

## Conference paper

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**Palladium-catalyzed microwave-assisted Hirao reaction utilizing the excess of the diarylphosphine oxide reagent as the P-ligand; a study on the activity and formation of the “PdP<sub>2</sub>” catalyst**<https://doi.org/10.1515/pac-2018-1004>

**Abstract:** The microwave-assisted Hirao reaction of bromobenzene and diarylphosphine oxides was performed at 120 °C using triethylamine as the base, and 5 % of palladium acetate as the catalyst in ethanol. 5 % Excess of the >P(O)H reagent served as the reducing agent, while another 10 % as the preligand (in the >POH tautomeric form). It was found that the P–C coupling reaction was significantly faster with (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>P(O)H (**A**) and (3,5-diMeC<sub>6</sub>H<sub>3</sub>)<sub>2</sub>P(O)H (**B**), than with Ph<sub>2</sub>P(O)H (**C**) and (4-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>P(O)H (**D**). Moreover, species **A** and **B** could be applied as selective P-ligands in the reaction of bromobenzene with **C** or **D**. Dependence of the effectiveness of “PdP<sub>2</sub>” catalysts with diarylphosphine oxide preligands on the methyl substituents followed a reversed order as the reactivity of the diarylphosphine oxide species in the P–C coupling itself. Formation of the “PdP<sub>2</sub>” catalyst from palladium acetate and diarylphosphine oxide has never been studied, but now it was evaluated by us at the B3LYP level of theory applying 6-31G(d,p) for C,H,P,O and SDD/MW28 for Pd including the explicit-implicit solvent model. The novel mechanism requiring three equivalents of the >P(O)H species for each of the palladium acetate molecule was in agreement with the preparative experiments. The ligation of palladium(0) with different P(III) species comprising the >POH form of the >P(O)H reagent was also studied, and the critical role of the steric hindrance on the ligation, and hence on the activity of the “PdP<sub>2</sub>” catalyst was substantiated. Last but not least, the influence of the Me substituents in the aromatic ring of the P-reagents on the energetics of the elemental steps of the Hirao reaction itself was also evaluated.

**Keywords:** *ab initio* calculations; cross-coupling; ICPC-22; microwave heating; P-ligands; palladium; reaction mechanisms.

## Introduction

The P–C coupling reaction of dialkyl phosphites, alkyl *H*-phosphinates or secondary phosphine oxides with bromoarenes carried out in the presence of a suitable Pd(0) – phosphine catalyst, and in most cases triethylamine as the base affords dialkyl arylphosphonates, alkyl aryl-phenylphosphinates and tertiary phosphine

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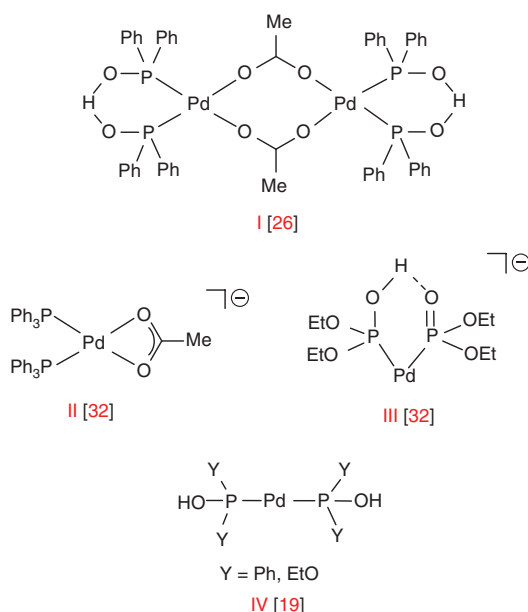


Fig. 1: Pd(0) complexes emerged in the Hirao reaction.

oxides, respectively [1–8]. In the early version of the Hirao reaction, Pd(PPh<sub>3</sub>)<sub>4</sub> was applied as the catalyst [1–3], later on, different Pd(0) precursors including Pd(OAc)<sub>2</sub> and PdCl<sub>2</sub> were used together with mono- or bidentate P-ligands [4–7]. Ni- and Cu complexes were also described as catalysts [4, 5]. Green chemical variations including phase transfer catalyzed methods [9–12], and microwave (MW)-assisted protocols [13–15] were also elaborated.

The Keglevich group found that the P–C coupling reaction under discussion may take place in the presence of Pd(OAc)<sub>2</sub> or NiCl<sub>2</sub> without the addition of the usual P-ligands [16–18]. It was observed and proved that the excess of the >P(O)H reagent may serve as the reducing agent to convert Pd(II) to Pd(0), and, in its trivalent tautomeric form >POH, as the two P-ligands [19]. Considering that the reduction of the Pd(II) salt and the ligation of the Pd(0) so formed requires three equivalents of the P-species to the catalyst applied in 5–10 %, all together 15–30 % of the >P(O)H reactant is necessary beyond its stoichiometric quantity covering the P–C coupling itself. It is well-known that the trivalent tautomeric form (Y<sub>2</sub>POH) of secondary phosphine oxides (Y<sub>2</sub>P(O)H) may be preligands in transition metal complexes that may serve as catalysts in different reactions [20–23]. In this respect, the ligation of Pd(0) [24–29] and Pt(0) [30, 31] is of special importance.

Existence of the [H(OPh<sub>2</sub>P)<sub>2</sub>PdOAc]<sub>2</sub> complex (Fig. 1/I) described by Buono *et al.* [26], and derived from the interaction of Pd(OAc)<sub>2</sub> and diphenylphosphine oxide is questionable on the basis of high level theoretical calculations, and also on the basis of our preparative experiences [19]. Kalek and Stawinski proposed another Pd complex (Fig. 1/II) as an active species in the Hirao reaction utilizing Pd(OAc)<sub>2</sub> as the catalyst precursor and PPh<sub>3</sub> as the P-ligand [32]. However, complex III (Fig. 1) was considered by them as an unreactive species in the catalytic cycle [32]. At the same time, Ackermann *et al.* described a similar species as an active catalyst in another kind of reaction [29]. On the basis of our theoretical calculations and experiments [19], the simple “PdP<sub>2</sub>” type complex (Fig. 1/IV) was suggested as, for the time being, the most probable catalyst in P–C coupling reactions.

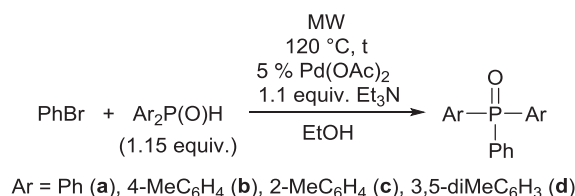
However, the formation of Pd complex IV from Pd(OAc)<sub>2</sub> and the excess of the Y<sub>2</sub>P(O)H reagent has so far never been investigated in details. For this, we wished to explore the formation of “PdP<sub>2</sub>” type complexes incorporating different diarylphosphine oxides as the P-ligands. We were interested in evaluating the effect of the substituents on the formation of the Pd catalyst, and on the energetics of the mechanism of the Hirao reaction as well.

