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Synthetic and Mechanistic Implications of Chlorine Photoelimination in Nickel/Photoredox C(sp^3)−H Cross-Coupling

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Cite This: https://dx.doi.org/10.1021/acs.accounts.0c00694

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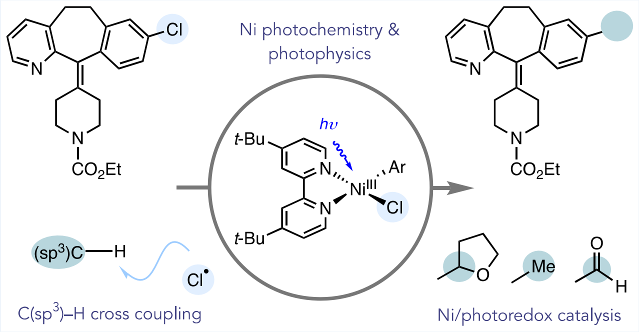

CONSPECTUS: In recent years, the development of light-driven reactions has contributed numerous advances in synthetic organic chemistry. A particularly active research area combines photoredox catalysis with nickel catalysis to accomplish otherwise inaccessible cross-coupling reactions. In these reactions, the photoredox catalyst absorbs light to generate an electronically excited charge-transfer state that can engage in electron or energy transfer with a substrate and the nickel catalyst. Our group questioned whether photo-induced activation of the nickel catalyst itself could also contribute new approaches to cross-coupling. Over the past 5 years, we have sought to advance this hypothesis for the development of a suite of mild and site-selective C(sp^3)−H cross-coupling reactions with chloride-containing coupling partners via photoelimination of a Ni−Cl bond.

On the basis of a report from the Nocera laboratory, we reasoned that photolysis of a Ni(III) aryl chloride species, generated by single-electron oxidation of a typical Ni(II) intermediate in cross-coupling, might allow for the catalytic generation of chlorine atoms. Combining this with the ability of Ni(II) to accept alkyl radicals, we hypothesized that photocatalytically generated chlorine atoms could mediate hydrogen atom transfer (HAT) with C(sp^3)−H bonds to generate a substrate-derived alkyl radical that is captured by the Ni center in cross-coupling. A photoredox catalyst was envisioned to promote the necessary single-electron oxidation and reduction of the Ni catalyst to facilitate an overall redox-neutral process. Overall, this strategy would offer a visible-light-driven mechanism for chlorine radical formation enabled by the sequential capture of two photons.

As an initial demonstration, we developed a Ni/photoredox-catalyzed α-oxy C(sp^3)−H arylation of cyclic and acyclic ethers. This method was extended to a mild formylation of abundant and complex aryl chlorides through selective 2-functionalization of 1,3-dioxolane. Seeking to develop a suite of reactions that introduce carbon at all different oxidation states, we explored C(sp^3)−H cross-coupling with trimethyl orthoformate, a common laboratory solvent. We found that trimethyl orthoformate serves as a source of methyl radical for a methylation reaction via β-scission from a tertiary radical generated upon chlorine-mediated HAT. Since chlorine radical is capable of abstracting unactivated C(sp^3)−H bonds, our efforts have also been directed at cross-coupling with a range of feedstock chemicals, such as alkanes and toluenes, along with late-stage intermediates, using chloroformates as coupling partners. Overall, this platform enables access to valuable synthetic transformations with (hetero)aryl chlorides, which despite being the most ubiquitous and inexpensive aryl halide coupling partners, are rarely reactive in Ni/photoredox catalysis.

Little is known about the photophysics and photochemistry of organometallic Ni complexes relevant to cross-coupling. We have conducted mechanistic investigations, including computational, spectroscopic, emission quenching, and stoichiometric oxidation studies, of Ni(II) aryl halide complexes common to Ni/photoredox reactions. These studies indicate that chlorine radical generation from excited Ni(III) is operative in the described C(sp^3)−H functionalization methods. More generally, the studies illustrate that the photochemistry of cross-coupling catalysts cannot be ignored in metallaphotoredox reactions. We anticipate that further mechanistic understanding should facilitate new catalyst design and lead to the development of new synthetic methods.

KEY REFERENCES

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Received: October 26, 2020

https://dx.doi.org/10.1021/acs.accounts.0c00694
Acc. Chem. Res. XXXX, XXX, XXX−XXX

ethers. Mechanistic studies supported that chlorine photoelimination occurs from excited Ni(III) complexes.

Kariofillis, S. K.; Shields, B. J.; Tekle-Smith, M. A.; Zacuto, M. J.; Doyle, A. G. Nickel/Photoredox-Catalyzed Methylation of (Hetero)aryl Chlorides Using Trimethyl Orthoformate as a Methyl Radical Source. *J. Am. Chem. Soc.* **2020**, *142*, 7683−7689.[2] *We pursued the application of chlorine photoelimination to the methylation of (hetero)aryl chlorides using trimethyl orthoformate as a source of methyl radical and found that the reaction is compatible with sensitive functional groups and late-stage compounds.*

Ackerman, L. K. G.; Martinez Alvarado, J. I.; Doyle, A. G. Direct C−C Bond Formation from Alkanes Using Ni-Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 14059−14063.[3] *Catalytic C−C bond formation from strong C(sp^3)−H bonds is a highly desired yet outstanding synthetic challenge. Here we demonstrated that chlorine photoelimination can serve as a platform for functionalization of unactivated C(sp^3)−H bonds via acylation of hydrocarbon substrates.*

Ting, S. I.; Garakyaraghi, S.; Taliaferro, C. M.; Shields, B. J.; Scholes, G. D.; Castellano, F. N.; Doyle, A. G. ^{3}d−d Excited States of Ni(II) Complexes Relevant to Photoredox Catalysis: Spectroscopic Identification and Mechanistic Implications. *J. Am. Chem. Soc.* **2020**, *142*, 5800−5810.[4] *We studied the photophysical and photochemical properties of Ni(II) complexes and found that upon initial excitation, an MLCT state is generated that decays to a long-lived ^{3}d−d state. This study provided insight into the behavior of Ni complexes in photoredox reactions.*

■ INTRODUCTION

The past decade has witnessed a dramatic rise in the application of photoredox catalysis in organic synthesis.[5] Integral to the success of this field is the photoredox catalyst, which becomes both a potent one-electron oxidant and reductant upon absorption of a visible-light photon (photoinduced electron transfer, or PET).[6] Single electron transfer (SET) between this reactive species and a small-molecule substrate affords access to radical intermediates under exceptionally mild reaction conditions.[5] Moreover, the resultant reduced or oxidized catalyst retains a strong thermodynamic driving force to return to the original oxidation state, thereby facilitating access to redox-neutral transformations. For these reasons, photoredox catalysis has enabled chemists to solve challenging problems in synthetic methodology development, organometallic catalysis, and medicinal chemistry.

Over the past decade, our lab has built a program in nickel-catalyzed cross-coupling.[7] Given the proclivity of nickel to both generate and accept reactive radical species, we postulated that merging nickel and photoredox catalysis could introduce a cooperative platform wherein a photoredox catalyst could supply substrate radicals as coupling partners to Ni and modulate Ni's oxidation state in catalysis (Figure 1A). In collaboration with the MacMillan laboratory, we reported a decarboxylative C(sp^3)−C(sp^2) cross-coupling of amino acids, as well as α-oxy- or α-phenyl-substituted carboxylic acids, with aryl halides.[8] This catalyst system was also applied to C(sp^3)−H arylation of dimethylanilines, demonstrating that Ni/photoredox catalysis can serve as a mild method for the direct functionalization of C(sp^3)−H bonds.[8,9] Independently, the Molander laboratory reported the merger of Ni and photoredox catalysis for the cross-coupling of aryl halides with benzyltrifluoroborate salts as aliphatic radical precursors.[10]

