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Regioselective Alkylative Cross-Coupling of Remote Unactivated C(sp^3)−H Bonds

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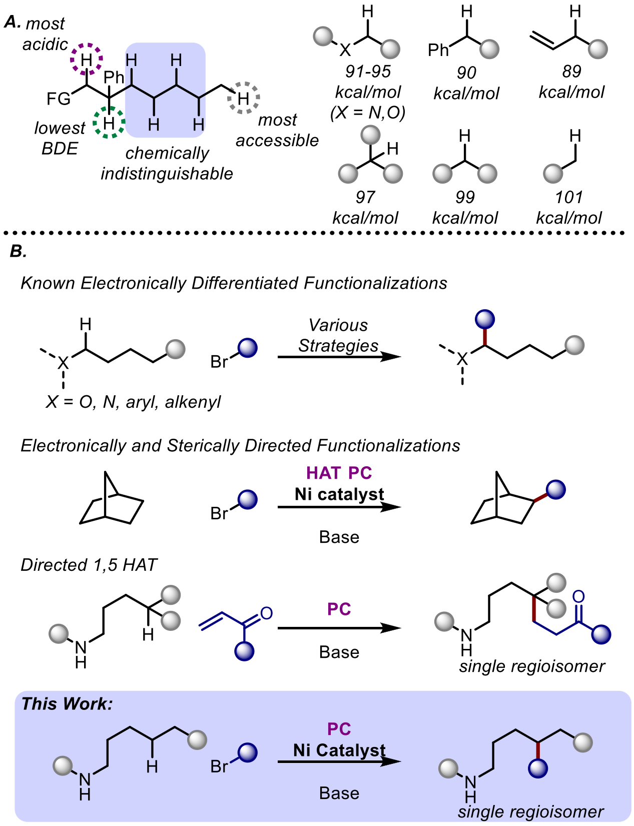
Supporting Information

ABSTRACT: The functionalization of unactivated C(sp^3)−H bonds poses a significant challenge due to their ubiquity and relative similarity in most organic frameworks. Herein, we describe the use of a combined photoredox and nickel catalytic system for the regioselective C(sp^3)−C(sp^3) coupling of unactivated C(sp^3)−H bonds and alkyl bromides. Positional selectivity is dictated by a 1,5-hydrogen atom transfer (HAT) reaction by a pendent amide. Interception of this radical by a Ni catalyst allows distal alkylation to occur in good yield and excellent selectivity.

The ubiquity of C−H bonds decorating organic molecules presents itself as the ultimate handle of chemical diversification. The ability to selectively and efficiently manipulate these C−H functionalities can greatly expedite and simplify synthetic routes through a greater diversity of potential bond disconnections. However, this ubiquity also poses a considerable selectivity challenge, as the differentiation between unbiased reactive sites can be marginal to largely indistinguishable.[1] Metal-catalyzed C−H activation has revolutionized our ability to quickly generate molecular complexity through the installment of new C−C, C−O, C−N, and C−X bonds.[2] While metal-catalyzed C−H activation has thrived on the functionalization of C(sp^2)−H bonds, the selective functionalization of C(sp^3)−H bonds poses an ongoing challenge.[3]

Techniques involving hydrogen atom transfer (HAT) have proven useful for the functionalization of intrinsically weak C(sp^3)−H bonds (Scheme 1).[4] Photoredox strategies that facilitate the generation of radical intermediates capable of HAT have expedited the growth of these avenues.[5] However, these radical intermediates target the weakest C−H bond in solution capable of a polarity matched transition state, which typically lie α to an existing functionality or heteroatom. In the absence of electronic positional bias, functionalization through these methods often occurs indiscriminately at chemically indistinguishable sites.[6] The coupling of a transition metal with these strategies has broadly expanded the breadth of bond disconnections through single-electron transmetalation.[7] This merger has culminated in the ability to cross-couple alkyl radicals generated from C−H bonds with metal-activated electrophiles to forge new C(sp^3)−C(sp^2) and C(sp^3)−C(sp^3) bonds.[8] Recent methodology has extended this reactivity to unactivated positions, although it requires a large excess of substrate and may generate mixtures of regioisomers.[9]

