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Perspective

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Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development

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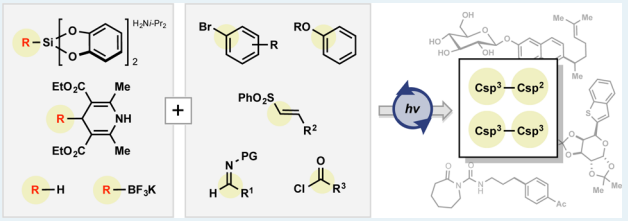
ABSTRACT: Photoredox catalysis has experienced a revitalized interest from the synthesis community during the past decade. For example, photoredox/Ni dual catalysis protocols have been developed to overcome several inherent limitations of palladium-catalyzed cross-couplings by invoking a single-electron transmetalation pathway. This Perspective highlights advances made by our laboratory since the inception of the photoredox/Ni cross-coupling of benzyltrifluoroborates with aryl bromides. In addition to broadening the scope of trifluoroborate coupling partners, research using readily oxidized hypervalent silicates as radical precursors that demonstrate functional group compatibility is highlighted. The pursuit of electrophilic coupling partners beyond (hetero)aryl bromides has also led to the incorporation of several new classes of C(sp^2)-hybridized substrates into light-mediated cross-coupling. Advances to expand the radical toolbox by utilizing feedstock chemicals (e.g., aldehydes) to access radicals that were previously inaccessible from trifluoroborates and silicates are also emphasized. Additionally, several organic photocatalysts have been investigated as replacements for their expensive iridium- and ruthenium-based counterparts. Lastly, the net C−H functionalization of the radical partner in an effort to improve atom economy is presented. An underlying theme in all of these studies is the value of generating radicals in a catalytic manner, rather than stoichiometrically.



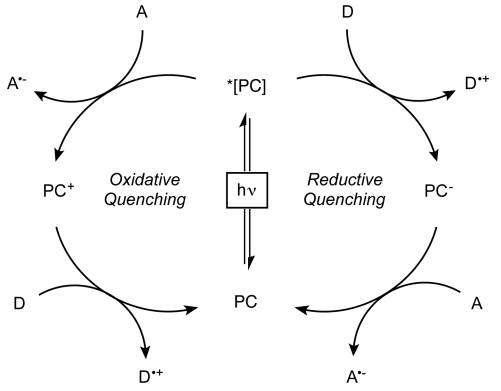
KEYWORDS: *photoredox, catalysis, cross-coupling, radicals, nickel, dual catalysis*

INTRODUCTION

Over the past eight years, a resurgence of interest in photoinduced electron transfer has resulted in a new class of organic transformations.[1] The ability to harness over 60 kcal/mol of visible light energy to activate redox-labile substrates—via the intermediacy of a photoredox catalyst—has enabled reactions under extraordinarily mild conditions compared to alternative two-electron modes of activation. Since the 1970s, the properties of transition metal photocatalysts (PC) have been studied, revealing that photoexcited transition metal catalysts can either undergo a single-electron oxidation or reduction (Scheme 1). One of the first synthetic applications of a photoredox catalyst was reported by Deronzier, wherein a ruthenium photocatalyst was used in a Pschorr-type transformation via a single-electron reduction of an aryl diazonium moiety.[2] More recently, Yoon,[3] MacMillan,[4] and Stephenson[5] employed $Ru(bpy)_3$ to perform cycloadditions, α-alkylation of aldehydes, and dehalogenation, respectively, through both oxidative and reductive quenching pathways. Following these seminal reports, numerous groups have developed creative applications with a variety of photocatalysts.[6]

Our group became interested in photoredox catalysis as a tool to generate alkyl radicals for use in cross-coupling reactions. In 2014, we disclosed the first example of photoredox/Ni dual catalysis to forge C(sp^2)−C(sp^3) bonds under unusually mild reaction conditions.[7] In this transformation, photoredox/Ni dual catalysis proceeds via the

Scheme 1. Oxidative and Reductive Pathways of Photocatalysts



single-electron oxidative fragmentation of *radical precursors* and *alkyl radical addition* to a nickel catalyst, a process we refer to as *single-electron transmetalation* (Scheme 2). The addition of the radical to the nickel complex using this protocol is the synthetic equivalent of the more traditional two-electron transmetalation, and the activation energy for this process is extraordinarily low.[8] This is in stark contrast to typical Pd- or Ni-catalyzed

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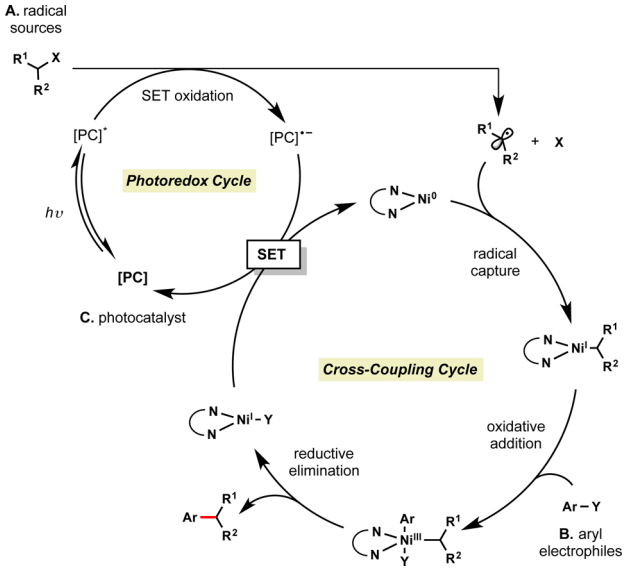
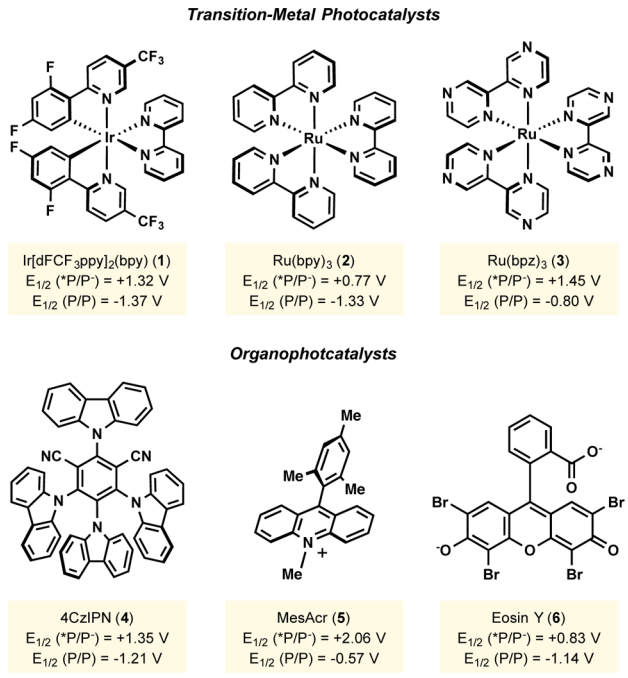
Scheme 2. Photoredox/Nickel Dual Catalysis Cycle



Scheme 3. Transition-Metal-Based and Organic Photocatalysts



processes, where transmetalation from an organometallic *nucleophile* to a metal center is often the rate-determining step with a high energy of activation.[9]

This Perspective details the efforts of our laboratory to expand the scope of photocatalytic routes to radicals by targeting three major components of the dual catalytic cycle for improvement (Scheme 2): the radical precursor (**A**), the electrophilic coupling partner (**B**), and the photocatalyst (**C**). Beyond trifluoroborate and hypervalent silicate reagents previously exploited,[1a] we sought complementary radical precursors derived from feedstock chemicals (e.g., aldehydes), to engage in *single-electron transmetalation* processes. Furthermore, the development of protocols for the inclusion of electrophiles other than hetero(aryl)bromides is discussed. Additionally, our efforts in the arylation of alkyl C(sp^3)−H bonds using photoredox/Ni dual catalysis are detailed.

Another important accomplishment was the inclusion of competent, inexpensive, and sustainable organic photoredox catalysts[10] (Scheme 3) in many of the developed protocols. Building upon Zhang's report that 4CzIPN (**4**) can serve as a surrogate of transition metal-based photocatalysts **1**, **2**, and **3** within the photoredox/Ni manifold,[11] we began to incorporate it into newly developed cross-couplings. We have also exploited the favorable properties of the mesityl acridinium dye (**5**)[12] and Eosin Y (**6**) to effect metal-free couplings.

An overarching theme that has evolved is the *catalytic* generation of radicals via photoredox processes that enables transformations that would be challenging, if not impossible, to carry out under conditions in which stoichiometric reagents were utilized to generate these same radicals.

