Evidence for Photocatalyst Involvement in Oxidative Additions of Nickel-Catalyzed Carboxylate *O*-Arylations

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ABSTRACT: Dual photo- and nickel-catalysis has can effect cross-coupling under mild conditions, but little is known about the *in situ* kinetics of this class of reactions. We report a comprehensive kinetic examination of a model carboxylate *O*-arylation, comparing the state-of-the-art homogeneous photocatalyst (Ir(ppy)$_3$) with a competitive heterogeneous photocatalyst (graphitic carbon nitride). Experimental conditions were adjusted such that the nickel catalytic cycle is emphasized, but differences between the systems still became apparent. Ir(ppy)$_3$ deactivates the nickel catalytic cycle and creates more side product. Kinetic data for this homogeneous reaction supports a rate-limiting reductive elimination. Graphitic carbon nitrides are more selective, even at high photocatalyst-to-nickel ratios. The heterogeneous reaction also shows a rate dependence on aryl halide, indicating that oxidative addition plays a role in rate determination. The results argue against the current mechanistic hypothesis, which states that the photocatalyst is only involved to trigger reductive elimination.

INTRODUCTION

Palladium catalysis is key to many conceptual and practical advances in modern organic chemistry, but its scarcity projects poorly for long-term use. As such, transferring well-defined reactivities of palladium to nickel, an isoelectronic and more abundant metal, has been an explicit goal of catalysis for more than fifty years. Low-valent nickel species are capable of undergoing oxidative additions readily, but the subsequent reductive eliminations (RE), particularly for Ni(II) complexes, are thought to be comparatively difficult.[1] Nickel couplings are hence believed to go through higher-valent intermediates,[2-3] accessed by stoichiometric redox modulators, such that the RE is more favorable.[4-5]

The combination of photocatalysis with nickel catalysis has provided an elegant pathway by which nickel can turn over without adding excessive reductants or harsh conditions.[6-7] Iridium polypyridyl complexes were found to act as photocatalysts (PCs) to effect C–N, C–O, and C–C couplings using nickel(II) precatalysts.[8-9] Subsequently, homogeneous iridium photocatalysts have been replaced with heterogeneous graphitic carbon nitride (g-CN) semiconductors, rendering the overall transformations noble-metal-free.[10-14]

The current mechanistic proposal for a relatively well-studied carboxylate *O*-arylation (Scheme 1A) in this family of reactions is depicted in Scheme 1B.[15] Numerous common nickel(II) precatalysts are viable, which are thought to undergo two single-electron transfers to a bipyridyl Ni(0) **4**. From this reduced species, oxidative addition to **5** is facile. The catalyst resting state **6** is unable to undergo the necessary reductive elimination. To close the cycle, **6** receives an energy transfer from the MLCT excited state of the photocatalyst, which enables C–O bond formation.[16-17] Stern-Vollmer quenching studies,[15] transient absorption spectros-
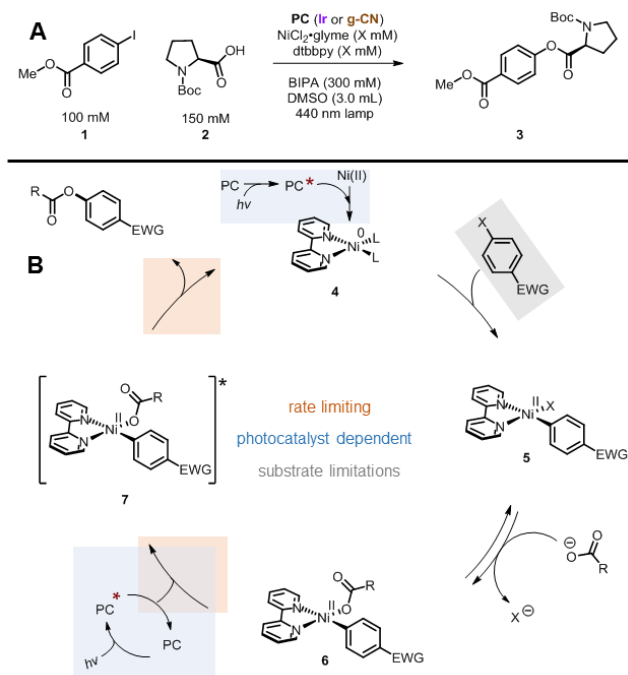
Scheme 1. A) The two dual photo- and nickel-catalyzed reactions studied in this work. Standard conditions shown. Deviations from these conditions in any subsequent figure will be noted. B) Mechanistic hypothesis (2017).

copy,[16] and computational studies[17] have been used to support quenching of Ir(ppy)$_3$ by a potential nickel(II) intermediate.

