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On the Role of Dppf Monoxide in the Transmetalation step of the Suzuki-Miyaura Coupling Reaction

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Suzuki Coupling • Palladium • Transmetalation • dppf • Diphosphine monoxide

ABSTRACT: Diphosphine ligands are frequently used in palladium-catalyzed Suzuki-Miyaura (S-M) reactions. Despite their widespread application in both academic and industrial settings, their role in the B-to-Pd transmetalation has not been firmly established. We combined electrochemistry, NMR spectroscopy and DFT calculations to elucidate the role of dppf (1,1'-bis(diphenylphosphino)ferrocene) in this key elementary step of the S-M reaction. We observed that excess dppf inhibits transmetalation involving $PhB(OH)_2$ and dppf-ligated arylpalladium(II) complexes, while an optimal [base]/[$PhB(OH)_2$] ratio maximizes the concentration of a [Pd-O-B] key intermediate. *In situ* oxidation of dppf to the diphosphine monoxide dppfO can take place in the presence of base, leading to dppfO-ligated arylpalladium(II) complexes, which readily undergo transmetalation at room temperature. These findings suggest guidelines for the rational optimization of diphosphine-promoted S-M reactions.

The metal-catalyzed cross-coupling of organoboron derivatives with electrophiles, known as the Suzuki-Miyaura (S-M) reaction, has become one of the most important synthetic transformations in modern organic chemistry.[1,2] It is widely applied on industrial scale to manufacture active pharmaceutical ingredients and fine chemicals.[3] The mechanism of this reaction has been the subject of several experimental and theoretical studies.[4,5,6,7] As displayed in Scheme 1, it is generally admitted to involve three elementary steps: an oxidative addition (OA), a transmetalation (TM), and a reductive elimination (RE). As it generally limits the rate of the overall cross-coupling process, the TM step has been the subject of several thorough mechanistic studies.

The TM can either proceed through the addition of the boronate [Ar'B(OH)₃]⁻ to OA product[5b, 6a-d, 6g-k] or from the association of the boronic acid with the Pd hydroxo complex (Scheme 1).[5g-i, 5l] The rate of this step can be finely tuned by the base/boronic acid ratio,[5g, 5i, 5l] and the Denmark group first gave experimental evidence of the key intermediate: the heterobimetallic **[Pd-O-B]** key species, which completed the description of the mechanistic scenario (Scheme 1).[5b, 5n, 5o, 5q]

Diphosphines such as 1,1'-bis(diphenylphosphino)ferrocene (dppf), 1,2-bis(diphenylphosphino)ethane (dppe), and 1,3-bis(diphenylphosphino)propane (dppp) are commonly used ligands in palladium-catalyzed Suzuki-Miyaura cross-couplings.[1k] The mechanistic picture emerging form existing studies, which almost exclusively focus on monodentate phosphine ligands, is difficult to extend to chelating diphosphines in a straightforward manner.
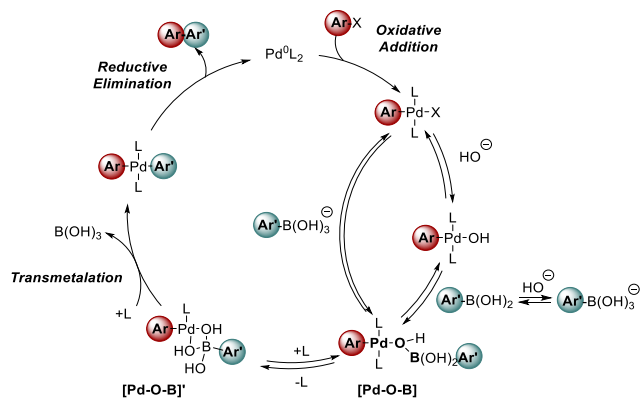
Scheme 1. General mechanism of the S-M cross-coupling reaction.

In particular, a mechanistic model should explain how bidentate ligands can accommodate the formation of the key **[Pd-O-B]** and **[Pd-O-B]'** species, both of which are necessary for the TM to occur according to the mechanism reported in Scheme 1. This issue has not been addressed systematically in the literature. Denmark and co-workers observed a slightly reduced transmetalation rate when dppf was employed instead of P*i*Pr₃, and conjectured the need of generating a coordinatively unsaturated intermediate,[5o] whose nature could not be firmly established. A theoretical study focusing on the S-M reaction promoted by complexes of the model ligand H₂PCH₂CH₂PH₂ investigated only an associative mechanism, for which very high energy barriers were computed.[6f]

Suzuki-Miyaura Cross-Coupling

Inhibition of TM by dppf

Competent catalytic species Hemilabile ligand
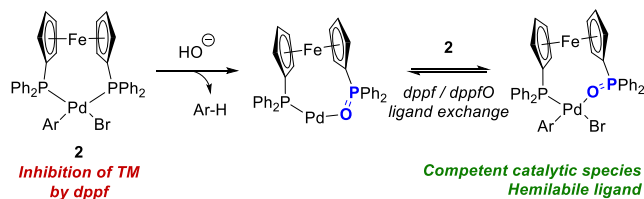
Scheme 2. Hypothesis on the role of dppfO in S-M reactions proposed in this paper.