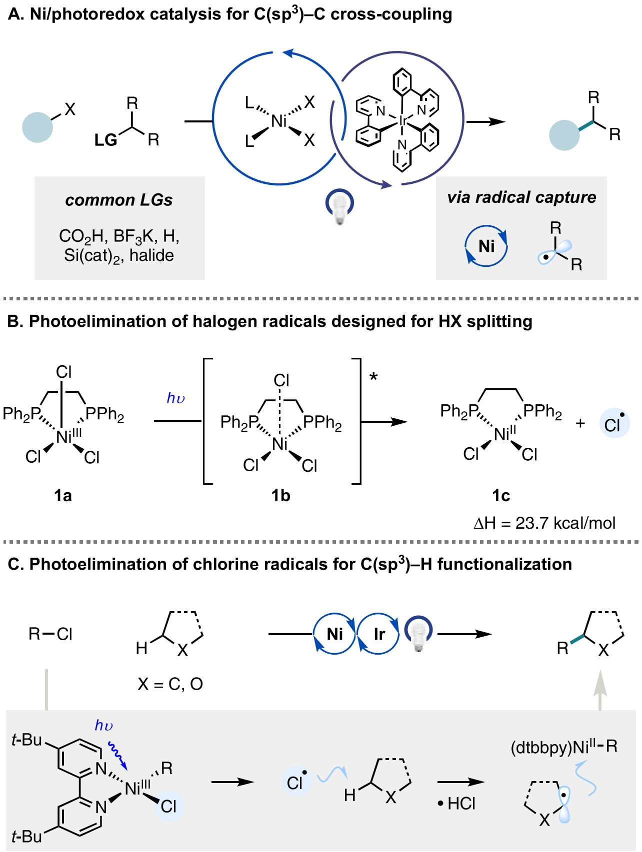


Figure 1. (A) Ni/photoredox cross-coupling. (B) Halogen photoelimination from Ni(III) trihalide complexes (HX = hydrohalic acid). (C) Photoelimination of chlorine radicals for C(sp^3)−H cross-coupling.

Since those initial reports, many researchers have made important contributions to this area, revealing that nickel/photoredox catalysis can serve as a platform for bond formation with traditionally unreactive coupling partners.[11]

The impact of PET on the field of Ni-catalyzed cross-coupling prompted our interest in exploring alternative mechanisms for harnessing visible light in catalysis. In this context, we were drawn to photoinduced ligand dissociation, or photoelimination, a mechanism by which light absorption by a transition metal complex leads to excited-state labilization of a metal−ligand bond.[12] A preeminent example is photoexcitation of metal carbonyl complexes with ultraviolet irradiation. Seminal work by Bergman and others demonstrated that photolysis of Ir− and Rh−CO complexes affords coordinatively unsaturated species responsible for activation of inert hydrocarbon C−H bonds.[13]

Because of its important implications for energy storage, photoelimination of halogen radicals has seen recent and growing interest. In 2015, the Nocera group reported a protocol for halogen photoelimination from mononuclear Ni(III) trihalide complexes, the first example from a first-row transition metal complex.[14] These Ni(III) complexes, supported by bidentate phosphine ligands, underwent photoelimination of chlorine or bromine radicals under visible-light irradiation (λ > 400 nm). The liberated chlorine atom is stabilized by an arene-to-chlorine-atom charge-transfer interaction. The formation of this relatively long-lived transient species arises from a dissociative LMCT excited state (**1b**), from which photoinduced cleavage of the apical Ni(III)−Cl bond produces Ni(II) species **1c** and a chlorine radical (Figure 1B).

Although work by Nocera and others focused upon halogen photoelimination for energy storage applications, we questioned whether the generation of halogen radicals by photoelimination could also offer interesting synthetic opportunities. Traditionally, chlorine radical generation requires employment of reagents that are oxidizing and challenging to handle, including chlorine gas and *N*-chlorosuccinimide. Furthermore, oxidation of chloride to chlorine is inaccessible with most conventional photocatalysts (E = 2.03 V vs SCE in MeCN). Instead, we envisioned that access to chlorine radical could be possible from abundant chloride-containing electrophiles by combining chlorine photoelimination from Ni with metallaphotoredox cross-coupling. By design, the chloride source would serve as both the reaction coupling partner and the source of chlorine radical for hydrogen atom transfer (HAT). If successful, this approach could facilitate cross-coupling with unactivated C(sp^3)−H bonds in the absence of a directing group: the thermodynamically favorable formation of H−Cl (bond dissociation energy (BDE) = 102 kcal/mol) would permit virtually any C(sp^3)−H bond to undergo abstraction (Figure 1C). This Account centers upon our studies in applying the concept of photoelimination of halogen radicals toward C(sp^3)−H cross-coupling and our mechanistic understanding of chlorine photoelimination in catalysis.

SYNTHETIC METHOD DEVELOPMENT

Initial Discovery of the Arylation of Ethers

In 2014 and 2015, our lab reported examples of C−H functionalization α to nitrogen atoms in anilines via an oxidation/deprotonation sequence (*N*-phenylpyrrolidine $E_{1/2}$ = 0.70 V vs SCE in MeCN)[15] (Figure 2A), wherein α-amino radicals were generated under photoredox conditions and intercepted by Ni for cross-coupling (Figure 2B).[8,9] However, this approach was unsuccessful for functionalization of C−H bonds α to ethers because of their high oxidation potentials (i.e., THF E = 1.75 V vs SCE; $E_{1/2}$[*Ir^{III}/Ir^{II}] = 1.21 V vs SCE in MeCN).[16] On the other hand, the C−H bonds adjacent to oxygen atoms in ethers are significantly weakened (bond dissociation free energy (BDFE) ~ 86−89 kcal/mol) such that activation with HAT agents, including chlorine radicals, could provide a route for functionalization (Figure 2C).[17] Thus, we initiated our investigation of halogen photoelimination in cross-coupling with this substrate class.

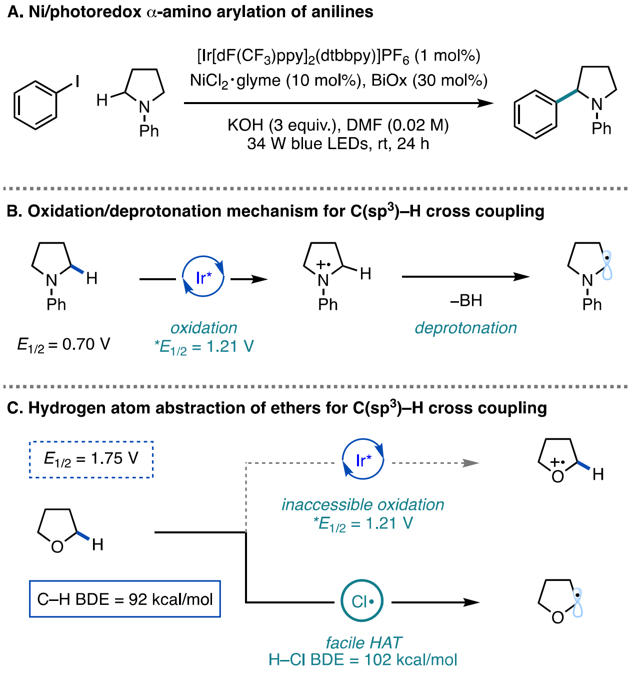


Figure 2. Strategies for Ni/photoredox C(sp^3)−H functionalization.

We proposed that the arylation of ethers could proceed via the mechanism shown in Figure 3.[1] Oxidative addition of Ni(0) complex **2** into an aryl chloride would produce Ni(II) aryl chloride intermediate **3**. Concurrently, irradiation of iridium(III) photocatalyst **4** would afford highly oxidizing, long-lived *Ir(III) triplet excited state **5** (τ_0 = 2.3 μs, *$E_{1/2}$ = 1.21 V vs SCE in MeCN), which could oxidize Ni(II) intermediate **3** to Ni(III) aryl chloride species **6**. The Ni(III)−chlorine bond is then rendered sufficiently weak that a photon of visible light can homolyze the bond (BDFE = 47 kcal/mol), resulting in Ni(II) aryl species **7** and a chlorine radical. The photocatalytically generated chlorine radical would then abstract a hydrogen atom from THF (THF BDE = 92 kcal/mol; H−Cl BDE = 102 kcal/mol), and rebound of the resulting carbon-centered radical into **7** would produce Ni(III) species **8**. Subsequent reductive elimination from Ni(III) would forge the product containing a new C(sp^3)−C(sp^2) bond and Ni(I) species **9**, which would be reduced by highly reducing Ir(II) species **10** ($E_{1/2}$ = −1.37 V vs SCE in MeCN) to regenerate both the Ni(0) and Ir(III) catalysts.