Broadly, the substrate scopes for both homogeneous and heterogeneous variations of carbon–heteroatom couplings

contain only electron-poor aryl halides and electron-neutral or electron-neutral or electron-rich coupling partners (HNR$_2$, HOR, HSR, *etc.*). To our knowledge these limitations have not been explicitly discussed in a mechanistic context. The Ir(ppy)$_3$-catalyzed homogeneous carboxylate *O*-arylation accommodates only electron-withdrawing aryl bromides, and electron-withdrawing carboxylic acids are absent. Such a combination could be explained by arguing that an S$_N$Ar-type reductive elimination is required.

However, tension between the existing mechanism and the resulting substrate scopes surfaced during our development of the heterogeneous congener using graphitic carbon nitride photocatalysts.[10] During a cursory kinetic study, methyl 4-iodobenzoate **1** (96%, 4h) coupled considerably faster coupling than methyl 4-bromobenzoate (88%, 48h) with *N*-Boc proline **2**. Once the nickel catalytic cycle is at the resting state **6**, the differences between an aryl iodide and bromide are irrelevant, as only the aryl ring remains on-cycle. This discrepancy in rate must therefore arise from the oxidative addition or ligand exchange step. As even aryl chlorides show facile proclivities towards oxidative addition with low-valent nickel in non-photochemical reactions,[18] and the homogeneous analogue converted aryl bromides efficiently, we began to question whether the existing mechanism is operational with the heterogeneous congener. Given that we found the same substituent limitations, albeit with iodides instead of bromides, we further wondered if there were mechanistic commonalities among the two *O*-arylations.

Electron deficiency of an aryl halide can accelerate oxidative additions, as the aryl halide is itself formally reduced. In this vein, aryl halide limitations in this class of reactions could be explained by scission of the aryl halide bond that pushes at the energetic boundaries of photocatalytic reductions. Reduction potentials of common aryl halides range from -1.0 to -3.5V[19-20], with electron-donating groups and higher-row halides ranking as more difficult. The iridium polypyridyl complex Ir(ppy)$_3$ used in the homogeneous *O*-arylation has a reduction potential of -1.73V, and substrate limitations could be a marker of the Ir(III)*/Ir(IV) potential within the aforementioned range.[21] Such logic has been invoked for the thiolation of aryl iodides[22] as well as dehalogenations[23-24] with this exact photocatalyst. Stern-Vollmer and transient absorption studies showed that aryl iodides could in fact quench the excited triplet state of Ir(ppy)$_{3}$,[22] forming an aryl radical.

With these considerations in mind, we set out to answer three basic questions: 1) do the heterogeneous and homogeneous reactions proceed by the same mechanism; if so, 2) do they both conform to the extant hypothesis, in which reductive elimination is rate-limiting; and 3) are the rate-limiting steps and the steps which require photocatalyst the same?

RESEARCH PLAN AND HYPOTHESES

Numerous mechanistic studies have been undertaken for photocatalytic reactions in general.[25] Inquiries on dual nickel- and photocatalyzed carbon–heteroatom cross-couplings have largely focused on the character of the interaction between photocatalyst and metal catalyst.[17, 26] However, no in-depth kinetics studies of any of these reactions have been disclosed.
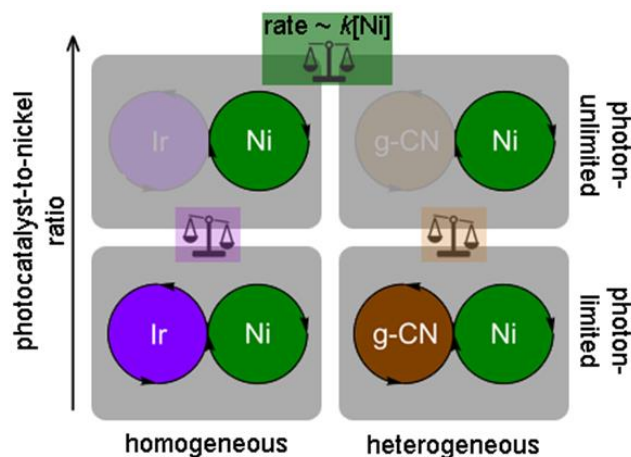
Figure 1. Four sets of data will be collected and compared. Our hypothesis is that the photon-unlimited data sets will be identical, and will corroborate a rate-limiting reductive elimination.

