

## Chapter 4

### Merging Photoredox with Nickel Catalysis: The Coupling of Carboxylic Acids with Aryl Halides

#### *I. Introduction to Nickel Catalysis*

Over the past fifty years, transition metal-catalyzed cross-coupling reactions have transformed the field of synthetic organic chemistry via the evolution of a wide variety of C–C and C–heteroatom bond-forming reactions.<sup>100</sup> During this time, the seminal studies of Negishi, Suzuki, Miyaura, Stille, Kumada, and Hiyama have inspired numerous protocols to construct carbon–carbon bonds using palladium, nickel, or iron catalysis.<sup>101</sup> These strategies enable highly efficient and regiospecific fragment couplings with high functional group tolerance, facilitating the application of modular building blocks in early- or late-stage synthetic efforts. Traditionally, cross-coupling methods have relied upon the use of organometallic nucleophiles such as aryl or vinyl boronic acids, zinc halides, stannanes, or Grignard reagents that undergo addition to a corresponding metal-activated aryl or vinyl halide.

An emerging strategy for C–C bond formation has been the application of native organic functionality as traceless activation handles for transition metal-mediated cross-couplings. In this context, the use of olefin, methoxy, and acetoxy moieties as organometallic replacements has enabled a variety of carbon–carbon bond formation protocols using feedstock materials.<sup>102</sup> We recently questioned whether it would be possible to deliver a mechanism by which feedstock chemicals that contain common yet non-traditional leaving groups could serve as useful coupling

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<sup>100</sup> (a) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis, Vol. 1*; Wiley-VCH: Weinheim, 2004. (b) De Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions, Vol. 1*; Wiley-VCH: Weinheim, 2004.

<sup>101</sup> For a review on nickel-catalyzed cross couplings, see: Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

<sup>102</sup> (a) Anka-Lufford, L. L.; Prinsell, M. R.; Weix, D. J. *J. Org. Chem.* **2012**, *77*, 9989. (b) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343.

Seeded Content – **Understanding nickel catalysis - March 5, 2015 by ScienceX**  
**<https://phys.org/news/2015-03-nickel-catalysis.html>**

Catalysis is a chemical phenomenon that increases the rate of a chemical reaction by spending only a tiny amount of additional substance, called a catalyst. Around 90 percent of all commercially manufactured products involve chemical substances processed in catalytic procedures at some stage. Whatever we are surrounded by in our everyday life was produced with the help of chemical catalysis – materials, dyes, textile, fuels, paper, devices, vehicle parts, food, pharmaceuticals, cosmetics and many others.

Since only a small amount of a catalyst is required to drive the production of [chemical substances](#), the [catalytic process](#) can be tuned to high cost efficiency. Polymerization is an excellent representative example of [catalytic efficiency](#). The manufactured products – polyethylene, plastics, etc. – are produced at a million tons scale every year and are consumed in all countries. Preparation of pharmaceuticals and drugs is another example. Being produced at much smaller scale, these unique chemicals require exceptional structural diversity. It is the area where an outstanding potential of catalysis is now comprehensively explored.

Such increasing growth of industrial production requires the development of more and more catalysts. The price of metal catalysts has significantly increased and even tiny amounts have become expensive. For example, the Nasdaq price for one widely used catalytic metal, palladium, increased by more than four times during the last six years. Production of catalysts is the main area of consumption of palladium with many demanding applications.

Today, the tendency is clearly shifting toward replacement of expensive metals by cheaper analogs. A brief comparison of [catalyst](#) prices shows that a simple metal like nickel is superior to Pd, Pt, Au, Rh (Figure 1). At the moment, these noble metals are ubiquitously used in catalytic applications.

So is it possible to replace noble metals with nickel in the catalytic applications? This appears to be rather difficult to achieve. Each metal has a unique set of chemical and physical properties that provide a particular catalytic transformation. Replacing one catalytic metal for another is in many cases a challenging task.

Of particular interest is the observation made about nickel a century ago by the famous chemist and Nobel Laureate Paul Sabatier: "It can be compared to a spirited horse, delicate, difficult to control, and incapable of sustainable work." (Sabatier, P. *Catalysis in Organic Chemistry*, NY, 1922, p. 15.). Thus, nickel catalysis is a long-standing question. Can the chemists force nickel to do a desired synthetic work? Although there are many successful nickel catalysts on the market, researchers are still facing the challenge.

