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Photoinduced Nickel-Catalyzed Deaminative Cross-Electrophile Coupling for $C(sp^2)$−$C(sp^3)$ and $C(sp^3)$−$C(sp^3)$ Bond Formation

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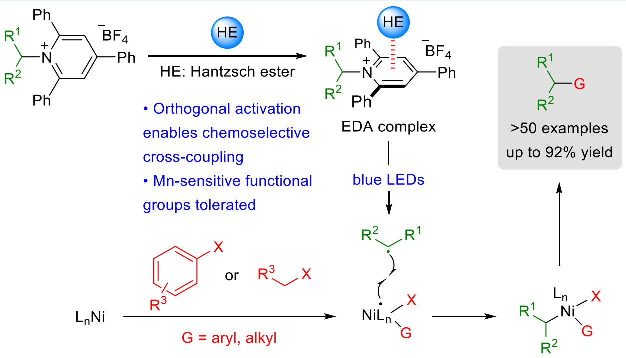
ABSTRACT: The construction of C−C bonds through cross-coupling between two electrophiles in the absence of excess metallic reducing agents is a desirable objective in chemistry. Here, we show that *N*-alkylpyridinium salts can be efficiently merged with aryl or alkyl halides in an intermolecular fashion, affording products in up to 92% yield at ambient temperature. These reactions harness the ability of *N*-alkylpyridinium salts to form electron donor−acceptor complexes with Hantzsch esters, enabling photoinduced single-electron transfer and fragmentation to afford alkyl radicals that are subsequently trapped by a Ni-based catalytic species to promote $C(sp^2)$−$C(sp^3)$ and $C(sp^3)$−$C(sp^3)$ bond formation. The operationally simple protocol is applicable to site-selective cross-coupling and tolerates diverse functional groups, including those that are sensitive toward metal reductants.



KEYWORDS: *photochemistry, nickel catalysis, pyridinium salts, cross-electrophile coupling, EDA complexes, deamination*

Transition-metal-catalyzed C−C bond forming cross-coupling[1] has revolutionized the way countless organic molecules are assembled, and it is an indispensable tool in the modern synthetic chemist's arsenal.[2] In particular, reductive cross-electrophile coupling has witnessed rapid development over the last two decades.[3] These transformations obviate the need to presynthesize organometallic reagents, allowing the direct union of two relatively more stable electrophilic organohalides,[4] pseudohalides,[5] or redox-active substrates[6] to deliver the product.

Because of the ubiquity, low cost, and ease of accessibility associated with aliphatic primary amines, recent advances have taken advantage of these feedstock chemicals to prepare air- and moisture-stable Katritzky pyridinium salts[7] as alkylating precursors in reductive coupling[8] (Scheme 1a). However, examples of these deaminative processes are limited and often involve elevated temperatures,[8a−d] and superstoichiometric amounts of an expensive organic reagent (such as tetrakis(dimethylamino)ethylene),[9] diboryl compound/base[10] or a metal (such as Mn, Zn)[8a−d] are required as terminal reducing agents. Consequently, problems such as reaction reproducibility that may arise from inconsistencies in the quality of commercially available metallic reductants,[4a,c,11] as well as environmental[12] and toxicity[13] issues during metal waste disposal, especially when the reactions are performed at large scale, are inevitable. Adding to these challenges is the incompatibility of certain reactive functional groups to metal reductive conditions (see below for further discussion). It merits mention that methods for deaminative alkylation[8b,14] are scarce, and the majority of these $C(sp^3)$−$C(sp^3)$ bond-forming processes rely on olefins as alkyl group precursors.

