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An Experimental and Theoretical Study on the “2,2’ Bipiridyl Ni Catalyzed” Hirao Reaction of >P(O)H Reagents and Halobenzenes; A Ni(0)#Ni(II) or a Ni(II)#Ni(IV) mechanism?

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An Experimental and Theoretical Study on the “2,2’-Bipiridyl-Ni-Catalyzed” Hirao Reaction of >P(O)H Reagents and Halobenzenes; A Ni(0)→Ni(II) or a Ni(II)→Ni(IV) mechanism?

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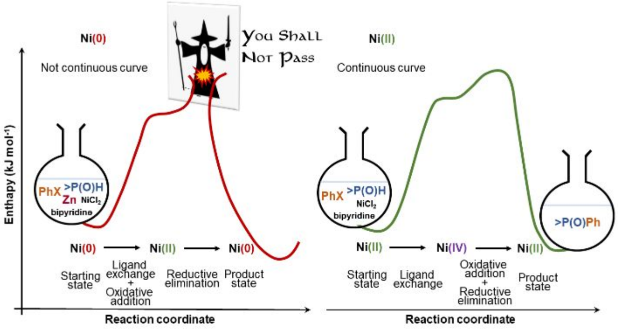


ABSTRACT

It was found by us that the P–C coupling reaction of >P(O)H reagents with PhX (X = I and Br) in the presence of $NiCl_2$/Zn as the precursors for the assumed Ni(0) complexant together with 2,2’-bipyridine as the ligand took place only with PhI at 50/70 °C. M06-2X/6-31G(d,p)//PCM(MeCN) calculations for the reaction of $Ph_2P(O)H$ and PhX revealed a favorable energetics only for the loss of iodide following the oxidative addition of PhI on the Ni(0) atom. However, the assumed transition states with Ni(II) formed after P-ligand uptake and deprotonation could not undergo reductive elimination meaning a “dead-end route”. Hence, it was assumed that the initial complexation of the remaining Ni^{2+} ions with 2,2’-bipyridine may move the P–C coupling forward *via* a Ni(II)→Ni(IV) transition. This route was also confirmed by calculations, and this mechanism was justified by preparative experiments carried out using $NiCl_2$/bipyridine in the absence of Zn. Hence, the generally accepted Ni(0)→Ni(II) route was refuted by us, confirming the generality of the Ni(II)→N(IV) protocol, either in the presence of bipyridine, or using the excess of the >P(O)H reagent as the *P*-ligand. The results of the calculations on the complex forming ability of Ni(0) and Ni(II) with 2,2'-bipyridine or the *P*-reagents were in accord with our mechanistic proposition.

Keywords: Hirao reaction, halogenobenzene, >P(O)H reagent, P–C coupling, Ni catalyst, 2,2'-bipyridine, reductant, mechanism, theoretical calculations

INTRODUCTION

The Hirao reaction that is a P–C coupling between vinyl and aryl halides (mostly bromides) and >P(O)H reagents, such as dialkyl phosphites, alkyl phenyl-*H*-phosphinates and secondary phosphine oxides is in the focus these days. On the one hand, it is a useful synthetic procedure to provide phosphonates, phosphinates and tertiary phosphine oxides,[1,2] on the other hand, its mechanism is also of interest. The Hirao P–C coupling is an up-do-date alternative of the Michaelis–Arbuzov reaction or Friedel–Craft arylation involving the interaction of bromoarenes with trialkyl phosphites, or the functionalization of arenes with phosphinoyl chlorides, respectively.

Originally, Hirao described the application of tetrakis(triphenylphosphine)palladium as the catalyst,[3–5] then different Pd(0) precursors, *e.g.* Pd(II) salts were also used together with mono- or bidentate *P*-ligands.[1,2,6] There is an agreement that the originally present, or the *in situ* formed Pd(0) undergoes oxidative addition with the vinyl- or aryl bromide. This step is followed by a ligand exchange connecting the >P(O)H reagent to the central Pd(II) ion. The final step of the catalytic cycle is reductive elimination to furnish the P–C coupled product and the regenerated Pd(0) catalyst.[7–9] A more general scheme of the metal-catalyzed P–C couplings is shown in Figure 1.

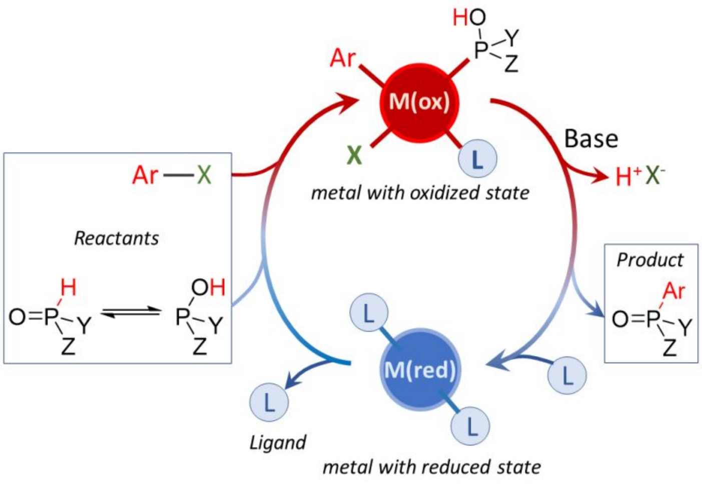


Figure 1. General scheme for the Hirao reaction of ArX and YZP(O)H species. The metal (M) can be Pd or Ni.

It was an important observation that a suitable excess of the >P(O)H reagent, via its >P-OH tautomeric form, may serve as the *P*-ligand, and hence, there is no need to add the usual phosphines.[10] And what is more, the excess of the *P*-reagent may also serve as the reducing agent to convert Pd(II) to Pd(0). A refined mechanism supported by experimental data and quantum chemical calculations was set up for the "*P*-ligand-free" accomplishment by us.[11] Moreover, the structure of the catalyst was identified as $(HO)Y_2P$---Pd(O)---$PY_2(OH)$ (where Y = aryl, alkyl or alkoxy), and its formation was also evaluated.[12] It is well-known that secondary phosphine oxides existing under the $Y^2P(O)H \rightleftharpoons Y^2POH$ tautomeric equilibrium (where Y = aryl or alkyl)[13] may be applied as preligands in transition metal complex catalysts.[14–17]

