

Deoxygenative $C(sp^3)$ – $N(sp^3)$ Cross-Coupling Enabled by Nickel Metallaphotoredox CatalysisRuizhe Chen,[#] Taehyun Kim,[#] Noah B. Bissonnette,[#] Robert T. Martin, Joseph R. Martinelli, Albert Cabré, and David W. C. MacMillan*Cite This: *J. Am. Chem. Soc.* 2025, 147, 37885–37892

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ABSTRACT: Metallaphotoredox catalysis has emerged as a powerful platform for generating high-energy radicals from native functionalities. This approach integrates radical reactivity with transition metal catalysis to enable controlled bond formation. However, the synthesis of tertiary amines remains a significant challenge due to their redox sensitivity under photoredox conditions and the inherent difficulty of $C(sp^3)$ – $N(sp^3)$ reductive elimination. Herein, we describe a deoxygenative C–N cross-coupling between alcohols and *N*-hydroxylamine esters to form tertiary amines. Oxidation of the tertiary amine products is kinetically suppressed under optimized conditions, while a sterically demanding ancillary ligand promotes reductive elimination. This methodology displays broad substrate scope, accommodating diverse functional groups, heterocycles, and pharmaceutical derivatives.

Molecular architectures rich in sp^3 -hybridized frameworks represent important synthetic targets in contemporary organic chemistry due to their favorable pharmacological properties and elevated clinical success rates.^{1–3} Tertiary amines bearing $C(sp^3)$ – $N(sp^3)$ bonds are of particular interest, as over 80% of recently FDA-approved drugs contain at least one saturated N-heterocycle, nearly half of which are fully saturated (Figure 1A).⁴ Notable examples include piperidines, pyrrolidines, piperazines, and morpholines—each among the ten most prevalent heterocycles in modern therapeutics.⁴ These ring systems are predominantly N-functionalized in marketed drugs.⁴

Nucleophilic substitution and carbonyl reductive amination are among the most widely used methods for synthesizing aliphatic amines. However, these approaches can suffer from limitations owing to steric constraints, forcing reaction conditions, and undesired side reactions such as elimination and overalkylation.⁵ Accordingly, considerable effort has been devoted to developing milder and more efficient methods to construct tertiary aliphatic amines from alkyl electrophiles. Notable examples merge open-shell intermediates with transition-metal catalysis, as in the net reductive cross-electrophile coupling reported by the Wang group⁶ and the photoexcited copper-mediated halogen atom transfer (XAT) activation developed by the Fu group.^{7,8} While these elegant methods achieve the conversion of alkyl halides to aliphatic amines, analogous approaches using alcohols—among the most abundant and structurally diverse classes of commercially available feedstocks⁹—remain limited by forcing conditions and narrow substrate scope.^{10–12} These limitations underscore the need for fundamentally new strategies for the direct conversion of alcohols to aliphatic amines.

N-heterocyclic carbene (NHC) precursors have recently emerged as mild, robust *in situ* activators of alcohols, enabling a wide range of deoxygenative metallaphotoredox cross-coupling

reactions.^{13,14} Within this framework, we recently introduced a net oxidative, copper-mediated deoxygenative C–N coupling of alcohols and $N(sp^2)$ coupling partners (Figure 1B).¹⁵ However, these conditions proved ineffective for $N(sp^3)$ -hybridized analogs. Indeed, the synthesis of tertiary amines via metallaphotoredox catalysis remains a longstanding challenge in synthetic chemistry, largely owing to two fundamental issues. First, the reductive elimination step required to forge the $C(sp^3)$ – $N(sp^3)$ bond is intrinsically disfavored due to the strength of the metal–nitrogen bond¹⁶ and the high kinetic barrier associated with the significant reorganization energy of $C(sp^3)$ – $N(sp^3)$ reductive elimination. Few examples exist of efficient $C(sp^3)$ – $N(sp^3)$ reductive elimination en route to tertiary amine products.^{6,17,18} Second, tertiary amines possess relatively low oxidation potentials ($E_{ox} \sim 1.0$ V vs SCE) and are prone to oxidation by photocatalysts, leading to product inhibition. Oxidation generates amino radical cations that are susceptible to decomposition, especially under basic environments. Current successful strategies either employ photocatalysts less prone to reductive quenching—such as the decatungstate anion¹⁷—or rely on rapid back electron transfer to mitigate decomposition without the need for strong bases.¹⁹

We sought to address these limitations by identifying new metallaphotoredox systems capable of facilitating $C(sp^3)$ – $N(sp^3)$ reductive elimination while mitigating deleterious oxidation of amine products (Figure 1C). Owing to its mild oxidation potential ($E_{ox} \sim 0.9$ V vs SCE), we posited that the

