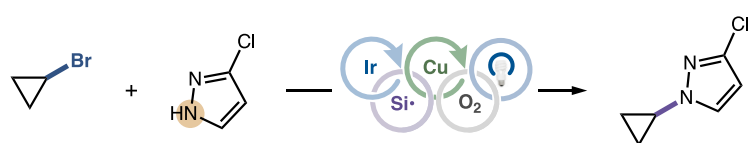


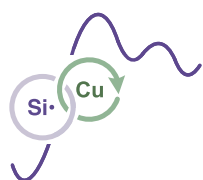
Article

A general *N*-alkylation platform via copper metallaphotoredox and silyl radical activation of alkyl halides

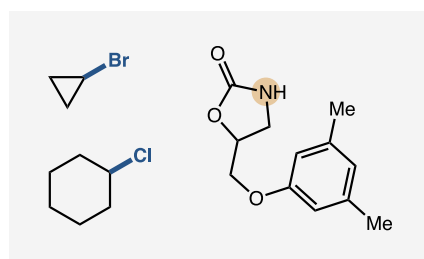
A metallaphotoredox approach to catalytic, open-shell *N*-alkylation



halogen abstraction-radical capture (HARC) platform



low-barrier reactions
at room temperature



- strained, hindered bromides
- alkyl chlorides
- drug-like heterocycles
- pharmaceutical agents

>60 examples of traditionally elusive S_N2 products

Nathan W. Dow, Albert Cabré,
David W.C. MacMillan

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Highlights

General, room temperature *N*-alkylation via copper metallaphotoredox catalysis

Broad reactivity across diverse alkyl bromides, *N*-heterocycles, and pharmaceuticals

Convenient approach to *N*-cyclopropylation using easily handled bromocyclopropane

Readily extended to functionalization of unactivated secondary alkyl chlorides

Traditional substitution reactions between nitrogen nucleophiles and alkyl halides feature well-established, substrate-dependent limitations and competing reaction pathways under thermally induced conditions. Herein, we report that a metallaphotoredox approach, utilizing a halogen abstraction-radical capture (HARC) mechanism, provides a valuable alternative to conventional *N*-alkylation. This visible-light-induced, copper-catalyzed protocol is successful for coupling >10 classes of *N*-nucleophiles with diverse primary, secondary, or tertiary alkyl bromides. Moreover, this open-shell platform alleviates outstanding *N*-alkylation challenges regarding regioselectivity, direct cyclopropylation, and secondary alkyl chloride functionalization.



Dow et al., Chem 7, 1–16
July 8, 2021 © 2021 Elsevier Inc.
<https://doi.org/10.1016/j.chempr.2021.05.005>

Article

A general *N*-alkylation platform via copper metallaphotoredox and silyl radical activation of alkyl halides

Nathan W. Dow,¹ Albert Cabré,¹ and David W.C. MacMillan^{1,2,*}

SUMMARY

The catalytic union of amides, sulfonamides, anilines, imines, or *N*-heterocycles with a broad spectrum of electronically and sterically diverse alkyl bromides has been achieved via a visible-light-induced metallaphotoredox platform. The use of a halogen abstraction-radical capture (HARC) mechanism allows for room temperature coupling of C(sp³)-bromides using simple Cu(II) salts, effectively bypassing the prohibitively high barriers typically associated with thermally induced S_N2 or S_N1 *N*-alkylation. This regio- and chemoselective protocol is compatible with >10 classes of medicinally relevant *N*-nucleophiles, including established pharmaceutical agents, in addition to structurally diverse primary, secondary, and tertiary alkyl bromides. Furthermore, the capacity of HARC methodologies to engage conventionally inert coupling partners is highlighted via the union of *N*-nucleophiles with cyclopropyl bromides and unactivated alkyl chlorides, substrates that are incompatible with nucleophilic substitution pathways. Preliminary mechanistic experiments validate the dual catalytic, open-shell nature of this platform, which enables reactivity previously unattainable in traditional halide-based *N*-alkylation systems.

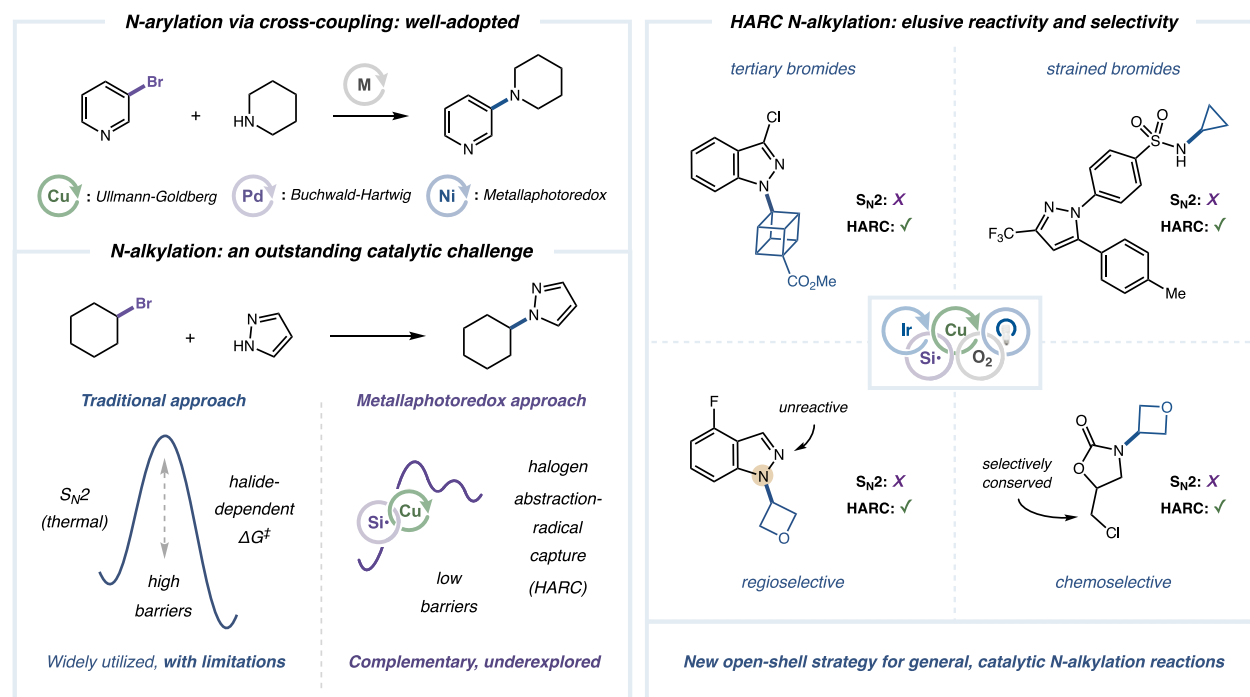
INTRODUCTION

The societal need to discover and produce pharmaceuticals, agrochemicals, and functional materials has long established a demand for new C–N bond-forming reactions that are successful across diverse combinations of complex substrates.^{1–3} Indeed, over the last 2 decades, palladium-, nickel- and copper-catalyzed protocols such as Buchwald-Hartwig,^{4,5} Ullmann-Goldberg,⁶ and Chan-Evans-Lam⁷ C(sp²)-N cross-couplings have emerged as mainstay strategies to generically access versatile *N*-aryl structural motifs (Scheme 1).^{8,9} In contrast, transition-metal-mediated couplings affording C(sp³)-N bonds are comparatively underdeveloped as broadly applicable synthetic technologies,¹⁰ despite growing recognition of the importance of C(sp³)-incorporation when designing new drugs and agrochemicals.^{11–13} Instead, practical approaches to forging C(sp³)-N bonds remain generally limited to classical methods, including Mitsunobu substitution,¹⁴ Curtius rearrangements,¹⁵ olefin hydroamination,^{16,17} or reductive amination.¹⁸