In addition to metal-catalyzed cross-coupling[7d,14b,15] and photocatalyzed C−C bond formation,[14d,e,g,16] the redox-active nature of *N*-alkylpyridinium salts was recently exploited in efficient photoexcitation of electron-donor−acceptor (EDA) complexes generated from the pyridinium salt with bis(catecholato)diboron (B_2cat_2),[17] Hantzsch ester,[18] or triethylamine[18] to deliver C−X (X = B, C, S) bonds under catalyst-free conditions (Scheme 1b). Inspired by these preceding observations, we speculated if we could leverage the photoactive EDA complex **I** formed between an *N*-alkylpyridinium salt **1** and a relatively inexpensive electron donor **3**, which, under visible-light irradiation, would furnish an unactivated alkyl radical species that could be captured in a nickel catalytic cycle (involving the reaction of organohalide **2**) to deliver the final adduct **4** (Scheme 1c). Through this new catalytic platform, stoichiometric metals or expensive reducing agents are avoided, enabling facile entry to a broader spectrum of multifunctional products that are otherwise inaccessible using previously established reductive regimes. Furthermore, the

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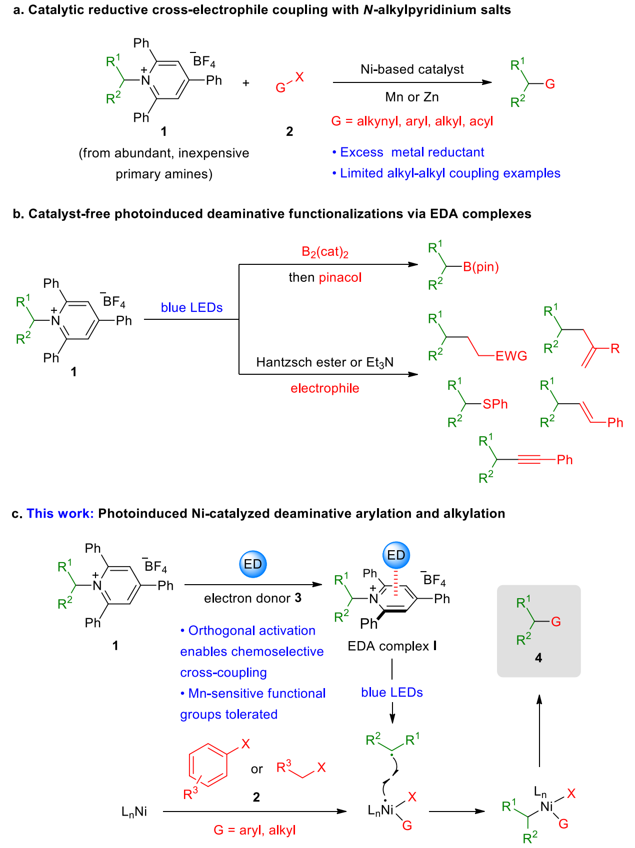
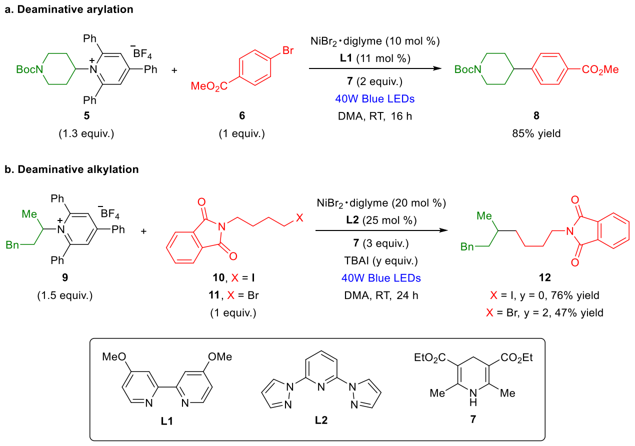
Scheme 1. Strategies for Deaminative Functionalizations with *N*-Alkylpyridinium Salts



Scheme 2. Conditions Identified for Photoinduced Ni-Catalyzed Deaminative Arylation and Alkylation[a]



[a] Yields are for isolated and purified products.

