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# Reimagining C($sp^3$)–N bond formation via a HARC strategy

Michael S. Crocker,[1,2] Reem Nsouli,[1,2] and Laura K.G. Ackerman-Biegasiewicz[1,*]

**Conventional *N*-alkylation methods have been limited to approaches with high energy barriers and low selectivity. In this issue of *Chem*, MacMillan and co-workers report an innovative halogen abstraction-radical capture (HARC) strategy via metallaphotoredox catalysis that couples strained and hindered alkyl halides with a diverse range of *N*-nucleophiles.**

The development of transition-metal-catalyzed cross-coupling has transformed the way synthetic routes are devised and implemented in both academia and industry. The development of reliable C–N bond-forming reactions has been paramount to these efforts. Reactions such as the Buchwald-Hartwig amination, Ullmann-Goldberg reaction, and Chan-Evans-Lam coupling provide modular strategies for efficiently accessing C($sp^2$)–N targets.[1–3]

Although amines are prevalent in natural products and bioactive compounds, accessing C($sp^3$)–N bonds can be challenging. Frequently, *N*-alkylation is accomplished through $S_N1$/$S_N2$ chemistry. However, this can require harsh conditions that lead to competitive elimination products, regioselectivity issues, and/or over-alkylation. Moreover, strained and hindered electrophiles are known to be recalcitrant to substitution methods, and electron-poor amines further increase the barrier to reactivity.[4]

To circumvent these limitations, several advances in C($sp^3$)–N coupling methods have capitalized on copper catalysis.[5,6] The proclivity of copper to coordinate to heteroatoms and effectively form Cu(II) or Cu(III) species allows for facile C($sp^3$)–N bond formation via reductive elimination.[7] This strategy has successfully utilized boronic acids and esters, carboxylic acids, alkenes, and hydrocarbons as substrates. However, organohalides, which are an abundant and versatile source of alkyl electrophile, have been comparatively underexplored. Reports by Fu, Peters, and colleagues[8] have established the use of open-shell copper catalysis for *N*-alkylation, providing evidence for the potential use of a halogen-abstraction strategy. The scarce application of organohalides and hindered flexibility with regard to nucleophiles in the established protocols highlights the need for complementary and innovative mechanisms to be employed for future C–N bond formations.

Recently, MacMillan and co-workers devised a halogen abstraction-radical capture (HARC) method[9,10] by using photoredox-generated silyl radicals for *N*-alkylation (Scheme 1). In this reaction, organohalides can be activated easily via a halogen-abstraction process, and copper is used to activate the nitrogen nucleophile, as well as to facilitate bond formation. By applying a HARC strategy to the coupling of alkyl halides with amines, the authors overcame the higher-energy oxidative addition step that is common in copper-catalyzed reactions.

In order to realize this transformation, the authors reacted 3-chloro-1*H*-indazole and bromocyclohexane in the presence of blue light (450 nm) for 4 h in an integrated photoreactor. This nucleophile possesses two reactive sites, whereas the alkyl bromide is resistant to nucleophilic displacement, making this model system representative of the challenges that face conventional

