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Communication

Free-Radical Deoxygenative Amination of Alcohols via Copper Metallaphotoredox Catalysis

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ABSTRACT: Alcohols are among the most abundant chemical feedstocks, yet they remain vastly underutilized as coupling partners in transition metal catalysis. Herein, we describe a copper metallaphotoredox manifold for the open shell deoxygenative coupling of alcohols with *N*-nucleophiles to forge C(sp^3)−N bonds, a linkage of high value in pharmaceutical agents that is challenging to access via conventional cross-coupling techniques. *N*-heterocyclic carbene (NHC)-mediated conversion of alcohols into the corresponding alkyl radicals followed by copper-catalyzed C−N coupling renders this platform successful for a broad range of structurally unbiased alcohols and 18 classes of *N*-nucleophiles.

Carbon−nitrogen bonds are prevalent in therapeutics, agrochemicals, natural products, and functional materials. Over 80% of unique FDA-approved small-molecule pharmaceuticals contain at least one nitrogen atom,[1] and 18% of transformations executed at the drug discovery stage involve the installation of a C−N bond.[2] The past two decades have seen dramatic advances in the construction of C(sp^2)−N bonds, largely attributable to the development of powerful transition metal catalysis platforms, such as the Buchwald-Hartwig,[3] Ullman-Goldberg,[4,5] and Chan-Evans-Lam[6] coupling reactions. Despite recent progress, introduction of a general platform to install medicinally relevant C(sp^3)−N linkages remains a high priority (Figure 1a).[7−9]

Molecules that possess a higher fraction of fully saturated carbon atoms exhibit enhanced physicochemical properties—including higher solubility and bioavailability—compared to their unsaturated analogs and are thus more likely to advance through clinical trials.[10,11] Given the ubiquity of carbon−nitrogen bonds in therapeutics, there is a strong impetus to develop general methods to construct C(sp^3)−N linkages. However, synthetic access to these motifs mainly relies on classical methods, such as reductive amination,[12] nucleophilic displacement with activated electrophiles,[13−15] Curtius rearrangement,[16] and olefin hydroamination.[17,18]

Copper catalysis has drawn attention for its unique ability to forge challenging bonds via facile reductive elimination from high-valent copper(III) complexes.[19] However, the sluggish oxidative addition of low-valent copper species into organic electrophiles precludes a more comprehensive expansion of conventional copper-based methods. Over the past decade, the merger of copper catalysis with free-radical chemistry emerged as a general approach to bypass the challenge of copper(I) oxidative addition. Specifically, it was demonstrated that copper(III) intermediates can be accessed by adding free radicals onto copper(II) species. Regarding amination chemistry, this merger of copper catalysis with free radical chemistry enabled C(sp^3)−N coupling of alkyl halides,[20−25] carboxylic acids,[26−28] and simple hydrocarbons.[29,30] However, no C(sp^3)−N cross-coupling method has been disclosed that features as a radical precursor the most widespread aliphatic functionality: the alcohol.

Alcohols are widely available, structurally diverse, and operationally convenient native alkyl building blocks (Figure 1b). Moreover, their extensive presence in pharmaceuticals and natural products provides opportunities for direct late-stage functionalization. However, alcohols are underutilized as alkylating reagents. Due to the low electrophilicity and innate strength of the C(sp^3)−O bond, alcohols must first be converted into more reactive species, and these activation platforms often require time- and resource-intensive chemical steps and challenging purifications.

Recent methods have been introduced for the orthogonal homolytic activation of alcohol C(sp^3)−O bonds. For instance, the redox chemistry of xanthate esters,[31] hemioxalates,[32] phosphoranyl radicals,[33,34] and low-valent oxophilic metals[35] has been leveraged to convert alcohols into alkyl radicals. However, combining these new activation modes with transition metal catalysis continues to pose a challenge.

