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Photoinduced Palladium-Catalyzed Negishi Cross-Couplings Enabled by the Visible-Light Absorption of Palladium–Zinc Complexes

*Irini Abdiaj, Lena Huck, José Miguel Mateo, Antonio de la Hoz, M. Victoria Gomez, Angel Díaz-Ortiz, and Jesús Alcázar**

Abstract: *A visible-light-induced Negishi cross-coupling is enabled by the activation of a Pd^0–Zn complex. With this photocatalytic method, the scope of deactivated aryl halides that can be employed in the Negishi coupling was significantly expanded. NMR experiments conducted 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 process for medicinal chemists to build C(sp^3)–C(sp^2)[3] bonds and synthesize 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 aryl chlorides are used.

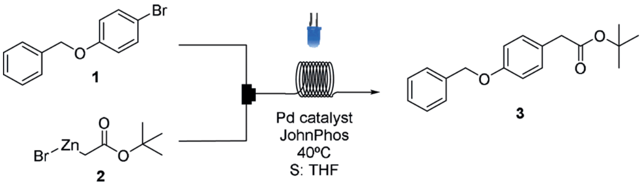
We have recently described a light-induced nickel-catalyzed Negishi reaction, and have demonstrated that the applicability of this method can be extended by using blue light.[7] We attempted the reaction of 4-benzyloxybromobenzene (**1**) with (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (**2**), which was prepared following our flow procedure,[8] under our nickel photo-Negishi conditions. However, the reaction failed in our hands, and the desired product was not detected in the crude mixture (see the Supporting Information).

Looking at the literature, we found that this substrate had never been successfully used in this transformation. Nevertheless, the reaction was attempted using a set of suitable ligands following procedures described for similar compounds[5] (see Table S1 in the Supporting Information). Unfortunately, none of the combinations tried provided reasonable conversion into the product even when Q-Phos, a well-established ligand for these transformations, was used.

Recently, it has been reported that visible light can induce palladium catalysis by direct absorption through Pd^0, facilitating the single electron transfers during the oxidative addition step. This has enabled Heck reactions of inactivated substrates.[9] Considering this antecedent, we decided to irradiate our reaction mixture with visible light. To start with, we selected JohnPhos as the ligand for the Pd catalyst. With this ligand, some conversion into the product was observed, and the lack of substitution on the biaryl moiety may allow for further derivatization in case more complex substrates are to be used.[10]

The first conditions that we attempted involved irradiation with a 450 nm lamp, the use of 10 mol % of palladium catalyst, and a residence time of 30 min at 40 °C. Full conversion into the product was observed under these conditions (Table 1, entry 1) whereas the conversion was low in the corresponding batch process (4 %). Reducing the

Table 1: Optimization of the light-induced palladium-catalyzed Negishi reaction.[a]



Entry	t_R [min]	Light	Pd [mol %]	Conv. [%]
1	30	on	10	100
2	30	on	5	100 (85)[b]
3	30	on	2.5	31
4	20	on	5	90
5	30	on	–	0
6	30	off	5	5
7	30	on	5[c]	28

[a] Reaction conditions: **1** (1 equiv, 0.2 mmol), **2** (2 equiv, 0.4 mmol), Pd(dba)$_2$ as the catalyst, and JohnPhos as the ligand. Conversions determined by LC-MS. [b] Yield of isolated product given in parentheses. [c] Pd(OAc)$_2$ as the catalyst.

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amount of catalyst to 5 mol% did not reduce the conversion (entry 2), but a further reduction to 2.5 mol% clearly decreased the turnover of the reaction (entry 3). Similarly, the conversion was reduced slightly when the residence time was decreased (entry 4).

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 to the reaction (entry 7).

With optimized reaction conditions in hand (Table 1, entry 2), the substrate scope of the reaction was explored (Figure 1). In all cases, the conversion was clearly boosted under blue light irradiation. In some cases, the difference between light and no light reactions is noteworthy, for instance, for compounds **7**, **11**, **14**, and **16–19**. A broad variety of aryl bromides containing a range of electron-donating and electron-withdrawing groups were used as cross-coupling partners and generated compounds **3–13**. The reaction is chemoselective as demonstrated by compound **4**, where the reaction took place only at the bromine substituent, and compound **6**, where only the Negishi coupling product was observed and not the corresponding Blaise reaction product.[11] Both monocyclic (**16–18**) and bicyclic (**14** and **15**) heteroaryl bromides with diverse substitution patterns are also suitable coupling partners.