## Results and discussion

### Experimental results on the P–C coupling reaction of bromobenzene and diarylphosphine oxides

In our experiments, 1.15 equivalents of diarylphosphine oxides were reacted with bromobenzene in the presence of 5 % of  $\text{Pd}(\text{OAc})_2$  and 1.1 equivalents of triethylamine in ethanol at 120 °C under MW irradiation. The results were summarized in Table 1. It can be seen that under the conditions applied, completion of the P–C coupling with diphenylphosphine oxide and di(4-methylphenyl)phosphine oxide required 1 h (Table 1,

**Table 1:** The Hirao reaction of bromobenzene and diarylphosphine oxides in the presence of  $\text{Pd}(\text{OAc})_2/\text{Ar}_2\text{P}(\text{O})\text{H}$  as the catalyst.



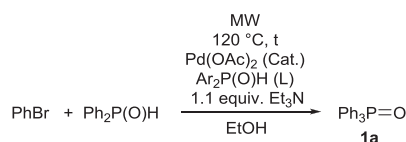
Ar	t (min)	Conversion (%) <sup>a</sup>	Yield (%) <sup>b</sup>	Entry
Ph	30	17		1
<b>Ph</b>	<b>60</b>	<b>100</b>	<b>83 (1a)</b>	<b>2</b>
4-MeC <sub>6</sub> H <sub>4</sub>	30	11		3
<b>4-MeC<sub>6</sub>H<sub>4</sub></b>	<b>60</b>	<b>100</b>	<b>83 (1b)</b>	<b>4</b>
<b>2-MeC<sub>6</sub>H<sub>4</sub></b>	<b>15</b>	<b>100</b>	<b>80 (1c)</b>	<b>5</b>
<b>3,5-diMeC<sub>6</sub>H<sub>3</sub></b>	<b>15</b>	<b>100</b>	<b>82 (1d)</b>	<b>6</b>

<sup>a</sup>Based on <sup>31</sup>P NMR.

<sup>b</sup>The average of 2 or 3 parallel measurements.

Text in bold represents the best experiments.

**Table 2:** Varying the P-ligand in the Hirao reaction of PhBr and Ph<sub>2</sub>P(O)H.



Ph <sub>2</sub> P(O)H (equiv.)	L (equiv.)	Ar	Cat. (%)	t (min)	Conv. (%) <sup>a</sup>	Yield (%) <sup>b</sup>	Entry
1	0.15	Ph	5	30	17		1
1.15							
1	0.15	Ph	5	60	100	83	2
1.15							
1	0.15	2-MeC <sub>6</sub> H <sub>4</sub>	5	15	20		3
1	0.15	2-MeC <sub>6</sub> H <sub>4</sub>	5	30	100	80 <sup>c</sup>	4
1	0.30	2-MeC <sub>6</sub> H <sub>4</sub>	10	30	100	82 <sup>c</sup>	5
1	0.15	3,5-diMeC <sub>6</sub> H <sub>3</sub>	5	30	39		6
1	0.15	4-MeC <sub>6</sub> H <sub>4</sub>	5	60	100	90 <sup>d</sup>	7

<sup>a</sup>Based on <sup>31</sup>P NMR.

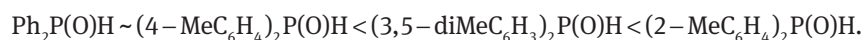
<sup>b</sup>The average of 2 or 3 parallel measurements.

<sup>c</sup>Purity: 95 % [by-product (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>P(O)Ph (**1c**)].

<sup>d</sup>Purity: 89 % [by-product (4-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>P(O)Ph (**1b**)].

entries 2 and 4). After 30 min, the conversions were only  $\leq 17\%$  (Table 1, entries 1 and 3). It is noteworthy that the similar reaction of di(2-methylphenyl)phosphine oxide and bis(3,5-dimethylphenyl)phosphine oxide took place much faster, both P–C couplings were complete after 15 min (Table 1, entries 5 and 6, respectively). From the best experiments (marked in boldface), the corresponding diaryl-phenylphosphine oxides (**1a–d**) were obtained in yields of 80–83 % after purification by column chromatography (Table 1, entries 2, 4–6).

The beneficial effect of the 2-Me or 3-Me group in the phenyl ring is obvious. However, it is a question if the formation of the active catalyst, or the P–C coupling reaction itself is enhanced by the 2- or 3-Me substituent. To evaluate this, 0.15 equivalents of di(2-methylphenyl)phosphine oxide was applied as the P-ligand in the Hirao reaction of diphenylphosphine oxide with bromobenzene that was carried out otherwise as above. As compared to the case, where diphenylphosphine oxide served both as the reagent and the preligand (Table 2, entries 1 and 2), the P–C coupling using di(2-methylphenyl)phosphine oxide as the catalyst ligand was significantly faster. Completion of the phosphinoylation required 30 min (Table 2, entries 3 and 4). The selectivity of the Hirao reaction was rather good, only 5 % by-product **1c** contaminated triphenylphosphine oxide **1a**. The application of 10 % of  $\text{Pd}(\text{OAc})_2$  together with 30 % of di(2-methylphenyl)phosphine oxide led to similar results (Table 2, entry 5). The catalyst formed from  $\text{Pd}(\text{OAc})_2$  and bis(3,5-dimethylphenyl)phosphine oxide as the P-ligand revealed an intermediate activity as compared to the complexes involving diphenylphosphine oxide or di(2-methylphenyl)phosphine oxide as the preligand (Table 2, entries 6, 1 and 4). The experiment applying di(4-methylphenyl)phosphine oxide as the preligand led to similar results as the reference reaction with the use of only diphenylphosphine oxide (Table 2, entries 7 and 2). It can be seen that the 4-Me substituent has practically no effect on the course of the reaction. Hence, the beneficial effect of di(2-methylphenyl)phosphine oxide is to promote the formation of a more active catalyst. The activity of the Pd complexes with the tautomeric form of diarylphosphine oxides as the P-ligands shows the following trend regarding the P-species:



After confirming that di(2-methylphenyl)phosphine oxide and bis(3,5-dimethylphenyl)phosphine oxide are more efficient preligands to  $\text{Pd}^0$  than diphenylphosphine oxide, we wished to explore the reactivity of the different secondary phosphine oxides in the Hirao reaction itself. For this, competitive P–C coupling reactions were carried out applying two different secondary phosphine oxides in quantities of 0.575–0.575 equivalents (all together 1.15 equivalents) to the bromobenzene. Experimental results were summarized in Table 3.