PHOTOREDOX/NICKEL DUAL CATALYSIS

The many challenges of transition metal-catalyzed cross-coupling of sp^3-hybridized nucleophilic species with sp^2-hybridized electrophiles led our group[6] and others[4] to develop cross-coupling protocols based upon single-electron transformations (Scheme 2). The major advantage of using radical intermediates in such catalytic cycles derived from the extraordinarily rapid capture of these open-shell species by the transition-metal cross-coupling catalysts in an event we termed "single-electron transmetalation". The success of these processes derived ultimately from the fact that these radicals were generated catalytically in a process that was tightly regulated and innately controlled by the intertwinement of the photoredox cycle and the cross-coupling cycle. Thus, adjustment of the electronic nature and concentration of the individual catalysts are used to regulate the concentration of the radicals generated. This is critical to the success of the overall process because such highly reactive intermediates, left to themselves, are subject to a variety of deleterious side-reactions, including dimerization and disproportionation. Catalytic generation of the key reactive intermediates was thus critical for the success of these intricately fused cycles and provided the crucial, enabling transformations that could not be accomplished using stoichiometric methods based, for example, on tin hydride or electrochemical processes.

Alkyltrifluoroborates and Alkylsilicates. Alkyltrifluoroborates are exceptional reagents for photoredox processes, primarily because of their low oxidation potentials, benchtop stability, and commercial availability.[13] Additionally, complex alkyltrifluoroborates can be accessed via a variety of complementary pathways, including β-borylation of conjugated carbonyl substrates,[14] substitution of halomethyltrifluoroborates, and so on.[15] From the seminal cross-coupling of benzyltrifluoroborates, the exploration of different classes of trifluoroborates has led to the fruitful incorporation of secondary alkyl,[16] α-alkoxy,[17] α-amino,[18] and α-trifluoromethyl[19] subunits into similar manifolds.

To expand the scope of radical precursors with complementary reactivity, the compatibility of bis(catecholato)-alkylsilicates was evaluated in photoredox-/Ni-catalyzed cross-couplings. Hypervalent silicon compounds have been shown to be readily oxidized, affording the corresponding alkyl radicals as initially demonstrated by Nishigaichi and co-workers.[20] The groups of Goddard, Ollivier, and Fensterbank also demonstrated that radicals derived from photooxidation of pentavalent bis(catecholato)silicates readily participated in allylation, vinyl-

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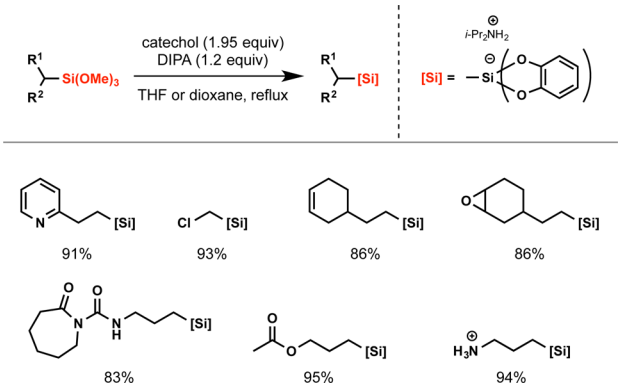
ation/alkynylation, conjugate addition, and nickel-catalyzed cross-coupling reactions.[21] With an improved synthetic route to access alkyl ammonium bis(catecholato)silicates, our group built a library of silicate radical precursors containing epoxide, amine, and chloride functional groups from the corresponding trimethoxysilanes (Scheme 4).[22]

Scheme 4. Building a Library of Silicates

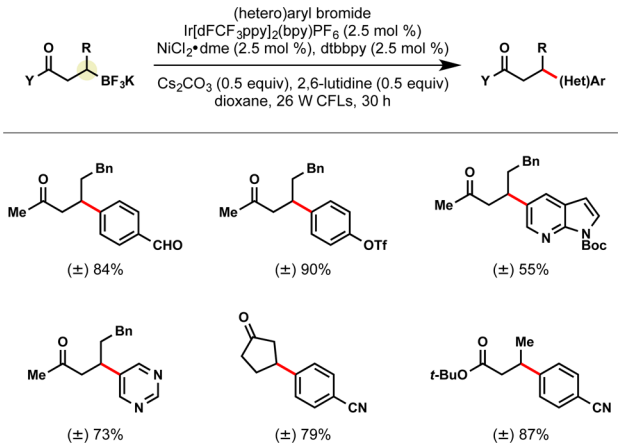


As with alkyltrifluoroborates, alkylsilicates are crystalline solids or free-flowing powders that are indefinitely bench-stable. Alkylsilicates have the added advantage of avoiding formation of the deleterious byproduct BF_3, which requires the use of basic sequestering agents in cross-coupling protocols. Furthermore, the lower oxidation potentials (E_{red} = +0.75 V vs SCE) allowed the transition from iridium photocatalysts to the significantly less expensive $Ru(bpy)_3(2PF_6)$[1b] and even organic photocatalysts. Additionally, alkylsilicates tend to be more soluble than trifluoroborate salts, which can be an important consideration in their adaptation to photoflow conditions. These advantages enabled photoredox/Ni dual cross-coupling with exquisite functional group tolerance (e.g., substrates containing amines and protic functional groups).

Secondary Alkyl β-Trifluoroborato Ketones. In 2011, our group reported the β-borylation of α,β-unsaturated amide and carbonyl compounds using a readily available copper catalyst with bisboronic acid.[14] Subsequently, we successfully engaged secondary alkyl β-trifluoroboratoamides in palladium-catalyzed cross-couplings.[23] Unfortunately, efforts to couple alkyl β-trifluoroborato ketones or -esters under similar conditions primarily resulted in β-hydride elimination. Other routes to similar synthons include the generation of organozinc and -lithium reagents, which also result in unproductive side reactions, specifically an intramolecular attack on the carbonyl to afford the corresponding cyclopropanolates.[24] Therefore, we hypothesized that coupling the secondary alkyl β-trifluoroborato ketones and -esters via single-electron transmetalation using photoredox/Ni dual catalysis could address this unsolved challenge.[25]

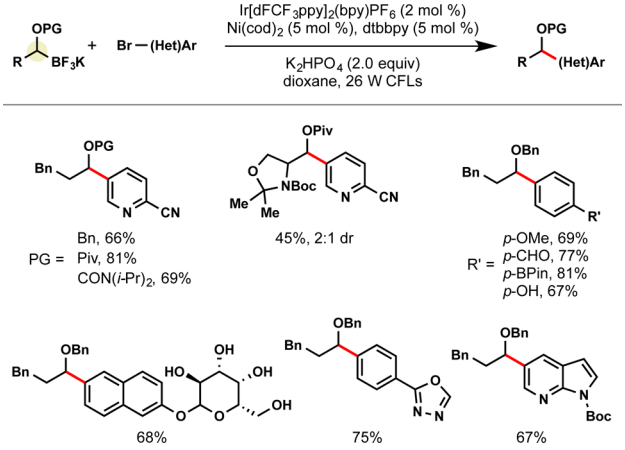
Optimization of reaction conditions revealed that the $Ir[dFCF_3ppy]_2(bpy)PF_6$ photocatalyst (2.5 mol %), $NiCl_2$·dme (2.5 mol %)/dtbbpy (2.5 mol %) cross-coupling catalyst, Cs_2CO_3 (0.5 equiv), and 2,6-lutidine (0.5 equiv) in dioxane afforded the highest conversion to product. Impressively, this coupling tolerated a wide range of potentially sensitive functional groups (e.g., aldehydes, ketones, esters, nitriles) and heteroaryl partners (e.g., pyridine, pyrimidine, azaindole) as shown in Scheme 5.

Scheme 5. Coupling of Alkyl β-Trifluoroborato Ketones



Secondary α-Alkoxy Alkyltrifluoroborates. Tackling another challenging substrate class in palladium-catalyzed Suzuki cross-couplings, we sought to utilize α-alkoxyalkyltrifluoroborates in the dual catalytic manifold. Previous palladium-catalyzed approaches toward the coupling of α-alkoxyalkyltrifluoroborates via two-electron transmetalation pathways were limited by the need for excess base (>5 equiv CsOH) and elevated temperatures (>100 °C), which resulted in extremely narrow functional group tolerance.[26] In fact, only a benzylic ether protecting group (PG) was compatible with the reaction conditions.[20] We postulated that single-electron transmetalation would facilitate a more general synthesis of protected secondary alcohol derivatives.[27] The mild, optimized reaction conditions associated with the dual catalytic cross-coupling manifold readily lent themselves toward a protecting group-independent and functional group-tolerant strategy to access a broad range of protected benzylic alcohol derivatives (Scheme 6). Notably, a fully unprotected carbohydrate was readily coupled in a synthetically useful 68% yield.

