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Activation Strategies for Alkyl Precursors in Achieving $C(sp^3)-C(sp^3)$ Cross-Coupling via Metallaphotoredox Catalysis

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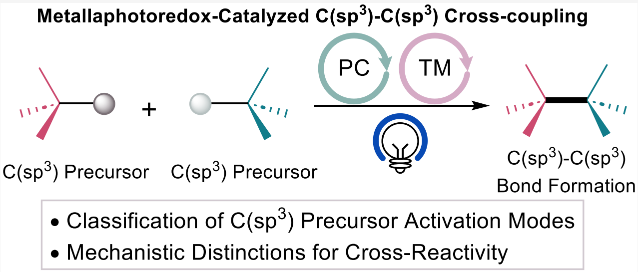
ABSTRACT: $C(sp^3)-C(sp^3)$ bond formation is gaining more prominence, especially with a growing emphasis on building three-dimensional chemical space in bioactive molecules, fine chemicals, and agrichemicals. Metallaphotoredox catalysis has emerged as an effective strategy for designing processes using diverse $C(sp^3)$ precursors well suited for $1e^-$ radical chemistry. This review summarizes the latest advancement in metallaphotoredox catalysis, addressing the long-standing challenges in $C(sp^3)-C(sp^3)$ cross-coupling, with a focus on the classification of reactions based on the distinct modes of activation of $C(sp^3)$ precursor upon entering the catalytic cycle.



1. INTRODUCTION

Carbon−carbon bond formation constitutes a foundational process within organic chemistry, enabling access to structurally complex molecules from simple starting materials. In this context, the impact of transition-metal-catalyzed cross-coupling reactions, particularly with that of Pd catalysis, has propelled advancements in synthetic methodologies applied in natural product synthesis, medicinal chemistry, fine chemicals, agrichemicals, and functional materials.[1−4] Representative C−C bond-forming catalysis methods such as Negishi reaction,[5] Suzuki−Miyaura reaction,[6,7] and Stille reaction[8] share a common mode of reactivity, where cross-reactivity of two carbons arises from a carbon electrophile and an organometallic reagent. Historically, these reactions have evolved around the cross-coupling of $C(sp^2)$-hybridized carbon atoms, where the cross-reactivity relies on $2e^-$ pathways via an oxidative addition with an electrophile and a transmetalation with an organometallic reagent and a subsequent reductive elimination to afford the C−C bond (Figure 1A).

Recently, the significance of the $C(sp^3)-C(sp^3)$ motif has been becoming increasingly recognized, especially for constructing medicinally relevant molecules.[9,10] Nonetheless, the incorporation of $C(sp^3)$ into cross-coupling processes presents a formidable challenge, primarily due to the inherent impediments of slow oxidative addition and reductive elimination or side reactions associated with β-hydride elimination in comparison to their $C(sp^2)$ counterparts.[11] Therefore, the realization of $C(sp^3)-C(sp^3)$ cross-coupling when adhering to the classical electrophilic and organometallic coupling partner paradigm can be challenging.

In contrast to these heterolytic $2e^-$ processes, metallaphotoredox catalysis typically employs a $1e^-$ process to introduce the alkyl precursor into the catalytic cycle. Upon irradiation of light, the photocatalyst can absorb a photon and transition into an excited state that can, in turn, facilitate a single electron oxidation, a reduction, or an energy transfer process to an organic molecule, resulting in the formation of a $C(sp^3)$ radical. Such reactivity can be merged with a transition metal that can undergo cross-coupling (Figure 1B). With this potential, a diverse array of methodologies for instigating the formation of carbon-centered radicals has emerged in recent years.

A notable difference in employing respective coupling partners for metallaphotoredox lies in the challenge of categorizing them as conventional "electrophiles" or "nucleophiles". Instead, their classification can be determined by the method of radical generation and integration into the transition-metal catalytic cycle. Consequently, a comprehensive understanding of the diverse modes of activation becomes paramount for designing novel reactions with elaborate mechanistic design.

This review aims to summarize the burgeoning field of metallaphotocatalyzed $C(sp^3)-C(sp^3)$ cross-coupling. This review commences with categorizing the $C(sp^3)$ precursors that have been employed in photocatalyzed $C(sp^3)-C(sp^3)$ cross-coupling, delineating whether they are activated via

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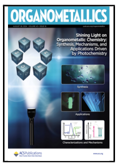

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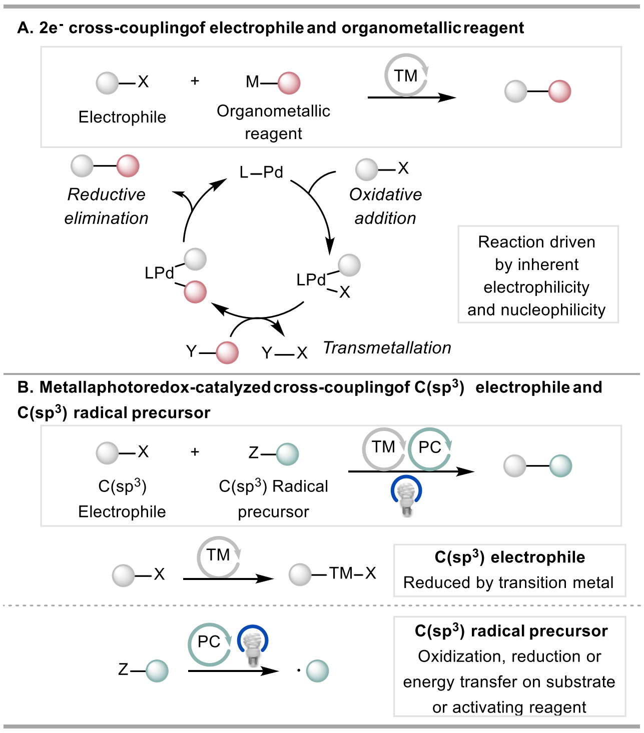


Figure 1. Transition-metal catalyzed cross-coupling to enable carbon−carbon bond formation. (A) Two-electron cross-coupling of electrophile and organometallic reagent. (B) Metallaphotoredox-catalyzed cross-coupling of $C(sp^3)$ electrophile and $C(sp^3)$ radical precursor.

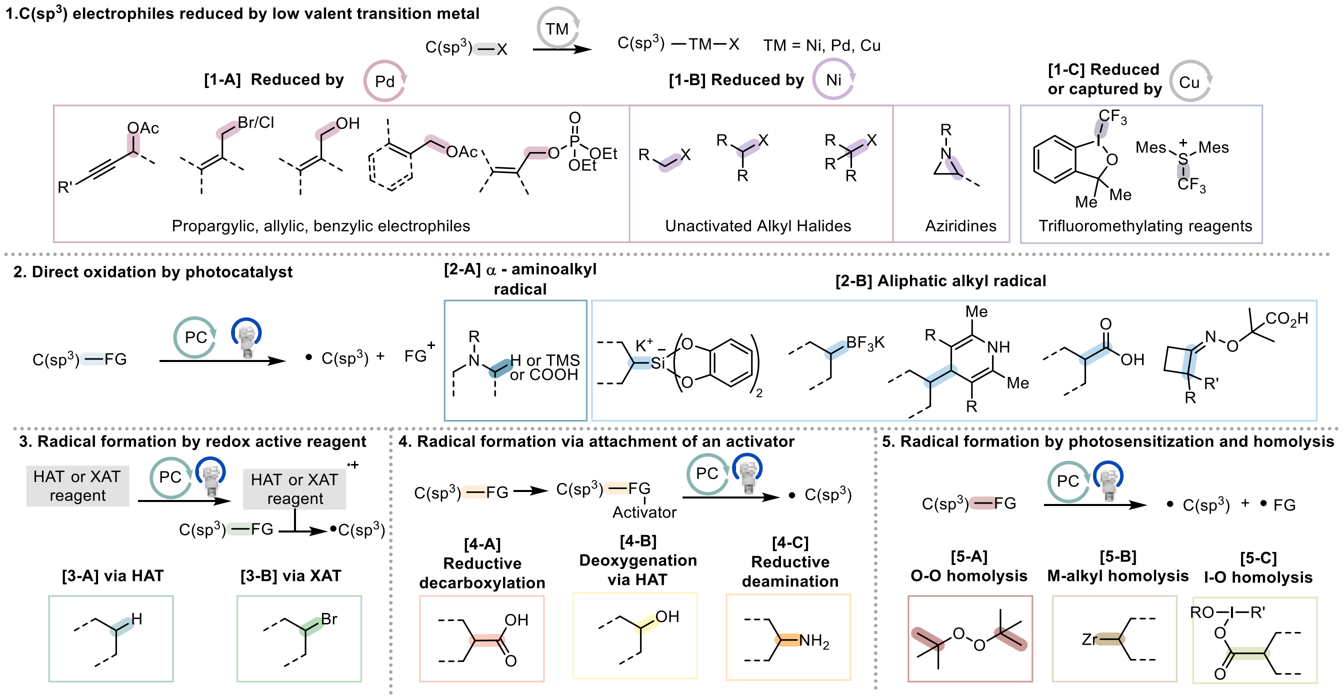
reduction of the transition metal (Table 1, 1), possess functional groups directly amenable to oxidation by an excited photocatalyst (Table 1, 2), generate a radical via a hydrogen atom transfer (HAT) or a halogen atom transfer (XAT) reagent (Table 1, 3), necessitate an attachment of an activating reagent prior to radical formation (Table 1, 4), or undergo photosensitization and subsequent homolytic cleavage (Table 1, 5). Each scheme will address the classification of each coupling partner based on these criteria. The narrative of different publications will be based on how these diverse combinations have resulted in mechanistic distinctions.

Topics on photocatalyzed $C(sp^3)-C(sp^3)$ bond formation resulting from the addition of radicals to π bonds or the leveraging of persistent radical effects are not covered in this review. For these subjects, we recommend referring to previous literature,[12,13] as the aim of this review is to focus on the metallaphotoredox dual catalysis enabling cross-coupling of two different $C(sp^3)$ precursors and highlight the underlying principle behind cross-selectivity.

2. ACTIVATION MODES FOR C(SP^3) PRECURSORS USED IN METALLAPHOTOREDOX C(SP^3)−C(SP^3) CROSS-COUPLING

The first class of $C(sp^3)$ coupling partners is the (pseudo)halide electrophiles that undergo reduction by the transition metal that enables the cross-coupling process (Table 1, 1). Within this class, further subdivision is possible based on the type of transition metal responsible for the reduction. Pd catalysts have been shown to reduce primarily activated alkyl species such as propargylic, allylic, or benzylic (pseudo)halides, encompassing diverse leaving groups including acetates, halides, and phosphates (Table 1, [1-A]). As for unactivated alkyl halides, relatively fewer examples have been reported to undergo oxidative addition with Pd, presumably due to the unstable nature of alkyl−Pd bonds (vide infra). Such challenge of employing Pd catalysts has prompted the recognition of Ni catalyst as the more optimal catalyst, owing to their enhanced electropositivity and reduced propensity to undergo β-H elimination (Table 1, [1-B]).[11] Furthermore, reduction with Ni has also been extended to unconventional $C(sp^3)$ electro-

Table 1. Activation Modes of C(sp^3) Precursors Employed in Metallaphotoredox-Catalyzed Cross-Coupling



philes such as aziridines as a precursor to accessing a β-functionalized amine. The third category of C(sp^3) precursors of trifluoromethyl groups has shown excellent compatibility with the reducing capability of Cu, which has been documented to be of challenge for both Pd and Ni catalysis (Table 1, [1-C]).[14]

The second class of C(sp^3) precursors possesses functional groups that can undergo single electron oxidation within the potential window of excited-state photocatalysts to generate an alkyl radical. C(sp^3) precursors of this class include α−C-H, silyl, or carboxylic amines, providing a route to α-amino carbon-centered radicals. As for the generation of unactivated alkyl radicals, silicates, potassium trifluoroborates, dihydropyridine, or carboxylic acids can be used, albeit necessitating a photocatalyst with a higher oxidation potential (Table 1, 2).

The third class of C(sp^3) precursor lacks functional groups directly activatable by the excited-state photocatalyst. Rather, they rely on a reagent capable of generating an open-shell species with the photocatalyst that can, in turn, trigger the formation of a C(sp^3) radical, either via a hydrogen atom transfer (HAT) or halogen atom transfer (XAT). For HAT, C−H bonds with high bond dissociation energies (BDE) including aliphatic or benzylic alkyl C−H bond, α-amide, and α-oxy C−H bonds serve as suitable substrates (Table 1, [3-A]). The HAT reagent is activated via an oxidation or energy transfer process, examples including chlorine or bromine radicals, DBU, or *N*-centered amidyl radicals. Alkyl bromides, on the other hand, can undergo homolytic cleavage of C−X bonds by employing XAT reagents such as a supersilanol that readily undergoes oxidation with photoredox catalyst to form a silyl radical. (Table 1, [3-B]).[15]

The fourth class of C(sp^3) precursors possesses functional groups capable of generating radicals upon attaching a photoactivatable group. For example, while carboxylic acids can be directly oxidized with the assistance of a base, as in the second mode of activation (Table 1, [2]), they can also be disguised as a *N*-hydroxyphthalimide (NHPI) esters using *N*-hydroxyphthalimide as an activator. Upon SET, NHPI esters undergo reduction at the O−N bond, leading to a subsequent decarboxylation event that produces an alkyl radical (Table 1, [4-A]). Deoxygenative approaches of alcohols require the addition of activators such as an aldehyde or NHC reagents to induce activated forms of alcohol. These activated forms can undergo a facile β-scission upon HAT or SET, resulting in the generation of an alkyl radical (Table 1, [4-B]). Amines can be condensed into pyridinium salts, also known as Katrizky salt, to obtain suitably low potentials to generate an equivalent of alkyl radical and pyridine upon reduction (Table 1, [4-C]).

The last class of C(sp^3) precursors is not redox active but can be photosensitized to undergo homolysis or undergo subsequent β-scission, resulting in the formation of a carbon-centered radical. Examples within this category include peroxides (Table 1, [5-A]), alkyl zirconium (Table 1, [5-B]), or iodoacetates (Table 1, [5-C]), which can initiate homolysis at the weakest sites, setting off a cascade of C−C bond-forming catalysis.

This classification framework sets the stage for an exploration of various publications, delineating the specific type of C(sp^3) precursor associated with each coupling. Such analysis hopefully provides insights into the mode of catalysis design and the efficiency of the cross-coupling reactivity.

