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Visible Light-Induced Nickel-Catalyzed Negishi Cross-Coupling. A New Approach to Exogenous Photosensitizer-free Photocatalysis.

Irini Abdiaj,[a] Alberto Fontana,[a] M. Victoria Gomez,[b] Antonio de la Hoz[b] and Jesús Alcázar*[a]

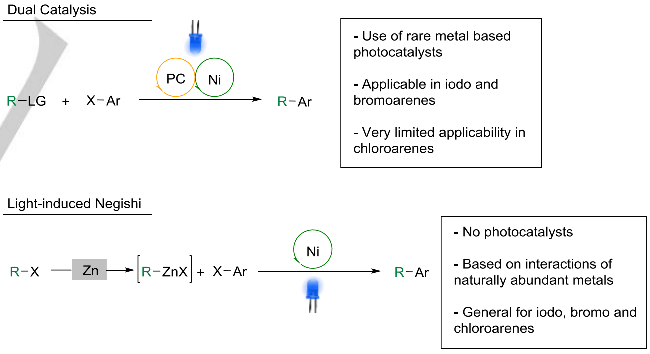
Dedication ((optional))

Abstract: The merging of photoredox and transition-metal catalysis has become one of the most attractive approaches for carbon-carbon bond formation. The procedure requires the use of two transition organometallic species, one of which acts as a photosensitizer and the other as a cross-coupling catalyst. We report here a new exogenous photosensitizer-free photocatalytic protocol that allows the formation of carbon-carbon bonds by direct acceleration of the well-known nickel-catalyzed Negishi cross-coupling using two naturally abundant metals. This finding will open new avenues in cross-coupling chemistry involving the direct visible light absorption of organometallic catalytic complexes.

The development of carbon-carbon bond formation through transition-metal mediated cross-coupling chemistry has changed the way that organic synthesis is carried out.[1,2] More recently, the advent of dual catalysis, where organometallic catalysis is combined with a photosensitizer, has opened new avenues in C(sp^3)–C(sp^2) bond formation.[3-5] However, the photocatalyst used is based on rare metals, such as ruthenium or iridium complexes, and this makes the protocols less suitable and sustainable for scalability purposes. Different alkyl boron,[6,7] ammonium alkylsilicates,[8] *O*-benzyl xanthates[9] and α-heteroatom-containing carboxylic acids[10] have been used to promote the formation of nucleophilic alkyl radicals.

Baran's group recently reported the use of organozinc derivatives in combination with light for C(sp^3)–C(sp^2) coupling but, as reported by the authors, the reaction is a pure thermal process and light did not add value to the reaction.[11] Beyond this article, other reports on the use of organozinc reagents in a photochemical reaction have not been published to date. Considering the lack of knowledge about the behavior of these intermediates in photochemical processes and given our experience in organozinc chemistry,[12-14] we decided to explore the use of these reagents in dual catalysis as a replacement for other organometallic reagents reported previously (Figure 1).[6-8]

Initially, we selected methyl 4-bromobenzoate **2** and benzylzinc bromide **1** as coupling partners and ran the reaction in the presence of 1 mol % of iridium photocatalyst and 2 mol % of nickel coupling catalyst in batch. There was clear evidence for the formation of the expected product in the crude mixture (see supporting information). Photochemical reactions are often enhanced on using flow[15,16] and it was therefore decided to apply this technology (Table 1). As anticipated, a higher conversion was achieved in flow than that detected in batch (entry 1). Control reactions were carried out in an effort to determine whether this process was driven by temperature or light. To our surprise, while irradiation was essential for the reaction (entry 3), the use of a photocatalyst was not (entry 2). A temperature of 60 ºC was required to achieve full conversion (entry 4). The use of our flow protocol for the formation of the organozinc derivative,[12] instead of the commercially available reagent, also led to full conversion, but in the absence of light a conversion of 78% was obtained (entry 5), so the thermally driven process was much higher for our zincate than for the commercial one.



R = alkyl subunit; Ar = aryl group; X = halogen atom; PC = iridium or ruthenium based photocatalysts

Figure 1. Comparison of dual catalysis with light induced Negishi coupling.