Ni-catalysis is another option to carry out P–C couplings. Typical cases for Ni-catalyzed Hirao reactions were summarized in Table 1. The first group includes $Ni(cod)_2$ as the catalyst precursor. Surprisingly, it could be used without any added ligand (Table 1, entry 1).[18] Recalling our experience with Pd $(OAc)_2$,[10] it is reasonable to assume that a part of the >P(O)H reagent may have served as the *P*-ligand. In most of the cases, $Ni(cod)_2$ was used together with *N*-[19] or *P*-ligands[20–22] (Table 1, entry 2 and entries 3–5, respectively). It is also a possibility that the P–C couplings are performed using Ni(0) catalysts prepared *in situ* from Ni(II) salts by reduction with Zn (or Mg). In these cases, 2,2'-bipyridine was applied as a suitable ligand (Table 1, entries 6 and 7).[23,24] There seems to be an agreement that in the above instances a Ni(0) → Ni(II) conversion is involved in the catalytic cycle. In just one case, a *P*-ligand was used together with Zn as the reductant (Table 1, entry 8).[25] Examples involving Ni(II) salts together with mostly *P*-, and occasionally *N*- and *O*-ligands in the absence of an external reducing agent represent special instances (Table 1, entries 9–12).[26–29] The question arises if the reduction of Ni(II) can be assumed or not in these cases. Two *P*-ligand-free protocols applying $Ni(NO_3)_2$-based nanoparticles[30] or just $NiCl_2$[31] (Table 1, entries 13 and 14) were also described. In the latter variation, the authors of this article proved experimentally and by high level quantum chemical calculations that, surprisingly, a Ni(II) → Ni(IV) transformation occurs in the catalytic cycle, and the >P-OH tautomer of the *P*-reagent provides the ligand.[32] Beside aryl derivatives, 1,1-dibromo-1-alkenes were also used as starting materials in Ni-catalyzed reductive type P–C couplings with diphenylphosphine oxide.[33]

In this paper, we wish to investigate the P–C coupling reaction of halogenobenzenes (PhX, X = Br or I) with diphenylphosphine oxide and ethyl phenyl-*H*-phosphinate using a Ni(II) salt together with 2,2'-bipyridine, in the presence or absence of Zn as the reducing agent. The purpose of this study is to clarify the oxidation state of Ni in the P–C coupling reactions under discussion, and to set up a reliable mechanism utilizing preparative experiments and high level quantum chemical calculations. It was also our aim to critically evaluate and interpret the literature data accumulated on the reductive type of Hirao reactions.

Table 1. Ni-Catalyzed P–C Coupling of Aryl Derivatives with >P(O)H Reagents

entry	aromatic substrate	Ni catalyst precursor	*N*-, *P*- or *O*-ligand	external reducing agent	base	solvent	T (°C)/t	yield (%)	ref.
1	$ArS(O)_nMe$ (n = 0–2)	$Ni(cod)_2$	–	–	$^tBuONa/K$	dioxane	100/≤1 day	30–98	20
2	ArCN	$Ni(cod)_2$	8-hydroxyquinoline (*N*)	–	^tBuOK	dioxane	90/16 h	13–90	21
3	ArOTf	$Ni(cod)_2$	dppf (*P*)	–	K_2CO_3	dioxane	80/20 h	56–96	22
4	$ArOC(O)^tBu$	$Ni(cod)_2$	dcype (*P*)	–	K_2CO_3	dioxane	~100/18 h	50–98	23
5	ArOPiv	$Ni(cod)_2$	dcype (*P*)	–	Cs_2CO_3	PhMe	~100/≥1 day	36–98	24
6	ArX	$NiCl_2$	2,2'-bipyridine (*N*)	Zn (2 equiv.)	–	H_2O	70/1 day	75–97	25
7	PhI	$NiCl_2$	2,2'-bipyridine (*N*)	Zn (2 equiv.)	–	DMF	50/1 day	75	26
8	ArOY (Y = Ms, Ts)	$NiCl_2$ /	dppf (*P*)	Zn (1 equiv.)	DIPEA	DMF	≤140/1.5 day	29–87	27
9	$ArB(OH)_2$	$NiBr_2$	pyridine (*N*)	–	K_2CO_3	DCE	100/1 day	50–98	28
10	ArX	$NiCl_2$ /	dppp (*P*)	–	K_3PO_4	dioxane	100/≤1 day	14–99	29
11	ArX	$NiCl_2$ /	PPh_3 or DME (*P* or *O*)	–	K_2CO_3 or ^tBuONa	DMF	≤90/≤10 h	46–87	30
12	ArO"act"[a]	$NiCl_2$ /	dppp (*P*)	–	K_2CO_3	MeCN	≤120/≤20 h	30–95	31
13	ArBr	$Ni(NO_3)_2$-based NP[b]	–	–	K_2CO_3	MeCN	100/18 h	3–86	32
14	ArBr	$NiCl_2$	–	–	TEA	MeCN	150 (MW)/≤1 h	31–92	33

[a] "act": activating group.

[b] NP: nanoparticle.

RESULTS AND DISCUSSION

1. P–C coupling reactions under reductive conditions

At first, we wished to compare the most important Ni(0)-catalyzed P–C coupling protocols described in the literature. In our experiments, the coupling of bromobenzene or iodobenzene with diphenylphosphine oxide served as the model reaction. In the first experiment, PhBr and $Ph_2P(O)H$ were reacted in the presence of 10% of $NiCl_2$ as the catalyst precursor, 2 equivalents of Zn as the reductant, and 2,2'-bipyridine (20%) as the *N*-ligand in water as the solvent. Applying the conditions (a 1 day heating at 70 °C) described by Zhao et al.,[23] and following the work-up suggested (filtration, extraction by DCM, drying and chromatography), triphenylphosphine oxide (TPPO) was obtained in a low yield of 5% that could be confirmed after a few repetitions (Table 2, entry 1). In comparison, the yield reported was 92%.[23] In the next experiment, iodobenzene was applied instead of PhBr. In this case, our confirmed yield for TPPO was much better, 65% (Table 2, entry 2) that was still lower than the reported outcome of 92%.[23] It is obvious that PhI is more reactive than PhBr in the P–C couplings investigated. Then, the similar "reductive" Hirao reaction of ethyl phenyl-*H*-phosphinate with PhI was performed in DMF as the solvent, and heating the mixture at 50 °C for one day in the presence of Zn, and in the absence of TEA as described by Japanese authors.[24] At 50 °C, the yield of ethyl diphenylphosphinate (76%), was almost the same reported (75%)[24] (Table 2, entry 3). At a somewhat higher temperature of 70 °C, the yield remained practically the same (78%). Then, the previous reactions were repeated in the presence of two equivalents of TEA as the base. At 50 °C, the experimental and literature yields were 85% and 99%,[24] respectively (Table 2, entry 4). Again no significant change could be observed after running the P–C coupling at 70 °C, as the yield was 84%. One can see that the presence of TEA has only a slight effect on the outcome (see Table 2, entry 3 versus entry 4). This may be due to the presence of 2,2'-bipyridine and Zn that may also act as bases.

As a new combination, PhEtOP(O)H was also reacted with PhBr under the previous conditions, but at 70 °C the reaction took place in a low useful conversion allowing a yield of only 15% for $Ph_2P(O)OEt$ (Table 2, entry 5). Then, $Ph_2P(O)H$ was reacted with PhI and PhBr in DMF in the presence of Zn as the reducing agent. These P–C couplings led to the formation of Ph_3PO in yields of 75% and 5%, respectively (Table 2, entries 6 and 7). The reaction of bis(4-methylphenyl)phosphine oxide with PhI and PhBr under similar conditions applied for the arylation of $Ph_2P(O)H$ led to similar results. The P–C coupling with PhI furnished $(4\text{-MePh})_2PhPO$ in a yield of 74%, but PhBr was found again to be unreactive allowing a yield of 8% (Table 2, entries 8 and 9).

