

Microwave Assisted Synthesis of Aryl Phosphonates and Tertiary Phosphine oxides by the Hirao Reaction †

Bianka Huszár*, Zoltán Mucsi and György Keglevich

Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary; zoltanmucsi@gmail.com (Z.M.); keglevich.gyorgy@vbk.bme.hu (G.K.)

* Correspondence: huszar.bianka@vbk.bme.hu

† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: <https://ecsoc-25.sciforum.net/>.

Abstract: Our group described a green, “P-ligand free”, Pd(OAc)₂- or NiCl₂-catalyzed synthesis under MW conditions. The reactivity of a few aryl derivatives in the Pd(OAc)₂-catalyzed, “P-ligand free” P–C coupling reactions under MW condition was also studied. An induction period was observed. Finally, the less known copper(I)-promoted reactions were investigated experimentally. The mechanism was explored by quantum chemical calculations.

Keywords: P–C coupling; Hirao reaction; microwave; palladium catalyst; nickel catalyst; copper(I) catalyst; ligand free

1. Introduction

The synthesis of tertiary phosphine oxides and aryl phosphonates, as important pharmaceutical and pesticide intermediates, catalyst ligand precursors, is a widely studied area in organophosphorus chemistry [1]. One way of forming P–C bond involves transition metal catalyzed cross coupling reactions. 40 years ago Hirao et al. was the first who discovered the protocol of the P–C coupling reactions between vinyl halides and dialkyl phosphites in the presence of Pd(PPh₃)₄ catalyst [2]. Then, the method was extended to give not just vinyl phosphonates, but aryl phosphonates, -phosphinates and tertiary phosphine oxides [3]. To avoid the use of the sensitive and high-cost catalyst, various Pd sources in combination with different mono- and bidentate P-ligands were used [4–6]. In these cases, the active catalyst was formed *in situ*. Later on, the microwave (MW) technology, as a greener tool for syntheses was applied in phosphorus chemistry [1,4–6]. Using MW conditions in the Hirao reaction instead of conventional heating resulted in high conversions and excellent yields during shorter reaction times. Since then, not just palladium but nickel and copper precursor catalyzed P–C coupling reactions have also been developed with added P- or N-ligands [4–6].

2. Pd(OAc)₂-Catalyzed P–C Coupling Reactions in the Absence of Directly Added P-Ligands

Our group, Keglevich and co-workers suggested a new Pd(OAc)₂-catalyzed, MW-assisted method for the Hirao reaction, when the >P(O)H-reagents were applied in excess (Scheme 1) [7,8]. The tautomeric form (>POH) of the >P(O)H-reagent served as the P-ligand. These reaction types were named “P-ligand free” coupling reactions because the generally applied P-ligands were not added to the reaction mixture. They found that any kind of substituents (electron-withdrawing e.g., halogeno, ethoxycarbonyl and acetyl or electron-donating e.g., alkyl and MeO) had an unfavourable effect on the course of the coupling reactions [8].

Citation: Huszár, B.; Mucsi, Z.; Keglevich, G. Microwave assisted synthesis of aryl phosphonates and tertiary phosphine oxides by the Hirao reaction. *Chem. Proc.* **2021**, *3*, x, <https://doi.org/10.3390/xxxxx>