Among the traditional *N*-alkylation strategies, direct S_N2 or S_N1 substitution of alkyl halides with *N*-nucleophiles remains the most adopted technology for generating alkylamine-bearing biomedical agents^{19,20} and among the most frequently utilized transformations across all chemical industries.^{21,22} Despite the long-standing popularity of this closed-shell *N*-alkylation pathway, substitution reactions typically face substantial halide-dependent activation barriers, which renders numerous

The bigger picture

Alkylamines and their *N*-heterocyclic derivatives are key structural features in molecules central to the medical, agroscience, and materials science industries. Although *N*-alkylation using nitrogen nucleophiles and halides has historically been accomplished via nucleophilic substitution, this process is frequently inefficient and poorly selective under thermal activation. We report a kinetically facile, room temperature *N*-alkylation achieved via underexplored halogen abstraction-radical capture pathways mediated by independent photoredox and copper catalytic cycles. With a broad scope and late-stage applicability, even for traditionally inert cyclopropane and chloride electrophiles, this protocol offers new and efficient strategies for modern amine synthesis. These developments can ideally provide medicinal chemists with single-step access to valuable sp³-rich chemical diversity in drug discovery, including alkylamine motifs unattainable via conventional *N*-alkylation methods.



Scheme 1. Catalytic N-alkylation via HARC coupling of alkyl bromides

substrates (in particular strained or hindered halides) inert to functionalization (Scheme 1).^{21,22} Even for reactive halides, elevated barriers for substitution result in high-temperature requirements that impose broad limitations, including low selectivity for a single constitutional isomer (or regioisomer), non-controlled overalkylation events, and competing elimination pathways.^{21,22} While in some cases, metal-mediated variants of halide N-alkylation have removed these limitations,^{23,24} there remains an outstanding need to identify new, robust mechanisms that allow such couplings across an expansive range of complex halide and N-heterocyclic systems while employing ambient, low-temperature conditions.

Within the select C(sp³)-N cross-coupling methods already disclosed, copper catalysis has increasingly been featured as a key component for enhancing efficiency and scope, exploiting the well-precedented capacity for high-valent Cu(III) states to induce carbon-heteroatom bond formation via reductive elimination.^{25,26} Buchwald, Hartwig, König, Watson, and others have elegantly engaged several abundant alkyl feedstocks in such protocols, including olefins,^{27,28} boronic acids and esters,^{29–32} hydrocarbons (activated *in situ* via hydrogen atom transfer),^{33,34} and carboxylic acids (typically deployed as redox-active electrophiles).^{35–38} However, platforms for copper-catalyzed N-alkylation using alkyl halides, which are readily available, and prototypical S_N2 electrophiles, are currently restricted by limited mechanistic approaches and reduced generality in substrate scope. Within this area, the groups of Fu and Peters have made notable advances by designing several distinct organohalide-based N-alkylation platforms, primarily using transiently generated Cu(I)-amido intermediates for aliphatic radical generation via single-electron transfer (SET).^{39–43} In these systems, successful activation of both coupling partners by a single (often photoactive) copper complex has frequently enabled N-alkylation using readily reducible electrophiles (i.e., iodides and α-halocarbonyls), with additional examples demonstrated using aliphatic bromides in

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<https://doi.org/10.1016/j.chempr.2021.05.005>

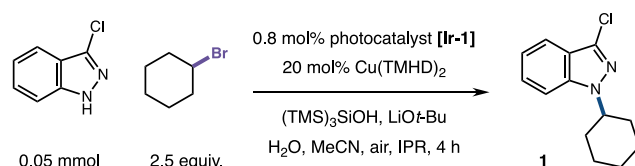
tandem with amide- or indole-derived nucleophiles.^{39–43} Ultimately, these reports from Fu and Peters have conclusively established that merging open-shell and copper-mediated activation modes can indeed facilitate catalytic C(sp³)-N bond formation.⁴⁴

Over the past decade, metallaphotoredox catalysis has emerged as a powerful platform to employ open-shell intermediates in concert with transition-metal-catalyzed cross-coupling under mild conditions.^{45,46} This approach has recently been combined with copper catalysis,⁴⁷ in particular for forging traditionally elusive C-CF₃^{48–52} and C-N^{35–37} bonds. In the context of organohalide functionalization, such strategies have most notably enabled Ullmann-Goldberg couplings of diverse (hetero)aryl bromides at room temperature using a previously unreported mechanistic approach.⁵³ This transformation utilizes photoredox-generated silyl radicals, which rapidly convert aryl bromides to radical intermediates via halogen atom transfer, to facilitate ambient or low-temperature coupling by replacing sluggish Cu(I) oxidative addition with a kinetically facile halogen abstraction-radical capture (HARC) sequence.^{54–56} Based on this new mechanism for C-N coupling, we hypothesized that an underexplored alkyl-HARC regime could generically provide aliphatic radicals from the corresponding bromides, ultimately enabling low-barrier *N*-alkylation via well-established copper-catalyzed C(sp³)-N bond formation (Scheme 1). Specifically, using these previously unexplored principles for *N*-alkylation, we anticipated that independent steps for halide activation (by photoredox-mediated halogen abstraction) and nucleophile activation (by copper ligation) would confer widespread structural and electronic generality with respect to each coupling partner, thereby addressing key limitations in halide-based catalytic C(sp³)-N coupling. Herein, we report the successful design and execution of this dual copper/photoredox *N*-alkylation platform, which demonstrates reactivity and selectivity surpassing that of traditional substitution due to synergistic copper and silyl radical-based activation modes.

RESULTS AND DISCUSSION

HARC *N*-alkylation of 3-chloroindazole using alkyl bromides

Our initial studies began by investigating the alkylation of a medically relevant 1*H*-indazole model *N*-nucleophile with bromocyclohexane (Figure 1). Gratifyingly, following optimization efforts (see Figures S1–S21), 93% yield of product 1 was obtained after 4 h of blue light irradiation (450 nm) using Ir(III) photocatalyst Ir[dF(CF₃)ppy]₂[4,4'-d(CF₃)bpy]PF₆ ([Ir-1]), commercial copper precatalyst Cu(TMHD)₂, tris(trimethylsilyl)silanol (supersilanol) as a silyl radical precursor, and acetonitrile as solvent (entry 1). Several elements proved critical for optimal reactivity, including a vent needle for air incorporation, the integrated photoreactor (IPR) as a standardized device for reaction vial irradiation,⁵⁷ LiOt-Bu as base, and water as an additive.^{58–60} Anhydrous systems were consistently detrimental (entry 2), even under conditions closely mimicking the previously reported HARC-Ullmann-Goldberg reaction (i.e., 1,1,3,3-tetramethylguanidine as base, entry 3).⁵³ Control reactions verified the importance of oxygen for catalytic turnover (entry 4), in addition to the superior performance of high-intensity IPR setups, as weaker blue light sources (i.e., Kessil lamps) were generally inadequate for robust product formation (entry 5). As expected, base, photocatalyst, copper, and supersilanol were all required for substantial reactivity (entries 6–9), consistent with the desired HARC mechanism that should require both photocatalytic halogen atom abstraction and copper-mediated bond formation to achieve coupling (see supplemental information and Figures S26 and S27 for additional control experiments and perturbation studies, which confirm the robustness of the optimized conditions).



