MICROWAVE ASSISTED SYNTHESIS OF ARYL PHOSPHONATES AND TERTIARY PHOSPHINE OXIDES BY THE HIRAO REACTION

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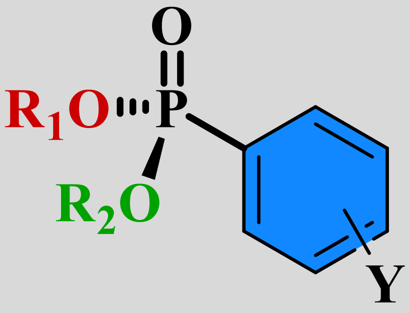
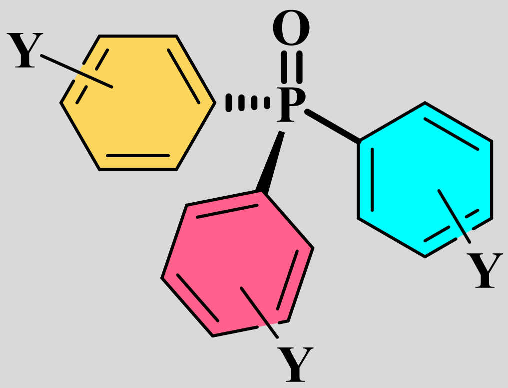
Aryl Phosphonates and Tertiary Phosphine Oxides

- **Aryl phosphonates**



Aryl phosphonates are important pharmaceutical, and pesticide intermediates, catalyst ligand precursors [1].

- **Tertiary phosphine oxides**



From tertiary phosphine oxides lots useful intermediates and reagents (e.g., catalyst ligands) could be produced by deoxygenation reactions [1].

One way of forming these products: using the P–C crosscoupling reactions.

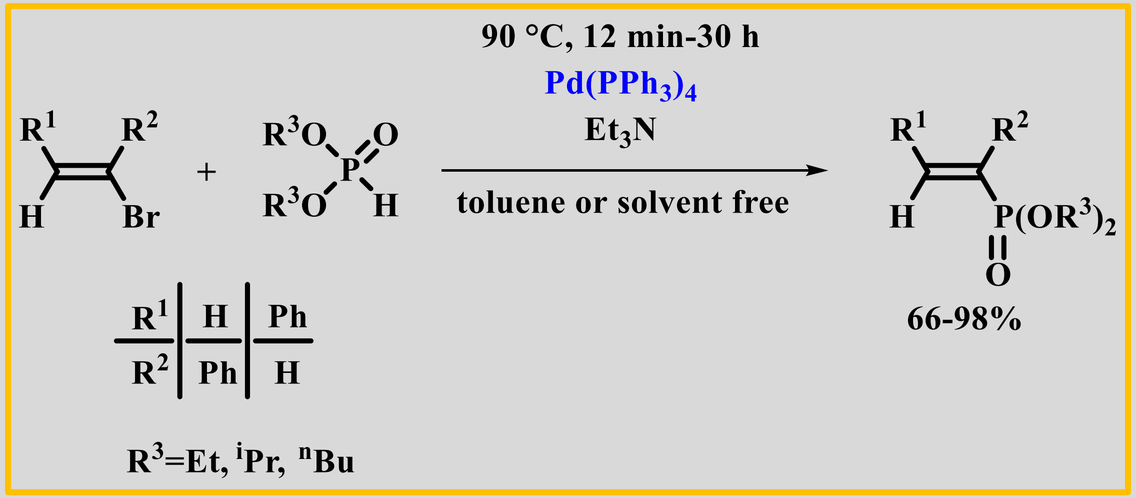
Let's see the literature background of the P–C reactions!

[1] Keglevich, G. Organophosphorus Chemistry - Novel Developments, De Gruyter, **2018**

The P–C Coupling Reactions – Literature review I.

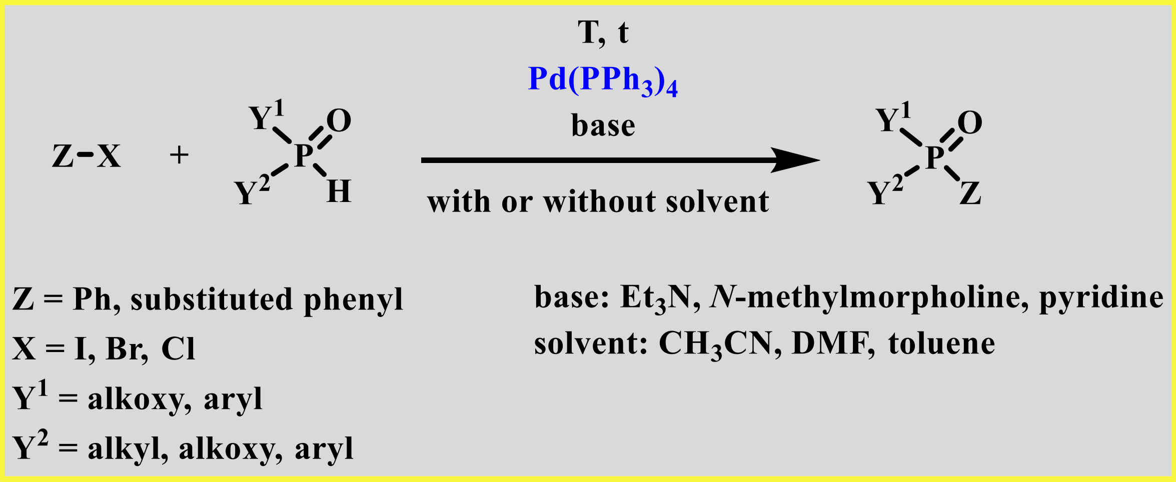
❑ *The Pd(PPh$_3$)$_4$ catalyst*

In 1980, new possibility of P–C bond formation was decribed the first time by Hirao *et al*. They applied Pd(PPh$_3$)$_4$ catalyst in the coupling reactions of vinyl halides and dialkyl phosphites [1,2]. After the success, this effective catalyst was also used several times in different coupling reactions between aryl halides and dialkyl phosphites, *H*-phosphinates or secondary phosphine oxides [3-5].