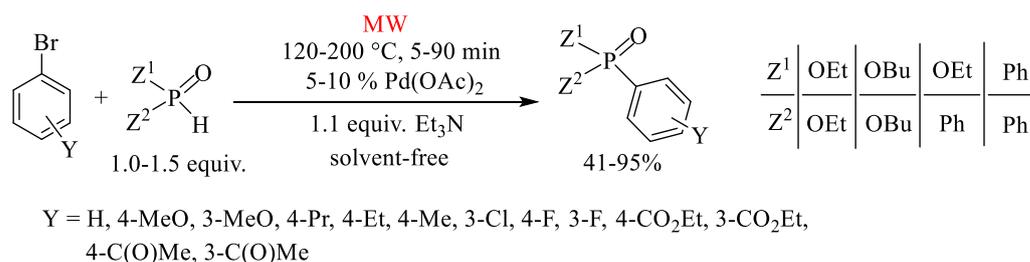
Academic Editor: Julio A. Seijas

Published: 15 November 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

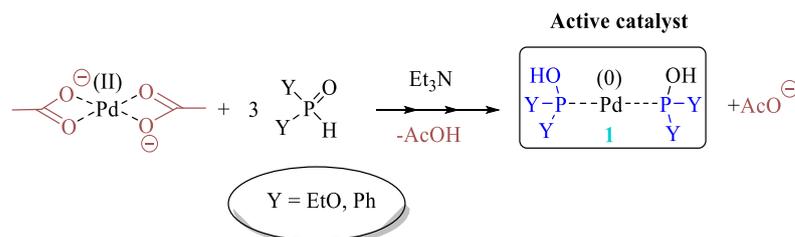


Copyright: © 2021 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).



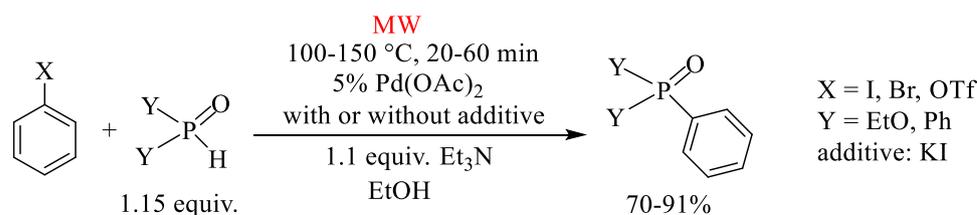
Scheme 1. Applying Pd(OAc)₂ as the catalyst precursor under MW-conditions in the “li-gand free” P–C coupling reactions.

Kalek and Stawinski published first that the general mechanism of the P–C coupling reactions is very similar to that of the C–C couplings [9,10]. It involves oxidative addition, ligand exchange and reductive elimination steps. The model reaction of the Pd(OAc)₂-promoted coupling of bromobenzene (PhBr) and diethyl phosphite (DEP) or diphenylphosphine oxide (DPPO) was investigated in the presence of triethylamine in ethanol as the solvent, the entire catalytic cycle by our group utilizing quantum chemical calculations [11]. It was found, the quantity of the P-reagent had to be 3 times of the catalyst precursor’s amount. It means, that if 5% of Pd(OAc)₂ is applied, 15% of the >P(O)H-reagent is needed, all together 1.15 equivalents. 5% as reducing agent for the Pd(II)→Pd(0) reduction, 10% as P-ligands to form the active catalyst (**1**) (Scheme 2) [11,12] and, of course, 1 equiv. as the reagent.



Scheme 2. Formation of the active catalyst in the “P-ligand free”, palladium acetate catalyzed coupling reactions.

Later on, we studied the reactivity of two aryl halides (such as PhI, PhBr) and phenyl trifluoromethanesulfonate (PhOTf) towards DEP and DPPO (Scheme 3) [13]. It was found that the iodobenzene (PhI) was the most reactive derivative. Under the same conditions (100 °C, 60 min) PhBr did not enter into reaction with DPPO, so we promoted the coupling with potassium iodide (KI). When the PhBr was pre-reacted with the KI in ethanol at 120 °C for 30 min, the coupling reaction was successful with the DPPO. PhOTf was the less reactive compound.



Scheme 3. Coupling reactions of PhI, PhBr and PhOTf with >P(O)H-compounds.

Then, we were interested in the kinetics of the Hirao reaction (Figure 1) [13]. It was found that in the first ~22 min the active catalyst (**1**) may be formed and the intrinsic coupling reaction started after 22 min. It means, reaction times described in the literature should be handled with care.