**Table 3:** Competitive P–C coupling reactions of PhBr with equimolar mixtures of two diarylphosphine oxides.

PhBr + Ar <sup>1</sup> <sub>2</sub> P(O)H + Ar <sup>2</sup> <sub>2</sub> P(O)H (0.575 equiv.) (0.575 equiv.)		MW T, t 5 % Pd(OAc) <sub>2</sub> 1.1 equiv. Et <sub>3</sub> N EtOH		Ar <sup>1</sup> <sub>2</sub> P(O)Ph + Ar <sup>2</sup> <sub>2</sub> P(O)Ph A B			
Ar <sup>1</sup>	Ar <sup>2</sup>	T (°C)	t (min)	Conversion (%)	Yield (%) <sup>a</sup>	(A/B) (%) <sup>a,b</sup>	Entry
Ph	2-MeC <sub>6</sub> H <sub>4</sub>	120	7	60 <sup>c</sup>		81 ( <b>1a</b> ) 19 ( <b>1c</b> )	1
Ph	2-MeC <sub>6</sub> H <sub>4</sub>	120	15	100	72 <sup>d</sup>	51 ( <b>1a</b> ) 49 ( <b>1c</b> )	2
Ph	3,5-diMeC <sub>6</sub> H <sub>3</sub>	120	15	85 <sup>c</sup>		63 ( <b>1a</b> ) 37 ( <b>1d</b> )	3
Ph	3,5-diMeC <sub>6</sub> H <sub>3</sub>	120	20	100	80 <sup>d</sup>	53 ( <b>1a</b> ) 47 ( <b>1d</b> )	4
2-MeC <sub>6</sub> H <sub>4</sub>	3,5-diMeC <sub>6</sub> H <sub>3</sub>	100	15	52 <sup>c</sup>		28 ( <b>1c</b> ) 72 ( <b>1d</b> )	5
2-MeC <sub>6</sub> H <sub>4</sub>	3,5-diMeC <sub>6</sub> H <sub>3</sub>	120	5	100	88 <sup>d</sup>	50 ( <b>1c</b> ) 50 ( <b>1d</b> )	6
Ph	4-MeC <sub>6</sub> H <sub>4</sub>	120	30	27 <sup>c</sup>		62 ( <b>1a</b> ) 38 ( <b>1b</b> )	7

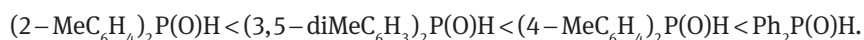
<sup>a</sup>The average of 2 or 3 parallel measurements.

<sup>b</sup>Based on <sup>31</sup>P NMR.

<sup>c</sup>Average conversion for the two components.

<sup>d</sup>Based on the average molar mass.

One can see from the interrupted reactions that diphenylphosphine oxide is more reactive than di(2-methylphenyl)phosphine oxide and bis(3,5-dimethylphenyl)phosphine oxide (Table 3, entries 1 and 3, respectively), and that the bis(3,5-dimethylphenyl)phosphine oxide is more reactive than the 2-methylphenyl P-reagent (Table 3, entry 5). This difference in the reactivity may be the consequence of steric hindrance. The results of the competitive reactions using the diphenylphosphine oxide – di(4-methylphenyl)phosphine oxide reactant pair suggested that the phenyl-reagent is somewhat more reactive than the 4-methylphenyl species (Table 3, entry 7). It is also seen that allowing complete conversions (Table 3, entries 2, 4 and 6), the ratio of products **1a/1c**, **1a/1d** and **1c/1d** was practically 1:1 in all cases. It should be noted that the reaction times listed in Table 3 cannot be compared strictly, as the diarylphosphine oxides also have an impact on the activity of the catalyst (as was shown above), and hence, this also influences the overall reaction time. However, within the pairs, the product ratio (**A/B**) of the incomplete reactions bears relevant information on the relative reactivity of the two diarylphosphine oxides involved. Our experiments suggest the following order of reactivity of the diarylphosphine oxides in the P–C couplings themselves:



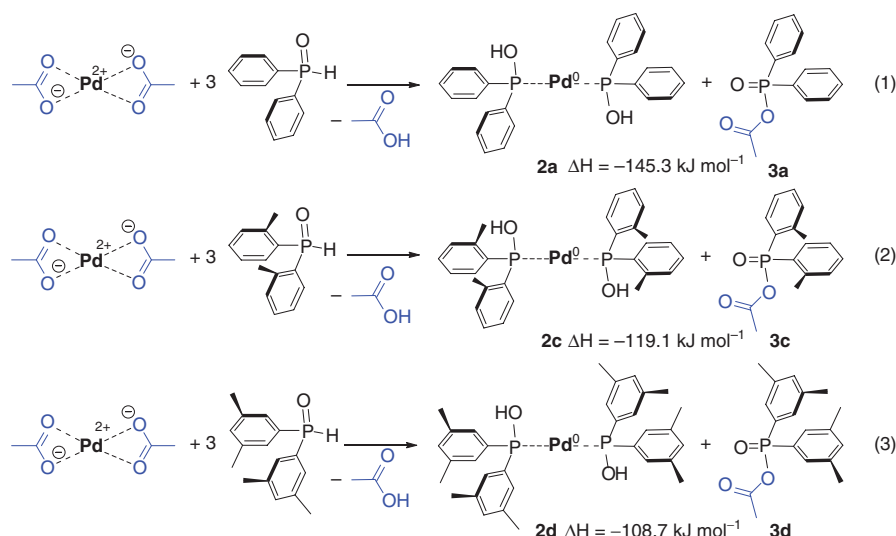
According to the experimental results, the activity of the catalyst influenced by the steric and electric properties of the preligand has a more significant effect on the overall rate, and hence on the reaction time than the reactivity of the  $\text{Ar}_2\text{P(O)H}$  species in the Hirao reaction itself.

## Theoretical calculations

### Formation of the Pd catalyst from $\text{Pd}(\text{OAc})_2$ and diarylphosphine oxides

#### Thermodynamics for the formation of the Pd catalyst from $\text{Pd}(\text{OAc})_2$ and diarylphosphine oxides

In our earlier paper [19], it was proposed that the interaction of  $\text{Pd}(\text{OAc})_2$  and diphenylphosphine oxide affords a complex of type  $[(\text{HO})\text{Ph}_2\text{P}]_2\text{Pd}$  (**2a**). The formation of species “ $\text{PdP}_2$ ” (**2**) for three aryl derivatives together with the energetics are represented in Scheme 1. Reaction enthalpies for the three specific conversions were calculated at the B3LYP level of theory applying 6-31G(d,p) for CHPO, and SDD(MWB28) for Pd

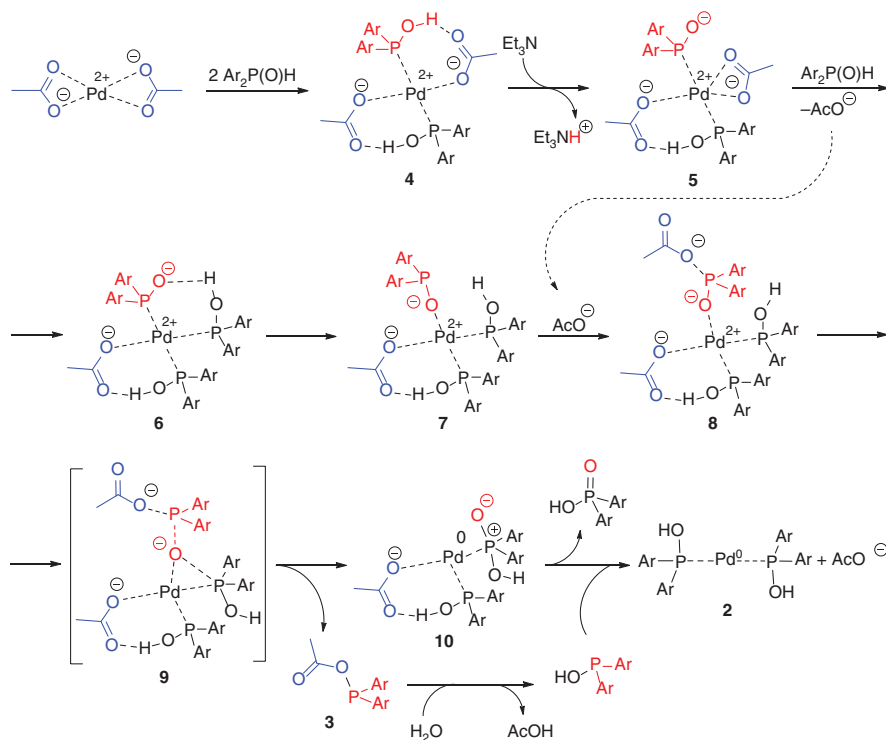


**Scheme 1:** Thermodynamics for the reaction of  $\text{Pd}(\text{OAc})_2$  with  $\text{Ar}_2\text{P(O)H}$  to afford  $[(\text{HO})\text{Ar}_2\text{P}]_2\text{Pd}$  complexes calculated by the B3LYP/genecp//PCM(EtOH) method using the 6-31G(d,p) basis set for CHOP, and SDD(MWB28) for Pd atoms including the explicit-implicit solvent model.