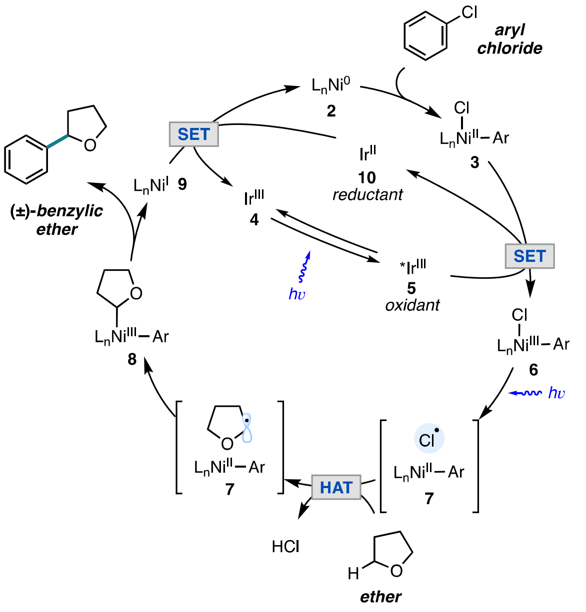


Figure 3. Proposed catalytic cycle for the arylation of ethers via chlorine photoelimination.

We found that employment of Ni(cod)$_2$ (cod = 1,5-cyclooctadiene) (10 mol %), 4,4′-di-*tert*-butylbipyridine (dtbbpy) ligand (15 mol %), [Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)]PF$_6$ photocatalyst (2 mol %), and potassium phosphate (2 equiv) under irradiation with blue LEDs enabled the cross-coupling of a variety of aryl chlorides with THF (0.04 M) (Figure 4).[1] (Hetero)aryl chlorides with varying electronic and steric

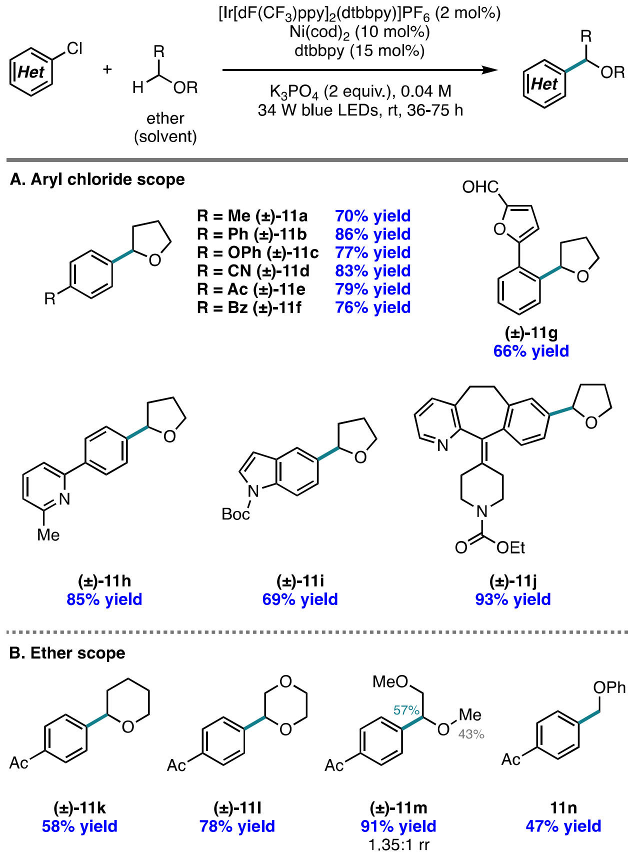


Figure 4. Representative (hetero)aryl chloride and ether substrate scopes.

properties also underwent efficient coupling to give α-arylated products (Figure 4A). Additionally, other cyclic as well as acyclic ethers could be used in the Ni/photoredox cross-coupling reaction with 4′-chloroacetophenone, including 1,4-dioxane ((±)-**11l**) and anisole (**11n**) (Figure 4B). In reactions with 1,2-dimethoxyethane to give product (±)-**11m**, cross-coupling occurred at both the secondary and primary C−H bonds in a 1.35:1 ratio, indicating moderate selectivity for the weaker C−H bond. Reactions performed in the absence of Ni catalyst, photoredox catalyst, or light resulted in the formation of no cross-coupled product, indicating that all three components were necessary. At the same time that this work was disclosed, the Molander group demonstrated the coupling of aryl bromides with ethers, leveraging bromine radical HAT with ethereal substrates using nickel/photoredox catalysis.[18]

Importantly, our platform for chlorine photoelimination allows for the use of aryl chlorides, the most ubiquitous, inexpensive, and biologically relevant aryl halide coupling partners. Generally, nickel/photoredox methodologies require aryl bromides or iodides as substrates for reactivity. In fact, at the time of the publication of this Account, more than 450 nickel/photoredox methodologies have been reported, but fewer than 10 of these reports employ aryl chlorides (>5 substrates).[19] In most nickel/photoredox cross-coupling methodologies that employ aryl halides, the generation of the radical species occurs independently of the nickel catalytic cycle, so radical addition to the Ni catalyst may occur prior to oxidative addition, furnishing a Ni(I) intermediate. Indeed, computational studies by Molander, Kozlowski, and Gutierrez favor Ni(0)/Ni(I)/Ni(III) catalytic cycles that proceed via oxidative addition to Ni(I) rather than to Ni(0).[20] Importantly, oxidative addition of an aryl chloride to Ni(I) is significantly more challenging than to Ni(0), which may explain why aryl chlorides are not competent coupling partners in other Ni/photoredox methodologies. In contrast, because in the proposed catalytic cycle aliphatic radical generation is dependent on Ni(III) photoelimination, which occurs only after oxidative addition, a Ni(0)/Ni(II)/Ni(III) sequence is likely favored.

Formylation of (Hetero)aryl Chlorides

The arylation of ethers served as an important proof of concept for chlorine photoelimination in a synthetic context. However, a number of other methods exist to effect α-arylation of ethers, including examples of redox-neutral methods.[21] Moving forward, we sought to develop synthetic applications of the photoelimination strategy that would capitalize on its unique features: redox-neutral C−H cross-coupling and employment of abundant and inexpensive chloride-containing coupling partners. One such application that we identified was a mild formylation of (hetero)aryl chlorides.

The versatility of aromatic aldehydes renders them important functional groups in the synthesis of pharmaceuticals, fragrances, fine chemicals, and natural products. One route for preparing benzaldehydes is electrophilic aromatic substitution, but both the regioselectivity and reactivity are dependent on the substrate identity. Challenges associated with regioselective formylation can be circumvented by employing traditional organometallic methods, but this strategy can compromise functional group tolerance. A more general approach to aryl formylation is Pd-catalyzed reductive carbonylation of aryl halides, first reported in 1974 by Heck and co-workers.[22] However, this approach presents implementation challenges on the laboratory scale and tends to be limited to aryl bromides or iodides. These limitations have restricted formylation reactions to early stages in synthesis. At the same time, there are far more commercial aryl chlorides than benzaldehydes, making them attractive substrates for formylation.

Thus, we envisioned that a mild formylation of aryl chlorides via chlorine photoelimination, using 1,3-dioxolane as a formyl source, would be an attractive alternative.[23] Site-selective C−H functionalization at the 2-position of 1,3-dioxolane, the weakest C−H bond in the molecule, followed by radical trapping by Ni would afford benzylidene acetal derivatives. Reaction optimization demonstrated that $[\mathrm{Ir}[\mathrm{dF}(\mathrm{CF}_3)\mathrm{ppy}]_2(\mathrm{dtbbpy})]\mathrm{PF}_6$ (1 mol %), $\mathrm{NiCl}_2\cdot$glyme (10 mol %), dtbbpy (15 mol %), and K_3PO_4 (2 equiv) under 34 W blue LED irradiation allowed the synthesis of acetal intermediates from (hetero)aryl chlorides and dioxolane as the reaction solvent (0.05 M). The resulting benzylidene acetals were not isolated but instead were directly subjected to acidic workup to provide the corresponding benzaldehyde products (Figure 5). Notably, a nickel/photoredox-catalyzed strategy similar to ours was concurrently reported by Mariano, Wang, and co-workers to enable formylation of aryl halides and triflates with diethoxyacetic acid as a formyl equivalent.[19a] While aryl chlorides underwent formylation in their report, only electron-deficient substrates were reactive in the method.

