Photoinduced Palladium Negishi Cross-Coupling Through Visible Light Absorption of Palladium-Zinc Complexes.

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Abstract: A visible light-induced Negishi cross-coupling, through activation of a Pd(0)-zinc complex, is reported. This new photocatalytic process allows the expansion of the scope of zinc enolates in the Negishi coupling reaction with deactivated aryl halides. NMR experiments in the presence and absence of light confirmed that the formation of the palladium-zinc complex is key for accelerating the oxidative addition step.

The discovery of transition metal catalyzed cross-coupling reactions has enhanced the synthetic chemist's toolbox and has allowed access to new chemical entities.[1,2] In particular, the Negishi reaction has been an important tool for medicinal chemists to build $C(sp^3)$-$C(sp^2)$ carbon-carbon bonds[3] and creating bioactive molecules with a higher $C(sp^3)$ fraction and improved physicochemical properties.[4]

One of the most challenging Negishi cross-couplings is the α-arylation of carbonyl compounds as the arylated product is more acidic than the starting material and quenches the starting enolate.[5] This reaction is of particular interest to medicinal chemists as this functionality is present in several pharmaceutical drugs, such as Naproxen, Ibuprofen, Flurbiprofen, Tolmentin, and Fexofenadine.[6] However, the reaction still remains a challenge when electron rich heterocycles and chloro-derivatives are used.

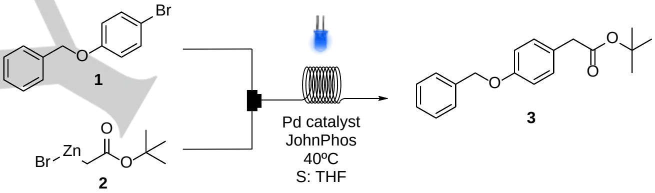
We have recently described the light induced nickel-catalyzed Negishi reaction, and have demonstrated extended applicability of this methodology using visible blue light.[7] We attempted the reaction of 4-benzyloxybromobenzene **1** with (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide **2**, prepared following our flow protocol,[8] under our nickel photoNegishi conditions. However, the reaction failed in our hands and product was not detected in the crude mixture (see supporting information).

Looking at the literature, this substrate was not reported previously in a Negishi coupling. Nevertheless, the reaction was attempted using a set of suitable ligands following the procedures described for similar compounds[5] (see Table S1 in supporting information). Unfortunately, none of the combinations tried provided reasonable conversion to product even using Q-Phos, a well-established ligand for these transformations.

Recently, it has been reported that visible light can induce palladium catalysis by direct absorption of Pd(0), facilitating the single electron transfers during the oxidative addition step. This enables the Heck reaction for inactivated substrates.[9] Considering this antecedent, we decided to irradiate our reaction with visible light. To start with, we selected JohnPhos as the ligand for the Pd catalyst. It showed some conversion to product and lacks substitution on the biaryl moiety that may allow further derivatization in case more complex substrates are required.[10]

The first conditions that we attempted was irradiating with a 450 nm lamp, using 10% of palladium catalyst, 30 min. of residence time at 40ºC. Full conversion to product was observed under these conditions (Table 1, entry 1) in comparison with the low conversion in batch (4%). Reducing the amount of catalyst to 5% did not reduce the conversion (entry 2), but further reduction to 2.5% clearly decreased the turnover of the reaction (entry 3). Similarly, conversion was reduced slightly if the residence time was decreased (entry 4).

Table 1. Optimization of the light induced Pd-Negishi reaction.



Entry	t_R (min)	Light	Pd (mol %)	Conv. (%)
1	30	On	10	100
2	30	On	5	100 (85)^a
3	30	On	2.5	31
4	20	On	5	90
5	30	On	---	0
6	30	Off	5	5
7	30	On	5^b	28

Reaction conditions: **1** (1 eq., 0.2 mmol), **2** (2 eq., 0.4 mmol), Pd(dba)$_2$ as catalyst and JohnPhos as ligand. [a] Isolated yield in brackets. [b] Pd(OAc)$_2$ as catalyst.