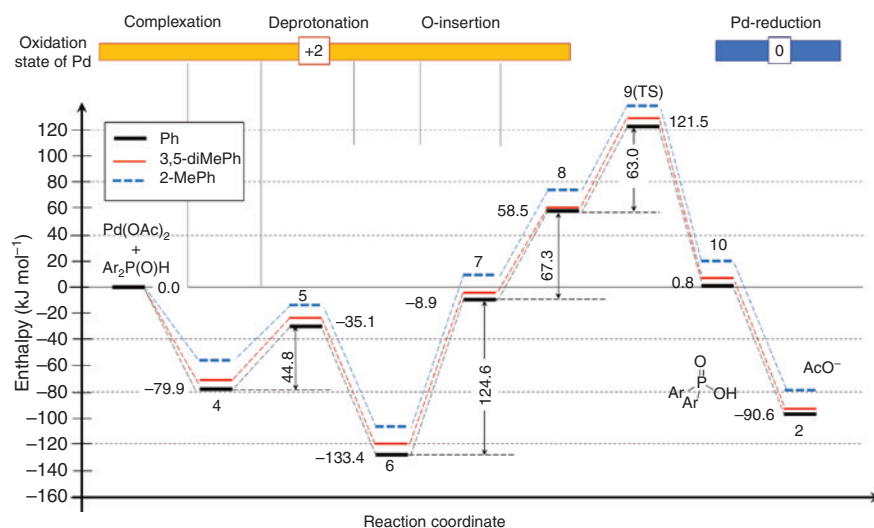
including the explicit-implicit solvent model [33]. It can be seen that the formation of complex  $[(\text{HO})\text{Ph}_2\text{P}]_2\text{Pd}$  (**2a**) is more favorable than that of  $[(\text{HO})(2\text{-MeC}_6\text{H}_4)_2\text{P}]_2\text{Pd}$  (**2c**) and  $[(\text{HO})(3,5\text{-diMeC}_6\text{H}_3)_2\text{P}]_2\text{Pd}$  (**2d**) referring to the role steric hindrance, and, as a consequence, to a somewhat looser Pd–P connection (see later) in the latter cases.

### Mechanism for the formation of the Pd catalyst from $\text{Pd}(\text{OAc})_2$ and diarylphosphine oxides

According to the general hypotheses and earlier findings [32], it was assumed that the active oxidation state of the Pd is the zero. The question arises, how  $\text{Pd}^{2+}$  of  $\text{Pd}(\text{OAc})_2$  added to the reaction mixture may be reduced to  $\text{Pd}(0)$ , and what the mechanism of the complex formation is. Diarylphosphine oxide may serve as the reducing agent. As a matter of fact, the corresponding diarylphosphinic acid by-products were identified from the crude mixtures by LC-MS ( $\text{Ar} = \text{Ph}$ :  $[\text{M} + \text{H}]^+ = 219.1$ ,  $\text{Ar} = 2\text{-MeC}_6\text{H}_4$ :  $[\text{M} + \text{H}]^+ = 247.1$  and  $\text{Ar} = 3,5\text{-diMeC}_6\text{H}_3$ :  $[\text{M} + \text{H}]^+ = 275.1$ ). After considering a few possibilities, the most probable reaction mechanism is shown in Scheme 2. The interaction of  $\text{Pd}(\text{OAc})_2$  and two units of  $\text{Ar}_2\text{P}(\text{O})\text{H}$  leads to Pd(II) complex **4**, which is then deprotonated by TEA to provide species **5**. In the next step, the acetate anion of the “PdOAc” moiety is replaced by a third  $\text{Ar}_2\text{P}(\text{O})\text{H}$  molecule affording complex **6**. Then, an intermolecular *O*-insertion into the P–Pd bond of intermediate (**6**) furnishes intermediate **7** with a P–O–Pd unit. In the next step, an acetate anion is connected to the P atom of the “ $\text{Ar}_2\text{POPd}$ ” moiety of complex **7** to give associate **8**. A reductive elimination from intermediate **8** via TS **9** affords complex **10** and  $\text{Ar}_2\text{POC}(\text{O})\text{Me}$  (**3**). A final stabilization of species **10** by the elimination of  $\text{Ar}_2\text{P}(\text{O})\text{OH}$  and  $\text{AcO}^-$ , and by the simultaneous incorporation of the  $\text{Ar}_2\text{POH}$  species formed by regeneration via hydrolysis of “acyloxyphosphine” **3** results in the formation of complex **2** that is the active form of the catalyst, as it was shown earlier [19]. The energetical background belonging to the mechanism illustrated in Scheme 2 is shown in Fig. 2, while the enthalpy values are listed in Table 4. It can be seen that, in the first approach, the level of enthalpies does not depend much on the nature of the aryl group of



**Scheme 2:** Proposed detailed mechanism for the formation of catalyst  $[(\text{HO})\text{Ar}_2\text{P}]_2\text{Pd}$  from  $\text{Pd}(\text{OAc})_2$  and  $\text{Ar}_2\text{P}(\text{O})\text{H}$  including the explicit-implicit solvent model.



**Fig. 2:** Energetics for the reductive formation of the  $\text{Pd}(\text{Ar}_2\text{POH})_2$  complex from  $\text{Pd}(\text{OAc})_2$  and  $\text{Ar}_2\text{POH}$  calculated by the B3LYP/genecp//PCM(EtOH) method using the 6-31G(d,p) basis set for CHOP, and SDD(MWB28) for Pd atoms including the explicit-implicit solvent model.

**Table 4:** Enthalpy ( $\Delta H$ ) changes in  $\text{kJ mol}^{-1}$  for the reaction sequence suggested for the formation of the  $\text{Pd}(\text{PAR}_2\text{OH})_2$  complex computed by the B3LYP/genecp//PCM(EtOH) method using the 6-31G(d,p) basis set for CHOP, and SDD(MWB28) for Pd atoms with the explicit-implicit solvent model.