Scheme 6. Coupling of Secondary α-Alkoxy Alkyltrifluoroborates



Construction of Functionalized Chromanones. In an effort to merge the β-trifluoroborato ketones and secondary α-alkoxyalkyltrifluoroborates, we next targeted the biologically significant chromanone core, found in myriad plant metabolites.[28] Although there have been a multitude of synthetic routes to access functionalized chromanones,[29] most dis-

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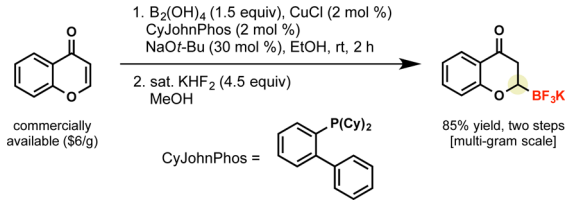
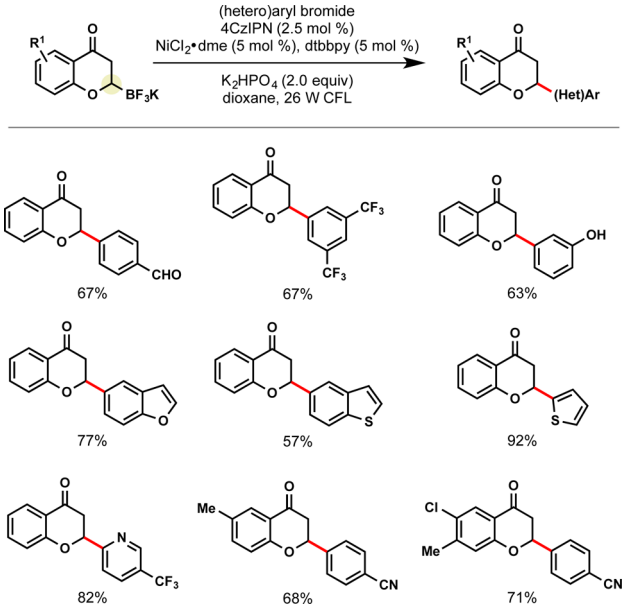
connections involve a chalcone intermediate, making derivatization of the C2-aryl ring difficult. Conjugate addition of various arylmetallics to chromones constitutes another logical approach, but from a diversity point of view, this tactic is less than ideal because it requires the synthesis of organometallic reagents, many of which are air- and moisture-sensitive. We envisioned an alternate route where a trifluoroboratochromanone serves as a radical precursor to access a wide array of 2-(hetero)aryl chromanones rapidly using the corresponding aryl or heteroaryl halide directly as coupling partners.[30] This strategy would take advantage of having access to thousands of commercially available, structurally diverse aryl- and heteroaryl halides to elaborate the chromanone core. The requisite 2-trifluoroboratochromanones were prepared via the β-borylation of commercially available chromone using an inexpensive copper catalyst and bisboronic acid on gram-scale (Scheme 7).[14]

Scheme 7. Gram-Scale Preparation of Trifluoroboratochromanone



A variety of 2-(hetero)aryl-substituted flavanones were synthesized in one step under the operationally simple and mild reaction conditions (Scheme 8). Aryl bromides bearing

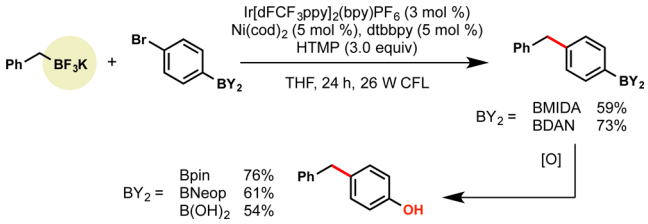
Scheme 8. Arylation of Trifluoroboratochromanones



electron-withdrawing substituents in the meta- and para-positions that may also subsequently serve as building blocks were well-tolerated. Additionally, a variety of heteroaryl bromides provided the desired flavanones in good yields. Lastly, chromones substituted on the aryl subunit were also readily borylated and then subsequently arylated, providing additional opportunities for diversification of the flavanone core.

Iterative Cross-Coupling Strategy. Although we demonstrated that several reactive functional groups were untouched in the photoredox dual cross-couplings (e.g., aldehydes, chlorides), our laboratory sought to determine if boronate groups would also remain intact for iterative cross-couplings.[31] The combination of photoredox/Ni dual catalysis at room temperature indeed allowed the differentiation of reactivity sites based on the preferential tendencies for tetracoordinate, C(sp^3)-hybridized organoboron reagents to engage in single-electron transmetalation, in contrast to their tricoordinate, C(sp^2)-hybridized counterparts. Thus, reactive, tricoordinate, C(sp^2)-hybridized organoboron reagents that succumb to decomposition pathways such as oxidation and protodeboronation during traditional Pd-mediated coupling conditions remained intact using the orthogonal photoredox/Ni cross-coupling protocols (Scheme 9).[32]

Scheme 9. Mechanism-Based Selective Coupling



Initially, benzyltrifluoroborate was coupled with aryl bromides bearing the C(sp^2)-hybridized organoboron *N*-methyliminodiacetic acid (BMIDA) and 1,8-diaminonaphthalene (BDAN) subunits to afford the desired products in 59% and 73% yields, respectively. Tricoordinate boronate reagents were also successfully coupled and then immediately oxidized to the corresponding alcohol because the intermediates were found to be unstable when subjected to column chromatography.

To demonstrate the utility of this orthogonal cross-coupling strategy, 2-(4-bromo-3-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was subjected to a series of modular functionalizations, beginning with photoredox/Ni dual-catalytic cross-coupling, to provide the C(sp^3)−C(sp^2) coupled product. The crude product was then directly diverted into either Suzuki or 1,4-addition manifolds that chemoselectively activated the sp^2-hybridized organoboron lynchpin. Additional elaboration of the aryl chloride by Buchwald−Hartwig or Suzuki cross-couplings provided expedient access to diversified products without the need for protecting group manipulations (Scheme 10).

A similar, iterative strategy was pursued with ammonium silicates to provide alkylated aryl- and heteroaryl boronates, providing a complementary approach (Scheme 11).[33] [Ru(bpy)$_2$](PF$_6$)$_2$, a significantly less expensive photocatalyst ($138/g) than the commonly used Ir[dFCF$_3$ppy]$_2$(bpy)PF$_6$ (>$1,000/g), was chosen because alkyl ammonium silicates possess lower oxidation potentials (E_{red} = +0.75 V vs SCE). Comparable yields were also obtained when the organophotocatalyst 4CzIPN ($6/gram) was utilized, which further improved the sustainability of the reaction. An additional advantage to employing ammonium silicate radical precursors with lower oxidation potentials is the incorporation of primary,

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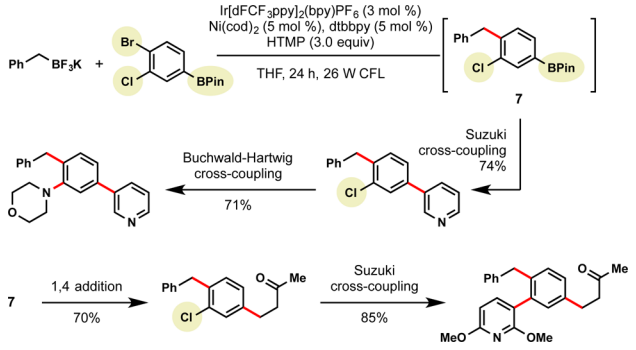
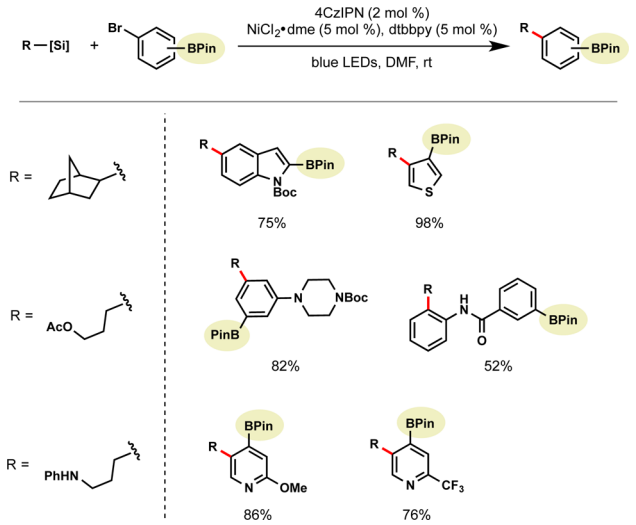
Scheme 10. Three-Step Iterative Cross-Couplings