Control experiments indicated that both light and palladium catalyst are essential for this transformation (entries 5 and 6). It is important to highlight that the palladium source is key as well. Replacing Pd(dba)$_2$, Pd(0), by Pd(OAc)$_2$, Pd (II), was detrimental for the reaction (entry 7).

With the optimized conditions in hand (Table 1, entry 2), the substrate scope of the reaction was explored (Figure 1). In all cases conversion was clearly boosted under blue light irradiation. In some cases, the difference between light and no light reactions is noteworthy, for instance compounds **7**, **11**, **14,** and **16**-**19**. A broad variety of bromo derivatives were used as cross-coupling partners and contained a variety of electron-donating and electron-withdrawing groups, compounds **3**-**13**. The reaction also

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) proved to be chemoselective as shown in compound **4**, where the reaction took place only at the bromo substituent, and compound **6**, where only the Negishi coupling product was observed and not the corresponding Blaise reaction product.[11] Bromo heterocycles are also suitable coupling reagents, either monocyclic (**16**-**18)** or bicyclic rings (**14** and **15)**, with diverse substitution.

The scope of suitable organozinc reagents is also broad and goes beyond the usual Reformatsky reagents. For instance, α-bromobutyrolactone and 3-bromo-N-methylpyrrolidnone provided the corresponding products **8**, **9** and **18** in high yields under light irradiation. Importantly, the protocol is also compatible with other organoalkyl zinc derivatives such as *Boc*-protected azetidine (compound **7**) or fluoroalkyl chains (compounds **14** and **15**), which are valuable substituents in medicinal chemistry.

For more demanding substrates, a bulkier phosphine, such as X-Phos, was required. This allowed us to access more deactivated bromo and chloro derivatives, compounds that are usually out of the scope for this reaction.[5] For instance, 2,3- and 2,4-dimethoxy analogues (**20** and **21**); or 3-bromopyridines (**22**, **23** and **25**). Remarkably, we were also able to functionalize five-membered heterocycles (pyrazoles **26** and **27**) with the halogen at the most electron-rich carbon of the heterocycle. Finally, 3-chloropyridines are usually not described as coupling partners for Negishi couplings and they were also accessible under light irradiation as exemplified with compounds **30** to **32**.

To examine the robustness of the new photoinduced reaction, we decided to scale up compound **13** using both shelf-stable halogenated starting materials. The organozinc reagent was prepared in flow, and the exiting stream was connected to a second solution stream containing the haloarene and the catalytic complex before entering the photoreactor. This process was run continuously for 5 h. In parallel the same reaction was performed in batch for the same time and the results of both reactions were compared (see supporting information). The flow protocol provided product **13** in 97% yield, with a productivity of 520 mg/h. Using the batch Negishi protocol, the product was only isolated in 36% yield. This example clearly demonstrated the value of the new light-driven reaction described herein.

Considering the difference observed above in conversion between the thermal Negishi reaction and the light induced coupling reaction, kinetic studies with compound **12** were performed following their conversion to product in flow at different residence times in the presence and absence of light. The light enhancement is notable from the initial moments of the reaction, and the difference in product formation remained stable over time (Figure 2). These results looked completely different to the ones obtained in our previous work with nickel catalysis,[7] probably indicating that activation may take place at a different step of the mechanism.

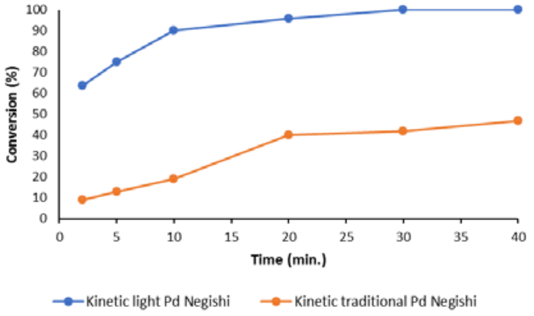

Figure 2. Kinetic studies of compound **12** for Pd Negishi reaction. THF as solvent.

