Transition metal-catalyzed, ligand free P–C coupling reactions under MW conditons

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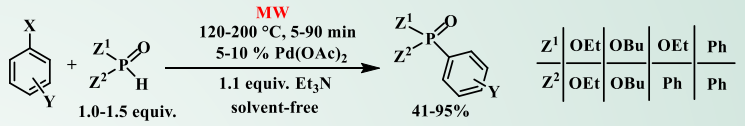
The Hirao P–C coupling reaction

The first P–C coupling reactions were described by *Hirao et al.* [1, 2]. They applied $Pd(PPh_3)_4$ as the catalyst. Due to the air- and moisture-sensitive $Pd(PPh_3)_4$, various Pd-precursors with directly added P-ligands, and later on, Ni- or Cu- precursors with P- and N-ligands were used. In these methods the active catalyst is formed *in situ* [3].

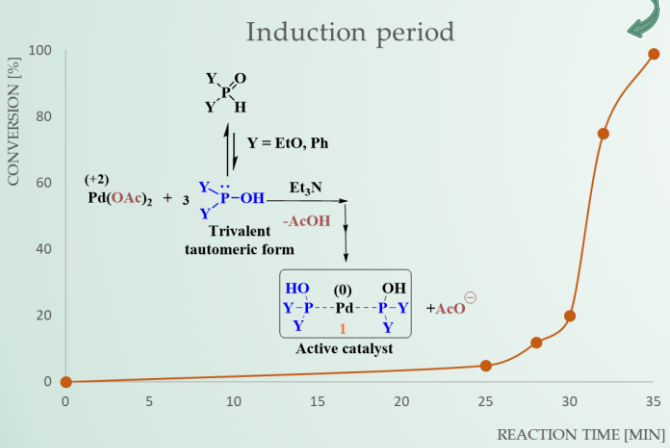
Using $Pd(OAc)_2$ as the catalyst – the "P-ligand free" reactions

- **The *Keglevich* group found that, the Hirao reaction may take place under MW conditions, in the presence of $Pd(OAc)_2$ without the addition of expensive P-ligands, if the P-reagent is used in an excess [4-8]. The catalytic cycle was evaluated by quantum chemical calculations [6, 7]. It was found, the necessary quantity of the >P(O)H-reagent's excess is three 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).**

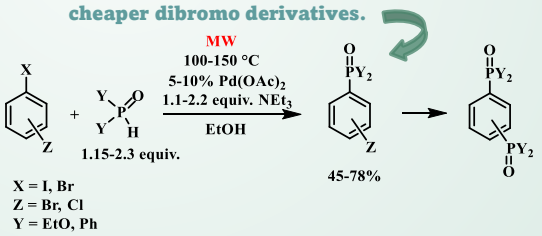


X = Br, I, OTf
Y = H, 4-MeO, 3-MeO, 4-Pr, 4-Et, 4-Me, 3-Cl, 4-F, 3-F, 4-CO_2Et, 3-CO_2Et, 4-C(O)Me, 3-C(O)Me

- **We studied the kinetics of the couplings. It was found that the Hirao reaction commenced after 22 min, during the induction period of 22 min the active catalyst (1) is formed from Pd-precursor and the tautomeric form of the P-reagent [8].**

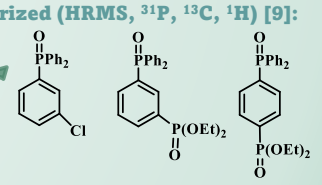


- **We investigated not just the reaction of the monohalogene benzenes, but also that of the dihalogene derivatives. 1,4-, 1,3- And 1,2-dibromobenzenes and the analogous bromo-iodo or bromo-chloro derivatives were reacted with DEP and DPPO too [9]. We found that in most cases, the costly bromo-iodobenzenes could be replaced by the cheaper dibromo derivatives.**



X = I, Br
Z = Br, Cl
Y = EtO, Ph

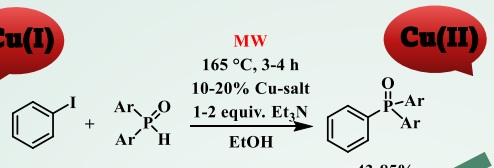
Three new products were prepared and characterized (HRMS, ^{31}P, ^{13}C, ^{1}H) [9]:



- **We also observed the phosphinoylation of PhI with $Ph_2P(O)H$ at 100 ·C was complete after 1 h, but in the case of PhBr, there was no reaction. So, we promoted the coupling between PhBr and $Ph_2P(O)H$ by KI additive [8]. Unfortunately, activation of the chlorobenzene was not efficient → Reactivity order: PhI>PhBr>>PhCl.**