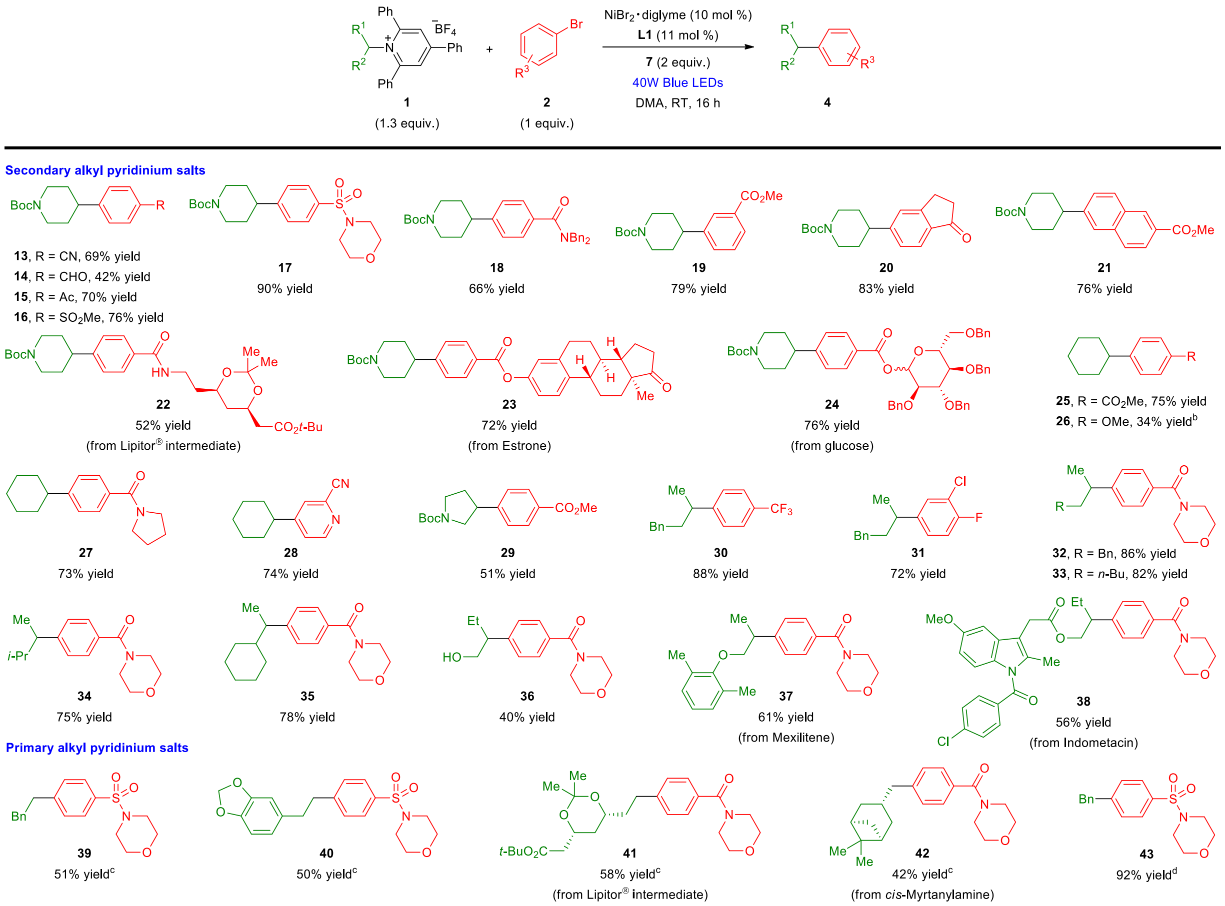
orthogonal activation of **1** and **2** means that difficult alkyl−alkyl cross-coupling reactions that are often susceptible to competitive homocoupling[4b,19] side pathways can be achieved under mild base-free conditions at ambient temperature without an exorbitantly large excess of either reactant, thereby reducing waste generation. Herein, we describe the successful implementation of a photoinduced deaminative strategy to facilitate $C(sp^2)-C(sp^3)$ and $C(sp^3)-C(sp^3)$ cross-electrophile coupling with readily available organohalides.