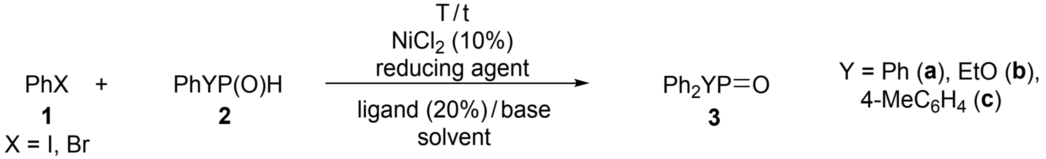
Then, driven by curiosity, the P–C coupling of PhI with PhEtOP(O)H, $Ph_2P(O)H$ and $(4\text{-MeC}_6H_4)_2P(O)H$ was performed in DMF at 70 °C for one day in the presence of TEA, but in the absence of Zn. To our surprise, the expected products, phosphinate [$Ph_2P(O)OEt$], and phosphine oxides [Ph_3PO and $(4\text{-MeC}_6H_4)_2PO$] were formed, and could be isolated in yields of 71%, 80% and 75%, respectively (Table 2, entries 10–12). This means that, as a matter of fact, there is no need for Zn as a reductant.

Changing for Hirao reactions performed in the absence of reducing agent and *N*-ligand, the $NiCl_2$-catalyzed P–C coupling of PhEtOP(O)H and $Ph_2P(O)H$ with PhBr was carried out in MeCN using K_2CO_3 or Cs_2CO_3 as the base under MW irradiation. In this cases, the excess of the >P(O)H reagent served as the *P*-ligand *via* its >P-OH trivalent form. After a MW irradiation at 150 °C for 30 min, in agreement with our earlier experience,[31,32] the corresponding products $Ph_2P(O)OEt$ and Ph_3PO were isolated in yields of 86% and 83%, respectively (Table 2, entries 13 and 14). Repeating the last experiment with the difference that 1.2 equivalents of Zn was also added to the mixture before irradiation, the reaction went wrong, and only triphenylphosphine could be isolated from the mixture. PPh_3 could be isolated in a yield of 23% (Table 2, entry 15). It means that the addition of Zn was harmful to the P–C coupling, and the

Ph_3PO formed in a lower conversion was reduced to PPh_3 by the Zn under the conditions of the reaction (150 °C/MW). The MW-assisted P–C coupling of PhBr with $Ph_2P(O)H$ was also attempted in the presence of 2,2'-bipyridine as the ligand to the Ni catalyst using triethylamine as the base and DMF as the solvent. After an irradiation at 150 °C for 1 h, the usual work-up afforded Ph_3PO in a yield of 71% (Table 2, entry 16).

It can be said that in the experiments applying P-ligand and marked by Table 2/entries 13–15, the Ni(II)→Ni(IV) protocol proposed earlier[32] governs these P–C couplings. It is noteworthy that 2,2'-bipyridine was also a suitable ligand in the reaction of PhBr with $Ph_2P(O)H$ under MW irradiation (Table2/entry 16). The question emerges if the earlier assumed Ni(0)→Ni(II) variation may remain valid for the "reductive" accomplishments, if the P–C couplings take place also in the absence of Zn as the reductant? The answer is unambiguous "no", and this problem is investigated by theoretical calculations (see below).

Table 2. Ni-Catalyzed P–C Couplings under Different Conditions



$$\underset{\substack{\mathbf{1}\\ X = I,\ Br}}{PhX} + \underset{\mathbf{2}}{PhYP(O)H} \xrightarrow[\substack{ligand\ (20\%)/base\\ solvent}]{\substack{T/t\\ NiCl_2\ (10\%)\\ reducing\ agent}} \underset{\mathbf{3}}{Ph_2YP{=}O} \quad \substack{Y = Ph\ (\mathbf{a}),\ EtO\ (\mathbf{b}),\\ 4\text{-}MeC_6H_4\ (\mathbf{c})}$$

entry	X	Y	*N*- or *P*-ligand (%)	external reducing agent (equivalent)	base	solvent	T (°C)/t	conversion to Ph_2YPO[a] (%)	yield (%)	yield^{lit} (%)
1	Br	Ph	2,2'-bipyridine	Zn (2)	–	H_2O	70/1 day[b]	[c]	5 (**3a**)	92 (**3a**)[25]
2	I	Ph	2,2'-bipyridine	Zn (2)	–	H_2O	70/1 day	90	65 (**3a**)	92 (**3a**)[25]
3	I	EtO	2,2'-bipyridine	Zn (1.2)	–	DMF	50[d]/1 day	95	76 (**3b**)	75 (**3b**)[26]
4	I	EtO	2,2'-bipyridine	Zn (1.2)	Et_3N	DMF	50[d]/1 day	96	85 (**3b**)	99 (**3b**)[26]
5	Br	EtO	2,2'-bipyridine	Zn (1.2)	Et_3N	DMF	70/1 day	[c]	15 (**3b**)	
6	I	Ph	2,2'-bipyridine	Zn (1.2)	Et_3N	DMF	70/1 day	100	75 (**3a**)	
7	Br	Ph	2,2'-bipyridine	Zn (1.2)	Et_3N	DMF	70/1 day	[c]	5 (**3a**)	
8	I	4-MeC_6H_4	2,2'-bipyridine	Zn (1.2)	Et_3N	DMF	70/1 day	100	74 (**3c**)	
9	Br	4-MeC_6H_4	2,2'-bipyridine	Zn (1.2)	Et_3N	DMF	70/1 day	[c]	8 (**3c**)	
10	I	EtO	2,2'-bipyridine	–	Et_3N	DMF	70/1 day	97	71 (**3b**)	
11	I	Ph	2,2'-bipyridine	–	Et_3N	DMF	70/1 day	100	80 (**3a**)	
12	I	4-MeC_6H_4	2,2'-bipyridine	–	Et_3N	DMF	70/1 day	100	75 (**3c**)	
13	Br	EtO	PhEtOP(O)H	–	K_2CO_3	MeCN	150 (MW)/30 min	100	86 (**3b**)	85[e] (**3b**)[33]
14	Br	Ph	$Ph_2P(O)H$	–	Cs_2CO_3	MeCN	150 (MW)/30 min	100	83 (**3a**)	79 (**3a**)[34]
15	Br	Ph	$Ph_2P(O)H$	Zn (1.2)	Cs_2CO_3	MeCN	150 (MW)/30 min	[c]	23 (**4**)[f]	
16	Br	Ph	2,2'-bipyridine	–	Et_3N	DMF	150 (MW)/30 min	92	71 (**3a**)	

[a] Based on relative ^{31}P-NMR intensities.

[b] No significant improvement in the yield on reaction at 100 °C for 2 days.

[c] Could not be detected.

[d] No significant change in the yield after carrying out the reaction at 70 °C for 1 day.

[e] In the presence of 5% of nickel chloride.

[f] PPh_3 (**4**) was the product.