These two reports and the frequent use of diphosphine ligands in S-M cross-couplings prompted us to investigate the B-to-Pd transmetalation in the case of diphosphines. We observed that oxidation of dppf, a diphosphine widely used in S-M reactions applied to the total synthesis of natural products,[1] could take place under conditions mimicking a typical catalytic reaction, yielding the monoxide dppfO. Our results highlight the potentially crucial role of this *in situ* generated species in diphosphine-mediated S-M reactions (Scheme 2).[8]
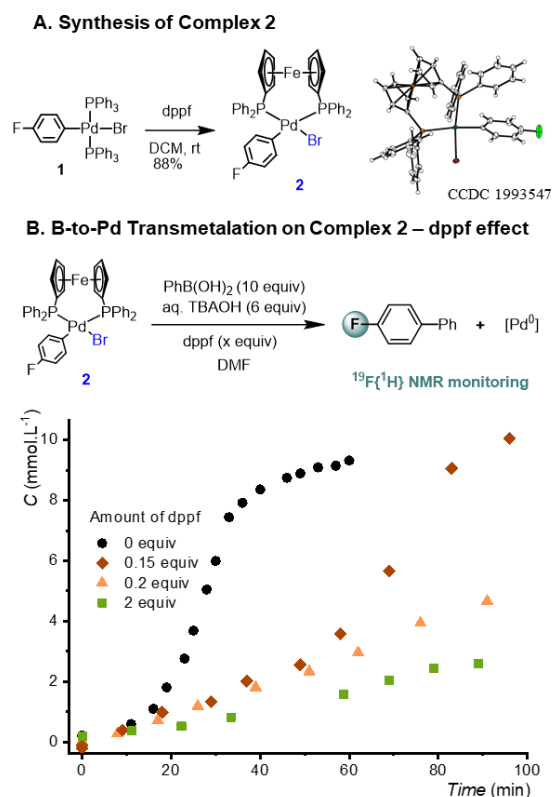
Results and Discussion

The oxidative addition complex *cis*-[Pd(Ar)Br(dppf)] (**2**, Ar = 4-F-C₆H₄) was prepared by ligand exchange between *trans*-[Pd(Ar)Br(PPh₃)₂] (**1**) and dppf (Figure 1A) to study TM involving PhB(OH)₂ using tetrabutylammonium hydroxide (TBAOH) as a base.

1. Inhibiting Effect of Extra Diphosphine on the TM

We first investigated the effect of excess ligand on the B-to-Pd TM starting from either the OA complex **1** or **2** and different amounts of added PPh₃ or dppf. The ratio [OH⁻]/[PhB(OH)₂] ≈ 0.6 (6 equiv / 10 equiv) previously reported to maximize the TM rate in the case of PPh₃-ligated complexes was used.[5g] Formation of the coupling product Ar-Ph was monitored by $^{19}F\{^1H\}$ NMR spectroscopy (Figure 1B).[10]