Scheme 1. Inspiration for the Development for the Regioselective Alkylation of C(sp^3)−H bonds: (A) Selectivity Challenges Present in the Functionalization of C−H Bonds in Organic Molecules; (B) Prior Art of Photoredox-Enabled HAT Strategies for the Functionalization of C(sp^3)−H Bonds in Comparison to This Work



Our group and the Knowles group has previously demonstrated selective functionalization of distal C(sp^3) sites with new C−C bonds through a 1,5-HAT strategy through a photoredox-catalyzed oxidation of a pendent amide moiety.[10] The remote carbon radical, generated through a six-membered transition state, is sufficiently long-lived to trap exogenous Michael acceptors to furnish a δ-functionalized amide. This strategy showcases the ability to regioselectively monofunc-

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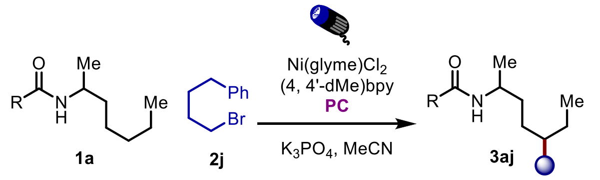
tionalize an unactivated distal methine or methylene in the presence of more electronically or sterically activated C−H bonds.

We sought to unify the selectivity imparted through 1,5-HAT with the versatility offered through nickel catalysis to selectively alkylate distal bonds. In doing so, one of numerous otherwise indistinguishable methylene sites can be coupled selectively to the wealth of commercially available or easily accessible alkyl bromides.

We first examined whether the distal alkyl radical generated through 1,5-HAT could be captured by a metal catalyst. Due to the well-established ability of nickel bipyridine complexes to participate in metallophotoredox cross-couplings,[11] we chose to screen these species in conjunction with our previously established methods[10a] for forming a distal alkyl radical (Table 1).[12] Alkyl trifluoroacetamides are particularly well-suited to directing the 1,5-HAT in the presence of a sufficiently strong base. Interestingly, the reaction only proceeds at remote sites bearing secondary C(sp^3)−H bonds (Scheme 2). Other directing groups which decrease the acidity of the N−H proton proved unreactive, including when these systems were run using conditions developed by Knowles[10b] relying on proton-coupled electron transfer (PCET; Table 1, entries 4−6). Additionally, all of the reactive components are necessary, as removal of light, the photocatalyst, Ni, ligand, or base all result in no product formation (Table 1, entries 7−11).

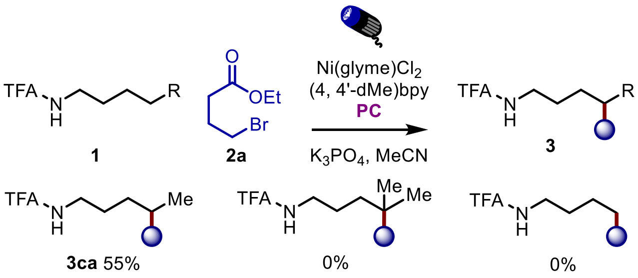
Table 1. Optimization and Control Studies



Entry	R Source	Deviation from Standard Conditions[a]	Yield (%)
1	**CF_3**	**none**	**79**
2	CHF_2	none	0
3	CF_2CF_3	none	61
4	Ph	PC-2, $NBu_4OP(O)(OBu)_2$	0
5	Ph	none	0
6	CF_3	PC-2, $NBu_4OP(O)(OBu)_2$	0
7	CF_3	Without Ni	0
8	CF_3	Without Ligand	0
9	CF_3	Without PC	0
10	CF_3	Without Light	0
11	CF_3	Without Base	0

[a] Optimizations were performed on 0.1 mmol scale using **1a** (1 equiv), **2j** (2 equiv), Ni source (10 mol %), ligand (12 mol %), base (4 equiv), and **PC** (1 mol %) over a period of 36 h. **PC** = $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$. PC-2 = $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$.