2. Theoretical calculations on the complexing ability

The complexation processes of Ni(0) and Ni(II) with 2,2’-bipyridine or the PhYP(O)H $\rightleftharpoons$ PhYPOH species (Y = Ph and EtO) were studied by computational method at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory (Figure 2). The two ligands [bipyridyl and PhYP(O)H] present in the mixture may compete for the same Ni species. It is noteworthy that a sharp difference can be observed between the complexation enthalpies of Ni(0) and Ni(II) towards the two kinds of ligands under discussion (Table 3). In most cases, Ni(II) forms significantly stronger complexes both with bipyridine, and the >P(O)H species, than Ni(0). The differences in the enthalpy values may be measured in hundreds of kJ mol^{-1}. According to the enthalpies of complexation, Ni(0) prefers the >P-OH ligands to bipyridine, while the situation is just the opposite for Ni(II). Ni with the higher oxidation state of II prefers the bipyridine ligand and forms a more stable complex with this bidentate ligand, as compared to the complex formation with *P*-ligands.

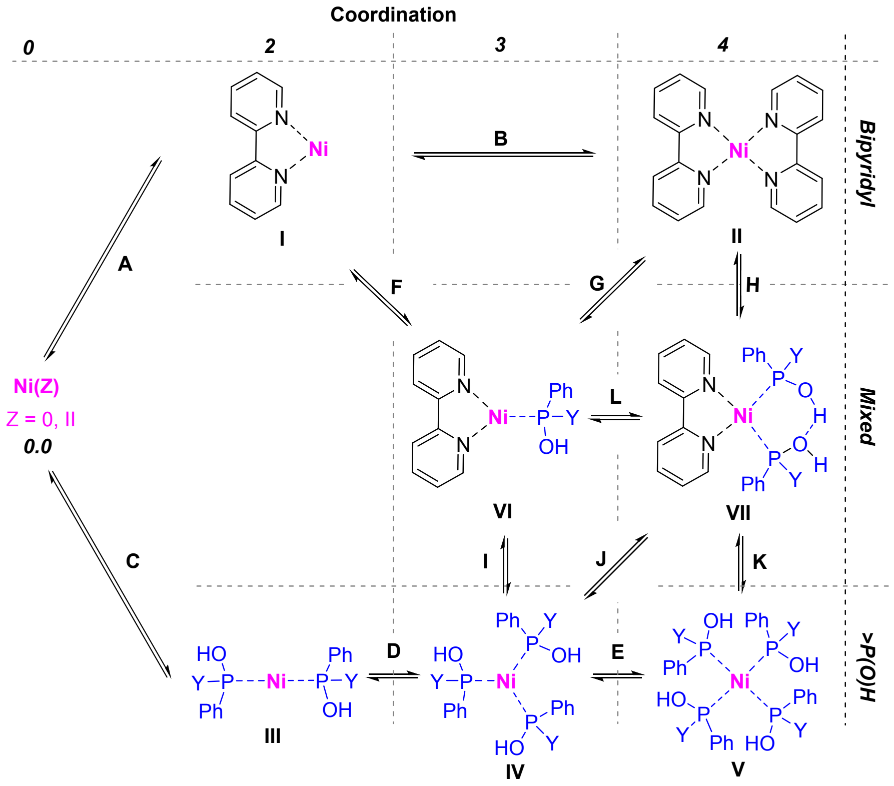


Figure 2. Summary of the complexation processes for Ni(0) and Ni(II). Letters **A**–**L** refer to the single steps.

Table 3. The enthalpy (Δ*H*) and Gibbs free energy values (Δ*G*) of the complexation of Ni(0) and Ni(II) by >P-OH or bipyridine computed at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory, given in kJ mol^{-1}. The meanings of letters **A–L** were defined in Figure 2.

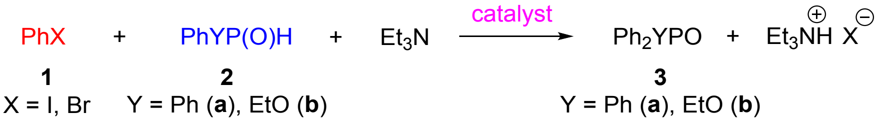
	Ni(0)				Ni(II)			
	Y = Ph		Y = OEt		Y = Ph		Y = OEt	
	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})
A	–64.5	–20.3	–64.5	–20.3	–440.0	–399.6	–440.0	–399.6
B	–301.1	–244.8	–301.1	–244.8	–343.7	–282.9	–343.7	–282.9
C	–123.8	–49.6	–108.6	–14.6	–310.9	–147.6	–312.6	–209.7
D	–132.8	–53.2	–168.3	–106.3	–263.3	–224.1	–181.1	–134.0
E	–180.8	–133.1	–119.1	–46.6	–171.6	–103.5	–191.7	–103.5
F	–118.8	–62.1	–130.0	–84.4	–143.0	–98.5	–118.8	–62.1
G	161.0	149.9	171.0	160.3	200.7	184.4	224.9	220.8
H	17.9	61.3	41.3	99.6	35.4	75.0	75.7	136.9
I	52.1	–12.3	82.3	16.1	–10.1	–63.4	–65.2	–118.0
J	–91.0	–100.9	–47.4	–44.7	–175.4	–172.8	–214.4	–201.9
K	89.8	32.2	71.7	2.0	–3.8	–69.3	–22.7	–98.4
L	–149.2	–83.9	–129.7	–60.7	–165.3	–109.4	–149.2	–83.9

3. Theoretical calculations on the mechanism of the Ni-catalyzed P–C couplings

3.1 Thermodynamics of the P–C coupling reaction of >P(O)H species with halogenobenzenes

M06-2X/6-31G(d,p) calculations suggested that the P–C couplings of $Ph_2P(O)H$ and PhEtOP(O)H with halogenobenzenes are exothermic, and that the reaction with PhI is more than two times exotermic than that with PhBr (Table 4).

Table 4. Thermodynamics of the Hirao reactions investigated.



X	Y = Ph			Y = OEt		
	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	Δ*S* (kJ mol^{-1})	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	Δ*S* (kJ mol^{-1})
Br^-	–64.2	–52.5	–39.1	–71.1	–51.8	–64.8
I^-	–153.9	–139.3	–49.0	–160.8	–138.5	–74.7

3.2 The course of the P–C couplings under reductive conditions [Ni(0)]

The reaction of $Ph_2P(O)H$ with PhI or PhBr served as the model reaction calculated by the M06-2X/6-31G(d,p)//PCM(MeCN) method (Figure 3). The catalytic cycle starts with the decomplexation of the rather stable bis[bipyridylNi(0)] complex (**II**) accompanied by the entry of the halogenobenzene (**1**) reactant. Immediately a π^2 complex (**5**) is formed, terminating the aromaticity of the phenyl ring. After the rearrangement of the complex, *i.e.* after an oxidative addition, the halogene is transferred and bound as an anion (Br^- or I^-) to the metal via a low energy transition state (**5***), and affords the corresponding intermediate (**6**) in an exothermic manner, meanwhile a phenyl anion is also generated. Theoretically, the two electrons required for the transformation outlined are covered by the oxidation of the Ni(0) to Ni(II). The energetics of the subsequent elimination of the halogenide anion depend on the nature of the halogene. The bromine anion is bound much stronger to the Ni atom than the iodine anion, hence the enthalpy demand for the debromination and deiodination is +235.4 kJ mol^{-1} and +80.1 kJ mol^{-1}, respectively. The resulting naked phenyl complex (**7**) is then attacked and complexed by the $Ph_2P(O)H$ reagent, gaining some enthalpy. The intermediates (**8**) are then deprotonated at the >P-OH moiety by TEA (that may be followed by a final rearrangement). However, the species (**9A** and **9B**) formed after deprotonation cannot undergo reductive elimination, as we could not find a reaction coordinate connecting directly the minimum of **9A** or **9B** and the state **I+3a**, meaning practically a “dead-end street”. Theoretically, in this elementary step a phenyl anion should approach and attack a negatively charged $>PO^-$ anion, which is prevented by the coulomb repulsion between them. Moreover, in this step, the Ni(II) should to be reduced by getting back two electrons, meanwhile the quasi P(III) should be oxidized to P(V). The enthalpy and energy values belonging to this dead-end street mechanism are listed in Table 5. Another invalid mechanism was observed, when the primary *P*-complex was not deprotonated, but directly attacked by the phenyl anion.