Scheme 11. Coupling Boronate-Containing Aryl Bromides

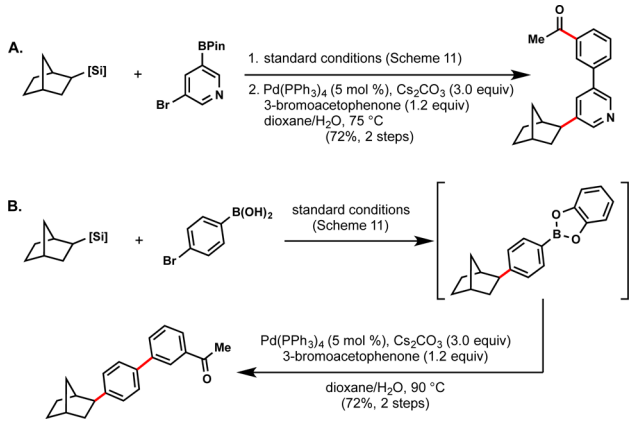


nonbenzylic radicals into the dual cross-coupling manifold. Examination of the scope of the electrophilic, iterative cross-coupling partners revealed that a variety of C(sp^2)-hybridized boronate esters were tolerated under the optimized reaction conditions, providing the target products in moderate to excellent yields.

The standard conditions for silicate coupling also proved to be fruitful for iterative C(sp^3)−C(sp^2) Suzuki cross-couplings. The crude, alkylated material could be carried directly on to the next step to provide multifunctionalized molecules in good yields (Scheme 12). When a bromo-substituted arylboronic acid was used, the catechol boronate ester that formed during the alkylation step could also be carried directly into a subsequent Suzuki reaction without purification.

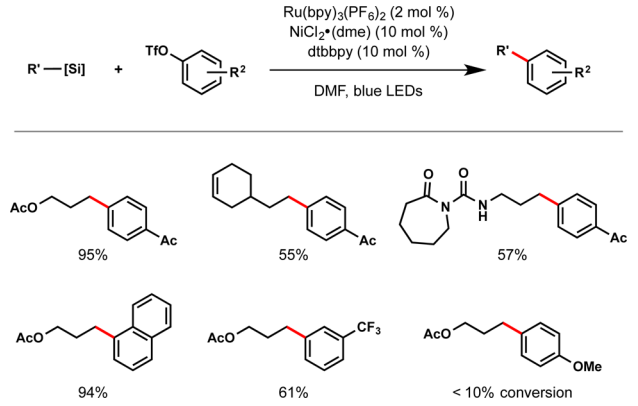
Engaging New Electrophiles in Dual Catalysis. *Cross-Coupling with Triflates.* Alternatives to aryl halide electrophiles were also pursued for incorporation into dual catalytic cross-coupling.[34] Aryl sulfonates, which are derived from different chemical feedstocks (phenols) than the corresponding halides, were examined because of their ability to undergo low-temperature oxidative addition toward ligated nickel species.[35] Preliminary screening revealed that 4-acetylphenyltrifluoromethanesulfonate readily participated in C(sp^2)−C(sp^3) cross-coupling with a variety of primary and secondary alkylbis(catecholato)silicates under conditions similar to those previously reported.[14] Exploration of the aryl triflate scope revealed that although electron-neutral and electron-poor

Scheme 12. One-Pot Iterative Cross-Couplings



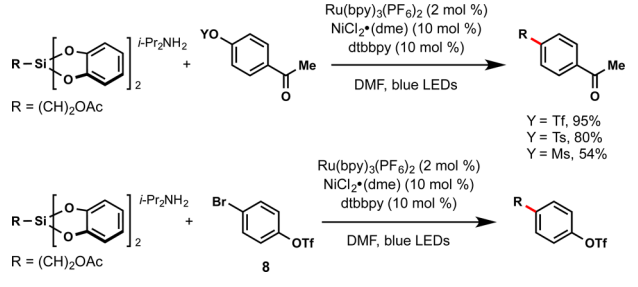
triflates provided product in acceptable yields, the use of electron-rich triflates resulted in lower reactivity (Scheme 13).

Scheme 13. Silicate Scope with Aryl Triflates



Aryl tosylates and -mesylates, which display improved bench stability compared to aryl triflates, were also successfully coupled, although lower yields were observed. Additionally, the relative rates of oxidative addition of aryl bromides and aryl triflates onto Ni(I) was also investigated using **8** (Scheme 14).

Scheme 14. Probing Chemoselectivity and Sulfonate Scope



In difunctionalized substrates, alkylation occurred exclusively at the position bearing the bromide, indicating that oxidative addition of aryl bromides is more rapid. This enables chemoselective transformations of poly functionalized starting materials using dual catalysis.

Acylation via Acid Chlorides. Further efforts to expand the scope of halide electrophiles in the dual catalytic manifold beyond aryl/heteroaryl moieties led to the examination of acyl

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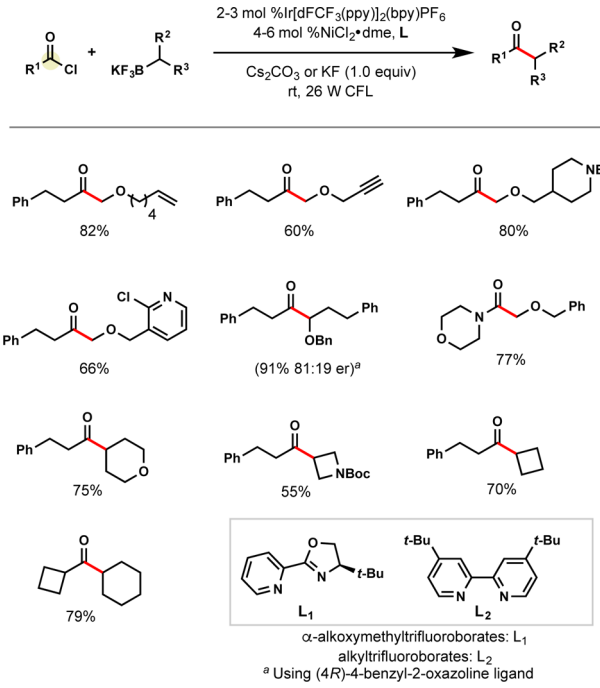
chlorides. Although acyl halides are known to react with organoboron "ate" complexes in an intermolecular fashion, either air-sensitive trialkylboranes or pyrophoric/toxic additives under forcing conditions were required.[36] In contrast, we recognized that the extremely mild conditions required to activate alkyltrifluoroborates for incorporation into Ni-catalyzed cross-coupling would allow the direct synthesis of alkyl ketones containing sensitive functional groups from bench stable starting materials.[37]

A variety of α-alkoxymethyltrifluoroborates containing versatile synthetic lynchpins (i.e., alkenes, alkynes, amines) and heterocycles were readily coupled under the optimized reaction conditions to provide aliphatic α-alkoxy ketones and amides (Scheme 15).[37a] Secondary alkyltrifluoroborates were

Scheme 15. Acylation of Trifluoroborates

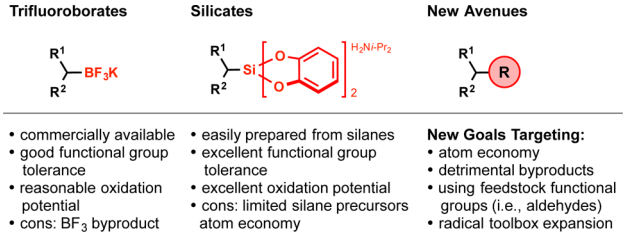


also readily transformed into the corresponding ketones under similar reaction conditions.[37b] For both sets of trifluoroborate coupling partners, the acyl chloride was also varied to afford access to various dialkyl ketones. Lastly, it was demonstrated that the use of (4*R*)-4-benzyl-2-oxazoline for the cross-coupling led to the formation of an enantioenriched ketone in modest er (81:19).