Scheme 2. Effect of Substitution at *δ*-Position



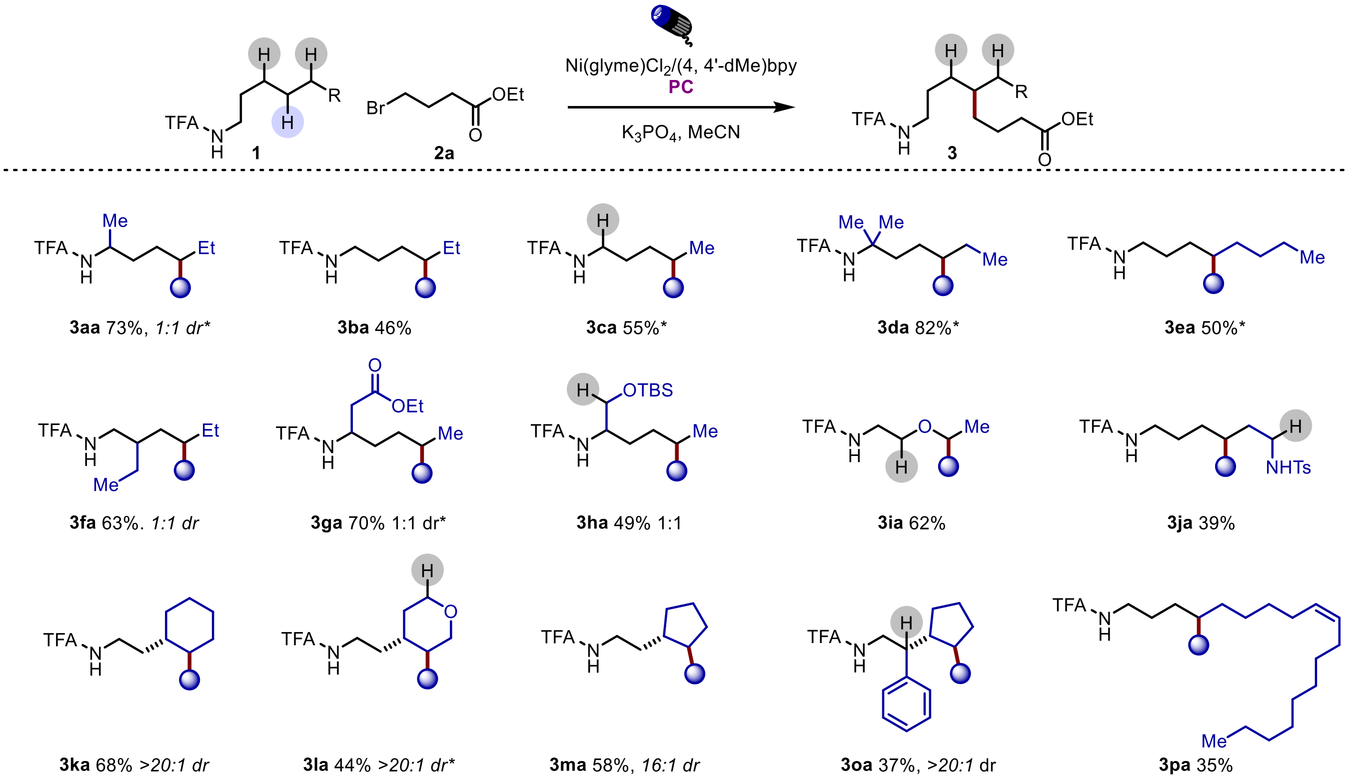
Having established that this strategy effectively forges a new C−C bond regioselectively at a distal C−H, we examined its scope. Aliphatic linear amides participate well and are monofunctionalized at the *δ*-methylene site (Scheme 3). Interestingly, even with the generation of a tertiary site at the *δ*-position, no second cross-coupling occurs at that site, which differs from the related capture of Michael acceptors.[10a] In the case of multiple functionalizable sites, secondary positions are selectively functionalized in preference over primary positions, **3fa**. In cyclic systems, cross-coupling tends to occur in a *trans* relationship, probably due to the preference of radical capture of the active Ni catalyst on the sterically less hindered side of the ring (see Supporting Information, p S5). This allows for alkylation of five- and six-membered ring systems with high diastereoselectivity. In substrates featuring more activated C(sp^3)−H bonds in positions other than those *δ* to the amide moiety, functionalization occurs solely at the unactivated, directed site in preference over the weaker, more reactive C(sp^3)−H bonds. This allows for the tolerance of sulfonamides (**3ja**), ethers (**3ia** and **3la**), arenes and alkenes (**3oa** and **3pa**), and their adjacent activated C−H bonds, albeit with occasionally diminished yields.

