The Palladium Acetate-Catalyzed Microwave-Assisted Hirao Reaction without an Added Phosphorus Ligand as a "Green" Protocol: A Quantum Chemical Study on the Mechanism

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Abstract: It was proved by our experiments that on microwave irradiation, the mono- or bidentate phosphorus ligands generally applied in the palladium(II)-catalyzed P–C coupling reaction of aryl bromides and dialkyl phosphites or secondary phosphine oxides may be substituted by the excess of the $>P(O)H$ reagent that exists under a tautomeric equilibrium. Taking into account that the reduction of the palladium(II) salt and the ligation of the palladium(0) so formed requires 3 equivalents of the P-species for the catalyst applied in a quantity of 5–10%, all together, 15–30% of the P-reagent is necessary beyond its stoichiometric quantity. In the coupling reaction of diphenylphosphine oxide, it was possible to apply diethyl phosphite as the reducing agent and as the P-ligand. The reactivities of the diethyl phosphite and diphenylphosphine oxide reagents were compared in a competitive reaction. The mechanism and the energetics of this new variation of the Hirao reaction of bromobenzene with $Y_2P(O)H$ reagents (Y=EtO and Ph) was explored by quantum chemical calculations. The first detailed study on simple reaction models justified our assumption that, under the conditions of the reaction, the trivalent form of the $>P(O)H$ reagent may serve as the P-ligand in the palladium(0) catalyst, and shed light on the fine mechanism of the reaction sequence. The existence of the earlier described bis(palladium complex) $\{[H(OPh_2P)_2PdOAc]_2\}$ was refuted by high level theoretical calculations. This kind of complex may be formed only with chloride anions instead of the acetate anion. The interaction of palladium acetate and $Y_2P(O)H$ may result in only the formation of the $[(HO)Y_2P]_2Pd$ complex that is the active catalyst in the Hirao reaction. The new variation of the Hirao reaction is of a more general value, and represents the greenest protocol, as there is no need for the usual P-ligands. Instead, the $>P(O)H$ reagent should be used in an excess of up to 30%. Hence, the costs and environmental burdens may be decreased.

Keywords: cross-coupling; energetics; microwave heating; palladium catalyst; phosphorus ligands; reaction mechanisms

Introduction

The best method for the synthesis of arylphosphonates is the Hirao reaction comprising a P–C coupling between a dialkyl phosphite (*H*-phosphonate) and an aryl or vinyl halide (mostly bromide) in the presence of $Pd(PPh_3)_4$ as the catalyst, and in most cases, tri- ethylamine as the base in different solvents.[1–8] Later on, different variations of the Hirao reaction were described including *in situ* formed Pd catalysts from suitable precursors [e.g., $Pd(OAc)_2$ and $PdCl_2$] and added mono- or bidentate P-ligands, and extension to *H*-phosphinates, as well as secondary phosphine oxides using different arenes.[9–14] Moreover, Ni and Cu com-

plexes were also applied as catalysts.[9,10] There were attempts to elaborate green chemical accomplishments including microwave (MW)-assisted methods,[15,16] and phase-transfer catalyzed protocols.[17–20]
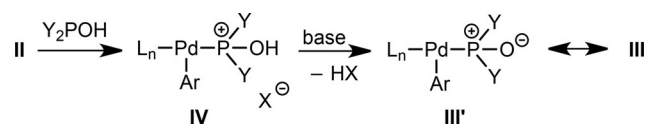
In respect of Pd catalysis, either Pd(PPh$_3$)$_4$, or, quite often, Pd(OAc)$_2$ together with a mono- and bidentate P-ligand may be applied in the P–C coupling reaction of aryl derivatives with >P(O)H reagents. The senior author of this article with co-workers found that under MW conditions the Hirao reaction may take place in the presence of Pd(OAc)$_2$ without the addition of a usual P-ligand. NiCl$_2$ could also be used under similar conditions.[21] This protocol was called as a "P-ligand-free" P–C coupling reaction.[22,23] However, the situation is that, in these cases, a part of the >P(O)H reagent present in the reaction mixture may have served as the reducing agent, and as the P-ligand. The "P-ligand-free" accomplishments mean a big step further, as the use of expensive and air-sensitive mono- and bidentate P-ligands may be avoided, thus the costs and environmental burdens can be decreased. Moreover, the realization of the Hirao reaction is simplified if a single species may be the reagent, and, at the same time, the reducing agent and the P-ligand.

The generally accepted catalytic cycle for the Pd(0)-catalyzed Hirao reaction is shown in Figure 1. According to this protocol, the main steps are the oxidative addition of the aryl halide to the Pd(0) complex (**I**) to give Pd(II) complex **II**, the change of ligands that leads to key intermediate **III**, and the reductive elimination providing the product [ArP(O)Y$_2$], and regenerating the Pd(0) catalyst.[24–30]

As a matter of fact, a few refinements of the above cycle were also proposed by several authors. One such is the incorporation of the P(III) tautomeric form of the >P(O)H species in the primary Pd-adduct (**II**) forming intermediate **IV** that undergoes a deprotonation by the base present in the mixture to
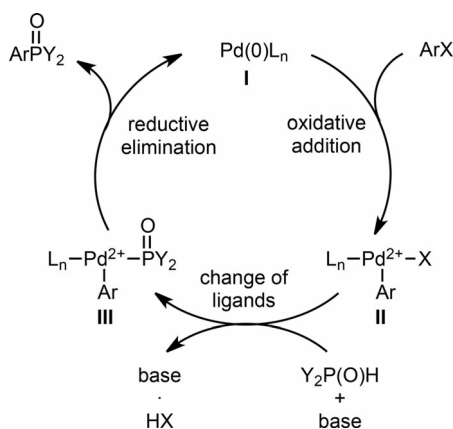
Scheme 1. Refinement of the **II**→**III** conversion in the general scheme of the Hirao reaction.

afford the secondary Pd-adduct (**III′/III**) (Scheme 1).[25,29,30]

Our aim was to study the "P-ligand-free" Pd(OAc)$_2$-catalyzed Hirao reaction for two simple models. On the one hand, we wished to investigate the role of the >P(O)H species. May it serve as the reducing agent and as the P-ligand beside being the reactant? On the other hand, we planned to evaluate the fine mechanism of the simplified ("P-ligand-free") Hirao reaction as a whole.