Kinetics studies of catalytic systems that track a reaction in their native reaction conditions throughout the entire course of a reaction can afford a wealth of qualitative and quantitative information usually inaccessible from studies of a narrower scope.[27-28] However, "native" reaction conditions are typically based on the methodology studies where the primary aim is the optimization of yield. Studies of dual photo- and nickel catalytic reactions under such conditions may give data obfuscated by rate-limiting processes derived from interaction between the PC and metal catalyst. Kinetically, this may paint an incomplete picture of the reaction, but this data could arguably be useful to synthetic chemists considering using such a method. We therefore sought to observe the homogeneous and heterogeneous dual photo- and nickel-catalyzed *O*-arylations in two regimes each (Figure 1). The first would be conditions closer to the standard conditions obtained during methodology development ("photon-limited"), geared toward understanding overall reaction behavior. The second would be in a regime in which the metal catalyst is saturated with excited photocatalyst species ("photon-unlimited"). Under such conditions photons are essentially treated as a reagent in high excess. Data obtained in this regime allows us to both evaluate the intrinsic kinetics of the nickel cycle, as well as enable a more rigorous comparison between data sets of different photocatalysts.

As no *in situ* studies exist to date any for dual nickel- and photocatalyzed cross-couplings, comparison of the photon-limited and photon-unlimited regimes with each other for each reaction would be of general interest. We anticipated that we would see differences between the photon-limited and photon-unlimited regimes, potentially in the magnitude of the reagents' coefficients in the rate laws.

Most importantly, the intrinsic, photon-unlimited kinetics of both reactions should be compared with each other and to the extant mechanistic hypothesis. The kinetics in photon-unlimited regimes of the homogeneous and heterogeneous reactions should be identical since the PC should drop out of the rate law. The extant hypothesis for the dual photo- and nickel-catalyzed carboxylate *O*-arylation, congruent with the accrued understanding of nickel catalysis, is that the PC enables a rate-limiting reductive elimination.[15]

Thus, we predicted that the photon-unlimited regime for both reactions would give rate ~ k[Ni].

RESULTS

I. Heterogeneous (graphitic carbon nitride) PC

*a. Photon-limited (3.33 mg/mL g-CN, 5 mM Ni•L, 50% lamp power)*

Initially, the kinetics of the carboxylate *O*-arylation of aryl iodides using the graphitic carbon nitride CN-OA-m[29] as a photocatalyst in photon-limited conditions were analyzed. These photocatalytic reactions can be tracked by attaching a custom vial to an *in situ* infrared probe.[10] Using a stronger LED lamp for increased photon flux and improved reproducibility, we ensured that the infrared technique tracked reaction progress by verification with an orthogonal method (Figure S2).

From a cursory, qualitative glance, these reactions at the native conditions display no unusual behavior, except for exhibiting a short induction period. A series of experiments were conducted to assess which reagents were responsible for this induction (Figure S5). Delaying the injection of NiCl$_2$•glyme and its bipyridyl ligand or aryl iodide **1** resulted in immediate productive catalysis. Delayed injection of carboxylic acid **2** retains the induction period. Conspicuously, delaying addition of the base *N-tert*-butylisopropylamine (BIPA) resulted in a reaction profile slightly suggestive of catalyst activation,[30] indicating that the secondary amine plays a role more significant than simply that of a Brønsted base.

Varying the nickel concentration from 5-20 mM unsurprisingly resulted in no rate change (Figure S6). At 5 mM Ni, no catalyst deactivation or product inhibition was observed (Figure S8), expected at such a high metal catalyst concentration. Surprisingly, modulation in [**1**] resulted in a fractionally positive order (Figure S9) for the aryl iodide. Carboxylic acid **2** showed a zero-order dependence (Figure S10). Reagent orders obtained in this regime should be considered with some measure of caution as the interactions between PC and Ni are ill-defined. However, we were curious if the reagent order of the aryl iodide would persist in the photon-unlimited regime, as it would be a significant clue to help resolve the questions posed below.

To switch from the photon-limited to the photon-unlimited regime, we needed to increase the ratio of photons and/or PC to nickel. Although numerous photocatalytic reactions with metal centers have been tracked with *in situ* apparatuses,[31] to our knowledge only one study has described finding a region in which nickel's access to excitation is carefully controlled to be unimpeded.[32] In the work of Lehnherr *et al.*, light directly excited a metal catalyst, with no photocatalytic intermediary. To find a region in which their metal catalyst was not limited by throughput of photons, initial rate was plotted against catalyst concentration, and at lower concentrations a roughly linear correlation is apparent. To make a comparable plot, we retained a high PC loading and maximum lamp power.