The scope with respect to suitable organozinc reagents is also broad and goes beyond the usual Reformatsky reagents. For instance, α-bromobutyrolactone and 3-bromo-*N*-methylpyrrolidinone provided the corresponding products **8**, **9**, and **18** in high yields under light irradiation. Importantly, the reaction is also compatible with other alkyl 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 use more deactivated aryl bromides and chlorides, compounds that are usually out of the scope of this reaction.[5] For instance, we obtained the 2,3- and 2,4-dimethoxy analogues **20** and **21** and the 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 atom of the heterocycle. Finally, 3-chloropyridines are usually not described as coupling partners for Negishi couplings but they could be employed under light irradiation as exemplified with compounds **30–32**.

To examine the robustness of the new photoinduced reaction, we decided to scale up the synthesis of compound **13** from the 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 period of time, and the results of both reactions were compared (see the Supporting Information). The flow procedure provided product **13** in 97% yield, with a productivity of 520 mg h^{-1}. Using the batch Negishi procedure, the product was only isolated in 36% yield. This example clearly demonstrates the value of the new light-driven reaction described herein.

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

As single electron transfer (SET) processes have been shown to be crucial in palladium-catalyzed photoinduced reactions,[12] a radical trap experiment using compound **30** was run. Owing to the limited number of scavengers that can be used with organozinc reagents, as shown in our previous work,[7] diphenylethylene and di-*tert*-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 light-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 owing to the tailing into the visible region 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 there 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 generating 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 experiments were run to observe changes at the level of the catalyst (Figure 4). Addition of Pd(dba)$_2$ to a solution of JohnPhos in THF led to the appearance of a new small resonance at 58.97 ppm (Figure 4b), which was assigned to the Pd^0 catalytic complex according to data reported in the literature for Pd^0 and Pd^{II} JohnPhos complexes.[14] Control experiments reproduced reported data for both species: $\delta = 58.97$ ppm for Pd(dba)$_2$ and JohnPhos, and $\delta = 69.70$ ppm for Pd(AcO)$_2$ and JohnPhos (see Figure S3). The addition of 6-bromo-7-fluoroquinoline to the catalytic complex did not induce appreciable changes in the chemical shift, but an increase in the intensity of this resonance (Figure 4c). Nevertheless, addition of the organozinc derivative to the catalytic complex produced a downfield shift of this resonance to 60.33 ppm and an increase in its intensity (Figure 4d). The downfield shift observed in the ^{31}P NMR spectrum indicates the formation of a complex between the Pd^0 catalyst and the organozinc reagent with concomitant reduction of the elec-