It is assumed that the Ni^{2+} ions that are present in a low concentration allowed by the thermodynamics of the red-ox system controlled by the Nernst equation may push the P–C coupling further via the corresponding bipyridyl complex (see below).

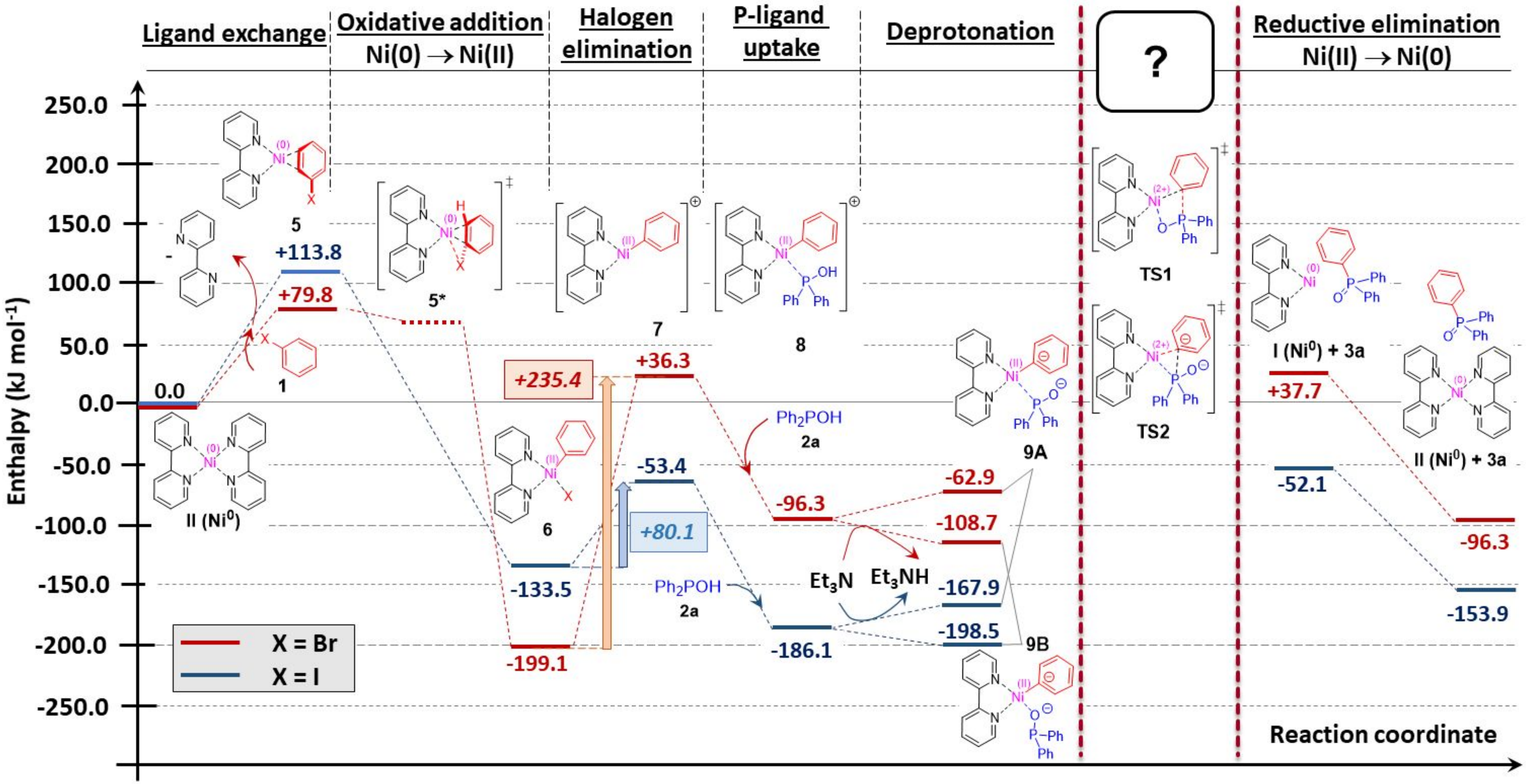


Figure 3. "Dead-end street" in the mechanism of the $Ph_2P(O)H$ +PhX (X = I, Br) reaction calculated by the M06-2X/6-31G(d,p)//PCM(MeCN) method.

Table 5. The enthalpy (Δ*H*) and Gibbs free energy values (Δ*G*) of the Hirao reaction with Ni(0), computed at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory, given in kJ mol^{-1}.

	X = Br		X = I	
	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})
5	79.8	69.8	+113.8	+102.0
6	–199.1	–212.8	–133.5	–150.6
7	36.3	–11.7	–53.4	–98.4
8	–96.3	–95.5	–186.1	–182.3
9A	–62.9	–58.7	–167.9	–161.7
9B	–108.7	–94.2	–198.5	–181.0
TS	DE*		DE*	
I + 3a	37.7	52.1	–52.1	–34.7
II + 3a	–64.2	–52.5	–153.9	–139.3

*DE = does not exist.

3.3 A study on the acidity of the naked and complexed PhYP(O)H reagents

According the computational results, the deprotonation of the PhYP(O)H (**2**) species (Y = Ph or EtO) by triethylamine (Figure 4, eq. 1 and Table 6, entry 1) is rather endothermic (Δ*H* = 140.0/150.8 kJ mol^{-1}), referring to their experimentally known weak acidic character. However, if the PhYP(O)H reagent is complexed with the (Bipy)Ni(II) (**VI/Ni(II)**), the acidity is significantly increased, and the deprotonation exhibits exothermic values (Δ*H* = -50.3/-73.2 kJ mol^{-1}) meaning a spontaneous loss of the proton (Figure 4, eq. 2 and Table 6, entry 2). In the case of (Bipy)Ni(0)–PPhY(OH) complexes (**VI/Ni(0)**), in accord with the Δ*H* values of 77.8 and 66.0 kJ mol^{-1}, the acidity is rather weak (Figure 4, eq. 3 and Table 6, entry 4). A deprotonation connected with the rearrangement of the *P*-complex (**VIII**) to the corresponding *O*-complex (**IX**) may also occur, and the enthalpy change for the formation of the rearranged product (**IX**) is more favorable than that for the corresponding *P*-complex (**VIII**) (Table 6, entries 3 and 5 *vs* entries 2 and 4).