In the case of complex **1** in the presence of additional PPh₃ (2 equiv), the coupling reaction was almost complete after 5 min (Figure S5a). Formation of Ar-Ph followed a first order law with an apparent rate constant of $k_{app} = 3.3 \ 10^{-3} \ s^{-1}$.[5g] No intermediate could be detected in this case, in agreement with TM being rate determining.[5g] In stark contrast, in the case of complex **2**, in the presence of 1 equiv of dppf (Figure 1B, green curve), TM is very slow and only 20% conversion was observed after 90 min. Under these conditions, the kinetics could be fitted by a first order rate law and the apparent rate constant was estimated to be $k_{app} = 3.2 \ 10^{-5} \ s^{-1}$ (Figures S5). The ratio between the two rate constants is about 100, which corresponds to a difference in activation energy of approximately 3 kcal mol⁻¹. These observations indicate that dppf strongly inhibits B-to-Pd transmetalation. The TM turns out to be the second elementary step of the S-M reaction to be inhibited by excess dppf, as it has been shown that extra diphosphine also inhibits OA by hampering the formation of the reactive 14-electron complex [Pd⁰(dppf)].[12]
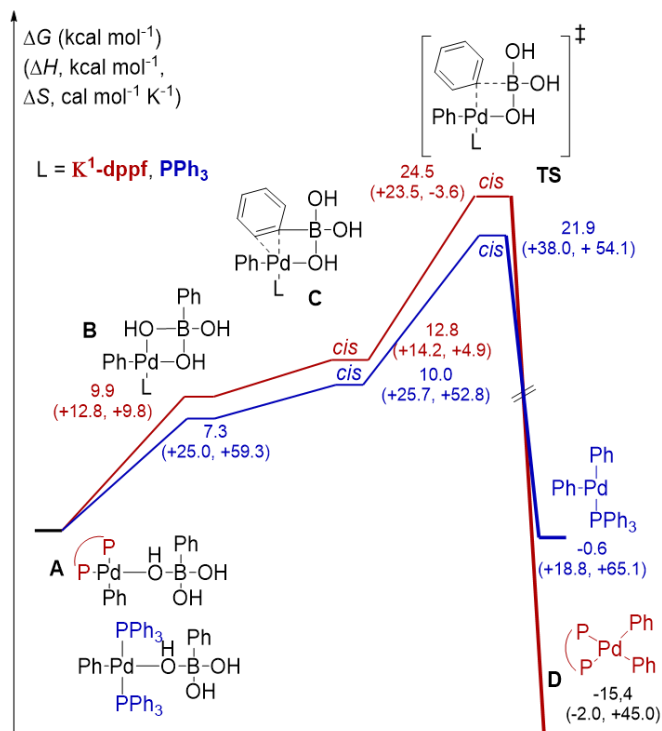
Figure 1. A. Synthesis of complex **2** by ligand exchange from **1**. **B**. Reaction monitoring of the formation of 4-fluoro-1,1'-biphenyl from **2** (20 mM in DMF) with PhB(OH)₂ (10 equiv) and 6 equiv of TBAOH (1.5 M in H₂O) at 20 °C, in the presence of varying amounts of dppf. **C.** Most favored pathways for the TM and RE with dppf and PPh₃ as ligands (see Figure S4 for the alternative *trans* pathway), studied by DFT calculations. Computed relative Gibbs free energies are reported in kcal mol⁻¹ at 298 K. Enthalpies (kcal mol⁻¹) and entropies (cal K⁻¹ mol⁻¹) are reported in parentheses.