To reduce the effect of the thermal component of the reaction, we selected 4-bromoanisole as a coupling partner, a substrate that has not been described in Negishi couplings using nickel as catalyst. Using the commercially available reagent no reaction was observed (see supporting information). Nevertheless, on using the flow zincate, a conversion of 53% was achieved with 2% catalyst loading (entry 7) and full conversion was achieved when the catalyst loading was increased to 5% (entry 8). The same conditions in the absence of light provided the compound with 55% conversion (entry 9).

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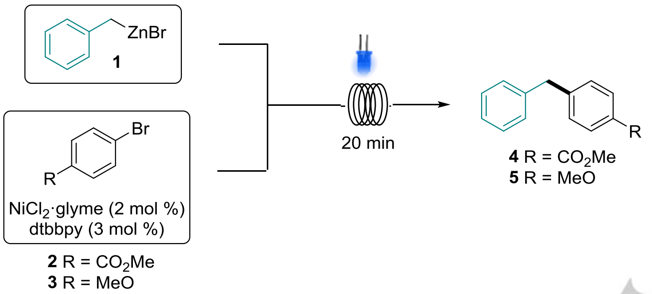
Even though the difference in conversion between the pure thermal Negishi and the new light-driven reaction was only 45%, we considered it sufficient to follow the conversion in flow at different time points either in the presence or absence of light (see Figure S1 in supporting information). This experiment proved the reaction is accelerated in the presence of light and that this acceleration is particularly marked at the beginning of the reaction. Based on the findings outlined above, the scope of the reaction was further explored by varying both reagents (Figure 2). This study was focused on bromo- and chloroarenes as they are rarely used in nickel-catalyzed Negishi cross-couplings.[17] To obtain comparable results, the reactions were performed under the same conditions either in presence or absence of light.

Table 1. Optimization of the flow reaction.



Entry	T (ºC)	R	Irradiation	Photocatalyst	Conv. (%)
1	40	CO₂Me	450 nm	fac-Ir(ppy)₃	64
2	40	CO₂Me	450 nm	----	70
3	40	CO₂Me	----	----	4
4	60	CO₂Me	450 nm	----	100
5	60	CO₂Me	----	----	78[a]
6	60	MeO	450 nm	----	0
7	60	MeO	450 nm	----	53[a]
8	60	MeO	450 nm	----	100[a, b]
9	60	MeO	----	----	55[a,b]

[a] Organozinc prepared in flow. [b] 5 mol % of nickel catalyst used.

Compounds with electron-withdrawing groups only required 2 mol % of nickel. The effect of the light on the reaction is specially highlighted when strong electron-donating groups were present in the molecule, compounds **8** and **10**, where conversion rocketed in the presence of light. Iodo-derivatives were also suitable but a strong donating group, such as a free amino group, is required to observe remarkable difference between the light irradiated and thermal reactions (e.g., compound **18**). The protocol is also applicable to different alkylzinc reagents, either freshly prepared or commercially available, beyond benzyl analogues, for instance compounds **6**, **7** and **12**.

It is important to highlight the ability of chloroarenes to participate in this reaction, since these coupling partners have only rarely been described in the literature in this context.[17] The case of compound **19** clearly illustrates the value of the new protocol, where irradiation with light became key to achieve a good yield of the expected product when the chloroarene was used. It is also important to highlight that compound **23** can only be obtained in the presence of light. In order to demonstrate the value of this methodology in a medicinal chemistry setting, compounds **25** and **26** were prepared using the corresponding chlorotriazolopyridine core previously described in a series of compounds with activity as positive allosteric modulators of the metabotropic glutamate receptor 2, but never reported in a Negishi cross-coupling.[18-22] Both examples clearly benefited from the light protocol and the products were obtained in good to excellent yields, whereas little or no conversion was observed in the absence of light. This finding will be key to introduce C(sp^3)-enriched motifs that could improve physicochemical parameters such as solubility.[23,24]