entry	deviation	yield ^a
1	none	93%
2	no water	58%
3	TMG as base, no water	41%
4	sparged under N ₂ atmosphere	8%
5	40 W Kessil Blue LEDs as light source	40%
6	no base	4%
7	no photocatalyst	<1%
8	no copper catalyst	<1%
9	no (TMS) ₃ SiOH	<1%

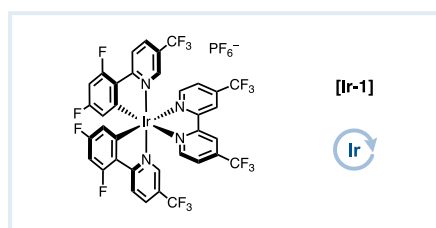


Figure 1. Control reactions of optimized HARC *N*-alkylation conditions

Reactions performed with (TMS)₃SiOH (2.5 equiv), LiOt-Bu (3.0 equiv), and H₂O (10 equiv) in MeCN (0.1 M), under IPR irradiation, unless otherwise indicated.

^aYields determined by ¹H NMR analysis. See [supplemental information](#) for specific experimental details. TMHD, 2,2,6,6-tetramethyl-3,5-heptanedionate; IPR, integrated photoreactor; TMG, 1,1,3,3-tetramethylguanidine.

With optimized conditions in hand, we next sought to examine the scope of bromides amenable to coupling (Figure 2). Strained cyclic bromides, which are often sluggish S_N1 or S_N2 partners,^{21,22} were effective substrates, delivering *N*-cyclobutyl and *N*-azetidynyl products in high yield (2 and 3, 87% and 90% yield, respectively). Larger cyclic bromides containing pyrrolidine (4, 55% yield), tetrahydropyran (5, 71% yield), or cycloheptane (6, 60% yield) cores could also be successfully functionalized. Acyclic bromides were also readily implemented in this protocol (7–9, 54%–75% yield), demonstrating complementarity to S_N2 methods via reactivity with neopentyl substrates.^{21,22} For more complex secondary cases, spirocyclic and bridged bicyclic frameworks (10–12, 47%–92% yield), an adamantyl system (13, 54% yield), a biologically relevant sterol scaffold (14, 56% yield), and a substrate bearing heterocyclic functionality (15, 87% yield) were all broadly competent for alkyl-HARC coupling.

To further illustrate the generality of this platform, we also evaluated a series of tertiary bromide electrophiles, which are typically challenging substrates in both metal-free and transition-metal-catalyzed *N*-alkylations.^{21–24} Although supersilanol was insufficient for accomplishing these couplings, we were delighted to find that the recently disclosed aminosilane (TMS)₃SiNHAd, which furnishes a more nucleophilic silyl radical with greater kinetic capacity for halogen atom abstraction,⁶¹ was

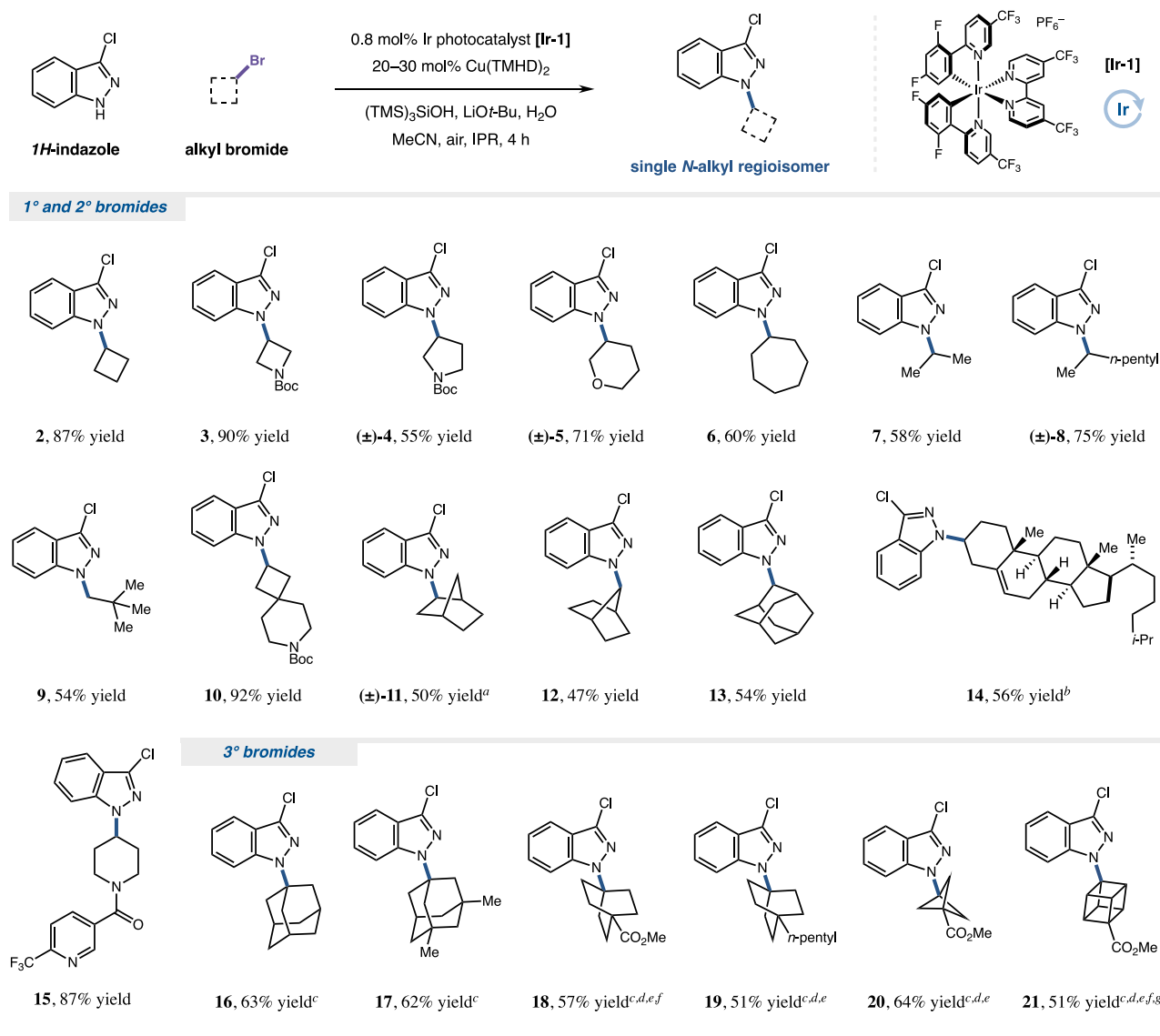


Figure 2. Alkyl bromide scope for copper-HARC *N*-alkylation

Isolated yields unless otherwise indicated. r.r. >20:1 in all cases. Reactions generally performed under air with photocatalyst [Ir-1] (0.8 mol %), Cu(TMHD)₂ (20–30 mol %), (TMS)₃SiOH (2.5 equiv), LiOt-Bu (3.0 equiv), H₂O (10 equiv), *N*-nucleophile (0.25 mmol, 1.0 equiv), and alkyl bromide (2.5 equiv) in MeCN (0.1 M) under IPR irradiation (450 nm) for 4 h. See [supplemental information](#) for specific experimental details.