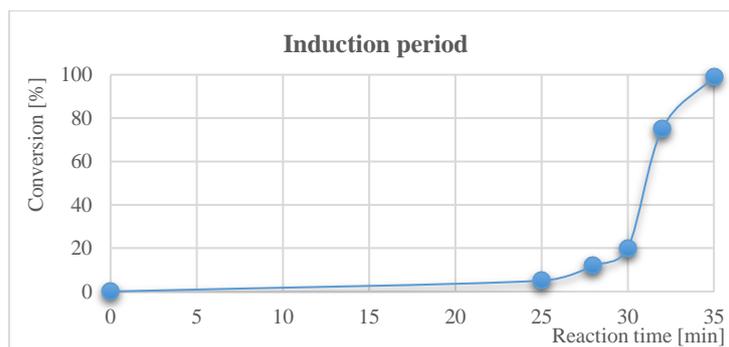
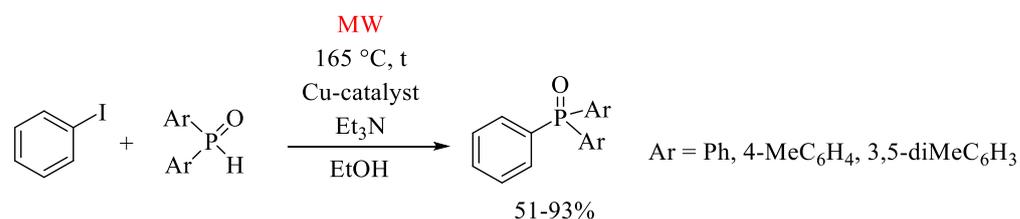


Figure 1. Induction period of the Hirao reaction at 120 °C.

In the next stage, efficient “ligand free” nickel-catalyzed (e.g., NiCl₂) syntheses were also elaborated by our group [14–17]. In these cases, surprisingly, Ni(II)→Ni(IV) oxidation happened instead of the Ni(0)→Ni(II) formation. Unfortunately, nickel is more toxic compound than the palladium, but more affordable.

3. Cu(I)-Catalyzed Hirao Reaction

In our latest work, we investigated the use of the less studied copper(I) catalysts (Scheme 4) [18]. The most reactive aryl halides, the PhI was chosen to compensate the copper’s lower reactivity. Bisligated P---Cu(I)---P (**A**), P---Cu(I)---N (**B**), and N---Cu(I)---N (**C**) complexes were considered as the catalysts. 20% of CuBr was found the most efficient catalyst precursor using with 2 equiv. of NEt₃ at 165 °C.



Scheme 4. Copper(I) catalyzed Hirao reaction of secondary phosphine oxides and iodobenzene.

The possible ligations of Cu(I) were also studied by calculations (Figure 2) [18], that suggested that complexes **A** and **B** may catalyze the P–C coupling, but the **B** is more advantageous both according to experiments. In the oxidative addition step a Cu(I)→Cu(III) oxidation takes place.