Results and Discussion

Experimental Results on the "P-Ligand-Free" Hirao Reaction

As it was mentioned in the Introduction, we elaborated a new version of the Hirao reaction. Our idea was that under MW conditions the P(III) form (**1′**) of the dialkyl phosphite or diphenylphosphine oxide reagents (**1**) may play the role of the mono- or bidentate P-ligands added in all earlier cases into the reaction mixtures.[21,22] The only requirement was to add the >P(O)H species in a sufficient quantity so that it should cover the stoichiometric quantity of the reagent of the P–C coupling, and it should be enough as P-ligand needed for the Pd complex (**2**) [0.20 equivalents if 10% of Pd(OAc)$_2$ is used] (Scheme 2). On this occasion, the possible reductive role of the P-reagent was neglected. To ensure an excess, 1.5 equivalents of the >P(O)H reagent were used in the first approach.[21]

The possible role of secondary phosphine oxides and related species as preligands in Pd complexes including Pd(OAc)$_2$ as the precursor was recognized by Ackermann.[31,32]

We wished to evaluate the optimal quantity of the >P(O)H species using Pd(OAc)$_2$ as the Pd precursor. For this, the MW-assisted P–C coupling reaction of bromobenzene and diethyl phosphite or diphenyl-

Figure 1. General scheme for the Pd-catalyzed Hirao reaction.
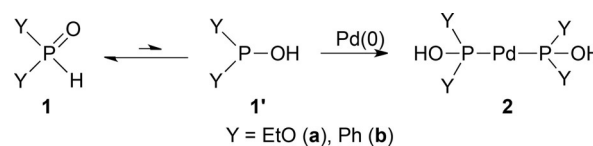
Scheme 2. *In situ* formation of the Pd(0) catalyst complex.
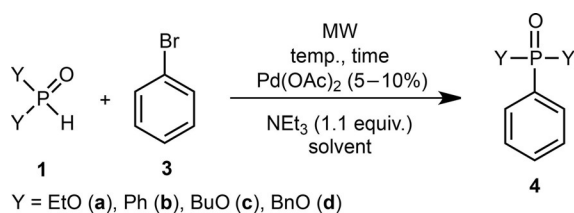
Scheme 3. The model reaction investigated at different molar ratios of the starting materials.

phosphine oxide was carried out using different quantities (1.15–1.5 equivalents) of the P-reagent in the presence of 1.1 equivalents of triethylamine and, in most cases, 10% of Pd(OAc)$_2$ in a solvent (ethanol or acetonitrile) (Scheme 3). The experimental data are listed in Table 1. The results of the solvent-free accomplishments were also included.

The experiments, where diethyl phosphite was measured in a 1.5 equivalents quantity, were carried out at 120°C for 0.5 h in the absence of any solvent using 5% of Pd(OAc)$_2$, or in ethanol using 10% of the catalyst to afford diethyl phenylphosphonate (**4a**) in yields of 80% and 73%, respectively (Table 1/entries 1 and 2). Under conventional heating, the P–C couplings remained incomplete. The thermal variation of the MW-assisted experiment marked by entry 1/footnote[b] of Table 1 led only to a conversion of 52%. This experience underlines the importance of MW irradiation in the protocol under discussion. The sol-

vent-supported P–C couplings were repeated at a molar ratio of 1 and 1.3. It was experienced that the use of only 1 equivalent of (EtO)$_2$P(O)H gave product **4a** in a lower yield of 54% (Table 1/entry 3). At the same time, the use of 1.3 equivalents of the P-reagent resulted in a yield of 74% (Table 1/entry 4) comparable with that obtained from the experiment applying 1.5 equivalents of (EtO)$_2$P(O)H. Using acetonitrile instead of ethanol, the yields were somewhat lower (Table 1/entry 5). Under the conditions applied, acetonitrile may not be an entirely inert solvent. It is noted that a series of solvents including toluene may serve as a medium for the Hirao reaction.[9] Applying only 5% of the Pd(OAc)$_2$ together with 1.15 equivalents of diethyl phosphite, there was the need for a somewhat longer reaction time of 1 h (Table 1/entry 6), but the yield (71%) was comparable with the case covered by entry 4.

Changing to diphenylphosphine oxide, in the first experiments it was applied in a quantity of 1.3 equivalents in the presence of 10% of the catalyst and EtOH as the solvent. Carrying out the reaction at 120°C for 1 h, the conversion was 95% (Table 1/entry 7), while the accomplishment at 150°C for 0.5 h furnished triphenylphosphine oxide (**4b**) in a yield of 87% (Table 1/entry 8). The decrease of the relative quantity of Ph$_2$P(O)H to 1 equivalent led to a lower yield of 54% (Table 1/entry 9), as this was observed also with (EtO)$_2$P(O)H. In case of 1.2 equivalents of Ph$_2$P(O)H, the yield of triphenylphosphine oxide was

Table 1. Results of the MW-assisted Hirao reaction of bromobenzene with (EtO)$_2$P(O)H or Ph$_2$P(O)H carried out under different molar ratios of the reagents using 1.1 equivalents of triethylamine as the base.

