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Communication

Aminoalkylation of Alkenes Enabled by Triple Radical Sorting

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ABSTRACT: The direct synthesis of C(sp^3)-rich architectures is a driving force for innovation in synthetic organic chemistry. Such scaffolds impart beneficial properties onto drug molecules that correlate with greater clinical success. Consequently, there is a strong impetus to develop new methods by which to access sp^3-rich molecules from commercial feedstocks, such as alkenes. Herein, we report a three-component aminoalkylation reaction that utilizes the principles of triple radical sorting to regioselectively add N-centered and C-centered radicals across alkenes. This process relies upon photoredox catalysis to transform alkyl bromides and reductively activated N-centered radical precursors into high-energy radical species in a redox-neutral fashion. A broad scope of coupling partners is demonstrated, with multiple synthetic applications, including facile syntheses of pharmacophoric substituted N-heterocycles.

The development of methods to access medicinally relevant scaffolds is a major focus of synthetic organic chemistry.[1] Two prominent features of modern drug molecules are nitrogen atoms and C(sp^3)-hybridized carbon atoms. Nitrogen is ubiquitous within drug molecules, demonstrated by its presence in 84% of approved pharmaceutical scaffolds.[2] Likewise, incorporation of C(sp^3)-rich architectures into pharmaceutical candidates is a key metric of clinical success, as exemplified by the increasing fraction of sp^3-hybridized carbon atoms through each phase of drug discovery.[3]

Thus, the ability to simultaneously introduce both a nitrogen atom and a C(sp^3)−C(sp^3) bond to a chemical feedstock would represent an attractive, practical advance in the synthesis of medicinally relevant molecules. One approach to this goal would involve the direct aminoalkylation of commercially abundant alkenes (Figure 1a). Recent reports have explored the ability of alkenes to serve as cross-coupling partners for transition-metal catalyzed C(sp^3)−C(sp^3) bond formation through a metal-hydride hydrogen atom transfer (MHAT) process.[4−9] Anti-Markovnikov C(sp^3)−N bond formation followed by HAT has also been widely explored through myriad hydroamination reactions.[10−18] Expanding on hydroamination, a variety of aminofunctionalization reactions have been developed, wherein the radical generated upon nitrogen addition can undergo a broad spectrum of transformations.[19−29] While methods for intramolecular aminoalkylation have been disclosed, including an elegant nickel-catalyzed method from Leonori and co-workers,[30] the direct intermolecular aminoalkylation of alkenes has remained challenging. Reported methods for this transformation include radical conjugate addition of the formed β-amino radical with styrenes and electrophilic alkenes,[31−33] and energy-transfer initiated chain processes to form carbonyl-containing compounds.[34,35]

Recent work from our group and others has shown the ability of various metal complexes to efficiently sort alkyl radicals toward C(sp^3)−C(sp^3) bond formation through bimolecular homolytic substitution (S_H2) mechanisms.[6−9,36−40] This manifold of radical sorting has been expanded to allow "triple radical sorting", wherein two transient carbon-centered radicals are simultaneously generated and sorted by both an alkene and an S_H2 catalyst.[41−43] These multicomponent couplings proceed through electrophilic carbon-centered radical addition to an unactivated alkene, generating a nucleophilic radical, which then undergoes S_H2 with an *in situ* formed alkyl metal species to deliver dicarbofunctionalized products. We wondered whether this triple radical sorting mechanism could be expanded to encompass highly reactive heteroatom radicals, such as nitrogen-centered radicals. Certain nitrogen-centered radicals are sufficiently electrophilic to add into alkenes,[20] but we hypothesized that deleterious side reactions, such as hydrogen atom transfer (HAT)[44] and addition to the metal catalyst,[24] could hinder effective alkene difunctionalization.