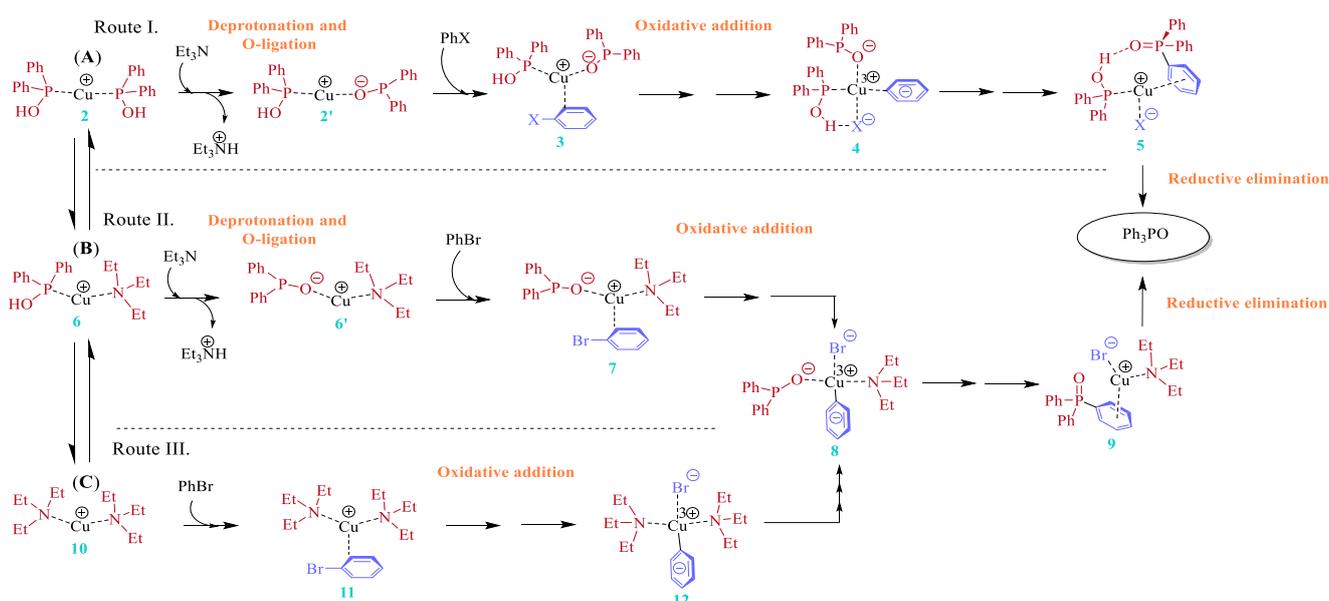


Figure 2. Three possible routes of the Cu(I)-salts catalyzed P-C coupling reactions.

4. Conclusions

It can be concluded that in the Pd(OAc)₂-catalyzed reaction the reactivity order was: PhI > PhBr > PhOTf. KI was a good choice to promote the coupling reaction between DPPO and PhBr. There is an induction period during the active catalyst may be formed. Nickel may also be an efficient catalyst precursor. It can be also seen that the copper could mean a cheaper option within transition metal catalysts without directly added ligands, in the presence of 2 equiv. triethylamine. However, a higher temperature and a longer reaction time were needed to reach ~90% conversion as compared to the case with Pd- or Ni-catalysts. Pd(0) → Pd(II), Ni(II) → Ni(IV), Cu(I) → Cu(III) oxidation processes took place in the different oxidative addition step.

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.

References

1. Keglevich, G. *Organophosphorus Chemistry—Novel Developments*; De Gruyter: Berlin, Germany, 2018.
2. Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. Stereoselective synthesis of vinylphosphonate. *Tetrahedron Lett.* **1980**, *21*, 3595–3598, [https://doi.org/10.1016/0040-4039\(80\)80245-0](https://doi.org/10.1016/0040-4039(80)80245-0).
3. Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. Palladium-catalyzed new carbon-phosphorus bond formation. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909–913, <https://doi.org/10.1246/bcsj.55.909>.
4. Jablonkai, E.; Keglevich, G. Advances and new variations of the Hirao reaction. *Org. Prep. Proced. Int.* **2014**, *46*, 281–316, <https://doi.org/10.1080/00304948.2014.922376>.
5. Jablonkai, E.; Keglevich, G. P-C bond formation by coupling reaction utilizing >P(O)H species as the reagents. *Curr. Org. Synth.* **2014**, *11*, 429–453, <https://doi.org/10.2174/15701794113109990066>.
6. Henyecz, R.; Keglevich, G. New developments on the Hirao reactions, especially from “green” point of view. *Curr. Org. Synth.* **2019**, *16*, 523–545, <https://doi.org/10.2174/1570179416666190415110834>.
7. Jablonkai, E.; Keglevich, G. P-Ligand-free, microwave-assisted variation of the Hirao reaction under solvent-free conditions; the P-C coupling reaction of >P(O)H species and bromoarenes. *Tetrahedron Lett.* **2013**, *54*, 4185–4188, <https://doi.org/10.1016/j.tetlet.2013.05.111>.
8. Keglevich, G.; Jablonkai, E.; Balázs, L. B. A “green” variation of the Hirao reaction: The P-C coupling of diethyl phosphite, alkyl phenyl-*H*-phosphinates and secondary phosphine oxides with bromoarenes using P-ligand-free Pd(OAc)₂ catalyst under microwave and solvent-free conditions. *RSC Adv.* **2014**, *4*, 22808–22816, <https://doi.org/10.1039/c4ra03292f>.
9. Kalek, M.; Stawinski, J. Pd(0)-catalyzed phosphorus-carbon bond formation. Mechanistic and synthetic studies on the role of the palladium sources and anionic additives. *Organometallics* **2007**, *26*, 5840–5847, <https://doi.org/10.1021/om700797k>.