Y	Y$_2$P(O)H Quantity [equiv.]	Pd(OAc)$_2$ [%]	Solvent	Temp. [°C][a]	Time [h]	Conv. [%]	Yield [%]	Remarks	Entry
EtO	1.5	5	–	120	0.5	97	80	ref.[21] [b]	1
EtO	1.5	10	EtOH	120	0.5	100	73		2
EtO	1.0	10	EtOH	120	0.5	not relevant	54		3
EtO	**1.3**	**10**	**EtOH**	**120**	**0.5**	**100**	**74**		**4**
EtO	1.3	10	MeCN	120	0.5	100	61		5
EtO	1.15	5	EtOH	120	1	100	71		6
Ph	1.3	10	EtOH	120	1	95			7
Ph	**1.3**	**10**	**EtOH**	**150**	**0.5**	**100**	**87**		**8**
Ph	1.0	10	EtOH	150	0.5	not relevant	54		9
Ph	1.2	10	EtOH	150	0.5	95	79		10
Ph	1.3	10	MeCN	150	0.5	100	67		11
Ph	1.0	10	EtOH	150	0.5	100	80	+30% (EtO)$_2$P(O)H[c]	12
Ph	1.0	10	EtOH	150	0.25[d]+0.5	100	79	+30% (EtO)$_2$P(O)H	13
BuO	**1.3**	**10**	**EtOH**	**120**	**0.5**	**100**	**74**		**14**
BnO	**1.3**	**10**	**BnOH[e]**	**110**	**0.25**	**100**	**68**	_[f]	**15**

[a] CEM Discover (300 W) applying 25–70 W.
[b] Comparative thermal experiment led to a conversion of 52% and yield of 41%.
[c] All components were reacted at once.
[d] A pre-reaction was allowed between Pd(OAc)$_2$ and (EtO)$_2$P(O)H for 15 min.
[e] To avoid transesterification.
[f] 7% of BnP(O)(OBn)$_2$ [δ_P (CDCl$_3$)=27.8 (δ_P=27.7[33]), [M+H]$^+$=353.1304, C$_{21}$H$_{22}$O$_3$P requires 353.1301) was also present in the crude mixture as a by-product.

79% (Table 1/entry 10). The use of acetonitrile as the solvent led again to a lower yield (Table 1/entry 11).

It can be seen that 1 equivalent of the $>P(O)H$ species (**1**) is not enough to ensure a complete reaction, as, using 10% of $Pd(OAc)_2$, 20% of the P-reagent is consumed by the formation of the Pd complex. Moreover, it also turned out that the presence of 1.3 equivalents of the P-reagent is more advantageous than that of 1.2 equivalents. This must be due to the fact that 10% of the $>P(O)H$ species should cover the reduction of Pd(II) to Pd(0). This was confirmed experimentally by us, as from one of the crude products (from the run covered by Table 1/entry 4) we could detect the presence of $(EtO)_2P(O)OH$ (LC-MS, $M + H = 154.04$), which may have formed as the oxidation product along with the reduction of Pd(II) to Pd(0). To date, only in one case was it suggested that a part of the P-ligand added to the Pd(II) precursor is involved in the redox reaction.[14] Theoretically, triethylamine used as the base may also act as a reducing agent, but applying it even in a 5-fold excess, the reduction was found to be much slower, than that with a trivalent P-species, in the given case PPh_3.[34] Comparison of the yields (87% and 79%) of the experiments marked by entries 8 and 10 of Table 1 refers to the role of $(EtO)_2P(O)H$ as a reductant.

The optimized P–C couplings were then extended to the reaction of dibutyl phosphite and dibenzyl phosphite with bromobenzene. The corresponding dialkyl phosphonates (**4c** and **4d**) were obtained in yields of 74% and 68%, respectively (Table 1/entries 14 and 15). In the latter case, benzyl alcohol was applied as the solvent to avoid transesterification, and the formation of $BnP(O)(OBn)_2$ as a minor by-product was inevitable. Dibenzyl phosphite is obviously more reactive than dialkyl phosphites.

In whole, the protocol elaborated by us seems to be of a more general value.

The message from our experiments is that in the "P-ligand-free" Hirao reaction, 1.3 equivalents of the $>P(O)H$ reagent should be used if the $Pd(OAc)_2$ catalyst is applied in a quantity of 10%. On a larger scale, starting from 2.0 mmol of bromobenzene instead of 0.05 mmol, 2.5% of the catalyst was enough. In this case, 1.075 equivalents of the diethyl phosphite were used, and the yield of phosphonate **4a** was 72%.

It is also noted that regarding the palladium salt precursors, $Pd(OAc)_2$ is the best choice due to its lipophilicity.[9] However, we plan to try out also $PdCl_2$ and that will be a subject of another study.

It was an interesting challenge to examine if, in the P–C coupling of PhBr and $Ph_2P(O)H$, it is possible to use $(EtO)_2P(O)H$ as the reducing agent of Pd(II) and as the P-ligand for the Pd formed. For this, the Hirao reaction was carried out in the presence of 1 equivalent of $Ph_2P(O)H$ and 0.3 equivalents of $(EtO)_2P(O)H$ in two variations. In the first case

(Table 1/entry 12), all components were measured in, and reacted. In the second instance (Table 1/entry 13) a 15 min pre-reaction was allowed for $Pd(OAc)_2$ and $(EtO)_2P(O)H$ at 150°C. As can be seen, the outcome of the two reactions was similar (the yield was *ca.* 80% in both cases), but the P–C couplings under discussion were somewhat less efficient as compared to the control experiments marked by Table 1/entry 8. Hence, it is possible to use $(EtO)_2P(O)H$ as the P-ligand and the reducing agent, when the coupling reagent is $Ph_2P(O)H$. In this way, a part of the expensive $Ph_2P(O)H$ may be substituted by $(EtO)_2P(O)H$. It is also obvious that there is no need for a pre-reaction to form the active $Pd[HOP(OEt)_2]_2$ (**2a**) catalyst.

The reactivity order of the two $>P(O)H$ species used in our study was also a question. The comparison of the reactivity of $(EtO)_2P(O)H$ and $Ph_2P(O)H$ is not easy, as there are three independent and consecutive reaction steps: reduction of the Pd(II) to Pd(0) (i), ligation of the Pd(0) so formed (ii), and the P–C coupling itself (iii). As regards the gross reactivity, $(EtO)_2P(O)H$ seems to be more reactive than $Ph_2P(O)H$, if the reaction times required at 120°C using 1.3 equivalents of the $>P(O)H$ species and 10% of the catalyst in EtOH as the solvent are compared (Table 1/entries 4 and 7). To be able to decide on the reactivity of the $>P(O)H$ species in the P–C couplings, concurrent reactions comprising 0.5 equivalents of both $Ph_2P(O)H$ and $(EtO)_2P(O)H$ to one equivalent of bromobenzene were performed in the presence of 10% of $Pd(PPh_3)_4$ and 1.1 equivalents of triethylamine in ethanol as the solvent. After a 20-min irradiation at 120°C, the reaction was interrupted, and analyzed. The ^{31}P NMR spectrum revealed the presence of 50% of triphenylphosphine oxide, 39% of diethyl phenylphosphonate and 11% $(EtO)_2P(O)H$, suggesting that $Ph_2P(O)H$ is slightly more reactive, than $(EtO)_2P(O)H$ in the intrinsic P–C coupling reaction.