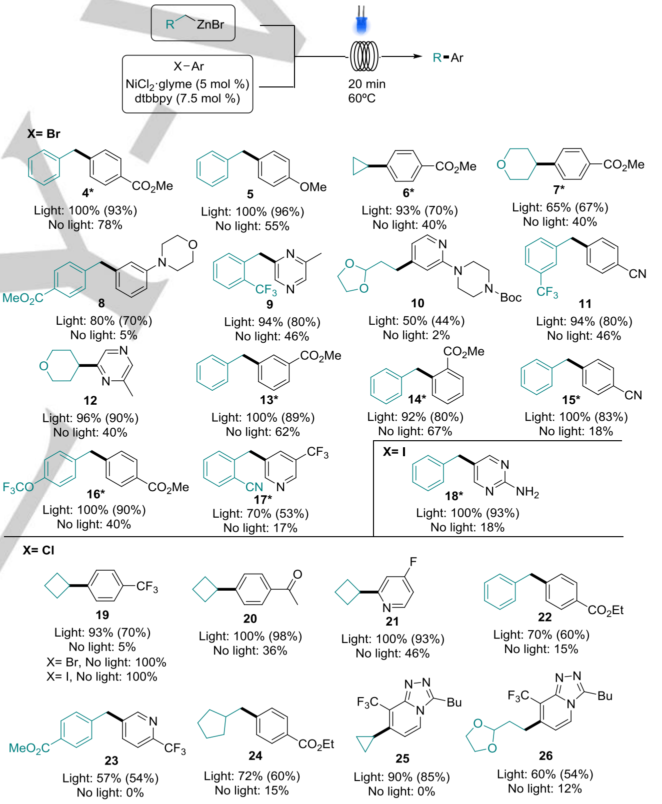


Figure 2. Scope of organozinc and haloarene coupling partners in the light-induced nickel-catalyzed Negishi coupling. Conversions by liquid chromatography. Isolated yields in brackets. *Reactions run with 2 mol % catalyst. See supplementary information for more details..

Preparation of compound **16** was selected to demonstrate the scalability of the protocol. Organozinc preparation was carried out in flow and the exiting stream was connected to a second solution stream containing the haloarene and the catalytic complex before entering in the photoreactor (see Figure S9 in supporting information). This process was run continuously for 8 h and compared with the same reaction in batch, by sampling at

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different timepoints (see Figure S10 in supporting information). The flow protocol provided 6.7 g of isolated product (93% isolated yield), with a productivity of 800 mg·h^{-1}. In contrast, only a 39% of isolated yield was achieved in batch. Considering the time and reaction volumes, the space/time yield[25,26] was calculated and this clearly favors the new flow process (see table of Figure S10 in supporting information).

Regarding the mechanism of the reaction, it is important to note that visible light-induced transition metal-catalyzed transformations are known in literature and have been recently reviewed.[27] Metals used for this reaction include cobalt, iron, copper, palladium, gold and platinum. However, nickel has not been described for this chemistry. The initial approach to clarify the light induction of the reaction was the study of UV-visible spectra for each component of the reaction and different mixtures. It was found that only when the catalytic complex was mixed with the organozinc reagent was a broad band observed in the visible region (Figure 3). When $NiCl_2$, i.e., Ni(II), was replaced by Ni(COD), Ni(0), absorption in the visible region was not observed and this demonstrates the need for nickel(II) species for light absorption.