^ad.r. 4:1.

^b0.05 mmol scale; toluene/MeCN (7:3, 0.1 M) as solvent; d.r. 1:1; yield determined by ¹H NMR analysis.

^c(TMS)₃SiNHAd as silyl radical source.

^d60 mol% Cu(TMHD)₂.

^eIsolated yield from five combined 0.05 mmol scale reactions (0.25 mmol total) due to reduced yields (>5% loss of yield) on typical 0.25 mmol scale.

^f[Ir(dFCF₃)ppy]₂(dtbbpy)PF₆ ([Ir-2]) as photocatalyst. ^g3.5 equiv (TMS)₃SiNHAd used. Ad, 1-adamantyl.

competent for accessing such tertiary *N*-alkyl products. Numerous scaffolds reacted efficiently under these conditions, including derivatives of adamantane (16 and 17, 63% and 62% yield, respectively), bicyclo[2.2.2]octane (18 and 19, 57% and 51% yield, respectively), bicyclo[1.1.1]pentane (20, 64% yield), and cubane (21, 51% yield).⁶² Evidently, this method can be readily applied to the formation of rigid bioisosteric alkylamines, structures of high value for medicinal chemistry programs

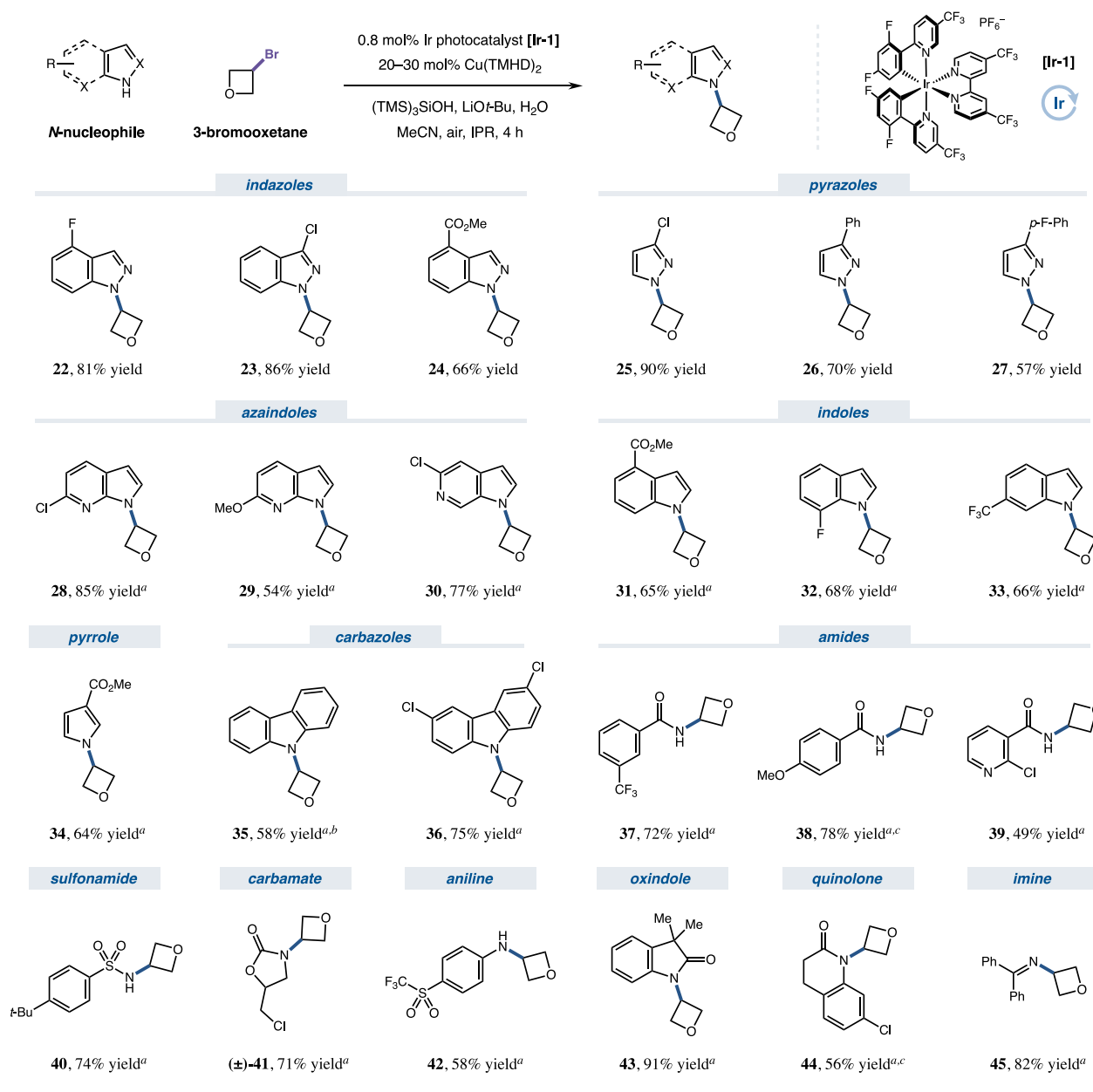


Figure 3. *N*-nucleophile scope for copper-HARC *N*-alkylation

Isolated yields unless otherwise indicated. See Figure 2 for general conditions and supplemental information for specific experimental details.

^aDBN (1.0 equiv) used as additive.

^b0.5 equiv LiOt-Bu used.

^cYield determined by ¹H NMR analysis. DBN, 1,5-diazabicyclo[4.3.0]non-5-ene.

which currently suffer from limited (or non-existent) synthetic approaches via modular cross-coupling techniques.⁶³

Evaluation of *N*-nucleophile and pharmaceutical agent scope

We then turned our attention to the scope of *N*-nucleophiles suitable for this transformation (Figure 3). Using a strained model halide substrate, a variety of indazoles (22–24, 66%–86% yield) and pyrazoles (25–27, 57%–90% yield) were alkylated in