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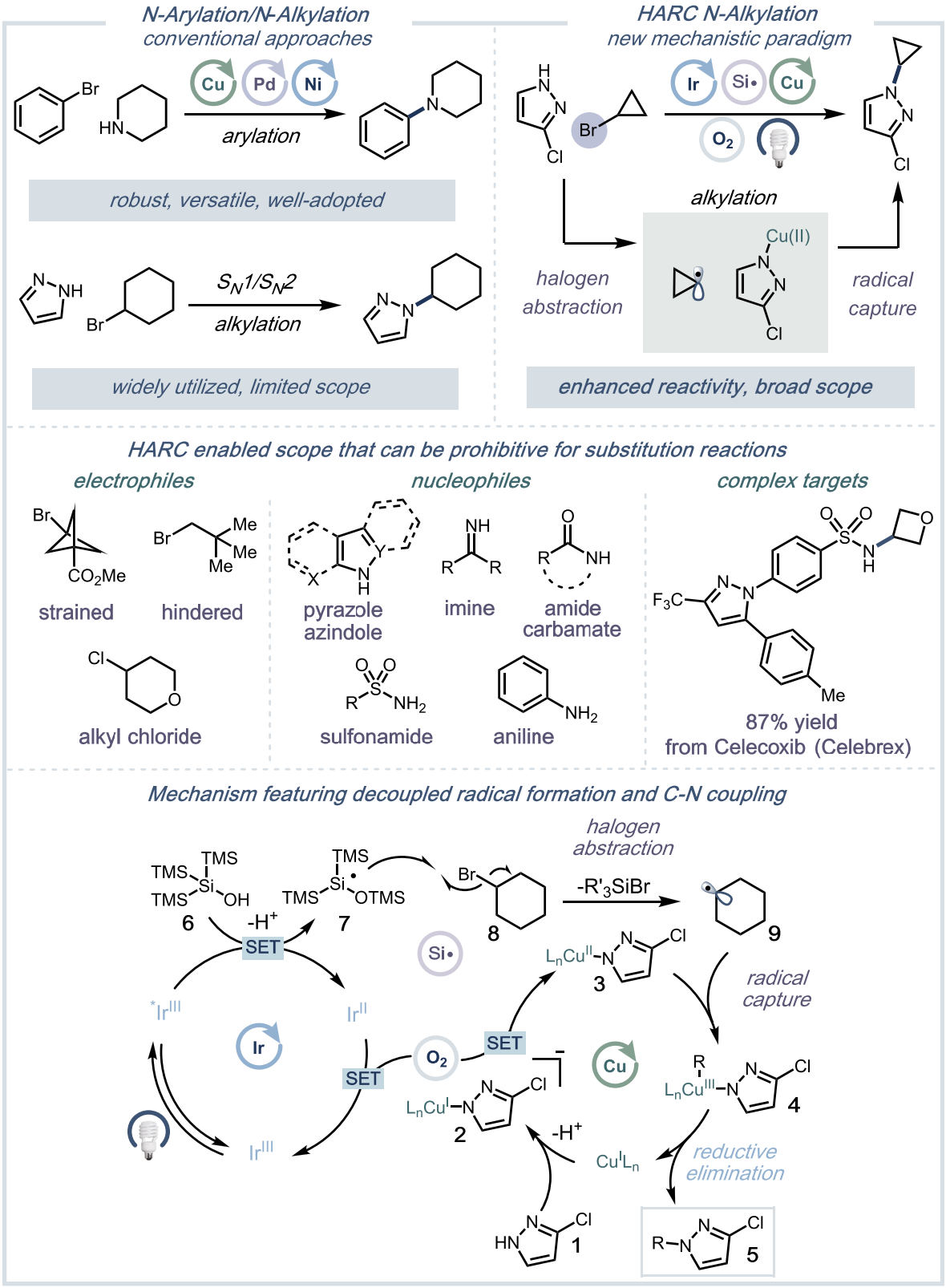


Scheme 1. HARC for *N*-alkylation: Utility, substrate scope, and proposed mechanism

methods. The standard conditions employed Ir[dF(CF$_3$)ppy]$_2$[4,4′-d(CF$_3$)bpy]PF$_6$ as the photocatalyst, bis(2,2,6,6-tetramethyl-3,5-heptanedionato)copper [Cu(TMHD)$_2$] as the copper catalyst, supersilanol (tris(trimethylsilyl)silanol) as the radical source, LiO$^t$Bu as the base, and MeCN as the solvent. Under optimal conditions, yields up to 93% were attained. Control reactions revealed that the photocatalyst, copper catalyst, silyl radical source, and base were all essential for high reactivity. Notably, yields were enhanced with the addition of water and an open atmosphere.[10]

One of the key features of the HARC strategy is its impressive scope, allowing for unprecedented activation of strained and hindered electrophiles with a variety of amine nucleophiles. Applying the optimized conditions to cyclic substrates such as cyclobutyl and azetidinyl bromides, which are slow to react under substitution conditions, led to product in 87% and 90% yields, respectively. Cyclopropyl bromide could be incorporated into a range of amines in 48%–85% yields. Additionally, complex acyclic, spirocyclic, and bridged bicyclic halide scaffolds were effectively applied in this reaction. Although activating tertiary bromides and secondary chlorides with the silanol radical precursor was challenging, applying the more nucleophilic radical generated from (TMS)$_3$SiNHAd furnished the corresponding alkylated products effectively. Derivatives of adamantane, bicyclo[2.2.2]octane, and cubane, which can be problematic for both substitution and metal-catalyzed reactions alike, proved successful with this HARC protocol.

In addition to allowing the electrophile scope, the HARC strategy also enabled alkylation of 13 different classes of *N*-nucleophiles, including carbazoles, pyrroles, indoles, and amides. Regioselectivity was observed with substrates such as indazoles, pyrazoles, and azaindoles, which bear more than one nucleophilic nitrogen. Electron-rich and -poor arenes and tertiary amines were tolerated, and benzophenone imine served as an entry point to primary amine derivatives. Notably, halogen abstraction was selective for alkyl bromides even in the presence of alkyl or aryl chlorides. To demonstrate the utility of this method for late-stage functionalization, the authors successfully *N*-alkylated commercial pharmaceutical drugs Celebrex, Navoban, Skelaxin, and Dogmatil in moderate to high yields (52%–87%).

The extensive substrate combinations demonstrated in this work exemplify the value of its underlying mechanism. The tolerance of this method to weak nucleophiles and strained or tertiary alkyl halides is in stark contrast to $S_N1/S_N2$ reactions. To further probe this dichotomy, experiments using (bromomethyl)cyclopropane suggest that an alkyl radical is formed in the reaction. The fast ring-opening rate of $k = 7.8 \times 10^7\ s^{-1}$ at 20°C for this substrate is consistent with the exclusive isolation of the ring-opened product. To investigate the possibility that β-elimination could also be operative, the authors ran the reaction in the presence of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), yielding primarily the trapped product. Together, these experiments support an open-shell pathway that could proceed through a halogen-abstraction mechanism.