We were successful in preparing the complex $[HO(EtO)_2]_2Pd$ (**2**, $Y = EtO$) in a separate experiment by reacting $Pd(OAc)_2$ with 1.3 equivalents of $(EtO)_2P(O)H$ at 120°C for 30 min. The ^{31}P NMR shift of the Pd complex (**2**, $Y = EtO$) was in agreement with that reported by Kalek et al.[11] This prepared complex was then tested in the reaction of $(EtO)_2P(O)H$ with PhBr carried out as above. Diethyl phosphonate (**4a**) was obtained in a yield of 72% proving that the *in situ* formed catalyst is identical to species **2** ($Y = EtO$).

It is worth noting that Buono et al. described the formation of another kind of complex from the reaction of $Pd(OAc)_2$ with a series of secondary phosphine oxides applied in a two equivalents quantity. The outcome is exemplified on the reaction of $Ph_2P(O)H$ performed in toluene at 60°C for 2 h. Complex **5** was isolated in a yield of 54% (Scheme 4).
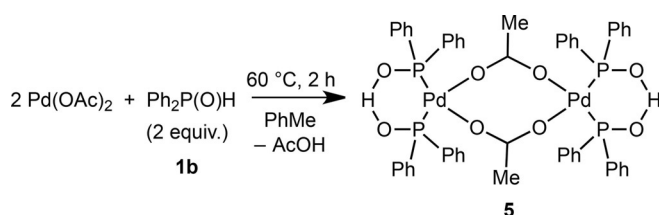
Scheme 4. Assumed formation of bis(palladium complex) **5** from Pd(OAc)$_2$ and Ph$_2$P(O)H.

However, due to the low solubility of complex **5** in most organic solvents, a complete characterization was not possible.[35]

The activity of complex **5** in a [2+1] cycloaddition model reaction was rather low.[35] Later on, when the complex was formed *in situ* by the reaction of Pd(OAc)$_2$ and Ph$_2$P(O)H, the [2+1] cycloaddition reaction was much more efficient according to the yield of 60% reported.[36] We believe that in the later cases not complex **5**, but the *in situ* formed [(HO)Ph$_2$P]$_2$Pd complex (**2**, Y = Ph) may have been the real catalyst.

Comparative theoretical calculations suggested that while complex **5** is not a stable formation, the dimer-like complex with two chloride anions (**5′**) may exist. Let us start with the latter complex. In the case of chloride as anion, the formation of the monomeric ($^-$OY$_2$P)(HOY$_2$P)Pd(II) Cl$^-$ species (where Y = Ph or MeO) and their dimerization calculated at the B3LYP/6-31G(d,p)//PCM(MeCN) level of theory are energetically favourable (Table 2), and the dimeric forms represent well-ordered and almost symmetrical structures for both variations (Figure 2). The high exothermicity provides enough driving force to overcome the unfavourable entropy factors (*ca.* 170/178 J mol^{-1} K^{-1}).

In the case of OAc$^-$ as anion, the formation of the monomeric ($^-$OY$_2$P)(HOY$_2$P)Pd(II) OAc$^-$ is energetically also favourable, however, the formation of the dimers is endothermic (for Y = Ph, $\Delta H = +82.3$ kJ mol^{-1}, for Y = MeO, $\Delta H = +20.7$ kJ mol^{-1}), hence they cannot exist in reality
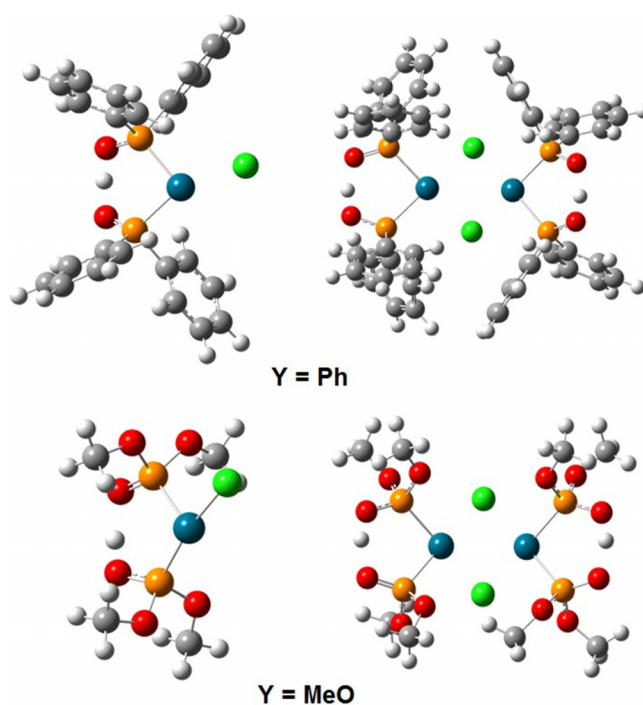
**Figure 2.** Stereostructure of the monomeric and dimeric chloride anion-containing palladium complexes.

(Table 3). In both cases, the dimeric forms represent disordered and unsymmetrical structures (Figure 3).

A Mechanistic Study of the Catalytic Cycle

It is generally accepted that in the cross-coupling reactions, a Pd(0) species is involved in the first stage of the catalytic cycle. For this, first of all, the Pd(II) should be reduced to Pd(0), presumably, a part of the >P(O)H component serves as the reducing agent. Then, the Pd(0) formed coordinates two >P–OH ligands. In our case, there was no added P-ligand in the reaction mixture.