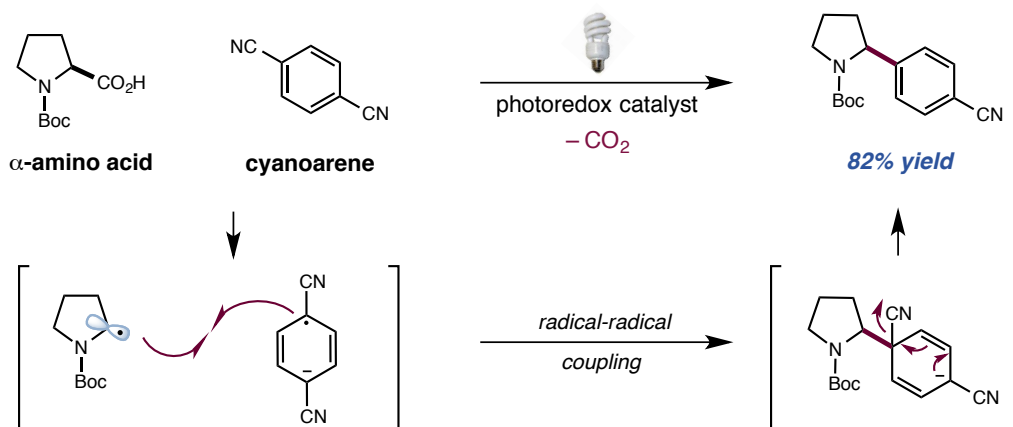
After multiple unsuccessful direct forcing attempts, chemists have made impressive progress in understanding the mechanisms of nickel-catalyzed reactions. New research provides the opportunity to understand the "spirit" of the metal and to make use of its advantages.

A recent article published in the *ACS Catalysis* journal highlights state-of-the-art in this field and emphasizes that we have reached a turning point in the studies of nickel catalysis. As it is discussed in the article, fundamental knowledge on reaction mechanisms can fully uncover the power of [nickel](#) catalysts and minimize plausible drawbacks for practical applications (Figure 2). The key advantages of [nickel catalysts](#), summarized in the article, include:

1. High performance in reactions for which other metals were not efficient;
2. Large variability of electronic states – Ni(0)/Ni(I)/Ni(II)/Ni(III);
3. New reactions and transformation beyond the known limits of other metals;
4. Facile activation and transformation of molecules that are chemically less reactive;
5. Excellent opportunities in photocatalytic and hybrid catalytic cycles.

Will a new hero appear soon on the catalysis team? Let's give it some time.

loss of CO<sub>2</sub>, which can then be trapped by aryl radicals (Scheme 17).<sup>103,104</sup> This concept has been expanded to show that carboxylic acids can be used generally as nucleophile partners in a range of transformations, including conjugate addition,<sup>105</sup> vinylation,<sup>106</sup> fluorination,<sup>107</sup> and reduction.<sup>108</sup> Based on this insight, we questioned whether carboxylic acids could be used broadly as latent nucleophiles in transition metal cross-coupling.



**Scheme 17.** Photoredox-Catalyzed Decarboxylation Accesses Nucleophilic Radicals.

### III. Merging Photoredox with Nickel Catalysis

With the recent growing interest in photoredox catalysis, there have been efforts within the synthetic community to combine this catalytic platform with transition metal catalysis. Several methods have been disclosed that utilize the reactivity of palladium, gold, and copper catalysis to accomplish the installation of unique functionality via the intermediacy of

<sup>103</sup> Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257.

<sup>104</sup> Sammis and coworkers reported a photoredox-catalyzed decarboxylation–fluorination reaction in early 2014: Rueda-Becerril, M.; Mahé, O.; Drouin, M.; Majewski, M. B.; West, J. G.; Wolf, M. O.; Sammis, G. M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2014**, *136*, 2637.

<sup>105</sup> Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886.

<sup>106</sup> Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602.

<sup>107</sup> Ventre, S.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654.

<sup>108</sup> Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 11340.

photoredox-generated radicals.<sup>109</sup> We recently questioned if visible light photoredox and nickel transition metal catalysis might be successfully combined to create a dual catalysis platform for general and modular C–C bond formation using simple feedstock chemicals.