The scope of the alkyl bromide coupling partner was also explored (Scheme 4). In nearly all cases, the alkyl halide is used in excess to the aliphatic amine, as the alkyl bromide is consumed in a competing reductive homocoupling. This reductive homocoupling outcompetes desired cross-coupling in low concentrations of amide, resulting in incomplete conversion of the amide but complete consumption of the alkyl bromide. Most aliphatic alkyl bromides, including ethyl, are tolerated under the reaction conditions (**3kb**). Other functionalities, including protected alcohols, **3kf**, nitriles, **3kg**, and alkenes, **3kh**, also participate well in the reaction. Interestingly, benzylic bromides are not tolerated, presumably due to the competing off-cycle reduction by the photocatalyst which generates free benzyl radicals. Other heterocycles are tolerated, including dioxolanes, **3ki**, phthalimides, **3kk**, and pyrroles, **3kl**. Aryl bromides are tolerated, **3km**, as the primary alkyl bromide is considerably more reactive. Alkyl bromides bearing electronically diverse arene rings are well tolerated under the standard conditions (**3kj**−**3ko**). Currently, alkyl bromides are the only productive alkyl halides as chlorides, iodides, and pseudohalides such as tosylates and triflates are either unreactive or lead to unproductive byproducts. Secondary and tertiary alkyl bromides show diminished yields under the optimized conditions and have thus far only shown modest levels of synthetic efficiency.[14]

Isotopically labeled tags can be easily incorporated under these conditions allowing for the isotopic differentiation of otherwise symmetrical groups. The reactivity can also be performed sequentially when there are more potential abstraction sites, allowing for the difunctionalization of **2k** with two distinct coupling partners in excellent diastereoselectivity. Alternatively, orthogonal reactivity can be performed to generate quaternary carbon centers through the direct radical capture of a suitable radicalophile.[10a] This allows for the selective, mild generation of a distal quaternary carbon from a previously unactivated or functionalized methylene site, **4b**.

A potential mechanism that accounts for the observed transformation and regioselectivity is represented by the

Scheme 3. Reaction Scope (Amides)[a]



[a]Reactions were run on 0.1 mmol scale with 2 equiv of **2a**, 10 mol % Ni(glyme)Cl_2, 12 mol % 4,4′-dimethyl-2,2′-bipyridine, 1 mol % PC ([Ir(dF-CF_3ppy)$_2$dtbbpy]PF_6), and 4 equiv of K_3PO_4 in 0.75 mL of MeCN for 36 h. *Product assay purity 93-96% (contains 4%−7% inseparable impurity of product-derived olefin) (see SI).

catalyst system depicted in Scheme 5A. The trifluoroacetamide directing group, which is sufficiently acidic to be deprotonated by the phosphate base, is oxidized by an excited-state photocatalyst to generate a neutral amidyl radical, **V**. This amidyl radical can then abstract a hydrogen atom in a 1,5-HAT fashion from the δ-methylene to afford a carbon-centered radical at the distal position, **VI**. Meanwhile, a low-valent nickel complex, **I**, can oxidatively insert into the alkyl bromide to generate a Ni^{III} alkyl species, **II**. This Ni^{III} can be reduced to a Ni^{II} species by the reduced-state photocatalyst which can then trap the distal carbon radical to afford a transient Ni^{III}, **VII**, which undergoes reductive elimination to afford the newly formed C−C bond and regenerate a catalytically active Ni^{I}.