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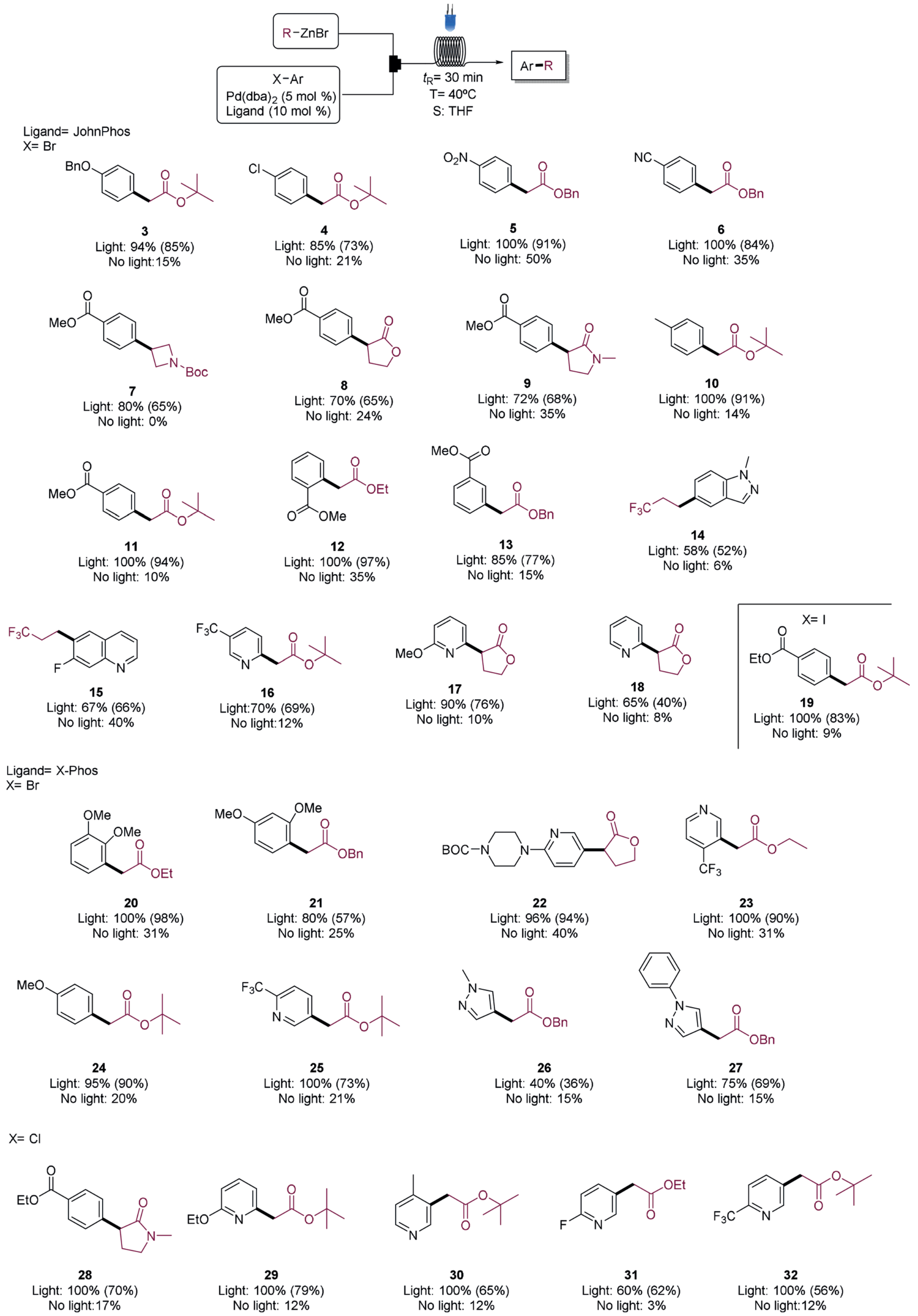

Figure 1. Scope of the light-induced palladium-catalyzed Negishi reaction. Yields of isolated products given in parentheses. Reaction conditions: ArX (1 equiv, 0.5 mmol), RZnBr (2 equiv, 1 mmol), Pd(dba)$_2$ (5 mol%), ligand (10 mol%).

tron density at the phosphorus atom. The formation of this potential complex is in line with the UV/Vis spectra shown in Figure 3.

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

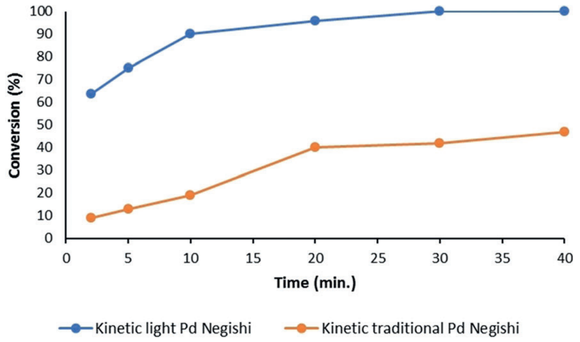

Figure 2. Kinetic studies of the generation of compound **12** in the palladium-catalyzed Negishi reaction in THF.