	Ar		
	Ph	3,5-diMeC <sub>6</sub> H <sub>3</sub>	2-MeC <sub>6</sub> H <sub>4</sub>
	$\Delta H$ (kJ mol <sup>-1</sup> )	$\Delta H$ (kJ mol <sup>-1</sup> )	$\Delta H$ (kJ mol <sup>-1</sup> )
$\text{Pd}(\text{OAc})_2 + 2 \text{Ar}_2\text{P}(\text{O})\text{H}$	0.0	0.0	0.0
4	-79.9	-70.1	-61.4
5	-35.1	-22.4	-16.5
6	-133.4	-120.6	-111.3
7	-8.9	-2.3	8.7
8	58.5	60.6	76.8
9	121.5	125.1	131.7
10	0.8	5.0	10.9
$2 + \text{Ar}_2\text{P}(\text{O})\text{OH} + \text{AcO}^-$	-90.6	-92.7	-79.8

diarylphosphine oxides. The formation of complexes **2** with methyl-substituted P-species is somewhat unfavored as compared to the case with phenyl ring. The relatively high overall enthalpy of activation values may be overcome by MW irradiation.

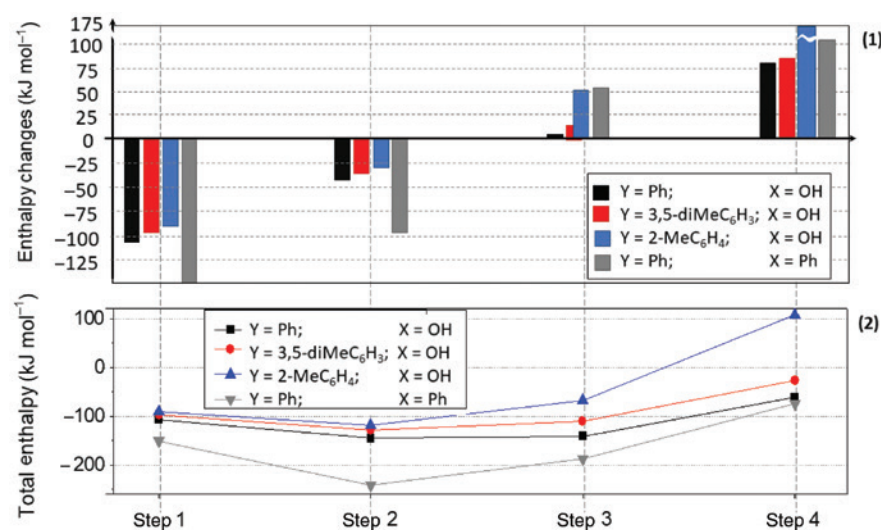
### A study on the ligation of Pd(0)

In our calculations carried out with the B3LYP method [34] using 6-31G(d,p) basis set for CHOP, and MWB28 for Pd [35] including the explicit-implicit solvent model, the complexation of Pd(0) with diarylphosphine oxides and triphenylphosphine was investigated. The enthalpy values for the complexations are listed in Table 5 and shown in Fig. 3. It was found that the mono- (**V**) and bis-ligated Pd(0) complexes (**IV**) may be formed in exothermic reactions for all the cases studied, as characterized by delta enthalpy values of  $-150.5$  to  $-90.6 \text{ kJ mol}^{-1}$  and  $-91.3$  to  $-27.7 \text{ kJ mol}^{-1}$ , respectively. Within series **IV**, the distances of  $2.298 \text{ \AA}$ ,  $2.300 \text{ \AA}$ , and  $2.309 \text{ \AA}$  calculated for the cases with Ph, 3,5-diMeC<sub>6</sub>H<sub>3</sub>, and 2-MeC<sub>6</sub>H<sub>4</sub> substituents, respectively, refer to



**Table 5:** Consecutive ligation of “Pd(0)” by phosphines computed by the B3LYP/genecp//PCM(EtOH) method using the 6-31G(d,p) basis set for CHOP, and SDD(MWB28) for Pd atoms with the explicit-implicit solvent model.

Y	X	Step 1 (V)		Step 2 (IV)		Step 3 (VI)		Step 4 (VII)	
		$\Delta H$ (kJ mol <sup>-1</sup> )	$d_1$ (Å)	$\Delta H$ (kJ mol <sup>-1</sup> )	$d_2$ (Å)	$\Delta H$ (kJ mol <sup>-1</sup> )	$d_3$ (Å)	$\Delta H$ (kJ mol <sup>-1</sup> )	$d_4$ (Å)
Ph	OH	-106.2	2.171	-39.1	2.298	4.8	2.322	79.1 <sup>a</sup>	2.384 <sup>b</sup>
3,5-diMeC <sub>6</sub> H <sub>3</sub>	OH	-97.2	2.173	-31.2	2.300	18.1	2.327	83.0 <sup>a</sup>	2.404 <sup>b</sup>
2-MeC <sub>6</sub> H <sub>4</sub>	OH	-90.6	2.181	-27.7	2.309	51.3	2.363	174.6 <sup>a</sup>	2.475 <sup>b</sup>
Ph	Ph	-150.5	2.198	-91.3	2.323	53.9	2.386	113.6	2.545

<sup>a</sup>Estimated values, optimized at loose convergence criteria.<sup>b</sup>Average values.**Fig. 3:** Enthalpy changes (1) and total enthalpy changes (2) for the mono-, bis- and tris-ligation of Pd(0) computed by the B3LYP/genecp//PCM(EtOH) method using the 6-31G(d,p) basis set for CHOP, and SDD(MWB28) for Pd atoms including the explicit-implicit solvent model.

somewhat elongated Pd–P bonds in the order mentioned. The tris-complexation (VI) is not favorable, and turned to endothermic in all cases. For Ph<sub>2</sub>POH, this value is quite low- and (3,5-diMeC<sub>6</sub>H<sub>3</sub>)<sub>2</sub>POH exhibits a somewhat larger value. With (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>POH and PPh<sub>3</sub>, the enthalpy of the tris-ligation proved to be rather high, and hence these processes are unfavorable, obviously as a consequence of steric hindrance. The gross energetics can be seen well in Fig. 3/(2). In case of the (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>POH and PPh<sub>3</sub> ligands, the real minima are at bis-ligation, while the complexation with Ph<sub>2</sub>POH may remain significant at tris-ligation in the presence of excess of the ligand. The situation regarding enthalpies is rather similar for the tetra-ligation (VII). The complex forming ability of PPh<sub>3</sub> is comparable with that of the (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>POH species. Furthermore, it can be said that while forms IV and VI are real complexes, VII is mainly a dissociated variation. It is noted that the complexation degree of a catalyst is a crucial parameter during the reaction it is involved in. An “under-com-