It should be noted that this reaction proceeds when using either Ni(cod)$_2$ or Ni(glyme)Cl_2 as the precatalyst. When using a Ni^{II} precatalyst, as in the optimized conditions, a reduction of the catalyst to a low valent Ni species is likely required before entering the catalytic cycle. In the cases where a Ni^0 catalyst is used, an increased amount of reductively homocoupled alkyl bromide is observed, which likely helps generate the necessary Ni^{I}.[15]

One perplexing caveat of the reactivity exhibited by the 1,5 HAT/Nickel cross-coupling is the lack of observed reactivity at tertiary positions, especially considering that these positions exhibit a multitude of functionalization methods through 1,5-HAT strategies.[13] This lack of reactivity also mirrors that of the more sterically demanding alkyl bromides, as the presumably more sterically encumbered Ni active species demonstrates diminished catalytic efficiency. Despite screening a number of ligands, none produced a cross-coupled product in either set of conditions.

In order to more thoroughly probe the fate of the tertiary radical, several mechanistic studies were performed (Scheme 5). We tested this hypothesis through deuterium labeling of the amidyl N−H and conducting the reaction in deuterated solvent to ensure that any alkyl radical abstraction or reversible 1,5-HAT would incorporate deuterium into the product. The absence of deuterium in the product demonstrates that C−C bond formation is diastereoselective rather than a result of epimerization to the more stable diastereomer after alkylation. Due to the low reactivity of tertiary reactive sites, we hypothesize that the reductive elimination of the tertiary alkyl group to generate a quaternary carbon is relatively slow (Scheme 5C). Instead, it is possible that the long-lived Ni^{III} intermediate could in turn be reduced by the photocatalyst and undergo elimination to generate Ni^0 and an alkene.[16] Olefinic products are observed with more sluggish substrates which supports the likelihood of this pathway. This was further corroborated by the fact that a variety of olefinic products, primarily the δ−ε alkene, are observed when utilizing substrate **1p**. This reactivity of the generated tertiary position enables the formation of unsaturated elimination products that remain as inseparable impurities in some isolated products. Deuteration of the activated position (**1c-d$_4$**) results in the conservation of the second deuteron in the alkylated product. This indicates that if 1,5-DAT occurs on the generated tertiary center then the process is reversible through either a retro-1,5-DAT or a Ni mediated delivery of a hydrogen atom to the alkyl radical through metalation, reduction, and protonation. It