We centered our scope evaluation on late-stage and biologically relevant (hetero)aryl chlorides as well as abundant aryl chlorides that are not available as commercial aryl bromides, iodides, and aldehydes. A common limitation of

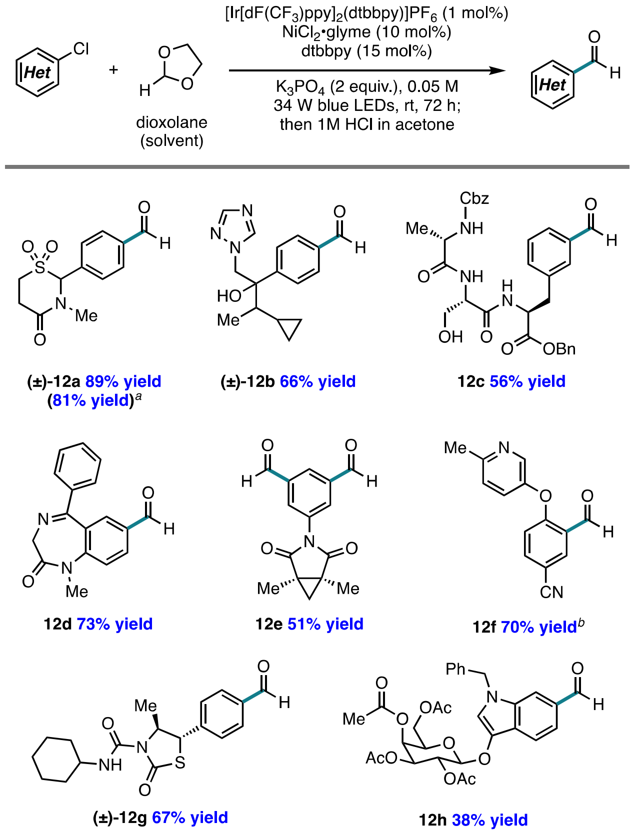


Figure 5. Representative substrate scope for the formylation of (hetero)aryl chlorides. [a]Yield using Schlenk technique. [b]Benchtop setup (gram scale).

photoredox reactions is their scalability, often due to issues of light penetration.[24] We therefore evaluated the formylations on a gram scale: a benchtop scale-up reaction provided **12f** in 70% yield.

Methylation of (Hetero)aryl Chlorides

Benzaldehydes are valuable intermediates in large part because they enable access to esters, amines, alcohols, and toluenes via oxidation or reduction. Nevertheless, redox manipulation is not ideal from a step economy perspective and requires stoichiometric oxidants or reductants that often have an adverse impact on functional group tolerance in late-stage modification.[25] Thus, we anticipated that direct installation of a single carbon substituent at different oxidation states would be attractive.

To accomplish this, we sought to extend chlorine photoelimination to a direct aryl esterification using trimethyl orthoformate as a methyl ester surrogate. Early experiments employing trimethyl orthoformate showed that the corresponding aryl methyl ester **14** was accessible from 4′-chloroacetophenone in 8% yield, which we attributed to coupling with the tertiary radical of trimethyl orthoformate (Figure 6A). Benzylic ether product **13**, derived from coupling at the primary C−H bonds of trimethyl orthoformate, was also obtained in 27% yield. Most surprising and intriguing to us, however, was the formation of methylated product **15** in 38% yield, demonstrating that three different oxidation states were accessible by cross-coupling from a single carbon unit.[2]

Formation of the methylated product was attributed to coupling with methyl radical, which we hypothesized to be generated via *β*-scission of the tertiary radical of trimethyl orthoformate after C−H abstraction by chlorine radical. While *β*-scission is well-studied for the generation of aliphatic radicals from oxygen-centered radicals,[26a−c] there is significantly less precedent for *β*-scission from carbon-centered radicals.[26d,e] Our computational investigation suggested that *β*-scission of the tertiary radical of trimethyl orthoformate is kinetically feasible ($\Delta G^{\ddagger}$ = 11.4 kcal/mol). Moreover, formation of dimethyl carbonate as a byproduct affords a thermodynamic driving force (ΔG = −25.1 kcal/mol) (Figure 6B).[27] Indeed, reaction progress analysis and methyl radical trapping experiments supported the intermediacy of methyl radical and the concurrent generation of dimethyl carbonate. The computations also predicted preferential HAT at the tertiary C−H bond over the primary sites (ΔBDFE = −1.2 kcal/mol).

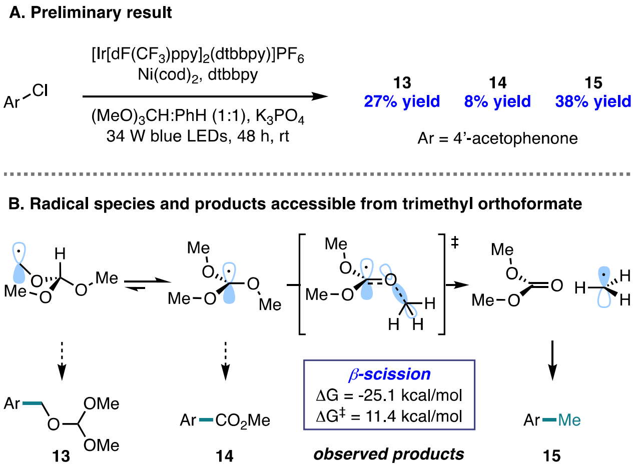


Figure 6. Design of a methylation reaction.

While our discovery of this methylation was serendipitous, we recognized that installation of a methyl substituent onto small molecules is an established and important strategy for obtaining compounds with improved biological properties, a phenomenon so pervasive it has been called the “magic methyl effect”.[28] However, most methylation methodologies require harsh reaction conditions or reactive electrophilic or nucleophilic methyl sources that are incompatible with late-stage functionalization of bioactive molecules.[28a] Recently, *N*-hydroxyphthalimide esters[29a] and methyl tosylate[29b,c] have been demonstrated to be competent methyl radical precursors in Ni cross-coupling with aryl iodides and bromides, respectively. Accordingly, these reactions require either preparation of the methyl radical source or employment of an electrophilic methylating reagent. In contrast, we were drawn to trimethyl orthoformate as an abundant, commercial, and functional group-tolerant methyl source.

In optimizing the initial lead result for methylation, we arrived at the reaction conditions shown in Figure 7, which delivered methylation over alkoxymethylation in a ratio of ∼4:1 while minimizing formation of the ester product. An extensive scope of heteroaryl chlorides and late-stage compounds was established. The abbreviated scope shown in Figure 7 demonstrates the remarkable tolerance of radical methylation for functionalities that are incompatible with nucleophilic and electrophilic methyl sources. We were also able to extend this method to acyl chlorides as a mild method for the generation of ketones, esters, and tertiary amides.[2]

While the nickel/photoredox-catalyzed methylation reactions are high-yielding with electron-deficient (hetero)aryl