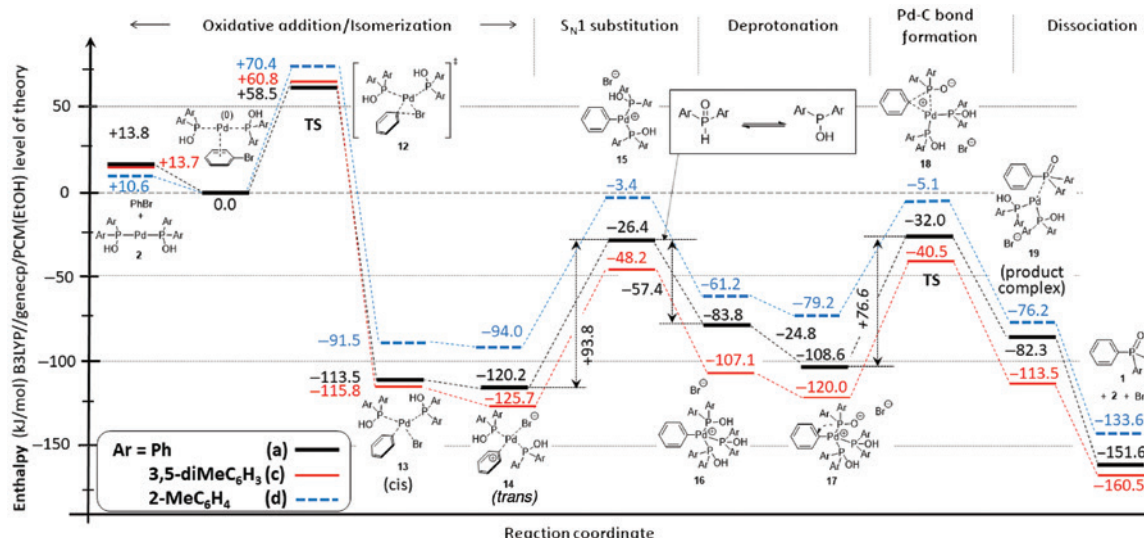


Fig. 4: Enthalpy diagram for the P-C coupling reaction of bromobenzene with diarylphosphine oxides in the presence of  $[(\text{HO})\text{Ar}_2\text{P}]_2\text{Pd}$  catalyst computed by the B3LYP/genecp//PCM(EtOH) method using the 6-31G(d,p) basis set for CHOP, and SDD(MWB28) for Pd atoms.

plexed" metal is not active and not stabilized sufficiently, so it may tend to precipitate as a black solid. At the same time, an overcrowded complex surrounded by more ligands deactivates the catalyst, hence preventing its assistance in the particular reaction. From among the species discussed, **IV** may be the best catalyst, **VI** and **VII** are hindered forms.  $\text{Pd}(\text{PPh}_3)_4$  may also exist in the  $\text{Pd}(\text{PPh}_3)_3 + \text{PPh}_3$  form not only in accord with our calculations, but also by as described by others [36].

## Mechanism of the Hirao reaction of bromobenzene and diarylphosphine oxides

Beside our detailed investigations on the mechanism [19], the literature mentions the usual mechanistic protocol comprising oxidative addition of the bromoarene of the  $\text{Pd}(0)$  complex, incorporation of the  $>\text{P}(\text{O})\text{H}$  reagent by exchange, deprotonation, and reductive elimination to provide the  $\text{ArP}(\text{O})<$  product [37–39]. The proposal of Kalek and Stawinski contains new elements regarding the "Pd"– $\text{ArX}$  adduct, and the coordination of the  $>\text{P}(\text{O})\text{H}$  species [40]. However, to date, the mechanism suggested by us (Fig. 4) on the basis of high level quantum chemical calculations is the most detailed version. According to this, the "Pd"– $\text{PhBr}$  adduct undergoes an S<sub>N</sub>1 substitution with the  $>\text{P}(\text{O})\text{H}$  reagent, and the formation of the Pd–C bond following a deprotonation takes place according to a new way [19].

The calculated values of the enthalpy of activation for the rate determining oxidative addition (58.5 kJ mol<sup>-1</sup>, 60.8 kJ mol<sup>-1</sup> and 70.4 kJ mol<sup>-1</sup> for the models Y = Ph, 3,5-diMeC<sub>6</sub>H<sub>3</sub>, 2-MeC<sub>6</sub>H<sub>4</sub>, respectively) are not in accord with the experimentally observed reaction times of 60, 15 and 15 min, respectively. As it was discussed above, the ligation of  $\text{Pd}(0)$  determines the activity of the catalyst that also has an impact on the course of the reaction. The sterically more hindered ligands ((2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>POH and (3,5-diMeC<sub>6</sub>H<sub>3</sub>)<sub>2</sub>POH) favor the dominance of the active  $\text{Pd}(\text{O})\text{L}_2$  form over the inactive  $\text{Pd}(\text{O})\text{L}_3$  species.

## Conclusions

Studying the Hirao reaction of bromobenzene with diarylphosphine oxide in the presence of 5% of  $\text{Pd}(\text{OAc})_2$  applying 15% excess of the P-reactant to ensure the reduction of  $\text{Pd}^{2+}$  and the bis-ligation of the  $\text{Pd}(0)$  so obtained, it was found that the P–C coupling was significantly faster with (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>P(O)H and

(3,5-diMeC<sub>6</sub>H<sub>3</sub>)<sub>2</sub>P(O)H, than with Ph<sub>2</sub>P(O)H and (4-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>P(O)H. Moreover, the first two species could be applied as selective P-ligands in the Hirao reactions of the later two P-reagents. Dependence of the efficiency of the Pd(PAr<sub>2</sub>OH)<sub>2</sub> catalyst on the methyl substituents of the aromatic ring followed a reversed order as the reactivity of the Ar<sub>2</sub>P(O)H in the P–C coupling reaction. The novel mechanism for the formation of the “PdP<sub>2</sub>” catalyst evaluated by theoretical calculations was in accord with preparative experiments, as required three equivalents of the >P(O)H species for each of the Pd(OAc)<sub>2</sub> molecules. The ligation of Pd(0) with the different diarylphosphine oxides was also investigated, and the critical role of the steric hindrance due to the methyl group in the aromatic ring affecting the activity of the catalyst was pointed out. The energetics for the sequence of the Hirao reaction was also evaluated for three different models.

## Experimental

### Preparation of the starting materials

#### The synthesis of bis(2-methylphenyl)phosphine oxide

To 1.9 g (80.0 mmol) of magnesium in 20 mL of diethyl ether was added a few crystals of I<sub>2</sub>. Then, a few drops of the solution of 9.6 mL (80.0 mmol) of 2-bromotoluene in 30 mL of diethyl ether was added. After the initiation, the remaining solution was added dropwise to maintain reflux. After the addition was complete, the mixture was stirred at the boiling point for 2.5 h. Then, the mixture was cooled to 0 °C, and 2.6 mL (20.0 mmol) of diethyl phosphite in 30 mL of diethyl ether was added dropwise to the solution of the Grignard reagent. The contents of the flask were stirred at 26 °C for 2.5 h. The mixture was then quenched with 10 % HCl solution at 0 °C. The aqueous phase was extracted twice with 80 mL of diethyl ether, and the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent provided a residue that was purified by column chromatography (silica gel, 1 % methanol in dichloromethane) to give bis(2-methylphenyl)phosphine oxide as pale-yellow white crystals.

#### Bis(2-methylphenyl)phosphine oxide

Yield: 63 %; mp.: 98 °C, mp. [41]: 97–98 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>, 121.5 MHz) δ 17.8, δ<sub>p</sub> lit [41] (CDCl<sub>3</sub>, 202 MHz) 17.8, δ<sub>p</sub> lit [42] (CDCl<sub>3</sub>, 162 MHz) 17.7; [M + H]<sup>+</sup> = 231.0940, C<sub>14</sub>H<sub>16</sub>OP requires 231.0939.

#### The synthesis of bis(4-methylphenyl)phosphine oxide

The preparation of bis(4-methylphenyl)phosphine oxide was performed according to our previously described method [18].