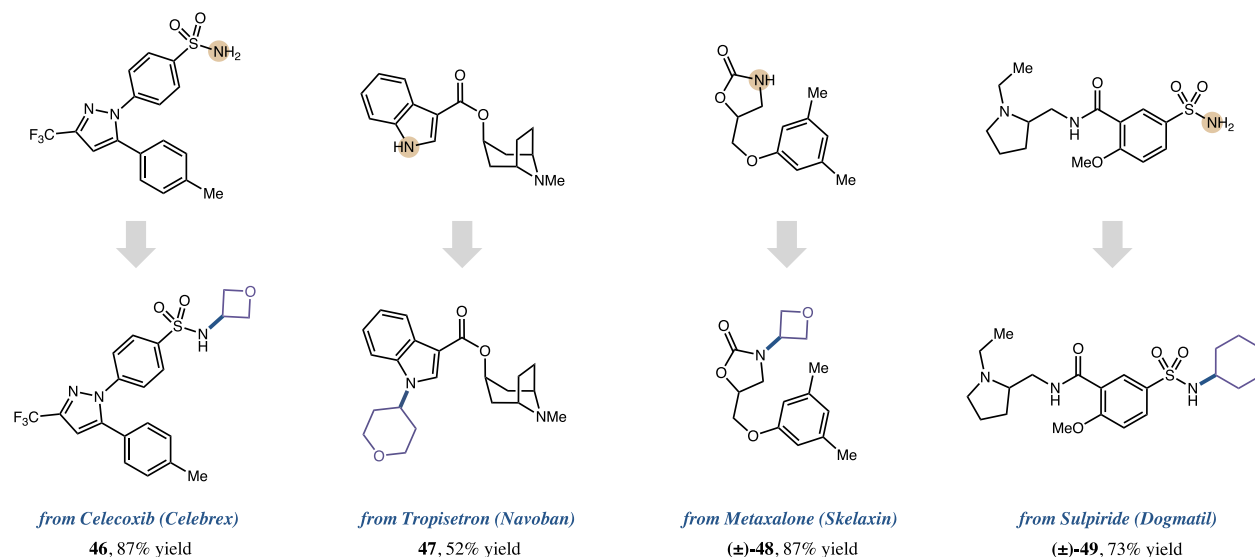


Figure 4. Late-stage N-alkylation of pharmaceutical agents

All yields are isolated. See [supplemental information](#) for specific experimental details.

high efficiency. Consistent with previous copper metallaphotoredox studies,³⁵ this method delivers all products as single regioisomers, an elusive selectivity trend for traditional nucleophilic substitution approaches.^{21,22,64,65} For heterocycles featuring one reactive site, azaindoles (**28–30**, 54%–85% yield), indoles (**31–33**, 65%–68% yield), pyrrole (**34**, 64% yield), and carbazoles (**35** and **36**, 58% and 75% yield, respectively) were readily functionalized, as were benzamide N-acyl partners bearing either electron-rich or electron-deficient arene frameworks (**37–39**, 49%–78% yield). Furthermore, sulfonamide (**40**, 74% yield), carbamate (**41**, 71% yield), aniline (**42**, 58% yield), oxindole (**43**, 91% yield), and dihydroquinolone nucleophiles (**44**, 56% yield) were also successfully coupled. Remarkably, exquisite chemoselectivity was observed for bromide abstraction in all cases, leaving aryl or alkyl chloride functionality intact and available for subsequent synthetic manipulation. Notably, benzophenone imine (**45**, 82% yield) could also be utilized for accessing derivatives of primary amines, motifs typically inaccessible via substitution due to predominant overalkylation when using nucleophiles (such as ammonia) containing several labile N–H bonds.^{21,22,24} In total, 13 diverse nucleophile classes were amenable to coupling, demonstrating the generality of alkyl-HARC mechanisms with independent silyl radical and copper-based activation steps (for additional examples and current limitations, see [Figure S30](#)).⁶⁶

To survey the utility of this method in drug discovery settings, we also employed this alkyl-HARC protocol to functionalize various commercial N-nucleophilic pharmaceutical agents ([Figure 4](#)). Celebrex (**46**, 87% yield), Navoban (**47**, 52% yield), Skelaxin (**48**, 87% yield), and Dogmatil (**49**, 73% yield) were all expediently converted to complex N-alkyl analogs using various bromide coupling partners, with basic and oxidation-prone⁶⁷ tertiary amines notably tolerated in several cases.⁶⁸ Given the prevalence of heterocyclic N-nucleophiles in drug candidates, this platform should provide medicinal chemists facile access to diverse pharmaceutical analogs via modular, late-stage N-alkylation.

Extension of HARC methodology to cyclopropyl and chloride electrophiles

Exploiting this complementary N-alkylation protocol, we further sought to couple halides broadly considered inert within S_N1 or S_N2 substitution platforms, initially

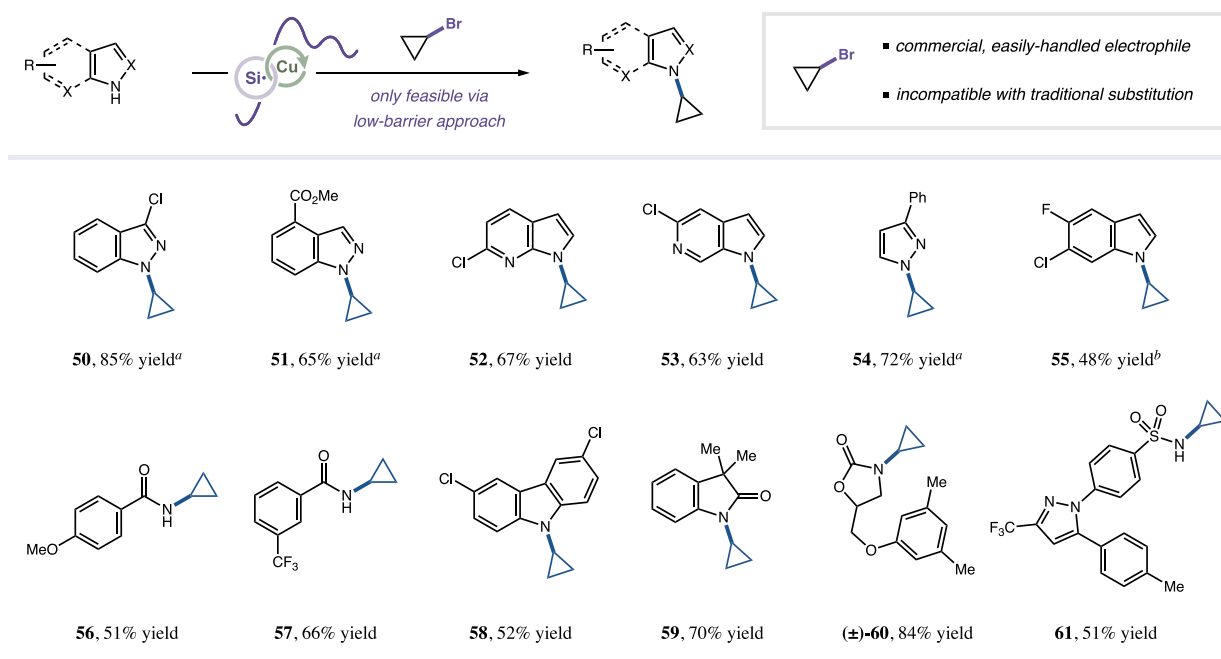


Figure 5. Direct cyclopropylation of N-nucleophiles using bromocyclopropane

Isolated yields unless otherwise indicated. See [supplemental information](#) for specific experimental details.

^ar.r. >20:1.

^bYield determined by ¹H NMR analysis.

targeting the generation of heterocyclic cyclopropylamine derivatives. These motifs, although pharmaceutically valuable,⁶⁹ are challenging to reliably access late-stage due to the generally inert nature of cyclopropane electrophiles to nucleophilic displacement,^{35,70–74} instead necessitating the use of preformed organometallic derivatives.^{75–79} Gratifyingly, alkyl-HARC cyclopropylation employing commercial and bench-stable bromocyclopropane was indeed achievable for various N-nucleophiles with good to excellent efficiency (50–59, 48%–85% yield, [Figure 5](#)). Moreover, this approach was applicable to more complex structures, providing Skelaxin (**60**, 84% yield) and Celebrex (**61**, 51% yield) analogs in expedient fashion. This accomplishment highlights the unique capabilities of HARC-based N-alkylations, permitting single-step syntheses of elusive drug-like cyclopropylamines.