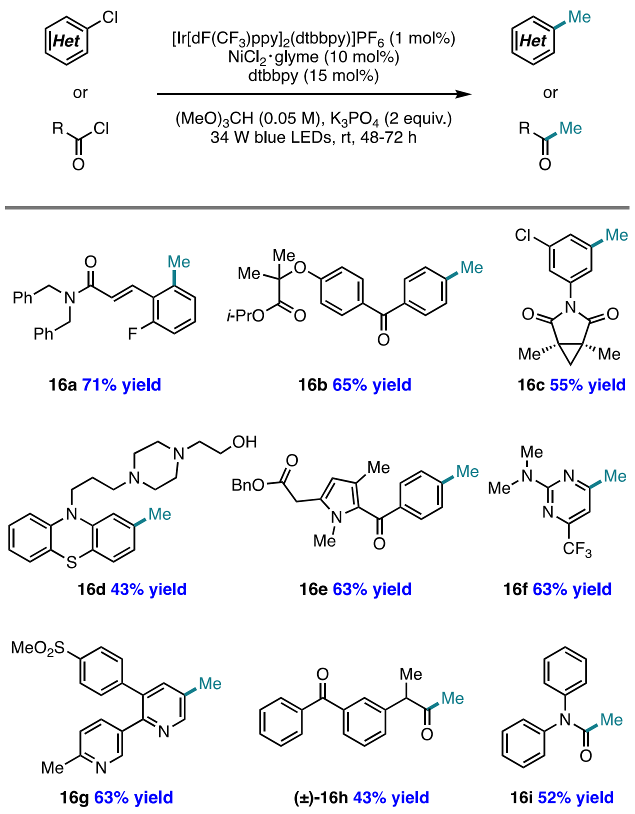


Figure 7. Representative substrate scope for the methylation of (hetero)aryl and acyl chlorides.

chlorides, electron-rich substrates are unreactive; however, electron-rich aryl chlorides are competent reaction partners in the formylation and etherification methods. For example, *p*-phenoxy- and *p*-methoxy-substituted aryl chlorides underwent etherification or formylation respectively in 77% ((±)-**11c**) or 58% yield (**17**); in contrast, methylation of 4-chloroanisole proceeded in less than 2% yield (Figure 8A). This limitation, consistent with a more challenging oxidative addition to Ni(0), could be circumvented by employing aryl bromides (vide infra) as substrates with the addition of tetrabutylammonium chloride (TBACl) as an exogenous chloride source for halide exchange, providing **18** in 56% yield (Figure 8B). While we do not yet understand the divergence in reactivity between the methods, we found that the electronic bias between methods could be used advantageously: for example, procymidone, which contains two equivalent aryl chlorides, underwent formylation at both positions to give product **12e** in Figure 5. Under the methylation protocol, only one aryl chloride underwent functionalization to provide **16c** in Figure 7, thereby preserving an additional reactive handle for further functionalization.

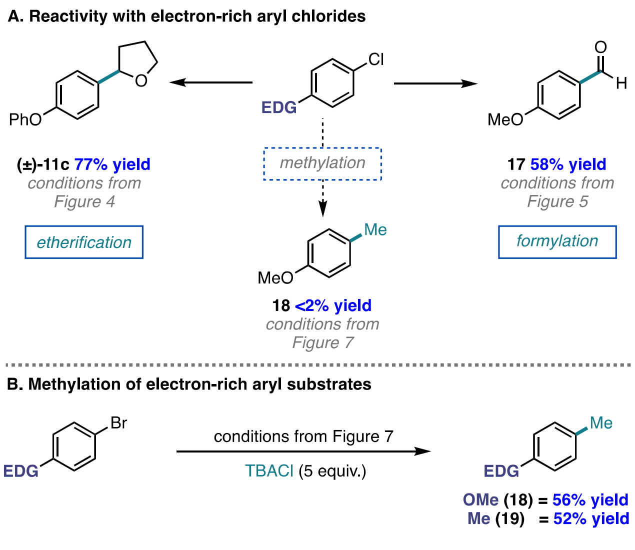


Figure 8. (A) Comparison of electronic tolerances across photoelimination methodologies. (B) Methylation of electron-rich aryl bromides via halide exchange at Ni.

Functionalization of Unactivated C–H Bonds

The use of ethereal solvents in aryl etherification, formylation, and methylation reactions provided a handle for reactivity and selectivity via the reduced bond strengths of C–H bonds adjacent to oxygen atoms. However, use of chlorine radical as a hydrogen atom abstractor should permit direct functionalization of entirely unactivated C(sp^3)–H bonds, a longstanding challenge in C–H functionalization. Most examples of C(sp^3)–H activation for C–C bond formation require substrates with coordinating directing groups or their employment in large excess, precluding their application in synthesis at both an early and a late stage.[30] Thus, the direct and modular functionalization of unactivated alkanes to form C–C bonds represents an unmet challenge in synthesis.[31]

To address this challenge, we aimed to apply chlorine photoelimination for the cross-coupling of 4′-chloroacetophenone with cyclohexane (BDFE = 91 kcal/mol); however, performing the reaction under the conditions shown in Figure 4 with 10 equiv of cyclohexane delivered the desired product in only 41% yield.[32] We recognized that the limited success of our initial attempts could be attributed to the C–H bond strengths and polarities of the starting materials and products. In arylation reactions, the benzylic C(sp^3)–H bonds in the products are considerably weaker (BDFE ~ 80 kcal/mol) than the unactivated C(sp^3)–H bonds of the starting materials (BDFE = 91–95 kcal/mol). This could lead to unproductive consumption of chlorine radical, particularly when C(sp^3)–H substrates are employed as limiting reagents. This problem was anticipated to be particularly acute for the photoelimination strategy since it provides only one chlorine radical per substrate activation, in contrast to methods where HAT catalysts are continuously regenerated.

We sought to exploit C–H bond polarity effects to overcome this issue.[33] We anticipated that installation of an electron-withdrawing group via C–C cross-coupling would reduce the rate of product α-C–H bond abstraction by chlorine radical, an electrophilic radical, even though the product would still possess a weaker C–H bond than the starting material. Thus, we chose the introduction of an ester from chloroformates as a more promising means of achieving C–C coupling from unactivated alkanes (Figure 9).[3] Such a

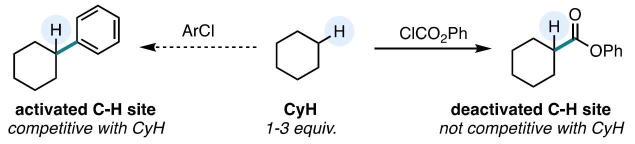


Figure 9. Designing a system for functionalizing unactivated C(sp^3)–H substrates.

strategy would not only deactivate the product toward overfunctionalization but also bestow a once-unreactive alkane with the great expanse of reactivity associated with the carbonyl group.

Upon optimization, we found that phenyl chloroformate underwent reaction with only a small excess of cyclohexane (3 equiv), furnishing the esterified product in 66% yield under the conditions shown in Figure 10.[34] Scope studies revealed that a variety of substrates containing unactivated C−H bonds underwent functionalization (Figure 10). For example, tetramethylsilane, which contains one of the strongest $C(sp^3)$−H bonds (BDFE = 96 kcal/mol), underwent esterification in 51% yield (**20d**) (Figure 10). Acyl chlorides could also be used as substrates to provide ketone products upon coupling with aliphatic reaction partners, such as cyclooctane (**20e**).[35] For substrates containing multiple chemically distinct $C(sp^3)$−H bonds, preferential esterification occurred at benzylic (**20f**, **20g**) or *α*-oxy or *α*-amino positions (**20h**), consistent with abstraction of weaker and more hydridic C−H bonds. More complex unactivated substrates underwent functionalization at a variety of positions. The regioselectivity observed generally was consistent with functionalization at positions with the most hydridic C−H bonds that would also result in the most stabilized radical species (tertiary > secondary > primary C−H bonds). The site selectivity could additionally be predicted with an Evans−Polanyi plot (vide infra).[33,36] In the case of product **20i**, functionalization occurred at only one position, consistent with chlorine radical abstraction at the most electron-rich and sterically accessible site. Esterification of late-stage molecules, such as sclareolide (**20k**), proceeded to give a mixture of regioisomers, again with a preference for the most electron-rich and sterically accessible C−H bonds. Additionally, this method for direct C−C bond formation represents one of the only methods by which a quaternary carbon center can be installed with Ni/photoredox catalysis (**20j**).[20b,29b,37]