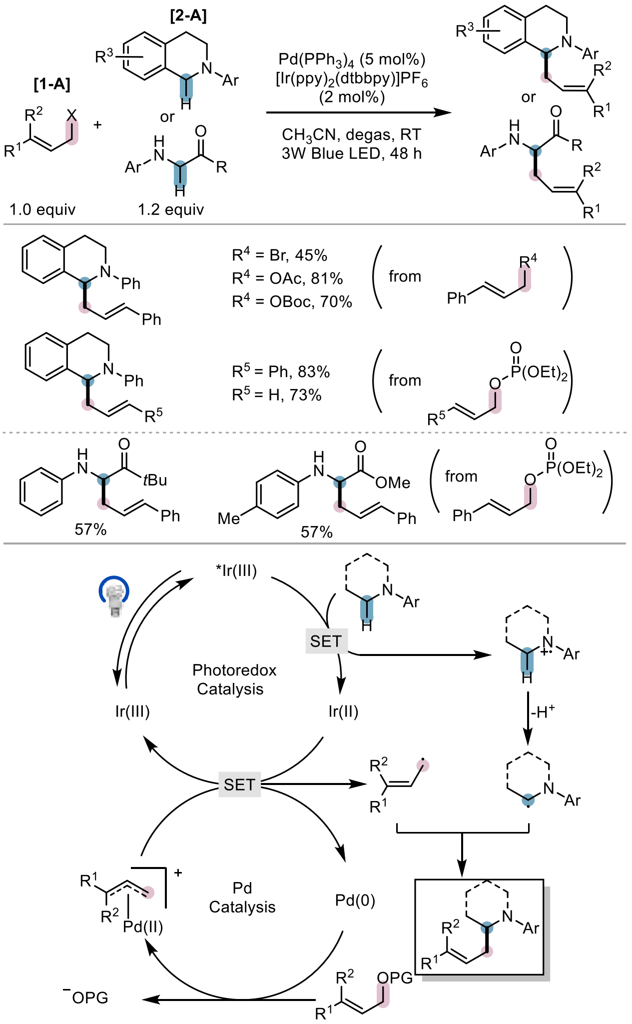
3. CROSS-COUPLING OF DIRECTLY PHOTOOXIDIZED C(SP^3) PRECURSORS

3.1. Cross-Coupling between Photooxidized α-Amino Carbon and Electrophiles Reduced by Transition Metals.

Amines can undergo a single electron oxidation by a visible-light-induced photocatalyst and access an α-amino C(sp^3) carbon-centered radical as a reactive intermediate.[16] A seminal publication by Macmillan and Doyle demonstrated that the photochemically generated α-amino carbon radical can be intercepted with a Ni catalyst, enabling cross-reactivity to afford a C(sp^3)−C(sp^2) bond.[17] This work paved the way in the incorporation of an α-amino carbon to engage in numerous C(sp^3)−C(sp^3) carbon coupling methodologies.

Among the pioneering instances is the work of the α-allylation of amines, reported by Xiao and Alper.[18] In this work, the authors employed a dual-catalytic system involving Pd(PPh_3)$_4$ and [Ir(ppy)$_2$(dtbbpy)]PF$_6$ to enable cross-coupling between allyl electrophiles and amines as an alkyl radical precursor (Scheme 1A). Prior to these findings, π-allyl Pd(II) complexes had been reported to generate allyl radicals by single electron reductions using chemical reductants, such as Cp_2TiCl_2.[19,20] However, the authors harnessed visible light and an Ir photocatalyst to enable the single electron reduction instead.

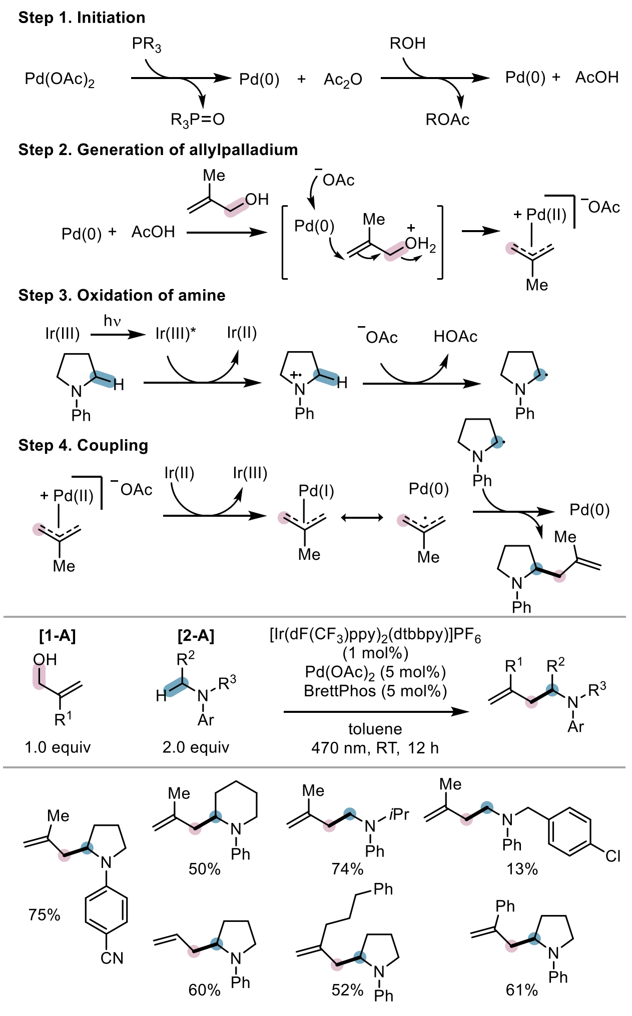
Scheme 1. Allylation of α-Amino C−H Using Pd/Photoredox Catalysis



A wide spectrum of allyl electrophiles, such as allyl halides, allyl phosphates, and allyl alcohols with protecting groups, exhibited successful reactivity for this transformation. The amine moiety, including tetrahydroisoquinolines or anilines, served as a successful substrate, although this reaction was not feasible for 2° benzylic amines and α-amino ketones. As for the mechanistic elucidations, the authors proposed that the visible-light-excited *Ir(III) can oxidize the amine to generate an α-amino alkyl radical and Ir(II). The resulting Ir(II) can, in turn, reduce the allyl Pd(II) complex generated in situ with an allyl electrophile to afford the allyl radical. The authors postulated that the α-amino radical, owing to its stability and bulkiness, precludes homocoupled products[21] and can selectively react with the allyl radical, which is relatively reactive.

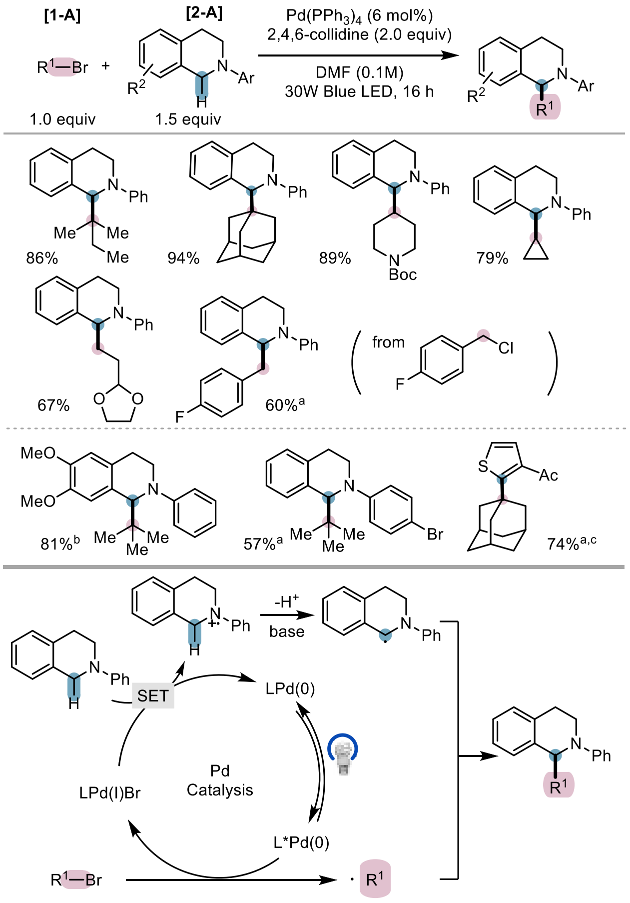
Recently, Murakami et al. contributed to expanding the scope of allyl species amenable to the α-allylation of amines. Their approach involved employing allylic alcohols to enable a dehydrogenative strategy, an atom-economic transformation compared to their protected analogs (Scheme 2).[22] The choice of using $Pd(OAc)_2$ as a precatalyst was found to be critical. After $Pd(OAc)_2$ generates Pd(0) and Ac_2O in situ from Pd(II) with a phosphine ligand, the anhydride engages in a reaction with the allylic alcohol to afford acetic acid. The acetic acid assists in the protonation of the allylic alcohol, thereby contributing to the generation of the Pd(II) allyl species. The resulting Pd(II) allyl complex is then reduced by Ir(II) photocatalyst originating from the photooxidized amine as the other coupling partner. This methodology enabled cross-coupling of 1° aniline and 2° pyrrolidine rings.

Scheme 2. Dehydrative Allylation of α-Amino C−H Using Pd/Photoredox Catalysis from Allylic Alcohols



Subsequently, Yu and co-workers extended the cross-coupling of α-amino C−H bonds, progressing from allyl (pseudo)halides to incorporating unactivated alkyl bromides (Scheme 3).[23] This methodology is noteworthy in that it enables cross-coupling between 1°, 2°, and 3° alkyl bromides and *N*-phenyl tetraisoquinolines to form the challenging $C(sp^3)-C(sp^3)$ bond. Interestingly, the reaction is carried out in the absence of a photocatalyst. Instead, the authors propose that $Pd(PPh_3)_4$ can be directly excited by visible light, which can facilitate bromide abstraction and yield a Pd(I)Br species. This oxidized Pd(I)Br species, in turn, can enable an efficient single electron oxidation of the amine to generate an α-amino carbon radical. This α-amino carbon radical can recombine with the alkyl radical stemming from the alkyl bromide to afford the $C(sp^3)-C(sp^3)$ bond. To substantiate this proposed mechanism, the authors conducted photophysical mechanistic experiments, such as fluorescence quenching experiments and Stern−Volmer studies, revealing that the alkyl bromide effectively quenches the excited-state $Pd(PPh_3)_4$ to undergo a single electron transfer (SET) process, consistent with the proposed catalytic cycle.

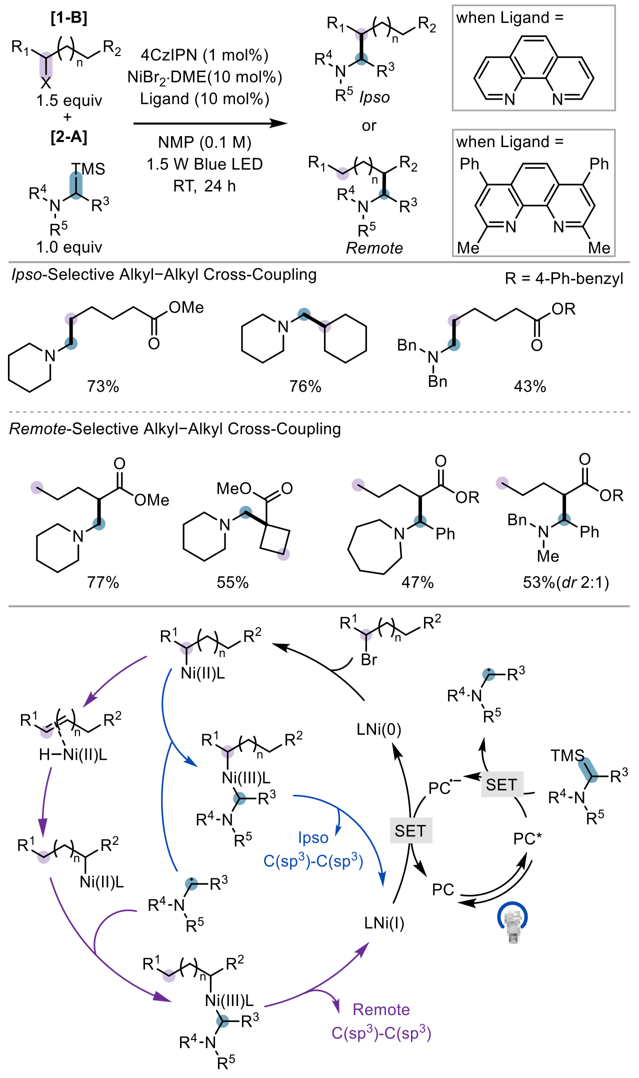
Scheme 3. 1°, 2°, and 3° Alkylation of α-Amino C−H Using Pd Catalysis



[a]Forty-eight hours. [b]Twenty-four hours. [c]Cs_2CO_3 (1.5 equiv) was used instead of 2,4,6-collidine; THF was used instead of DMF.

Recently, a novel Ni/photoredox-catalyzed aminoalkylation was reported (Scheme 4).[24] This methodology employs α-silyl amines which upon undergoing single electron oxidation generate α-amino carbon radicals. These radicals subsequently engage in coupling reactions with unactivated 1° and 2° alkyl bromides, which enter the catalytic cycle by oxidative additions to low-valent Ni catalyst. Interestingly, the regioselectivity of the cross-coupling reactivity was dependent on the specific ligand employed. The parent phenanthroline ligand facilitated a direct cross-coupling with the aliphatic 1° or 2° alkyl group at the carbon site to which the halide was attached (ipso-selective alkyl−alkyl cross-coupling). Conversely, the use of a tetrasubstituted 9,9′-dimethyl 1,10-phenanthroline resulted in a regiodivergent $C(sp^3)-C(sp^3)$ cross-coupling (remote alkyl−alkyl cross-coupling). The remote alkyl−alkyl cross-coupling is proposed to occur via a chain-walking event, leading to a thermodynamically stable position adjacent to the ester group, wherein the product affords the biologically relevant β-amino acid ester.