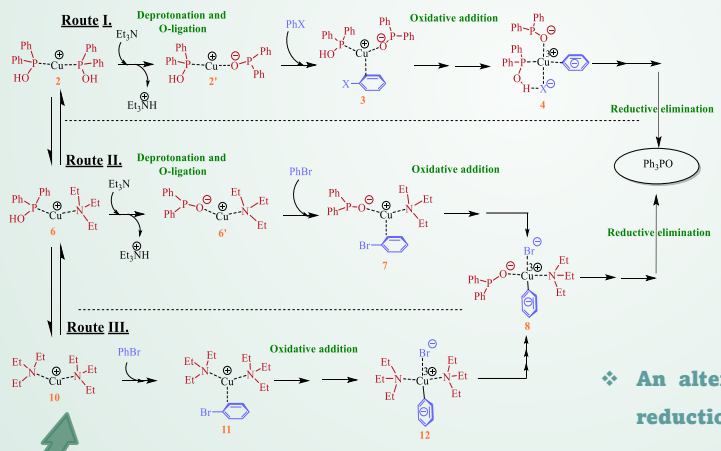
Using different copper-salts as the catalyst

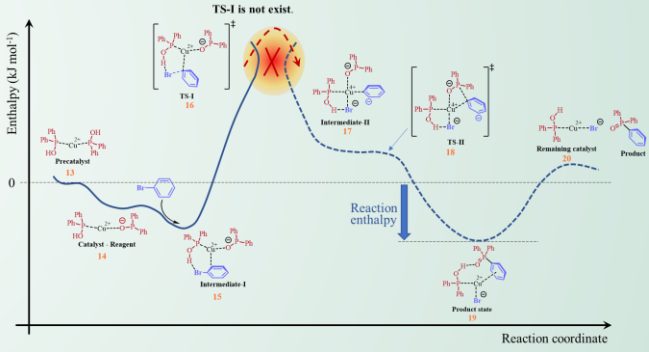
- **In this work, we investigated the use of copper catalysts, which could be a cheaper option. Due to the copper's lower reactivity, the most reactive aryl halide PhI had to be used.**
- **First experiments were carried out in the presence of Cu(I)-salts (*e.g.* CuI, CuCl and CuBr) at 165 °C under MW conditions [10]. Using 20% of CuBr as the catalyst precursor, and 2 equiv. of NEt_3 as the base, seemed to be the best.**



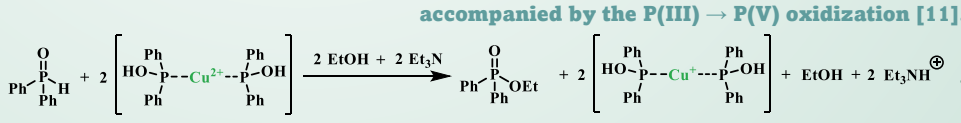
Ar = Ph, 4-MeC_6H_4, 3,5-diMeC_6H_3
Cu(I)-salts: CuI, CuCl, CuBr
Cu(II)-salts: $CuSO_4$, $Cu(OAc)_2xH_2O$, $CuCl_2x2H_2O$, $CuSO_4x5H_2O$

- **Later on, Cu(II)-salts (*e.g.* $CuSO_4$, $Cu(OAc)_2xH_2O$, $CuCl_2x2H_2O$, $CuSO_4x5H_2O$) were studied [11]. It was concluded that applying 20% of $CuSO_4$ or $Cu(OAc)_2xH_2O$ 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 [11].**
- **The mechanism of the reaction was calculated. We studied the possible ligations of Cu(I). Bisligated P—Cu(I)—P (2), P—Cu(I)—N (6) and N—Cu(I)—N (10) complexes were considered as the catalysts. Complex 6 may catalyze the P–C coupling, both according to experiments and calculations [10].**





- **An alternative interpretation was looked for: a Cu(II) → Cu(I) reduction was assumed by the secondary phosphine oxide, accompanied by the P(III) → P(V) oxidization [11].**



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 NEt_3 were used in a 1:2 molar ratio. The mechanisms were studied by quantum chemical calculations.**

References:

[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] Henyecz, R.; Keglevich, G. *Curr. Org. Synth.* **2019**, *16*, 523.
[4] Jablonkai, E.; Keglevich, G. *Tetrahedron Lett.* **2013**, *54*, 4185.
[5] Keglevich, G.; Jablonkai, E.; Balázs L. B. *RSC Adv.* **2014**, *4*, 22808.
[6] Keglevich, G.; Henyecz, R.; Mucsi, Z.; Kiss, N. Z. *Adv. Synth. Catal.* **2017**, *359*, 4322.
[7] Henyecz, R.; Mucsi, Z.; Keglevich, G. *Pure Appl. Chem.* **2019**, *91*, 121.
[8] Henyecz, R.; Huszár, B.;.Grenitzer V.; Keglevich, G. *Curr. Org. Chem.*. **2020**, *24*, 1048.
[9] Huszár, B., Varga, P.R., Szűcs, N.Á., Simon, A., Drahos, L., Keglevich, G. *Catalysts*, **2022**, *12*, 1080.
[10] Huszár, B.; Henyecz, R.; Mucsi, Z.; Keglevich, G. *Catalysts*, **2021**, *11*, 933.
[11] Huszár, B., Mucsi, Z.; Szolga, R., Keglevich, G. *J. Organomet. Chem.*, **2022** *published online*