In 2021, our laboratory introduced *N*-heterocyclic carbene (NHC)-based reagents that condense with alcohols under mild conditions to yield redox-active adducts.[36] Without purification or workup, these preactivated intermediates directly engage in metallaphotoredox transformations, enabling the deoxygenative generation of alkyl radicals from a range of structurally unbiased alcohols. This alcohol activation mode is compatible with multiple transition-metal catalysis platforms and has been

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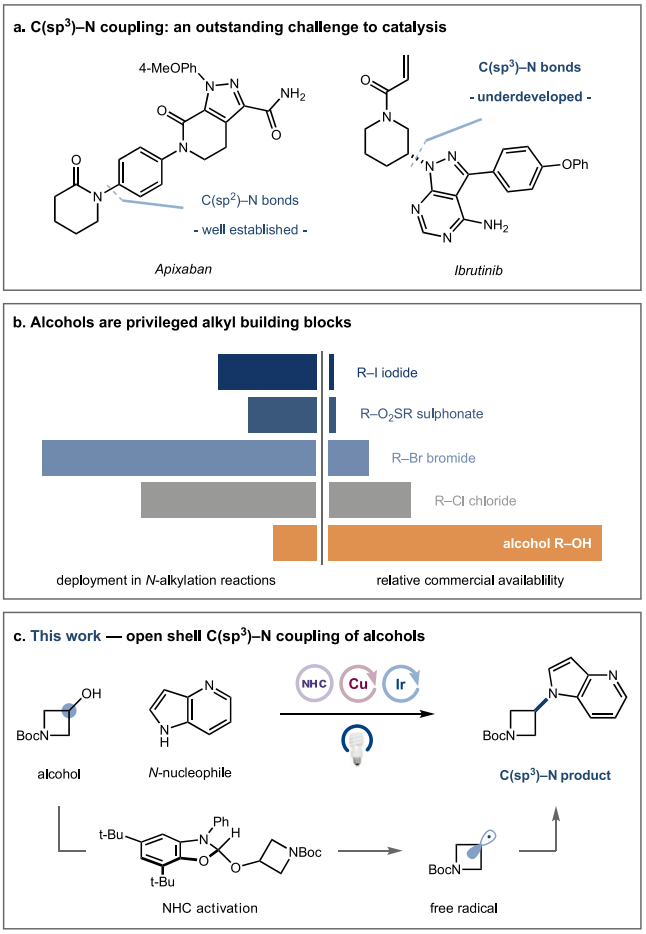


Figure 1. Deoxygenative amination of alcohols. Abbreviations: 4-MeOPh, 4-methoxyphenyl; Boc, *tert*-butoxycarbonyl; Ph, phenyl; t-Bu, *tert*-butyl.

harnessed for various deoxygenative transformations, including arylation,[36] alkylation,[37,38] and trifluoromethylation.[39] Inspired by these studies, we sought to merge copper metallaphotoredox catalysis with NHC-alcohol activation to develop a general C(sp^3)−N cross-coupling platform that utilizes alcohols as alkylating reagents (Figure 1c). An open-shell route from alcohols to C−N bonds would streamline the construction of these highly functional biorelevant linkages.

The plausible mechanism for the C(sp^3)−N cross-coupling reaction is outlined in Figure 2. First, alcohol **1** reacts with *N*-arylbenzoxazolium salt **2** under mildly basic conditions, forming NHC-alcohol adduct, **3**. Upon photoexcitation with visible light (450 nm), [Ir(Fmppy)$_2$(dtbpy)][PF$_6$] complex **4** (Fmppy = 2-(4-fluorophenyl)-4-(methylpyridine), dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) generates a long-lived triplet excited state (τ = 1.2 μs). This photoexcited *Ir(III) **5** ($E_{1/2red}$ [$^*Ir^{III}/Ir^{II}$] = +0.94 V versus saturated calomel electrode (SCE) in CH$_3$CN)[40] is readily quenched by NHC-alcohol adduct **3** *via* single-electron transfer (SET) ($E_{1/2}$ = 1.0 V versus SCE in CH$_3$CN),[36,41] yielding reduced Ir(II) species **6** and the radical cation of the adduct. The methine C−H bond in this radical cation is deprotonated with stoichiometric base, producing α-oxy radical **7**. Next, **7** undergoes β-scission of the C−O bond, affording an inert carbamate byproduct and free alkyl radical **8**. Independently, an *N*-nucleophile, **9**, reacts with copper(II) acetate and stoichiometric base to produce Cu(II) amido complex, **10**. Complex **10** intercepts free alkyl