The mechanism of the Hirao reaction was calculated by the B3LYP/genecp//PCM(MeCN) method. The

Table 2. Theoretical study on the formation of monomeric and dimeric Pd(II) complexes from PdCl$_2$ and Y$_2$POH calculated at the B3LYP/6-31G(d,p)//PCM(MeCN) level.
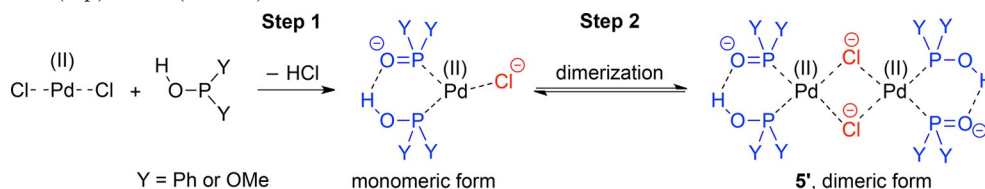
Y	Step 1: PdCl$_2$+2 Y$_2$POH→monomeric form			Step 2: 2 monomeric forms→dimeric form (**5′**)		
	ΔH_1 [kJ mol^{-1}]	ΔG_1 [kJ mol^{-1}]	ΔS_1 [J mol^{-1} K^{-1}]	ΔH_2 [kJ mol^{-1}]	ΔG_2 [kJ mol^{-1}]	ΔS_2 [J mol^{-1} K^{-1}]
Ph	−254.5	−189.8	−217.1	−118.9	*ca.* −70.5	−170.2
MeO	−273.0	−214.7	−195.4	−153.8	−100.6	−178.4

Table 3. Theoretical study on the formation of monomeric and dimeric Pd(II) complexes from Pd(OAc)$_2$ and Y$_2$POH calculated at the B3LYP/6-31G(d,p)//PCM(MeCN) level.
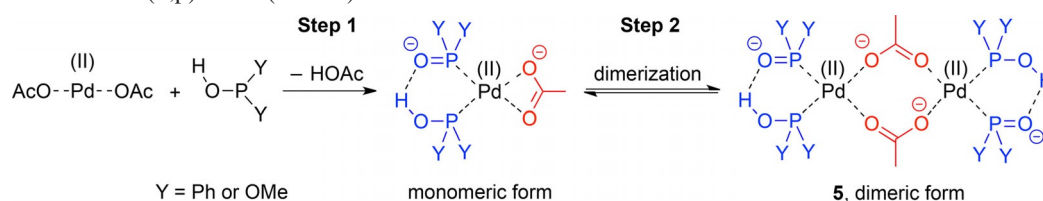
Y	Step 1: Pd(OAc)$_2$+2Y$_2$POH→monomeric form			Step 2: 2 monomeric forms→dimeric form (**5**)		
	ΔH_1 [kJ mol^{-1}]	ΔG_1 [kJ mol^{-1}]	ΔS_1 [J mol^{-1} K^{-1}]	ΔH_2 [kJ mol^{-1}]	ΔG_2 [kJ mol^{-1}]	ΔS_2 [J mol^{-1} K^{-1}]
Ph	−252.0	−201.0	−170.0	+82.3*	+153.6*	−237.5*
MeO	−222.9	−171.9	−170.2	+20.7*	+86.8*	−220.2*

* Thermodynamic corrections were calculated from IR frequency calculations *in vacuo* and added to the PCM energy values.
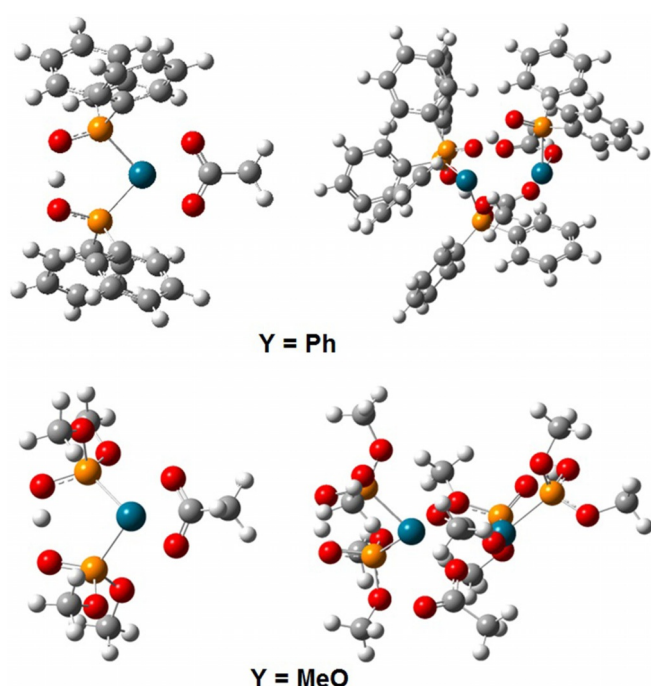

Figure 3. Stereostructure of the monomeric and dimeric acetate anion-containing palladium complexes.

6-31G(d,p) basis set was chosen for CHOBrP, while SDD(MWB28) was used for the Pd atom. The schematic representation of the catalytic cycle is shown in Figure 4, while the energy diagram is shown in Figure 5. The energetics calculated are summarized in Table 4.

In the first step of the catalytic cycle, which is the oxidative addition sub-process, the active form of the catalyst {**2**, Pd(0)[P(OH)Y$_2$]$_2$} and the reagent PhBr (**3**) form a weak complex by coordination of the phenyl ring and the Pd. This state may be considered as the starting point of the catalytic cycle. Then, the Pd is inserted into the C–Br bond *via* a low energy (*ca.* 57 kJ mol^{-1}) TS (**7TS**) resulting in species **8** in an

exothermic manner. In this structure, the two Pd ligands are in the *cis* disposition, but this complex (**8**) is transformed into the more stable *trans* variant (**9**).