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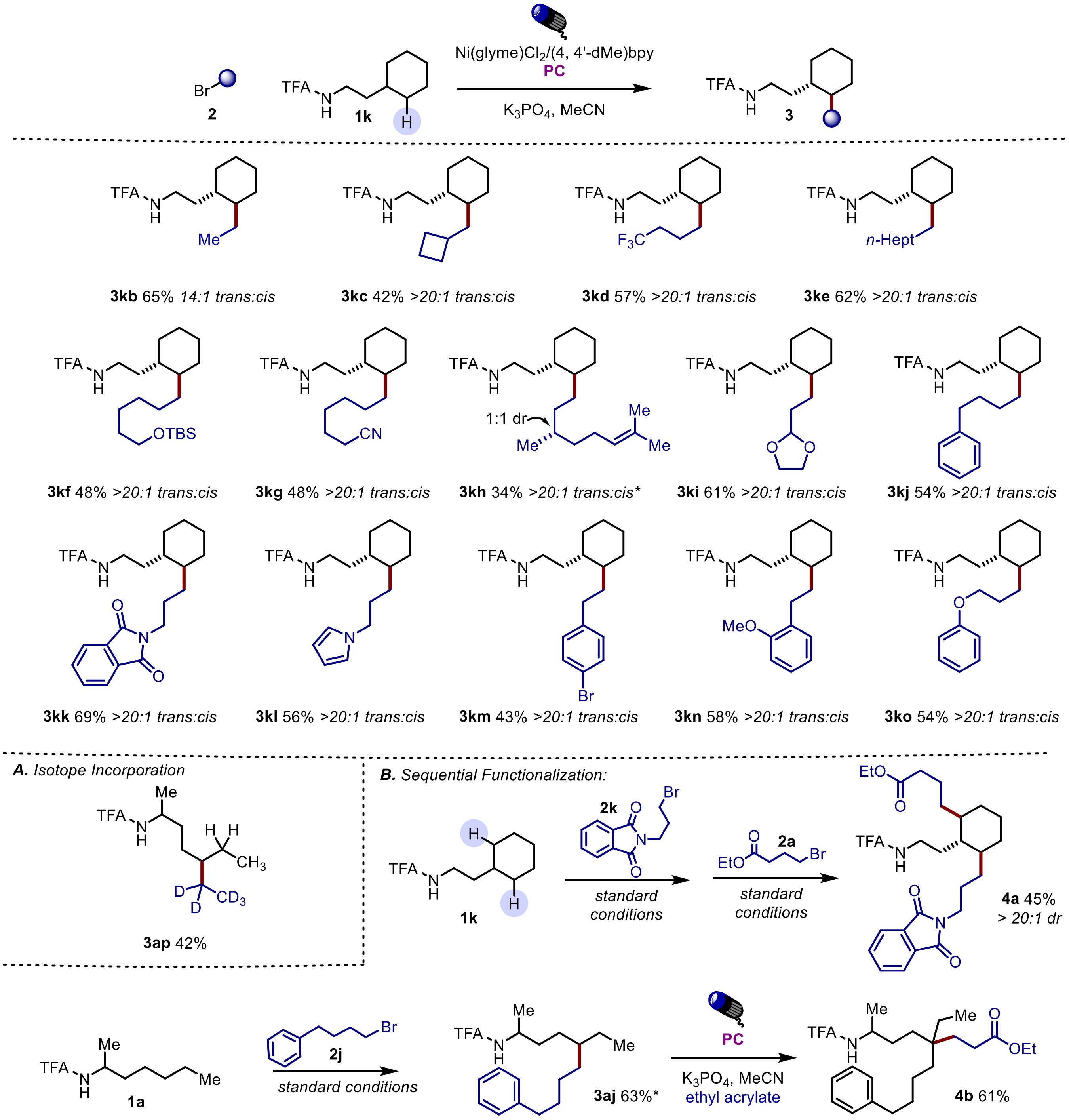
Scheme 4. Representative Examples of Alkyl Bromides[a]