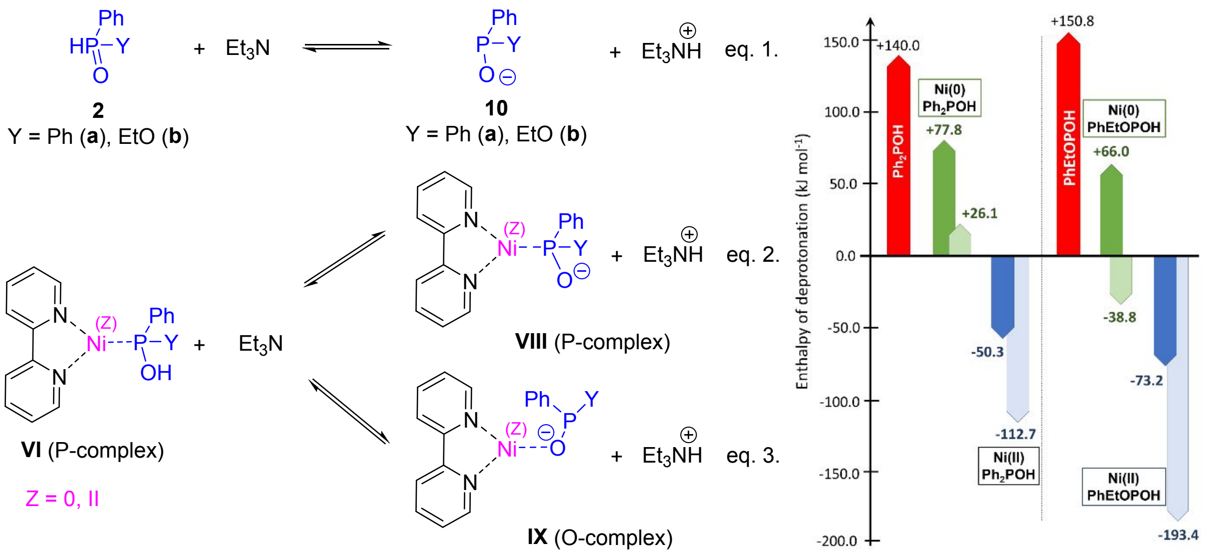


Figure 4. The acid-base equilibria for species **2** and **VI** in the presence of triethylamine. The corresponding enthalpy values visualized in the right side are listed in Table 6, computed at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory.

Table 6. The enthalpy (ΔH) and Gibbs free energy values (ΔG) (in kJ mol^{-1}) for the deprotonation of species **2** and **VI** in the presence of triethylamine, computed at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory.

entry	Ni(Z)			Y = Ph		Y = OEt	
				ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})
1	–	eq. 1.	**2→10**	+140.0	+133.0	+150.8	+152.6
2	Ni(II)	eq. 2.	**VI→VIII**	–50.3	–48.3	–73.2	–63.7
3		eq. 3.	**VI→IX**	–112.7	–101.9	–193.4	–190.0
4	Ni(0)	eq. 2.	**VI→VIII**	+77.8	+79.6	+66.0	+72.7
5		eq. 3.	**VI→IX**	+26.1	+35.1	–38.8	–30.4

3.4 The course of the P–C couplings in the absence of reductant

It was shown under point 3.2 that the Ni(0)→Ni(II)→Ni(0) sequence is not operable under the reductive conditions applied, as the reaction pathway is disrupted in the last step. It was assumed that the Ni(II)→Ni(0) process does not have the sufficient electrochemical potential to oxidate P(III) to P(V) in the final step. We decided to return to the Ni(II)→Ni(IV)→Ni(II) protocol, which was proved to be a realistic route applying *P*-ligands.[32] The catalytic process starting with Ni(II)-bipyridyl complex **II** was also evaluated by the M06-2X/6-31G(d,p)//PCM(MeCN) method. The **II→VII→VI→VIII→11→12→13→(14+3a)** route proposed was summarized in Figure 5, while the energetics are listed in Table 7. The reaction starts with an endothermic ligand exchange process (**II→VII**), followed by the elimination of one of the *P*-ligands (**VII→VI**) and a deprotonation (**VI→VIII**) by NEt_3. The next step involves the coordination of the halogenobenzene reactant, which is much more favorable in case of X=Br than in the instance with X=I. This refers to the much weaker C–I bond, which is dissociated easier. It was found that the oxidative addition of PhX within Ni(II)-bipyridyl complex **11** is realized *via* high energy state **12** with Ni(IV), affording the complex of product (as **13**) in a single step. The reduction of Ni(IV) in TS **12** to Ni(II), as in intermediate (**13**), is connected with the oxidation of P(III) to P(V) (again in **13**). It is worthy to mention that the enthalpy barrier is much lower for the addition of PhI than that for PhBr (+58.1 kJ mol^{-1} *vs* +201.3 kJ mol^{-1}). This is in full agreement with our experimental findings (see Table 2, entries 2, 6 *vs* entries 1, 7). An efficient P–C coupling of PhBr with $Ph_2P(O)H$ applying 2,2'-bipyridine as the ligand was possible only at a higher temperature of 150 °C under MW conditions (see Table 2, entry 16). The enthalpy requirement of 201.3 kJ mol^{-1} for the **11→12** transformation may be covered by MW irradiation. It was found earlier that the direct esterification of *P*-acids characterized by $\Delta H^{\#}$ of up to 186 kJ mol^{-1} can be performed under MWs.[34,35]

The Ni(II)→Ni(IV) protocol discussed above using the bipyridine ligand has not only been confirmed by our experiments and calculations, but it is also in agreement with the findings of other authors, especially Zhao *et al.,* who described a Ni(II)-catalyzed P–C coupling in the presence of pyridine as the *N*-ligand in the absence of a reductant.[26]

Our observation that the $NiCl_2$/2,2'-bipyridine-catalyzed P–C couplings take place *via* the Ni(II)→Ni(IV) route and not *via* the Ni(0)→Ni(II) protocol is in some respect groundbreaking, as till date the latter possibility was assumed. Considering our earlier finding that the Ni(II)/>P-OH-catalyzed Hirao reactions take also place *via* the surprising Ni(II)→Ni(IV) conversion,[32] this realization may be of general value.