A survey of various Ni-based salts, ligands, electron donors, and solvents was performed to merge pyridinium salt **5** with aryl bromide **6** under blue light irradiation at ambient temperature (see the Supporting Information (SI) for details). We then found that the desired deaminative arylation product **8** was obtained in 85% isolated yield within 16 h, using 10 mol % of $NiBr_2$·diglyme and 11 mol % of bipyridine **L1** in the presence of Hantzsch ester **7** as a reductant and DMA as a solvent (see Scheme 2a). Replacing the Ni complex, ligand, or solvent with other alternatives led to lower yields, and no product was detected in the absence of the catalyst, **7** or light (see the SI for details). Reaction conditions were separately evaluated for the more-challenging union of pyridinium salt **9** with alkyl iodide **10** (see the SI for details), and 20 mol % of the Ni-based complex derived from $NiBr_2$·diglyme and **L2** was revealed to be optimal to furnish **12** in 76% isolated yield (83% GC yield; see Scheme 2b). Decreasing the catalyst loading to 10 mol % resulted in diminished efficiency (62% GC yield). Remarkably, performing the alkylation using a 1:1 ratio of **9** and **10** delivered **12** with a respectable GC yield of 55% (see the SI for details). This compares favorably with other reductive cross-electrophile protocols that employ super-stoichiometric quantities of one cross-partner (2−3 equiv) to suppress adventitious homocoupling,[8c] or entail strongly basic[7d,14b] and cryogenic conditions.[5g] Note that the analogous alkylation with bromoalkane **11**, in the presence of tetrabutylammonium iodide (TBAI) as an additive, could also generate **12** in 47% yield.

With the established conditions in hand, we first examined the scope of deaminative arylation using a diverse array of pyridinium salts **1** (secondary and primary alkyl, cyclic, and acyclic) as well as bromoarenes **2** (see Scheme 3). Generally, various electronically modified aryl bromides served as effective substrates in cross-coupling, affording products in up to 92% yield. These include molecules containing a nitrile (**13**), an alcohol (**36**), an aldehyde (**14**), a ketone (**15**, **20**), an ester (**19**, **21**, **25**, **29**), an amide (**18**, **27**, **32**−**36**), a sulfone (**16**) and a sulfoamide (**17**, **39**, **40**, **43**). Synthesis of Lewis basic heterocycle **28**, as well as products derived from multifunctional bioactive compounds (**22**−**24**, **37**, **38**, **41**, **42**) further underscores the exceptional functional group compatibility of the photoinduced catalytic reaction system. Benzylpyridinium salts are also amenable substrates, although purple light irradiation was required to give the product (**43**). Reactions with functionalized aliphatic iodides were subsequently investigated (see Scheme 4). Deaminative alkylation was found to proceed efficiently to deliver **44**−**57** in up to 73% yield. Commonly occurring functional groups such as a phthalimide (**44**, **46**, **47**, **53**, **54**), an amino ester (**49**), an ether (**55**) as well as an electron-deficient enoate (**45**, **56**) are tolerated. Chemoselective cross-coupling with the iodoalkane motif enables access to **48**, which bears a reactive aryl bromide handle that could be subjected to further transformations. Similar to the processes in Scheme 3, deaminative alkylation with substrates appended to complex molecules could be effected to generate the corresponding products **50**−**52**. Of particular note, the formation of **57** demonstrates a key advantage of the present photoinduced catalytic manifold, since alkyl-substituted aldehydes are found to be sensitive toward excess metallic reductants[8b,d] (see the SI for details).