R^1	H	Ph
R^2	Ph	H

R^3=Et, ^{i}Pr, ^{n}Bu



Z = Ph, substituted phenyl
X = I, Br, Cl
Y^1 = alkoxy, aryl
Y^2 = alkyl, alkoxy, aryl

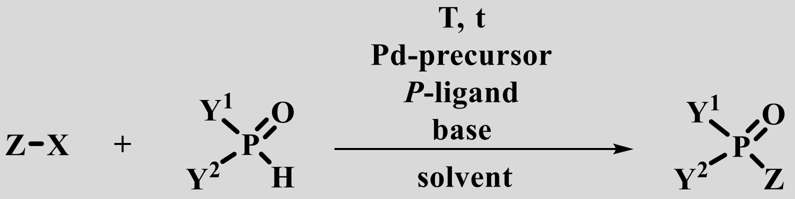
base: Et$_3$N, *N*-methylmorpholine, pyridine
solvent: CH$_3$CN, DMF, toluene

[1[Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T.; *Tetrahedron Lett.* **1980**, *21*, 3595.
[2] Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T.; *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.
[3] Jablonkai, E.; Keglevich, G.; *Org. Prep. Proced. Int.* **2014**, *46*, 281.
[4] Jablonkai, E.; Keglevich, G.; *Curr. Org. Synth.* **2014**, *11*, 429.
[5] Henyecz, R.; Keglevich, G.; *Curr. Org. Synth.* **2019**, *16*, 523.

The P–C Coupling Reactions – Literature review II.

❑ ***Pd-precursors and P-ligands***

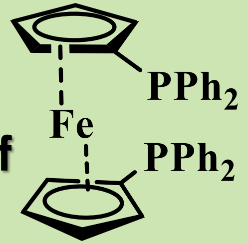
Unfortunately, the $Pd(PPh_3)_4$ catalyst had a high price and had sensitivity to air and moisture, so researchers started to use Pd-salts with directly added mono- or bidentate *P*-ligands. In these cases, the active catalyst was formed *in situ* [1-3].



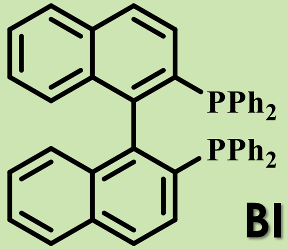
Z = Ph, subtituted phenyl, naphtyl, pyridyl
X = I, Br, Cl
Y^1 = alkoxy, phenyl $\quad$ Y^2 = alkyl, alkoxy, phenyl

Pd-precursor: $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$
base: Et_3N, $^iPr_2NEt$, pyridyne
solvent: DMSO, CH_3CN, toluene

P*-ligands: *e.g.

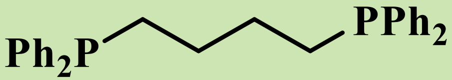


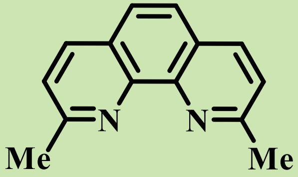
dppf



BINAP

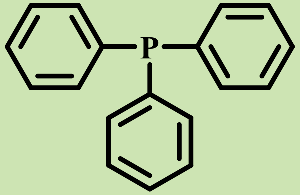
dppb

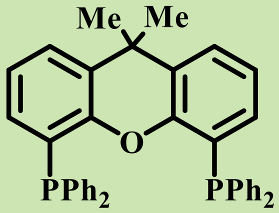




dmphen

PPh_3





Xantphos

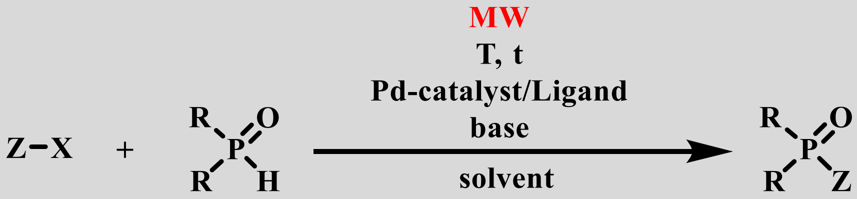
[1] Jablonkai, E.; Keglevich, G.; *Org. Prep. Proced. Int.* **2014**, *46*, 281.
[2] Jablonkai, E.; Keglevich, G.; *Curr. Org. Synth.* **2014**, *11*, 429.
[3] Henyecz, R.; Keglevich, G.; *Curr. Org. Synth.* **2019**, *16*, 523.

like a greener variation of the synthesis took place in phosphorus chemistry [1, 4-6]. Using MW-conditions in the Hirao reaction instead of the conventional heating resulted high conversions and good yields during s

The P–C Coupling Reactions – Literature review III.

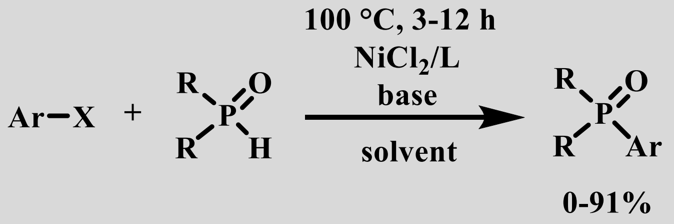
❑ *Microwave and palladium catalyst*

MW technology, as a greener way of carrying out syntheses has also appeared in phosphorus chemistry [1]. Using MW conditions in the Hirao reaction instead of conventional heating resulted in high conversions and excellent yields during shorter reaction times [2-4].