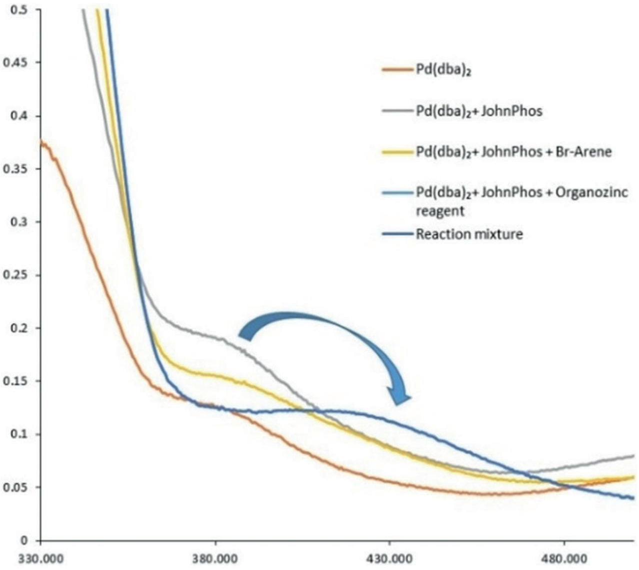

Figure 3. Absorption spectra of different components of the reaction mixture. Arrows indicate band shifts. THF was used as the solvent.

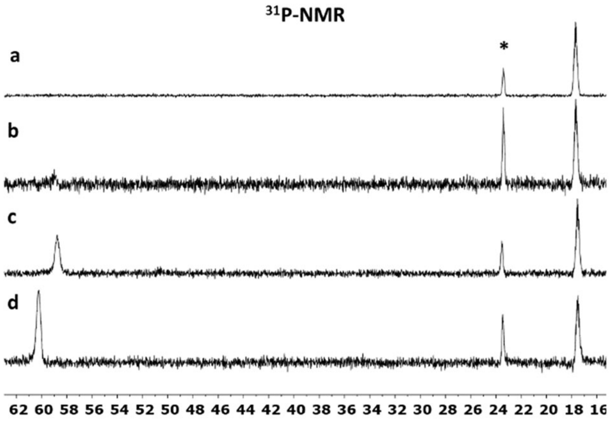

Figure 4. ^{31}P NMR spectra of a) JohnPhos, b) JohnPhos and Pd(dba)$_2$, c) JohnPhos, Pd(dba)$_2$, and 6-bromo-7-fluoroquinoline, and d) JohnPhos, Pd(dba)$_2$, and (3,3,3-trifluoropropyl)zinc(II) iodide. * Triphenylphosphine oxide (23.39 ppm) was placed in a capillary tube and used as the internal standard.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

presence and absence of light (Figure 5). In the absence of light, the reaction proceeded very slowly as the complete consumption of the complex required up to two days (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 had completely disappeared after 75 min (Figure 5c), and the resonance of the product started to appear after 15 min (Figure 5d). This experiment clearly showed the relationship between the complex observed in the ^{31}P NMR spectrum and the formation of the product. A separate experiment was run in the absence of 6-bromo-7-fluoroquinoline, and the resonance of the complex remained in the NMR spectra even in the presence of light (Figure S4). These data support the hypothesis that the Pd^0–organozinc complex is formed before the oxidative addition step.

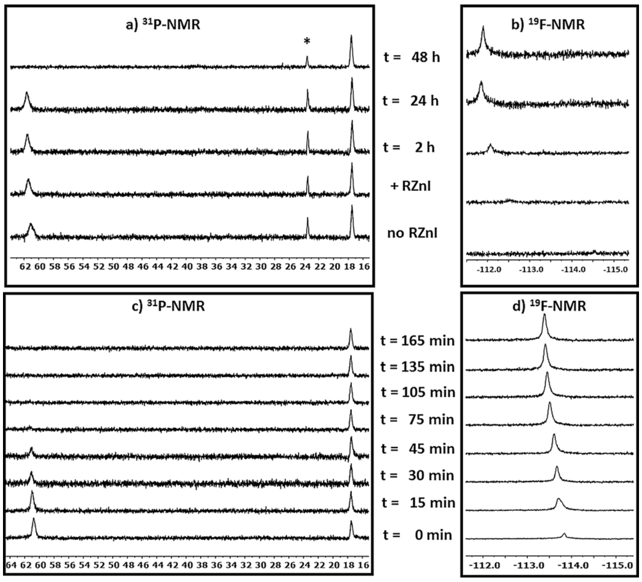

Figure 5. Reaction monitoring for the generation of compound **15**. Reaction in the absence of light: a) Evolution of the Pd^0–organozinc complex by ^{31}P NMR analysis, b) evolution of the product by ^{19}F NMR analysis. Reaction in the presence of light: c) Evolution of the Pd^0–organozinc complex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

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 was clearly favored in the presence of light. Moreover, the amount of dimer of the organozinc reagent, a common side product of the reaction, did not increase under light irradiation (Figure S5).