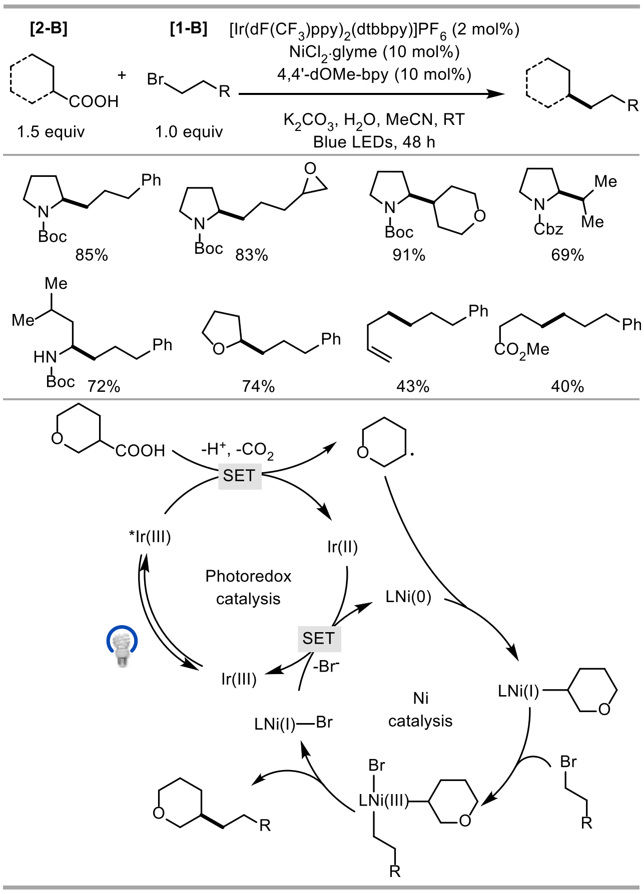
Scheme 4. Regiodivergent Alkylation of α-Silyl Amine Using Alkyl Bromides via Ni/Photoredox Catalysis



3.2. Cross-Coupling between Alkyl Precursors Undergoing SET Oxidation and Electrophiles Reduced by Transition Metals.

The initial $C(sp^3)$ cross-coupling methodologies mentioned in section 3.1 were predominantly reliant on the intrinsic electron richness of the amine for the single electron oxidation to generate the alkyl radical intermediate. However, subsequent evolution in $C(sp^3)$ precursors emerged for $C(sp^3)-C(sp^3)$ cross-coupling featuring functional groups that can generate unactivated aliphatic radicals upon a single electron redox event.

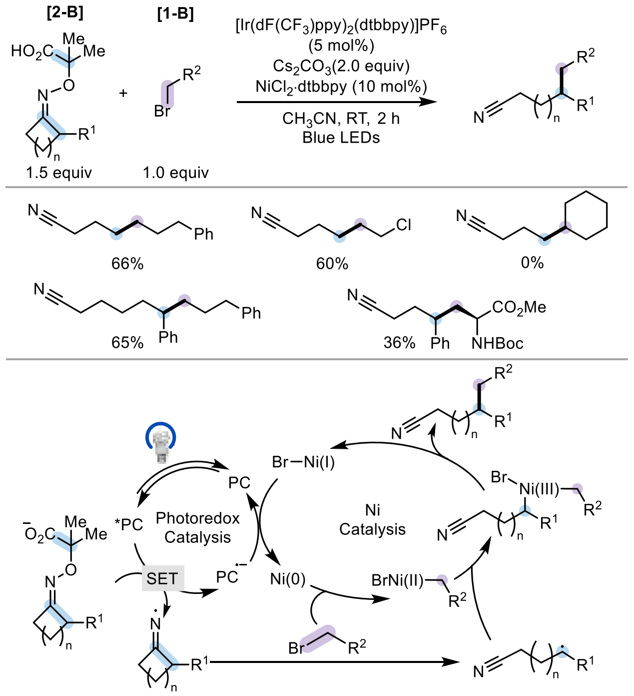
Scheme 5. Ni/Photoredox-Catalyzed Cross-Coupling of Two Unactivated Aliphatic Alkyl Groups from Carboxylic Acids and Alkyl Bromide



In a seminal contribution in 2016, Macmillan and co-workers presented a method for cross-coupling of two unactivated aliphatic alkyl groups, employing carboxylic acid and primary alkyl halides via Ni/photoredox catalysis (Scheme 5).[25] In this reaction, the carboxylic acid undergoes deprotonation, and the resulting acetate undergoes decarboxylative single electron oxidation by the *Ir(III) photocatalyst, $*[Ir(dF(CF_3)\text{-}ppy)_2(dtbbpy)]PF_6$. This process yields a carbon-centered radical, which is proposed to be captured by the low-valent Ni(0) coordinated with a bipyridyl ligand. This interaction generates a Ni(I) alkyl species capable of reducing the second coupling partner, the alkyl bromide, to form Ni(III). The oxidation state of Ni(III) facilitates the formation of the $C(sp^3)-C(sp^3)$ bond through reductive elimination. The resulting Ni(I) is then reduced back to Ni(0), with Ir(II) serving as the reductant, thus completing the catalytic cycle for both catalysts. This pivotal work vastly expanded the type of $C(sp^3)$ that we typically invoke in $C(sp^3)-C(sp^3)$ cross-coupling. It enabled the cross-coupling reactivity between 1°−1°/1°−2°/2°−2° aliphatic alkyl groups using carboxylic acids such as those tethered to *N*-Boc-protected pyrrolidines and amines, α-ethers, and 1° and 2° aliphatic alkyl bromides.

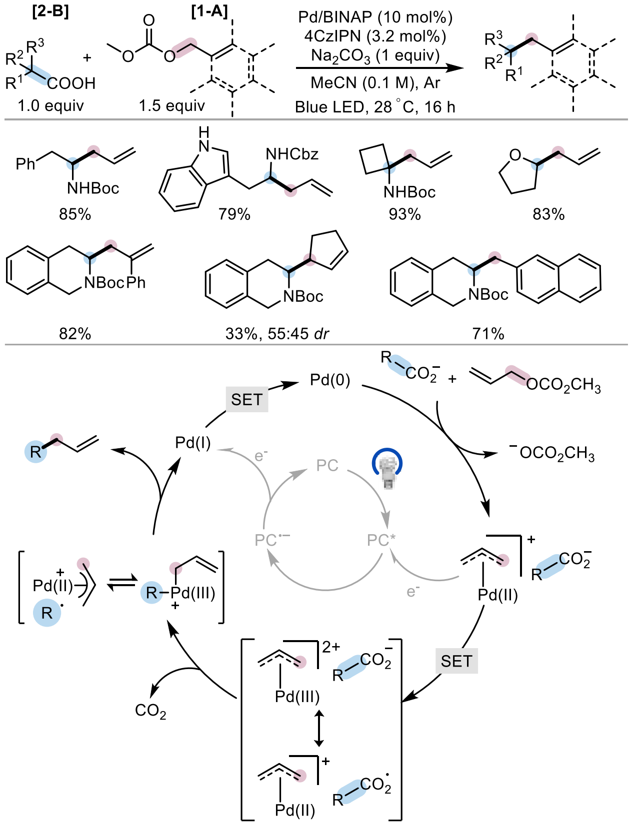
In 2019, Leonori and colleagues introduced another notable example of using decarboxylation to afford alkyl radicals from photoexcited generation of cyclic iminyl radical and a subsequent ring-opening reaction (Scheme 6).[26] In this strategy, a visible-light-excited photocatalyst promotes the SET oxidation of oxime−carboxylate, where the decarboxylation induces formation of the C═O double bond, concomitantly allowing homolytic cleavage between the O−N bond to afford an iminyl radical. This iminyl radical then initiates β-scission, where the driving force for homolytic C−C bond cleavage is the formation of a distal nitrile radical and the release of ring strain. This nitrile radical then can engage in alkylation with 1° aliphatic alkyl bromides When using a four-membered ring, the ring strain proves sufficient to cleave and generate a 2° nitrile radical. Conversely, the unstrained rings necessitate somewhat activated benzylic radicals as a driving force for C−C bond cleavage. While this methodology showcased commendable reactivity with 1° alkyl bromides, its application faced limitations for 2° alkyl bromides.

Scheme 6. Cross-Coupling between 1° Alkyl Bromide and 2° Aliphatic Alkyl/Benzylic Radicals Generated via Decarboxylation/Imidyl Radical Formation/β-Scission



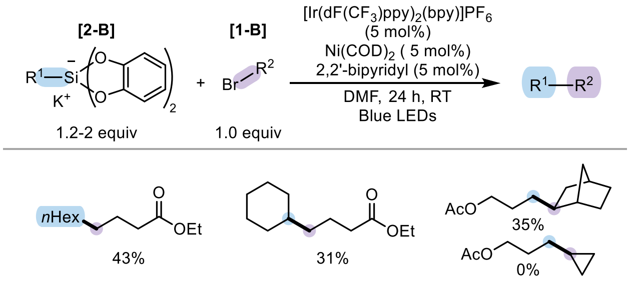
Tunge and co-workers applied the decarboxylation strategy to effect cross-coupling with allylic/benzylic carbonates with 1° and 2° carboxylic acids, employing Pd for the cross-coupling catalyst and 4CzIPN as the photocatalyst (Scheme 7).[27] The authors achieved cross-coupling of α-amino and α-oxy alkyl radicals with allyl or benzyl carbonates in a redox-neutral fashion. The proposed mechanism involves the formation of the Pd(II) π-allyl carboxylate species from Pd(0)/BINAP, carbonate, and carboxylate. SET from carboxylate to Pd facilitates decarboxylation and carbon-centered radical formation. This radical is then intercepted by Pd(II) π-allyl species, undergoing an inner-sphere reductive elimination pathway to afford the C(sp^3)−C(sp^3) bond.

Scheme 7. Allylation/Benzylation of 2° α-Amino/Oxy, Unactivated Alkyl Groups or 3° Unactivated Aliphatic Alkyl Groups via Pd/Photoredox Catalysis



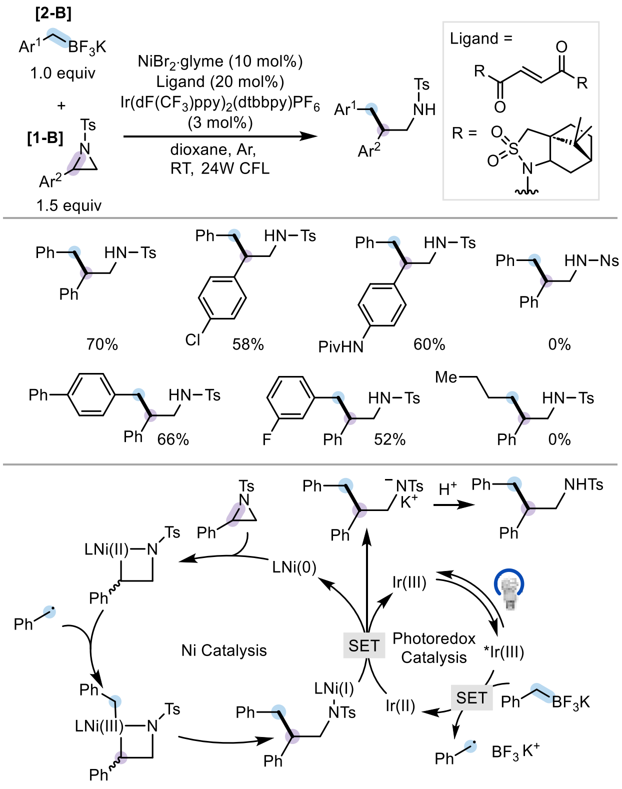
The oxidative activation pathway to generate alkyl radicals extended beyond carboxylic acids and found application in cross-coupling with alkyl precursors, such as alkyl silicates, as reported by Ollivier and Fensterbank (Scheme 8).[28] Prior studies have shown that silicates are a versatile source of aliphatic alkyl radicals for previous C(sp^3)−C(sp^2) cross-coupling,[29,30] from which they applied the same strategy in achieving C(sp^3)−C(sp^3) bond formation with aliphatic alkyl bromides. The reaction employed Ni(COD)$_2$ and a bipyridyl ligand as the cross-coupling catalyst and [Ir(ppy)$_2$(dtbbpy)]PF$_6$ as the photocatalyst. While the methodology demonstrated cross-coupling reactivity with certain examples of 1° or 2° aliphatic alkyl bromides, the yields, when compared to its performance in cross-coupling with aryl halides, were relatively modest.

Scheme 8. Cross-Coupling of Two Aliphatic Alkyl Groups from Alkyl Silicates and 1° Alkyl Bromide via Ni/Photoredox Catalysis



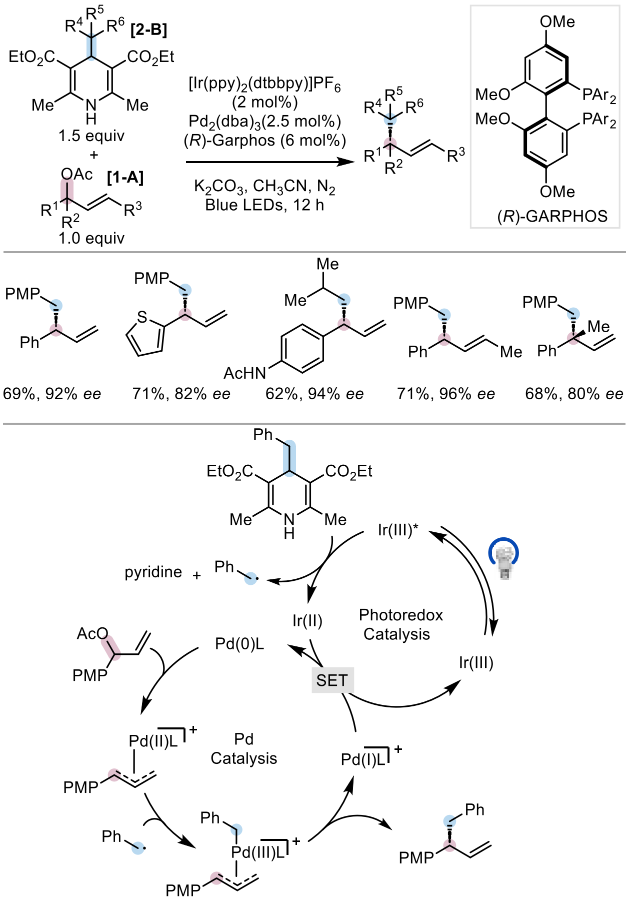
Potassium trifluoroborates stand out as another valuable source of C(sp^3) precursors activated upon single electron oxidation. These benchtop-stable alkyl radical precursors have previously demonstrated cross-coupling reactivity with aryl halides using photoredox catalysis.[31] In a study conducted by Xiao and Chen and colleagues, this reactivity was extended to the alkylation of aziridines, a versatile class of C(sp^3) electrophiles known to be amenable to Ni catalysts,[32] serving as valuable precursors for the synthesis of medicinally relevant β-functionalized amines (Scheme 9).[33,34] In this work, the authors reported that while benzyl trifluoroborates exhibited reactivity, unactivated aliphatic alkyl trifluoroborates did not give any notable reactivity. Regarding the scope of aziridines, most substrates showed reactivity with tosyl-protected monosubstituted styrenyl aziridines. However, similar reactivity was not observed with other protecting groups (Ns or Ac) or disubstituted styrenyl aziridines. For the mechanistic proposal, the authors postulated that aziridines, known to undergo oxidative addition with Ni(0), presumably form the Ni(II) azametallacycle species, capable of trapping the benzylic radical generated from the trifluoroborates. This high-valent Ni(III) species likely undergoes a facile reductive elimination to generate the C(sp^3)−C(sp^3) bond.