Our design plan involves three distinct phases of radical sorting (Figure 1b). First, an electrophilic N-centered radical and a nucleophilic C-centered radical are simultaneously generated and electronically sorted by the unactivated alkene. Unactivated alkenes are typically π-nucleophilic,[45] so the electrophilic N-centered radical should outcompete the nucleophilic C-centered radical for alkene addition. This N-centered radical addition generates a sterically hindered tertiary radical, which is disfavored from adding to the nickel radical sorting catalyst due to the weaker bond strengths of more hindered nickel−alkyl species.[38] In contrast, the unhindered primary radical should form a significantly stronger nickel−carbon bond,[38] allowing sorting of the two nucleophilic radicals based on steric parameters. The final phase of the

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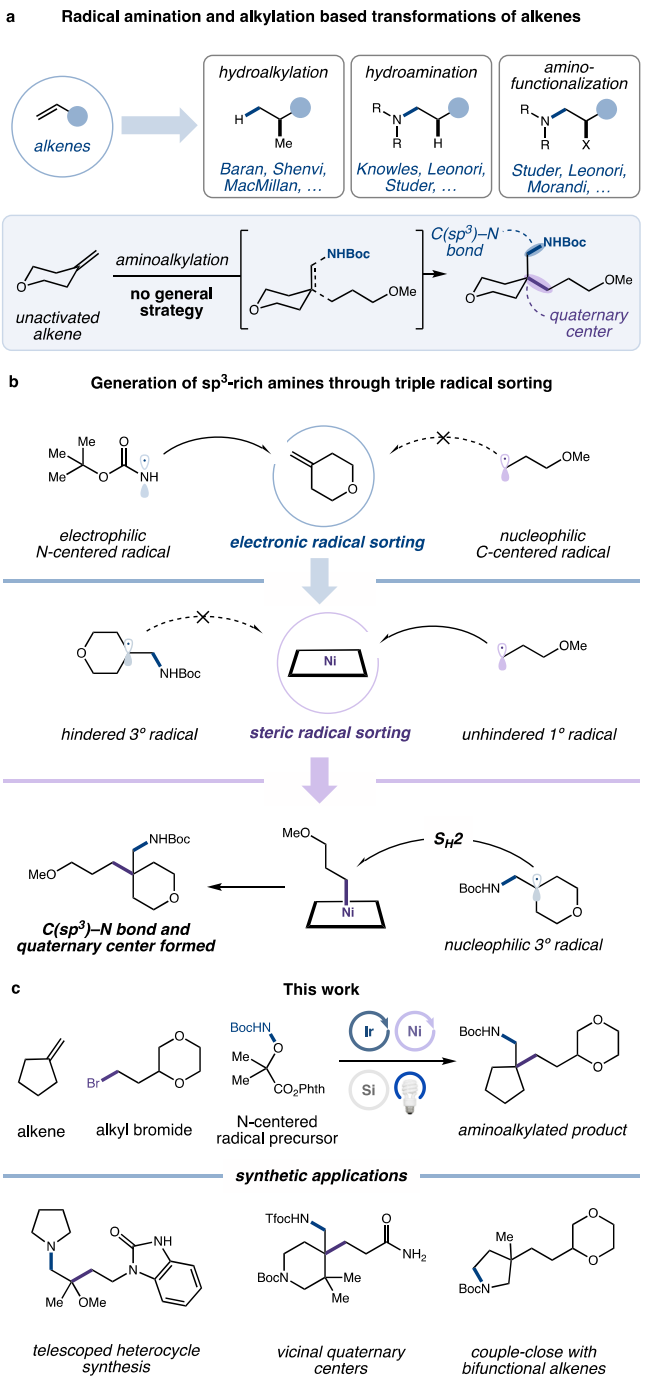


Figure 1. Aminoalkylation of alkenes.