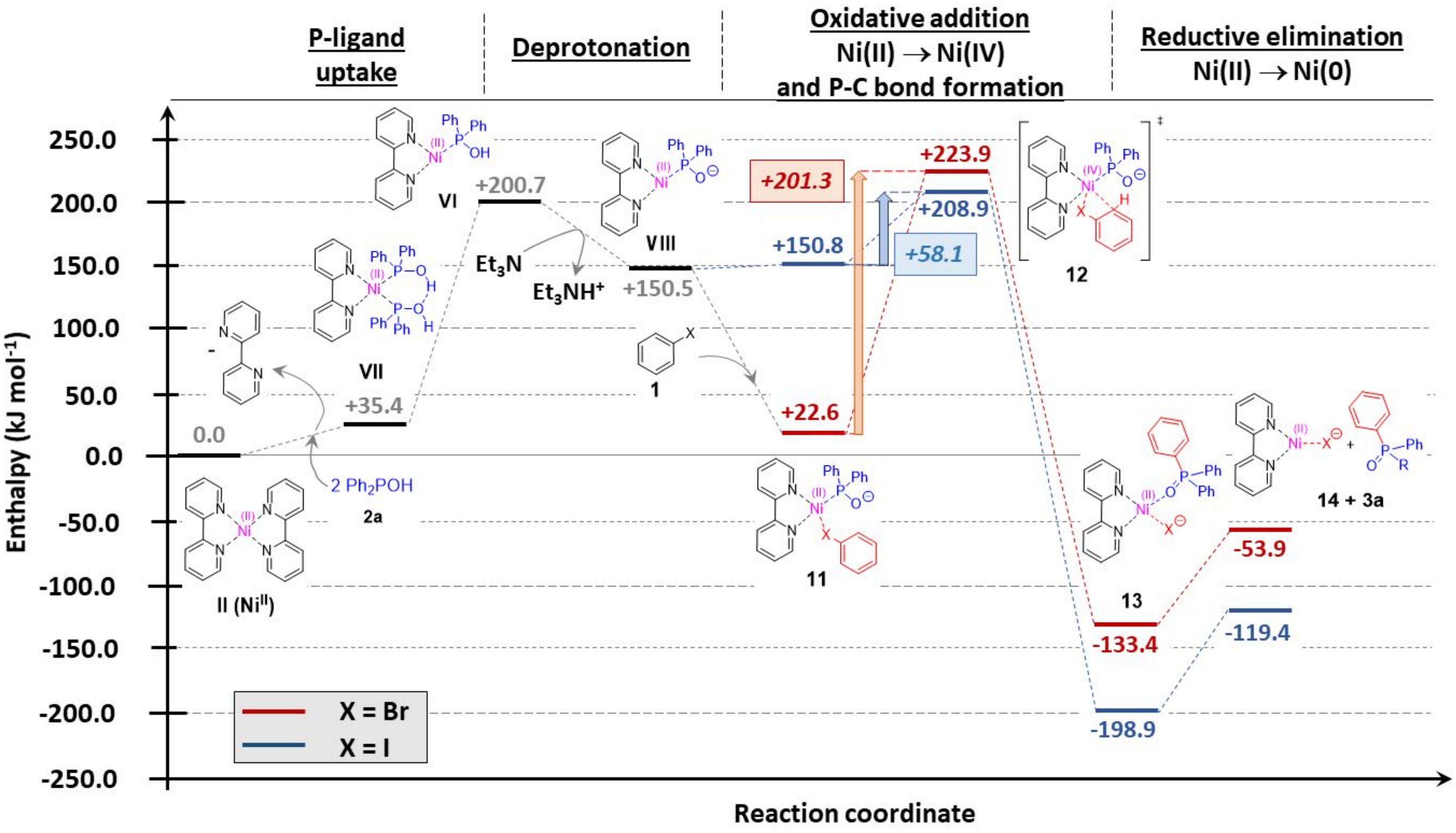


Figure 5. Reaction mechanism of the Hirao reaction of $Ph_2P(O)H$ +PhBr or PhI, calculated at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory.

Table 7. The enthalpy (ΔH) and Gibbs free energy values (ΔG) of the Hirao reaction with Ni(II), computed at M06-2X/6-31G(d,p)//PCM(MeCN) level of theory, given in kJ mol^{-1}.

	X = Br		X = I	
	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})
VIII	35.4	75.0	35.4	75.0
VII	200.7	184.4	200.7	184.4
IX	150.5	136.1	150.5	136.1
11	22.6	69.8	150.8	195.4
12	223.9	205.2	208.9	187.2
13+3a	–133.4	–87.5	–198.9	–153.0
14+3a	–53.9	–66.3	–119.4	–131.8

CONCLUSIONS

In summary, we found that the Hirao reaction of iodobenzene with diphenylphosphine oxide or ethyl phenyl-*H*-phosphinate in the presence of $NiCl_2$, 2,2'-bipyridine and Zn, as well as triethylamine in DMF at 50/70 °C afforded the corresponding P–C coupled products Ph_3PO and PhEtOPO *via* the Ni(II)→Ni(IV) protocol. Preparative experiments showed that the presence of Zn as a reductant had no impact on the course of the P–C coupling. Without Zn, the outcome of the reaction was practically the same as that in the presence of the reductant. Moreover, high level M06-2X/6-31G(d,p)//PCM(MeCN) calculations did not justify the Ni(0)→Ni(II) transition assuming the reductive variation of the Hirao reaction. This kind of approach simply led to a "dead-end street". However, the Ni(II) →Ni(IV) driven P–C coupling was justified, when 2,2-bipyridine was applied as the *N*-ligand. The enthalpy requirement of the oxidative addition of PhX (X=Br and I) on the "*N*,*N*,*P*–Ni(II)" complex depended on the nature of the halogene: PhI was more reactive than PhBr. It is recalled that the P–C coupling reactions of PhBr and >P(O)H reagents took also place, when some excess of the reagent served as the *P*-ligand (*via* the >P-OH tautomeric form) for $NiCl_2$. Heating at 150 °C under MW conditions allowed efficient phosphinoylation of PhBr. It can be concluded that the Ni(II)→Ni(IV) mechanism seems to be general, no matter if a *N*- or *P*-ligand is used. The results of the calculations on the competitive complexation of Ni(0) or Ni(II) with >P-OH or bipyridine were in agreement with our mechanistic calculations. Our experimental and theoretical results refuted the earlier assumed, but never proved Ni(0)→Ni(II) mechanism.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased in purities of >98% from Sigma-Aldrich or TCI, and were used without further purification. The reactions under traditional heating were performed in an oil bath.

The MW-assisted experiments were carried out in a CEM® Discover Model SP (300 W) focused microwave reactor equipped with a stirrer and a pressure controller using 100 W irradiation under isothermal conditions. The reaction mixtures based on batches of 0.5 mmol quantities were irradiated in sealed borosilicate glass vessel (with a volume of 10 mL) available from the supplier of CEM®. The reaction temperature was monitored by an external IR sensor. A scale-up to 1 mmol was not possible due to the limit of the MW device.

The ^{31}P, ^{13}C and ^{1}H NMR spectra were taken in $CDCl_3$ solution on a Bruker AV-300 spectrometer operating at 121.5, 75.5 and 300 MHz, respectively. The ^{31}P chemical shifts are referred to H_3PO_4, while the ^{13}C and ^{1}H chemical shifts are referred to TMS. The couplings are given in Hz. The melting point of products **3a** and **3c** was determined using a Bibby Scientific SMP10 Melting Point Apparatus.

General Procedure A: The Nickel-catalyzed P–C Coupling of Bromo-, or Iodobenzene with >P(O)H reagents in the Presence of $NiCl_2$ as the Catalyst Precursor and 2,2'-Bipyridine as the *N*-Ligand.

