*Proceeding Paper*

# Transition Metal-Catalyzed, "Ligand Free" P–C Coupling Reactions under MW Conditions [†]

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**Abstract:** A method of a "P-ligand free", Pd(OAc)$_2$-catalyzed P–C coupling reactions under MW conditions was investigated in our group. In our latest work this procedure was extended to dihalogenobenzenes. Copper-promoted reactions were studied experimentally and by quantum chemical calculations.

**Keywords:** P–C coupling reactions; microwave; palladium catalyst; nickel catalyst; copper catalyst

## 1. Introduction

The transition metal-catalyzed, P–C cross coupling reactions between vinyl halides and dialkyl phosphites were described 40 years ago by Hirao. The first reactions were carried out between vinyl/aryl halides and dialkyl phosphites in the presence of Pd(PPh$_3$)$_4$ catalyst [1,2]. Then, more phosphorus compounds, e.g., aryl phosphonates, -phosphinates and tertiary phosphine oxides were also prepared effectively [3–6]. Later on, several Pd compounds in combination with different types of P-ligands were applied [3–6]. In these reactions, the active catalyst was formed in situ. In the past years, microwave (MW) technology was also applied in organic chemistry, that resulted in excellent yields during shorter reaction times [3–6]. Some nickel and copper salt catalyzed coupling reactions with added P- or N-ligands were also published [3–6].

## 2. Pd(OAc)$_2$-and NiCl$_2$-Catalyzed, Directly Added "P-ligand Free" P–C Coupling Reactions

Our group suggested a new Pd(OAc)$_2$-catalyzed, MW-assisted method for the P–C coupling reactions in 2013. These reactions were named "P-ligand free" Hirao reactions because of the lack of typically applied mono- or bidentate P-ligands [7]. They studied the coupling reactions between aryl derivatives and different >P(O)H-reagents, when the P-reagents were applied in some excess (Scheme 1) [7,8].
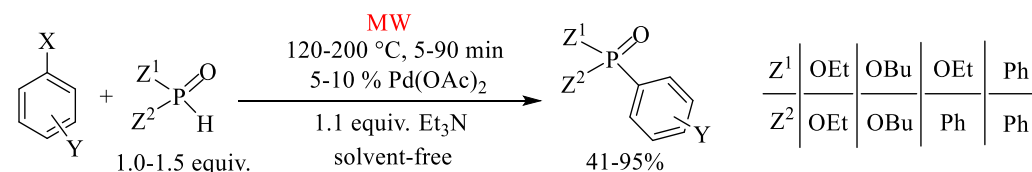


X = Br, I, OTf

Y = H, 4-MeO, 3-MeO, 4-Pr, 4-Et, 4-Me, 3-Cl, 4-F, 3-F, 4-CO$_2$Et, 3-CO$_2$Et, 4-C(O)Me, 3-C(O)Me