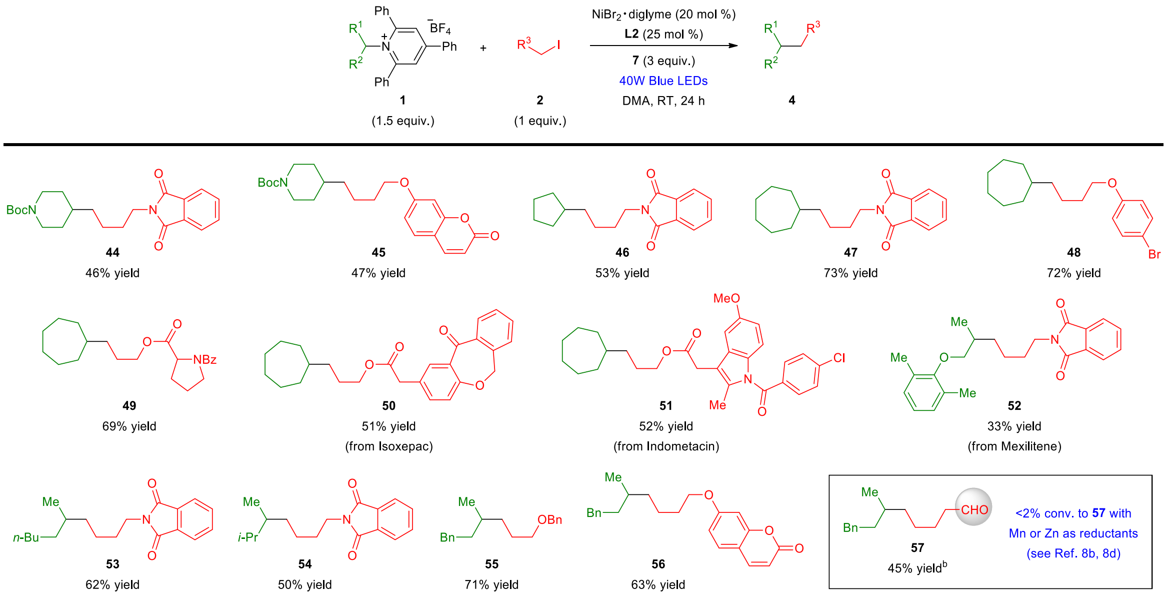
Formation of photoactive EDA complexes between *N*-alkylpyridinium salts **1** and **7** have already been documented in previous studies.[18] Further control experiments were per-

Scheme 3. Scope of Deaminative Arylation[a]



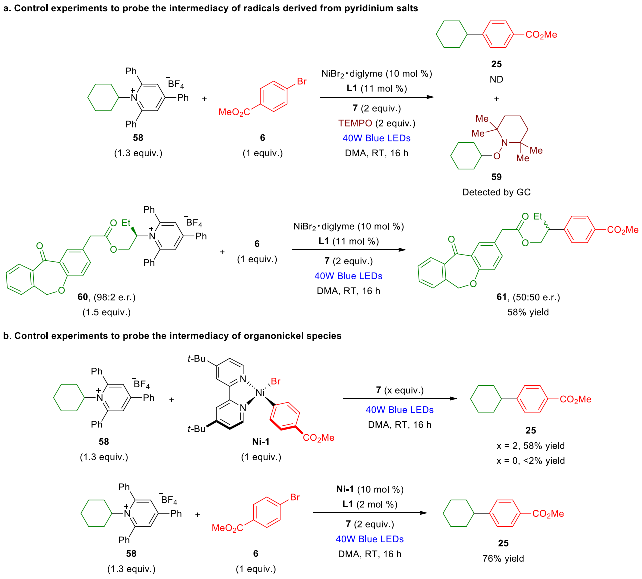
[a]Yields are for isolated and purified products. **4n** was obtained in a 1:1 diastereomeric ratio. [b]The reaction was conducted with 20 mol % Ni complex, 25 mol % **L1** and 2 equiv of pyridinium salt. [c]The reactions were conducted with 12 mol % 4,4′-di-*t*-Bu-bpy, 1.5 equiv pyridinium salt, and 3 equiv Et_3N. [d]The reaction was conducted with 20 mol % $NiBr_2$·diglyme, 25 mol % 4,4′-di-*t*-Bu-bpy, and 1.5 equiv of pyridinium salt under 40 W purple LEDs (390 nm) irradiation.