Additionally, we anticipated that (TMS)₃SiNHAd, originally designed by our laboratory for organochloride abstraction,⁶¹ could activate typically unreactive non-primary alkyl chlorides toward HARC N-alkylation ([Figure 6](#)). We were pleased to find that, under modified conditions, conversion of secondary alkyl chlorides to the corresponding radicals using (TMS)₃SiNHAd provided facile N-alkylation reactivity (**62** and **1**, 52% and 50% yield, respectively). The significance of this discovery was further verified via rapid generation of trans-amino alcohol **63** (40% yield) for which the necessary bromohydrin partner is unavailable in gram-scale quantities from chemical vendors, thus demonstrating single-step entry into chemical space unattainable from commercially available bromides (for control reactions verifying the mechanism that enables the formation of **63**, see [Figure S28](#)). The chlorocyclohexanol stereoisomeric mixture employed ultimately furnished **63** in a diastereoconvergent fashion, a notable consequence of

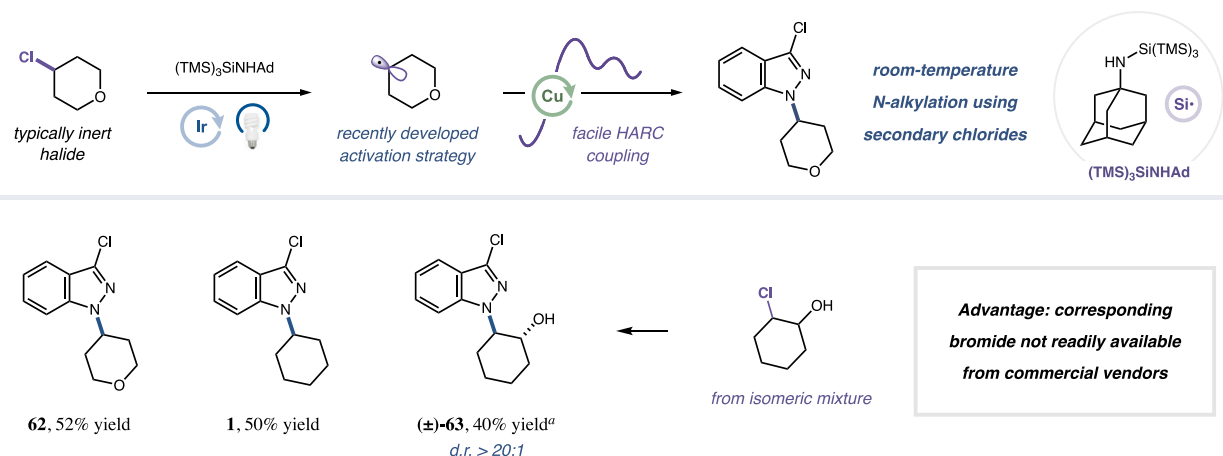


Figure 6. Extension of HARC coupling to unactivated alkyl chlorides

All yields are isolated. r.r. >20:1 in all cases. ^aInitial alkyl chloride d.r. 1:1. See [supplemental information](#) for specific experimental details.

exploiting copper-mediated bond formation as an elementary step to facilitate N-alkylation. We expect this new metallaphotoredox N-alkylation strategy to enable a variety of previously unachievable chloride substitution reactions, and further expansion of this variant of the copper-HARC protocol is currently underway.

Mechanistic proposal and comparisons to traditional substitution methods

Following our studies on the applicability of this HARC N-alkylation to various synthetic contexts, we also sought to investigate the mechanism of coupling. In particular, we set out to verify that the achievements of this platform, with respect to the breadth of scope, are in fact complimentary to those possible within established substitution conditions and that the HARC design principle is utilized to accomplish these advances. We started by identifying products 1, 18, and 50 as representative examples for comparing our metallaphotoredox method against prototypical substitution approaches. Previous reports indicate that these adducts are formed in trace or modest yield (with moderate N1-regioselectivity) under traditional substitution conditions when using 3-chloroindazole and the corresponding bromide electrophiles (Figure 7),³⁵ presumably due to prohibitively high kinetic barriers for halide displacement which cannot be overcome using thermal activation. Consequently, efficient and regioselective generation of 1, 18, and 50 under HARC N-alkylation conditions (57%–93% yield, see Figures 1, 2, 5, and 7) signifies that this new platform will indeed enable reactivity not attainable from standard two-electron processes, implying that alternative reaction pathways must be operative. Furthermore, when subjecting 3-chloroindazole and bromocyclohexane to the optimized HARC coupling conditions using only ambient light as a photon source, product 1 was not detected (Figure 7), eliminating the possibility of background non-photonic substitution pathways (these trends were consistent across all 13 classes of nucleophiles subjected to coupling, see Figure S29). Collectively, these results indicate both that unique mechanisms beyond those of traditional nucleophilic substitution are responsible for the robust performance observed in HARC N-alkylation reactions and that such N-alkyl products are otherwise inaccessible when using conditions designed to best facilitate classical S_N2 or S_N1 processes.