Since single electron transfer (SET) processes have been shown to be crucial in palladium photoinduced reactions,[12] a radical trap experiment using compound **30** was run. Due to the limited scavengers that can be used with organozinc reagents, according to our previous work,[7] diphenylethylene and ditert-butylhydroxytoluene (BHT) were chosen for this purpose. None of them quenched the formation of the expected product. Although these results may indicate the absence of radicals, their presence cannot be entirely ruled out.

In an effort to identify the photo-absorbing species, absorption spectra of different components of the reaction were recorded. Previous reports showed that Pd(0) complexes can be photoactivated into Pd(0)* with visible light irradiation due to tailing absorption into visible spectra of a small band centered at 380 nm.[9,12] A similar profile was observed when the complex between $Pd(dba)_2$ and JohnPhos was formed. However, when the organozinc reagent was added, this band moved to 430 nm and remained when all reaction components were present in the mixture (Figure 3).

With the aim of understanding the mechanism, ^{19}F and ^{31}P NMR spectroscopic studies of the reaction to get compound **15** were performed in the presence and absence of light.[13] This experiment allowed us to monitor not only the consumption of the cross-coupling partners to form the reaction product, but also the involvement of the catalytic complex in the reaction.

First, ^{31}P NMR studies were run to observe the changes at the level of the catalyst (Figure 4). Addition of $Pd(dba)_2$ to a solution of JohnPhos in THF produces the appearance of a new small signal at 58.97 ppm (Figure 4b), assigned to the Pd (0) catalytic complex according to the data reported in literature for Pd(0) and Pd(II) JohnPhos complexes.[14] Control experiments reproduced reported data for both species: 58.97 ppm for $Pd(dba)_2$ + JohnPhos and 69.70 for $Pd(AcO)_2$ + JohnPhos (see Figure S3 supporting information). Addition of 6-bromo-7-fluoroquinoline to the catalytic complex does not produce appreciable changes in the chemical shift, but an increase in its intensity (Figure 4c). Nevertheless, addition of the organozinc derivative to the catalytic complex produces a downfield shift of this signal to 60.33 ppm and an increase in its intensity (Figure 4d). The downfield shift observed in ^{31}P NMR indicates the formation of a complex between the Pd(0) catalyst and the organozinc reagent with concomitant reduction of the electron density at the phosphorous atom. The formation of this potential complex is in line with the observation of the UV-visible spectra shown in Figure 3.

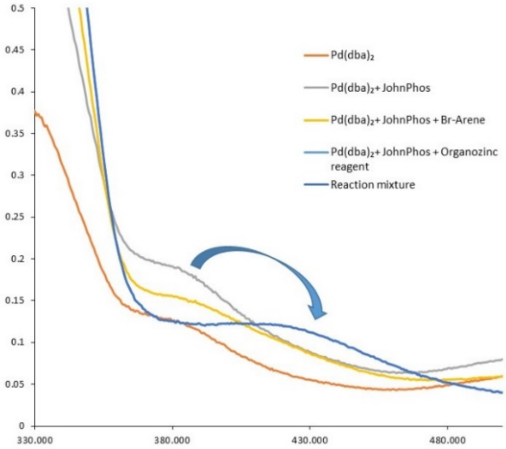

Figure 3. Absorption spectra of different components of the reaction mixture. Arrow indicates band shift. THF as solvent.