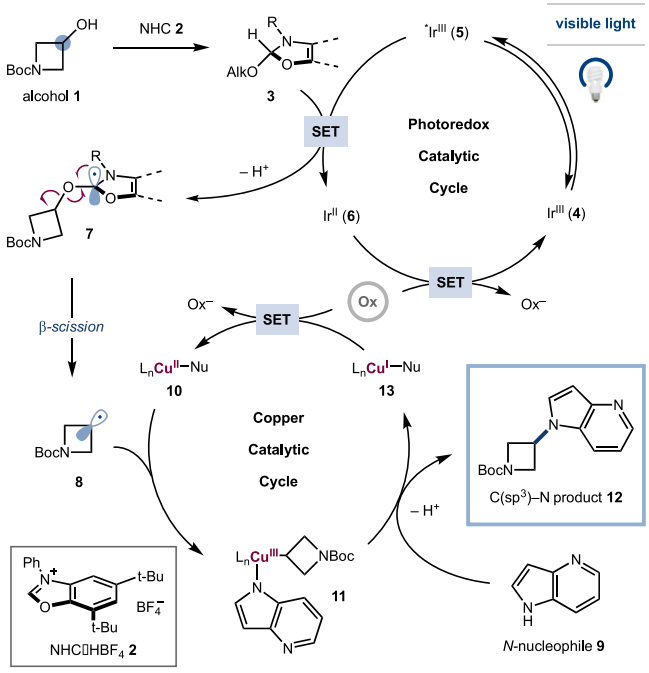
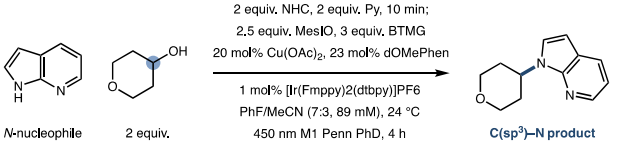


Figure 2. Plausible mechanism for the deoxyamination reaction. Abbreviations: Alk, alkyl; Nu, nucleophile; Ox, oxidant.

radical **8** at near-diffusion rates, generating a putative Cu(III) alkyl intermediate, **11**.[42,43] The high-valent copper complex **11** undergoes reductive elimination to produce the C(sp^3)−N coupled product **12** and low-valent copper(I) species **13**. Finally, both catalytic cycles are turned over *via* reaction of exogenous stoichiometric oxidant with the reduced iridium catalyst, **6** ($E_{1/2red}$ [Ir^{III}/Ir^{II}] = −1.50 V versus SCE in CH$_3$CN) and copper catalyst, **13**.

We began our investigations by examining the coupling between 7-azaindole and 4-tetrahydropyranol. Following an extensive campaign, we identified optimal conditions for this reaction (Table 1). The deoxygenative amination was successfully performed with commercially available copper(II) acetate, 4,7-dimethoxy-1,10-phenanthroline ligand, BTMG

Table 1. Control Experiments for the C(sp^3)−N Coupling



entry[a]	deviation	yield[b]
1	none	81% (62%[c])
2	no Ir photocatalyst	<1%
3	no Cu(OAc)$_2$ catalyst	<1%
4	no BTMG base	<1%
5	no light	<1%
6	no dOMePhen ligand	10%
7	no MesIO oxidant	7%
8	1 equiv. alcohol	28%

[a]0.1 mmol scale. [b]^{1}H NMR assay yields. [c]Isolated yield on 0.5 mmol scale. Abbreviations: Ac, acetyl; BTMG, 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine; dOMePhen, 4,7-dimethoxy-1,10-phenanthroline; Mes, mesityl; Py, pyridine. See the Supporting Information (SI) for further details.

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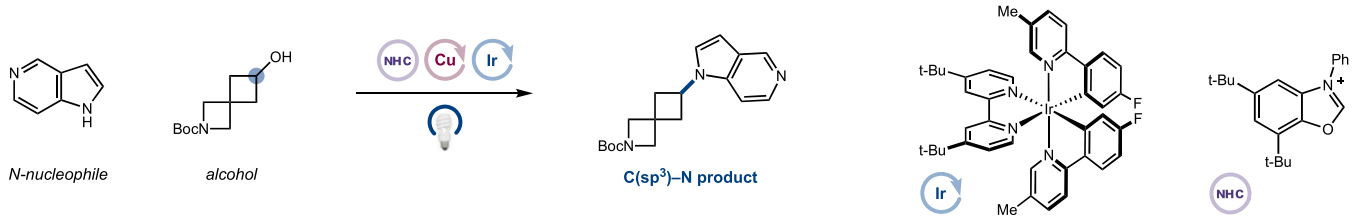
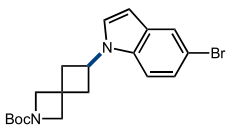
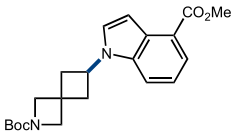
Table 2. *N*-Nucleophile Scope of the Deoxyamination Reaction