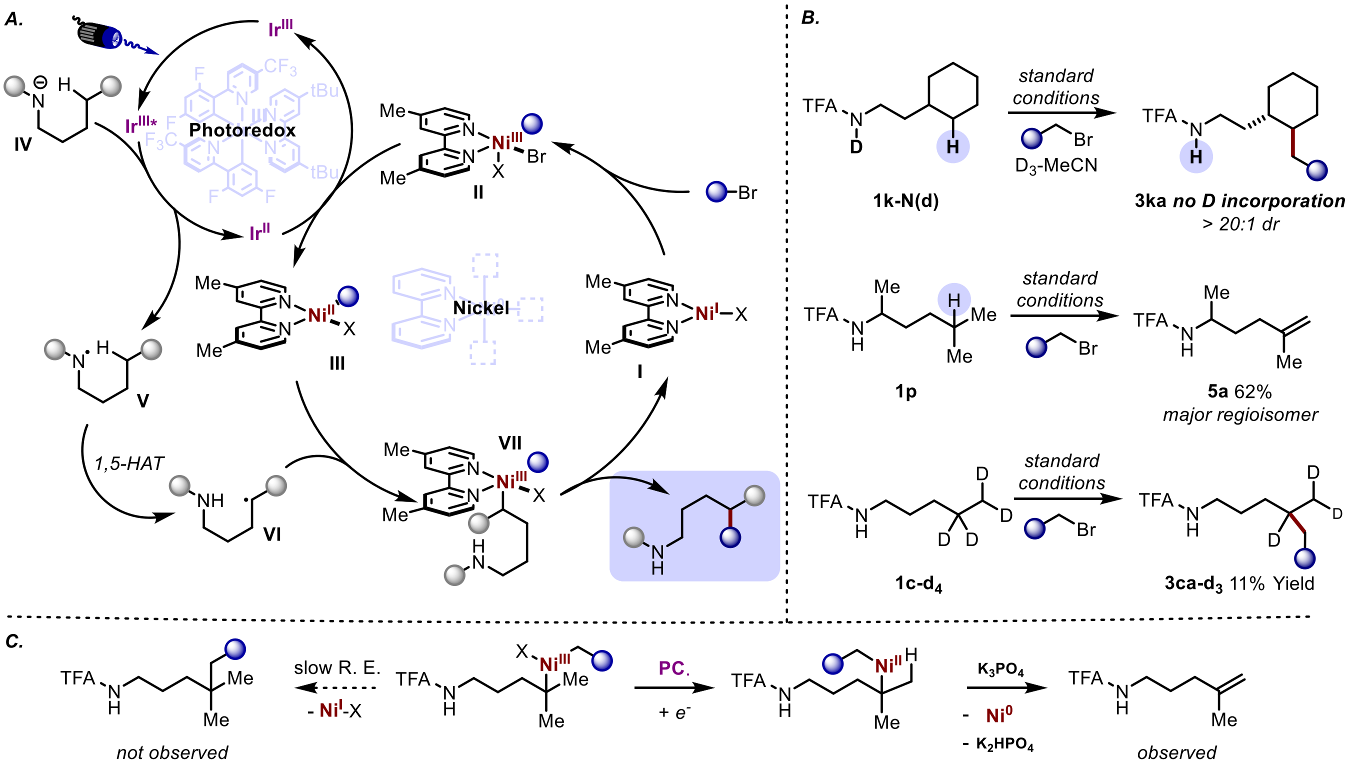


[a] Reactions were run on 0.1 mmol scale with 2 equiv of alkyl bromide, 10 mol % Ni(glyme)Cl$_2$, 12 mol % 4,4′-dimethyl-2,2′-bipyridine, 1 mol % PC ([Ir(dF-CF$_3$ppy)$_2$dtbbpy]PF$_6$), and 4 equiv of K$_3$PO$_4$ in 0.75 mL of MeCN for 36 h. (A) Deuterotopically labeled alkyl bromides can be utilized to incorporate deuterated fragments into substrates otherwise lacking reactive handles. (B) Sequential functionalization is available through this reactivity, as symmetrical reactive sites can be functionalized without degradation of diasteroselectivity. The reactivity can also be paired with prior disclosed methods to effectively furnish quaternary sites. *Product assay purity 95-98% (contains 2-5% inseparable impurity of product-derived olefin) (see SI).

seems likely, therefore, that the 1,5-abstraction and Ni capture may occur in the case of δ-methines, but then results in elimination upon reduction or other unproductive side reactions.

We have demonstrated functionalization of distal unactivated C(sp^3)−H bonds through a photoredox mediated 1,5-HAT and nickel cross-coupling strategy. This allows for the broad diversification of possible synthetic building blocks that can be selectively incorporated at an unactivated distal methylene site. Studies indicate that this coupling is selective for monoalkylation, resulting in distal tertiary carbon centers.

Scheme 5. Mechanistic Insights into the Distal C−H Alkylation: (A) Potential Mechanism; (B) Deuteration Studies and Reactivity with Tertiary Substrates; (C) A Proposed Reaction Pathway Describing the Fate of Tertiary Nickel Intermediates in Which Slow Reductive Elimination Allows for Competing Substrate Oxidation



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07014.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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