**Scheme 1.** "Ligand free" P–C coupling reactions in the presence of Pd(OAc)$_2$ precursor.

It is known that the catalytic cycle of the P–C coupling reactions is very similar to C–C couplings; the main steps are oxidative addition, ligand exchange and reductive elimination [9,10]. However, by our group, the entire, detailed catalytic cycle was calculated on the model reaction of the Pd(OAc)$_2$-promoted coupling of bromobenzene (PhBr) and diethyl phosphite (DEP) or diphenylphosphine oxide (DPPO) [11–13]. It was found, the necessary quantity of the >P(O)H-reagent's excess is 3 times of the catalyst precursor's amount. The P-reagent served as reduction agent and as the catalyst ligands via its trivalent tautomeric form (>POH). It all means, that if 10% of Pd(OAc)$_2$ is applied, 30% of the >P(O)H-reagent is needed, all together 1.3 equivalents [11–13]. We also studied the kinetics of the coupling reactions, and an induction period was found (Figure 1) [14]. In the first ~22 min the active catalyst (**1**) may be formed in situ from the Pd-precursor and the tautomeric form of the P-compoud. We confirmed the reactivity order of the aryl halides: iodobenzene (PhI) was the most, PhBr was less, and chlorobenzene (PhCl) was the least reactive. We successfully promoted the PhBr and DPPO coupling reaction with potassium iodide (KI) at 100 °C [14].
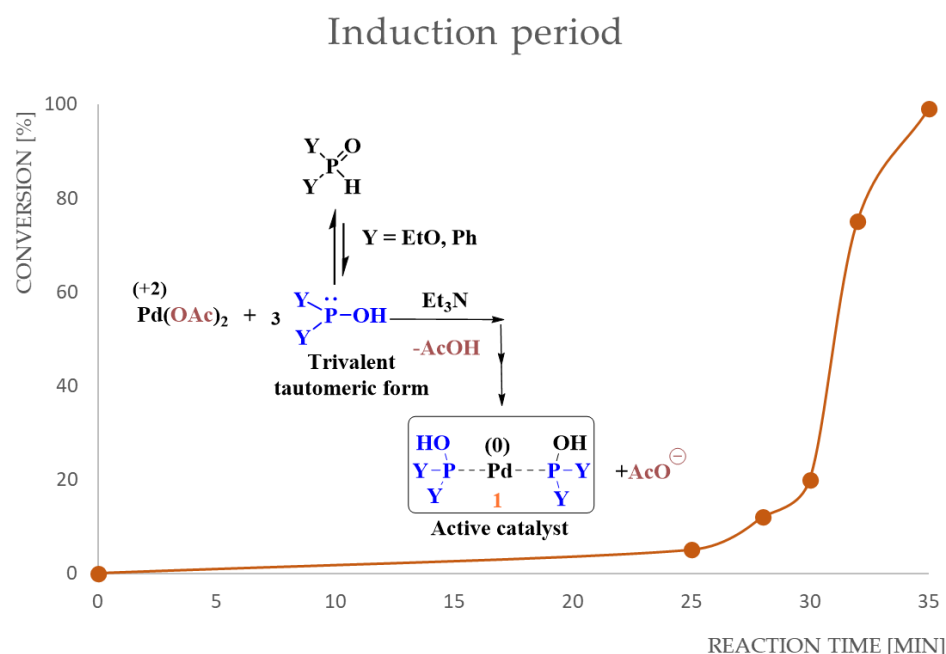


**Figure 1.** Induction period of the Hirao reaction with forming the active catalyst.

After the previous results, we extended this, Pd(OAc)-catalyzed, "P-ligand free", MW-assisted method to different bromo-halogenobenzenes. 1,4-, 1,3- And 1,2-dibromobenzenes and the analogous bromo-iodo or bromo-chloro derivatives were reacted with DEP and DPPO too (Scheme 2.) [15]. We found that in most cases, the costly bromo-iodobenzenes could be replaced by the cheaper dibromo derivatives. The bis(>P(O)-benzene) species were synthesized directly or from the isolated mono(>P(O)-bromophenyl) derivatives. Three new products were prepared and characterized.
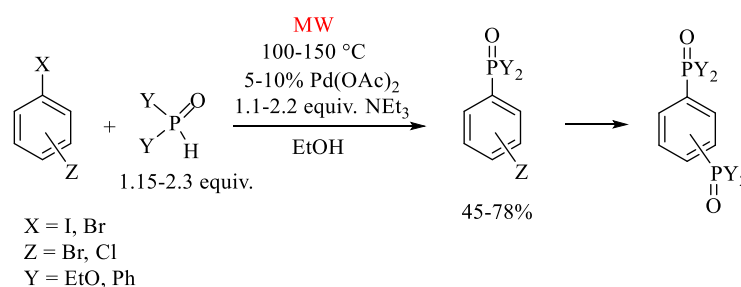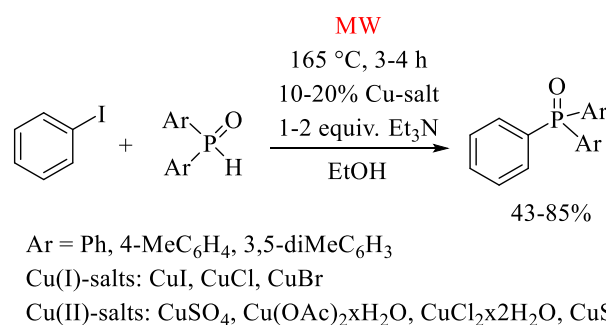
**Scheme 2.** The "ligand free" P–C coupling reactions of different bromo-halogenobenzenes.