To rationalize these kinetic results, we estimated the energy barriers of the TM by DFT calculations (see the computational details in the Supporting Information) (Figures 1C and S6). The slower TM rate with dppf than that with PPh$_3$ could possibly be due to a dissociative mechanism in contrast with the working hypothesis previously formulated by Huang *et al.*[6f] Indeed, as first demonstrated by Goossen and Thiel[6c] the TM with PPh$_3$-ligated Pd(II) requires partial phosphine decoordination and takes place via a four-centered transition-state involving the concerted formation of Pd-C bond and cleavage of Pd-B bonds. Similar behavior is predicted for dppf (Figures 1C and S6).
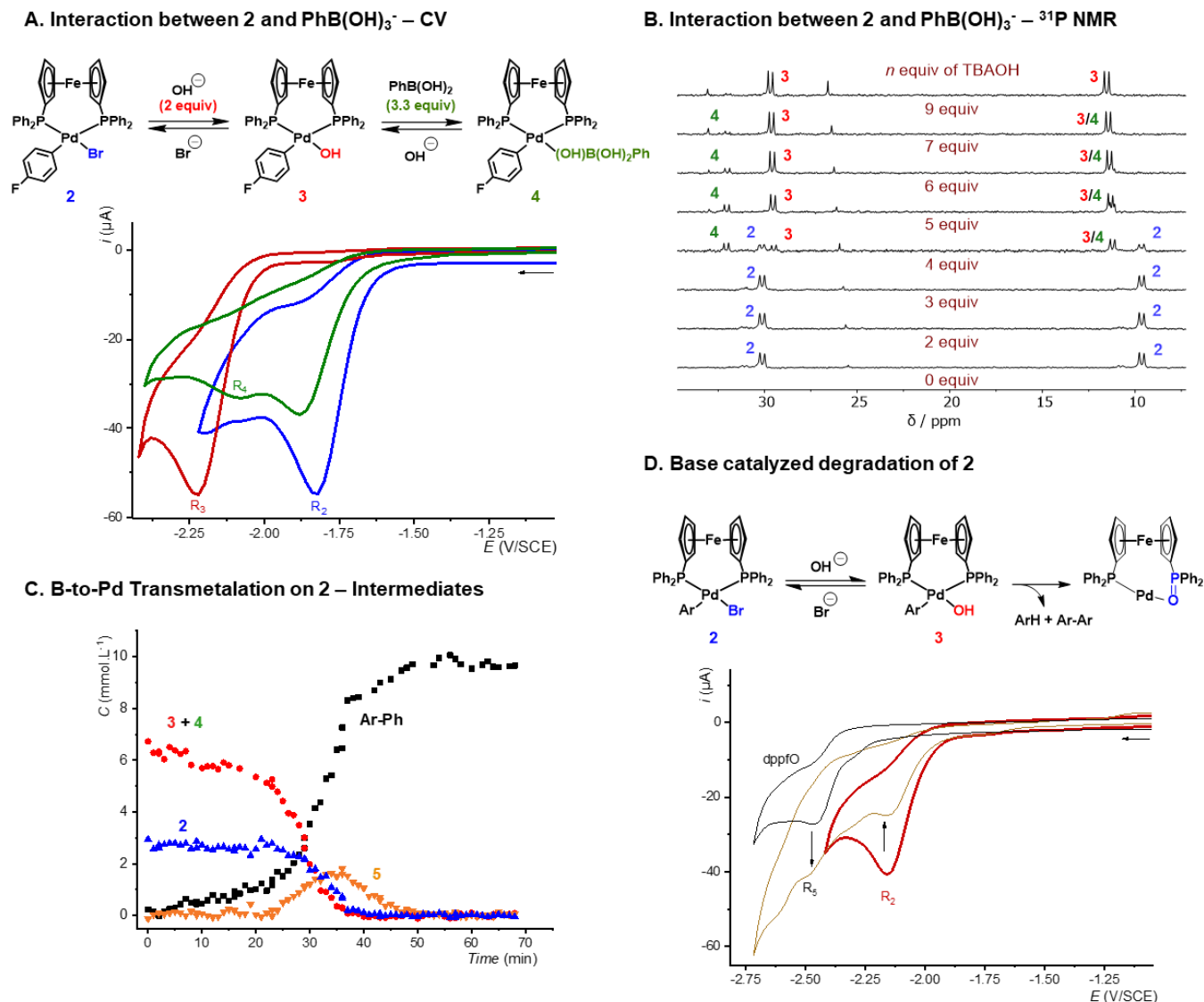
Starting from complex [Pd-O-B] **A**, the cleavage of one P-Pd bond can be assisted by one OH of the boronate moiety to form complex **B**. This release is endothermic (+12.8 kcal mol^{-1}) and almost entropically neutral (+9.8 cal mol^{-1} K^{-1}), leading to an overall endergonic process. For comparison, the same process involving PPh$_3$ lies 2.6 kcal mol^{-1} lower in energy (+7.3 kcal mol^{-1}) driven by the strong positive entropic contribution (+59.3 cal mol^{-1} K^{-1}). Nonetheless, complex **B** cannot directly take part into TM since the phenyl moiety on the boron center is too far from the Pd-center ($d_{(C-Pd)}$ = 3.42 Å). Therefore, prior to TM a ligand exchange between the OH and Ph linked to the boron atom is thus required, leading to the formation of complex **C**. Two pre-TM complexes **C-cis** (+12.8 kcal mol^{-1}) and **C-trans** (+15.7 kcal mol^{-1}) can be formed depending on the relative position of the two aromatic rings with respect to the Pd-center. For clarity, in the main text and figures we will refer only to the most stable *cis* conformer, while all data corresponding to the *trans* conformer are available in the Supporting Information. In the case of dppf, both isomers are 4-5 kcal mol^{-1} higher in free energy compared to the PPh$_3$ analogues. Finally, both *cis* and *trans* transition states were optimized, lying at 24.5 and 27.5 kcal mol^{-1} respectively. The energy barrier for phosphine decoordination directly impacts these transition states. In the case of PPh$_3$, the most favourable **TS-cis** was localized at +21.9 kcal mol^{-1}, i.e. about 3 kcal mol^{-1} lower compared to dppf, corresponding roughly to a factor 10^2 on the kinetics of the reaction.[13] Both experimental and theoretical studies, thus, point towards a slower transmetalation rate when using diphosphine ligands. However, when the formation of the coupling product Ar-Ph was monitored in the absence of added dppf, the reaction proceeded faster, and it was essentially complete after 30 min (Figure 1B, black curve). In the latter case, kinetic curve of formation of Ar-Ph displayed an induction period, which is either typical of an autocatalytic reaction or hints at the *in-situ* generation of an active species from a less reactive precursor.[11] The induction period varies from nearly 1 h at low base concentration to a few seconds at high base concentration (Figure S23). This is in agreement with the instantaneous reaction reported by Denmark and co-workers,[5n] as the TM was studied starting from complex **3** with 1 equiv of boronic acid (corresponding to [OH$^-$]/[PhB(OH)$_2$] = 1). Consistently with the concentration profiles (Figure 2C), this induction period probably results from the formation of a reactive species generated from either complex **3** or **4**. To shed light on this surprising behavior, we investigated in more details the nature of potential intermediates of the dppf-mediated S-M coupling.