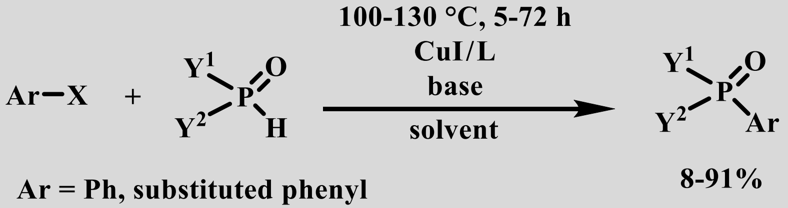
Z = Ph, substituted phenyl, naftyl, vinyl
X = I, Br, Cl R = alkoxy, phenyl
Pd-catalyst/Ligand: $Pd(PPh_3)_4$, $Pd(OAc)_2$/dmphen
base: Et_3N, K_2CO_3, Na_2CO_3
solvent: CH_3CN, DMF, H_2O

❑ *Nickel and copper catalyzed coupling reactions [2-4]*



X = Br, Cl
Y = OMe, Ph
Ar = substituted phenyl or naphthyl
L = PPh_3, P^cHex_3, dppe, dppp, dppf, $AsPh_3$

base: K_3PO_4, K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOAc, KO^tBu, $^iPr_2EtN$
solvent: dioxane, DMF, THF, MeCN



Y^1	OEt	Ph	OEt	O^iPr
Y^2	Ph	Ph	OEt	O^iPr

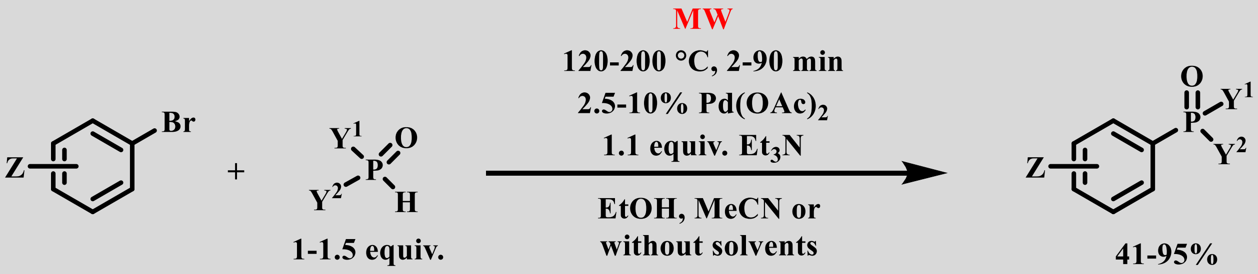
Ar = Ph, substituted phenyl
X = I, Br
L = 2,2'-bipyridine, proline, pipecolic acid, phenanthroline, 1-methylimidazole, α-benzoin oxime, salicylaldehyde oxime

base: Cs_2CO_3, K_2CO_3, K_3PO_4, NaO^tBu, DMAP
solvent: toluene, dioxane, DMF

[1] Keglevich, G. Organophosphorus Chemistry - Novel Developments, De Gruyter, **2018**
[2] Jablonkai, E.; Keglevich, G.; *Org. Prep. Proced. Int.* **2014**, *46*, 281.
[3] Jablonkai, E.; Keglevich, G.; *Curr. Org. Synth.* **2014**, *11*, 429.
[4] Henyecz, R.; Keglevich, G.; *Curr. Org. Synth.* **2019**, *16*, 523.

“*P*-ligand Free”, Pd(OAc)$_2$ Catalyzed Coupling Reactions

The Keglevich group developed a MW-assisted, Pd(OAc)$_2$-catalyzed method for the Hirao reaction without the usual applied *P*-ligands [1-4]. They added the >P(O)H-reagents in excess to the reaction mixture. It is cheaper and greener implementation. The catalytic cycle was evaluated by quantum chemical calculations [3-4]. The >P(O)H-compounds served as ligands in the formation of the active catalyst and were involved in the Pd(II)→Pd(0) reduction.



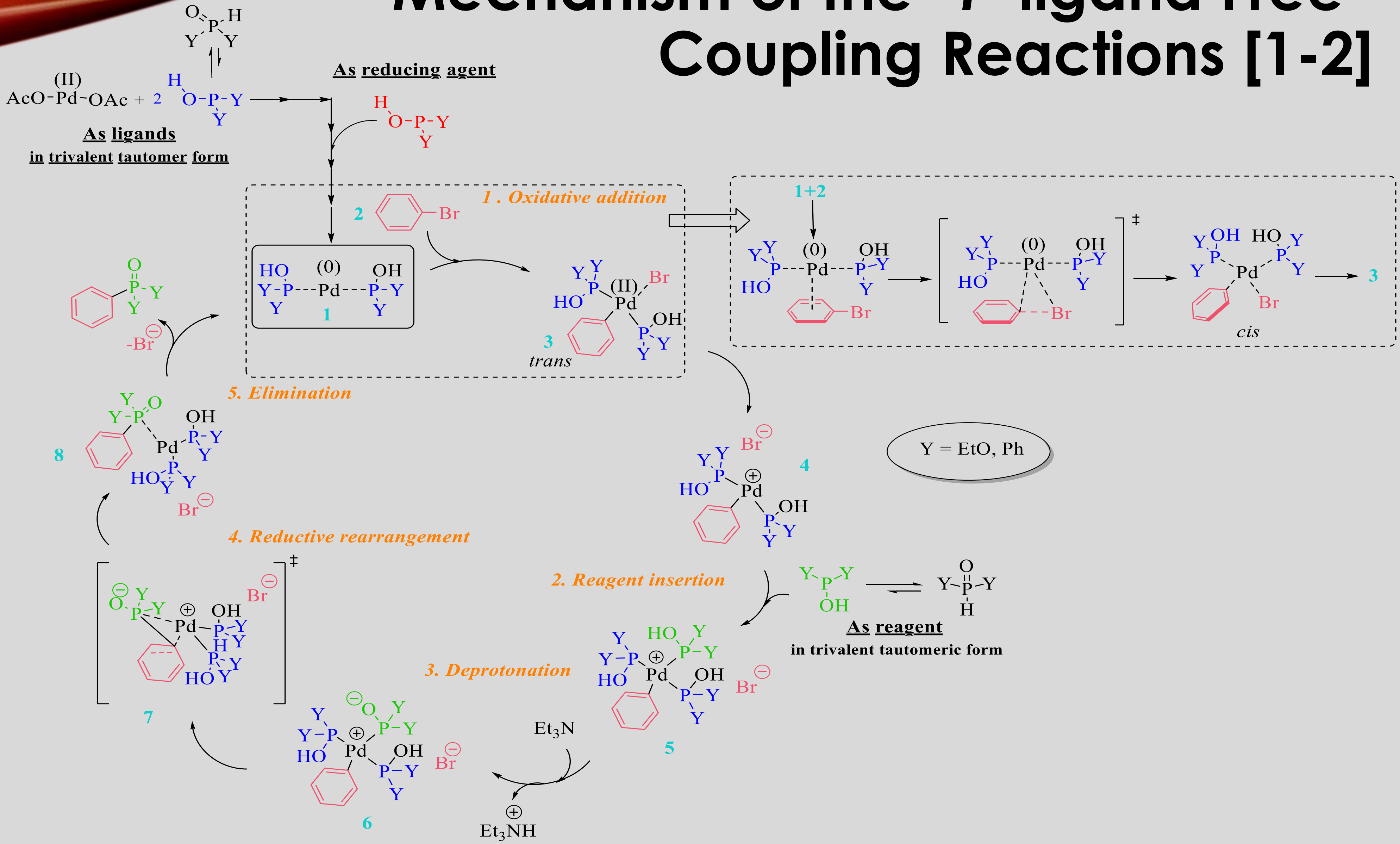
Y^1	OEt	OBu	OEt	OPr	O^{i}Pr	OBu	O^{i}Bu	Ph	Pr	Bu	Bn
Y^2	OEt	OBu	Ph	Ph	Ph	Ph	Ph	Ph	Pr	Bu	Bn