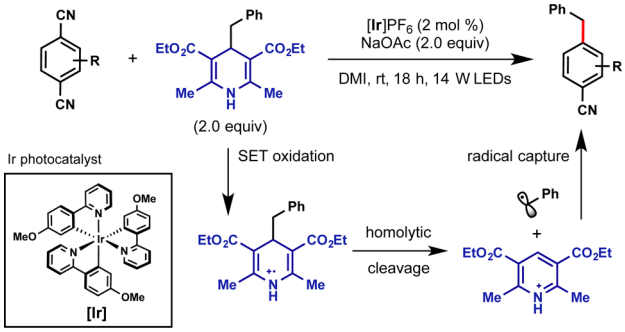
New Radical Precursors. Our group hoped to access additional chemical space via the development and implementation of novel radical precursors. Recognizing several potential drawbacks of alkyltrifluoroborates (e.g., formation of BF_3) and silicates (poor atom economy, limited commercial availability of silanes), we initially focused our attention on the incorporation of readily available feedstock chemicals bearing desirable functional groups (Scheme 16).

Hantzsch Esters From Aldehyde Feedstock Chemicals. Currently, there are 12 000+ commercially available aldehydes, underlining their potential as an important chemical feedstock for the generation of radical precursors.[38] Nishibayashi and co-workers reported the synthesis of 4-alkyl-1,4-dihydropyridines for use as latent radicals from various aldehydes.[39] As shown in Scheme 17, the Hantzsch ester presumably undergoes a single-

Scheme 16. Comparing Radical Sources



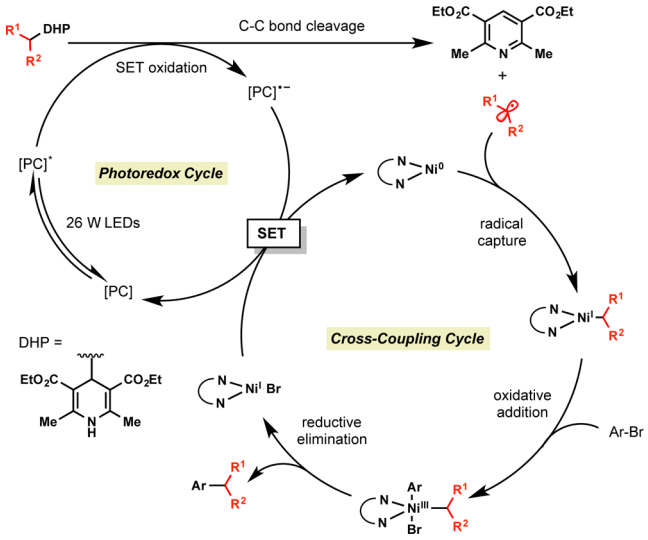
Scheme 17. SET and C−C Bond Cleavage of DHPs



electron oxidation to the radical cation followed by homolysis of the C−C bond to form an alkyl radical. The resulting benzylic radicals were then captured by a variety of 1,4-dicyanobenzenes. Additionally, the Nishibayashi group moved beyond benzylic radicals to heteroatom-stabilized, carbon-centered radicals (i.e., α-alkoxy, α-amino subunits).

We surmised that the alkyl 1,4-dihydropyridines (DHPs) could also serve as an alternative radical source in a Ni/photoredox dual catalytic manifold.[40] A plausible mechanism is outlined in Scheme 18. To initiate the cycle, the DHP

Scheme 18. Proposed Mechanism for DHP Coupling



undergoes a single-electron oxidation followed by concomitant C−C bond cleavage, forming a radical intermediate. As described above, the radical is captured by ligated Ni(0), which then undergoes oxidative addition toward the aryl bromide to provide a Ni(III) intermediate. Reductive elimination to provide the product and Ni(I) is followed by reduction of Ni(I) to Ni(0), closing both catalytic cycles.

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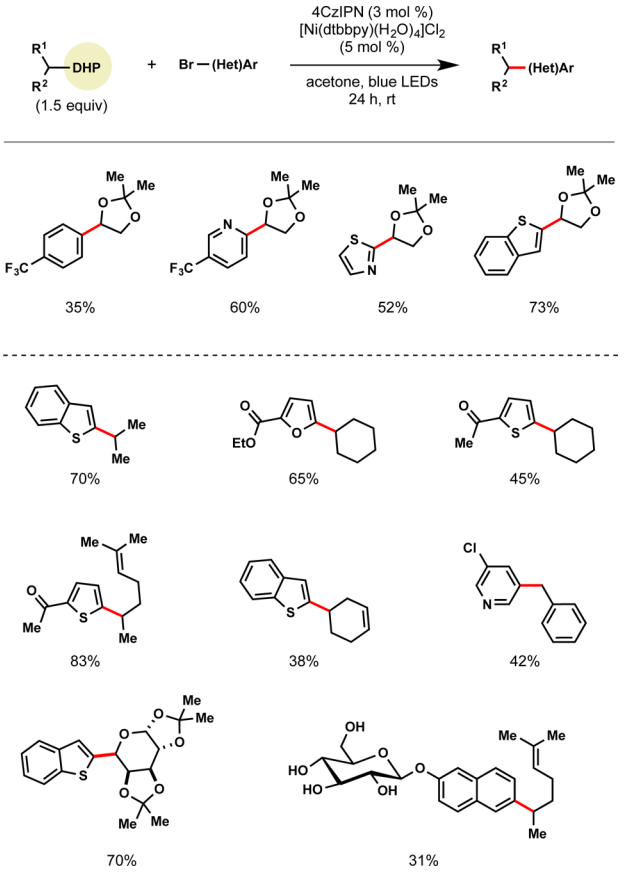
During the optimization process, we discovered that acetone was a suitable solvent for the reaction, and additives were not required because the DHP pyridine byproduct is unreactive under the dual catalytic conditions. Additionally, the iridium photocatalyst was replaced with the inexpensive organophotocatalyst 4CzIPN. To simplify the reaction conditions even further, $NiCl_2$·dme was precomplexed with dtbbpy to form the bench- and air-stable nickel precatalyst Ni(dtbbpy)Cl_2·$4H_2O$ on multigram scale.

With dioxolane DHP in hand, a wide variety of aryl and heteroaryl bromides was examined. A few notable examples are showcased in Scheme 19. A variety of DHPs and (hetero)aryl

Scheme 19. Aryl Bromide and DHP Scope



bromides were also explored. Benzothiophenes proved to be robust partners with unstabilized secondary radicals. Electron-poor furans were also successfully coupled in decent yield with cyclohexyl DHP. Surprisingly, alkene-containing DHPs afforded excellent yields with acyclic and cyclic systems. 3-Bromo-5-chloropyridine was coupled with benzyl DHP in 42% yield, affording the chloride functional handle for further derivatization.

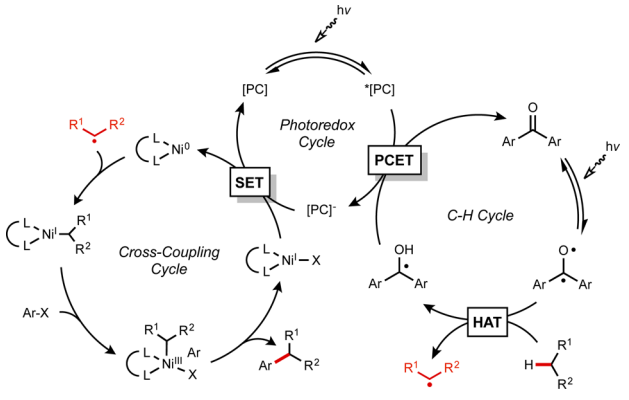
The robust nature of the transformation was demonstrated by using a protected carbohydrate derivative. This particular example, in which the product was isolated in 70% yield, demonstrates the complementarity between the single electron protocol and processes based on traditional organometallic species. In the latter, any metalation on the carbohydrate core would lead to rapid β-elimination of the neighboring alkoxide. Photoredox/Ni dual catalysis thus provides rapid entry to novel chemical space. Finally, unprotected glycoside moieties were tolerated, albeit a modest yield was achieved. Previous methods based on organometallic nucleophiles would typically require protection of the free hydroxyl groups before coupling, followed by a global deprotection.