2. Intermediates of the TM Step

When treated with TBAOH at –20°C, complex **2**, characterized by its reduction potential R$_2$ at –1.75 V *vs* SCE in DMF, evolved to a new complex with a reduction peak R$_3$ at –2.2 V (Figures 2A and S8). This new peak was assigned to the corresponding hydroxo complex [Pd(Ar)(OH)(dppf)] **3** and the structure was confirmed by ^{31}P{^{1}H} and ^{19}F{^{1}H} NMR (Figures S9 to S11).[5o] While the hydroxo complex **3** was stable at –20 °C, it rapidly decomposed at room temperature in the absence of PhB(OH)$_2$, thereby generating dppfO, as attested by CV showing the characteristic reduction peak of the latter compound (R$_5$ at -2.46 V *vs* SCE, Figure 2D). At the same time, the formation of fluorobenzene and 4-fluoro-1,1'-biphenyl was also observed by ^{19}F{^{1}H} NMR (Figures S10 and S24). In analogy with the well-described reduction of Pd(II) pre-catalysts in basic media,[9] complex **3** probably evolved through a reductive elimination to give dppfO-ligated Pd(0) along with the protodemetalation product ArH and the homocoupling one Ar-Ar, which were detected by ^{19}F{^{1}H} NMR (Figure 2D).[14]

When PhB(OH)$_2$ was added to the *in situ* generated [Pd(Ar)(OH)(dppf)] **3**, a new reduction peak R$_4$ was detected at –2.09 V *vs* SCE (Figure 2A). The latter was attributed to the formation of the mixed complex **[Pd-O-B] 4**, in analogy with the data reported by the Denmark group as the ligand (Figures S12 to S19).[5o] The ^{31}P{^{1}H} NMR titration of a solution containing complex **2** and 10 equiv of PhB(OH)$_2$ with TBAOH demonstrated that the optimal [OH$^-$]/[PhB(OH)$_2$] ratio is about 0.5-0.6 so as to maximize the formation of the productive intermediate **4** (Figure 2B). Worthy of note, this optimal ratio can also vary depending on the quantity of boroxine present as an impurity in the boronic acid (Figures S20 and S21).[4b]

The TM process was monitored by ^{19}F{^{1}H} NMR using a ratio [OH$^-$]/[PhB(OH)$_2$] = 0.5. Immediately after the addition of TBAOH, both **3** and **4** could be observed (Figure 2C, red curve) while some of the starting complex **2** remained (Figure 2C, blue curve). After an induction period of about 25 min, the cross-coupling product rapidly formed (Figure 2C, black curve). Interestingly, an additional intermediate Pd(II) complex **5** could be detected as a triplet at -124.4 ppm (Figure 2C, orange curve). Complex **5** accumulated during the reaction monitoring in parallel of a dramatic increase of the TM reaction rate (orange curve, Figure 2C). This behaviour seems to point out complex **5** as the active form of aryl-Pd toward transmetalation.

A. Interaction between 2 and PhB(OH)$_3^-$ – CV

B. Interaction between 2 and PhB(OH)$_3^-$ – ^{31}P NMR

C. B-to-Pd Transmetalation on 2 – Intermediates

D. Base catalyzed degradation of 2

Figure 2. A. CV performed towards reduction potentials of a DMF solution containing 0.1 M of TBABF$_4$ at –20 °C, at a scan rate of 0.2 V s^{-1} with **2** (2 mM) (blue), with 2 equiv of TBAOH (1.5 M in H$_2$O) (red), after addition of PhB(OH)$_2$ (3.3 equiv corresponding to a ratio [base]/[boronic acid] of 0.6) (green). **B.** ^{31}P{^{1}H} NMR of a solution of complex **2** (20 mM) in DMF in the presence of PhB(OH)$_2$ (10 equiv), upon increasing amount of TBAOH (1.5 M in H$_2$O). A coaxial insert containing a solution of H$_3$PO$_4$ in DMSO-d_6 was used for locking and as an internal standard for integration. **C.** Reaction monitoring of complex **2** (10 mM in DMF) with PhB(OH)$_2$ (10 equiv) in the presence of TBAOH (5 equiv) at 20 °C, monitored by ^{19}F{^{1}H} NMR. **D.** Formation of dppfO from **2** and **3** (Ar = 4-F-C$_6$H$_4$). CV performed towards reduction potentials of a DMF solution containing 0.1 M of TBABF$_4$ at rt, at a scan rate of 0.2 V s^{-1} with isolated complex **3** (2 mM (red), after 4 min (brown); CV of 2 mM of isolated dppfO (black).