Z = H, 4-MeO, 3-MeO, 4-Pr, 4-Et, 4-Me, 4-F, 3-F, 4-Cl, 3-Cl, 4-EtO(O)C, 3-EtO(O)C, 4-Me(O)C, 3-Me(O)C

[1] Jablonkai, E.; Keglevich, Gy.; *Tetrahedron Lett*., **2013**, 54, 4185.
[2] Keglevich, Gy.; Jablonkai, E.; Balázs, L. B.; *RSC Adv*., **2014**, 4, 22808.
[3] Keglevich, G.; Henyecz, R.; Mucsi, Z.; Kiss, N.Z., *Adv. Synth. Catal*., **2017**, 359, 4322.
[4] Henyecz, R.; Keglevich, G.; Mucsi, Z.; *Pure Appl. Chem*., **2019**, 91, 121.

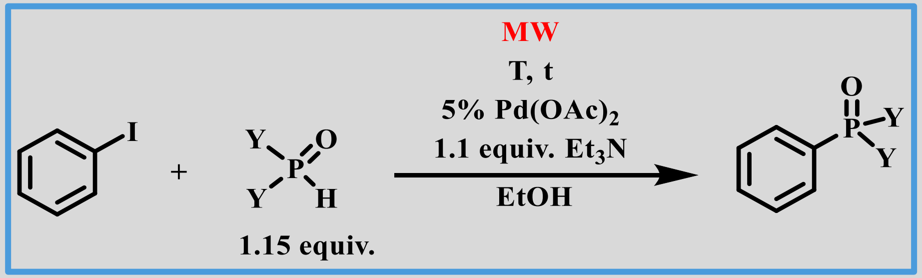
Mechanism of the “*P*-ligand Free” Coupling Reactions [1-2]

Quantum chemical calculations were made by **Dr. Zoltán Mucsi.**

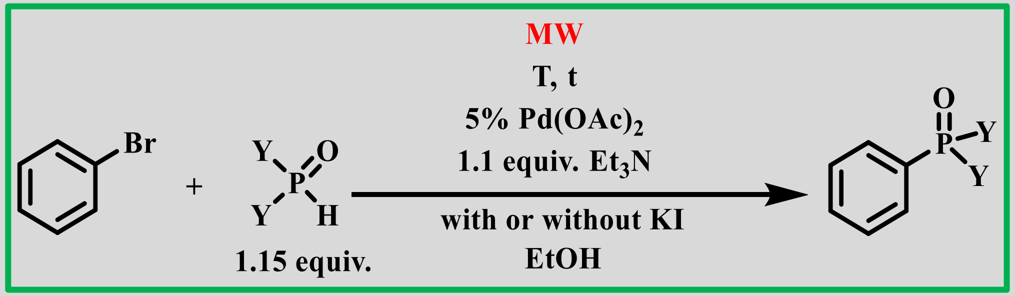


[1] Keglevich, G.; Henyecz, R.; Mucsi, Z.; Kiss, N.Z., *Adv. Synth. Catal.*, **2017**, *359*, 4322.
[2] Henyecz, R.; Keglevich, G.; Mucsi, Z.; *Pure Appl. Chem.*, **2019**, *91*, 121.

Reactivity of Different Aryl Derivatives [1]

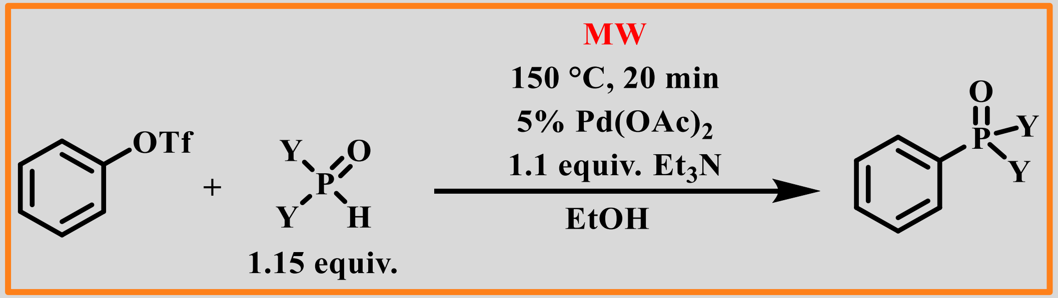


	Y	T [°C]	t [min]	Conversion [%]	Yield [%]
1.	Ph	100	60	100	91
2.	EtO	120	30	100	75



	Y	KI	T [°C]	t [min]	Conversion [%]	Yield [%]
1.	Ph	–	120	60	100	83 [2]
2.	Ph	–	100	60	0	–
3.	Ph	20%	100	60	49[a]	–
4.	Ph	1 equiv.	100	60	92[b]	85
5.	EtO	–	120	30	100	71

[a] There was no significant change in the presence of 50% of KI.
[b] Pre-reaction of PhBr and KI at 120 °C-on for 30 min in ethanol.