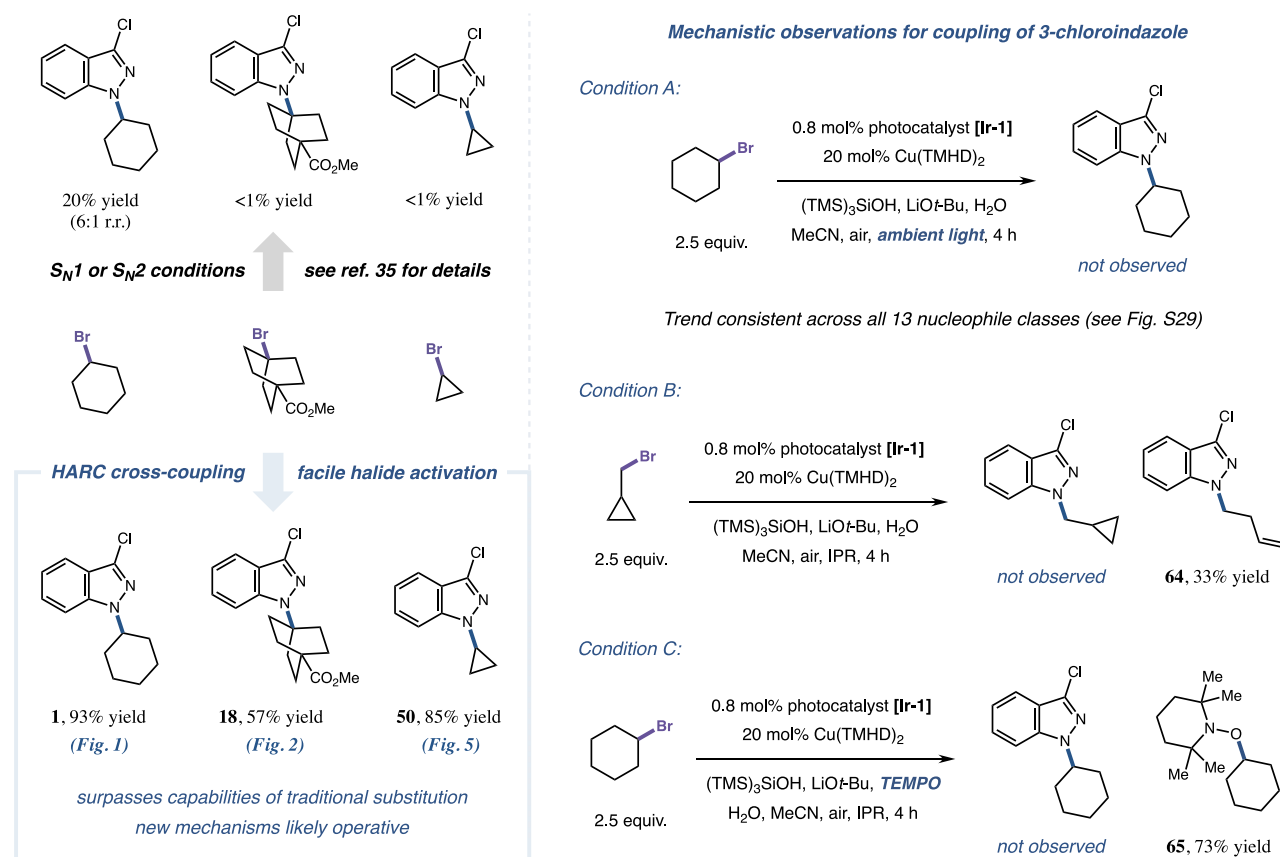
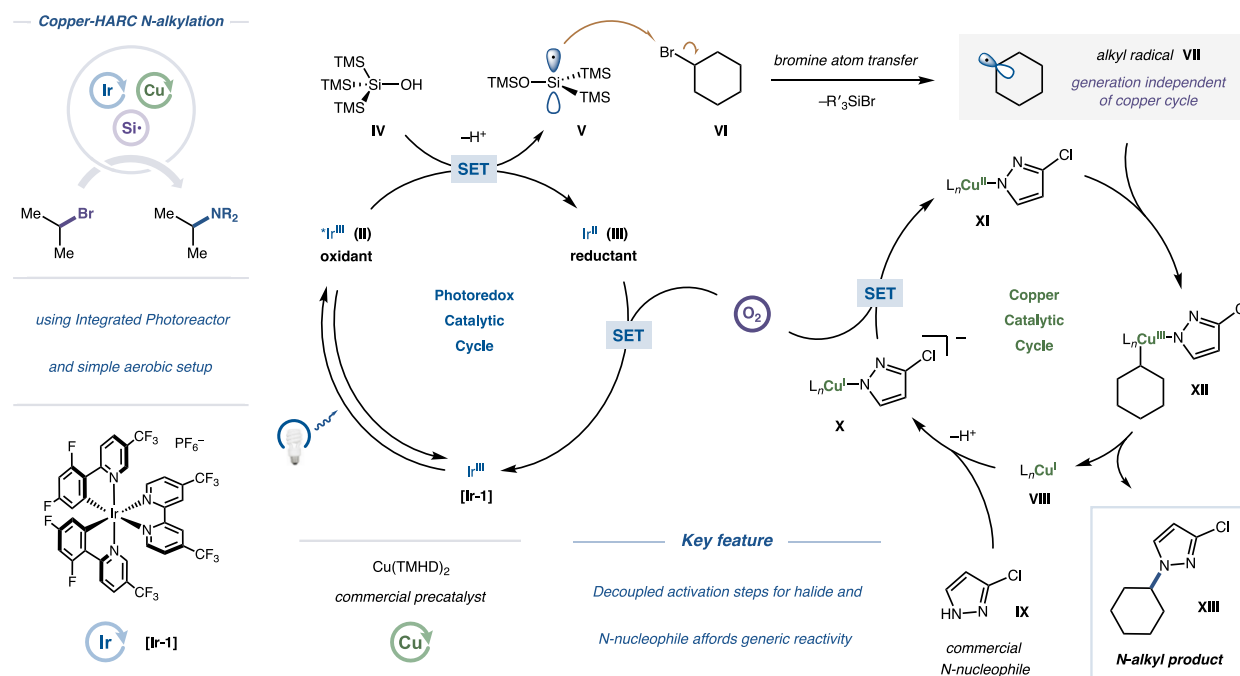


Figure 7. Comparisons with traditional substitution approaches and preliminary mechanistic experiments

All products formed using HARC conditions displayed r.r. >20:1. See Liang et al.,³⁵ indicated main text figures, or Figures S22–S25 and S29 for additional experimental details. TEMPO, 2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

To validate the hypothesized open-shell nature of this transformation, we further subjected 3-chloroindazole to coupling conditions designed to indicate the presence of radical intermediates. When using (bromomethyl)cyclopropane as the halide coupling partner, no direct coupling was observed, with *N*-homoallyl indazole **64** instead generated as the primary product in 33% yield (Figure 7). Given the rapid rate for unimolecular ring-opening of the cyclopropylmethyl radical ($k = 7.8 \times 10^7 \text{ s}^{-1}$ at 20°C)⁸⁰ to generate homoallylic isomers, this outcome is consistent with the intermediacy of alkyl radicals (presumably generated via halogen atom transfer, as supersilanol is required for detectable product formation, see Figure 1) in the HARC *N*-alkylation protocol. However, to further distinguish between the possibilities of radical ring-opening and copper-mediated β -carbon elimination (which would not necessarily proceed via open-shell intermediates),⁸¹ TEMPO-trapping studies were also conducted. When adding the persistent radical 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to the standard bromocyclohexane coupling reaction, product **1** was not detected, and the major species observed from bromocyclohexane conversion was TEMPO-trapped adduct **65** (Figure 7). Given that adduct **65** is well-established to be forged via radical-radical coupling of TEMPO with the transient cyclohexyl radical,⁸² these results, in tandem with ring-opening studies and control experiments (Figures 1, 7, and S22–S25), denote the anticipated open-shell pathways needed to enable HARC-type coupling.



Scheme 2. Plausible mechanism and summary of conditions for copper-HARC N-alkylation

Based on the above findings and preceding literature regarding the behavior of copper complexes in systems containing open-shell intermediates, a plausible mechanism and summary of optimal conditions for copper-HARC N-alkylation is detailed in [Scheme 2](#). Initial photoexcitation of Ir(III) photocatalyst [Ir-1] with blue light from IPR irradiation and subsequent intersystem crossing would generate the long-lived triplet excited state II (lifetime $\tau = 280$ ns), a potent single-electron oxidant ($E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.65$ V versus SCE in MeCN).⁸³ Consistent with previous aerobic photocatalytic transformations featuring silyl radical activation of halides,⁵³ ensuing SET between complex II and a silyl radical precursor such as supersilanol (IV; $E_{\text{pa}}[\text{IV}/\text{IV}^{\bullet}] = +1.54$ V versus SCE in MeCN)⁴⁸ would afford reduced Ir(II) photocatalyst III and, upon deprotonation and radical Brook rearrangement, silicon-centered radical V. This nucleophilic silyl radical can perform facile halogen atom abstraction, converting alkyl bromide VI to aliphatic radical intermediate VII.⁸⁴ Concurrently, reduced Ir(II) complex III ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -0.79$ V versus SCE in MeCN)⁸³ can be re-oxidized by molecular oxygen to regenerate ground-state Ir(III) photocatalyst [Ir-1]. Independently, Cu(I) catalyst VIII, N-nucleophile IX, and base would combine to produce anionic Cu(I)-amido complex X, eventually affording neutral Cu(II)-amido intermediate XI following SET with oxygen. Such copper complexes are well-documented to furnish C(sp³)-N bonds upon encountering alkyl radicals,^{33–36,44} presumably beginning with capture of radical VII (predicted to proceed at near-diffusion rates)^{85–87} to afford HARC-generated Cu(III)-alkyl complex XII. Subsequent reductive elimination from XII would deliver N-alkyl product XIII while regenerating Cu(I) catalyst VIII, ultimately closing both catalytic cycles.^{88–92} Unique to this platform is the decoupled nature of halide activation (by photocatalytic halogen atom transfer) and nucleophile activation (by copper catalysis). This design principle is evidently responsible for conferring generality (with respect to scope) across both coupling partners and for offering reactivity and selectivity surpassing that of previously reported halide-based N-alkylation systems.