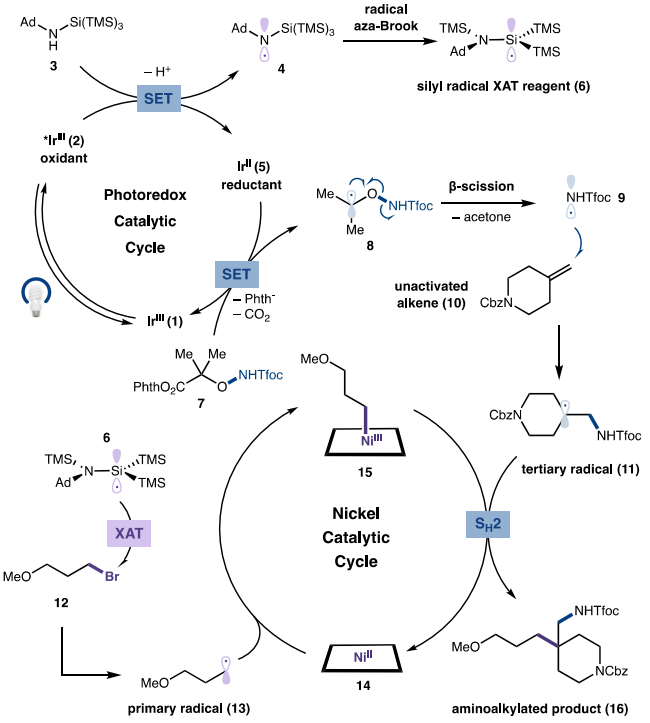
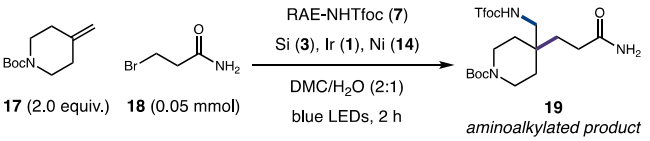


Figure 2. Proposed mechanism.

Table 1. Control Reactions for Aminoalkylation[a]



17 (2.0 equiv.) 18 (0.05 mmol) 19 aminoalkylated product

Entry	Deviation	Yield[b]
1	none	62%
2	no light	0%
3	no photocatalyst	0%
4	no nickel catalyst	5%
5	no Si (**3**)	0%
6	no N_2 sparge	21%
7	1.0 equiv of **3**, **7**, **17**	40%

[a]Reactions were performed with **7** (1.5 equiv), **3** (1.5 equiv), **1** (1 mol %), **14** (25 mol %), DMC/H_2O (2:1, 0.067 M), integrated photoreactor (450 nm, 50% light intensity). [b]Yields were determined by uHPLC analysis versus mesitylene as an internal standard. See SI for experimental details.

proposed sequence involves quaternary C(sp^3)–C(sp^3) bond formation via S_H2 reaction of the nucleophilic tertiary radical with the metal alkyl species. This step would furnish the final aminoalkylated product, featuring a new C(sp^3)–N bond and a C(sp^3)–C(sp^3) bond regioselectively forged across a degree of unsaturation.

To accomplish our goal of alkene aminoalkylation, we envisioned using metallaphotoredox catalysis, which has been extensively applied in the generation and subsequent cross-coupling of free radical species from traditionally inert partners.[46] The requisite alkyl radicals would be generated from feedstock alkyl bromides through halogen-atom transfer (XAT) by an oxidatively activated silane species.[47−49] To ensure a redox-neutral catalytic cycle, we required a reductive mode of N-centered radical generation. Inspired by reports of oxidative N-centered radical formation through decarboxylation and carbonyl β-scission,[21,26] we sought to invert the redox cycle by appending a redox-active *N*-hydroxyphthalimide ester to the carboxylic acid, rendering the species reductively activated.[50] Herein, we report the metallaphotoredox-mediated, three-component coupling of alkyl bromides, alkenes, and nitrogen-centered radical precursor substrates to forge a broad scope of aminoalkylated products. Synthetic applications of this method include formal N-heterocycle aminoalkylation through a telescoped heterocycle synthesis protocol, the formation of vicinal quaternary centers, and couple-close[43,51] sequences for ring synthesis (Figure 1c).