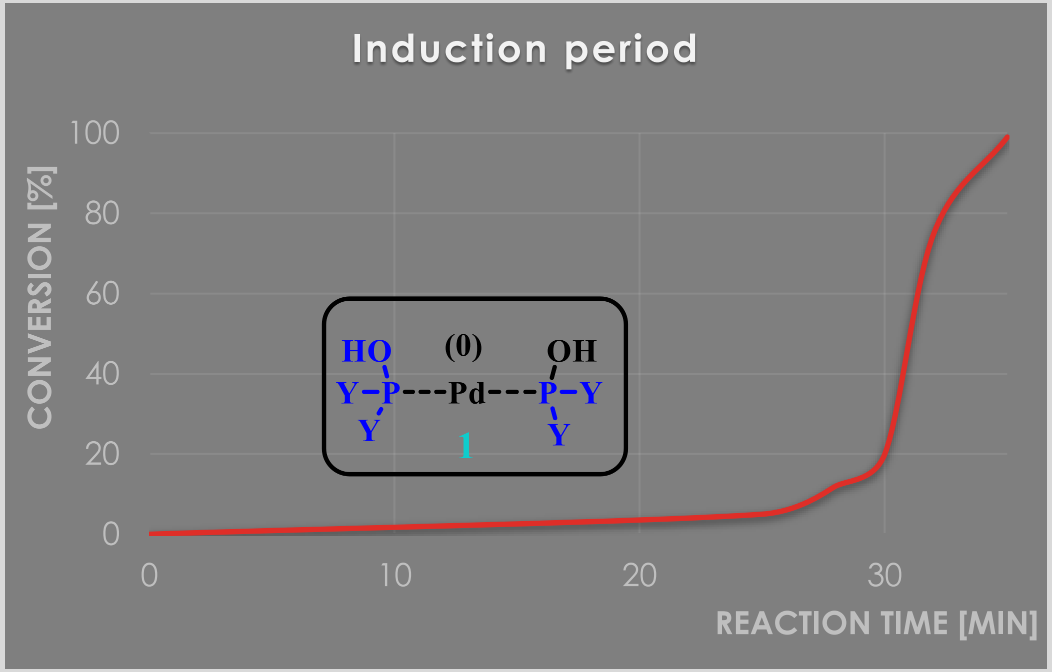
	Y	T [°C]	t [min]	Conversion [%]	Yield [%]
1.	Ph	150	20	100	86
2.	EtO	120	60	100	78

[1] Henyecz, R.; Huszár, B.;.Grenitzer V.; Keglevich, G.; *Curr. Org. Chem.*. **2020**, 24, 1048.
[2] Henyecz, R.; Keglevich, G.; Mucsi, Z.; *Pure Appl. Chem.*, **2019**, 91, 121.

Palladium and Nickel in the Absence of *P*-ligands

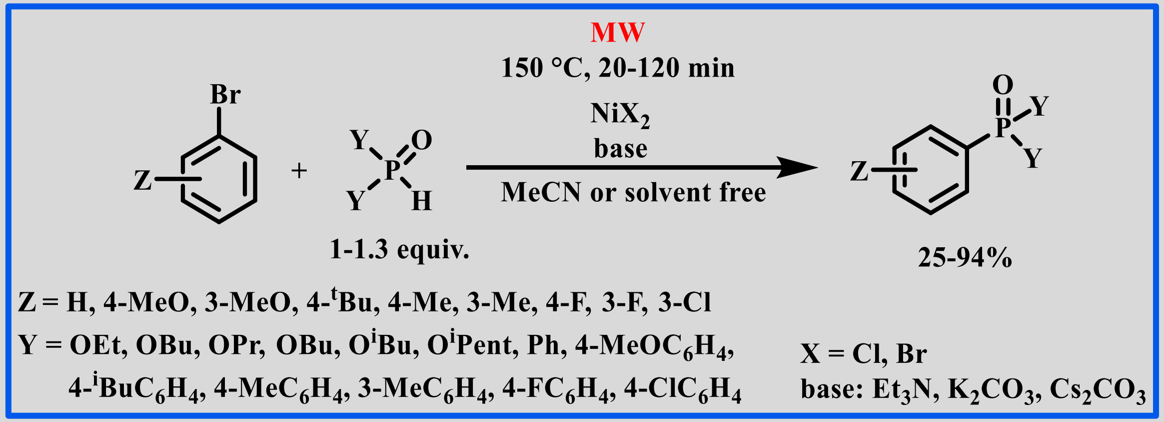
☐ ***The induction period***

We studied the kinetics of the Pd(OAc)$_2$-catalyzed Hirao reaction [1]. It was found that the Hirao reaction commenced after 22 min, during the induction period of 22 min the active catalyst is formed.



☐ ***”P-ligand free”, NiX$_2$-catalyzed coupling reactions***

Quantum chemical calculations confirmed that Ni(II) was not reduced in the reduce agent free and the *P*-ligand free coupling reactions [2-4]. It entered to the catalytic cycle after catalyst formation only in the +2 oxidation state. This was followed by oxidative addition steps - the oxidation state changed from +2 to +4, and reductive elimination steps. The ligands for Ni(II) were the excess of the >P(O)H-compounds.