To a test tube was added 0.0065 g (0.050 mmol) of nickel chloride, 0.60 mmol of the aryl halide (**1**) (0.063 mL of bromobenzene or 0.067 mL of iodobenzene), 0.50 mmol of the >P(O)H reagent [0.10 g of diphenylphosphine oxide (**2a**), 0.075 mL of ethyl phenyl-*H*-phosphinate (**2b**) or 0.11 g of bis(4-methylphenyl)phosphine oxide (**2c**)], 0.016 g (0.10 mmol) of 2,2′-bipyridine, 1 mL water or DMF as the solvent. At certain cases (for details, see Table 2) zinc powder [0.039 g (0.60 mmol) or 0.065 g (1.0 mmol)] and 0.14 mL (1.0 mmol) triethylamine was also measured in. The resulting mixture was stirred in an oil bath at the temperatures and for the times shown in Table 2. The crude reaction mixture was filtrated and passed through a thin (2-3 cm) layer of silica gel using ethyl acetate as the solvent. The crude product was analyzed by ^{31}P NMR spectroscopy and further purified by column chromatography (see below).

As a representative example, the experiment covered by entry 11 of Table 2 was scaled up to a double amount. In this case, the yield of **3a** was 83%.

General Procedure B: The MW-assisted Hirao Reaction of Bromobenzene with Diphenylphosphine Oxide or Ethyl Phenyl-*H*-phosphinate in the Presence of $NiCl_2$.

The MW-assisted reactions were performed according to our earlier methods.[31,32] To a MW glass vessel was added 0.0065 g (0.050 mmol) of nickel chloride, 0.052 mL (0.50 mmol) of bromobenzene, 0.12 g (0.60 mmol) of diphenylphosphine oxide (**2a**) or 0.090 mL (0.60 mmol) of ethyl phenyl-*H*-phosphinate (**2b**), 0.16 g (0.50 mmol) of cesium carbonate and 1 mL of acetonitrile. In one case (Table 2, entry 15) 0.039 g of (0.6 mmol) zinc powder was also added. The resulting mixture was irradiated in the MW reactor at 150 °C for 30 min for (see Table 2, entries 13–15). The crude reaction mixture was filtrated and passed through a thin (2-3 cm) layer of silica gel using ethyl acetate as the solvent. The crude product was analyzed by ^{31}P NMR spectroscopy and further purified by column chromatography using silica gel and ethyl-acetate – hexane as the eluent.

In one case (Table 2, entry 16), a mixture of 0.063 mL (0.60 mmol) of bromobenzene, 0.10 g (0.50 mmol) of diphenylphosphine oxide (**2a**), 0.0065 g (0.050 mmol) of nickel chloride, 0.016 g (0.10 mmol) of 2,2′-bipyridine and 0.14 mL (1.0 mmol) triethylamine in 1 mL of DMF as the solvent was irradiated at 150 °C for 1 h as above. Following a similar work-up, triphenylphosphine oxide (**3a**) was obtained in a yield of 71%.

Triphenylphosphine Oxide (3a): Following the *General Procedure A*. (Table 2, entries 2 and 11) or the *General Procedure B*. (Table 2, entry 14) and after purification by column chromatography (silica gel and hexane–acetone (6:4) as the eluent), **3a** was obtained as white crystals in yields of 65/80/83% (0.090/0.11/0.12 g) (see Table 2, entries 2, 11 and 14, respectively) and in purity of >98%. ^{31}P NMR (CDCl$_3$, 121.5 MHz) δ 29.1; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.41–7.58 (m, 9H), 7.60–7.74 (m, 6H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz) δ 128.5 (d, *J* = 12.1), 131.9 (d, *J* = 2.7), 132.1 (d, *J* = 9.9), 132.6 (d, *J* = 103.2); mp. 155–156 °C; all identical to those described in the literature.[12,20,23]

Ethyl Diphenylphosphinate (3b): Following the *General Procedure A*. (Table 2, entries 4 and 10) or the *General Procedure B*. (Table 2, entry 13) and after purification by column chromatography (silica gel and ethyl acetate–hexane (7:3) as the eluent, **3b** was obtained as colorless oil in yields of 85/71/86% (0.10/0.087/0.11 g) (see Table 2, entries 4, 10 and 13, respectively) and in purity of ≥98%. ^{31}P NMR (CDCl$_3$, 121.5 MHz) δ 31.4; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.37 (t, *J* = 7.1, 3H), 4.11 (quint, *J* = 7.1, 2H), 7.39–7.56 (m, 6H), 7.75–7.90 (m, 4H) ; ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz) δ 16.5 (d, *J* = 6.6), 61.1 (d, *J* = 5.9), 128.5 (d, *J* = 13.1), 131.6 (d, *J* = 10.1), 131.8 (d, *J* = 137.0), 132.1 (d, *J* = 2.8); all identical to those described in the literature.[10,24,25]

Bis(4-methylphenyl)phenylphosphine Oxide (3c): Following the *General Procedure A*. (Table 2, entries 8 and 12) and after purification by column chromatography (silica gel and hexane–acetone (6:4) as the eluent, **3c** was obtained as white crystals yields of 74/75% (0.11/0.12 g) (see Table 2, entries 8 and 12) and in purity of ≥96%. ^{31}P NMR (CDCl$_3$, 121.5 MHz) δ 27.8; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.39 (s, 6H), 7.18–7.35 (m, 4H), 7.36–7.76 (m, 9H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz) δ 21.6 (d, *J* = 1.4), 128.4 (d, *J* = 12.1), 129.2 (d, *J* = 12.5), 129.3 (d, *J* = 106.7), 131.7 (d, *J* = 2.8), 132.0 (d, *J* = 9.8), 132.1 (d, *J* = 10.3), 133.1 (d, *J* = 104.2), 142.4 (d, *J* = 2.8); mp. 76-77 °C; all identical to those described in the literature.[12,19,25]

Triphenylphopsphine (4): Following the *General Procedure B*. (Table 2, entry 15) and after purification by column chromatography (silica gel and hexane–acetone (6:4) as the eluent, **4** was obtained as a by-product as white crystals in a yield of 23% (0.030 g) and in a purity of ≥98%. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ –5.7; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.35 (m, 4H), 7.26–7.37 (m, 15H); ^{13}C{^{1}H} NMR ($CDCl_{3,}$ 75.5 MHz) δ 128.6 (d, *J* = 7.0), 128.8, 133.9 (d, *J* = 19.5), 137.3 (d, *J* = 10.7); mp. 79–80 °C; all identical to those described in the literature.[19,36]

For the spectroscopic data of compounds **3a–c** and **4** see the Supporting Information.

Theoretical calculations

All computations were carried out with the Gaussian16 program package (G16),[37] using standard convergence criteria for the gradients of the root mean square (RMS) Force, Maximum Force, RMS displacement and maximum displacement vectors (3.0×10^{-4}, 4.5×10^{-4}, 1.2×10^{-3} and 1.8×10^{-3}). Computations were carried out at M06-2X level of theory.[38] The basis set of 6-31G(d,p) was applied for C, H, O, P, N, Br, Ni and SDD/MWB46 for iodine.[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 398.15 K. Beside the vacuum calculations, the IEFPCM method was also applied to model the solvent effect, by using the default settings of G16, setting the $\varepsilon = 35.688$.[40] See the Supporting Information for details.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information (^{31}P, ^{1}H and ^{13}C NMR spectra of the products, energetics and geometrical data belonging to the theoretical calculations) is available free of charge on the ACS Publications website at DOI: …….

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Notes

The authors declare no competing financial interest.

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