3. Role of Diphosphine Monoxide dppfO

To assess a potential catalytic role of dppfO or dppfO-ligated Pd species and shed light on the structure of complex **5**, the TM in the presence of 0.15 equiv of dppfO was studied (Figure 3B, purple curve). An induction period similar to that observed in the absence of additives was found (Figure 3B, blue curve). Importantly, the effect of extra dppfO is less pronounced than that of dppf (Figure 3B, green curve). This suggests that the addition of dppfO alone does not lead to an active species. When introducing 0.1 equiv of Pd(dba)$_2$ (with or without 0.1 equiv of dppfO, Figure 3B black and brown curves), no induction period could be detected and both reactions were complete within less than 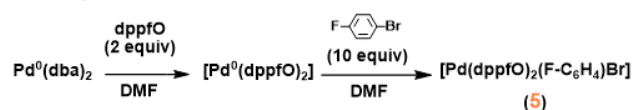20 min. In both cases, the protodemetalation product Ar-H and the homocoupling product Ar-Ar were observed, suggesting the concomitant decomposition of **3**.

We hypothesized that the presence of Pd(0) promotes the dppf/dppfO ligand exchange to form the less coordinated dppfO-ligated aryl Pd(II) complex. When adding *in situ* generated [Pd^0(dppfO)$_2$] (prepared by mixing Pd^0(dba)$_2$ and dppfO, *vide infra*) to a DMF solution of complex **2**, the ^{31}P{^{1}H} spectrum was quite complex, most probably due to a rapid exchange of ligands on the NMR timescale, but the signal corresponding to complex **5** was clearly observed by ^{19}F{^{1}H} NMR (Figure S31) and no induction period was apparent in this case (Figure 3B). This suggested that complex **5** is the active complex for TM and that it is formed in the presence of dppfO-ligated Pd^0.
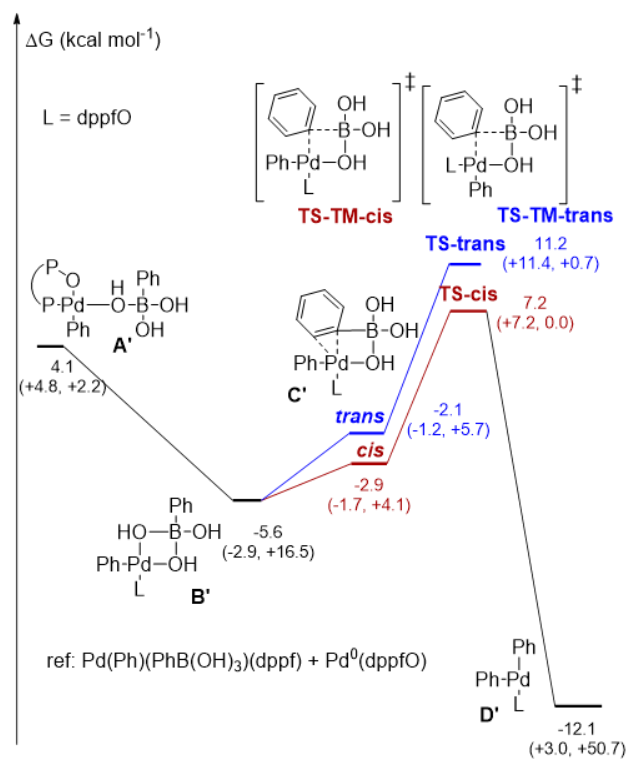
A CV analysis of a mixture Pd(dba)$_2$ with 2 equiv of dppfO demonstrated that a stoichiometric amount of dppfO was able to displace all the dba from the coordination sphere of Pd(0) (Figures S25 to S27), thus suggesting a strong affinity of dppfO for Pd(0). This contrasts with what was observed with dppf, since addition of 2 equiv of dppf on Pd(dba)$_2$ resulted in the formation of the mixed complex [Pd(dba)(dppf)] (Figure S28).[15] The resulting [Pd(dppfO)$_2$] was characterized for the first time by ^{31}P{^{1}H} NMR (Figure S29), and by CV (oxidation peak O$_1$ at +0.5 V vs SCE). This peak disappeared after addition of an excess of 4-F-C$_6$H$_4$Br, confirming that this Pd(0) species is able to perform the initial OA step (Figure S30).[16] [Pd(Ar)Br(dppfO)$_2$] could be prepared and characterized by ^{1}H, ^{13}C, ^{19}F{^{1}H} and ^{31}P{^{1}H} NMR and by ESI-MS (Figures 3A and S3). Spectral data of this complex were identical to those of the previously observed complex **5** (*vide supra*, part 2), which kinetics data indicated as a crucial intermediate. When isolated complex **5** was treated with PhB(OH)$_2$ and TBAOH no induction period was observed and the TM was completed within 10 min (Figures 3C and S32).