As a variation, "ligand free" nickel-catalyzed (e.g., NiCl$_2$), MW-assisted methods were also published earlier by our group [13,16–18]. The mechanism was calculated, and unexpectedly, a Ni(II)→Ni(IV) transition was observed instead of the earlier assumed Ni(0)→Ni(II) formation.

### 3. Cu-Catalyzed Hirao Reactions

After the Pd- and Ni-catalyzed accomplishments, we investigated the use of copper catalysts, which could be a cheaper option. Due to the copper's lower reactivity, the most reactive aryl halide PhI had to be used. First experiments were carried out in the presence of Cu(I)-salts (e.g., CuI, CuCl and CuBr) at 165 °C under MW conditions [19]. Using 20% of CuBr as the catalyst precursor, and 2 equiv. of NEt$_3$ as the base, seemed to be the best (Scheme 3). The mechanism of the reaction was also studied by quantum chemical calculations.



Ar = Ph, 4-MeC$_6$H$_4$, 3,5-diMeC$_6$H$_3$
Cu(I)-salts: CuI, CuCl, CuBr
Cu(II)-salts: CuSO$_4$, Cu(OAc)$_2$xH$_2$O, CuCl$_2$x2H$_2$O, CuSO$_4$x5H$_2$O

**Scheme 3.** Hirao reaction of iodobenzene and secondary phosphine oxides in the presence of different Cu-precursors.

The three different ways of possible ligations of Cu(I) may be seen in Figure 2. The calculation results suggested that complexes **2** and **6** may catalyze the coupling reaction, but complex **6** is more dominant according to experiments. It can be seen, Cu(I) → Cu(III) oxidation happens in the oxidative addition step [19].
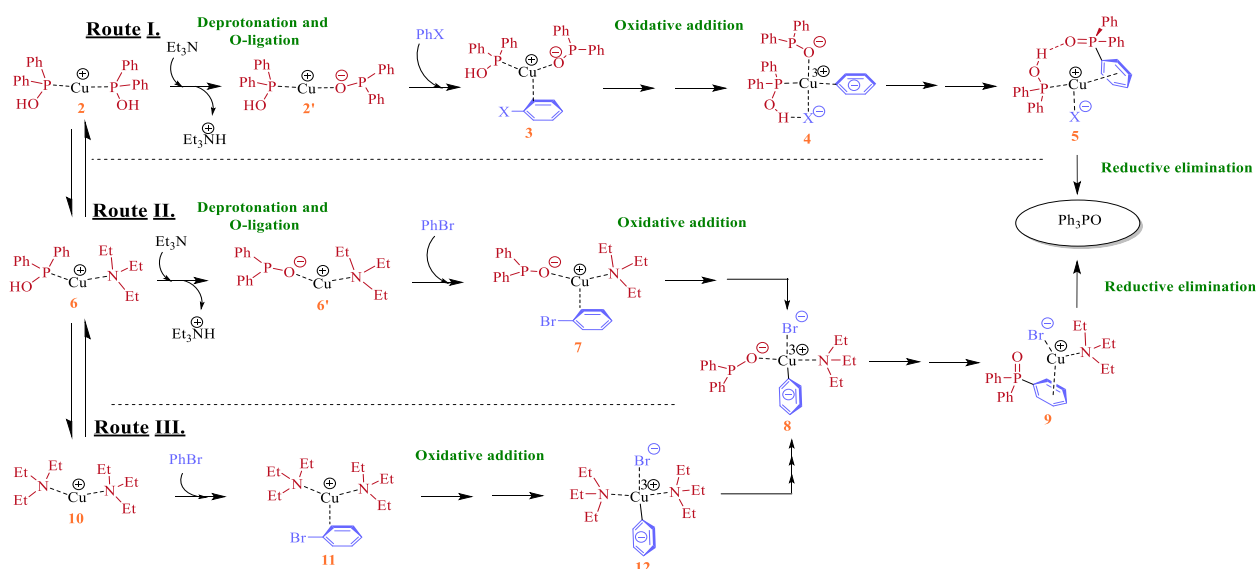
**Figure 2.** Three possible routes of Cu(I)-salts catalyzed, P–C coupling reactions.