Scheme 9. Cross-Coupling of Benzyltrifluoroborates with Styrenyl Aziridnes via Ni/Photoredox Catalysis



While the single electron oxidation of amines has been showcased to enable α-amino alkylation, as exemplified in section 3.1, an alternative strategy involves the use of amine radicals as precursors to form aliphatic alkyl radicals coupled with an aromatization event. A notable illustration of this concept is found in the work of the Yu group, where they reported a Pd-catalyzed allylation of benzylic bonds (Scheme 10).[35] The crucial component in this process is alkyl-1,4-dihydropyridines (DHP), serving as a C(sp^3) precursor capable of facile single electron oxidation with excited-state Ir(III) species to generate an alkyl radical and pyridine as a side product. In this pathway, the alkyl radical derived from DHP is anticipated to undergo ligation to Pd(II) allyl species, accessed via the allylation of Pd(0) with allyl acetates. Subsequent reductive elimination of Pd(III) species yields Pd(I) species, which in turn facilitates turning over of the reduced Ir(II) species to Ir(III), effectively closing the photoredox and Pd catalytic cycles. The authors identified (*R*)-Garphos as the optimal chiral ligand, enabling the production of chiral allyl products from various aryl-substituted or aryl-, alkyl-substituted allyl acetates. DHP precursors derived from unactivated 1° aliphatic alkyl or benzyl compounds were proven to be successful in this transformative process. It is worth mentioning that the same group published a subsequent report showcasing an asymmetric cross-coupling of *N*-methyl anilines and allyl acetates, resulting in the synthesis of chiral homoallylic amines enriched with tri- and tetrasubstituted stereogenic centers.[36]

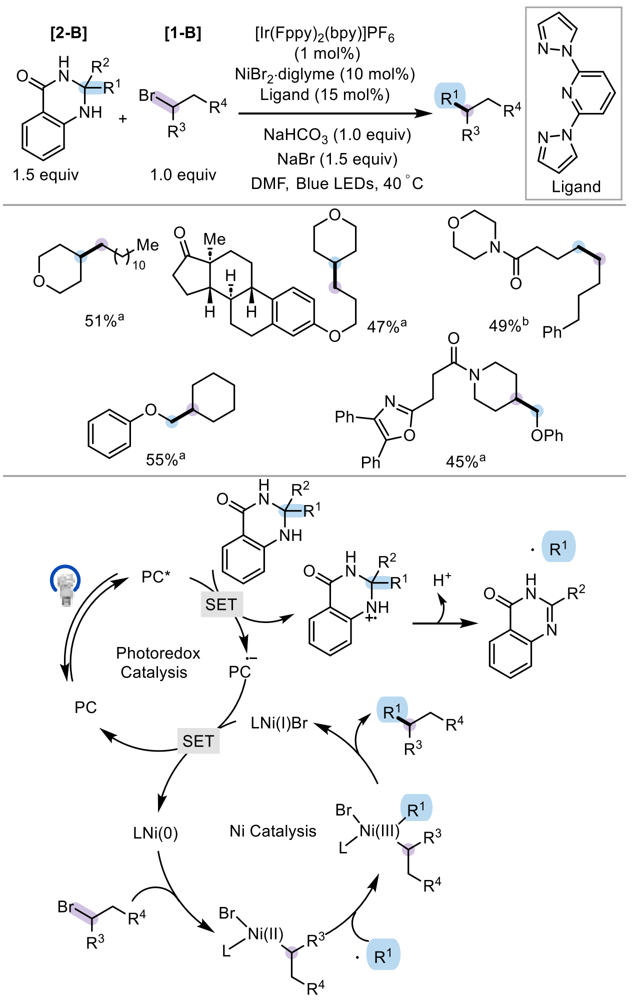
Scheme 10. Allylation of Benzylic, Aliphatic Alkyls from DHPs Using Pd/Photoredox Catalysis[a]



[a]Ar = 4-OMe-3,5-(tBu)$_2$-C_6H_2, PMP = p-methoxyphenyl.

Another versatile source of alkyl precursor is from direct oxidation of dihydroquinazolinones (Scheme 11). Martin and co-workers demonstrated that dihydroquinazolinones are easily prepared substrates, synthesized from ketones and anthranilamides, which can undergo a SET to enable C−C bond cleavage driven by the formation of aromaticity.[37] The alkyl radical generated includes unactivated 1° and 2° alkyl radicals, which exhibit cross-coupling reactivity with 1° alkyl bromides. The paper also presents a singular example of cross-coupling with a

Scheme 11. Cross-Coupling between 1° or 2° Aliphatic Alkyl Bromides and Dihydroquinazolinones via Ni/Photoredox Catalysis



[a]R2 = Me in the ketone derivative. [b]R2 = Ph in the ketone derivative.

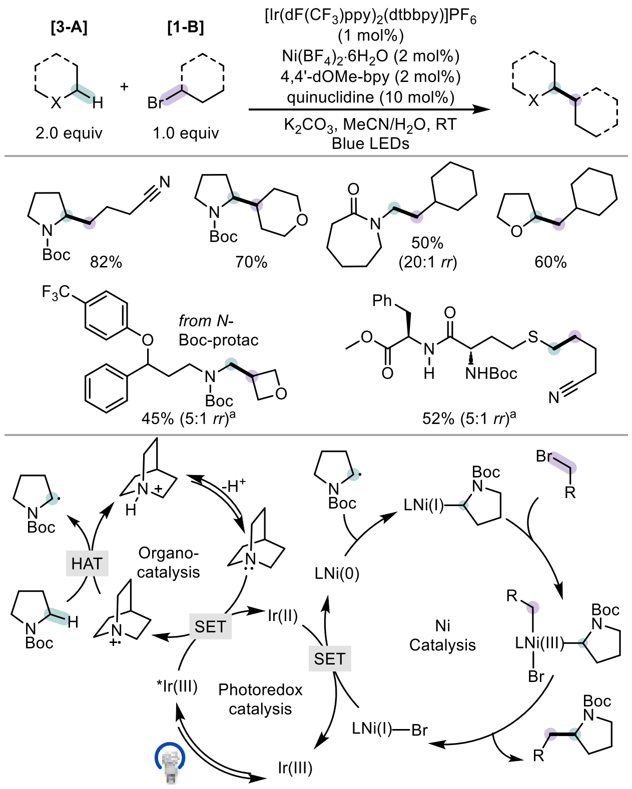
2° alkyl bromide. The authors emphasized the importance of using the bipyrazolepyridine ligand for enabling C(sp^3)−C(sp^3) cross-coupling.

4. CROSS-COUPLING BETWEEN CARBON RADICALS GENERATED BY HAT AND ELECTROPHILES REDUCED BY TRANSITION METALS

4.1. HAT Reagents Generated by Single Electron Oxidation. In preceding instances, the intrinsic functional groups were amenable to facile single electron oxidation by a suitably oxidizing photocatalyst. Another avenue for generating alkyl radical precursors involves direct hydrogen atom transfer (HAT). In this scenario, the HAT reagent can undergo a direct single electron oxidation with the photocatalyst, thereby engendering the C(sp^3) alkyl radical from the substrate's C−H bond. This methodology is particularly attractive due to the extensive pool of available substrates that can be facilitated by C−H bond activation, exhibiting an atom-economic transformation. However, the challenge inherent in the formation of alkyl radicals via HAT resides in achieving high site selectivity. In these instances, the nature of the HAT reagent and its resulting radical dictates the regioselectivity of the C−H bond of interest. While numerous HAT strategies have been documented, only a limited number of instances involving the cross-coupling of C−H bond substrates with alkyl electrophiles have been recently elucidated.

One of the seminal contributions that paved the way for cross-coupling through HAT involving a C−H bond substrate and an alkyl halide was elucidated in a work presented by Macmillan and colleagues in 2017 (Scheme 12).[38] Advancing beyond their precedent on native-group functionalization, such as decarboxylation, they demonstrated the efficacy of employing a hydrogen abstractor, quinuclidine. Quinuclidine (E_p = +1.1 V versus the saturated calomel electrode in MeCN),[39] serving as an electrophilic HAT reagent, possesses the capacity to generate an alkyl radical through single electron oxidation when engaged with an Ir photocatalyst. Specifically, quinuclidine exhibits selective abstraction of hydridic C−H bonds, demonstrating a pronounced preference over neutral or acidic C−H. This HAT selectivity is achieved by capitalizing on the polarity matching effect, wherein the ionic compatibility between the HAT catalyst and the hydrogen atom being abstracted dictates the selectivity. C−H bond substrates included *α*-amino C−H nucleophiles protected by easily cleavable Boc, Cbz, and Ac groups as well as diverse acyclic systems, cyclic ethers, and thioethers. These C−H bond substrates demonstrated successful coupling with both primary and secondary unactivated alkyl bromides.

Scheme 12. Alkylation of C−H Bond Substrates via HAT with Unactivated 1° or 2° Alkyl Bromide via Ni/Photoredox Catalysis



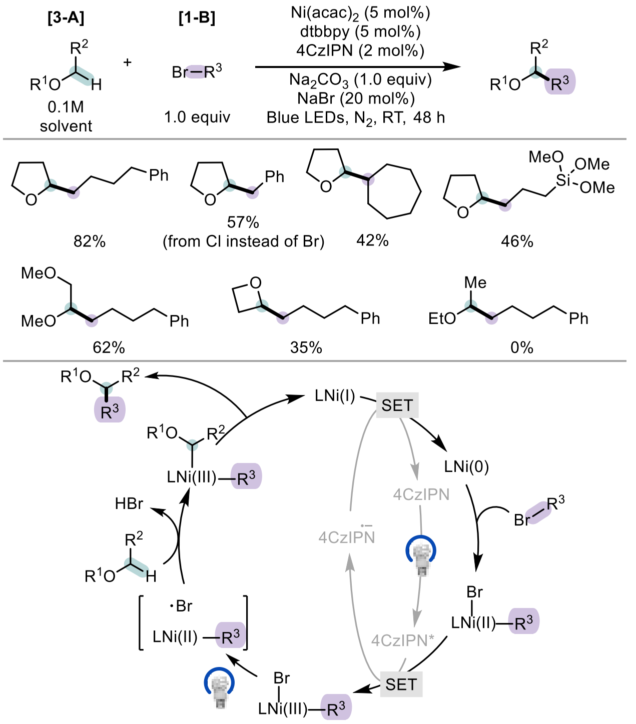
[a]Ten mole percent of Ni and ligand was used instead.

It is noteworthy that the same group subsequently published a late-stage methylation strategy using a C−H bond substrate with more elaborate functional groups to cross-couple with methyl bromides using sodium decatungstate as a HAT reagent.[40]

Alternative sources of HAT reagents encompass chlorine radicals ($Cl^\bullet$) or bromine radicals ($Br^\bullet$). While a conventional approach to accessing these radicals involves the homolysis of Cl_2 or Br_2, Doyle and colleagues introduced a safer and more efficient method for generating a chlorine radical by effecting the homolysis of a Ni−Cl bond through photoelimination.[41] This Ni−Cl bond is initially formed via the oxidative addition of an aryl halide. This strategy demonstrated that ethereal C−H bonds can undergo HAT and subsequent cross-coupling with aryl groups, resulting in the synthesis of benzylic ethers via Ni catalysis. Notably, the reaction enables HAT of C−H bond substrates that possess high oxidation potentials, such as tetrahydrofuran (THF) with an oxidation potential of E_p = 1.75 V versus the saturated calomel electrode (SCE). Concomitantly, Molander and co-workers also reported the arylation of ethereal C−H bonds using aryl bromides instead of aryl chlorides.[42]

Advancing upon these strategies, Konig and co-workers employed a 1° alkyl bromide instead of aryl halides to cross-couple with ethereal C−H bonds (Scheme 13).[43] After the alkyl bromide undergoes oxidative addition with Ni(0), a SET is suggested to occur on Ni(II) alkylBr to allow the photoelimination process, which results in the transformation of Ni(II) alkylBr to a Ni(III) alkylBr. This Ni(III) species then undergoes Ni−Br homolysis to generate a catalytic amount of bromine radical in situ which serves as a HAT reagent. From this HAT event, α-oxy alkyl radicals hop onto the Ni(II) species to generate Ni(III), which can undergo reductive elimination to afford the $C(sp^3)-C(sp^3)$ cross-coupled product. While 1° and 2° alkyl bromides reacted with THF, other ethereal C−H bond substrates such as dimethoxy ether, dioxolane, or dioxane did not show any reactivity.

Scheme 13. Alkylation of α-Oxy C−H Bond Substrates via Hydrogen Atom Transfer (HAT) with Unactivated 1° Alkyl Bromide via Ni/Photoredox Catalysis

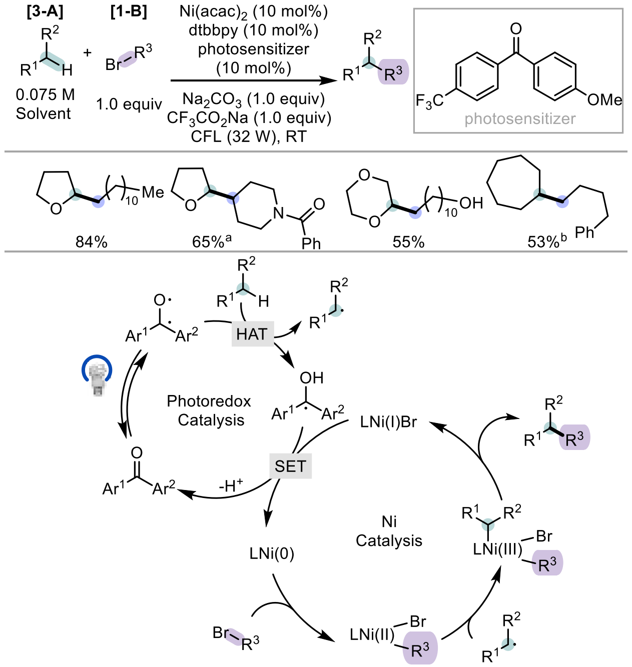


4.2. HAT Reagents Generated by Photosensitization.

Another method for generating a radical on the HAT reagent is via photosensitization, as opposed to single electron oxidation as discussed in section 4.1. A case in point is the photosensitization of *n* electrons of the C=O bond in an aryl ketone, which ascends to their corresponding π* orbital, followed by intersystem crossing (ISC) to generate a long-lived triplet state. The resulting long-lived triplet state behaves as a 1,2-biradical, imparting electrophilic radical properties at the oxygen radical.

The Martin group harnessed the potential of the photosensitization of diaryl ketones to facilitate HAT of C−H bond substrates, engendering alkyl radicals amenable to cross-coupling with alkyl bromides through Ni catalysis (Scheme 14).[44] During the development of this reactivity, the authors discerned the pivotal role of the arene backbone identity. The specific substituents on the arene ring dictated the requisite wavelength for photosensitization, the longevity of the triplet excited state, as well as the stability of the ketyl radical. The authors found that diaryl ketones possessing one *p*-methoxy group and another with a *p*-CF_3 group showed the best reactivity.