Moving from high to low nickel concentrations surprisingly did not provide an identical shape to that of the literature precedent (Figure 2A). Specifically, we observed an unexpected "peak" where catalysis has a much higher rate,
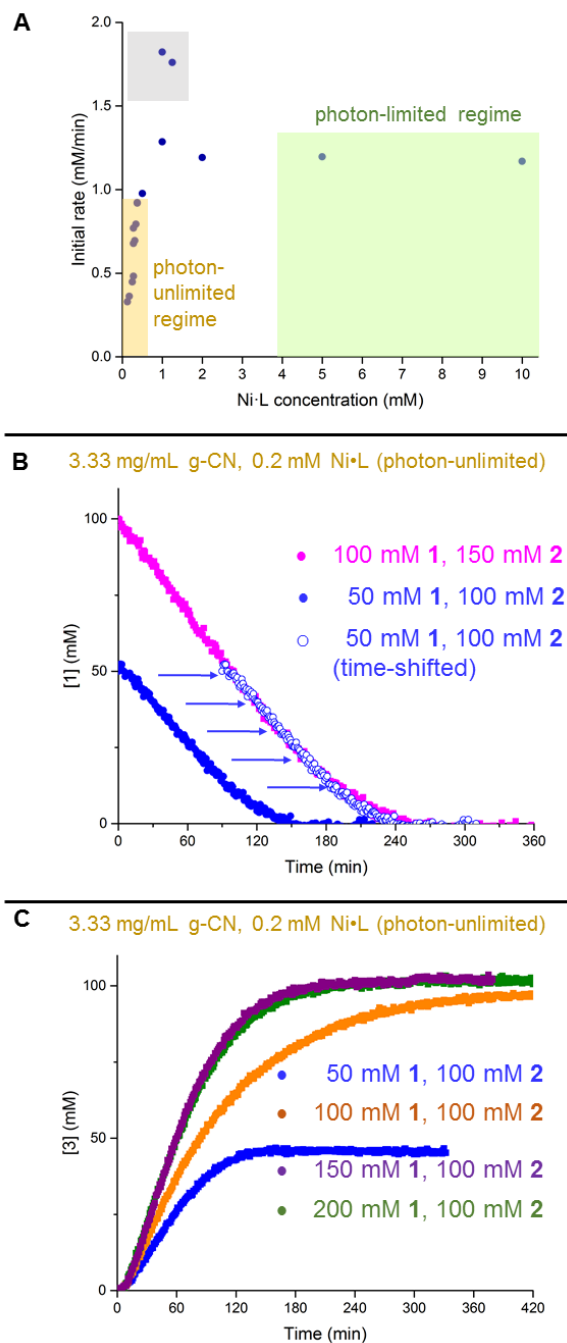
Figure 2. Key experiments of heterogeneous congener. A) Overview of where the photon-limited and unlimited regimes could be identified. B) Time-shifted same excess experiments. Overlay indicates lack of catalyst deactivation or product inhibition. C) Positive-order dependence of aryl iodide observed.

around 1 mM. Although further studies are required to account for this behavior, it is possible that metal catalyst above a certain threshold engages in some combination or comproportionation, disproportionation, and/or higher-order nickel species known to form in the presence of carboxylic acids.[33]

The area at very low concentration of nickel likely would provide a regime in which the nickel catalytic cycle was not limited by access to an excited photocatalytic species. To

confirm this was the case, at low concentrations we used Variable Time Normalization Analysis (VTNA)[34] to find a first-order dependence on nickel between 0.15-0.25 mM (Figure S11). Kinetics studies in this area are expected to produce data that reflect the intrinsic characteristics of the nickel cycle.

b. Photon-unlimited (3.33 mg/mL g-CN, 0.2 mM Ni•L, 100% lamp power)

To probe the robustness of the nickel catalyst, two "same excess" experiments were conducted[27, 35] under photon-unlimited conditions and the less concentrated was time-shifted on the x-axis (Figure 2B). Overlay here indicates that the product does not inhibit catalysis, nor does meaningful or disproportionate catalyst deactivation occur.

Experiments to determine the reagent orders of the substrates revealed that aryl iodide again exhibited a positive order dependence (Figure 2C). Due to the induction period, first attempts at VTNA overlay were found to be problematic (Figure S12). Elegant mathematical solutions to this common issue have been disclosed,[36] but the most rigorous would require spectroscopic determination of the active catalyst concentration. Repeating the different excess experiments with delayed catalyst injections (Figure S13), which bypass the induction period as described above, cleanly leads to a reagent order of 0.3.