DFT calculations further confirmed that TM is favored with dppfO compared to TM with dppf (Figures 3D *versus* 1D). In agreement with the experimental results, the ligand exchange reaction between [Pd(dppfO)] and the dppf-ligated **[Pd-O-B]** to form dppfO-ligated complex **A'** is only slightly endergonic (+4.1 kcal mol^{-1}) and the formation of complex **B'** is favored (−9.7 kcal mol^{-1}). Coordination of the aromatic moiety to form complexes *cis-* or *trans-***C'** is even more favorable and, as expected, the transition states for the TM step are very low lying (+7.2 and +11.2 kcal mol^{-1} for the *cis* and *trans* isomers respectively) accounting for the high activity of hemilabile-ligated Pd species for TM. Additionally, the RE step was also predicted to be faster with monocoordinated dppfO-ligated Pd species when compared to the dppf analogue (Figure S35).
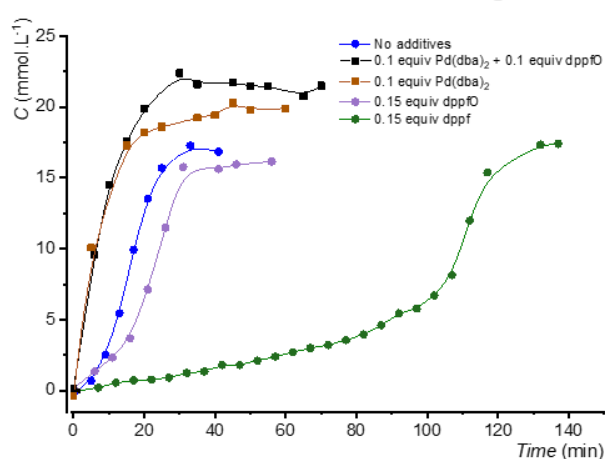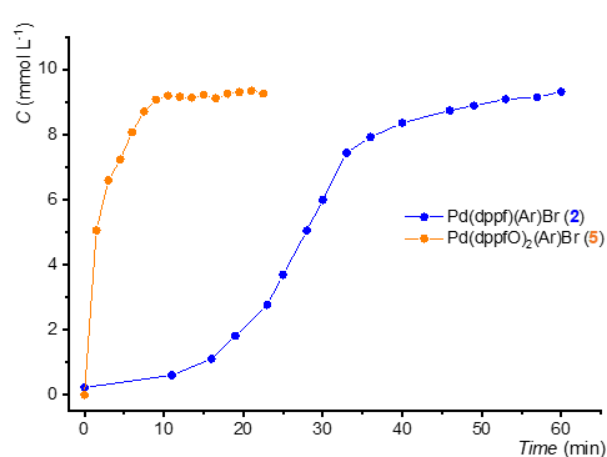
Figure 3. A. Oxidative addition with Pd^0(dppfO)$_2$. **B.** ^{19}F{^{1}H} NMR monitoring of the formation of 4-fluoro-1,1'-biphenyl from 2 (20 mM in DMF) with 10 equiv of PhB(OH)$_2$ and 6 equiv of TBAOH at 20 °C. **C.** ^{19}F{^{1}H} NMR monitoring of the formation of 4-fluoro-1,1'-biphenyl from 2 (blue, 10 mM in DMF) and 5 (orange, 10 mM in DMF), both with 10 equiv of PhB(OH)$_2$ and 6 equiv of TBAOH at 20 °C. D. Pathway for the TM process with dppfO as ligand studied by DFT calculations. Computed relative Gibbs free energies are reported in kcal mol^{-1} at 298 K. Enthalpies (kcal mol^{-1}) and entropies (cal K^{-1} mol^{-1}) are reported in parentheses.