indoles

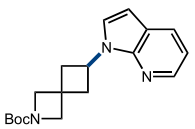


14 70% yield

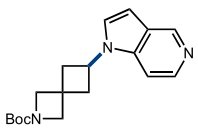


15 71% yield

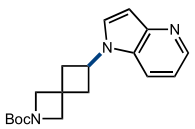
azaindoles



16 79% yield[a]

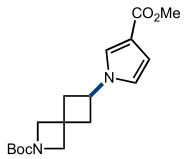


17 81% yield



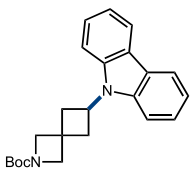
18 61% yield

pyrrole



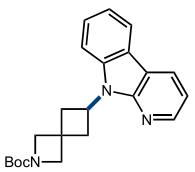
19 62% yield[a]

carbazole



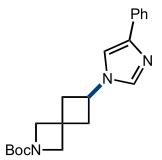
20 77% yield

azacarbazole



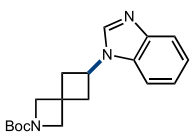
21 65% yield

imidazole



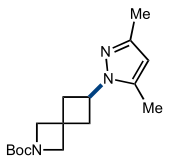
22 53% yield, >20:1 r.r.

benzimidazole

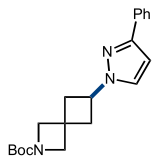


23 61% yield

pyrazoles

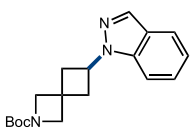


24 72% yield

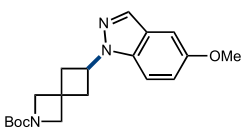


25 74% yield, >20:1 r.r.

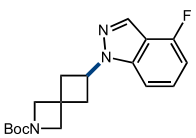
indazoles



26 76% yield, >20:1 r.r.[a]

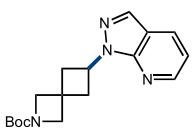


27 68% yield, >20:1 r.r.[a]

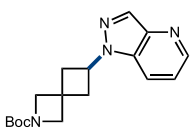


28 78% yield, >20:1 r.r.[a]

azaindazoles

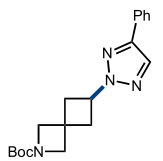


29 63% yield, >20:1 r.r.[a]



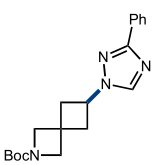
30 61% yield, >20:1 r.r.[a]

triazoles



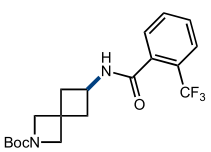
31 67% yield, 9:1 r.r.

triazoles

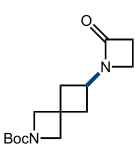


32 57% yield, 11:1 r.r.

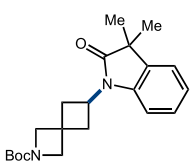
amides



33 60% yield

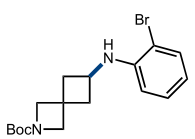


34 73% yield[a]

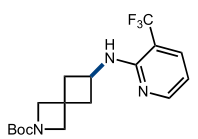


35 74% yield[a]

anilines

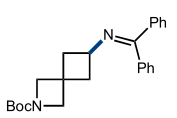


36 79% yield



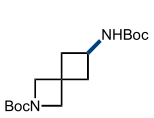
37 77% yield

imine



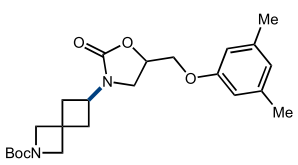
38 69% yield[a]

carbamate



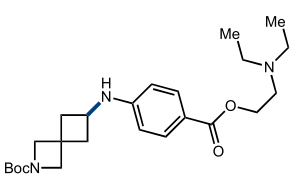
39 79% yield

Skelaxin



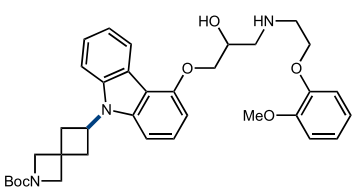
40 61% yield

Procaine



41 42% yield

Carvedilol



(±)-42 28% yield (42%)