A fourth experiment was performed using all components of the reaction but replacing the organozinc reagent with zinc chloride. In the presence of this salt, the signal of the Pd^0–JohnPhos complex was shifted again to $\delta = 61.8$ ppm. Interestingly, this resonance evolved over time to a new one at 67.7 ppm, close to the one reported for the Pd^{II} JohnPhos complex.[14] This process was completed after 180 min in the

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absence of light. Remarkably, in the presence of light, the full interconversion between both resonances only took 15 min (Figure S6). Furthermore, subsequent addition of the organozinc reagent to the reaction mixture generated the final coupling product, as an indication of the participation of a new intermediate in the reaction.

In summary, the NMR experiments demonstrated the formation of a complex between Pd^0 and the zinc derivatives that absorbs at 430 nm and accelerates the oxidative addition step as product only evolved in the presence of the haloarene reagent. The presence of Pd^0–Zn complexes in Negishi reactions was recently reported in the literature,[15] but 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.

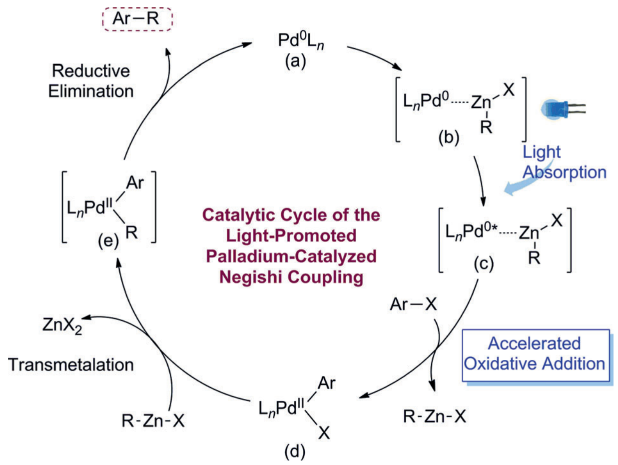

Figure 6. Plausible reaction mechanism for the visible-light-induced palladium-catalyzed Negishi reaction.

In conclusion, we have shown that palladium-catalyzed Negishi reactions are accelerated under blue light irradiation. This finding has a clear synthetic application as the coupling of Reformatsky-type reagents was expanded to electron-rich aryl bromides as well as aryl chlorides, substrates that are usually out of the scope of this reaction. The reaction is easily scalable and clearly superior to the traditional batch process. Kinetic, spectroscopic, and NMR studies demonstrated the formation of a Pd^0–zinc complex that absorbs visible light and accelerates the oxidative addition step of the catalytic cycle. This work provides new insight into Pd-driven photocatalysis and opens new avenues within this field. Follow-up work to characterize the intermediates and applications of the current method to medicinal chemistry will be the matter of future publications.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · flow chemistry · Negishi coupling · palladium catalysis · photocatalysis

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Communications

Photocatalysis

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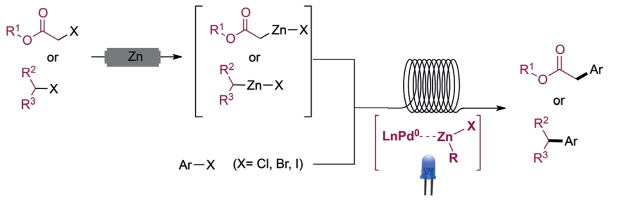
Photoinduced Palladium-Catalyzed Negishi Cross-Couplings Enabled by the Visible-Light Absorption of Palladium–Zinc Complexes



Much better with light: Complexes between palladium and zinc can absorb blue light. This process facilitates the oxidative addition of challenging substrates, opening new avenues in palladium cross-coupling chemistry and photocatalysis.