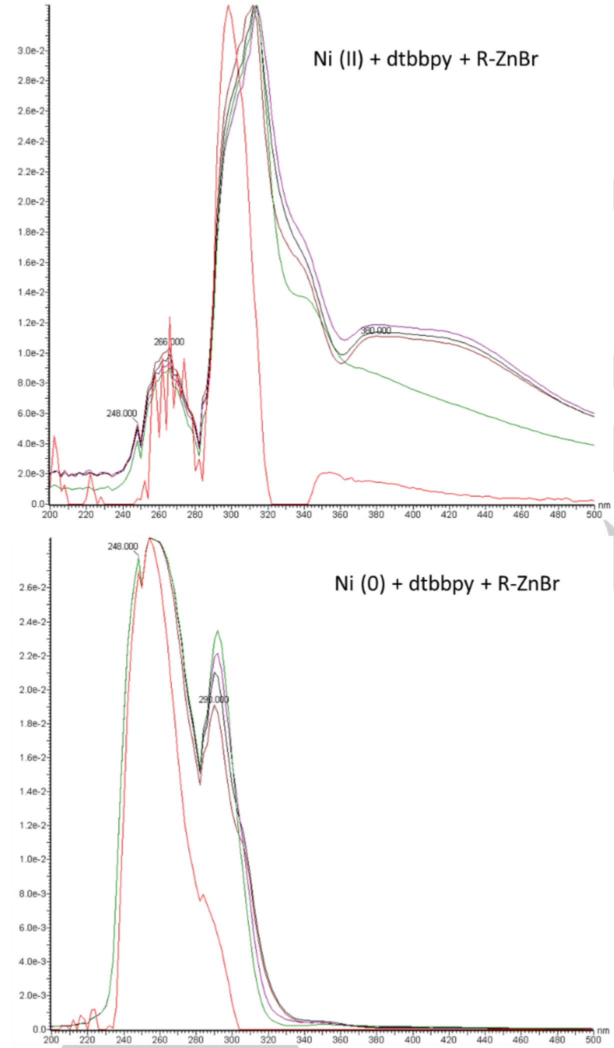

Figure 3. Absorption spectra of mixtures of nickel complexes with the organozinc reagent. Evolution of the absorption recorded over 20 minutes.

Considering the spectra of Figure 3, preparation of compound **1a** was performed at different wavelengths to determine the effect on the reaction outcome. The best conversion was obtained when the reaction mixture was irradiated at 450 nm (blue light). Lower conversions were achieved when the reaction was irradiated either at 360 nm (black light) or 520 nm (green light) (see table S8 in supporting information). These results are consistent with the absorption spectra.

Key aspects for dual catalysis and light-induced reactions are the single electron transfer processes (SET) and the formation of radicals. In this respect, different reactions were carried out to identify the presence of such radicals. However, conclusive results were not obtained in these experiments (see Table S7 in supporting information). Either traps reacted with the organozinc derivative in the absence of catalyst or light, so the reaction was quenched because of the reactivity of the zincate, or no trapping was observed. Rearrangements of radical probes, also known as radical clocks, cannot be used in the reaction discussed here as radicals had been detected during the organozinc formation in batch.[28] The use of flow did not make any difference in this respect (see supporting information). None of the assays provided suitable data to support the presence of radicals during the coupling process, although the absence of radicals cannot be ruled out.

With the aim of shedding additional light on the mechanism of the reaction, NMR spectroscopy was employed as an analytical tool given its potential to elucidate molecular structures. The aim was to study the reaction for the synthesis of compound **9** following the signal of the trifluoromethyl group close to the reactive site by ^{19}F NMR spectroscopy. The laser-diode based illumination device previously reported by us[29] was used to activate the reaction mixture in a 5 mm-NMR tube for *in situ* NMR monitoring.[30]

Reaction mixtures were freshly prepared and transferred quickly to a 5 mm-NMR tube to record the ^{19}F NMR spectrum. Consecutive NMR experiments were recorded as a function of monitoring time and light was switched on or off at different monitoring times (see supporting information for more details of the NMR experiments).

To try to detect the intermediate that is absorbing in the blue region (Figure 3), a very rapid addition of equimolar amounts of zincate derivative and nickel complex in an NMR tube allowed us to see a new signal in the spectrum at -61.0 ppm. It should be noted that the new signal is deshielded and appears around 2 ppm downfield from the signal of the original zincate, indicating a reduction in the electron density on this reagent. The analysis of consecutive NMR experiments turning the light on and off showed that this signal is decreasing only in the presence of light (Figure 4, left). As this signal is decreasing in intensity, the signal corresponding to dimer **28** clearly increased and followed the same pattern observed for previous intermediate (Figure 4, right). It has been widely reported that dimerization of organozinc reagents is linked to the reduction of Ni(II) precatalyst to Ni(0) as the first step to form the real catalytic complex.[17,31] The results from this experiment demonstrated that this step is clearly accelerated in the presence of light. Similar acceleration for the