Scheme 14. Alkylation of α-Oxy C−H Bond Substrates Activated by Hydrogen Atom Transfer (HAT) from Photosensitizer and Ni Catalysis



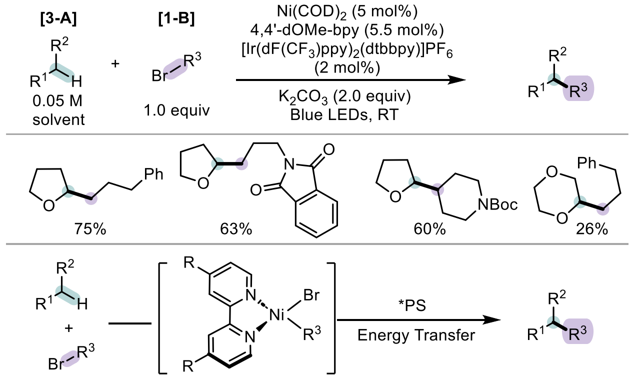
[a]Without CF_3CO_2Na. [b]Benzene as a cosolvent, 50 mol % of photosensitizer.

When using Ni(acac)$_2$, 4,4′-ditertbutylbipyridine, and CFL (32 W) as the light source, the authors found that the 1° and 2° unactivated alkyl bromides could engage in cross-coupling with C−H bond substrates subject to HAT by the photosensitized ketone. The spectrum of C−H bond substrates included α-oxy ethereal C−H bonds such as THF, cyclooxetane, dimethoxyethane, as well as aliphatic cycloalkanes. Mechanistic studies illustrate that the triplet excited ketones serve as the HAT and SET catalysts to enable the catalytic turnover in conjunction with the Ni catalyst.

The Hashmi group reported an analogous system using benzaldehyde as a photosensitizer, serving as a HAT reagent to generate radicals from an ethereal C−H bond.[45] Under UVA light, benzaldehyde engages in a HAT process, yielding an α-hydroxybenzyl radical, which would further abstract a hydrogen atom from the solvent to give an alkyl radical. The alkyl radical, in turn, can be elaborated to facilitate the construction of C−C bond formation via Ni-catalyzed cross-coupling with alkyl bromides. The versatility of this approach extends not only to ethereal bonds but also to amides and thio-containing substrates.

In specific instances, determining whether the HAT reagent is activated through SET or photosensitization can be a subject of inquiry. One noteworthy case illustrating this complexity is presented by the Rueping group[46] (Scheme 15) as it contradicts the SET pathway previously suggested in Scheme 13.[43] While both approaches involve the utilization of a bromine radical to enable HAT of C−H bond substrates, forming an alkyl radical that subsequently undergoes cross-coupling with alkyl bromides using Ni catalysis, Rueping and co-workers suggested that the SET pathway from Ni(II) to Ni(III) for generating a bromine radical via homolytic cleavage is unlikely. This proposal is rooted in their experimental data of comparing the reactivity of various redox potentials of photocatalysts (Table 2).

Scheme 15. Alkylation of α-Oxy C−H Bond Substrates by Ni−Br Photosensitization/Br-Mediated HAT and 1° or 2° Aliphatic Alkyl Bromides



The authors demonstrated that the optimal photosensitizer $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (Ir(III)*/Ir(II) = +1.21 V vs SCE) afforded the cross-coupled product in 75% yield. Conversely, photosensitizers with higher oxidizing potentials such as $[Ru(bpz)_3](PF_6)_2$ or $(9\text{-MesAcr})ClO_4$ did not form any product, leading them to reject the possibility of the reaction proceeding through SET mediated photoelimination. Furthermore, through DFT and TD-DFT calculations and nanosecond transient absorption spectroscopy, the authors suggest that a mechanism that involves a Dexter triplet−triplet energy transfer from the *Ir(III) photosensitizer to the Ni(II) species is more probable. This interaction forms the Ni(II) triplet state, triggering the breaking of the Ni−Br bond by the promotion of one electron from an occupied molecular orbital to the Ni−Br σ*. This ultimately generates a bromine radical that can facilitate the HAT and initiate the cross-coupling event with alkyl bromides. This methodology primarily showed good reactivity with 1° and 2° alkyl bromide with THF as the C−H bond substrate. A single example with dioxane was shown in a modest yield (26%).

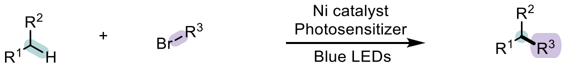
4.3. Amidyl Radical HAT Reagents and 1,5-HAT. In 2016, Knowles and Rovis concurrently disclosed a photoredox-catalyzed variation of the classical Hoffmann−Loffler−Freytag reaction.[47,48] In this reaction, an amidyl radical is generated by a photoexcited *Ir(III) catalyst with the assistance of deprotonation by a base. This electrophilic amidyl radical can enable a 1,5-hydrogen atom transfer (1,5-HAT) event of a distal unactivated aliphatic C−H bond facilitated by a favorable six-membered cyclic transition state. In both of their seminal contributions, the resulting radical was added to an electron-deficient alkene to afford a new C−C bond formation.

Expanding upon these findings, the Rovis group introduced a novel strategy of cross-coupling alkyl radicals generated through 1,5-HAT from an amidyl radical with alkyl bromides using a Ni catalyst (Scheme 16).[49] This strategy enabled a broad scope of TFA-protected amides with a variety of aliphatic 1° alkyl bromides. The authors proposed that after generating an amidyl radical, this can facilitate a 1,5-HAT to result a 2° alkyl radical. This radical can be captured by Ni(II) alkylBr, originating from the oxidative addition of the alkyl bromide to Ni(0). The resulting Ni(III) would undergo reductive elimination to regenerate Ni(I) and close the catalytic cycle.

In the same year, the Tambar group reported an allylation of an alkyl radical generated by a 1,5-HAT of an amidyl radical (Scheme 17). This transformation employs allylic chloride using nickel catalysis.[50] Notably, the proposed mechanism deviates from the previous nickel-catalyzed mechanism. The authors suggested that upon generation of the alkyl radical from 1,5-HAT, it adds to the alkene of the allylic chloride, forming a carbon-centered radical at the β-position of the chloride. The resulting alkyl radical undergoes a facile β-scission to afford the product along with the liberation of a chlorine radical. The chlorine radical is then postulated to participate in the reoxidation of the reduced photocatalyst Ir(II) catalyst, completing the catalytic cycle. This reaction encompassed 1,1-disubstituted allyl chlorides, including functional groups such as a silyl, ester, or phenyl moiety.

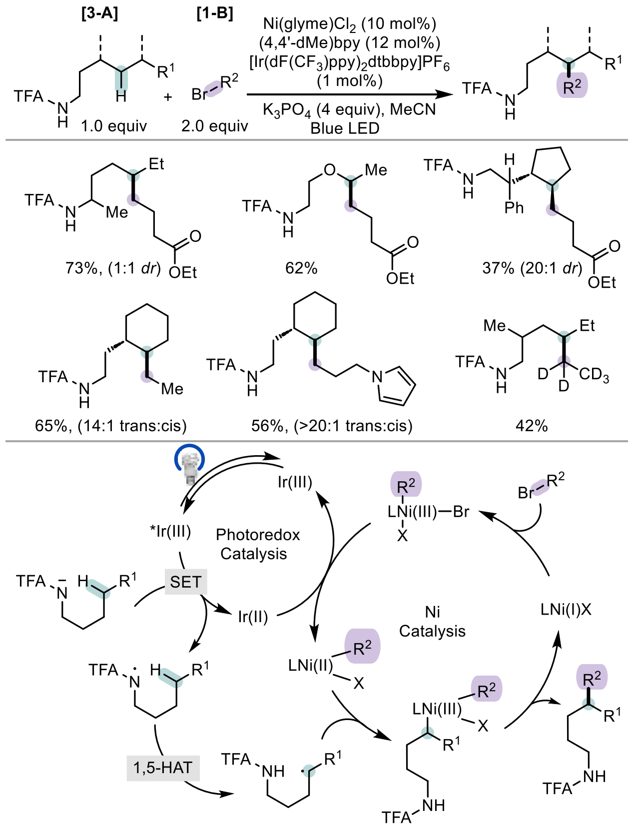
In 2020, the Montgomery and Martin group contributed to the field with further work on the α-alkylation of aryl amide substrates using Ni catalysis with 1° alkyl bromides (Scheme 18).[51] In their publication, the authors acknowledged that the

Table 2. Comparison of Reactivity with Photosensitizers of Varying Triplet−Singlet Energy and Oxidation Potentials

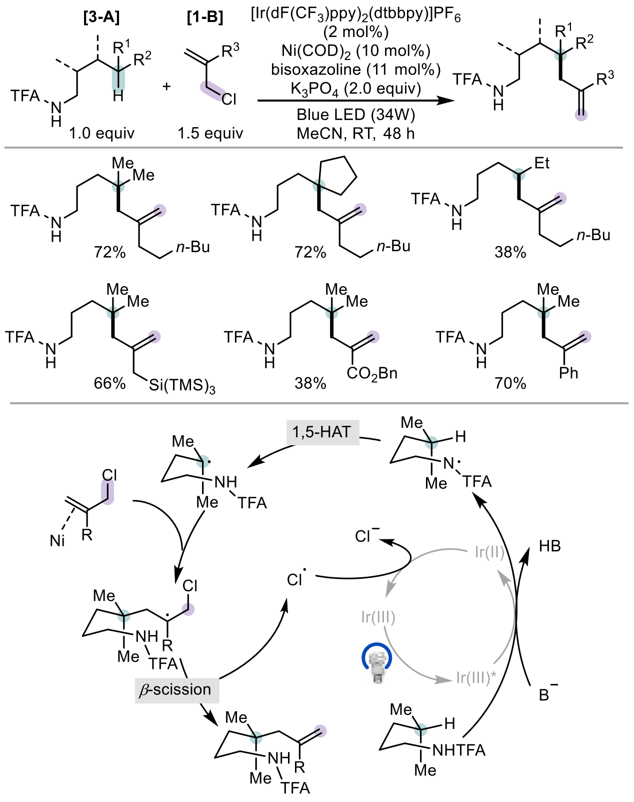


entry	photosensitizer	$\Delta E_{T1\text{-}S0}$ (kcal/mol)	$E1/2M^*/M^{\bullet-}$	λ_{Em} (nm)	result
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	60.7	1.21 V	472	formed
2	$[Ir(ppy)_2(dtbbpy)]PF_6$	50.5	0.66 V	581	n.r.
3	$[Ru(bpz)_3](PF_6)_2$	44.7	1.45 V	591	n.r.
4	$(9\text{-MesAcr})ClO_4$	44.5	2.06 V	590	n.r.

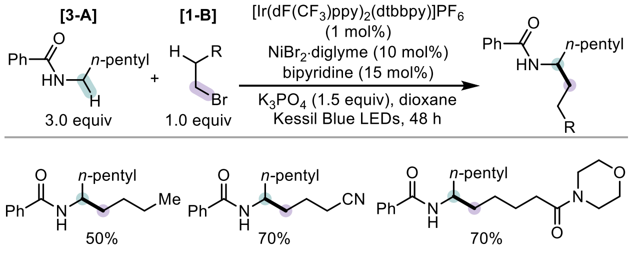
Scheme 16. Ni/Photoredox-Catalyzed Cross-Coupling between 1° Aliphatic Alkyl Bromides and 2° Alkyl Radicals Generated via Intramolecular 1,5-HAT



Scheme 17. Ni/Photoredox-Catalyzed Allylation from Allyl Chlorides and 2° Alkyl Radicals Generated via Intramolecular 1,5-HAT



Scheme 18. Ni/Photoredox-Catalyzed Alkylation from 1° Alkyl Bromides and 2° Alkyl Radicals Generated via HAT



precise mechanism of the reaction necessitates further investigation and emphasized that it is not likely to go through a 1,5-HAT from the amidyl radical followed by capturing of the carbon-centered radical with Ni to enable chain walking to the *α*-position. This conclusion was drawn from the observation that substituents lacking methylene and C—H bonds for 1,5-HAT were amenable to the reaction conditions.

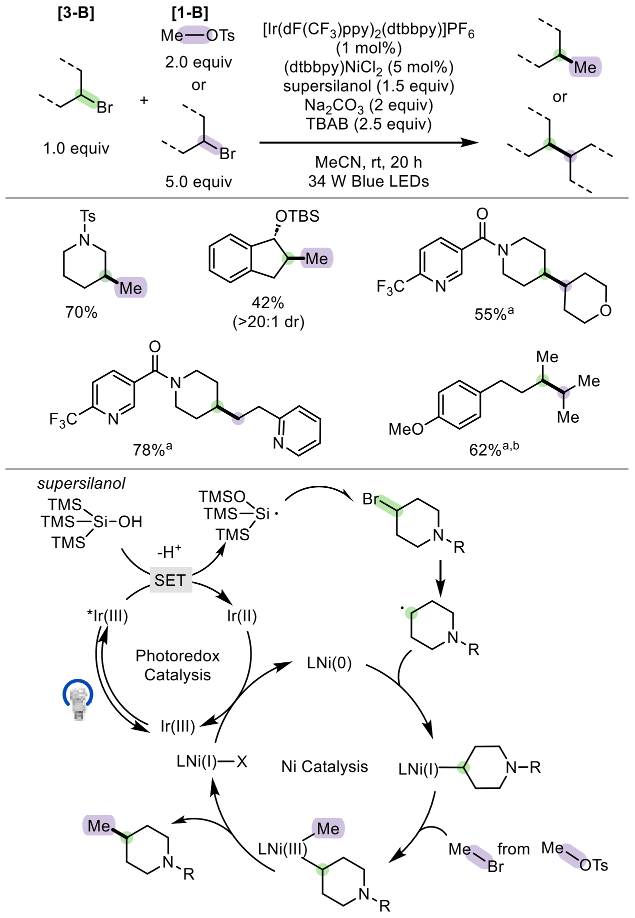
5. CROSS-COUPLING BETWEEN CARBON RADICALS GENERATED BY OXIDATIVELY INDUCED DEHALOGENATION AND ELECTROPHILES REDUCED BY TRANSITION METALS

Although alkyl bromides have predominantly served as electrophiles amenable to reduction through the mediation of low-valent transition-metal catalysts thus far, it is also feasible to employ a photoactivatable halogen atom transfer (XAT) reagent that can abstract the bromine to generate a carbon-centered radical. The XAT reagent can be generated via oxidation by a photocatalyst, thereby enabling a redox-neutral system when aiming to cross-couple with an electrophile activated by reduction.