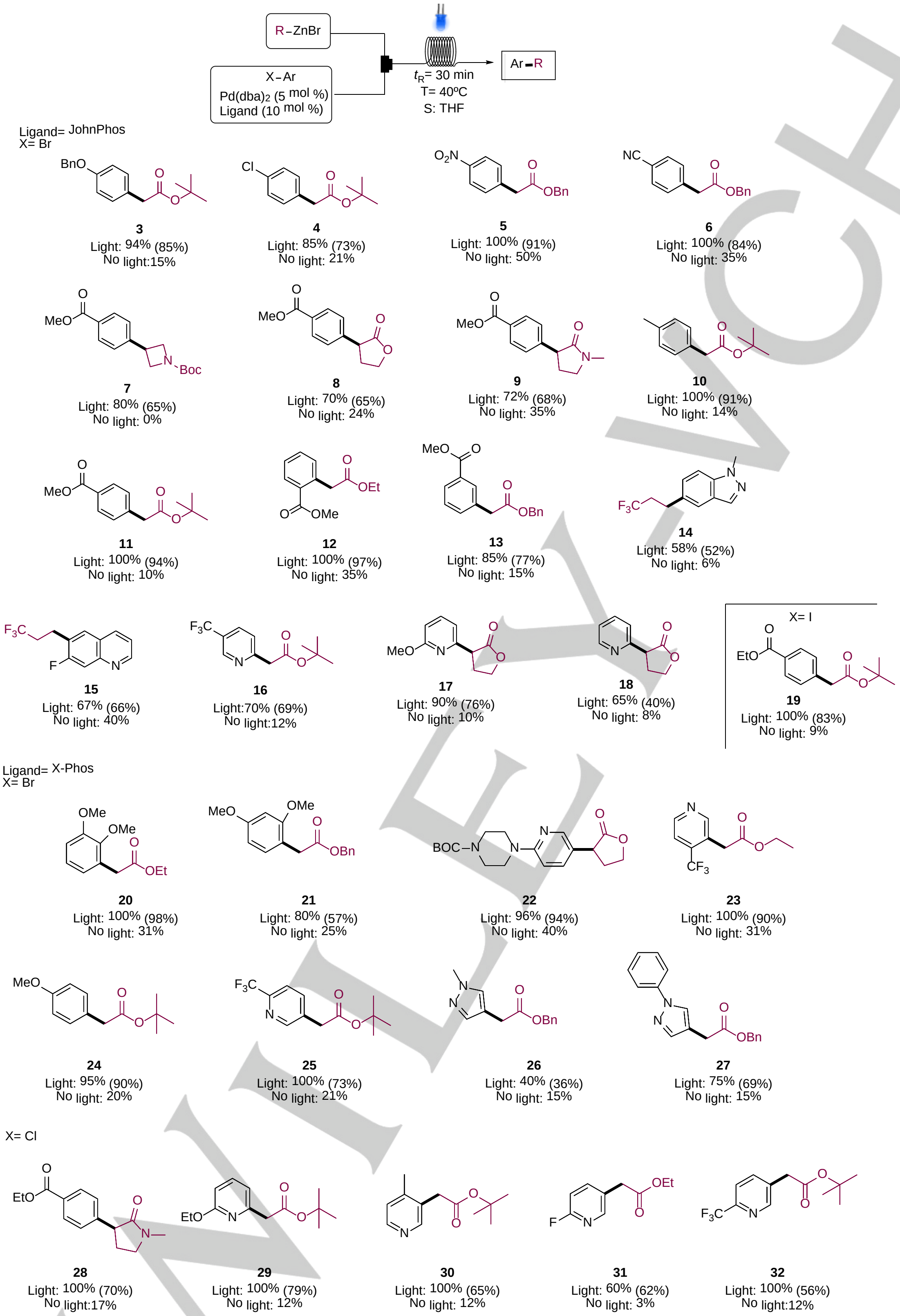

Figure 1. Scope of the light induced Pd-Negishi reaction. Isolated yields in brackets. Reaction conditions: Ar-X (1 eq., 0.5 mmol), R-ZnBr (2 eq., 1 mmol), $Pd(dba)_2$ (5 mol%), ligand (10 mol%).