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conversion of Pd(II) to Pd(0) has been observed in light-induced Heck reactions.[32,33]

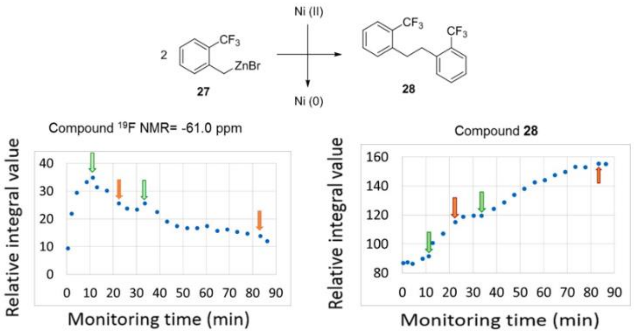

Figure 4. Effect of light in the degradation of an intermediate signal and in the acceleration of the formation of dimer **28**. Green arrows mark when the light was turned on and orange arrows when the light was turned off.

In a second experiment, a standard reaction was performed by adding in the NMR tube all the components at the required concentrations. The evolution of the signal of the product was then followed. At the beginning of the reaction, with the light off, there was a slow evolution to product and this was clearly accelerated once the light was switched on after around 5 minutes (see Figure S8 in supporting information). The data obtained from these two experiments is consistent with light acceleration of the overall reaction at two distinct points in the catalytic cycle. First, light accelerates the reduction of Ni(II) to Ni(0) complex with the concomitant oxidation of the zincate to the dimer **28**. Then, product formation is also accelerated by light. MacMillan *et al.* described the acceleration of the reductive elimination step of the catalytic cycle by an energy transfer from the iridium photocatalyst to a Ni(II) intermediate.[34] Similarly, the UV-visible spectra shown in Figure 3 may indicate that a direct light absorption of a complex between the two metals would accelerate the reductive elimination step of the catalytic cycle (see Scheme S3 in supporting information). Nevertheless, further work will be required to unveil the species formed and to fully elucidate the mechanism.

In conclusion, nickel-catalyzed Negishi cross coupling can be accelerated by visible light. This can be considered as a new photocatalytic process involving two naturally abundant metals. The use of freshly prepared organozinc derivatives in flow is key for the successful outcome of the reaction. The scope of the reaction is broader than that of traditional batch Negishi and dual catalytic reactions, especially considering aryl chlorides. The catalyst loading can be reduced to only 2 mol % nickel. This method allows access to new derivatives with potential value from a medicinal chemistry point of view. As the reaction is carried out in flow, direct scalability is easily achieved and the overall approach is superior to batch protocols. Even though further work will be required to study the mechanism in more detail, it seems to be accelerated in two steps: formation of the catalyst and catalytic cycle itself. We believe that the current findings will provide new insights into photocatalysis and open new avenues within this field. Further work to explore the potential of this new approach in other bimetallic reactions is currently ongoing in our laboratories.

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

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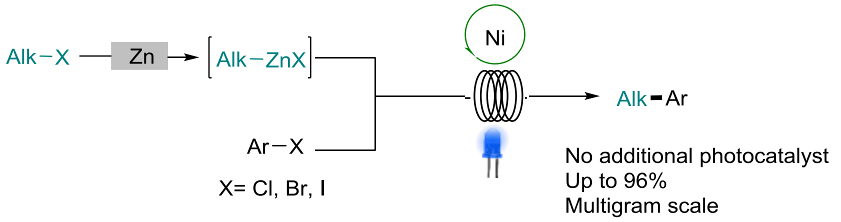

Visible acceleration: This new photocatalytic process involving two naturally abundant metals expands the current scope of both Negishi and dual catalysis cross-couplings. The methodology is applicable to drug discovery and scalable to multigram amounts.

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