C–H Arylation. Alkyltrifluoroborates, -silicates, and -DHPs exhibit many desirable traits as partners in photoredox/Ni dual catalysis, but the coupling of prefunctionalized, redox-active substrates is inherently limited by atom, step, and redox economy. For example, one must adjust the redox profile of unreactive species (e.g., boronic acids, silanes, or aldehydes) into their active forms, adding mass and molecular complexity that is ultimately lost upon coupling. In principle, direct functionalization of a $C(sp^3)$–H bond would provide optimal atom economy while reducing step and redox inefficiency en route to $C(sp^3)$–$C(sp^2)$ coupling products.[41] Efforts toward general approaches to Ni-catalyzed $C(sp^3)$–H arylation in the literature are limited by extreme conditions (greater than 100 °C), peroxide reagents/oxidants that often lead to unwanted byproducts, and the need for directing groups.[42] Given that photoredox catalysis is a powerful tool for accessing reactive intermediates demonstrated by numerous synthetic groups,[43] we sought to apply photoredox/Ni dual catalysis to the difficult challenge of effecting $C(sp^3)$–H arylation at room temperature.[44]

In the context of photoredox catalysis, $C(sp^3)$–H functionalization has been achieved through oxidation of *N,N*-dialkylanilines[4,45] because the formation of a nitrogen-centered radical cation significantly weakens the adjacent $C(sp^3)$–H bond. Our group envisioned targeting *redox-inactive* $C(sp^3)$–H bonds, from which we hoped to form alkyl radicals that could participate in dual catalytic systems. For a C–H bond to replace a stoichiometric, redox-active radical precursor within the established mechanism, an additive would need to serve two roles: (1) act as a single-electron reductant of the excited-state photocatalyst and (2) generate an alkyl radical. To accomplish this, we sought a mediator that could serve as an electron donor as well as facilitate radical generation via H atom transfer from $C(sp^3)$–H bonds. Although our group focused on diaryl ketones to facilitate direct arylation of $C(sp^3)$–H bonds, the MacMillan group identified quinuclidine derivatives as highly efficient additives for a related transformation.[46]

On the basis of the well-established reactivity of excited state diaryl ketone diradicals, which form ketyl radicals upon hydrogen atom abstraction (HAT) from both activated and unactivated $C(sp^3)$–H bonds,[47] we envisioned a tricatalytic mechanism for net C–H arylation (Scheme 20). Early studies employing THF as H atom donor and solvent with one

Scheme 20. Tricatalytic Mechanistic Proposal



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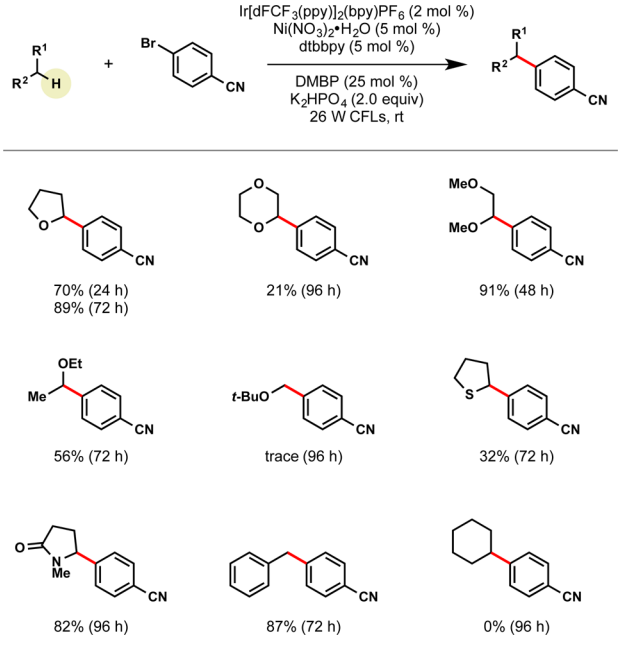
equivalent of benzophenone under standard coupling conditions afforded the desired product, albeit in moderate conversion. Addition of Brønsted bases significantly improved conversion, presumably by quenching the HBr byproduct. Additional optimization provided adequate conditions and represented an unprecedented example of directing group-free, Ni-catalyzed C(sp^3)–H arylation at room temperature. Control studies confirmed the necessity for nickel catalyst, photocatalyst, and light, but we were surprised to discover significant conversion to the desired product *without the diaryl ketone HAT mediator*. The ability of iridium and nickel to cocatalyze C(sp^3)–H arylation was concurrently discovered by Doyle, who developed conditions to couple aryl chlorides using higher loadings of a Ni(0) source and a stronger phosphate base.[48]

Although control studies demonstrated our initial mechanistic hypothesis was not responsible for the observed reactivity, we opted to examine the reaction scope, hoping that the limitations therein would provide insight into the nature of the bond-activating species. Unfortunately, the alkylation scope with respect to C(sp^3)–H substrates was narrow, requiring activated partners to be used as solvent. Ethereal solvents, such as THF, 1,4-dioxane, DME, and Et_2O, were effective (Scheme 21). Arylation of C(sp^3)–H bonds

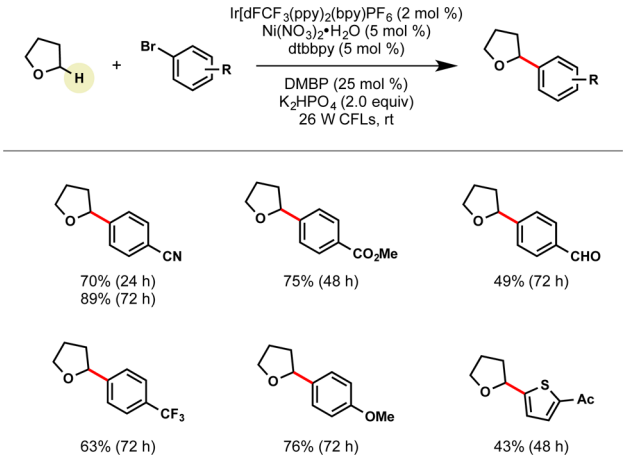
Scheme 21. C(sp^3)–H Partner Scope



adjacent to nitrogen- and sulfur-based heterocycles was also observed, with *N*-methylpyrrolidinone and tetrahydrothiophene undergoing α-arylation. Furthermore, toluene was effectively coupled at the benzylic position. Although the scope of the reaction with respect to the C(sp^3)–H is unquestionably specific, it is also surprisingly effective given the stringent requirements for the substrate-solvent to (1) donate an activated C(sp^3)–H, (2) effectively solvate the reaction mixture, and (3) be sufficiently volatile for removal upon completion. Similar limitations were observed by Doyle, though they reported three examples of direct C(sp^3)–H coupling with 10 equiv of H atom donor in benzene, including an appreciable reactivity of cyclohexane's unactivated C(sp^3)–H bonds.

Subsequently, THF was coupled with a variety of aryl bromides under the established conditions. Both electron-deficient and electron-rich (hetero)aryl bromides were coupled successfully (Scheme 22). Although bromides bearing homo-

Scheme 22. Aryl Bromide Scope in Ni/Ir Cross-Coupling



lytically weak C–H bonds were well-tolerated, protic functional groups were detrimental. Notably, in the presence of difunctionalized bromo- and chloroarenes, the conditions developed provided exclusive alkylation of the bromide. Although the scope is limited, this transformation represents an undirected, room-temperature coupling of C(sp^3)–H and aryl bromides, underlining the advantages of photoredox/Ni dual catalysis.

Approaching reaction development with an incomplete or inaccurate mechanistic understanding greatly biases the steps that can be taken to improve upon underlying limitations. Thus, mechanistic studies were necessary to develop a better understanding of the unexpected reactivity in the absence of a diaryl ketone. A representative transformation was thus carried out in a 1:1 mixture of THF:d_8-THF, and this reaction displayed a kinetic isotope effect of 6:1, which is indicative of a thermodynamically neutral H atom transfer[49] rather than formal C–H activation by a metal center. As a result of the observed KIE and the need for activated C(sp^3)–H bonds, we suspected a bromine radical, which is capable of activating weak C(sp^3)–H bonds, was generated under the photocatalytic conditions (Scheme 23).

We first speculated that the Ni(II) oxidative addition intermediate could be oxidized to a Ni(III) state by the iridium photocatalyst. The C(sp^3)–H activation steps would occur via (1) homolysis of the Ni(III)–Br bond to generate a bromine radical, (2) H atom transfer by the resulting bromine radical, and (3) alkyl radical addition to Ni(II). To provide support for this hypothesis, a series of photocatalysts were compared with higher oxidation potentials than the iridium photocatalyst. We first confirmed that **1** led to product and that no product formed under visible light excitation in the absence of photocatalyst. Next, to our surprise, no product was observed using the highly oxidizing ruthenium and acridinium photocatalyst **3** and **5**, respectively. This suggests that simple oxidation of the Ni(II) complex by a photocatalyst may not be sufficient to explain the observed C(sp^3)–H arylation.