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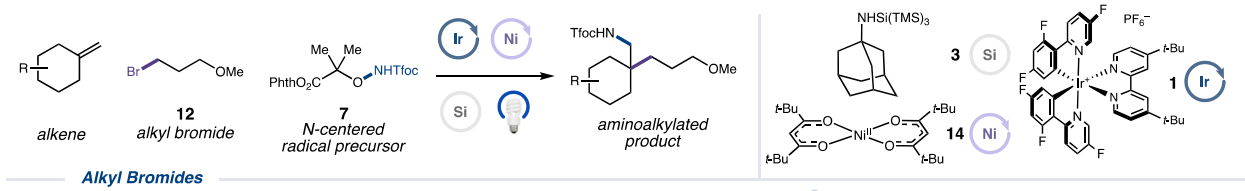
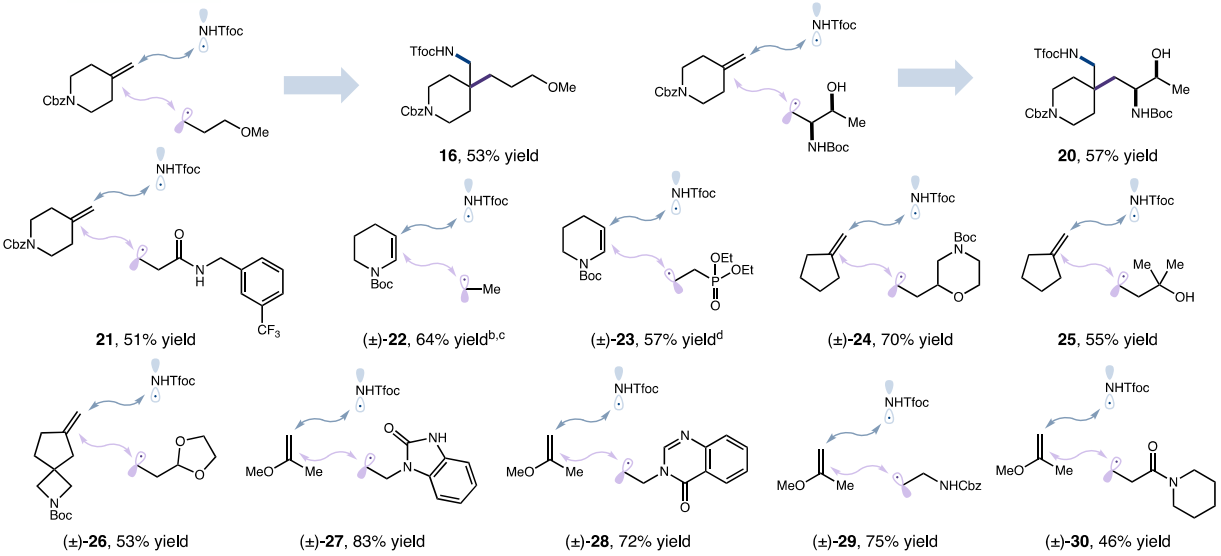
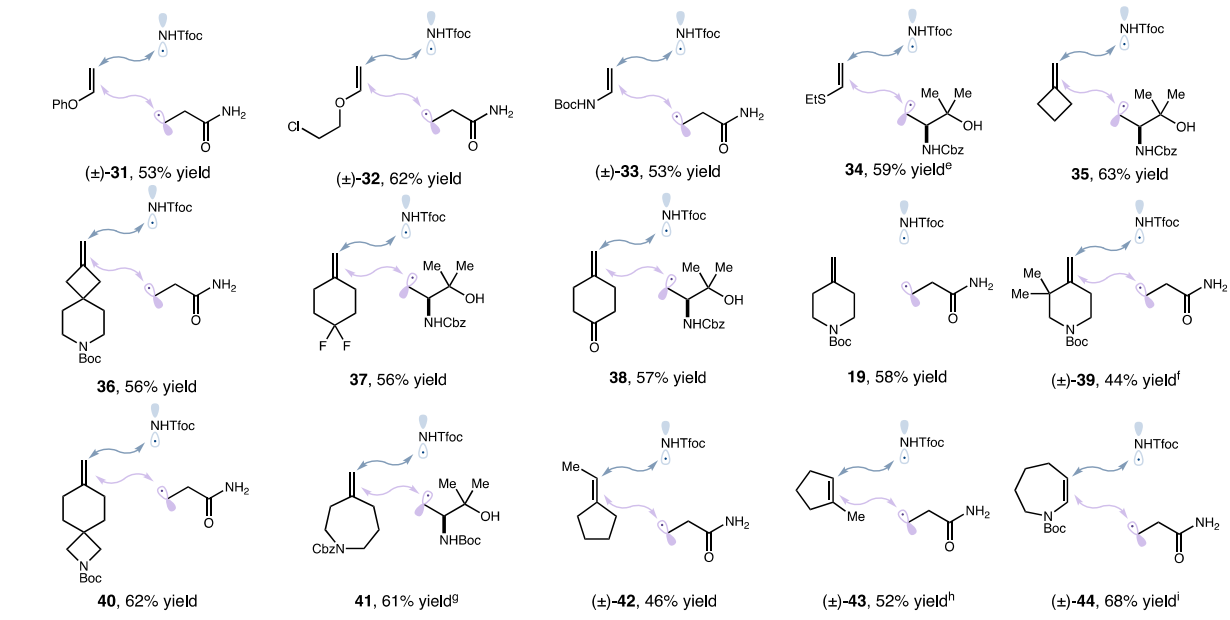
Table 2. Substrate Scope[a]