[a]With $Cu(OAc)_2$ (40 mol %), dOMePhen (45 mol %), and $[Ir(Fmppy)_2(dtbpy)][PF_6]$ (2 mol %). All other reactions were performed with alcohol (2 equiv), NHC (2 equiv), and pyridine (2 equiv) in PhF (0.25 M), then *N*-nucleophile (0.5 mmol, 1 equiv), $Cu(OAc)_2$ (10 mol %), Bphen (11.5 mol %), $[Ir(Fmppy)_2(dtbpy)][PF_6]$ (1 mol %), BTMG or DBN (3 equiv), and MesIO (2.5 equiv) in PhF/MeCN (7:3, 89 mM); irradiation with 450 nm light for 4 h. All yields are isolated (yields in parentheses are assay yields determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard). Abbreviations: Me, methyl; r.r., regioisomer ratio. See SI for details.

base, and $[Ir(Fmppy)_2(dtbpy)][PF_6]$ photocatalyst, with iodosomesitylene (MesIO) as the stoichiometric oxidant. Under optimized conditions, the alcohol substrate underwent efficient *in situ* activation with benzoxazolium reagent NHC (**2**) using pyridine as a base in fluorobenzene solvent. The resulting precipitate of pyridinium tetrafluoroborate salt was filtered off, and the crude solution of the NHC-alcohol adduct was directly subjected to cross-coupling with 7-azaindole, affording the *N*-alkyl product in excellent yield (Table 1, entry 1). Control experiments revealed that exclusion of the

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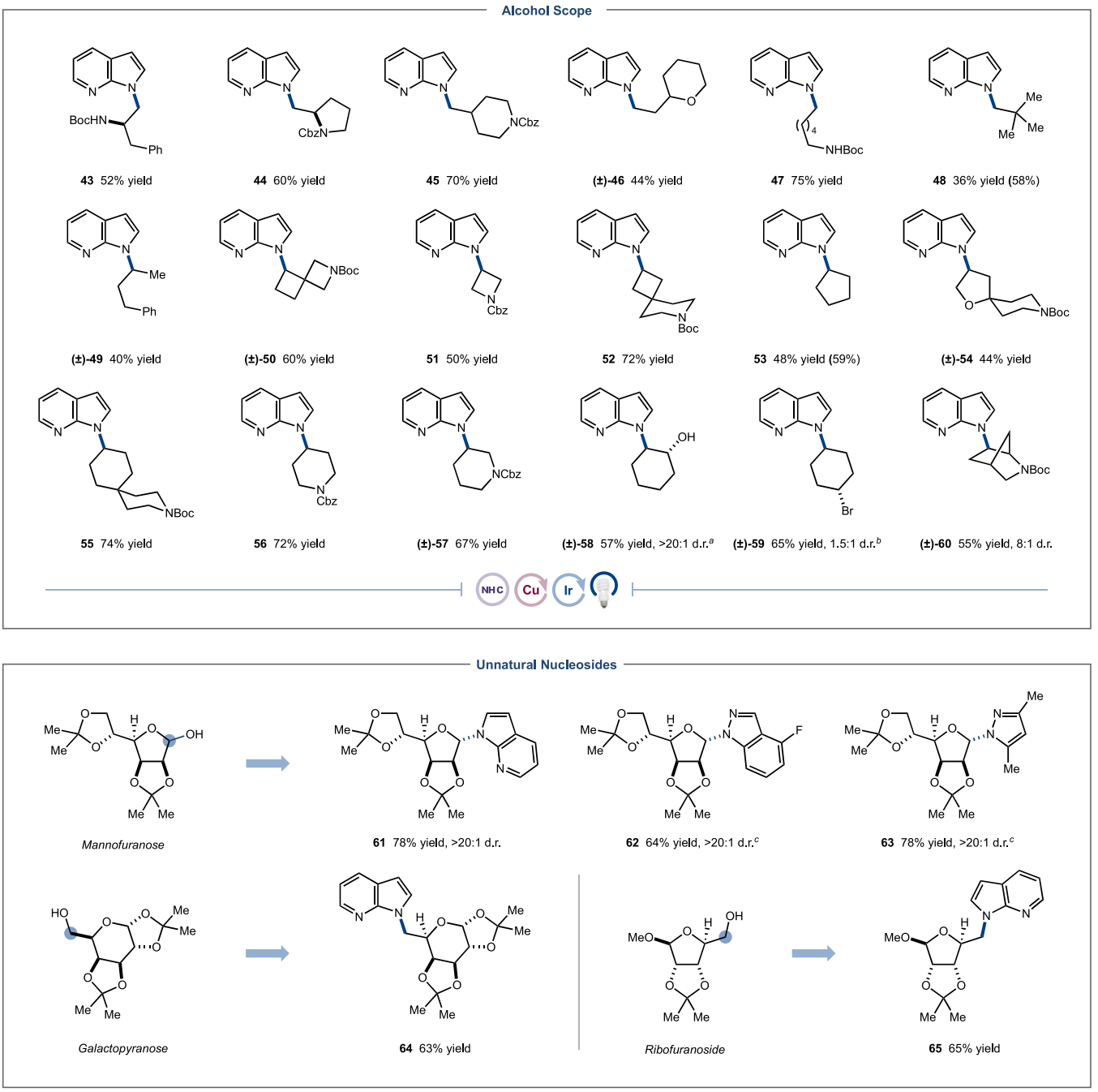
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Alcohol Scope of the Deoxyamination Reaction