One pioneering example was reported by MacMillan and co-workers, where they showed a C(sp^3)—C(sp^3) cross-coupling with two distinct alkyl (pseudo)bromides. One coupling partner is a small alkyl electrophile such as methyl tosylate or alkyl bromide introduced in excess, and the other partner incorporates a more valuable drug-like motif used as the limiting reagent (Scheme 19).[52] This reaction employs an Ir photocatalyst with a di-*tert*-butylbpy-ligated Ni catalyst with TBAB and supersilanol as additives. Under visible light, the supersilanol undergoes SET to generate a silyl radical, which is then capable of abstracting bromine from the valuable alkyl bromide species. The resulting alkyl radical can be ligated onto the Ni(0) to generate Ni(I) species, which can undergo oxidative addition with the simpler alkyl bromide, strategically introduced in excess. The reaction scope is quite broad, providing a methylation reaction and cross-coupling of 2°—2° alkyl groups, which is a challenging disconnection.

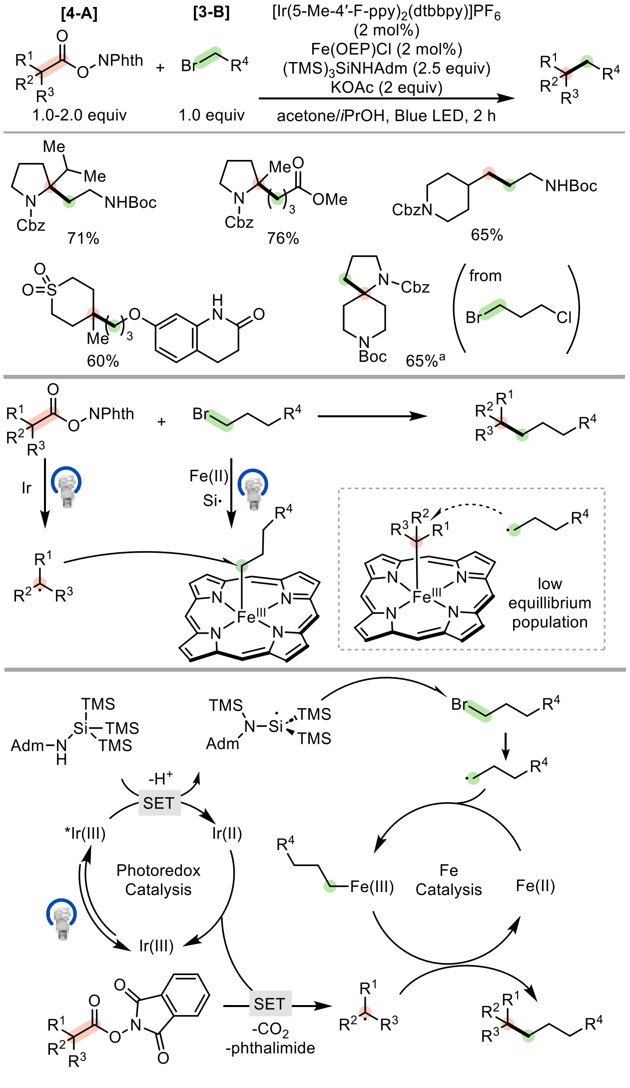
MacMillan and co-workers next invoked a biomimetic Fe-catalyzed S_H2 mechanism to facilitate C(sp^3)—C(sp^3) cross-coupling to furnish quaternary carbon centers from aliphatic 1° alkyl bromides and 3° NHPI esters, a disconnection that was not reported using a previously Ni-catalyzed method (Scheme 20).[53] This methodology involved the use of aminosilane as the XAT reagent to form a 1° radical from alkyl bromides. This alkyl radical would then be captured by the Fe(II) porphyrin catalyst at near diffusion-controlled rates to furnish the primary alkyl—Fe(III) intermediate. Concurrently, the reduced Ir(II) species can reduce the NHPI ester via SET to furnish a 3° radical upon

Scheme 19. Redox-Neutral Cross-Coupling of Two Alkyl Bromides via Ni/Photoredox Catalysis



[a]Three equivalents of supersilanol and 3 equiv of K_3PO_4 were used. [B]GC yields, 3 equiv of Na_2CO_3 used instead.

Scheme 20. Cross-Coupling of 1° and 3° Aliphatic Alkyl Groups via Fe/Photoredox Catalysis from Reductive Decarboxylation from NHPI Esters and Dehalogenation Using Supersilanol



[a]Reaction with alkyl bromide then NaH at 60 °C.

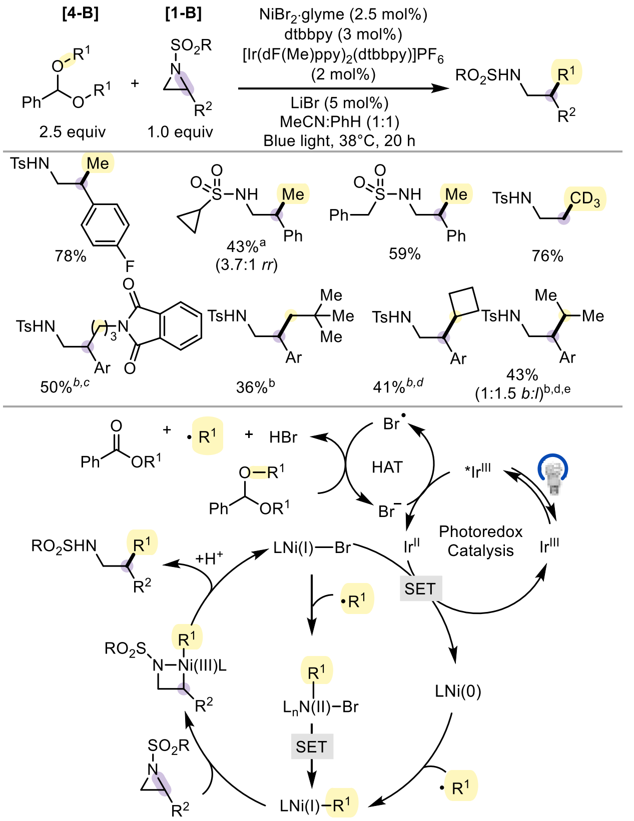
extrusion of CO_2 and phthalimide. The origin of the cross-reactivity is rooted in that the 1° alkyl group is expected to be ligated to the Fe first, while the more stable 3° radical can form a C−C bond via an outer-sphere mechanism. Accordingly, the 3° alkyl metal porphyrin complex is not formed in measurable equilibrium concentrations, and the S_H2 displacement with other radicals is kinetically slow.

6. Cross-Coupling of Alkyl Radicals Generated by Oxidatively Induced Deoxygenations. Due to its abundance in nature, alcohol can serve as a useful source of alkyl precursors; however, its functionalization remains a challenge due to the high BDE of C−O bonds. With an appropriate activating group, however, the C−O bond can be homolytically cleaved via *β*-scission. An illustrative instance of deoxygenative $C(sp^3)-C(sp^3)$ cross-coupling was reported by Doyle and co-workers using benzaldehyde to activate alcohols into acetals for a facile C−O homolytic cleavage (Scheme 21).[54] In their strategy, bromide salts are introduced as additives, which undergo oxidation by photoexcited *Ir(III) to generate a bromine radical that can function as an HAT reagent to abstract the benzylic C−H of the acetal. The resulting 3° radical enables a *β*-scission to occur, leading to generation of an equivalent of an aliphatic alkyl radical. This alkyl radical was proposed to be captured by Ni(0) species to afford Ni(I), from which aziridines can undergo oxidative addition via a Ni(I)−Ni(III) pathway. The authors highlight the novelty of the oxidative addition of aziridines at Ni(I), as stoichiometric studies and previous cross-coupling have exclusively identified aziridines to undergo oxidative addition at Ni(0), as suggested in Scheme 9. This methodology formally delivers *β*-alkylated amines, a prevalently used drug motif.

Soon after, Martin and co-workers published the cross-coupling of cyclic benzaldehyde acetals that can undergo a HAT event with quinuclidine as the HAT reagent to generate an alkyl radical. In this publication, the alkyl radical generated from acetals was showcased to enable coupling with two examples of cross-coupling with unactivated 1° and 2° alkyl bromides.[55]

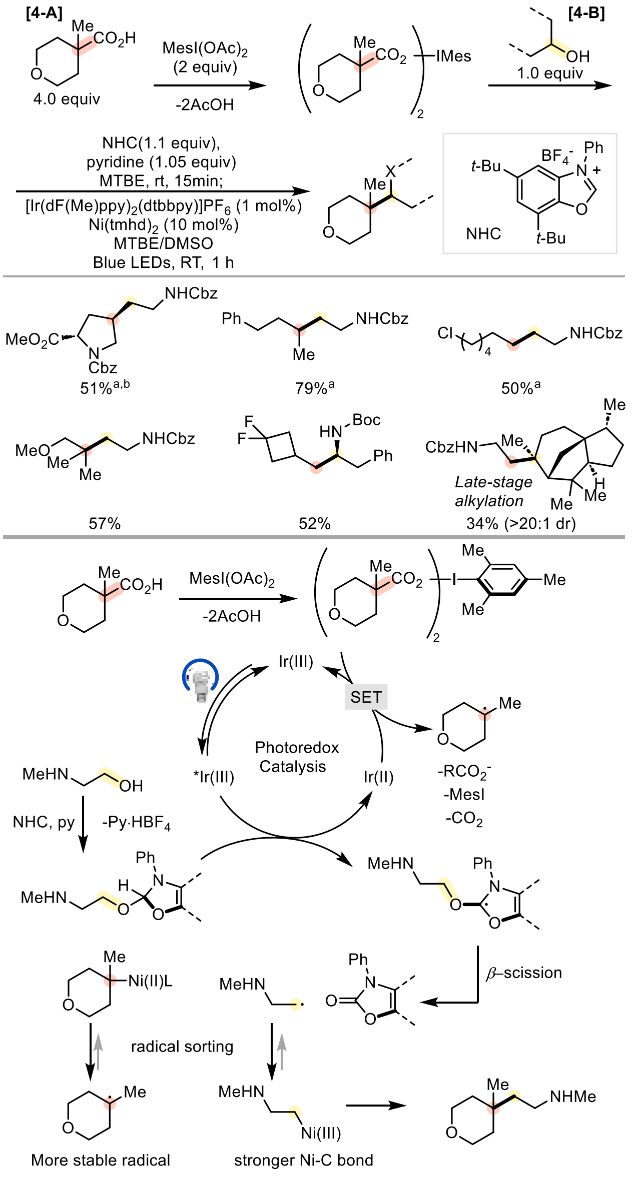
Expanding upon their previously reported S_H2 strategy (see section 5),[53] MacMillan and co-workers have introduced a cross-coupling method that employs alcohol as one variant of the alkyl radical precursor and carboxylic acids as the other coupling partner with the latter undergoing decarboxylative reduction, with both substrates necessitating an activator to transition to a redox-active state (Scheme 22).[56] In this methodology, the researchers employed a *N*-heterocyclic

Scheme 21. Cross-Coupling between Aziridines and Acetals Derived from Condensation of Benzaldehyde and Aliphatic Alkyl Alcohols



[a]rr refers to regioisomers of the substituted C−N bond vs an unsubstituted C−N bond. [b]Ar refers to *p*-F-phenyl. [c]One mole percent PC and 1.1 equiv of acetal at 25 °C. [d]5,5′-Difluoro-2,2′-bipyridine was used instead of dtbbpy. [e]Diisopropyl benzaldehyde acetal was used as the coupling partner. b:l refers to branched:linear.

Scheme 22. Cross-Coupling between Carboxylic Acid and Alcohols via Ni/Photoredox Catalysis via Using Differences in Substitution of the Aliphatic Alkyl Group



[a]A 1.30 equiv amount of NHC-1 and 1.25 equiv of pyridine. [b]A 2.7:1 dr.

carbene (NHC) to which the alcohol can add, generating a tertiary C−H bond that is susceptible to cleavage upon single electron oxidation of the adjacent amine. This oxidative process induces a *β*-scission, generating an aliphatic alkyl radical. Conversely, the carboxylic acid is first activated with MesI(OAc)$_2$, which subsequently undergoes a SET reduction by Ir(II). Although two aliphatic alkyl radicals are generated, the authors propose the cross-reactivity arises from the differences in substitution patterns. While a 1° alkyl group forms a stronger Ni−C bond, a 2° or 3° group forms a more stable radical, thereby enabling cross-coupling through a process aptly termed "radical sorting". The authors suggest that it is likely that "outer-sphere" C−C bond formation to form quaternary carbon centers is more plausible than an inner-sphere reductive elimination.

Using an analogous deoxygenative strategy, MacMillan and co-workers also presented cross-coupling with alkyl bromide instead (Scheme 23).[57] In this instance, although the alcohol is activated in the same way using NHC to enable SET to undergo *β*-scission to generate an alkyl radical, the authors proposed that it goes through an inner-sphere mechanism, where the alkyl radical ligates first onto Ni(0) to generate Ni(I) followed by oxidative addition of alkyl bromide to generate Ni(III). The product is obtained from reductive elimination at Ni(III). Impressively, they were able to demonstrate that 2°−2° can be cross-coupled. Through this they were able to show a number of different cross-coupling of two rings. To enable this reactivity, they extensively surveyed several different ligands, where they found that a monopyridylbioxazoline ligand was found to afford fruitful yields.

Following up on this publication, the same group reported a method for generating quaternary centers using the S$_H$2 bond-forming mechanism adhering to deoxygenation of alcohols using NHCs with alkyl bromide.[58] As for the activation of alkyl bromides, however, they employed a dehalogenative strategy by a reductively activated XAT reagent to enable halogen atom transfer (XAT) to occur. A wide variety of sterically congested quaternary products can be accessed through this protocol, including products derived from both alkylation and benzylation of tertiary fragments.