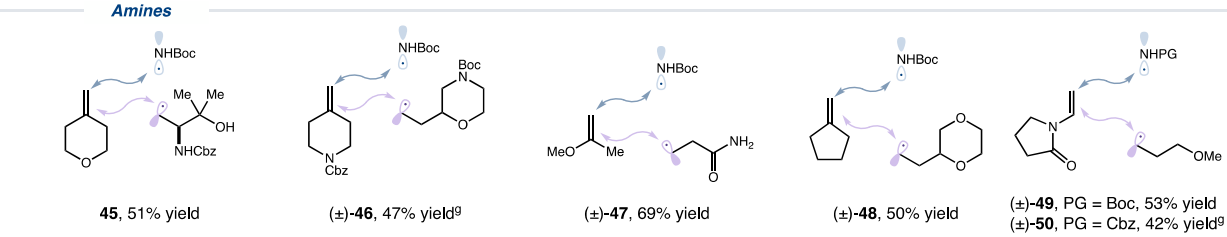
Alkyl Bromides



Alkenes



Amines



[a]Reactions performed on 0.5 mmol scale unless otherwise noted with alkene (2.0 equiv), alkyl bromide (1.0 equiv), N-centered radical precursor (1.5 equiv), **3** (1.5 equiv), **1** (1 mol %), **14** (25 mol %), 2:1 DMC/H_2O (0.067 M), integrated photoreactor (450 nm, 50% light intensity), 2 h. Isolated yields are reported unless otherwise noted. [b]Nickel(II) acetylacetonate (25 mol %) and potassium trispyrazolylborate (25 mol %) used instead of **14**. [c]2:1 d.r. [d]2.3:1 d.r. [e]1:1 d.r. [f]Yield determined by uHPLC analysis versus mesitylene as an internal standard. [g]See SI for experimental details. [h]3.4:1 d.r. [i]4.1:1 d.r.

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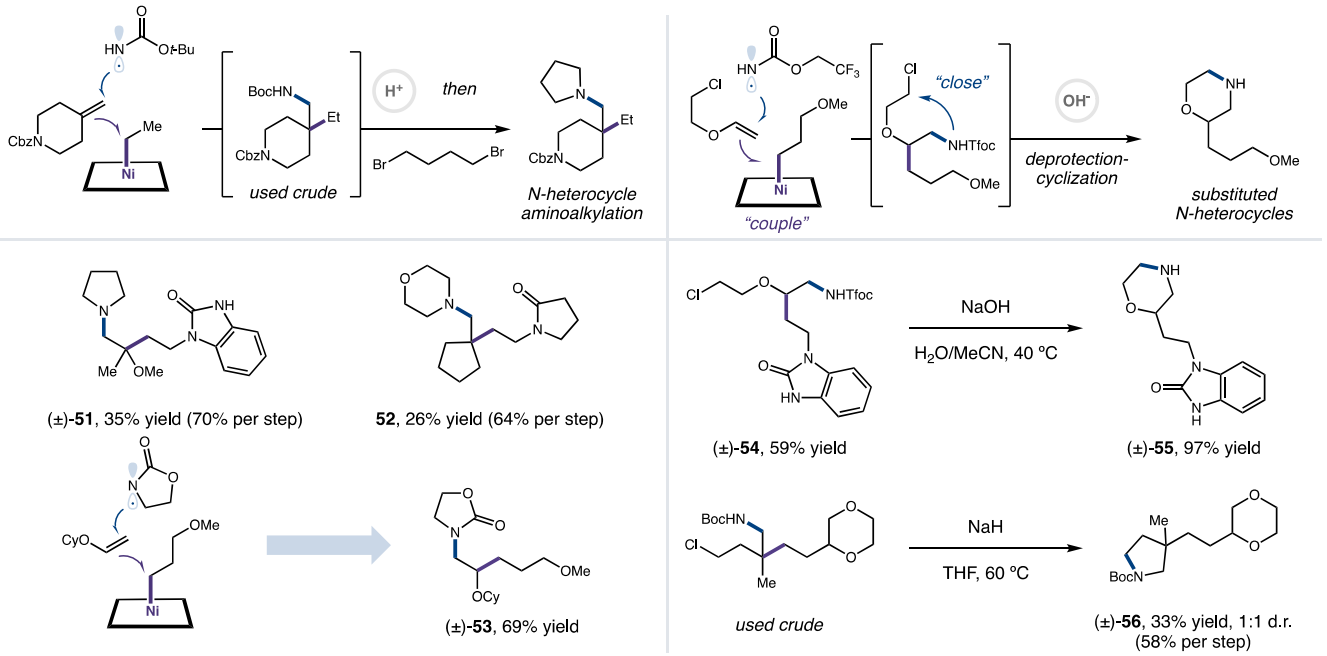
Table 3. Synthetic Applications[a]