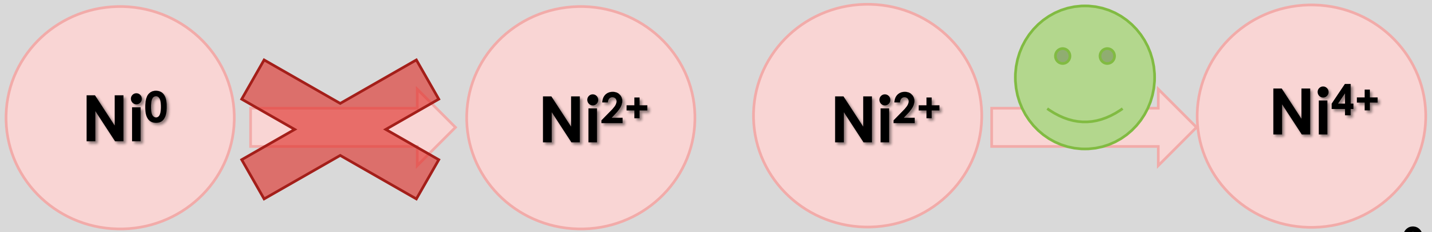


Z = H, 4-MeO, 3-MeO, 4-^{t}Bu, 4-Me, 3-Me, 4-F, 3-F, 3-Cl

Y = OEt, OBu, OPr, OBu, O^{i}Bu, O^{i}Pent, Ph, 4-MeOC$_6$H$_4$, 4-^{i}BuC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$

X = Cl, Br

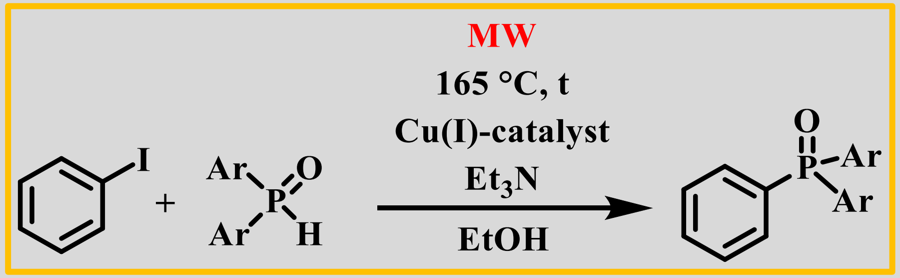
base: Et$_3$N, K$_2$CO$_3$, Cs$_2$CO$_3$



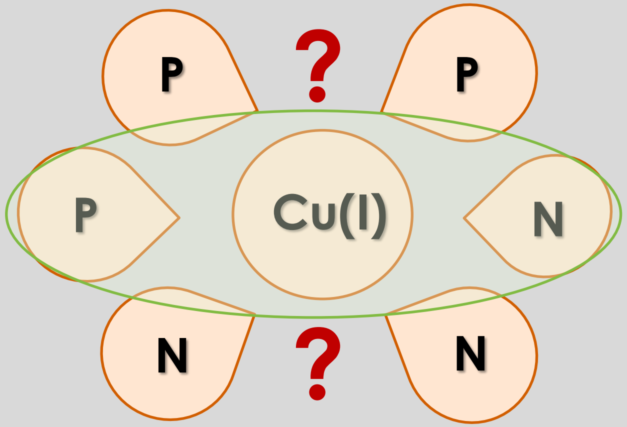
[1] Henyecz, R.; Huszár, B.;.Grenitzer V.; Keglevich, G.; *Curr. Org. Chem.*. **2020**, *24*, 1048.
[2]Jablonkai, E.; Balázs, L. B.; Keglevich, G.; *Curr. Org. Chem.* **2015**, *19*, 197.
[3] Henyecz, R.; Mucsi, Z.; Keglevich, G.; *Pure Appl. Chem.* **2020**, 92, 493.
[4] Keglevich, G.; Henyecz, R.; Mucsi, Z.; *J. Org. Chem.* **2020**, *85*, 14486.

Cu(I)-promoted reactions [1]

After palladium and nickel, the less known copper(I)-promoted reactions were investigated experimentally using iodobenzene and a few secondary phosphine oxides. We also studied the mechanism of the couplings and the possible *P*- or *N*-ligation of Cu(I).



	Catalyst [20%]	Ar	Ar_2POH [equiv.]	Et_3N [equiv.]	t [h]	Conversion [%]	Yields [%]
1.	CuI	Ph	1	2	4	75^a	68
2.	CuCl	Ph	1	1	3	71^a	60
3.			1,4	1	3	47^a	–
4.			1	2	3	93^a	86
5.			1	2	4	97^a	71
6.		$4\text{-}MeC_6H_4$	1	2	4	80^b	71
7.		$3,5\text{-}diMeC_6H_3$	1	2	4	87^c	81
8.	CuBr	Ph	1	1	3	75^a	65
9.			1,4	1	3	50^a	–
10.			1	2	3	99^a	93
11.		$4\text{-}MeC_6H_4$	1	2	4	83^b	78
12.		$3,5\text{-}diMeC_6H_3$	1	2	4	90^c	84