[a]With $Cu(OAc)_2$ (40 mol %), dOMePhen (45 mol %) in PhF/MeCN (5:1, 52 mM). [b]With dOMePhen (23 mol %). [c]With $Cu(OAc)_2$ (40 mol %), dOMePhen (45 mol %). All other reactions were performed with alcohol (2 equiv), NHC (2 equiv), and pyridine (2 equiv) in PhF (0.25 M), then *N*-nucleophile (0.5 mmol, 1 equiv), $Cu(OAc)_2$ (20 mol %), dOMePhen (25 mol %), $[Ir(Fmppy)_2(dtbpy)][PF_6]$ (1 mol %), BTMG or DBN (3 equiv), and MesIO (2.5 equiv) in PhF/MeCN (7:3, 89 mM); irradiation with 450 nm light for 4 h. All yields are isolated (yields in parentheses are assay yields determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard). Abbreviations: Bn, benzyl; Cbz, benzyloxycarbonyl. d.r., diastereomeric ratio. See SI for details.

photocatalyst, copper salt, base, or irradiation step failed to produce the desired product altogether (entries 2−5). Additionally, excluding the ligand or oxidant or utilizing only one equivalent of alcohol resulted in significantly diminished yields (entries 6−8). These results are consistent with the proposed mechanistic picture.

With optimized experimental protocols in hand, we sought to establish the scope of the deoxygenative C(sp^3)−N cross-coupling reaction. First, to evaluate the nucleophilic reaction partners, we selected a strained spirocyclic alcohol substrate that has proven challenging for nucleophilic substitution chemistry. Gratifyingly, the new method was found to be robust and general: deoxygenative amination was achieved with 18 classes of medicinally relevant *N*-nucleophiles (Table 2). A spectrum of azole heterocycles was engaged in the reaction. Indoles (**14** and **15**, 70 and 71% yield), azaindoles

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(**16**−**18**, 61−81% yield), pyrrole (**19**, 62% yield), carbazole (**20**, 77% yield), and azacarbazole (**21**, 65% yield) afforded alkylated products in good yields. Notably, the reaction tolerated aryl bromides (**14**) due to the high barrier for oxidative addition of low-valent copper(I) species into Ar−Br bonds. This chemoselectivity highlights the prospect of employing the transformation for rapid, modular assembly of biorelevant molecules.

Next, we turned our attention to diazole heterocycle substrates. Exposure of imidazole (**22**, 53% yield), benzimidazole (**23**, 61% yield), pyrazoles (**24** and **25**, 72 and 74% yield), indazoles (**26**−**28**, 68−78% yield), and azaindazoles (**29** and **30**, 63 and 61% yield) to the reaction conditions delivered the coupled products in good yields. Remarkably, the reaction proceeded with excellent regioselectivity for *N1* alkylation: regioisomeric ratios (r.r.) of >20:1 were observed for imidazole, pyrazole, indazole, and azaindazole substrates; this result is attributed to the preference of heterocycles to ligate to the copper center at the *N1*-position. The observed selectivity contrasts with conventional alkylation methods, which typically deliver complicated mixtures of regioisomeric *N1* and *N2*-products. Furthermore, triazoles (**31** and **32**, 67 and 57% yield, 9:1 and 11:1 r.r.) were alkylated in good yields and regioselectivities.