Scheme 4. Scope of Deaminative Alkylation[a]

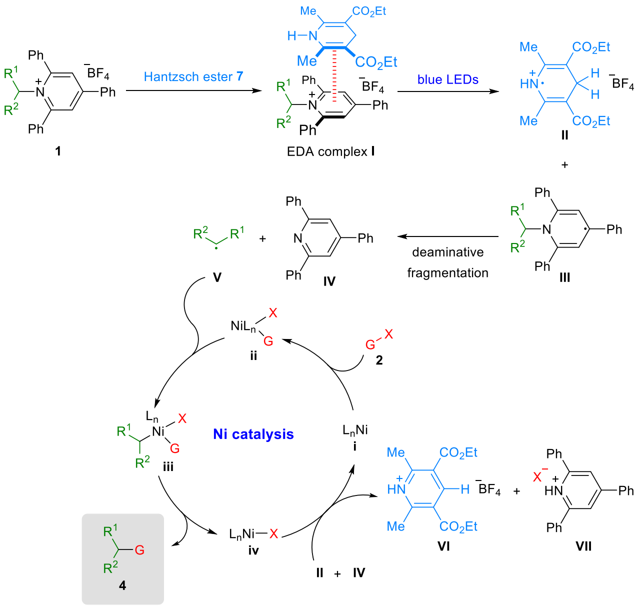


[a]Yields are for isolated and purified products. [b]The reaction was conducted with 20 mol % Ni complex and 25 mol % **L2**.

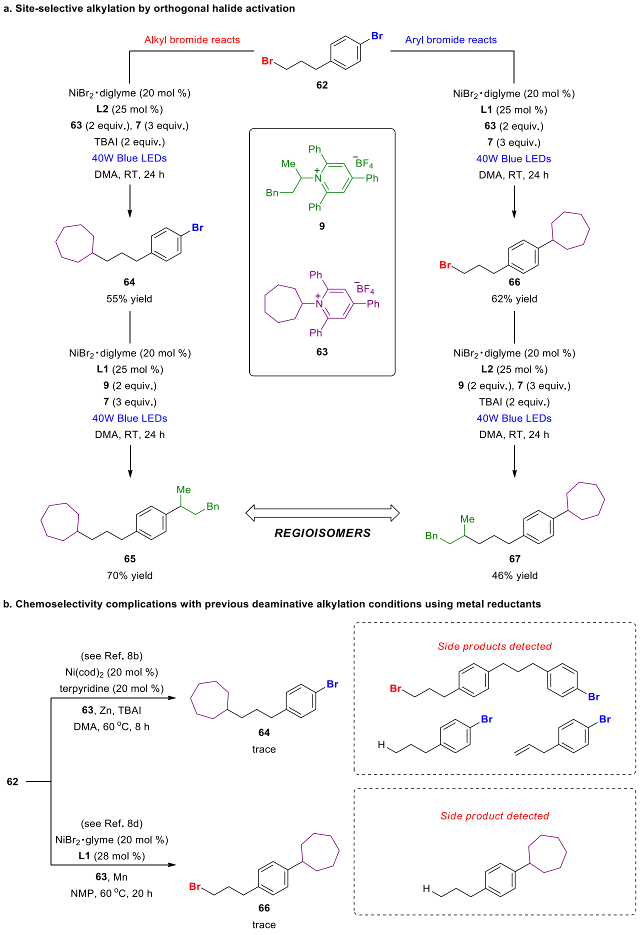
Scheme 5. Mechanistic Studies



Scheme 6. Proposed Mechanism for Photoinduced Ni-Catalyzed Deaminative Cross-Coupling