Later on, Cu(II)-salts (e.g., $CuSO_4$, $Cu(OAc)_2 \cdot xH_2O$, $CuCl_2 \cdot 2H_2O$, $CuSO_4 \cdot 5H_2O$) were studied in the coupling reactions (Scheme 3) [20]. It was concluded that applying 20% of $CuSO_4$ or $Cu(OAc)_2 \cdot xH_2O$ as catalysts, together with 2 equiv. of $NEt_3$ is the best combination.

The earlier mentioned Cu(I) analogous reaction mechanism was assumed also in the Cu(II) case: in the oxidative addition step, the $Cu^{2+}$ would be oxidized formally to $Cu^{4+}$. However, this step was not feasible, between intermediates **15** and **17** no real TS (**16**) was found on the potential energy surface (Figure 3) [20].
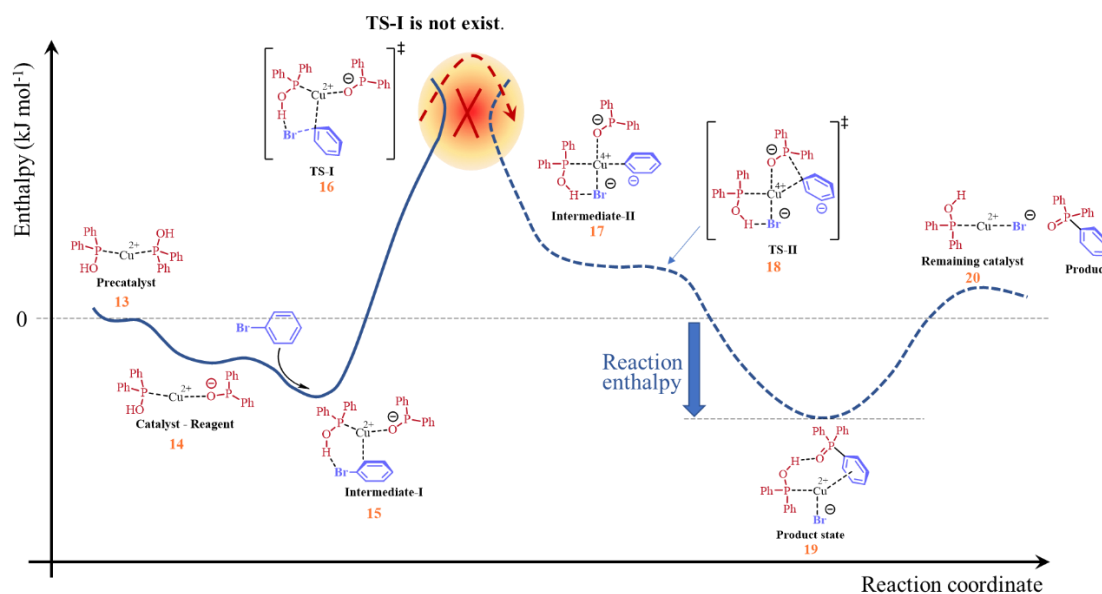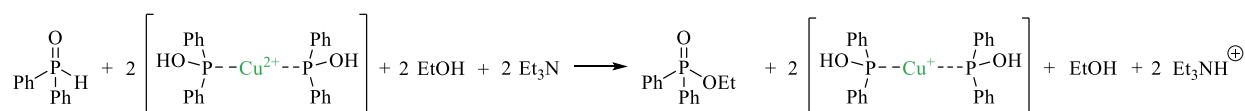


**Figure 3.** A "broken" mechanism.

Searching for a valid mechanism for the Cu(II)-precursors-catalyzed reactions, we looked for an alternative interpretation: a Cu(II) → Cu(I) reduction was assumed by the secondary phosphine oxide, accompanied by the P(III) → P(V) oxidization (Scheme 4) [20].

**Scheme 4.** The assumed $Cu^{2+} \rightarrow Cu^+$ reduction.

## 4. Conclusions

The "ligand free", Pd(OAc)₂-catalyzed method was successfully used for synthesis of bromophenylphosphine oxides and phosphonates. The neglected Cu(I) and Cu(II)-salts catalyzed P–C coupling reaction of iodobenzene with secondary phosphine oxides (diarylphosphine oxides) was elaborated under MW irradiation. The investigated reactions were the most efficient, when the P-reagent and NEt₃ were used in a 1:2 molar ratio. The mechanisms were studied by quantum chemical calculations.

**Author Contributions:** All authors have read and agreed to the published version of the manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

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