We also found that benzamide (**33**, 60% yield), *β*-lactam (**34**, 73% yield), oxindole (**35**, 74% yield), aniline (**36**, 79% yield), and aminopyridine (**37**, 77% yield) could be engaged in the transformation. Moreover, ammonia surrogates, such as benzophenone imine (**38**, 69% yield) and *tert*-butyl carbamate (**39**, 79% yield), delivered products that could be easily deprotected to reveal the corresponding primary amines. Finally, to underscore the utility of the C−N coupling for drug-discovery purposes, we examined a range of active pharmaceutical ingredients. Skelaxin (**40**, 61% yield), procaine (**41**, 42% yield), and Carvedilol (**42**, 42% yield) delivered alkylated products in useful to good yields. The compatibility of unprotected amines (**41 and 42**) with the reaction conditions is noteworthy for medicinal chemistry programs, considering the ubiquity of this functionality among lead compounds.

Having established the scope of the C(sp^3)−N cross-coupling reaction for the nucleophilic partners, we turned our attention to the alcohol coupling partners. We selected 7-azaindole as a nucleophile to interrogate the alcohol scope. As illustrated in Table 3, a wide variety of structurally unbiased primary and secondary alcohols could be harnessed for this transformation. Amino acid-derived primary alcohols are viable substrates (**43** and **44**, 52 and 60% yield). Piperidine- and tetrahydropyran-containing primary alcohols were also well tolerated (**45** and **46**, 70 and 44% yield), and a long-chain primary alcohol performed well (**47**, 75% yield). Moreover, a sterically hindered neopentyl alcohol was coupled in good yield (**48**, 58% yield).

Next, we evaluated secondary alcohols. Gratifyingly, an acyclic secondary alcohol (**49**, 40% yield) was well-tolerated, as were a series of four-membered (**50**−**52**, 50−72% yield), five-membered (**53** and **54**, 59 and 44% yield), and six-membered (**55**−**59**, 57−74% yield) carbocyclic and aliphatic heterocyclic alcohols. Notably, the reaction tolerated secondary alcohol and alkyl bromide moieties (**58** and **59**), underscoring the mild nature of the protocol. This finding raises the possibility of deploying bromoalcohols as bifunctional linchpins to rapidly assemble biorelevant aliphatic scaffolds. Moreover, we demonstrated the coupling of a bicyclic motif to the nitrogenated heterocycle (**60**, 55% yield, 8:1 d.r.). The capacity to directly employ the bicyclic alcohol in the C(sp^3)−N cross-coupling reaction is noteworthy given that few functionalized polycyclic building blocks are commercially available.

Unnatural nucleosides are widely utilized in anticancer and antiviral therapies due to their ability to interrupt cellular and viral replication.[44] However, the synthesis of these scaffolds is often challenging.[45] We wondered whether our deoxygenative amination platform would be amenable to the direct coupling of sugar hemiacetals and aromatic heterocycles. We were pleased to observe that mannofuranose acetonide could be converted to a series of single-diastereomer unnatural nucleosides using 7-azaindole (**61**, 78% yield), 4-fluoroindazole (**62**, 64% yield), and 3,5-dimethylpyrazole (**63**, 78% yield) as nucleophilic coupling partners. Moreover, 7-azaindole was coupled with galactopyranose acetonide (**64**, 63% yield) and ribofuranoside acetonide (**65**, 65% yield).

In summary, we disclosed an efficient protocol for the copper metallaphotoredox-enabled alkylation of *N*-nucleophiles with simple alcohols. This transformation was found to be amenable to an extensive range of substrates, including nitrogenated heterocycles, anilines, amides, primary and secondary alcohols, diols, monosaccharides, and complex drug-like molecules. Given the importance of C(sp^3)−N linkages in bioactive molecules, we anticipate this reaction will be of value to the medicinal chemistry community.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c04477.

Experimental details, optimization studies, compound characterization data, and spectra (PDF)

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Notes

The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS.

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

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