#### Bis(4-methylphenyl)phosphine oxide

Yield: 60 %; white crystals; mp.: 96–97 °C, mp. [43]: 95–96 °C; <sup>31</sup>P NMR (CDCl<sub>3</sub>, 121.5 MHz) δ 21.9, δ<sub>p</sub> lit [42] (CDCl<sub>3</sub>, 162 MHz) 21.7; δ<sub>p</sub> lit [43] (CDCl<sub>3</sub>, 121 MHz) 20.5; [M + H]<sup>+</sup> = 231.0941, C<sub>14</sub>H<sub>16</sub>OP requires 231.0939.

### General procedure for the reaction of bromobenzene with diarylphosphine oxides

To 0.0056 g (0.025 mmol) of palladium acetate was added 0.053 mL (0.50 mmol) of bromobenzene, 0.58 mmol of diarylphosphine oxide [0.12 g of diphenylphosphine oxide, 0.13 g of bis(4-methylphenyl)phosphine oxide,

0.13 g of bis(2-methylphenyl)phosphine oxide or 0.15 g of bis(3,5-dimethylphenyl)phosphine oxide], 0.077 mL (0.55 mmol) of triethylamine, and 1 mL of ethanol as the solvent. 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. Then, the solvent was removed, and the mixture was purified by column chromatography (silica gel, ethyl acetate – hexane). Products **1a** (83 %), **1b** (83 %), **1c** (80 %) and **1d** (82 %) were obtained as white or pale yellow crystals.

### Triphenylphosphine oxide (**1a**)

Appearance: white crystals; mp.: 156–158 °C, mp. [17]: 156–157 °C, mp. [44]: 156–157 °C;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  29.1,  $\delta_{\text{p}}$  lit [44] ( $\text{CDCl}_3$ , 162 MHz) 29.5,  $\delta_{\text{p}}$  lit [18] ( $\text{CDCl}_3$ , 121.5 MHz) 30.3;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  128.6 (d,  $J=12.1$ ,  $\text{C}_2$ )<sup>a</sup>, 132.0 (d,  $J=2.8$ ,  $\text{C}_4$ ), 132.2 (d,  $J=9.9$ ,  $\text{C}_3$ )<sup>a</sup>, 132.7 (d,  $J=103.8$ ,  $\text{C}_1$ ), <sup>a</sup>may be reversed,  $\delta_{\text{c}}$  lit [44] ( $\text{CDCl}_3$ , 100 MHz) 128.4 (d,  $J=12.1$ ), 131.9 (d,  $J=2.2$ ), 132.5 (d,  $J=9.9$ ), 132.8 (d,  $J=104.6$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.38–7.48 (m, 6H, ArH), 7.48–7.56 (m, 3H, ArH), 7.59–7.72 (m, 6H, ArH),  $\delta_{\text{H}}$  lit [44] ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.43–7.48 (m, 6H), 7.52–7.56 (m, 3H), 7.64–7.70 (m, 6H);  $[\text{M} + \text{H}]^+ = 279.0941$ ,  $\text{C}_{18}\text{H}_{16}\text{OP}$  requires 279.0939.

### Bis(4-methylphenyl)phenylphosphine oxide (**1b**)

Appearance: white crystals; mp.: 76 °C, mp. [18]: 78–79 °C;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  27.8,  $\delta_{\text{p}}$  lit [18] ( $\text{CDCl}_3$ , 162 MHz) 29.4,  $\delta_{\text{p}}$  lit [44] ( $\text{CDCl}_3$ , 162 MHz) 30.5;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  21.6 ( $\text{CH}_3$ ), 128.5 (d,  $J=12.1$ ,  $\text{C}_2$ )<sup>a</sup>, 129.3 (d,  $J=12.5$  Hz,  $\text{C}_2$ )<sup>b</sup>, 129.4 (d,  $J=106.6$  Hz,  $\text{C}_1$ ), 131.8 (d,  $J=2.7$  Hz,  $\text{C}_4$ )<sup>a</sup>, 132.1 (d,  $J=9.8$  Hz,  $\text{C}_3$ )<sup>a</sup>, 132.1 (d,  $J=10.3$  Hz,  $\text{C}_3$ )<sup>b</sup>, 133.1 (d,  $J=104.1$  Hz), 142.4 (d,  $J=2.8$  Hz) <sup>a,b</sup>may be reversed,  $\delta_{\text{c}}$  lit [45] ( $\text{CDCl}_3$ , 100 MHz) 21.7, 128.6 (d,  $J=11.8$  Hz), 129.4 (d,  $J=12.6$  Hz), 129.4 (d,  $J=106.9$  Hz), 131.9 (d,  $J=3.2$  Hz), 132.0 (d,  $J=8.7$  Hz), 132.2 (d,  $J=10.2$  Hz), 133.0 (d,  $J=102.5$  Hz), 142.6 (d,  $J=2.9$  Hz);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  2.39 (s, 6H,  $\text{CH}_3$ ), 7.18–7.32 (m, 4H, ArH), 7.37–7.47 (m, 2H, ArH), 7.47–7.61 (m, 5H, ArH), 7.61–7.73 (m, 2H, ArH);  $\delta_{\text{H}}$  lit [45] ( $\text{CDCl}_3$ , 400 MHz) 2.38 (s, 6H), 7.24 (dd,  $J=8.4$ , 2.4 Hz, 4H), 7.48 (m, 1H), 7.53 (dd,  $J=11.8$ , 8.0 Hz, 4H), 7.62–7.68 (m, 2H);  $[\text{M} + \text{H}]^+ = 307.1254$ ,  $\text{C}_{20}\text{H}_{20}\text{OP}$  requires 307.1252.

### Bis(2-methylphenyl)phenylphosphine oxide (**1c**)

Appearance: white crystals; mp.: 86–87 °C, mp. [46]: 82–85 °C;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  35.0,  $\delta_{\text{p}}$  lit [47] ( $\text{CDCl}_3$ , 202 MHz) 39.4,  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  21.9 (d,  $J=4.3$ ,  $\text{CH}_3$ ), 125.4 (d,  $J=12.8$ ,  $\text{C}_5$ )<sup>a</sup>, 128.6 (d,  $J=12.0$ ,  $\text{C}_3$ )<sup>a</sup>, 130.9 (d,  $J=102.3$ ,  $\text{C}_1$ )<sup>a</sup>, 131.8 (d,  $J=2.7$ ,  $\text{C}_4$ ), 132.0 ( $\text{C}_4$ )<sup>a</sup>, 132.1 (d,  $J=13.2$ ,  $\text{C}_3$ )<sup>b</sup>, 132.3 (d,  $J=9.6$ ,  $\text{C}_6$ )<sup>b</sup>, 132.7 (d,  $J=104.6$ ,  $\text{C}_1$ ), 133.0 (d,  $J=12.9$ )<sup>b</sup>, 143.4 (d,  $J=8.2$ ,  $\text{C}_2$ )<sup>a</sup>, <sup>a,b</sup>may be reversed,  $\delta_{\text{c}}$  lit [47] ( $\text{CDCl}_3$ , 125 MHz) 21.8 (d,  $J_{\text{p-c}}=4.5$ ), 125.3 (d,  $J_{\text{p-c}}=12.7$ ), 128.5 (d,  $J_{\text{p-c}}=12.7$ ), 130.8 (d,  $J_{\text{p-c}}=101.7$ ), 131.7 (d,  $J_{\text{p-c}}=2.7$ ), 131.8 (d,  $J_{\text{p-c}}=2.7$ ), 131.9 (d,  $J_{\text{p-c}}=10.9$ ), 132.2 (d,  $J_{\text{p-c}}=10.0$ ), 132.7 (d,  $J_{\text{p-c}}=102.6$ ), 132.9 (d,  $J_{\text{p-c}}=12.7$ ), 143.4 (d,  $J_{\text{p-c}}=8.2$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz) 2.51 (s, 6H,  $\text{CH}_3$ ), 6.96–7.09 (m, 2H, ArH), 7.09–7.18 (m, 2H, ArH), 7.27–7.35 (m, 2H, ArH), 7.37–7.52 (m, 4H, ArH), 7.52–7.66 (m, 3H, ArH),  $\delta_{\text{H}}$  lit [47] ( $\text{CDCl}_3$ , 500 MHz) 2.52 (s, 6H), 7.01–7.06 (m, 2H), 7.12–7.17 (m, 2H), 7.29–7.33 (m, 2H), 7.41–7.45 (m, 2H), 7.46–7.50 (m, 2H), 7.54–7.59 (m, 1H), 7.59e7.64 (m, 2H);  $[\text{M} + \text{H}]^+ = 307.1531$ ,  $\text{C}_{20}\text{H}_{20}\text{OP}$  requires 307.1252.