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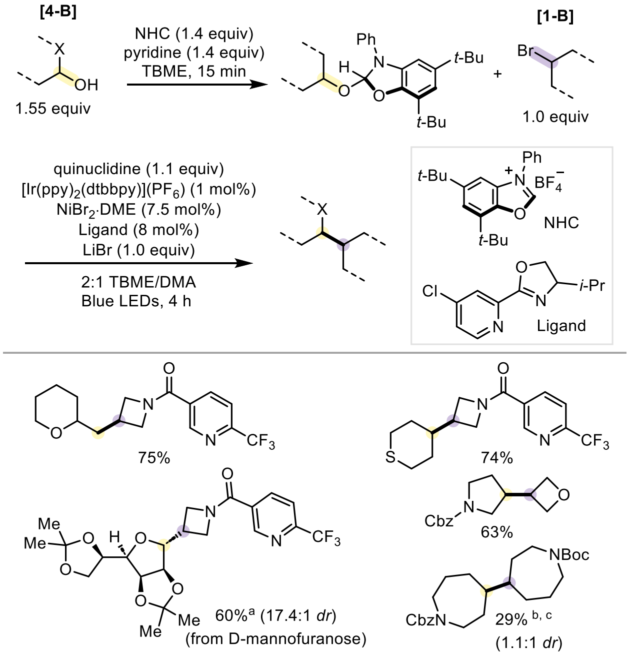
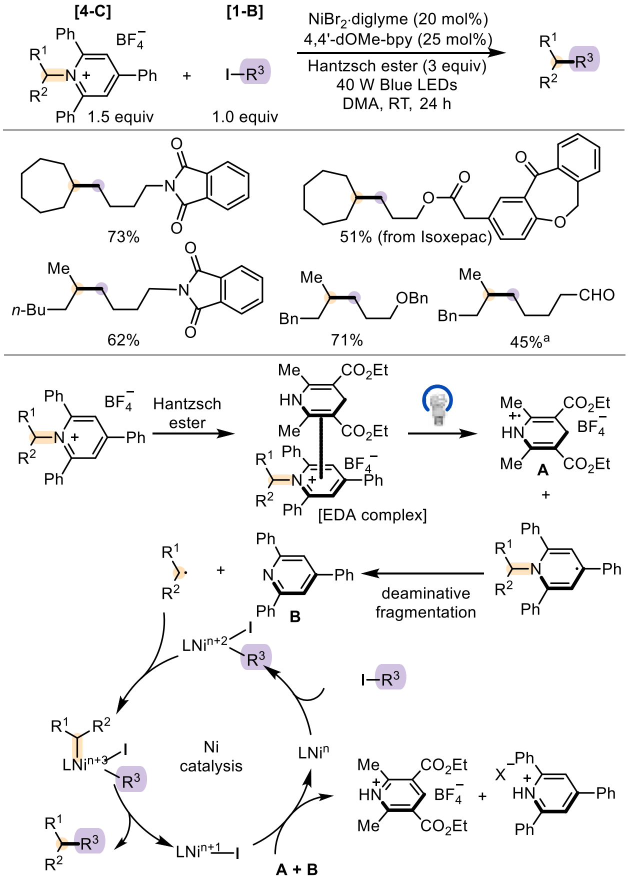
Organometallics 2024, 43, 1662−1681

Scheme 23. Cross-Coupling between Carboxylic Acid and 1° or 2° Aliphatic Alkyl Bromides



[a]The reaction was performed with alcohol (1.75 equiv), NHC (1.6 equiv), pyridine(1.6 equiv), and K_2CO_3 instead of LiBr (1.0 equiv). Dioxane was used instead of TBME. [B](±)- 4-Isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole (8 mol %). [C]K_2CO_3 was used instead of LiBr.

Scheme 24. Net-Reductive Cross-Coupling from Pyridinium Salt and 1° Aliphatic Alkyl Bromides



7. NET-REDUCTIVE CROSS-ELECTROPHILE COUPLING

The net-reductive elimination process employing photoredox, wherein both cross-coupling partners necessitate reduction, mandates a stoichiometric reductant to facilitate turnover in the catalytic cycle. This realm of net-reductive coupling remains relatively underexplored when compared with the previously mentioned redox-neutral catalytic cycles.

A noteworthy and rare illustration of cross-electrophile coupling involving C(sp^3)−C(sp^3) is exemplified in the deaminative coupling of pyridinium salts with alkyl iodides, as reported by Koh and colleagues (Scheme 24).[59] In this reaction, Hantzsch ester was reported to be the choice of reductant, enabling the formation of an EDA complex with the pyridinium salt, wherein the irradiation of visible light can lead to a deaminative fragmentation, concomitantly forming a pyridine and the alkyl radical to be coupled. The alkyl radical can coordinate to the Ni(II) alkylBr species. The resulting Ni(III) can undergo reductive elimination into Ni(I). This Ni(I) is then reduced back to Ni(0) in the presence of the oxidized Hantzsch ester and pyridine, affording protonated pyridine byproducts. This reaction afforded a number of cross-couplings of 1° or 2° alkyl pyridinium salts with 1° aliphatic alkyl bromides.

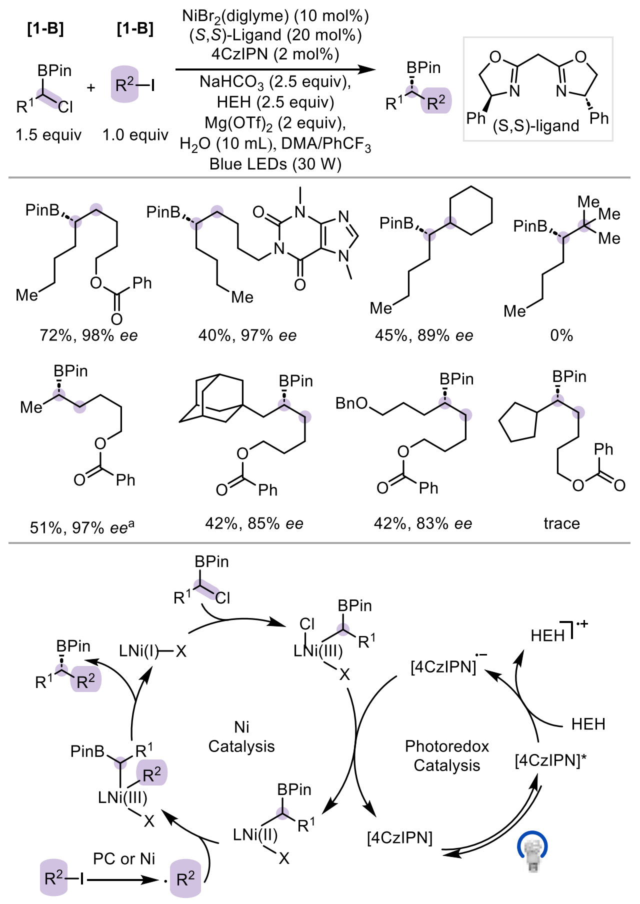
Xu and colleagues have contributed to the domain of net-reductive and enantioselective cross-electrophile strategies through their noteworthy work employing α-chloroboronate and alkyl iodide as the coupling partners, facilitated by a Ni catalyst and 4CzIPN as a photocatalyst (Scheme 25).[60] This study holds particular significance as high enantiomeric excess (ee) was achieved through the incorporation of a chiral bisoxazoline-type ligand. This reaction yields valuable chiral secondary alkyl boronic esters, serving as crucial intermediates in organic synthesis. The reaction's scope demonstrates tolerance toward diverse functional groups, encompassing 2° alkyl boronates and both 1° and 2° alkyl iodides, albeit the secondary cross-coupling instances yielded slightly lower yields.

Based on previous works, the authors suggested α-chlorobornate cannot be reduced by the single photoredox due to its strong reductive potential ($E = -2.8$ V vs SCE). Instead, they posit that it likely proceeds through oxidative addition with a Ni(I)X species, generating Ni(III) species capable of engaging in subsequent ring-opening or -closing processes. This Ni(III) species undergoes reduction to Ni(II) through the reduced 4CzIPN with the Hantzsch ester serving as the stoichiometric reductant. The reduced Ni(II) species is then postulated to capture the alkyl radical originating from the alkyl iodide, generating Ni(III). The resulting Ni(III) species undergo reductive elimination, and the catalytic cycle is closed. It is noteworthy that the authors do not incorporate Ni(0) into the proposed reaction mechanism, as $Ni(COD)_2$ failed to yield the desired product.

8. CROSS-COUPLING OF ALKYL RADICALS GENERATED BY PHOTOSENSITIZATION AND HOMOLYSIS

In addition to single electron reduction or oxidation of a redox-active substrate or reagent, an alternative modality of generating C(sp^3) radical precursors is through light-initiated triplet energy transfer from the photocatalyst to an organic molecule. Specifically, this applies to molecules capable of undergoing homolysis of a weak bond, resulting in the generation of a carbon radical.

Scheme 25. Net-Reductive Cross-Coupling from 2° Chloroboronates and 1° and 2° Aliphatic Alkyl Iodides

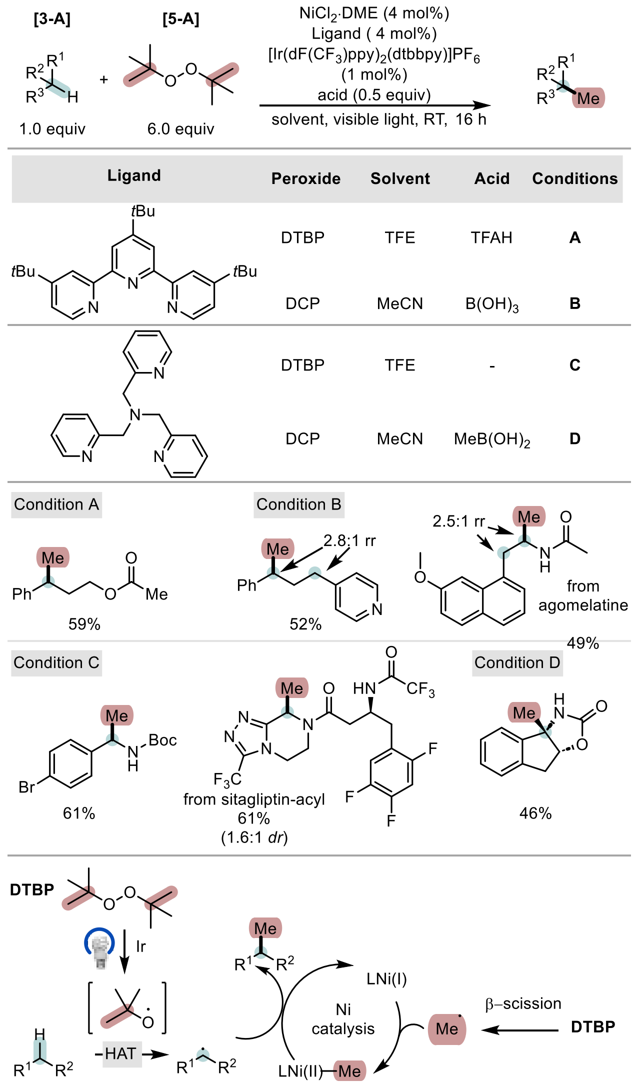


[a]Two equiv of α-chloroboronate used.

Recently, $C(sp^3)-C(sp^3)$ cross-coupling via photosensitization was demonstrated by Stahl and co-workers, where they showcased methylation of $C(sp^3)-H$ bonds in diverse drug-like molecules (Scheme 26).[61] In this publication, the authors employed peroxides, such as di-*tert*-butyl peroxide (DTBP), to generate an alkoxy radical via a visible-light- and photocatalyst-initiated triplet energy transfer, promoting the homolysis of the O−O bond. The resulting alkoxy can engender dual outcomes: (i) enable HAT from a C−H bond substrate and (ii) undergo *β*-scission to liberate a methyl radical. Consequently, the control of the relative rate of HAT vs generation of a methyl radical was particularly important in enabling cross-reactivity.

In doing so, Ni catalyst was employed to lead to productive methylation of the C−H bond. It was postulated that Ni(I) could sequester the methyl radical generated via *β*-scission, while an alkyl radical generated via HAT would ligate to the Ni(II)Me species, which would afford the methylated product. With the insight that the reaction conditions are amenable to modulation for equilibrium between the relative rates of HAT and methyl-radical formation, the authors carried out a high-throughput experimentation to optimize the methylation reaction for a diverse spectrum of substrates. Depending on the C−H substrate classes, whether it was for activated C−H bond substrates (benzylic C−H bonds, *α*-amido, benzylic bonds, *α*-oxy and benzylic bonds) or *α*-amino substrate scope, the authors demonstrated that each class necessitates different ligands, peroxides, solvent, and acid as additives.

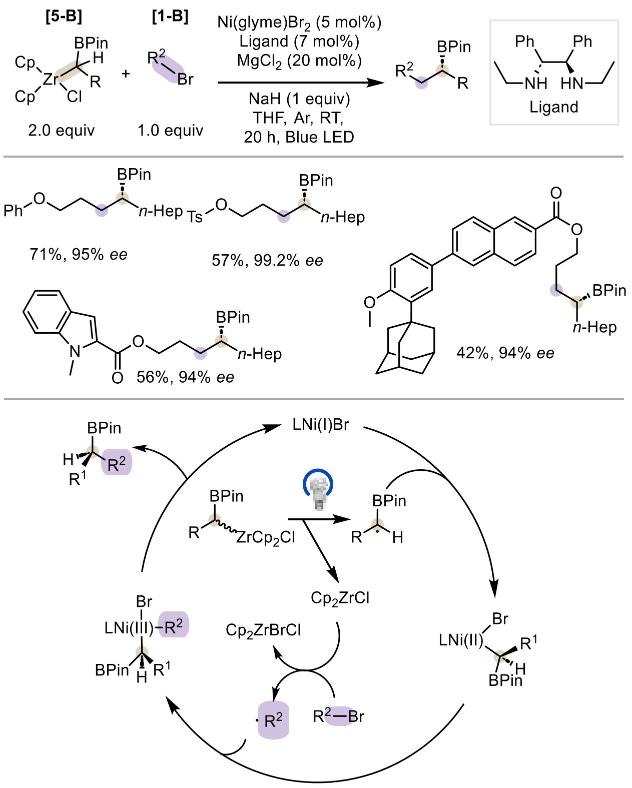
Scheme 26. Ni/Photoredox-Catalyzed Methylation of C−H Bond Substrates via Photosensitization of Peroxides and Subsequent Homolysis/*β*-Scission



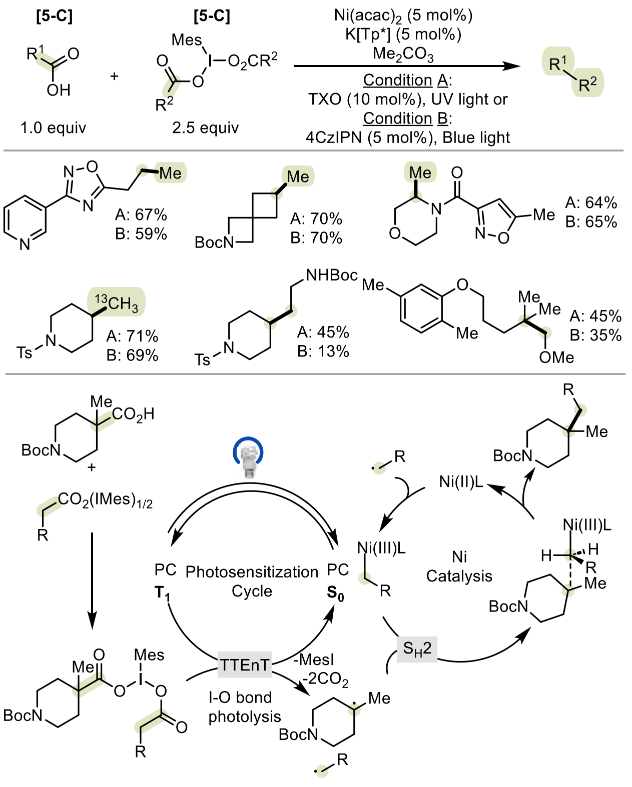
Recently, Qi and co-workers published a $C(sp^3)-C(sp^3)$ bond-forming methodology leveraging photosensitization and Ni catalysis for the synthesis of chiral borane compounds, which are highly valuable building blocks in chemical synthesis (Scheme 27).[62] In this work, alkyl zirconocene was employed as a photosensitizable radical precursor, which enables a photolytic homolysis via visible light to generate an alkyl radical. This alkyl radical ultimately undergoes Ni-catalyzed asymmetric cross-coupling with unactivated alkyl bromides with the assistance of a chiral diamine ligand. In this mechanistic scenario, the authors proposed a sequential oxidative addition step. The $C(sp^3)-C(sp^3)$ cross-coupling is a single electron addition process with alkyl radicals, generated by the reaction between alkyl halides and $Cp_2Zr(III)Cl$ species. While 1° unactivated alkyl bromides included substrates with functional groups such as aryl ethers, indoles, and esters, alkyl zirconium showed reactivity with 2° alkyl borane.