An alternative explanation is a triplet–triplet energy transfer facilitated by photocatalyst **1**, which has a higher triplet energy than **3** and **5** based on a comparison of their emission

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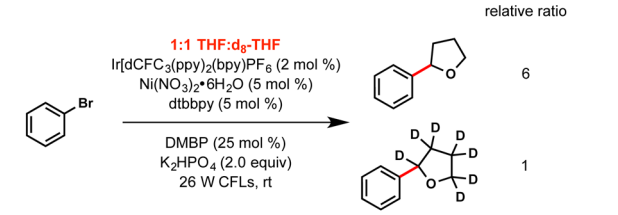
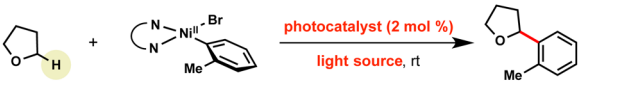
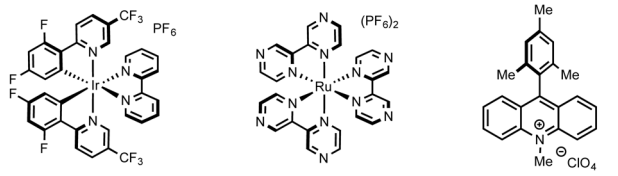
Scheme 23. KIE and Energy-Transfer Experiments





entry	photocatalyst	E_{M^*/M^-} (V)	Em λ (nm)	light source	result
1	**1**	1.21	470	26 W CFL	product formed
2	**3**	1.45	591	26 W CFL	n.r.
3	**5**	2.05	590	26 W CFL	n.r
4	none	n/a	n/a	26 W CFL	n.r.
5	none	n/a	n/a	UV light	product formed



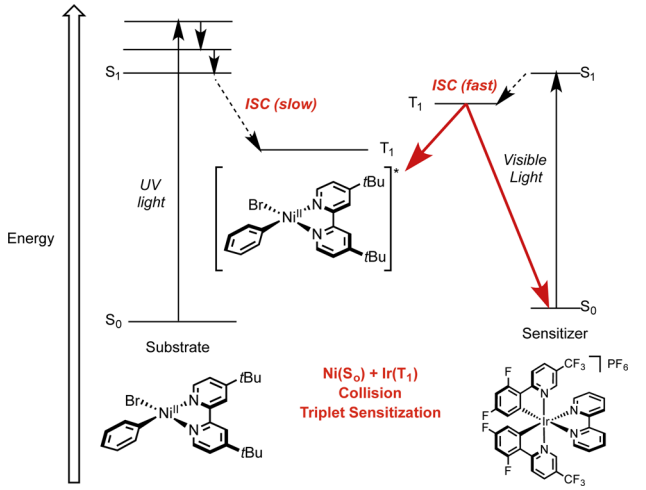
1 **3** **5**

wavelengths (Scheme 23). To test this new hypothesis, the Ni(II) complex was subjected to UV−B irradiation with emission wavelengths between 290−315 nm. Indeed, as shown in entry 5, product was observed. These results suggest that a Ni(II) excited state, which forms in the absence of an oxidant, is sufficient to facilitate the observed C(sp^3)−H arylation. As a result, a mechanism based upon energy transfer was favored.

We proposed that irradiation with UV light could promote Ni to a high-energy state that relaxes and undergoes intersystem crossing to a Ni(II) triplet that eliminates a halide radical.[50] Alternatively, the same Ni(II) excited state could be reached through a photocatalytic process: (1) photocatalyst excitation by visible light, (2) efficient intersystem crossing by the photocatalyst, and (3) triplet−triplet energy sensitization of the Ni(II) oxidative addition intermediate by a sufficiently high-energy photocatalyst triplet state (Scheme 24). Importantly, in the energy transfer scenario, the operative Ni excited state would be inaccessible in the presence of photocatalysts with insufficiently energetic triplet states (such as those exhibited by photocatalysts **3** and **5**) or by irradiation with inadequately energetic wavelengths of light (i.e., visible light). Preliminary computational work shows that the formation of a formal Ni(II) triplet state would elongate the Ni−Br bond and also result in transfer of electron density from the Ni center to the ligand, resulting in an excited-state species that may exhibit some similarities to the formal Ni(III) intermediates that are commonly invoked in photoredox/Ni cross-coupling.

Although we favor a mechanism based on energy transfer, we are admittedly unable to rule out the electron transfer-based mechanism favored in concurrently published work by Doyle et al.[51] It should be noted that the Doyle group has shown that Ni(II) oxidative addition complexes have redox potentials within **1a**'s oxidation window and also display Stern−Volmer quenching of the iridium photocatalyst. However, Stern−Volmer quenching is insufficient to distinguish between energy-

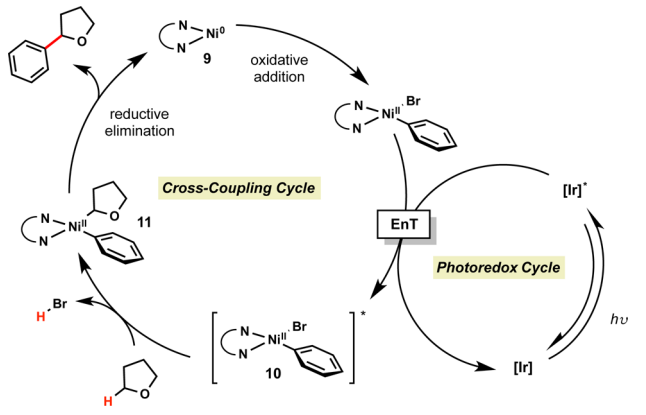
Scheme 24. Jablonski Diagram of High-Energy Nickel Complex



and electron-transfer processes. Transient absorption spectroscopic studies may be able to address this question[51] and provide a stronger basis for further development. Importantly, the mechanistic difference may strongly bias efforts in catalyst development to improve the efficiency of these reactions. The prevailing focus of photocatalyst development on redox potentials (SET) reflects the more typical mode of activation in organic synthesis, but optimizing for less commonly invoked energy transfer processes is largely underdeveloped.[43] Recently, Weaver et al. studied the important relationship between catalyst structure and cis/trans isomerization of alkenes via energy transfer,[52] but energy transfer between metals is particularly challenging given the lack of systems thought to operate by this mechanism and the difficulty in studying catalytic intermediates that may be transient in nature.[53]

The proposed mechanism is thus depicted in Scheme 25. Ni(0) **9** undergoes oxidative addition with the aryl bromide

Scheme 25. Current Mechanistic Proposal



followed by energy transfer (EnT) to form an excited Ni(II) complex **10**. We surmise that complex **10** can facilitate C−H abstraction from THF to form intermediate **11**, which can then undergo reductive elimination to form the corresponding product. It should be noted that the transformation from **10** to **11** is currently under investigation using computational methods. Currently, the KIE studies suggest the formation of bromine radical followed by a HAT process to form the alkyl

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radical. Alternatively, there is the possibility of a concerted step involving a four-membered transition state structure that is also consistent with experimental data.

Although functionalizing C(sp^3)−H bonds has historically been a challenging transformation, these preliminary results may provide a platform for further studies involving less-reactive C−H bonds. Toward this end, the ability to channel visible light energy selectively into synthetically useful C(sp^3)−H activation reactions through elementary radical H atom transfer steps has already enabled a recent, rapid growth in methods for functionalization of unactivated C−H bonds at room temperature.[54]

PHOTOREDOX PROCESSES

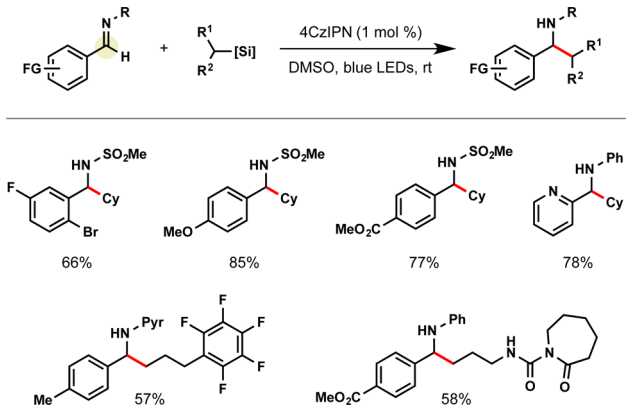
Seeing the value of *catalytic* radical generation in various cross-coupling reactions, we next sought to apply the same principle to other transformations wherein the stoichiometric generation of radicals provided suboptimal outcomes. Protocols developed within these previous paradigms typically resulted in the use of huge excesses of radical precursors and radical-generating reagents, which we were able to avoid using photoredox-generated radicals.