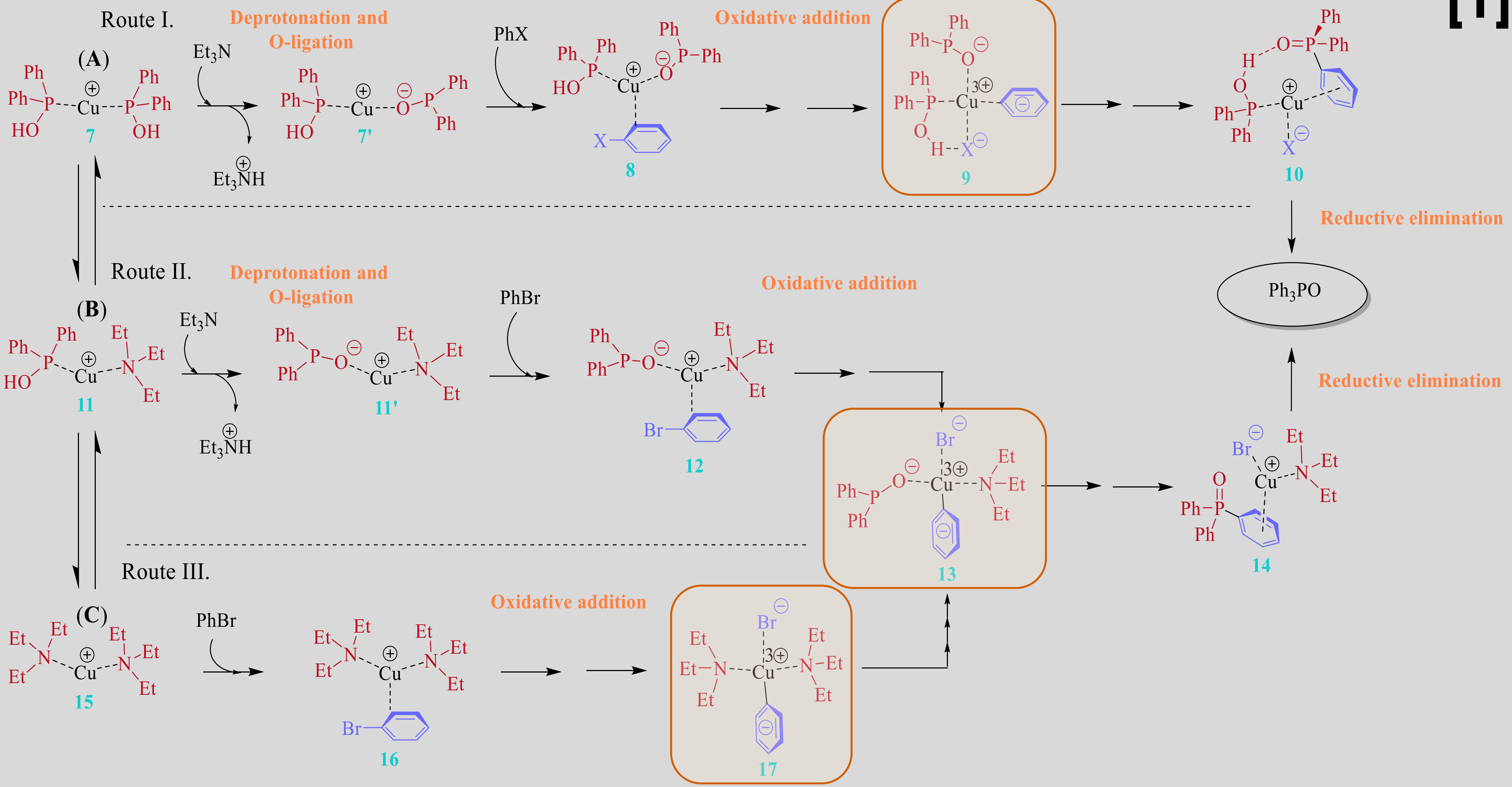
The theoretical calculations proved that the >P(OH)---Cu(I)---NEt_3 "mixed" complex may be the primary catalyst.

[1] Huszár, B.; Henyecz, R.; Mucsi, Z.; Keglevich, G.; *Catalysts*, **2021**, *11*, 933.

[a] $(EtO)Ph_2P(O)$ was detected as a side-product. [b] $(4\text{-}MeC_6H_4)_3P(O)$ was detected as a side-product. [c] $(3,5\text{-}diMeC_6H_3)_3P(O)$ was detected as a side-product.

Mechanisms of the Cu(I)-promoted reactions [1]

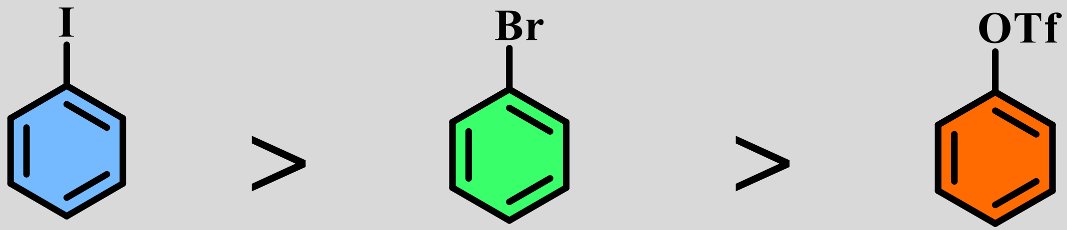
Quantum chemical calculations were made by **Dr. Zoltán Mucsi.**



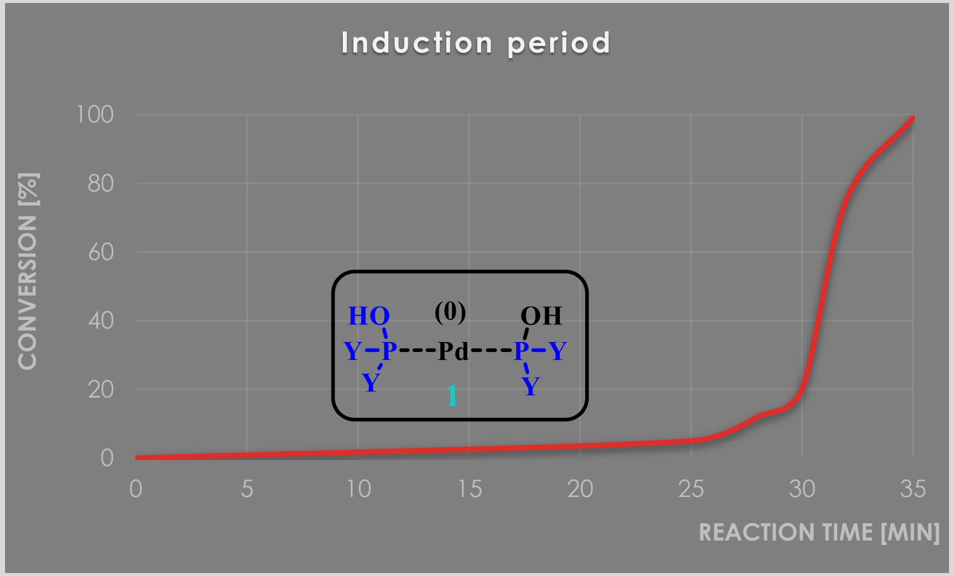
[1] Huszár, B.; Henyecz, R.; Mucsi, Z.; Keglevich, G.; *Catalysts*, **2021**, *11*, 933.