Examination of the dependence on reagents for **2**, the base, and the photocatalyst provided a much less straightforward picture. All three reagents exhibit positive order dependence at lower concentrations and inhibitory effects at higher concentrations (Figures S14-16).

II. Homogeneous (Ir(ppy)₃) PC
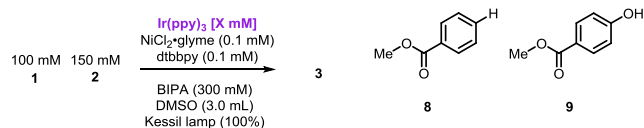
mM PC	3	1	8	9	Mass balance
1	62	0	18	6	86
0.5	83	0	10	4	97
0.25	82	0	8	3	94
0.125	90	0	5	5	100

Table 1. Screening to determine photocatalyst loading for photon-unlimited and photon-limited regimes of the homogeneous reaction.

We began the homogeneous studies by attempting to determine a proper photocatalyst loading. Initial experiments with 0.1 mM Ni•L and the standard (1 mM) photocatalyst concentration[15] gave unsatisfactory yields. We observed dehalogenation accompanying productive catalysis (Table 1). Formation of the phenol side product **9** appears to be independent of an unfavorable PC-to-Ni ratio.

Finding the photon-unlimited regime required a two-dimensional guess-and-check, in which the amount of PC and

Ni were modulated in turn to find a ratio in which 1) the interaction between the two was not rate-limiting and 2) formation of side products was not playing an outsized role in the nickel catalyst's activity. Visualization of Table 1 was via product formation reveals that despite its superior side product ratio, experiments with 0.125 mM PC loading are likely limited by the relay of energy from PC to Ni (Figure 3A). High concentrations of Ir(ppy)₃ accelerates the consumption of **1** but not significantly the rate of product formation. This finding is in striking contrast to the heterogeneous analogue, where slower product formation is a function of slower consumption of **1** at higher PC loading (Figure S16).

Based on these tradeoffs we decided to use 0.5 mM Ir(ppy)₃, given that it effects maximum product-forming rate, and approaches the maximum consumption of **1**, while the side processes are not overly competitive. From a qualitative standpoint these reactions do not share the induction period easily identifiable in the heterogeneous reaction. We performed an initial rate study (Figure S17) to identify a region where the nickel catalyst would be saturated with excited photocatalyst. Contrary to the heterogeneous equivalent, this graph matched closely with the literature precedent for finding a linear absorption regime.[32] VTNA confirmed that the nickel catalyst is first-order in this region (Figure S18), the middle of which is 0.075 mM Ni, the basis for further mechanistic studies.

a. Photon-unlimited (0.5 mM Ir(ppy)₃, 0.075 mM Ni•L, 100% lamp power)