After the oxidative addition, the bromide anion is eliminated from complex **9** in an endothermic way (*ca.* +90 kJ mol^{-1}), resulting in cationic intermediate **10**. During our study, the bromide anion is kept on the side of the complex as a counter ion. In the next step, the empty position of species **10** is occupied by another unit of P(OH)Y$_2$ to afford complex **11**, gaining 70.0 kJ mol^{-1} and 46.7 kJ mol^{-1} enthalpies for the cases of Y=OEt (**a**) and Y=Ph (**b**), respectively. Here, the more exothermic process (**10a→11a**) may be explained by the lowers steric hindrance for the ethoxy intermediate **11a**. Then, the P–OH function of the entering P-reagent is deprotonated in an exothermic way by the triethylamine present in the mixture, resulting zwitterionic complex **12**. The significant difference between the enthalpy of the deprotonation of **11a** (−41.9 kJ mol^{-1}) and that of **11b** (−0.30 kJ mol^{-1}) may be explained by considering the stability of the zwitterions **12a** (R=OEt) and **12b** (R=Ph) formed. Due to the better electron-donating ability of the ethoxy groups, the formation of intermediate **12a** is more favourable. It is noted that the deprotonation of catalyst **2** would be highly unfavourable. (For the transformation **2→2–H$^+$**, when Y=EtO, a ΔH of 33.2 kJ mol^{-1}, while when Y=Ph, a ΔH of 60.2 kJ mol^{-1} was calculated in our preliminary study.) The species with the deprotonated P-ligand then undergoes a rearrangement *via* transition state **13TS** to form the C–P bond through a moderate activation barrier (**13TS**). Here, the lower activation enthalpy is exhibited by **13TSb** meaning that intermediate **12b** with phenyl groups may be stabilized faster. In contrast to this, the preceding deprotonation of species **11** is more favourable for the ethoxy substituted case. Finally, the complex of the product (**14**) is dissociated to PhP(O)Y$_2$ (**4**), catalyst **2** and the bromide anion in
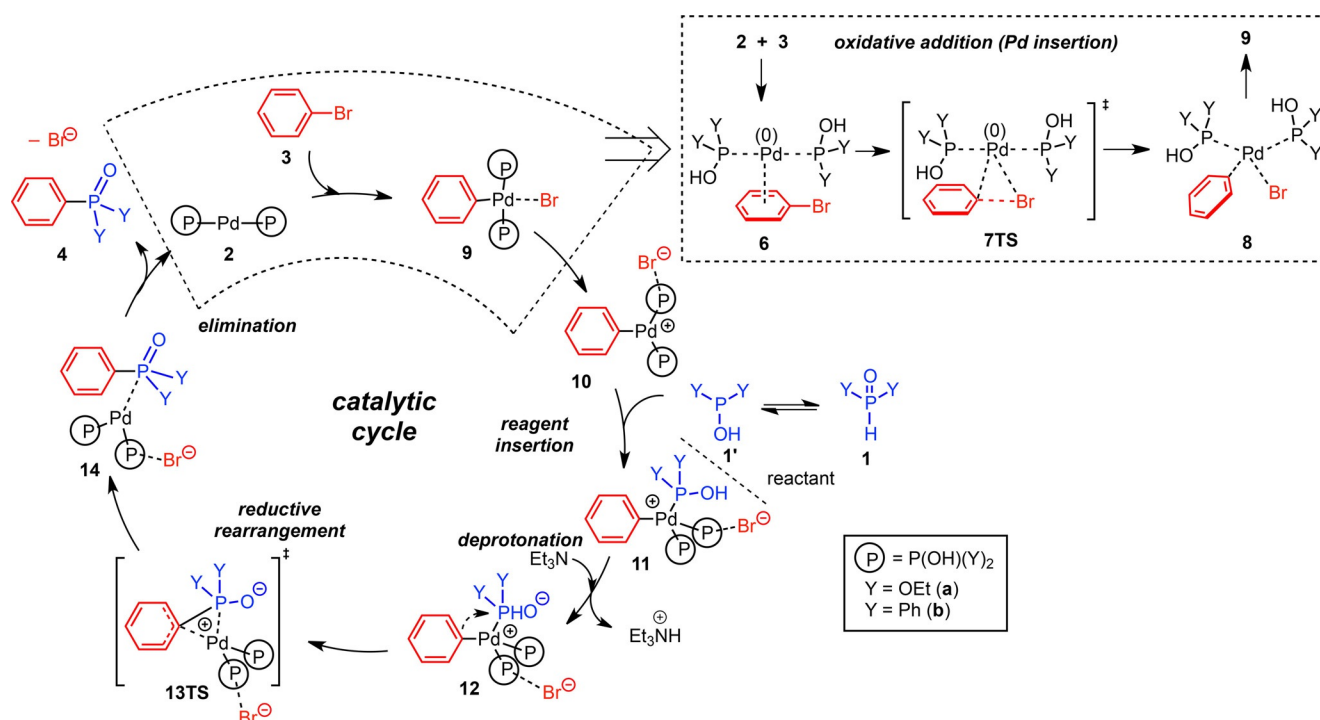
Figure 4. Schematic representation of the detailed catalytic cycle of the Hirao cross-coupling.
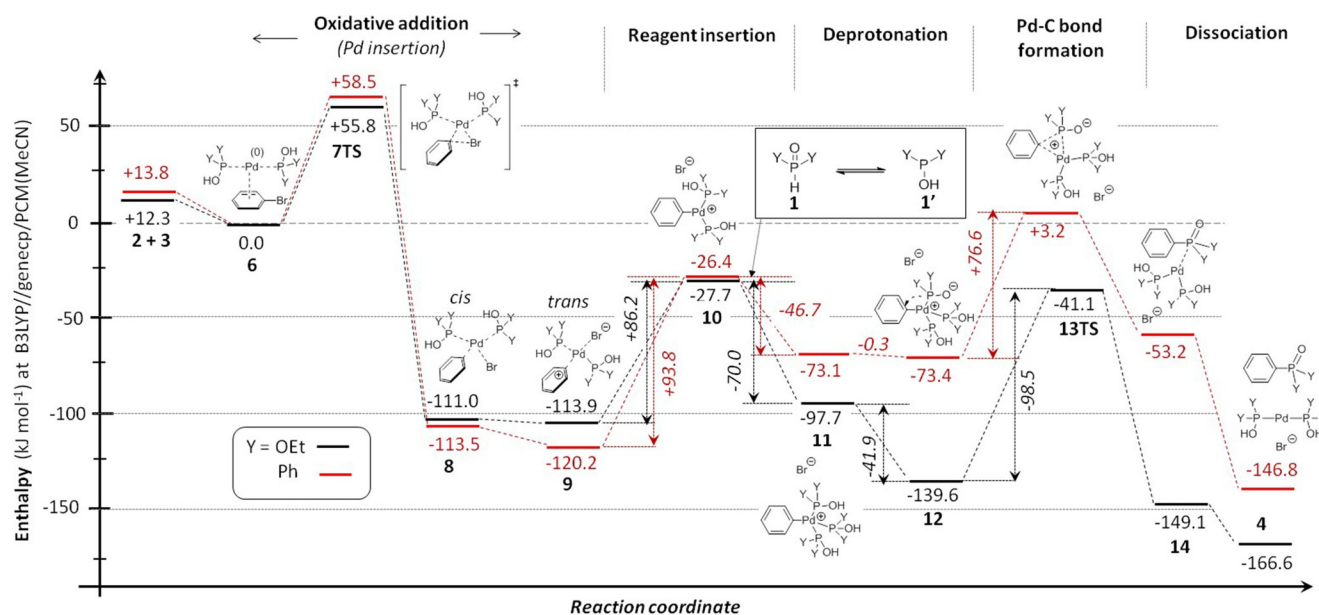
Figure 5. Schematic representation of the enthalpy change in the course of the reaction mechanism for Y = OEt (black) and Y = Ph (red). Enthalpy values were calculated by the B3LYP/genecp//PCM(MeCN) method. The 6-31G(d,p) basis set was chosen for CHOBrP, while SDD(MWB28) was used for the Pd atom. Italized numbers represent the differences of several selected transformations.