Conclusion

In summary, an underexplored HARC strategy has been applied to the copper metallaphotoredox alkylation of *N*-nucleophiles using alkyl halides as convenient electrophilic partners. This coupling method requires no substrate preactivation, operates under mild aerobic conditions, and provides reactivity with a broad range of alkyl bromides and *N*-heterocycles, including those typically recalcitrant within thermally induced S_N1 or S_N2 settings. The demonstrated late-stage utility of this method, as well as the compatibility of substrates traditionally inert to substitution (such as bromocyclopropane and various alkyl chlorides), makes this technology particularly promising for exploring diverse sp^3 -rich chemical space in medicinal chemistry settings. We anticipate that HARC coupling mechanisms, including those demonstrated for *N*-alkylation, will continue to be developed and deployed for complex molecule synthesis, ideally providing synthetic chemists access to elusive alkylamines (or other motifs) that cannot be generated through conventional approaches.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, David W. C. MacMillan (dmacmill@princeton.edu).

Materials availability

This study did not involve the design of unique reagents or catalysts for chemical synthesis.

Data and code availability

There is no dataset or code associated with this publication. All relevant procedures and experimental data are provided in the [supplemental information](#).

General procedure for HARC *N*-alkylation of indazoles and pyrazoles

To an oven-dried 40 mL vial equipped with a Teflon stir bar was added indazole or pyrazole nucleophile (0.25 mmol, 1.0 equiv), $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2[4,4'\text{-d}(\text{CF}_3)\text{bpy}]\text{PF}_6$ (**[Ir-1]**, 2.3 mg, 2.0 μmol , 0.008 equiv), bis(2,2,6,6-tetramethyl-3,5-heptanedionato)copper(II) ($\text{Cu}(\text{TMHD})_2$, 22–32 mg, 0.05–0.075 mmol, 0.2–0.3 equiv), LiOt-Bu (60 mg, 0.75 mmol, 3.0 equiv), MeCN (2.5 mL, 0.1 M), and water (45 μL , 2.5 mmol, 10 equiv). The resulting solution was stirred for 1–2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, alkyl halide (0.625 mmol, 2.5 equiv) and $(\text{TMS})_3\text{SiOH}$ (165 mg, 0.625 mmol, 2.5 equiv) were added to the mixture, after which the vial was capped and an 18G vent needle was inserted through the Teflon-lined septum. The reaction mixture was subsequently stirred under air within the integrated photoreactor (450 nm irradiation) for 4 h. After 4 h, the reaction mixture was diluted with EtOAc (5 mL), followed by the addition of KF on alumina (40 wt % from Sigma-Aldrich, 1.0 g) and tetrabutylammonium bromide (500 mg) to the vial. This suspension was stirred under air for 2–24 h, then filtered into a separatory funnel, using an additional 25 mL EtOAc wash to ensure complete transfer from the vial. The organic layer was subsequently washed with saturated Na_2CO_3 (10 mL), water (10 mL), and brine (10 mL), and the collected aqueous layer was extracted with EtOAc (10 mL). The combined organics were dried over MgSO_4 and concentrated *in vacuo* to obtain the crude product. This residue was then purified by silica gel chromatography to afford the desired *N*-alkylated product.

General procedure for HARC *N*-alkylation of other *N*-nucleophiles

To an oven-dried 40 mL vial equipped with a Teflon stir bar was added *N*-nucleophile (0.25 mmol, 1.0 equiv), Ir[dF(CF₃)ppy]₂[4,4'-d(CF₃)bpy]PF₆ ([Ir-1], 2.3 mg, 2.0 μmol, 0.008 equiv), MeCN (2.5 mL, 0.1 M), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 31 μL, 0.25 mmol, 1.0 equiv). The resulting homogeneous solution was stirred for 5 min, after which LiOt-Bu (60 mg, 0.75 mmol, 3.0 equiv) and water (45 μL, 2.5 mmol, 10 equiv) were added to the vial. This suspension was then sonicated under air for 1 min until the mixture became homogeneous. Cu(TMHD)₂ (22–32 mg, 0.05–0.075 mmol, 0.2–0.3 equiv) was then added to the vial, and the solution was stirred for 1–2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, alkyl halide (0.625 mmol, 2.5 equiv) and (TMS)₃SiOH (165 mg, 0.625 mmol, 2.5 equiv) were added to the mixture, after which the vial was capped and an 18G vent needle was inserted through the Teflon-lined septum. The reaction mixture was subsequently stirred under air within the integrated photoreactor (450 nm irradiation) for 4 h. After 4 h, the reaction mixture was diluted with EtOAc (5 mL), followed by the addition of KF on alumina (40 wt %, 1.0 g) and tetrabutylammonium bromide (500 mg) to the vial. This suspension was stirred under air for 2–24 h, then filtered into a separatory funnel, using an additional 25 mL EtOAc wash to ensure complete transfer from the vial. The organic layer was subsequently washed with saturated Na₂CO₃ (10 mL), water (10 mL), and brine (10 mL), and the collected aqueous layer was extracted with EtOAc (10 mL). The combined organics were dried over MgSO₄ and concentrated *in vacuo* to obtain the crude product. This residue was then purified by silica gel chromatography to afford the desired *N*-alkylated product.

Other experimental details and examples (Figures S1–S31), as well as characterization data (Figures S32–S184), can be found in the [supplemental information](#).

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.chempr.2021.05.005>.

ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS), the NIH (under award R35GM134897-01), the Princeton Catalysis Initiative, and kind gifts from Merck, Janssen, BMS, Genentech, Celgene, and Pfizer. N.W.D. acknowledges Princeton University, N. Brink, and the Brink Family for a Brink Graduate Fellowship and acknowledges Princeton University, E. Taylor, and the Taylor family for an Edward C. Taylor Fellowship. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS. The authors thank M.N. Lavagnino, Y. Liang, W. Liu, H.A. Sakai, and X. Zhang for helpful scientific discussions.

AUTHOR CONTRIBUTIONS

D.W.C.M., N.W.D., and A.C. conceived the research. N.W.D. and A.C. designed the experiments. N.W.D. and A.C. carried out the experiments and analyzed results under the guidance of D.W.C.M. N.W.D. and D.W.C.M. prepared the manuscript with input from all authors.

DECLARATION OF INTERESTS

D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

Received: February 22, 2021

Revised: April 6, 2021

Accepted: May 11, 2021

Published: June 15, 2021

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