We proposed that two interwoven catalytic cycles might be engineered to simultaneously generate (i) an organometallic nickel(II) species via the oxidative addition of a Ni(0) catalyst to an aryl, alkenyl, or alkyl halide coupling partner, and (ii) a carbon-centered radical generated through a photo-mediated oxidation event. Given that organic radicals are known to rapidly combine with Ni(II) complexes,<sup>110</sup> we hoped that this dual catalysis mechanism would successfully converge in the form of Ni(III)(Ar)(Alkyl), that upon reductive elimination would deliver our desired C–C fragment coupling product. As discussed earlier, The MacMillan group has previously demonstrated that photoredox catalysis affords access to nucleophilic  $\alpha$ -amino radicals via decarboxylation of a carboxylic acid. The research group of Abigail Doyle has explored Ni-catalyzed cross-coupling reactions with iminium ions that proceed via a putative  $\alpha$ -aminonickel intermediate.<sup>111</sup> Given our respective research areas, we sought to jointly explore the capacity of a nickel(II) aryl species to intercept a photoredox-generated  $\alpha$ -amino radical, thereby setting the stage for the fragment coupling. We recognized that the sum of these two

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<sup>109</sup> (a) Osawa, M.; Nagai, H.; Akita, M. *Dalton Trans.* **2007**, 827. (b) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (c) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (d) Rueping, M.; Koenigs, R. M.; Poschary, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem. Eur. J.* **2012**, *18*, 5170. (e) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505. (f) Shu, X.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844.

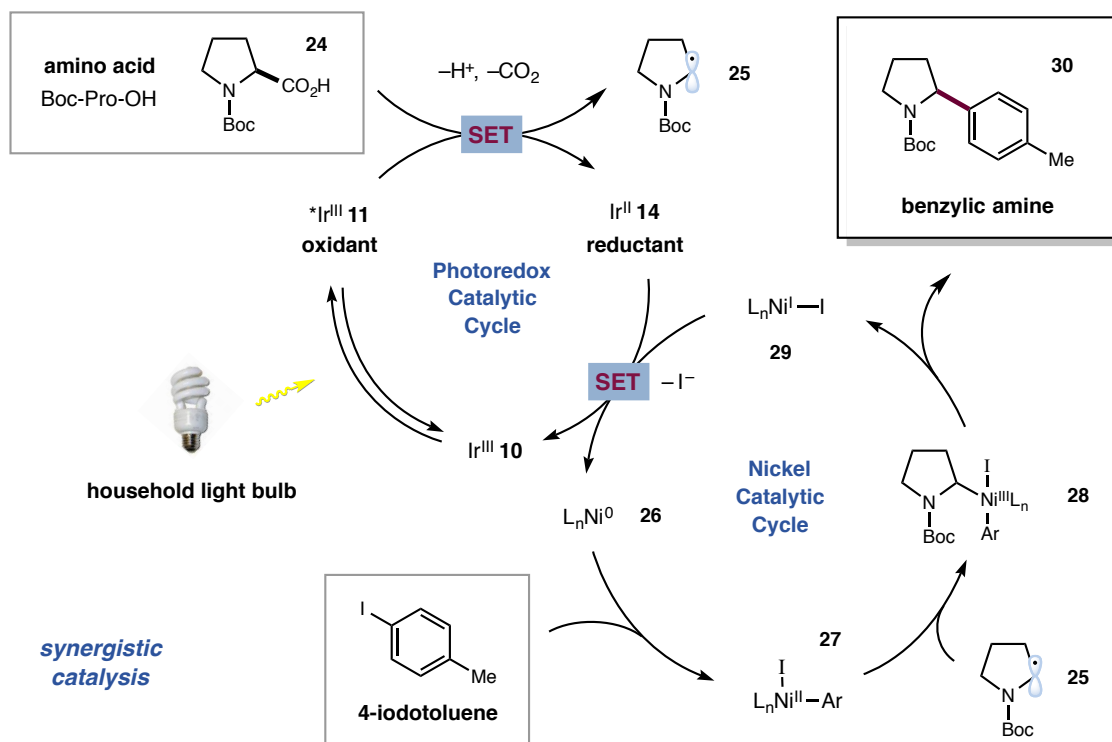
<sup>110</sup> (a) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624. (b) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192.

<sup>111</sup> (a) Graham, T. J. A.; Shields, J. D.; Doyle, A. G. *Chem. Sci.* **2011**, *2*, 980. (b) Sylvester, K. T.; Wu, K.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 16967. (c) Shields, J. D.; Ahneman, D. T.; Graham, T. J. A.; Doyle, A. G. *Org. Lett.* **2014**, *16*, 142.

catalytic processes could potentially overcome a series of limitations that exist for each of these catalysis methods in their own right.