Conclusions

- The order of reactivity of the derivatives we studied:

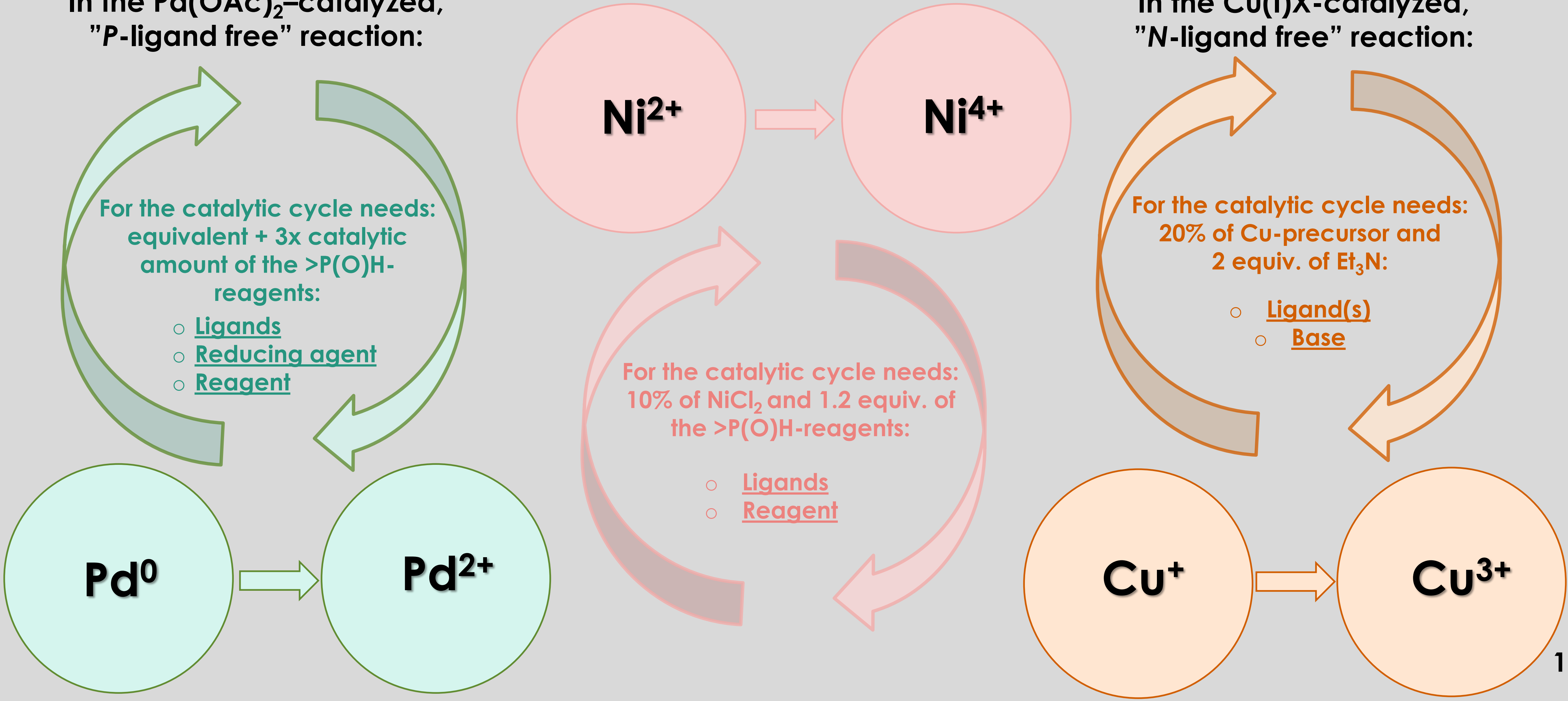


- The coupling of $Ph_2P(O)H$ and PhBr was successfully enhanced at 100 °C by KI additive.
- An induction period of 22 min was observed at 120 °C.



- Cu(I)-catalyzed reactions needed a higher temparature (165 °C), a longer reaction time (3 or 4 h) and 20% of the copper salt with 2 equiv. of Et_3N. CuBr was the most efficient precursor.
- The theoretical calculations proved that the P---Cu(I)---N “mixed” complex may be the primary catalyst.

Conclusions



In the Pd(OAc)$_2$–catalyzed, ”*P*-ligand free” reaction:

For the catalytic cycle needs: equivalent + 3x catalytic amount of the >P(O)H-reagents:

- Ligands
- Reducing agent
- Reagent

In the NiCl$_2$–catalyzed, ”*P*-ligand free” reaction:

For the catalytic cycle needs: 10% of NiCl$_2$ and 1.2 equiv. of the >P(O)H-reagents:

- Ligands
- Reagent

In the Cu(I)X-catalyzed, ”*N*-ligand free” reaction:

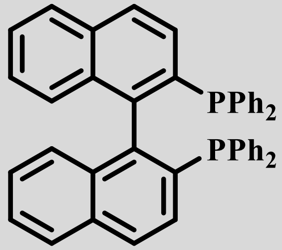
For the catalytic cycle needs: 20% of Cu-precursor and 2 equiv. of Et$_3$N:

- Ligand(s)
- Base

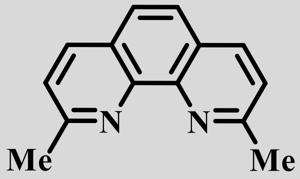
THANK YOU FOR YOUR ATTENTION!

List of the *P*-ligands

BINAP: 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl

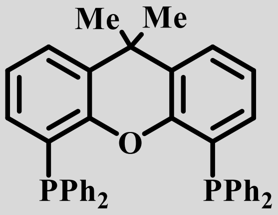


dmphen: 2,9-dimethyl-1,10-phenanthroline



dppb: 1,4-bis(diphenylphosphino)butane

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene



dppf: 1,1’-bis(diphenylphosphino)ferrocene