Scheme 7. Site-Selective and Chemoselective Incorporation of Aliphatic Groups by Photoinduced Catalytic Cross-Coupling



formed to provide evidence for the formation of radical intermediates (from **1**) in our system (Scheme 5a). When excess TEMPO was added to the standard reaction mixture, cross-electrophile coupling was suppressed and the TEMPO-trapped product **59** was detected by GC analysis. On the other hand, deaminative arylation of enantiomerically enriched **60** (prepared from commercially available (*R*)-2-amino-1-butanol) with **6** led to complete erosion of stereochemistry in the final product **61** (isolated in 58% yield as a racemic mixture), suggesting the formation of a radical species through a putative single-electron transfer (SET) pathway from **60**.[7d,8c]

To probe the supposed intermediacy of organonickel species, a separately synthesized bipyridine-Ni(II) complex **Ni-1** (derived from oxidative addition of the corresponding Ni(0) complex with **6**) was reacted with **58** under the established photoinduced cross-coupling conditions, and **25** was produced in 58% yield (Scheme 5b). As expected, <2% conversion to **25** was observed in the absence of the electron donor **7**. Furthermore, deaminative arylation of **58** with **6** was found to proceed smoothly in the presence of catalytic amounts of **Ni-1** and **L1**. These results substantiate the occurrence of an oxidative insertion process involving the organohalide **2** prior to alkylation with the pyridinium salt **1**.

Based on our studies, as well as past observations, we propose a tentative reaction mechanism, as shown in Scheme 6. An EDA complex **I**[18] is likely formed between *N*-alkylpyridinium salt **1** and Hantzsch ester **7**, which then undergoes photoexcitation and SET to give dihydropyridine radical cation **II** and **III**. Subsequent deaminative fragmentation of **III** yields triphenylpyridine **IV** and alkyl radical **V**, which presumably enters a Ni catalytic cycle by associating with Ni(II) complex **ii**, the oxidative insertion adduct derived from Ni(0) species **i** and organohalide **2** (either by direct oxidative addition or halogen atom abstraction/radical recombination[3a]). The resulting alkylnickel species **iii** is poised to undergo reductive elimination to furnish **iv** with concomitant release of the desired product **4**. To turn over the cycle, we surmised that **iv** is reduced back to **i** in the presence of **II** and **IV**, affording protonated pyridine byproducts **VI** and **VII**. Overall, the chemoselective activation of **1** and **2** enables the photoinduced catalytic cross-coupling to occur under mild ambient conditions. Further investigations to shed light on the exact nature of the in-situ-generated organonickel species are ongoing and will be disclosed in due course.

To showcase the value of our reaction system, dibromide **62** was subjected to sequences of photoinduced deaminative cross-coupling using *N*-alkylpyridinium salts **9** and **63** (Scheme 7a). Here, the alkyl bromide motif within **62** selectively underwent alkylation with **63** to give **64** in 55% yield. Following another alkylation with **9**, **65** was obtained in 70% yield. In a second set of transformations, **62** was selectively alkylated at the bromoarene site, using **63** to furnish **66** in 62% yield, which was further converted to **67** in 46% yield. Thus, access to both regioisomers **65** and **67** could be readily achieved without the need for tedious protection/deprotection strategies. In stark contrast, treatment of **62** to previously reported reductive deaminative conditions (with Mn or Zn)[8b,d] only led to complex product mixtures (Scheme 7b). These results highlight the unique capability of our photoinduced catalytic regime to effectively discriminate the multiple reactive sites of a substrate, which is crucial for attaining site-selective cross-coupling.[20]

In conclusion, we have developed a new catalytic manifold for deaminative arylation and alkylation that operates under mild reaction conditions. Central to this approach is the facile generation of aliphatic radicals from photoexcitation of pyridinium salt EDA complexes, and their subsequent engagement with an appropriate organonickel species to promote C−C bond formation. The present method demonstrates excellent functional group tolerance and offers a reliable avenue for site-selective installation of carbogenic motifs through orthogonal halide activation. Further extension of the strategy to other related transformations is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01416.

General information; optimization of reaction conditions; prepartion of starting materials; synthesis and characterization of products; mechanistic studies; associated references and NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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