonitrile since it requires 70 equivalents just to form an still unobservable amount of **Ib** in the ligand substitution equilibrium. It is reasonable to presume that an appreciable deal of $\Delta G^{\ddagger}_{(E\text{-}to\text{-}Z\ isom.)}$ is invested in the release of the double bond and only the rest pertains to the configurational isomerization.

In general the barrier to rotation in regular olefins is very high, and different catalytic mechanisms have been proposed,[18] but the aryl-EWO moiety in our phosphines is an α,β unsaturated

chalcone type olefin. The double bond in chalcones is electron-deficient due to the polarization induced by the C=O group. This feature of chalcone derivatives is very well documented.[19] Chalcone itself shows $\Delta G^{\ddagger}_{(isom.)}$ = 31.5 kcal.mol^{-1} in water, and activation energies about 15 kcal.mol^{-1} are common.[19c] Depending on substituents on the aryls and the solvents used, experimental values as low as $\Delta G^{\ddagger}_{(isom.)}$ 9 kcal.mol^{-1} have been found. In our RPEWO-F$_4$ (**1$_{a-c}$**) ligands the double bond is submitted to an additional source of electron polarization, due to the presence of the highly electronegative F atoms (Scheme 5). The consequence is a very electron-deficient double bond and a low activation barrier to rotation.

Scheme 5. Resonant forms contributing to high electron-deficiency of the double bond.



CONCLUSIONS

The progressive degree of H for F substitution in the sequence of phosphines RPEWO-H$_4$ < RPEWO-H$_2$F$_2$ < RPEWO-F$_4$ produces increasing electron-deficiency in the non-coordinated double bond and, consequently, increasing electron withdrawing strength in the chelated complexes.

The uncoordinated ligands, the P-monodentate PdCl$_2$ complexes, and the P-chelate complexes are all *E/Z* conformational equilibria in solution with reasonably low isomerization barriers, higher for the P-chelate complexes because it requires releasing the double bond.

The two isomers in equilibrium are observed only in the chelate complexes because the *E* and *Z* complexes have only very small differences (< 1 kcal.mol^{-1}). For the others, the *E* isomer is observed.

These observations are interesting in the context of catalysis because they suggest that the E/Z isomerizations can be occurring quite efficiently between main steps (e.g. coupling) along the catalytic cycle. They also point to experimental differences of stability between configurational isomers in the chelate Pd complexes that are lower than the acceptable uncertainty in DFT calculations. This difficulty should be taken into consideration when combining theoretical calculations and experiment in this kind of systems.

ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of the new phosphines and complexes; X-ray diffraction structures; kinetic measurements; (PDF, 91 pages). The Supporting Information is available free of charge on the ACS Publications website.

Notes

The authors declare no competing financial interests.

AUTHOR INFORMATION

Corresponding Author

*Pablo Espinet, IU CINQUIMA/Química Inorgánica, Universidad de Valladolid, 47071-Valladolid (Spain) Fax: (+)34 983 423013.
E-mail: espinet@qi.uva.es
http://gircatalisishomogenea.blogs.uva.es

ACKNOWLEDGMENT

The authors thank the Junta de Castilla y León (projects VA051P17 and VA062G18) and the Spanish MINECO (projects CTQ2016-80913-P and CTQ2017-89217-P) for financial support. M. N. P.-D. gratefully acknowledges the Spanish MECD for a FPU scholarship. Thanks are given to Jonathan Martínez-Laguna for help in the syntheses of several *o*-Tol derivatives.

REFERENCES

(1) Braunstein, P.; Naud, F. Hemilability of Hybrid Ligands and the Coordination Chemistry of Oxazoline-Based Systems. *Angew. Chem. Int. Ed.* **2001**, *40*, 680–699.

(2) Stradiotto, M.; Lundgren, R. J.; Buchwald, S. L.; Milstein, D. *Ligand Design in Metal Chemistry: Reactivity and Catalysis.* WILEY, 2016.