Another noteworthy example of photosensitization and homolysis is found in the work reported by Macmillan and colleagues, where they employed iodomesitylene carboxylate as an alkyl radical precursor (Scheme 28).[63] In this scenario,

Scheme 27. Visible-Light-Induced Enantioselective Radical Cross-Coupling of $C(sp^3)$−Borazirconocene and Alkyl Bromides via Ni Catalysis



Scheme 28. S_H2-Mediated Cross-Coupling of Two Respective Carboxylic Acids via Ni Catalysis and TTEnT[a]



[a]K[Tp*]: potassium tri(3,5-dimethyl-1-pyrazolyl)borohydride.

photosensitizers thioxanthone (TXO) or 4CzIPN undergo irradiation with UV or visible light, respectively, to access a long-lived, high-energy triplet state. This photoexcited state imparts the triplet energy to hypervalent iodine(III) species where two different alkyl carboxylates are ligated. The triplet energy leads to the homolysis of both I−O bonds to form carboxyl radicals, which subsequently undergo decarboxylation to form two alkyl radicals simultaneously. The cross-reactivity of two alkyl radicals arises from radical sorting, which allows preferential binding of the alkyl radical with a lower substitution to the catalyst. Subsequently, bimolecular homolytic substitution (S_H2) at a high-valent nickel−alkyl complex occurs, generating access to Me-1°, Me-2°, Me-3°, as well as 1°−3° alkyl cross-coupling. The synthetic utility is demonstrated in the late-stage methylation of biologically relevant molecules, such as artesunate or bezafibrate.

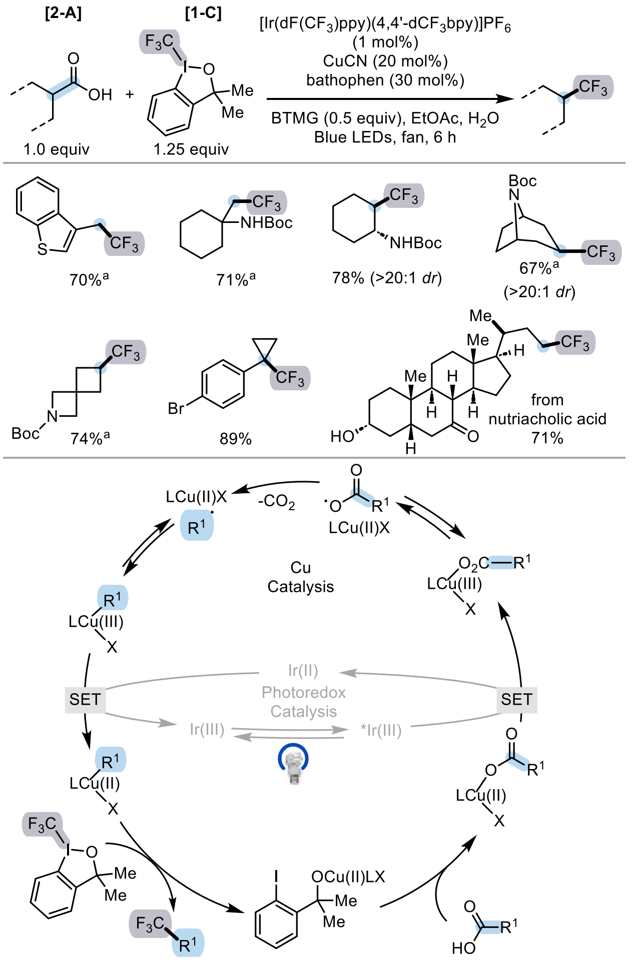
9. CROSS-COUPLING OF TRIFLUOROMETHYL GROUPS BY COPPER CATALYSIS

Another valuable $C(sp^3)$ functional group is the trifluoromethyl group (CF_3), a particularly important structural motif in medicinal candidates.[64] Cross-coupling of CF_3 radicals has been typically feasible with Cu as challenges of reductive elimination to form a C−CF_3 bond have been reported with Pd or Ni.[14] Another challenge with incorporating a C−CF_3 bond is that CF_3 radical additions have been typically reported with stoichiometric copper for the activation of CF_3 radical precursors.[65]

In efforts to address these challenges, MacMillan and co-workers reported an efficient method for the conversion of carboxylic acids to trifluoromethyl groups via Cu/photoredox catalysis,[66] taking advantage of Cu(III) to undergo facile reductive elimination with CF_3 (Scheme 29). The reaction conditions consist of the carboxylic acid substrate, Togni's reagents as the CF_3 source, Ir photocatalyst, CuCN with bathophen as the ligand, and BTMG as an additive with irradiation of blue light. Under basic reaction conditions, the carboxylic acid is expected to form a Cu(III) carboxylate species which can undergo oxidation with the photoexcited *Ir(III) species. The oxidized Cu(III) carboxylate species can undergo decarboxylation to generate an equivalent of an alkyl radical that can rapidly recombine to form Cu(III). At this point, the Cu(III) can be reduced by Ir(II), which could engage with the Togni's reagent to deliver the C−CF_3 product from Cu(III) reductive elimination. The resulting Cu(II) species would undergo ligand exchange with a new substrate to complete the catalytic cycle. Various (hetero)benzylic carboxylic acids, 2° carboxylic acids, as well as 3° cyclopropyl carboxylic acids were amenable to this reaction. It is worth noting that carboxylic acid-bearing natural products and medicinal agents were successfully transformed into their trifluoromethyl analogs.

Following this report, trifluoromethylation of alkyl halide was reported by the same group using a dehalogenative approach using supersilanol as the XAT reagent (Scheme 30).[67] In this mechanistic scenario, the excited-state *Ir(III) species generates a silicon-centered radical from a deprotonation and radical Brook rearrangement with the tris(trimethylsilyl)silanol. The silyl radical can then abstract a bromine radical from the alkyl bromide, while a SET between Ir(II) and an electrophilic trifluoromethylation reagent would generate a CF_3 radical and regenerate Ir(III). This trifluoromethyl radical can be captured by Cu(I) to produce Cu(II)−CF_3. This resulting Cu(II)−CF_3 species is then expected to capture the alkyl radical to generate

Scheme 29. Trifluoromethylation via Cu/Photoredox Catalysis with Carboxylic Acids and Togni's Reagent I[b]

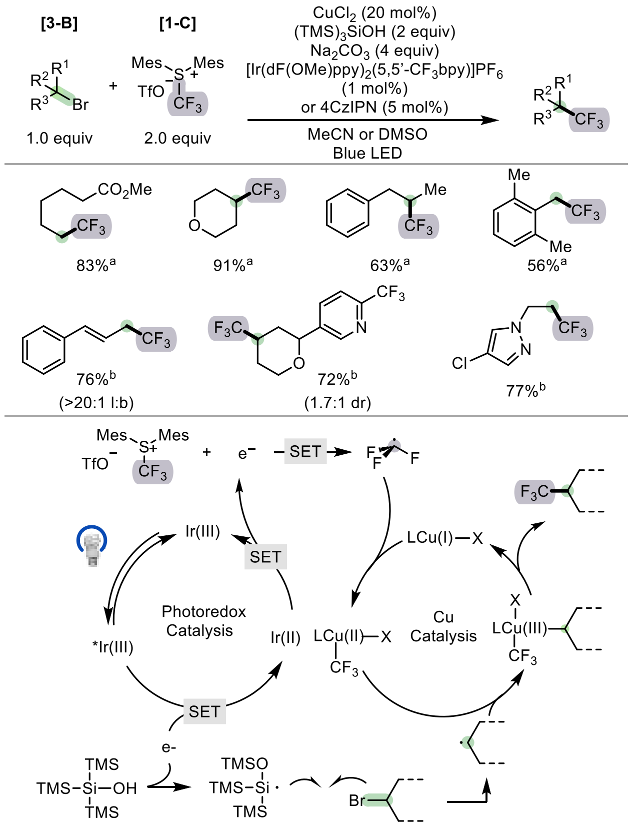


[a]Prepared with $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, $CuCl_2$, di(2-pyridyl)ketone (25 mol %), and TMG (0.5 equiv) instead. [b]All yields are based on ^{19}F NMR analysis of the crude reaction mixtures using an internal standard. BTMG refers to 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.

Cu(III) species followed by reductive elimination to afford the desired alkyl$-CF_3$ product. This methodology enabled a facile cross-coupling of CF_3 radicals with 1° benzylic, allylic alkyl bromides, including substrates that have heterocyclic arene systems. Trifluoromethylation was also showcased to drug derivatives, such as Celecoxib, Ticagrelor, or Pregabalin.

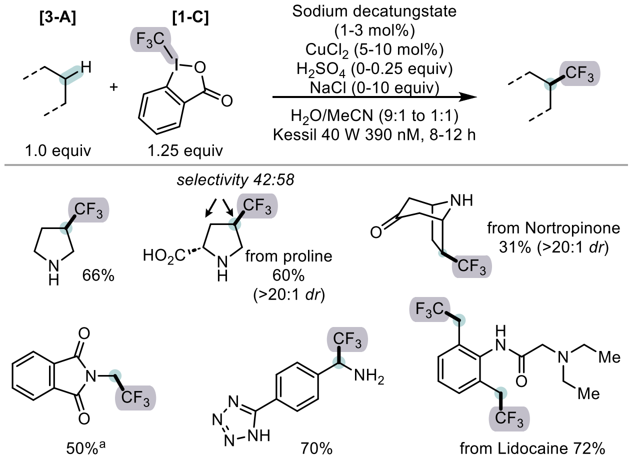
With such established tools to enable $C(sp^3)-CF_3$ bond formation, the Macmilllan group reported the development of a dual-catalytic $C(sp^3)-H$ trifluoromethylation through the merger of light-driven, decatungstate-catalyzed HAT and copper catalysis (Scheme 31).[68] This work employed Togni's reagent II as the trifluoromethylating reagent, selectively delivering CF_3 to several possible C$-$H bond sites. The scope included various secondary C$-$H or benzylic sites. For heteroatom-containing aliphatic rings, the C$-$H was abstracted at the most neutral site compared to the hydridic or protic sites. Furthermore, this methodology was applicable for late-stage trifluoromethylation on primary benzylic sites, such as Lidocaine, Prilocaine, Celecoxib, and Torsemide.

Scheme 30. Trifluoromethylation of 1° and 2° Unactivated Alkyl Bromides via Cu/Photoredox Catalysis



[a]Performed with 4CzIPN instead in DMSO for 1 h. [b]Performed with MeCN for 4 h.

Scheme 31. Cu/Photoredox-Catalyzed Trifluoromethylation of C−H Bond Substrates Activated by HAT



[a]Twenty percent CD_3CN in H_2O as solvent.

Advancing on these works, the same group published a deoxytrifluoromethylation utilizing benzoxazolium salts to activate alcohol substrates in situ for enabling $C(sp^3)-CF_3$ bond formation.[69]

10. SUMMARY AND OUTLOOK

The once deemed unattainable $C(sp^3)-C(sp^3)$ bond-forming cross-coupling reactions have witnessed significant advances in the past decade, overcoming challenges associated with closed-shell pathways. Dual catalysis involving transition metals and photoredox has played a pivotal role in introducing diverse alkyl coupling partners, breaking away from the conventional electrophile−nucleophile categorization of cross-coupling.

Numerous strategies incorporating orthogonal activation methods have been employed to facilitate the challenging formation of C(sp^3)−C(sp^3) bonds; however, substantial opportunities for further development persist. Efficient catalytic designs are warranted to address the inherent formation of alkyl radicals and homocoupling, necessitating exploration into novel C(sp^3) radical precursors. Furthermore, while existing methodologies propose reaction mechanisms, a comprehensive investigation into each of the elementary steps of the catalytic cycle remains elusive, accentuated by the diversity of reactions, suggesting a disparate reaction mechanism, prompting a need for meticulous analysis. Such mechanistic understandings may especially be helpful in the development of 2°−2°, 2°−3°, or 3°−3 °C(sp^3)−C(sp^3) cross-coupling, which remains still underdeveloped.

Moreover, the exploration of asymmetric reactions in C(sp^3)−C(sp^3) cross-coupling is a promising avenue, yet achieving stereoselective transformations at each stereocenter remains underexplored. In addition, the choice of catalysts offers further room for development with an emphasis on diversifying beyond the commonly used transition metals like Pd, Ni, and Cu. Additionally, exploring less costly alternatives to the precious-metal photocatalysts commonly reported in the literature presents a valuable opportunity.

Despite ongoing developmental needs, metallaphotoredox-catalyzed C(sp^3)−C(sp^3) reactions have opened novel chemical landscapes, particularly in the underexplored realm of medicinally relevant organic molecules.

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Notes

The author declares no competing financial interest.

Biography

Sun Dongbang received her B.S. and M.S. degrees in Chemistry from Korea University, Seoul, South Korea, where she worked on synthesizing fluorescent probes for intracellular imaging of drug localization. Later, she joined the lab of Jonathan A. Ellman at Yale University, where she worked on the total synthesis of (−)-naltrexone and the development of methodologies involving Co-catalyzed multicomponent reactions for accessing quaternary carbons. In 2020, she joined the laboratory of Abigail G. Doyle as a postdoctoral fellow at Princeton University, where she focused on developing Ni/photoredox-catalyzed C(sp^3)−C(sp^3) cross-coupling strategies. In 2023, she began her independent career at Sogang University, South Korea as an assistant professor, where her research interests lie in the development of new transition-metal and photoredox-catalyzed synthetic methods and total synthesis of complex natural products.

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