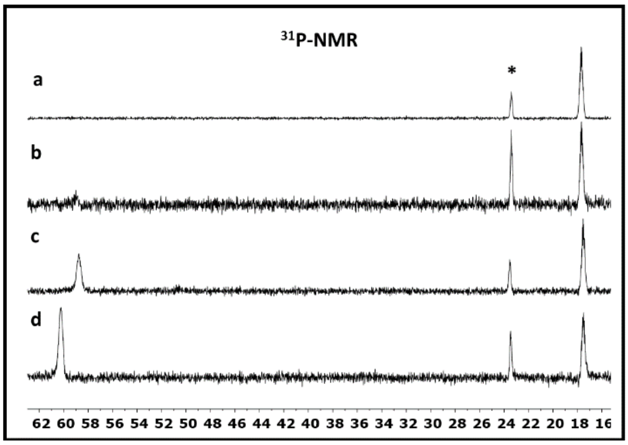

Figure 4. ^{31}P NMR spectra: a) JohnPhos; b) JohnPhos + Pd(dba)$_2$; c) JohnPhos + Pd(dba)$_2$ + 6-bromo-7-fluoroquinoline; d) JohnPhos + Pd(dba)$_2$ + (3,3,3-trifluoropropyl)zinc(II) iodide. *Triphenylphosphine oxide (23.39 ppm) placed in a capillary tube used as internal standard. THF as solvent.

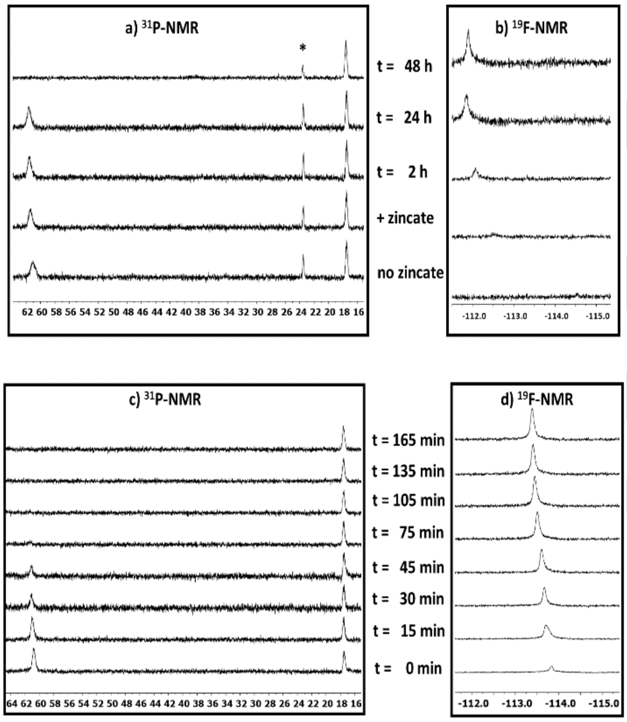

Figure 5. Reaction monitoring for compound **15**. Reaction in the absence of light: a) evolution of Pd(0)-organozinc complex by ^{31}P NMR, b) evolution of product by ^{19}F NMR. Reaction in the presence of light: c) evolution of Pd(0)-organozinc complex by ^{31}P NMR, d) evolution of product by ^{19}F NMR. *Triphenylphosphine oxide (23.39 ppm) placed in a capillary tube used as internal standard in 5a. THF as solvent.

Second, reactions with equimolar amounts of all components were performed to study the evolution of new signals as well as the formation of the cross-coupling product in the presence and absence of light (Figure 5). In the absence of light, the reaction proceeds very slowly, since it requires up to two days for the complete consumption of the complex (Figure 5a). The cross-coupling product started to appear after 2 h of reaction (Figure 5b). In the presence of light, the signal of the complex was completely consumed after 75 min. (Figure 5c), and the signal of the product started to appear at 15 min. (Figure 5d). This experiment clearly showed the relationship between the complex observed in ^{31}P NMR with the formation of product. A separate experiment was run in the absence of 6-bromo-7-fluoroquinoline and the signal of the complex remained in the NMR spectra even in the presence of light (see Figure S4 supporting information). These data supported the formation of the Pd(0)-organozinc complex previous to the oxidative addition step.

To further corroborate the role of light, the reaction was run under catalytic conditions in the presence and absence of light. In these experiments, formation of the cross-coupling product is clearly favoured in the presence of light. Moreover, the amount of dimer of the organozinc reagent, a common by-product of the reaction, did not increase under light irradiation (see Figure S5 supporting information).