(3) Pérez-Rodríguez, M.; Braga, A. A. C.; García-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Álvarez, R.; Maseras, F.; Espinet, P. C−C Reductive Elimination in Palladium Complexes, and the Role of Coupling Additives. A DFT Study Supported by Experiment. *J. Am. Chem. Soc.* **2009**, *131*, 3650−3657.

(4) (a) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. Superior Effect of a π-Acceptor Ligand (Phosphine−Electron-Deficient Olefin Ligand) in the Negishi Coupling Involving Alkylzinc Reagents. *Org. Lett.* **2007**, *9*, 4571–4574. (b) Shi, W.; Luo, Y.; Luo, X.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. Investigation of an Efficient Palladium-Catalyzed C(sp)−C(sp) Cross-Coupling Reaction Using Phosphine−Olefin Ligand: Application and Mechanistic Aspects. *J. Am. Chem. Soc.* **2008**, *130*, 14713–14720. (c) Zhang, H.; Luo, X.; Wongkhan, K.; Duan, H.; Li, Q.; Zhu, L.; Wang, J.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. Acceleration of Reductive Elimination of [Ar-Pd-C$_{sp3}$] by a Phosphine/Electron-Deficient Olefin Ligand: A Kinetic Investigation. *Chem. –Eur. J.* **2009**, *15*, 3823–3829.

(5) For hybrid phosphine-olefin ligands other than PEWO used in Pd-catalysis see, for example: (a) Cao, Z; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. Pd-Catalyzed Asymmetric Allylic Alkylation of Indoles and Pyrroles by Chiral Alkene-Phosphine Ligands. *Org. Lett.* **2011**, *13*, 2164–2167. (b) Liu, Z.; Du, H. Development of Chiral Terminal-Alkene−Phosphine Hybrid Ligands for Palladium-Catalyzed Asymmetric Allylic Substitutions. *Org. Lett.* **2010**, *12*, 3054–3057. (c) Williams, D. B. G.; Shaw, M. L. P–alkene bidentate ligands: an unusual ligand effect in Pd-catalysed Suzuki reactions. *Tetrahedron* **2007**, *63*, 1624−1629.

(6) (a) Gioria, E.; Martínez-Ilarduya, J. M.; García-Cuadrado, D.; Miguel, J. A.; Genov, M.; Espinet, P. Phosphines with Tethered Electron-Withdrawing Olefins as Ligands for Efficient Pd-Catalyzed Aryl-Alkyl Coupling. *Organometallics* **2013**, *32*, 4255−4261. (b) Gioria, E.; Martínez-Ilarduya, J. M.; Espinet, P. Experimental Study of the Mechanism of the Palladium-Catalyzed Aryl–Alkyl Negishi Coupling Using Hybrid Phosphine–Electron-Withdrawing Olefin Ligands. *Organometallics* **2014**, *33*, 4394–4400.

(7) Gioria, E.; del Pozo, J.; Martínez-Ilarduya, J. M.; Espinet, P. Promoting Difficult Carbon-Carbon Couplings: Which Ligand Does Best? *Angew. Chem., Int. Ed.* **2016**, *55*, 13276–13280.

(8) See for example: (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. The palladium-catalyzed trifluoromethylation of aryl chlorides. *Science,* **2010**, *328*, 1679–1681. (b) Cho, E. J.; Buchwald, S. L. The Palladium-Catalyzed Trifluoromethylation of Vinyl Sulfonates. *Org. Lett.* **2011**, *13*, 6552–6555.

(9) Functionally three-coordinate species refer to species where one of the coordination positions is either free or protected by a weak interaction to some atom, whether intramolecular or intermolecular. Examples are agostic interactions or weakly coordinating ligands. These species can have lower coupling barriers, either because they break that fourth interaction at a low energy cost, or because the coupling on the tetracoordinate species has a low barrier than for those with two strong ligands: Espinet, P.; Echavarren, A. M. The mechanisms of the Stille reaction. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704 – 4734.