A major difference between the heterogeneous and homogeneous reaction was apparent from the same excess experiment, where no overlay was observed (Figure 3B). Should the product inhibit catalysis, an effect in the heterogeneous reaction would have been observed, so we can attribute this behavior to catalyst deactivation. This analysis is complicated by the fact that dehalogenation accounts for a non-
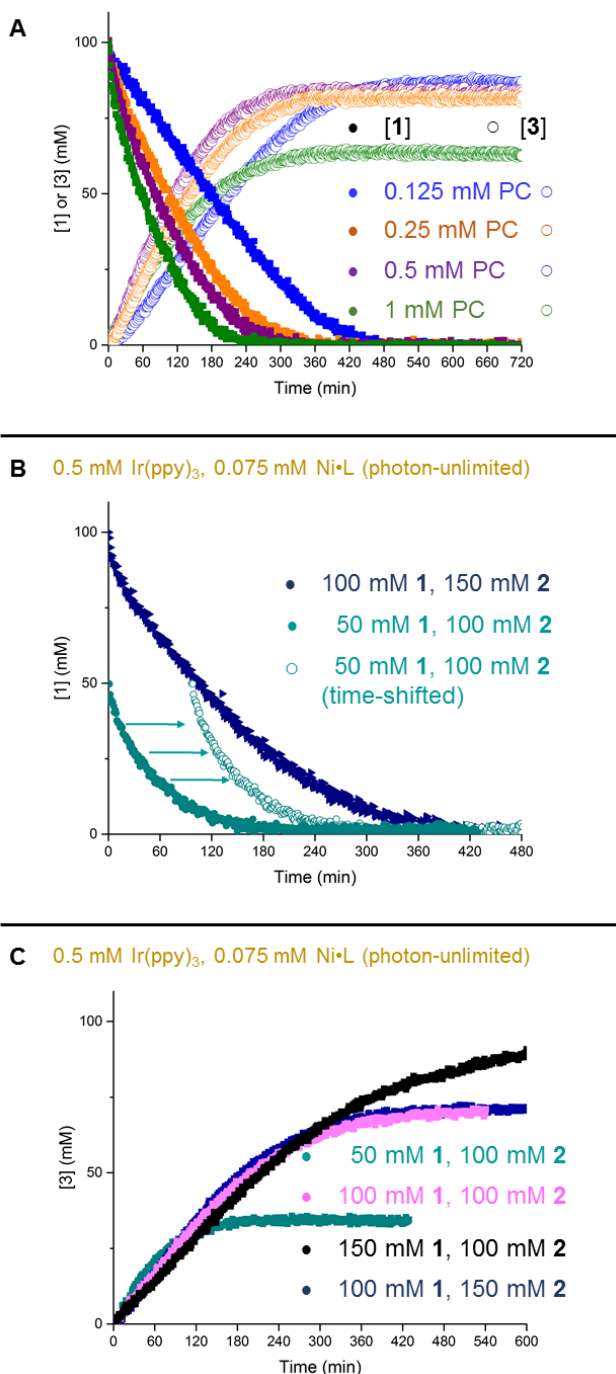
Figure 3. Key experiments of homogeneous congener. A) Increasing photocatalyst loading increases rate of starting material consumption, but product formation is found to be competitive with dehalogenation. B) Same excess experiment shows catalyst deactivation intrinsic to iridium photocatalysis. C) Rate is independent of [**1**] and [**2**].

negligible amount of the consumption of **1**. A same-excess graph in which the aryl iodide concentration was divided by product formation, to approximate only productive catalysis, also did not show overlay (Figure S19).

Experiments varying the amounts of substrate and coupling partner were conducted to obtain the reagent orders of our reactants. We found the rate to be essentially independent

of the concentration of **1** or **2** (Figure 3C). Such dependencies are congruent with a reductive elimination rate-limiting step. Last, we modified the amount of base while keeping all other reagents constant. This change was the sole factor that accelerates the homogeneous reaction (Figure S20).

a. Photon-limited (0.125 mM Ir(ppy)₃, 0.1 mM Ni•L, 100% lamp power)

Repeating all of the above experiments at lower concentration of homogeneous iridium photocatalyst and higher concentration of nickel catalyst resulted again in a dependence on nickel and zero-order dependencies on **1** and **2** (Figures S21 and S23). Increasing concentration of base again increases rate. The main difference between the photon-limited and photon-unlimited regimes was apparent in the same excess experiment, where no catalyst deactivation was observed in the photon-limited regime (Figure S22).

DISCUSSION

The most conspicuous finding of this study was the rejection of the hypothesis that the kinetics of both systems would give identical rate laws. In other words, as particular care was taken such that the nickel cycle was saturated with excited photocatalyst species for both systems, the intrinsic kinetics of a nickel cross-coupling cycle should have been identical between the two.

The chief quantitative finding of this study is the fractional dependence of aryl iodide **1** in the heterogeneous rate law. To some degree in the heterogeneous congener, oxidative addition is rate-limiting. We propose that this is a result of direct photocatalytic activation of the substrate (Figure 4B). The fractional order arises as this activation occurs off-cycle. Nickel is first-order as it intercepts the radical species on-cycle.

This process may have been overlooked because it is not necessarily rate-limiting. Ir(ppy)₃, having a favorable reduction potential of -1.76V vs. SCE, is readily able to donate an electron to the aryl halide **1**;[23, 37-38] this step is photocatalyst-dependent but fast for aryl iodides (Figure 4B). In contrast, the graphitic carbon nitride used in this study has a lower reduction potentials (up to -1.65V vs. SCE). The capacity for electron transfer is worse, and therefore even in conditions that can be considered photon-unlimited, formation of oxidative addition intermediate **5** is still limited by the kinetically relevant halide fragmentation.