Conclusions

This work addressed three key points regarding the use of diphosphine ligands in the Suzuki-Miyaura reaction concerning: i) their effect on TM rate, ii) the need for decoordination prior TM, and iii) the possible inhibitory effects of diphosphine ligands. In the course of our study, we observed that TM involving [PdArBr(dppf)] and PhB(OH)$_2$ in the presence of OH$^-$ proceeds with an induction period, suggesting that this complex needs to be converted to a more reactive species, which could be the actual intermediate of the catalytic cycle in S-M reactions. We have proved that dppf actually inhibits the TM and DFT calculations pointed out the need of partial decoordination of dppf for the TM to occur. Moreover, we showed that the dppfO generated from the *in situ* oxidation of dppf has a high affinity for Pd(0) species. Pd^0(dppfO)$_2$ is able to perform oxidative addition to ArBr to give a dppfO-ligated aryl Pd(II), which in turn is very reactive in the TM with PhB(OH)$_2$, as confirmed both experimentally and theoretically.

Finally, this study accounts for the widespread use of [Pd(dppf)Cl$_2$] as pre-catalyst for Suzuki-Miyaura cross-couplings, which is a direct precursor of dppfO-ligated Pd(0).[9] The diphosphine ligand is required for the reduction of most commercially available Pd(II) pre-catalysts,[9] but diphosphine monoxides could constitute efficient ligands to stabilize Pd(0) species and promote both the oxidative addition and the transmetalation steps.

Experimental Section

Synthesis of [Pd(dppfO)$_2$(4-F-C$_6$H$_4$)(Br)] (**5**). The reaction was carried out under argon. To a stirred mixture of [Pd(dba)$_2$] (50 mg, 0.087 mmol) in degassed CH$_2$Cl$_2$ (5 mL) was added 1-bromo-4-fluorobenzene (95 µL, 0.7 mmol) and 2.1 equiv of dppfO[17] (104 mg, 0.18mmol). After vigorous stirring at ambient temperature (red-brown color), the flask was fitted with a reflux condenser and heated in an oil bath at 50 °C overnight. The reaction mixture was allowed to warm to room temperature, then the solution was evaporated to a volume of approx. 1 mL and treated with degassed petroleum ether (5 mL). The dark red precipitate was filtered under inert atmosphere, washed with petroleum ether and dried *in vacuo* to produce complex **5** (100 mg, 80%). ^{31}P{^{1}H} NMR (121 MHz, DMF): δ = 25.3 (br s), 16.1 (d, $J_{\text{P-F}}$ = 3.0 Hz) ppm. ^{19}F{^{1}H} NMR (282 MHz, DMF): δ = -124.4 (t, $J_{\text{P-F}}$ = 3.0 Hz) ppm. MS (ESI+, MeCN) *m/z* (%): 1341.1 (100) [(M-Br)$^+$].

Computational Details

All DFT calculations were performed using the Gaussian 09 program (Rev. A02).[9] The structure of all minima and transition states were optimized using the M06 functional[10] and the following basis set: 6-31G for C, H, F, and B; 6-31+G(d) for O and P; LANL2DZ for Pd and Fe with the associated effective core potential LANL2.[11] Bulk solvent effects were taken into account using the PCM method as implemented in Gaussian.[12] The default cavity parameters, static and optical dielectric constants for DMF were used. The nature of all stationary points was checked by analytical frequency calculations. Computed harmonic frequencies were employed to calculate free energies at 298 K and 1 atm pressure with the usual approximations.

ASSOCIATED CONTENT

Supporting Information

Tables of experimental ^{31}P NMR chemical shifts and calculated shielding constants, additional data on the effect of computational parameters on structures and shielding constants. (PDF) Cartesian geometries and absolute energies. (xyz file)
The Supporting Information is available free of charge on the ACS Publications website.

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The authors declare no competing financial interests.

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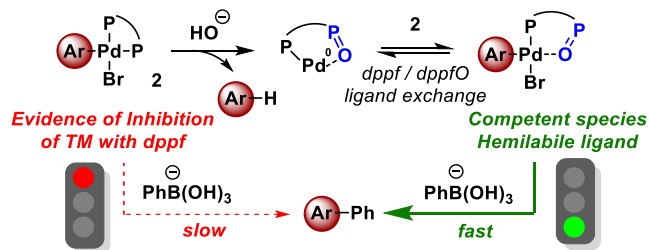
In situ oxidation of 1,1'-bis(diphenylphosphino)ferrocene (dppf) to the diphosphine monoxide (dppfO) accelerates the transmetalation step of the Suzuki-Miyaura coupling catalyzed by dppf-ligated Pd complexes.