(10) This has been explained in detail for related P-olefin hybrid ligands: (a) Tuxworth, L. W.; Baiget, L.; Phanopoulos, A.; Metters, O. J.; Batsanov, A. S.; Fox, M. A.; Howard J. A. K.; Dyer, P. W. Phosphine–alkene ligand-mediated alkyl–alkyl and alkyl–halide elimination processes from palladium(II). *Chem. Commun.* **2012**, *48*, 10413–10415. (b) Estévez, L.; Tuxworth, L. W.; Sotiropoulos, J. M.; Dyer, P. W.; Miqueu, K. Combined DFT and experimental studies of C–C and C–X elimination reactions promoted by a chelating phosphine–alkene ligand: the key role of penta-coordinate Pd^{II}. *Dalton Trans.* **2014**, *43*, 11165–11179.

(11) It is commercially available under the CAS number 1088-00-2.

(12) The acronyms used for the ligands are easy to understand. For instance, taking a complex case, [$PdCl_2${*Z*-(PhPEWO-F_4-chel)}], this is a $PdCl_2$ complex with (by order) a *Z* ligand with two Ph groups in the P atom, and 4 F atoms in the aryl of the chalcone skeleton, and is coordinated as chelate.

(13) The species [$PdCl_2${*E*-(PhPEWO-F_4)}] (***E*-8a**) and [$PdCl_2${*E*-(CyPEWO-F_4)}] (***E*-8c**) could not be isolated pure but they were detected as intermediates mixed with the corresponding *Z* isomers and the firstly formed *trans*-[$PdCl_2L_2$] (more details in SI).

(14) This is a close reference because in fact the aryl-olefin substituent of the P atom is a fluorinated chalcone (PhCH=CHC(O)Ph) radical.

(15) For comparison we calculated the difference in ΔG between *E*-C_6F_5CH=CHC(O)Ph and *Z*-C_6F_5CH=CHC(O)Ph in CH_2Cl_2, and the former is 3.0 kcal.mol^{-1} more stable, which means that the Z-conformation in equilibrium would be undetectable by NMR (0.6%).

(16) (a) Reichardt, C. Solvatochromic Dyes as Solvent Polarity Indicators. *Chem. Rev* **1994**, *94*, 2319–2358. (b) Cerón-Carrasco, J. P.; Jacquemin, D.; Laurence, C.; Planchat, A., Reichardt, C.; Sraïdi, K. Solvent polarity scales: determination of new $E_T(30)$ values for 84 organic solvents. *J. Phys. Org. Chem.* **2014**, *27*, 512−518.

(17) S is extremely unlikely to be an empty coordination site, and could be instead weakly coordinated water present in the solvent, the Cl bridge if dimerization to generate a small amount of an analogous of *E*-**10** occurs, or some other weak intramolecular interaction.

(18) Tan, E. H. P.; Lloyd-Jones, G. C.; Harvey, J. N.; Lennox, A. J. J.; Mills, B. M. [$(RCN)_2PdCl_2$]-Catalyzed *E*/*Z* Isomerization of Alkenes: A Non-Hydride Binuclear Addition–Elimination Pathway. *Angew. Chem. Int. Ed.* **2011**, *50*, 9602–9606.

(19) (a) Pina, F.; Melo, M. J.; Maestri, M.; Ballardini, R.; Balzani, V. Photochromism of 4‘-Methoxyflavylium Perchlorate. A “Write−Lock−Read−Unlock−Erase” Molecular Switching System. *J. Am. Chem. Soc.* **1997**, *119*, 5556−5561. (b) Pina, F.; Melo, M. J.; Maestri, M.; Passaniti, P.; Balzani, V. Artificial Chemical Systems Capable of Mimicking Some Elementary Properties of Neurons. *J. Am. Chem. Soc.* **2000**, *122*, 4496−4498. (c) Roque, A.; Lima, J. C.; Parola, A. J.; Pina, F. Substitution and solvent effects in the chalcones isomerization barrier of flavylium photochromic systems. *Photochem. Photobiol. Sci.* **2007**, *6*, 381−385. (d) Gaonkar, S. L.; Vignesh, U. N. Synthesis and pharmacological properties of chalcones. *Res. Chem. Intermed.* **2017**, *43*, 6043–6077.