an exothermic way rendering the overall process irreversible. After regeneration, Pd(0) catalyst **2** is ready for the next catalytic cycle. The considerable enthalpy gain accompanying the **6→4** transformation means an irreversible process.

Kalek and Stawinski proposed another possibility according to which the coordination of the dialkyl phosphite to Pd *via* the P=O group facilitates its deprotonation, and formation of the ligand exchange product.[27]

Table 4. Enthalpy, Gibbs free energy (kJ mol^{-1}) and entropy (J mol^{-1} K^{-1}) values of the reaction mechanism (see Figure 4 and Figure 5) of the Hirao cross-coupling calculated by the B3LYP/genecp//PCM(MeCN) method. The 6-31G(d,p) basis set was chosen for CHOBrP, while SDD(MWB28) was used for the Pd atom.

	Y = OEt			Y = Ph		
	ΔH [kJ mol^{-1}]	ΔG [kJ mol^{-1}]	ΔS [J mol^{-1} K^{-1}]	ΔH [kJ mol^{-1}]	ΔG [kJ mol^{-1}]	ΔS [J mol^{-1} K^{-1}]
6	0.0	0.0	0.0	0.0	0.0	0.0
7TS	55.8	69.6	−46.6	58.5	83.9	−85.3
8	−111.0	−93.8	−57.8	−113.5	−82.3	−104.6
9	−113.9	−96.8	−57.3	−120.2	−93.5	−89.6
10	−27.7	−17.2	−35.5	−26.4	−10.3	−89.6
11	−97.7	−26.3	−239.5	−73.1	15.1	−296.0
12	−139.6	−60.3	−266.1	−73.4	19.5	−311.7
13TS	−41.1	39.9	−271.9	3.2	92.5	−299.3
14	−149.1	−88.3	−203.8	−53.2	46.6	−335.0
4 + 2 + Br^{-}	−166.6	−150.5	−53.9	−146.8	−128.7	−60.6

Conclusions

Investigating the MW-assisted Hirao reaction of bromobenzene and (EtO)$_2$P(O)H or Ph$_2$P(O)H in the presence of triethylamine in ethanol, it was found that the trivalent form of the >P(O)H reagent may serve as the P-ligand in the Pd(0) catalyst formed by the reduction of Pd(OAc)$_2$ by the effect of the >P(O)H. This means that if 10% of the catalyst precursor is used, there is need for 1.3 equivalents of the >P(O)H reagent. It is noteworthy that the protocol elaborated requires MW irradiation, as on conventional heating, the P–C couplings remain incomplete. It was also possible to use (EtO)$_2$P(O)H as the reducing agent and the P-ligand in the coupling reaction of Ph$_2$P(O)H. The reactivities of (EtO)$_2$P(O)H and Ph$_2$P(O)H were evaluated by a competitive reaction. The novel role of the >P(O)H species was justified by a detailed experimental and theoretical study. This latter shed light on the fine mechanism of the Hirao reaction involving the >P(O)H reagent as the P-ligand. The existence of the earlier described [H(OPh$_2$P)$_2$PdOAc]$_2$ was refuted by theoretical calculations. Only the [(HO)Ph$_2$P]$_2$Pd complex, an *in situ* formed catalyst in the Hirao reaction investigated by us, may be formed from Pd(OAc)$_2$ and Ph$_2$P(O)H. The new and simplified version of the Hirao reaction is of general value, and represents the greenest protocol. Costs and environmental burdens are saved, as there is no need for mono- and bidentate P-ligands.

the >P(O)H reagent (diethyl phosphite: 0.08 mL, dibutyl phosphite: 0.13 mL, dibenzyl phosphite: 0.14 mL, or diphenylphosphine oxide: 0.13 g), 0.08 mL (0.60 mmol) of triethylamine and 1 mL of ethanol (or benzyl alcohol) as the solvent. [In the case of 5% of Pd^{2+} salt, 0.0055 g (0.025 mmol) of palladium acetate and 0.07 mL (0.60 mmol) of diethyl phosphite were measured in.] The resulting mixture was irradiated in a closed vial in a CEM Discover (300 W) microwave reactor at the temperatures and for the times shown in Table 1, entries 4, 6, 8, 14 and 15. The reaction mixture was purified by column chromatography using silica gel and hexane-ethyl acetate as the eluent to give dialkyl phenylphosphonates **4a**, **4c** and **4d** as colourless oils, or triphenylphosphine oxide **4b** as white crystals. For compound characterization, see Table 5. See also the Supporting Information for more spectroscopic data.