According to previous work by MacMillan and co-workers, halogen abstraction can afford organic radicals that can combine with copper.[9] The proposed catalytic reaction in this *N*-alkylation method begins with a Cu(I) species that reacts with the nucleophile and base to generate anionic Cu(I)-amido complex **2** (Scheme 1). Simultaneously, excitation of the Ir photocatalyst with visible light generates a long-lived oxidant ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.65 V versus saturated calomel electrode [SCE] in MeCN) that can react with supersilanol **6** ($E_{pa}$ [**6**/**6**$^{\cdot+}$] = +1.54 V versus SCE in MeCN).[10] After radical Brook rearrangement, a silyl radical that affords alkyl radical **9** via a halogen-abstraction mechanism is generated. Subsequent addition of **9** to Cu generates the Cu(III)-amido complex **4**. Reductive elimination ultimately yields the C–N-coupled product **5**, regenerating the Cu(I) catalyst. In both the Ir and Cu cycles, molecular oxygen serves as the oxidant.

In conclusion, the HARC *N*-alkylation reported by the MacMillan group represents a strategic advance in transition-metal-mediated cross-coupling reactions. The decoupling of organohalide activation and C–N bond formation leads to a uniquely broad substrate scope. In this work, the incorporation of hindered and strained aliphatic electrophiles, as well as electronically differentiated amines, yields products otherwise unattainable with previous methods. As chemistry continues to progress toward C(sp$^3$)-rich frontiers, synthetic strategies such as HARC under metallaphotoredox conditions can enable a myriad of opportunities for accessing molecular diversity.

## DECLARATION OF INTERESTS

L.K.G.A.-B. is a member of the *Chem Catalysis* advisory board.

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# Harnessing the reactivity of borenium for methane activation

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**Methane ($CH_4$) functionalization is an important field that is traditionally dominated by transition-metal catalysis. In this issue of *Chem*, Wang and colleagues report the exceptional reactivity of an N-heterocyclic carbene (NHC)-stabilized hydroborenium cation that allows for the selective C–H activation of $CH_4$, affording value-added borylated products in a transition-metal-free fashion.**

Methane, the major component of natural gas, is the simplest and arguably most abundant hydrocarbon found both below ground and under the seafloor. Its abundance and clean combustion nature make it an attractive candidate for fuel applications. Despite these advantages, there are a number of issues associated with methane utilization from both environmental and economical perspectives. A significant portion of naturally occurring $CH_4$ is found in remote locations, making its capture, storage, and transportation challenging. The current industry method to turn methane into transportable liquid fuel relies on a two-step process that first converts $CH_4$ into $CO/H_2$ syngas and subsequently transforms the mixture into methanol and other hydrocarbons. This process requires high temperatures and pressures to overcome the activation barriers for the cleavage of the inert C–H bonds of $CH_4$, which is expensive, energy intensive, and only viable on a large plant scale.

To tackle these challenges, ongoing effort has been directed to C–H activation and functionalization of $CH_4$ under milder conditions, especially with transition-metal catalysis.[1,2] In 2016, the Sanford[3] and Mindiola[4] groups reported two elegant examples of catalytic borylation of $CH_4$ with bis(pinacolato)diboron ($B_2pin_2$), thus taking advantage of the weak B–B bond as the enthalpic driving force, with Ru, Rh, and Ir as the transition-metal catalysts (Scheme 1A). Despite the notable advances presented in these reports, there has been a push to investigate metal-free catalytic systems in order to decrease the cost and reduce overall dependence on these precious metals. As such, the development of metal-free methane activation is highly desirable from an economic and environmental standpoint; however, it has been complicated by high activation barriers and low inherent reactivity. One potential strategy for developing a metal-free process was revealed in 2000, when Goldfuss et al. calculated that the barrier to methane activation by borane was notably lowered by exploitation of a four-center transition state analogous to σ-bond metathesis,[5] which drew attention to the possibility of using organoboron compounds in metal-free methane activation.

Organoboron compounds are indispensable stoichiometric reagents and (co)catalysts for organic transformations and polymer synthesis thanks to their diverse reactivity displayed in Lewis acid, hydride reduction, transmetalation, and cross-coupling chemistry.[6] In particular, they have been an important part of recent developments in main-group catalysis, showcasing their unique ability to activate and transform small molecules such as $H_2$, CO, $CO_2$, and $N_2$ into value-added chemicals.[7] Typically, the reactivity of boron(III) species relies on the associated vacant p orbital as a one- or two-electron acceptor. Among different organoborane species, boron compounds bearing a formal positive charge represent an emerging class of compounds because of their highly tunable Lewis acid properties. Depending on the coordination numbers of boron, such borocations can be categorized into boriniums (two coordinate), boreniums (three

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