Formation of Secondary Amines. The expansion of the chemical toolbox to include mild, bench-stable radical precursors as alkylating reagents under photoredox conditions was considered an attractive alternative to organometallics utilized in other C−C bond-forming reactions. The reaction of Grignard and organolithium reagents with C═O and C═N electrophiles has extensive value, but the instability and functional group intolerance of these highly reactive organometallics has always framed their use.[55] To address this issue, we imagined that nucleophilic alkyl radicals generated via photoredox catalysis could serve as mild alkylating agents to facilitate Grignard-type additions to electrophilic imines.[56] Previously reported radical-based approaches in which the radicals were generated *stoichiometrically* relied on conditions that were far from ideal [e.g., large excesses of flammable Et_3B/O_2 initiators, radical precursors (typically alkyl iodides), and reductants such as tin reagents or Zn], owing to the byproducts formed upon generation of the radicals.

Further, although the addition of α-heteroatom-stabilized radicals to imines has been reported, we recognized that silicate radical precursors would provide access to a broader range of alkyl radicals. A variety of nitrogen-substituted imines were transformed into the corresponding α-aryl-α-alkyl secondary amines utilizing alkyl radicals generated from bis(catecholato)-silicates. The transformation occurred readily under mild, redox neutral conditions without additives. The relatively low oxidation potentials of the silicate radical precursors facilitated the use of the organic photocatalyst 4CzIPN instead of Ru or Ir species, rendering the entire process metal-free. A variety of primary and secondary alkyl radicals bearing synthetically useful functional groups were readily intercepted by electronically varied α-(hetero)aryl imines under the optimized reaction conditions (Scheme 26).

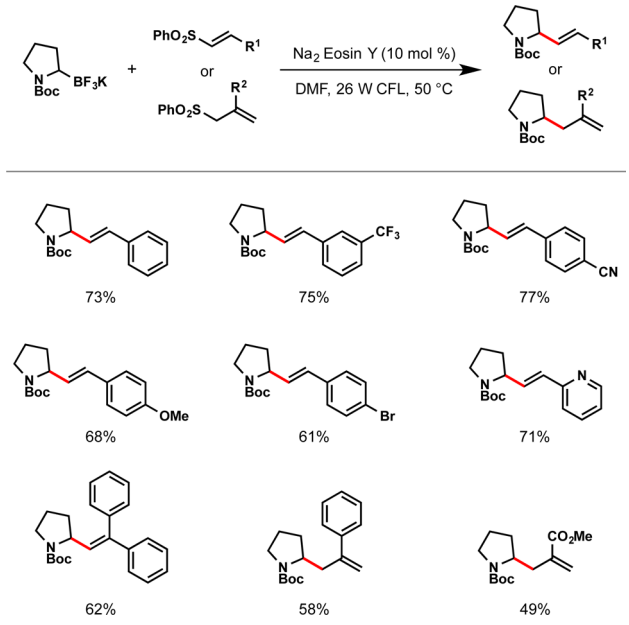
Allylation, Alkenylation, and Cyanation. We also explored the incorporation of readily available organophotocatalysts in allylation and alkenylation reactions.[57] Alkenyl sulfones were employed as electrophilic reagents to effect the transition metal-free alkenylation and allylation of Boc-protected potassium α-aminomethyltrifluoroborates. The inexpensive sodium salt of the organic photocatalyst Eosin Y (E_{red} = +0.83 V vs SCE) was found to be a suitable oxidant for

Scheme 26. Alkylation of Diverse Imines



potassium α-pyrrolidinyltrifluoroborate (E_{red} = +0.78 V vs SCE) under the reaction conditions developed. Conversely, the related cesium carboxylate (E_{red} = +0.95 V vs SCE) required the use of an iridium photocatalyst. Exploring the scope of the alkenyl sulfones revealed that stabilization of the radical intermediates following radical addition was required. Various electron-neutral, electron-withdrawing, and electron-donating substituents on the aryl ring were well-tolerated under the reaction conditions (Scheme 27). Protected homoallylic amines bearing styrene and acrylate groups were also generated from the corresponding allylic sulfones, although lower yields were observed.

Scheme 27. Alkenylation and Allylation of Pyrrolidinyltrifluoroborate



A wide range of primary and secondary alkyltrifluoroborates was also incorporated into an organic photocatalyst-mediated deboronative cyanation reaction using the highly oxidizing $MesAcr^+$ photocatalyst and tosyl cyanide (TsCN) as a radical trap (Scheme 28). Classically, alkyl nitriles are synthesized via S_N2 displacement of halides with nucleophilic cyanide sources.[58] As a result, the formation of primary nitriles is favored over secondary and tertiary analogues. On the basis of the coupling of alkyltrifluoroborates with alkenyl and allylic

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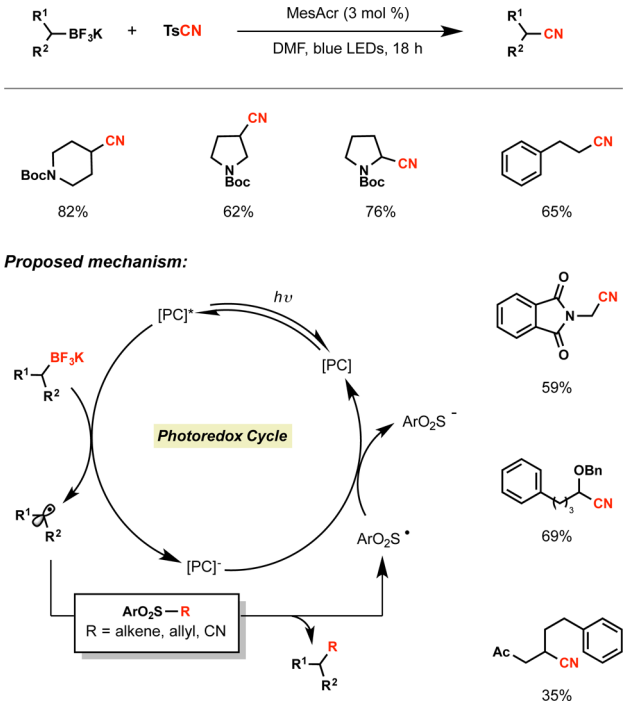
Scheme 28. Mild Cyanation of Alkyltrifluoroborates



sulfones, we sought to capture alkyl radicals (generated from photoinduced oxidation of alkyltrifluoroborates) with TsCN. By proceeding through radical intermediates, we anticipated that regiospecific cyanation should occur with mechanistic preference for less electrophilic carbon centers. The optimized reaction conditions provided access to primary and secondary as well as α-alkoxy-, γ-, β-, and α-amino alkyl nitriles under extremely mild reaction conditions. Notably, cyanation of an α-alkoxy alkyltrifluoroborate afforded a protected cyanohydrin, which can be difficult to synthesize by other methods given the reversibility of cyanohydrin formation.[59] A plausible mechanism is presented in Scheme 28. A visible-light-excited organic catalyst oxidizes the potassium alkyltrifluoroborate via a single-electron oxidation to provide an alkyl radical. The resulting radical then forms a new C−C bond in the presence of a suitable sulfonyl coupling partner while expelling a sulfonyl radical. The resultant sulfonyl radical is then reduced by one electron to close the catalytic cycle.[60]

CONCLUSIONS AND FUTURE OUTLOOK

Since establishing photoredox/Ni dual catalysis in 2014, our group has successfully modified both radical precursors and electrophiles in further efforts to expand access to underexplored chemical space. Beyond aryl bromides, our group has demonstrated triflates, tosyl cyanide, imines, acid chlorides, and sulfones as feasible "electrophilic" partners in both dual catalytic and metal-free manifolds. Additionally, since the initial demonstration of silicates as complementary radical precursors, a wider range of functionally rich alkyl radicals have been successfully cross-coupled. Although alkyltrifluoroborates and -silicates are fantastic reagents, step and atom economy is poor. Furthermore, the photoredox/Ni dual catalytic mechanism has led to a redefinition of alkyl coupling partners from traditional organometallic *nucleophiles* to redox-active *radical precursors*. Therefore, our group has searched for routes to access radical precursors from readily available functional groups. As demonstrated with DHPs (derived from aldehydes), feedstock functional groups hold great potential as latent radicals with wide commercial availability. Although DHPs are often more easily accessed than alkyltrifluoroborates and -silicates, there is room for improvement in atom economy. In related work, we uncovered an energy-transfer pathway targeting activated C(sp^3)−H bonds, which may inspire further related reaction design.

Finally, these studies bear witness to the value of generating highly reactive radical intermediates catalytically, in a tightly orchestrated, controlled manner to avoid deleterious side-reactions and lead to processes that are more efficacious and sustainable than those in which the radicals are created en mass by stoichiometric protocols.

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Notes

The authors declare no competing financial interest.

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