### Bis(3,5-dimethylphenyl)phenylphosphine oxide (**1d**)

Appearance: white crystals; mp.: 159 °C; mp. [45]: 158.6–159.2 °C;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  29.6,  $\delta_{\text{p}}$  lit [45] ( $\text{CDCl}_3$ , 162 MHz) 30.9;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  21.4 ( $\text{CH}_3$ ), 128.4 (d,  $J=12.0$  Hz,  $\text{C}_3$ )<sup>a</sup>, 129.7 (d,  $J=9.8$  Hz,  $\text{C}_2$ ), 131.7 ( $\text{C}_4$ )<sup>a</sup>, 132.1 (d,  $J=9.9$  Hz,  $\text{C}_3$ )<sup>a</sup>, 132.4 (d,  $J=105.3$  Hz,  $\text{C}_1$ ), 133.1 (d,  $J=103.1$  Hz,  $\text{C}_1$ )<sup>a</sup>, 133.7 (d,  $J=2.8$  Hz,  $\text{C}_4$ ),

138.1 (d,  $J=12.7$  Hz,  $C_3$ ),  $\delta_c$  lit [45] ( $CDCl_3$ , 100 MHz) 21.56, 128.6 (d,  $J=11.7$  Hz), 129.8 (d,  $J=10.0$  Hz), 131.9 (d,  $J=2.2$  Hz), 132.3 (d,  $J=9.7$  Hz), 132.4 (d,  $J=102.6$  Hz), 133.1 (d,  $J=102.7$  Hz), 133.9 (d,  $J=2.3$  Hz), 138.3 (d,  $J=12.2$  Hz);  $^1H$  NMR ( $CDCl_3$ , 300 MHz) 2.31 (s, 12H,  $CH_3$ ), 7.15 (s, 2H, ArH), 7.28 (d,  $J=12.2$  Hz, 4H, ArH), 7.39–7.55 (m, 3H, ArH), 7.62–7.73 (m, 2H, ArH),  $\delta_H$  lit [45] ( $CDCl_3$ , 400 MHz) 2.31 (s, 12H), 7.15 (s, 2H), 7.26 (d,  $J=12.4$  Hz, 4H), 7.42–7.47 (m, 2H), 7.51–7.55 (m, 1H), 7.63–7.68 (m, 2H);  $[M+H]^+ = 335.1567$ ,  $C_{22}H_{24}OP$  requires 335.1565.  $^{31}P$ ,  $^{13}C$  and  $^1H$  NMR spectra of compounds **1a–d** can be found in the Supplementary Material.

### The P–C coupling of bromobenzene with $Ph_2P(O)H$ in the presence of $(2-MeC_6H_4)_2P(O)H$ as the P-ligand

To 0.0056 g (0.025 mmol) of palladium acetate was added 0.053 mL (0.50 mmol) of bromobenzene, 0.10 g (0.50 mmol) of diphenylphosphine oxide, 0.017 g (0.075 mmol) of bis(2-methylphenyl)phosphine oxide, 0.077 mL (0.55 mmol) of triethylamine, and 1 mL of ethanol as the solvent [in the case of 0.011 g (0.050 mmol) palladium acetate 0.035 g (0.15 mmol) of bis(2-methylphenyl)phosphine oxide was used]. 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 2. After the reaction, the solvent was removed, and the residue so obtained purified by column chromatography (silica gel, ethyl acetate – hexane). Product **1a** (80/82 %), was obtained as white crystals.

### Concurrent Hirao reaction of diaryl phosphine oxides

To 0.0056 g (0.025 mmol) of palladium acetate was added 0.053 mL (0.50 mmol) of bromobenzene, 0.29–0.29 mmol of two diarylphosphine oxides [0.059 g of diphenylphosphine oxide and 0.067 g of bis(2-methylphenyl)phosphine oxide or 0.059 g of diphenylphosphine oxide and 0.075 g of bis(3,5-dimethylphenyl)phosphine oxide or 0.067 g of bis(2-methylphenyl)phosphine oxide and 0.075 g of bis(3,5-dimethylphenyl)phosphine oxide], 0.077 mL (0.55 mmol) of triethylamine, and 1 mL of ethanol as the solvent. 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 3. Then, the solvent was removed, and the residue was passed through a thin (ca. 1–2 cm) layer of silica gel using ethyl acetate. Volatile components were removed in vacuo, and the pale yellow crystals so obtained were analyzed by  $^{31}P$  NMR spectroscopy.

### Quantum chemical calculations

All computations were carried out with the Gaussian09 program package (G09) [48] using convergence criteria of  $3.0 \times 10^{-4}$ ,  $4.5 \times 10^{-4}$ ,  $1.2 \times 10^{-3}$  and  $1.8 \times 10^{-3}$ , 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 [34] using/6-31G(d,p) basis set for nuclei CHNOPBr and MWB28 for Pd [35] including the explicit-implicit solvent model [33]. 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, IEFPCM method was also applied to model the solvent effect, by using the default settings of G09 (radii = UFF), modeling EtOH solvent [49]. 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.

It was found that the calculated entropy values rather depend on the change of the number of molecules than the intrinsic structural modifications in the course of the sequence of reactions. This is due to the large and overestimated value of the translational and rotational entropy contributions coming from the single

molecule computations. However, this distorted entropy change modify significantly the Gibbs free energy changes ( $\Delta G$ ) as well, for this, the  $\Delta G$  values obtained were ignored. Consequently, only the enthalpy changes ( $\Delta H$ ) were considered in the discussion, which are considered to provide a more reliable picture and description of the complex reaction mechanism than  $\Delta G$ . It is noted that in a few cases, where the size of the molecule is rather large, the geometries were not fully optimized due to the complicated solvent model (PCM). Here, the geometry optimization could reach only the loose convergence criteria instead of the thigh one. These values are marked in Table 5. Details for the theoretical calculations are listed in the Supplementary Material.

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