[a]Isolated yields are reported. See SI for experimental details.

The proposed mechanism for this transformation is detailed in Figure 2. First, blue light excitation of iridium-based photocatalyst [Ir(dFFppy)$_2$(dtbbpy)](PF$_6$) (**1**, dFFppy = [3,5-difluoro-2-(5-fluoro-2-pyridinyl)phenyl], dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) yields an oxidizing triplet excited state (**2**, $E_{1/2}^{red}[Ir^{III}*/Ir^{II}]$ = +1.48 V versus saturated calomel electrode (SCE)).[52] Aminosilane reagent **3** can be readily oxidized by this excited state photocatalyst, resulting in reduced photocatalyst **5** and N-centered radical **4**, which is proposed to spontaneously undergo radical aza-Brook rearrangement to furnish silyl radical XAT reagent **6**.[49] Subsequently, **5** can directly reduce N-centered radical precursor **7** ($E_{1/2}^{red}[Ir^{III}/Ir^{II}]$ = −1.32 V versus SCE),[52] thereby closing the photocatalytic cycle and, upon extrusion of CO$_2$ and phthalimide anion, generating tertiary radical **8**. This radical intermediate can undergo β-scission to form acetone and N-centered radical **9**, which readily adds to unactivated alkene **10**, generating tertiary radical **11**.[22,26] Concurrently, XAT reagent **6** can undergo a facile bromine atom transfer with alkyl bromide **12** to supply primary radical **13**.[53] Capture of this intermediate by Ni(TMHD)$_2$ (**14**, TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate) affords Ni^{III}-alkyl species **15**.[37] Finally, tertiary radical **11** is proposed to undergo a C(sp^3)−C(sp^3) bond forming S$_H$2 reaction to form amino-alkylated product **16** and close the nickel catalytic cycle.[37,41] Radical clock and TEMPO trapping studies (see SI section 6 for details) support the radical nature of this proposed mechanism.

Optimization studies showed the capability of multiple commercially available photocatalysts to promote reactivity (see Table S2 for details). Additionally, several nickel-based radical sorting catalysts gave similar levels of product formation, with Ni(TMHD)$_2$ (**14**) proving to be optimal (see Table S3 for details). Control experiments (Table 1) support our mechanistic hypothesis: no reaction was observed in the absence of light, photocatalyst, or silane (entries 2, 3, and 5), and only 5% yield was obtained in the absence of nickel catalyst (entry 4). Under our optimal conditions, product **19** was obtained in 62% yield (entry 1). The yield is drastically lowered in the presence of oxygen (entry 6, 21% yield). Finally, utilizing just 1.0 equiv of each stoichiometric reaction component provided a diminished yet synthetically useful 40% yield (entry 7).