Table 5. Identification of the products.

Comp.	δ_P (CDCl$_3$)	δ_P^{lit}	[M+H]$^+_{found}$	[M+H]$^+_{requires}$
4a	18.8[a]	19.7[21]	215.0838	215.0837
4b	29.5[b]	30.3[21]	279.0941	279.0939
4c	18.8[c]	19.4[22]	271.1461	271.1463
4d	19.8[d]	19.8[15]	339.1133	339.1145

[a] From the experiments covered by entry 4 of Table 1.
[b] From the experiments covered by entry 8 of Table 1,
[c] From the experiments covered by entry 14 of Table 1.
[d] From the experiments covered by entry 15 of Table 1.

Experimental Section

General Procedure for the Reaction of Bromobenzene with >P(O)H Reagents

To 0.05 mL (0.50 mmol) of bromobenzene were added 0.011 g (0.05 mmol) of palladium acetate and 0.65 mmol of

In a scaled-up procedure, 2.0 mmol (0.21 mL) of bromobenzene, 2.15 mmol (0.28 mL) of diethyl phosphite, 0.05 mmol (0.011 g) of palladium acetate, 2.2 mmol (0.31 mL) of triethylamine and 4 mL of ethanol were measured in, otherwise the reaction was performed as above. The work-up afforded diethyl phenylphosphonate **4a**; yield: 0.31 g (72%).

The P–C Coupling of Bromobenzene with Diphenylphosphine Oxide in the Presence of Diethyl Phosphite as the P-Ligand

To 0.011 g (0.05 mmol) of palladium acetate were added 0.02 mL (0.15 mmol) of diethyl phosphite and 0.25 mL ethanol, then a pre-reaction was carried out in a closed vial in a CEM Discover (300 W) microwave reactor at 120 °C for 30 min. After that, 0.05 mL (0.50 mmol) of bromobenzene, 0.10 g (0.50 mmol) of diphenylphosphine oxide, 0.08 mL (0.60 mmol) of triethylamine and 0.75 mL of ethanol were added. In the case of Table 1/entry 12, all components were reacted at once. The resulting mixture was further irradiated at 150 °C for 30 minutes. The reaction mixture was purified by column chromatography using silica gel and hexane-ethyl acetate as the eluent to give triphenylphosphine oxide **4b** as white crystals.

Concurrent P–C Couplings of Bromobenzene with Diphenylphosphine Oxide and Diethyl Phosphite in the Presence of Pd(PPh$_3$)$_4$

To 0.11 mL (1.0 mmol) of bromobenzene were added 0.12 g (0.10 mmol) of Pd(PPh$_3$)$_4$, 0.06 mL (0.50 mmol) diethyl phosphite, 0.10 g (0.50 mmol) diphenylphosphine oxide, 0.16 mL (1.2 mmol) of triethylamine and 2 mL of ethanol as the solvent. The resulting mixture was irradiated in a closed vial in a CEM Discover (300 W) microwave reactor at 120 °C for 20 minutes. The reaction mixture was purified by column chromatography using silica gel and ethyl acetate as the eluent. The dense oil so obtained was analyzed by ^{31}P NMR spectroscopy.

Isolation of the *in situ* Formed Complex [HO(EtO)$_2$]$_2$Pd (2, Y = EtO) and Test of its Catalytic Activity

To 0.1 g (0.45 mmol) of palladium acetate was added 0.75 mL (5.85 mmol) of diethyl phosphite, then the reaction mixture was irradiated in a closed vial in a CEM Discover (300 W) microwave reactor at 120 °C for 30 min. The excess of diethyl phosphite was removed by distillation under vacuum. The residue so obtained was purified by column chromatography using silica gel and ethyl acetate as the eluent. Complex (**2**, Y = EtO) was obtained as a dense brown oil; yield: 0.13 g (78%); ^{31}P NMR (CDCl$_3$): $\delta_P = 96.0$, ($\delta_P = 95.1^{[11]}$).

Then, 0.05 mL (0.50 mmol) of bromobenzene, 0.06 mL (0.50 mmol) of diethyl phosphite, 0.08 mL (0.60 mmol) of triethylamine and 1 mL of ethanol were added to 0.02 g (0.05 mmol) of the above isolated complex [HO(EtO)$_2$]$_2$Pd (**2**, Y = EtO). The resulting mixture was irradiated at 120 °C for 30 minutes. The mixture was purified by column chromatography using silica gel and hexane-ethyl acetate as the eluent to give diethyl phenylphosphonate **4a** as colourless oil; yield: 0.08 g (72%).

Quantum Chemical Calculations

All computations were carried out with the *Gaussian09* program package (G09),[37] using convergence criteria of 3.0×10^{-4}, 4.5×10^{-4}, 1.2×10^{-3} and 1.8×10^{-3}, for the gradients of the root mean square (RMS) Force, Maximum Force, RMS displacement and maximum displacement vectors, respectively. Computations were carried out at B3LYP level of theory,[38] using the /6-31G(d,p) basis set for nuclei CHNOPBr and MWB28 for Pd.[39] The vibrational frequencies were computed at the same levels of theory, in order to confirm properly all structures as residing at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions U, H, G and S were computed at 298.15 K. Beside the vacuum calculations, the IEFPCM method was also applied to model the solvent effect, by using the default settings of G09 (radii = UFF), modelling MeCN solvent.[40] In a few cases, the frequency calculations could not be achieved at the standard level, due to the high memory demand, here the IR frequencies from the vacuum calculations were used. See the Supporting Information for details.

Acknowledgements

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