10. Kalek, M.; Stawinski, J. Palladium-catalyzed C–P bond formation: Mechanistic studies on the ligand substitutio and the reductive elimination. An intramolecular catalysis by the acetate group in Pd^{II} complexes. *Organometallics* **2008**, *27*, 5876–5888, <https://doi.org/10.1021/om800641n>.
11. Keglevich, G.; Henyecz, R.; Mucsi, Z.; Kiss, N.Z. The palladium acetate-catalyzed microwave-assisted Hirao reaction without an added phosphorus ligand as a “green” protocol: A quantum chemical study on the mechanism. *Adv. Synth. Catal.* **2017**, *359*, 4322–331, <https://doi.org/10.1002/adsc.201700895>.
12. Henyecz, R.; Mucsi, Z.; Keglevich, G. 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 “PdP₂” catalyst. *Pure Appl. Chem.* **2019**, *91*, 121–134, <https://doi.org/10.1515/pac-2018-1004>.
13. Henyecz, R.; Huszár, B.; Grenitzer V.; Keglevich, G. A study on the reactivity of monosubstituted bentenes in the MW-assisted Pd(OAc)₂-catalyzed Hirao reaction with Ph₂P(O) and (EtO)₂P(O)H reagents. *Curr. Org. Chem.* **2020**, *24*, 1048–1054, <https://doi.org/10.2174/1385272824999200403170827>.
14. Jablonkai, E.; Balázs, L.B.; Keglevich, G. A P-ligand-free nickel-catalyzed variation of the Hirao reaction under microwave conditions. *Curr. Org. Chem.* **2015**, *19*, 197–202, <https://doi.org/10.2174/1385272819666150114235413>.
15. Henyecz, R.; Mucsi, Z.; Keglevich, G. A surprising mechanism lacking the Ni(0) state during the Ni(II)-catalyzed P–C cross-coupling reaction performed in the absence of a reducing agent—An experimental and a theoretical study. *Pure Appl. Chem.* **2020**, *92*, 493–503, <https://doi.org/10.1515/pac-2019-1004>.
16. Keglevich, G.; Henyecz, R.; Mucsi, Z. Experimental and theoretical study on the “2,2′-bipyridyl-Ni-catalyzed” Hirao reaction of >P(O)H reagents and halobenzenes: A Ni(0)→Ni(II) or a Ni(II)→Ni(IV) mechanism? *J. Org. Chem.* **2020**, *85*, 14486–14495, <https://doi.org/10.1021/acs.joc.0c00804>.
17. Keglevich, G.; Henyecz, R.; Mucsi, Z. Focusing on the catalysts of the Pd- and Ni-catalyzed Hirao reactions. *Molecules* **2020**, *25*, 3897, <https://doi.org/10.3390/molecules25173897>.
18. Huszár, B.; Henyecz, R.; Mucsi, Z.; Keglevich, G. MW-promoted Cu(I)-catalyzed P–C coupling reactions without the addition of conventional ligands; an experimental and a theoretical study. *Catalysts* **2021**, *11*, 933–948, <https://doi.org/10.3390/catal11080933>.