We next set out to explore the scope of the aminoalkylation reaction. We first evaluated a variety of unique alkyl bromides across several different model alkenes using a Tfoc (2,2,2-trifluoroethoxy carbonyl) protected N-centered radical precursor (**7**). As shown in Table 2, ether, amino alcohol, and amide-containing alkyl bromides were well tolerated, forming medicinally relevant quaternary centers[54] (**16**, **20**, **21**, 51−57% yield). Ethyl and phosphonate groups were readily employed in this transformation, delivering 2,3-substituted piperidine cores (**22** and **23**, 64% and 57% yield, respectively). Morpholine, tertiary alcohol, and acetal-containing alkyl bromides also served as viable substrates, affording quaternary centers on five-membered ring alkenes with good yields (**24**−**26**, 53−70% yield). Moreover, medicinally relevant heterocycles, such as benzimidazolone[55] and quinazolinone,[56] were incorporated into aminoalkylated products with excellent yields (**27** and **28**, 83% and 72% yield, respectively).

We next probed the alkene scope of the transformation. Both phenoxy- and alkoxy-substituted terminal alkenes performed well, providing heteroatom-rich products in good yields (**31** and **32**, 53% and 62% yield, respectively). Terminal vinyl carbamates and sulfides served as competent substrates (**33** and **34**, 53% and 59% yield, respectively). Moreover, 1,1-disubstituted alkenes, including the four-membered rings, cyclobutyl and azaspiro[3.5]nonane, were smoothly functionalized (**35** and **36**, 63% and 56% yield, respectively). Six-membered rings also performed well, including those containing *gem*-difluoro and ketone functional groups (**37** and **38**, 56% and 57% yield, respectively). Construction of

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sterically demanding vicinal quaternary centers was readily accomplished, with only a minor loss in efficiency compared to a nondimethyl substituted substrate (**39** and **19**, 44% and 58% yield, respectively). Next, a seven-membered 1,1-disubstituted alkene was functionalized, providing **41** in 61% yield. The scope was then expanded to trisubstituted alkenes, yielding highly substituted cyclopentane products in good yields (**42** and **43**, 46% and 52% yield, respectively).

Finally, we evaluated the impact of installing different protecting groups on the N-centered radical. The NHBoc radical performed well in the system, forming quaternary center-containing products across a variety of alkenes and alkyl bromides with good yields (**45**−**48**, 47−69% yield). Both NHBoc and NHCbz radicals were incorporated into a pyrrolidinone scaffold, showcasing the ability of this method to accommodate a variety of protecting groups with similar efficiencies (**49** and **50**, 53% and 42% yield, respectively).

In a demonstration of the synthetic utility of this method, we next constructed a series of saturated N-heterocycles (Table 3). First, the NHBoc radical was subjected to aminoalkylation, and subsequent Boc deprotection and cyclization yielded the formal N-heterocycle aminoalkylation product. Notably, this reaction sequence was telescoped, with chromatography only occurring after the final cyclization step. This protocol was utilized to synthesize *N*-alkylated pyrrolidine and morpholine products, both of which are commonly occurring[57] heterocycles in approved drugs (**51** and **52**, 35% (70% per step) and 26% (64% per step) yield, respectively). To our delight, a cyclic N-centered radical performed well in the reaction, providing oxazolidinone **53** in 69% yield. Next, alkyl chloride-containing alkenes were subjected to a "couple-close" sequence. First, aminoalkylated product **54** was synthesized and subjected to a highly efficient base-mediated deprotection[58]−cyclization cascade to furnish substituted morpholine product **55** in near quantitative yield. Then pyrrolidine **56**, containing a quaternary center, was smoothly constructed in a telescoped fashion via intramolecular alkyl chloride cyclization.

In conclusion, we have developed a method to forge both a C(sp^3)−N and a C(sp^3)−C(sp^3) bond across commercial feedstock alkenes with perfect regioselectivity. A broad scope of alkene and alkyl bromide cross-coupling partners are well tolerated, and multiple different protecting groups on the N-centered radical are competent in the reaction. Finally, we highlighted the ability of this technology to form substituted N-heterocycles through "couple-close" sequences. We anticipate that this work will find use in the pharmaceutical industry for the rapid synthesis of nitrogen and C(sp^3)-rich molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c14965.

Additional experimental details, characterization, and spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a financial interest with respect to the Integrated Photoreactor.

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