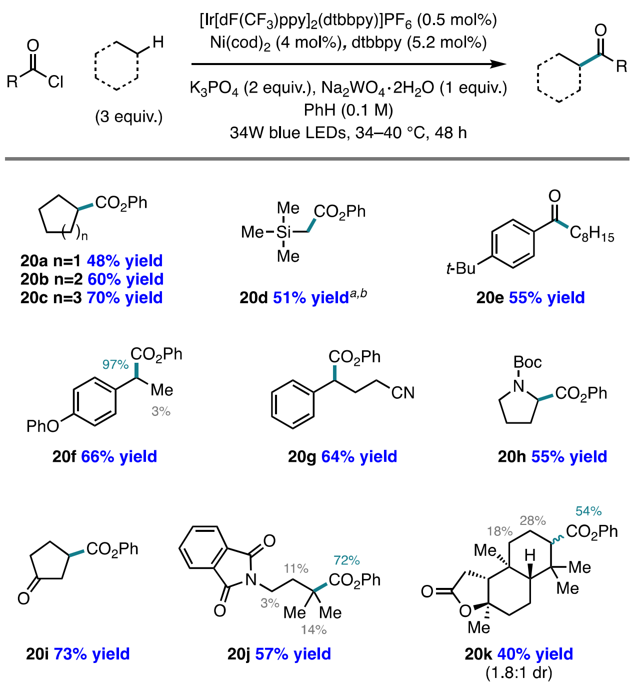


Figure 10. Representative scope for the acylation of unactivated C−H bonds. [a]6 equiv of C−H substrate was used. [b]Yield reported postdesilylation.

■ MECHANISTIC INVESTIGATIONS

Since our initial report, a variety of methods using halogen photoelimination in cross-coupling have been reported.[11] However, different mechanistic proposals have been put forth to account for the generation of halogen radicals, namely between photoelimination from excited Ni(II) or excited Ni(III). Our original mechanistic proposal invoked a process similar to Nocera's[14] in the light-induced generation of chlorine radicals from Ni(III) complexes (Figure 3). Aligned with our proposal, a $C(sp^3)$−$C(sp^3)$ cross-coupling of alkyl bromides with ethers was recently disclosed by König and co-workers, wherein photoelimination of bromine radicals is proposed to proceed from a Ni(III) species.[38] Wu has also invoked oxidation of Ni(II) to Ni(III) by a photocatalyst followed by photolysis to generate chlorine radicals.[39] Photoluminescence quenching studies and UV irradiation control reactions supported excitation of Ni(III) for chlorine radical elimination.

Alternatively, other researchers have proposed an energy transfer mechanism to access excited Ni(II) for halogen radical formation. Molander and co-workers leveraged bromine photoelimination in the cross-coupling of aryl bromides with ethers, which was proposed to proceed via excited-state Ni(II)−Br homolysis.[18] The researchers proposed energy transfer between the photocatalyst and the Ni catalyst as the operative mechanism on the basis of their observation that photocatalysts possessing high excited-state oxidation potentials but lower triplet energies failed to deliver cross-coupled product. Additionally, in the cross-coupling of allylic $C(sp^3)$−H bonds with aryl and vinyl bromides, Rueping proposed bromine radical generation from excited Ni(II) species using an acridinium photocatalyst.[40] The researchers deemed oxidation to Ni(III) prior to halogen elimination unlikely because, after oxidation, the reduced state of the photocatalyst

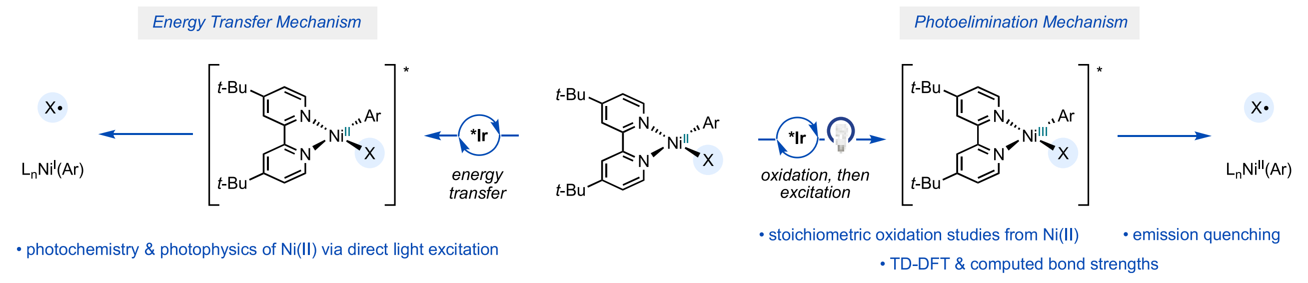


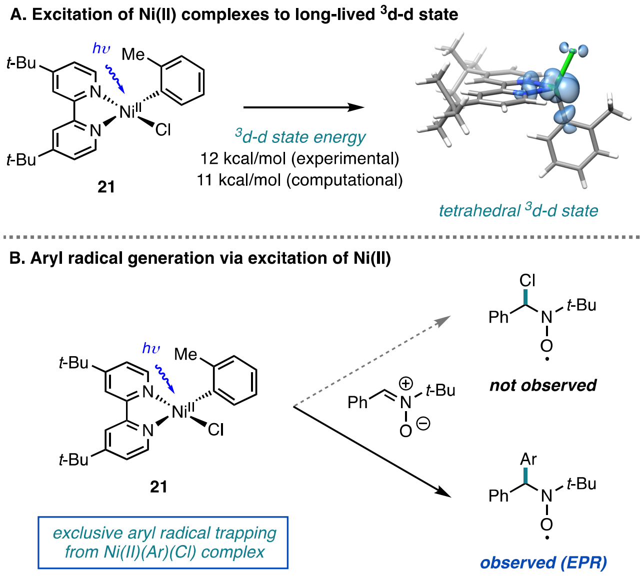
Figure 11. Proposed mechanisms for halogen photoelimination.

may not be sufficiently reducing to regenerate the Ni(0) catalyst.

Thus, our mechanistic studies on chlorine photoelimination have largely focused on discerning between these two possibilities in the synthetic methods that we have reported: (1) elimination from excited Ni(II) via energy transfer or (2) elimination from excited Ni(III) via light-induced bond homolysis (Figure 11).

Photophysical, Photochemical, and Computational Studies of Ni(II) Complexes

Despite the tremendous advances that have been made in synthesis with Ni/photoredox catalysis, little is known about the photophysics and photochemistry of the Ni(II) complexes relevant to these processes. Thus, we prepared a series of aryl halide complexes and investigated their interaction with visible light using steady-state and ultrafast spectroscopy.[4] Upon excitation, these complexes were found to relax into a long-lived ^{3}d−d excited state (Figure 12A). Although this transition features bond weakening of the Ni−ligand bonds, we found that this ^{3}d−d state is too low in energy (12 kcal/mol above the ground state) to enable elimination of a chlorine or bromine radical at temperatures relevant to the synthetic reactions (DFT at the M06/TZVP//B3LYP/TZVP level of theory).


A. Excitation of Ni(II) complexes to long-lived ^{3}d-d state

B. Aryl radical generation via excitation of Ni(II)

Figure 12. (A) Irradiation of **21** gives rise to a ^{3}d−d excited state. (B) Aryl radical capture in the presence of a radical trap.

To further probe the feasibility of chlorine photoelimination at Ni(II), we turned to a computational investigation. We found that while Ni(II)−Cl has a BDFE of 77 kcal/mol, oxidation of Ni(II) induces significant bond weakening (Ni(III)−Cl BDFE = 47 kcal/mol), making the Ni(III)−Cl bond sufficiently weak for visible-light-induced homolysis. The bond weakening is consistent across different carbon substituents: in the oxidation of (dtbbpy)Ni^{II}(CO$_2$Ph)(Cl) to [(dtbbpy)Ni^{III}(CO$_2$Ph)(Cl)]$^+$, the computed Ni−Cl BDFE is reduced from 65 to 37 kcal/mol. The significantly stronger Ni(II)−X bonds provide evidence that bond homolysis for halogen radical generation is unlikely, at least from the lowest-energy Ni(II) excited state.