A detailed description of our proposed mechanistic cycle for the decarboxylative coupling is outlined in Scheme 18. We presumed that initial irradiation of heteroleptic iridium(III) photocatalyst  $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$  [ $\text{dF}(\text{CF}_3)\text{ppy}$  = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine,  $\text{dtbbpy}$  = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**10**) would produce the long-lived photoexcited  $^*\text{Ir}^{\text{III}}$  state **11** ( $\tau = 2.3 \mu\text{s}$ ).<sup>63</sup> Deprotonation of the  $\alpha$ -amino acid substrate **24** with base and oxidation by the excited-state  $^*\text{Ir}^{\text{III}}$  complex ( $E_{1/2}^{\text{red}} [^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V vs. SCE in CH}_3\text{CN}$ )<sup>63</sup> via a single-electron transfer event (SET) would then generate a carboxyl radical, which upon rapid loss of  $\text{CO}_2$  would deliver the  $\alpha$ -amino radical **25** and the corresponding  $\text{Ir}^{\text{II}}$  species **14**. Given the established oxidation potential of prototypical amino acid carboxylate salts, we expected this process to be thermodynamically favorable (Boc-Pro-OCs,  $E_{1/2}^{\text{red}} = +0.95 \text{ V vs. SCE in CH}_3\text{CN}$ ).<sup>103</sup> Concurrently with this photoredox cycle, we hoped that oxidative addition of the  $\text{Ni}(0)$  species **26** into an aryl halide would produce the  $\text{Ni}(\text{II})$  intermediate **27**. We anticipated that this  $\text{Ni}(\text{II})$ -aryl species would rapidly intercept the  $\alpha$ -amino radical **25**, forming the organometallic  $\text{Ni}(\text{III})$  adduct **28**. Subsequent reductive elimination would forge the requisite C–C bond, while delivering the desired  $\alpha$ -amino arylation product **30** and expelling the  $\text{Ni}(\text{I})$  intermediate **29**. Finally, single-electron transfer between the  $\text{Ir}^{\text{II}}$  species **14** and the  $\text{Ni}$  complex **29** would accomplish the exergonic reduction of  $\text{Ni}(\text{I})$  to  $\text{Ni}(0)$  (based on the established two electron reduction potential of  $\text{Ni}(\text{II})$  to  $\text{Ni}(0)$ , we presume that reduction of  $\text{Ni}(\text{I})$  to  $\text{Ni}(0)$  should be thermodynamically favorable,  $E_{1/2}^{\text{red}} [\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2 \text{ V vs. SCE in}$

DMF)<sup>112</sup> by the Ir<sup>II</sup> species **14** ( $E_{1/2}^{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V vs. SCE in CH}_3\text{CN}$ ),<sup>63</sup> thereby completing both the photoredox and nickel catalytic cycles simultaneously.



**Scheme 18.** Proposed Mechanism for the Decarboxylative Arylation.

In collaboration with post-doctoral researchers Dr. Zhiwei Zuo and Dr. Lingling Chu, and graduate student Derek Ahneman, we first examined the proposed coupling using *N*-Boc proline, *para*-iodotoluene, and a wide range of photoredox and ligated nickel catalysts. To our delight, we found that the combination of Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> and NiCl<sub>2</sub>•glyme, dtbbpy, in the presence of 1.5 equivalents of Cs<sub>2</sub>CO<sub>3</sub> base and white light from a 26 W compact fluorescent bulb, achieved the desired fragment coupling in 78% yield. During our optimization studies, we found that use of a bench-stable Ni(II) source, such as NiCl<sub>2</sub>•glyme, was sufficient to generate

<sup>112</sup> Durandetti, M.; Devaud, M.; Perichon, J. *New J. Chem.* **1996**, *20*, 659.

the arylation product with comparable efficiency to a Ni(0) source. We attribute this result to *in situ* photocatalytic reduction of Ni(II) to Ni(0) via two discrete single electron transfer events, with excess amino acid likely serving as the sacrificial reductant to access the active Ni-catalyst ( $E_{1/2}^{\text{red}} [\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2 \text{ V vs. SCE in DMF}$ ).<sup>112</sup> We believe it is unlikely that the Ni(II)(Ar)X intermediate **27** undergoes a SET event to form Ni(I)Ar, given the poorly matched reduction potentials of the species involved (cf.  $E_{1/2}^{\text{red}} [\text{Ni}^{\text{II}}\text{ArX}/\text{Ni}^{\text{I}}\text{Ar}] = -1.7 \text{ V vs. SCE in CH}_3\text{CN}$  and  $E_{1/2}^{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V vs. SCE in CH}_3\text{CN}$ ).<sup>63,113</sup> We do, however, recognize that an alternative pathway could be operable wherein the oxidative addition step occurs from the Ni(I) complex to form a Ni(III) aryl halide adduct.<sup>114</sup> In this pathway, photocatalyst-mediated reduction of the aryl-Ni(III) salt to the corresponding Ni(II) species followed by the  $\alpha$ -amino radical addition step would then form the same productive Ni(III) adduct **28** as shown in Scheme 18. Given that (i) Ni(0) complexes undergo oxidative addition more readily than Ni(I) complexes with aryl halides,<sup>115</sup> and (ii) Ni(II) complexes are believed to rapidly engage with  $\text{sp}^3$  carbon-centered radicals to form Ni(III) species (enabling  $\text{sp}^3\text{-sp}^2$  and  $\text{sp}^3\text{-sp}^3$  C–C bond formations),<sup>110</sup> we favor the dual catalysis mechanism outlined in Scheme 18.