We reject the hypothesis that photocatalysts are required only as a late-cycle trigger for RE. We contend that the photocatalyst is required at *least* one point on the catalytic cycle, namely for single-electron transfer to the aryl halide. Substrate limitations for dual photo- and nickel-catalyzed carbon–heteroatom cross-couplings derive from this elementary step. The most obvious example is the far superior conversion of aryl bromides in this homogeneous *O*-arylation compared to the heterogeneous congener. Such a framework also harmonizes the mechanisms by which these transformations occur with the existing body of photocatalytic dehalogenations and radical-based transformations.[20, 23]

To augment our understanding of the heterogeneous reaction, we created a Hammett plot examining rate dependencies on aryl iodides with substituents of varying electronic character (Figure 4C). Qualitatively, this shape is also seen
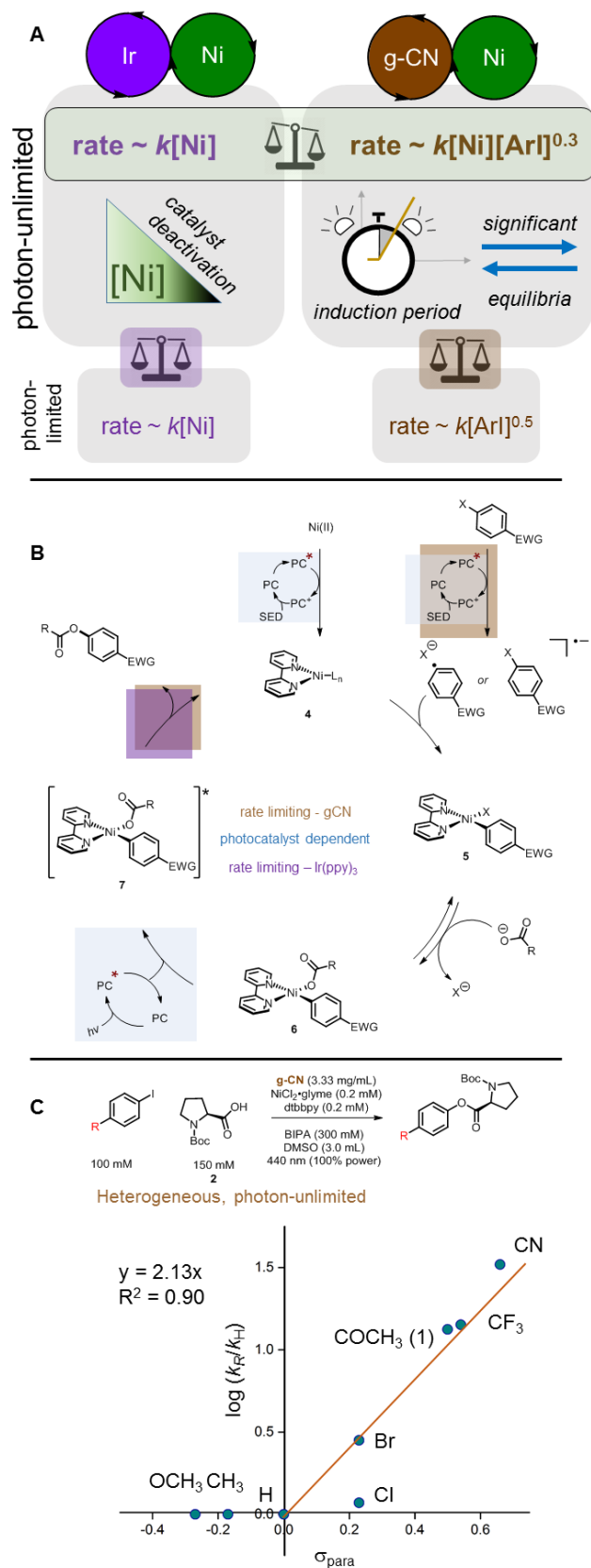
Figure 4. (A) Key findings of this study. (B) Updated mechanistic proposal. Secondary amine base is proposed to close the photoredox cycle by serving as single electron donor (SED). (C) Hammett plot for heterogeneous congener supports that oxidative addition is to some degree rate-limiting.

for the oxidative addition of tris(triphenylphosphine)nickel(0) to aryl chlorides.[18] The ρ value (2.1) is far below that of this more traditional oxidative addition (8.8), thought to proceed through an S_NAr-type mechanism. This could be explained by differences in ligand systems and halides, but also could point to a lowered dependence on the electronic substituent due to a nonconcerted oxidative addition.

With a rate law proportional only to the nickel concentration, data for the homogeneous reaction could reasonably fit three rate-limiting steps: a unimolecular rearrangement, ligand dissociation, or reductive elimination. We have observed nothing to support or reject the first two. Given that the incumbent hypothesis is that RE is rate-limiting, our data supports the existing proposals. As we had originally predicted, our kinetic data here likely reflects the limitations inherent to nickel catalysis.