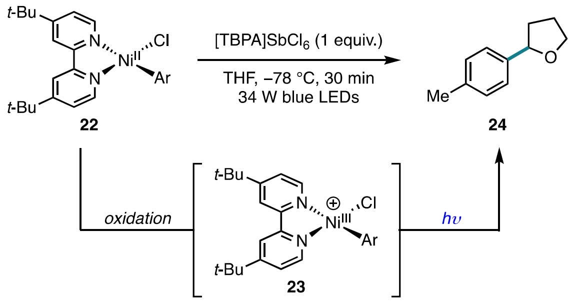
Ni(II) aryl chloride complexes can exist as stable and isolable species, providing a platform to study their photochemistry (Figure 12B). Irradiation of isolated (dtbbpy)Ni^{II}(*o*-Tol)(Cl) (**21**) in the presence of a radical trap[41] provided no evidence of chlorine radical generation by electron paramagnetic resonance (EPR) spectroscopy, although this does not necessarily reflect a lack of chlorine radical formation.[42] Instead, irradiation of this isolated Ni(II) aryl chloride complex resulted in exclusive trapping of *aryl* radicals in low conversion (Ni(II)−Ar BDFE = 35 kcal/mol).[43] Therefore, we expect that other pathways, specifically oxidation of Ni by the photocatalyst, could be outcompeting this step under catalytically relevant conditions.

Contrasting Photochemistry at Ni(II) with Chlorine Photoelimination from Ni(III)

Instead of chlorine radical photoelimination from excited Ni(II), we propose that the excited state of the Ir photocatalyst oxidizes the Ni(II) aryl halide species formed by oxidative addition. Because **21** was found to be competent in the cross-coupling with THF in the presence of light and photocatalyst, we chose to examine its properties to distinguish between energy transfer and oxidation pathways. Cyclic voltammetry of this complex indicated that *Ir(III) should be a suitable oxidant for accessing Ni(III) (E_p = 0.85 V vs SCE in THF). Importantly, Stern−Volmer quenching studies revealed that the Ni(II) complex is the most likely species responsible for quenching of the excited state of the photocatalyst. These data, in addition to the relative stability of the isolated Ni(II) complexes under visible-light irradiation, provide evidence for the generation of Ni(III) by photoinduced electron transfer from the Ir photocatalyst, consistent with the Ni(III) photoelimination proposal.

We then sought to explore the feasibility of photoelimination from excited Ni(III) complexes computationally. Using time-dependent density functional theory (TD-DFT), we found that the calculated absorption spectrum for [(dtbbpy)Ni^{III}(Ph)(Cl)]$^+$ contains high-energy features that are characterized by significant Ni−Cl $\sigma \rightarrow \sigma^*$ character. Along with the greatly weakened Ni(III)−Cl bond (BDFE = 47 kcal/mol), these states are expected to be dissociative.

To gain experimental data on photoelimination from Ni(III), we pursued stoichiometric studies. The proposed catalytic reaction requires two photons to enable chlorine radical generation: one photon for photocatalyst excitation to enable oxidation of Ni(II) to Ni(III) and a second photon for homolytic cleavage of the Ni(III)−Cl bond. Since the first of these steps could be accomplished using a chemical oxidant without light, the necessity of oxidation and irradiation could be interrogated separately. In a reaction employing stoichiometric (dtbbpy)Ni^{II}(Ar)(Cl) (Ar = 4-methylphenyl) (**22**) and the single-electron oxidant tris(4-bromophenyl)ammoniumyl hexachloroantimonate ([TBPA]SbCl$_6$) (E = 1.16 V vs SCE in dichloromethane) under visible-light irradiation, cross-coupled product **24** was obtained in 28% yield (Figure 13). When the reaction was conducted with oxidant but without irradiation, a requirement for photoelimination from Ni(III), no cross-coupling was observed. Additionally, when reactions were performed with light but without oxidant, the formation of **24** was again not observed. These experiments demonstrate that from the isolable Ni(II) aryl chloride complex, *both oxidant and light are necessary for chlorine photoelimination.*



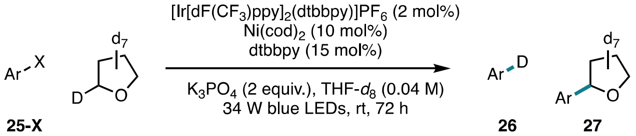
Deviation	Yield 24
none	28%
no oxidant	0%
no 34 W Blue LEDs	0%

Figure 13. Stoichiometric studies using the catalytically competent Ni(II) complex. Ar = 4-methylphenyl.

Evidence for Chlorine Radical in Hydrogen Atom Transfer

According to the mechanistic proposal, chlorine radicals mediate HAT with C(sp^3)−H substrates. However, in light of our observation of aryl radical generation upon photolysis of Ni(II) complex **21**, we also considered the possibility that aryl radicals could mediate HAT. To probe for their intermediacy in the catalytic system, we examined the coupling of aryl halides with a deuterium-labeled substrate (THF-d_8). Experiments using aryl chloride **25-Cl** provided strong evidence against aryl radical generation, as minimal deuterodehalogenation was observed (Table 1, entry 1). Moreover, only a 50% yield of the cross-coupled product **27** could be formed if aryl radical was mediating HAT. The observation of greater than 50% yield in the cross-coupling (68% yield) with **25-Cl** provides further evidence against aryl radicals acting as the operative HAT agents. Although the Ni(III)−Ar BDFE is likely sufficiently low for this bond to be cleaved with visible light, these findings indicate that aryl radical generation from Ni(III) does not take place, possibly because the Ni complex geometry and orbital considerations disfavor bond homolysis.

Table 1. Deuterium Labeling Experiments across Aryl Halides (Ar = 2-(4-Halophenyl)-6-methylpyridine)

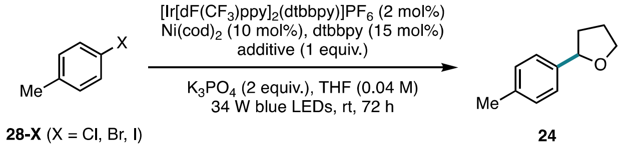


Entry	25-X	Yield 26	Yield 27
1	Cl	3%	68%
2	Br	2%	5%
3	I	66%	4%

If aryl radicals were operative in HAT, aryl bromides and iodides should perform comparably to aryl chlorides since the former substrates undergo facile oxidative addition to Ni. However, when an aryl bromide was used as the cross-coupling partner, only a trace amount of cross-coupled product was observed (Table 1, entry 2). The reaction performed with an aryl iodide also delivered a trace yield of the cross-coupled product, but with this substrate class deuterodehalogenation proceeded in 66% yield (Table 1, entry 3). This result suggests that when aryl iodides are used, aryl radicals are generated and mediate deuterium abstraction from THF-d_8. The generation of aryl radicals with aryl iodides could be attributed to the photochemistry of Ni(II) but most likely proceeds via oxidative addition and radical cage escape as described by Kochi.[44] Therefore, hydrogen atom abstraction by aryl radicals is significant only with aryl iodides and is consistent with chlorine photoelimination in the mechanistic proposal.

The fact that **25-Br** and **25-I** were unreactive is consistent with the role of halogen radical as the HAT agent: the weak H−I bond (BDE = 71 kcal/mol) renders an iodine radical incapable of abstracting even an activated C(sp^3)−H bond (Table 2, entry 3). However, reactivity could be restored when using aryl iodides and bromides as substrates via the addition of exogenous chloride for halide exchange (Table 2, entry 4).[45]

Table 2. Halide Additive Studies

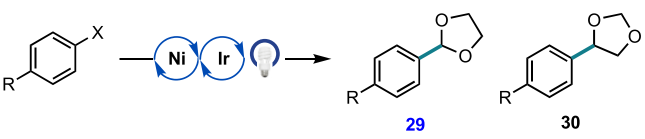


Entry	28-X	Additive	Yield 24
1	Cl	none	68%
2	Br	none	10%
3	I	none	5%
4	I	TBACl	51%
5	I	TBABr	37%
6	I	TBAI	6%

While the reaction yields are lower with aryl bromides than with the analogous aryl chlorides, we observed that the selectivity for C(sp^3)−H abstraction is higher when these substrates are employed, consistent with the Hammond postulate, wherein the later transition state by bromine radical abstraction (H−Br BDE = 88 kcal/mol vs H−Cl BDE = 102 kcal/mol) results in higher selectivity for the thermodynamically favored alkyl radical product. For example, reactions conducted in 1,3-dioxolane delivered two regioisomeric products, generally in a 9:1 ratio between the desired and undesired isomers (Table 3). The selectivity for C−H abstraction was 2 times higher when aryl bromides were employed as substrates.