<sup>113</sup> Budnikova, Y. H.; Perichon, J.; Yakhvarov, D. G.; Kargin, Y. M.; Sinyashin, O. G. *J. Organomet. Chem.* **2001**, 630, 185.

<sup>114</sup> Computational studies by Molander and coworkers suggest that for a related system, the mechanism proceeds via radical addition to a Ni(0) complex, followed by oxidative addition to form a Ni(III) intermediate: Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, 137, 4896.

<sup>115</sup> Amatore, C.; Jutand, A. *Organometallics* **1988**, 7, 2203.



#### *IV. Substrate Scope in the Photoredox–Nickel Decarboxylation Arylation*

Having established the optimal conditions for this photoredox–nickel decarboxylative arylation, we focused our attention on the scope of the aryl halide fragment. As shown in Table 10, a wide range of aryl iodides are amenable to this dual catalysis strategy, including both electron-rich and electron-deficient arenes (**1–4**, 65–78% yield). A variety of aryl bromides function effectively as well, including those that contain functional groups as diverse as ketones, esters, nitriles, trifluoromethyl groups, and fluorides (**5–9**, 75–90% yield). Heteroaromatics, in the form of differentially substituted bromopyridines, are efficient coupling partners as well (**10–13**, 60–85% yield). Moreover, aryl chlorides are competent substrates if the arenes, such as pyridines and pyrimidines, are electron-deficient (**14** and **15**, 64% and 65% yield). Notably, only products **6** and **10** in Table 10 would be accessible using the previously reported photoredox decarboxylation arylation strategy.<sup>116</sup> Moreover, we are unaware of the general use of sp<sup>3</sup> C-bearing carboxylic acids as reaction substrates in transition metal catalysis, an illustration of the tremendous scope expansion that is attainable using this dual catalysis technology. It should be noted that these reactions are typically complete in 72 h at larger scale, and 48 h on smaller scale.

#### V. Anilinic $\alpha$ -Amino C–H Bonds in Cross-Coupling

To further demonstrate the utility of this dual catalysis strategy, we sought to demonstrate the direct functionalization of  $\text{sp}^3$  C–H bonds with coupling partners derived from aryl or alkyl halides. Given that our decarboxylation-arylation mechanism involves the rapid addition of an  $\alpha$ -amino radical to a Ni(II) salt, we sought to generate an analogous  $\alpha$ -nitrogen centered carbon radical via a photoredox driven *N*-Ph oxidation,  $\alpha$ -C–H deprotonation sequence using aniline-based substrates.<sup>116</sup> We presumed that this photo-mediated *N*-Ph oxidation mechanism would provide an alternative pathway to the open-shell carbon intermediate (corresponding to **25**, Scheme 18), and should similarly intercept the putative Ni(II) intermediate **27**. Assuming that the remaining dual catalysis mechanism would be analogous to that shown in Scheme 18, we expected that a range of direct  $\text{sp}^3$  C–H functionalization protocols should be possible. Indeed, we were able to demonstrate that dimethylaniline undergoes  $\alpha$ -amine coupling with a variety of aryl halides in the presence of  $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$  and  $\text{NiCl}_2\cdot\text{glyme}$ , as shown in Table 12. Electron-deficient and electron-rich iodoarenes give good to excellent yields (**1–3**, 72–93% yield). Moreover, aryl bromides are competent coupling partners, enabling the installation of medicinally important heterocyclic motifs (**4**, 60% yield). Lastly, control experiments have revealed that the combination of light, photoredox catalyst **10**, and the  $\text{NiCl}_2\cdot\text{dtbbpy}$  complex is essential for product formation in all examples listed in Tables 10–12. This reaction represents a powerful foray into direct C–H activation using orthogonal cross-coupling reactivity.

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<sup>116</sup> McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.