Whether or not **6** requires photocatalyst to trigger RE likely depends on the oxidation state of this intermediate. It has been clearly demonstrated that a Ni(II) resting state cannot undergo RE without photocatalytic excitation.[15-17] However, extensive literature precedent points to the viability of multiple nickel oxidation states in cross-coupling reactions in very different conditions,[39-41] and the oxidation state of the on-cycle intermediate for these photochemical reactions has yet to be convincingly resolved. Should an energy or electron transfer be required at this intermediate in the homogeneous reactions, it would not be rate-limiting, given the photon-unlimited environment.

Of note is the fact that the only way to accelerate the homogeneous reaction was by addition of more secondary amine base, which is already in large excess. We offer three potential explanations. First, and most likely, the secondary amine donates an electron to $Ir(ppy)_3^+$ to regenerate the photocatalytic cycle. As increasing PC beyond our loading did also increase consumption of **1**, adding more base also increases the effective PC concentration. We can assume that the concentration of **2** requires equimolar amounts of base for deprotonation, and extra amine beyond that point fulfills various roles including weak ligand and electron source. Second, the base is potentially involved in the organization of the nickel catalyst to some degree, evinced by the "reaction fingerprint" of the heterogeneous reaction when the base is injected after a delay (Figure S5). As such, it is possible that its presence does not outright accelerate the reaction as much as it is as guard against decelerating or deactivating processes. Alternatively, or additionally, weak coordination of the base to the square planar pre-RE complex could create a more encumbered five-coordinate complex that is more prone to elimination,[42-43] or is better tuned to absorb an energy transfer.[26]

Qualitatively, two main observations stand out for iridium-catalyzed carboxylate *O*-arylations. First, this system inherently tends to be less selective. In the photon-unlimited regime, at reactions with reasonable concentrations of substrates, yields were frequently in the 70-80% range, often accompanied by significant dehalogenation of the aryl iodide. We believe that this results from speeding up photocatalytic activation of the aryl iodide beyond the capacity of the nickel species to trap the radical on-cycle.

Second, the homogeneous reactions have an intrinsic propensity for catalyst deactivation. Kinetics for the photon-limited and photon-unlimited regimes were essentially the same outside of the fact that catalyst deactivation was not observed in the photon-limited regime. We contend that all dual iridium- and nickel-catalyzed processes operate at inflated nickel concentrations to compensate for this inherent deactivation.

Qualitatively, the induction period in the heterogeneous congener notably differs from the homogeneous reaction. We observe small amounts of consumption of aryl iodide during the delay before product begins to form. If reduction of the Ni(II) precatalyst to a lower-valent species is requisite for productive catalysis, it is possible that this reduction is parallel to or intertwined with dehalogenation.

An unexpected revelation of the heterogeneous reaction is seen in the studies modulating the photocatalyst loading (Figure S16). In contrast to the homogeneous reaction, in which additional PC accelerates consumption of **1** indiscriminately, excess g-CN loading shows slower catalysis but with reasonable preservation of selectivity. We again attribute this to the weaker reduction potential of graphitic carbon nitrides, and is a potential upside to the more limited scope. Such a finding portends well for scalability as well as for sensitive or late-stage functionalization. Careful optimization of the ratios of photocatalyst, nickel, and substrate is far less likely to be necessary with graphitic carbon nitrides.

CONCLUSION

Efforts to swap photocatalysts in dual photo- and metal-catalytic systems may not preserve the inherent reactivity of the metal catalytic cycle. Homogeneous and heterogeneous esterifications differ primarily in that the heterogeneous congener showed a rate dependence on the aryl halide substrate. We ascribe this to the nickel trapping an off-cycle radical anion generated by the photocatalyst and the aryl halide. In this sense the requirements for electron-withdrawing substrates may be ascribed to an energetic barrier that is independent of the nickel catalytic cycle. The choice of photocatalyst may, among other things, be determined by the electronic character of the substrate. Graphitic carbon nitrides show remarkable selectivity even in very high PC-to-Ni ratios, whereas extra nickel catalyst is used in iridium-catalyzed cross-couplings to compensate for catalyst deactivation. We believe that photocatalysts with weaker reduction potentials, such as graphitic carbon nitrides, are less likely to participate in a Ni(0)/Ni(II) cycle.

ASSOCIATED CONTENT

Supporting Information.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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