A fourth experiment was performed using all components of the reaction but replacing the organozinc reagent by zinc chloride. In the presence of this salt, the signal of the Pd(0)-JohnPhos complex was shifted again to 61.8 ppm. Interestingly, this signal evolved over time to a new one at 67.7 ppm, close to the one reported for Pd(II)-JohnPhos complex.[14] This process is completed after 180 min. in the absence of light. Remarkably, in the presence of light the full interconversion between both signals only took 15 min (See Figure S6 supporting information). Furthermore, subsequent addition of organozinc reagent to the reaction mixture rendered the final coupling product as an indication of the participation of new intermediate in the reaction.

In summary, NMR experiments demonstrated the formation of a complex between Pd(0) and the zinc derivatives that absorbed at 430 nm and accelerates the oxidative addition step as product only evolved in the presence of the haloarene reagent. Pd(0)-Zn complexes in Negishi reactions have been recently reported in literature,[15] however their photochemical behavior remained unknown. Even though further experiments will be required to fully confirm the structures of the intermediates formed, the mechanism shown in Figure 6 can be tentatively proposed.

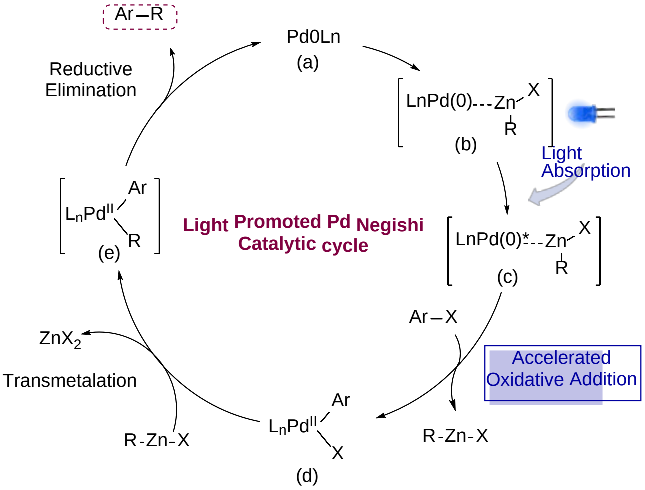

Figure 6. Plausible reaction mechanism for visible light induced Pd-catalyzed Negishi reaction.

In conclusion, palladium catalyzed Negishi reactions are accelerated in the presence of visible blue light. This finding has a clear synthetic application as the coupling of Reformatsky-type reagents is clearly expanded to electron rich and chloro heterocycles, substrates that are out of the scope of this reaction. The protocol is easily scalable and clearly superior to the traditional batch reaction. Kinetic, spectroscopic and NMR studies demonstrated the formation of a Pd(0)-zinc complex that allows the absorption of the visible light and accelerates the oxidative addition step of the catalytic cycle. This work will provide new insights into Pd-driven photocatalysis and opens new avenues within this field. Follow up work to characterize the intermediates found and applications of the current methodology to medicinal chemistry will be the matter of future publications.

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Keywords: Photocatalysis • Visible light • Pd Negishi coupling • C(sp^3)–C(sp^2) coupling • Flow Chemistry

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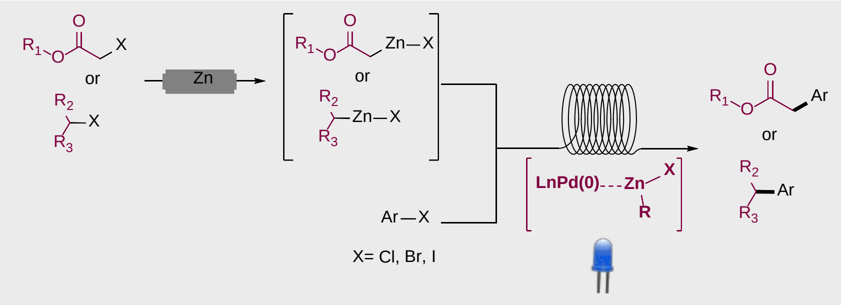

Much better with light: Complexes between palladium and zinc are able to absorb visible blue light and facilitate oxidative addition of really challenging substrates, opening new avenues in palladium cross-coupling chemistry and photocatalysis.

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