The involvement of chlorine radicals in hydrogen atom transfer was also indirectly examined via an Evans−Polanyi analysis (Figure 14A).[33,36] While hydrogen atom abstraction can occur in a variety of positions in unactivated alkanes, functionalization of alkanes with chemically distinct C−H bonds revealed regioselectivity consistent with the influence of BDFE on the rate of C−H abstraction. For example, esterification of 2-methylbutane occurred in a 53% combined yield with a preference for the tertiary C−H bond (α:β:γ:δ 1.3:9:6.3:1). An Evans−Polanyi plot for 2-methylbutane exhibited a linear correlation with an α value of 0.44, which

Table 3. Arylation of 1,3-Dioxolane with Aryl Chlorides and Bromides



Entry	R	X	Yield 29	29 : 30
1	CN	Cl	73%	7.1 : 1
2	CN	Br	52%	15.8 : 1
3	Ph	Cl	65%	9.0 : 1
4	Ph	Br	36%	18.1 : 1

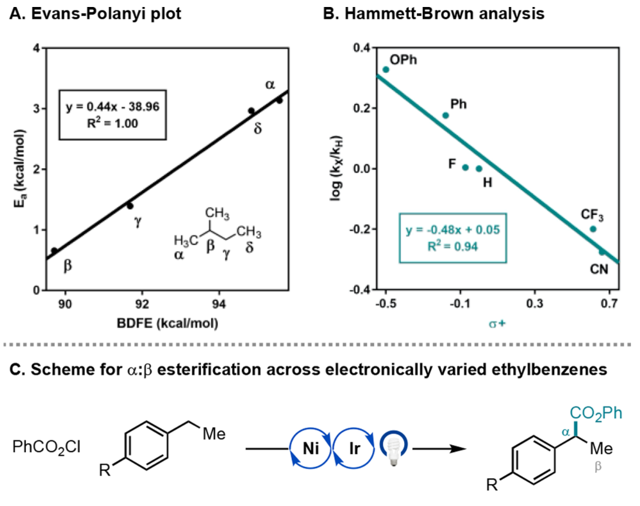


Figure 14. (A) Evans–Polanyi plot for the reaction of phenyl chloroformate with 2-methylbutane. (B) Hammett–Brown analysis of the relative rates of benzylic functionalization of ethylbenzenes. (C) Reaction scheme for Hammett–Brown analysis.

is in agreement with tabulated α values for hydrogen atom abstraction by chlorine radical (α_{Cl} = 0.45).[36]

Furthermore, selectivity in C–H abstraction by chlorine radical demonstrated a clear trend in polarity for the most electron-rich site. This influence was directly studied with a series of para-substituted ethylbenzenes, wherein the ratio of benzylic to methyl functionalization decreases with electron-withdrawing substituents (Figure 14C). Additionally, Hammett–Brown analysis revealed that electron-rich ethylbenzenes undergo benzylic C–C bond formation faster than electron-deficient substrates (Figure 14B). The small ρ value determined from this series is consistent with a highly exothermic abstraction step and in agreement with free-radical chlorination of toluenes (ρ values ranging from −0.5 to −1.0).[46]

The requirement for both light and oxidant in our system, in addition to trends observed via Evans–Polanyi and Hammett–Brown analyses, lend support to the generation of chlorine radicals for hydrogen atom transfer.[47] Key experimental studies, namely stoichiometric oxidation from Ni(II), Stern–Volmer emission quenching experiments, studies of the photophysics of excited Ni(II) complexes, and halide identity studies, support the photoelimination of chlorine radicals from excited Ni(III). Computational studies, including TD-DFT and computed bond strengths, lend additional support for the feasibility of chlorine photoelimination. Notably, a recent report demonstrated that DFT calculations are inadequate for describing the electronic structure of certain (bpy)Ni systems, with multireference calculations being necessary for this purpose.[43] These theoretical findings emphasize the need for experimental mechanistic studies, including those presented here for chlorine photoelimination, in elucidating reaction mechanisms in Ni/photoredox-catalyzed processes.

■ CONCLUSION AND OUTLOOK

We have shown that the photocatalytic generation of halogen radicals from Ni complexes has value in achieving otherwise-challenging C(sp^3)–H bond functionalization reactions. By invoking chlorine radicals in hydrogen atom transfer, virtually any C(sp^3)–H bond can be activated and functionalized under exceptionally mild conditions, as has been demonstrated in etherification, formylation, methylation, and acylation reactions. Our mechanistic understanding of this process leaves several potential extensions of these methods. Ligand design could facilitate catalyst-controlled site-selective C–H cross-couplings. Stabilization of chlorine radicals by aryl groups on ligands, as demonstrated by Nocera, indicates one such promising route.[14] Our studies to date have focused on the photoelimination of chlorine radicals and their use as hydrogen atom transfer agents; the photoelimination of other reactive ligands could have broad implications for catalysis and cross-coupling. For example, the generation of *N*- or *O*-centered radicals could provide an opportunity to use alcohol- or amine-based coupling partners.

Considering the ability of a variety of first- through third-row metal complexes to interact with visible light and photoredox catalysts, it may become feasible to use other metals for photoelimination processes in cross-coupling. Very recently, Castellano demonstrated that irradiation of phenanthroline-ligated Cu(II) species with blue light results in Cu–Cl bond homolysis to generate chlorine radicals.[48] That study, in addition to our studies on Ni, suggests that the photochemistry of cross-coupling catalysts themselves must not be ignored in metallaphotoredox systems and rather could serve as a design principle for the development of new catalytic reactions.

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Author Contributions

The manuscript was written through contributions of both authors. Both authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Stavros K. Kariofillis obtained a B.S. in Biochemistry from Lafayette College in 2013, where he worked with Professor Roxy Swails on developing new water-soluble palladium catalysts for cross-coupling. As an undergraduate student, he also worked with Professor Melanie Sanford at the University of Michigan studying the organometallic properties and reactivity of copper(I)−difluoromethyl complexes. He is currently an NSF Predoctoral Fellow in Professor Abigail Doyle's group at Princeton University, where his research focuses on methodology development within Ni/photoredox catalysis.

Abigail G. Doyle is the A. Barton Hepburn Professor of Chemistry in the Chemistry Department at Princeton University. She obtained her Ph.D. in catalysis and physical organic chemistry at Harvard University in 2008 under the direction of Prof. Eric Jacobsen after receiving her A.B. and A.M. in chemistry and chemical biology from Harvard in 2002. She joined the faculty at Princeton University in 2008 and is currently a co-PI for the NSF CCI Center for Computer Assisted Synthesis (C-CAS) and the DOE EFRC Bioinspired Light-Escalated Chemistry (BioLEC). The Doyle laboratory is interested in developing new approaches to chemical synthesis and catalysis, with a focus on Ni-catalyzed cross-coupling and nucleophilic fluorination methodology.

■ ACKNOWLEDGMENTS

We are grateful to the past and present members of our research group for their contributions to this work and to our collaborators from Celgene, the Scholes laboratory (Princeton), and the Castellano laboratory (NC State). This material is based on work supported by the National Science Foundation Graduate Research Fellowship Program under Grant DGE-1656466 (to S.K.K.). A.G.D. gratefully acknowledges Celgene, NIGMS (R35 GM126986), the Princeton Innovation Fund, and BioLEC, an Energy Frontier Research Center (U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Award DE-SC0019370) for funding. We thank Jesus Martinez Alvarado and Stephen Ting for helpful discussions.

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https://dx.doi.org/10.1021/acs.accounts.0c00694
Acc. Chem. Res. XXXX, XXX, XXX−XXX