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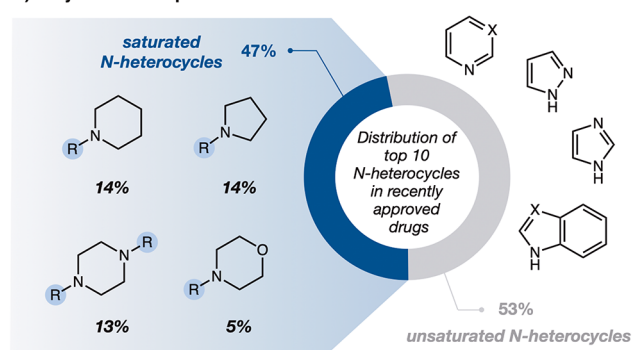
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A) Alkyl amines in pharmaceuticals



B) Our laboratory - 2024



C) This work

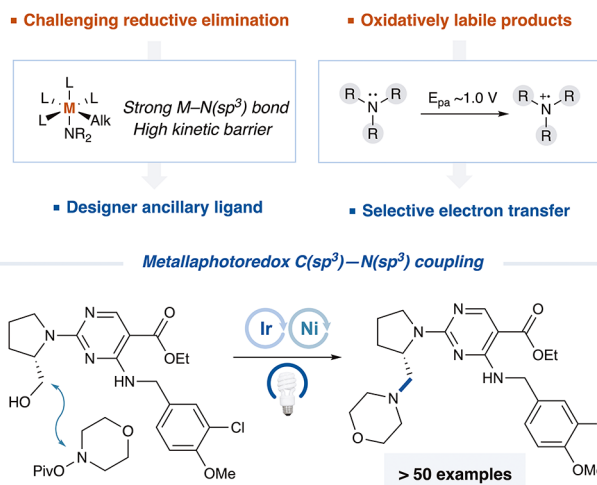
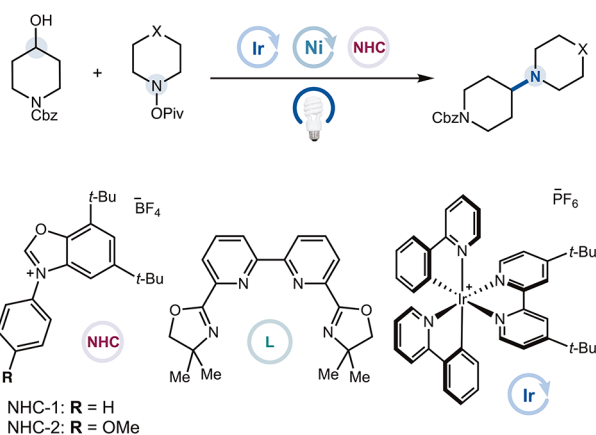


Figure 1. Alkyl amine synthesis via deoxygenative metallaphotoredox $C(sp^3)-N(sp^3)$ coupling.

NHC-alcohol adduct might be able to outcompete deleterious oxidation of the tertiary amine product under suitable redox conditions. We further aimed to use reductively activated $N(sp^3)$ -coupling partners as a means to avoid the net-oxidative conditions that promote product degradation. With these considerations in mind, *N*-hydroxylamine esters were identified as easily accessible precursors to aliphatic amines, whose weak $N-O$ bond undergoes facile oxidative addition by low valent metals.²⁰

In developing the reaction, *N*-Cbz-piperidin-4-ol and *N*-hydroxyl morpholine ester were selected as the model substrates. As shown in Figure 2, the desired $C(sp^3)-N(sp^3)$ coupling product was formed under nickel metallaphotoredox conditions in the presence of commercially available nickel(II) chloride catalyst, alcohol activator, NHC-1, quinuclidine base, and 1:1 MTBE/MeOH solvent. Among the hydroxylamine esters examined, pivaloyl esters outperformed their benzoyl, acetyl, and adamantanecarbonyl counterparts (Figure S03). Critical to our optimization campaign was the evaluation of



Entry ^a	$X=O$	Yield ^b
1	no deviation	78%
2	no light	0%
3	no photocatalyst	0%
4	no nickel	0%
5	no phthalimide	68%
6	N-OBz instead of N-OPiv	44%
$X=CH_2$		
7	no deviation	26%
8	<i>n</i> -PrOH for MeOH, NHC-2 for NHC-1, succinimide for phthalimide	68%

Ligand evaluation

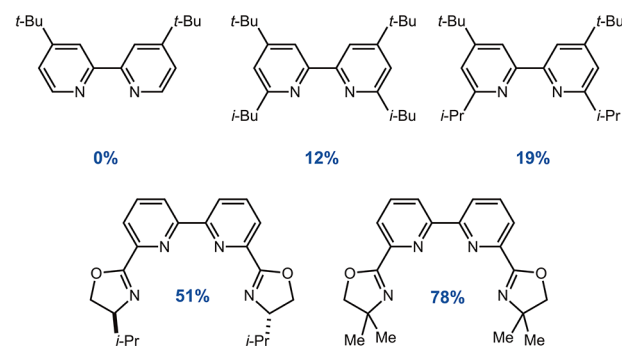


Figure 2. Control experiments and optimization. Reactions performed with alcohol (1.0 equiv), *N*-hydroxylamine ester (2.0 equiv), NHC-1 (1.2 equiv), pyridine (1.2 equiv), $NiCl_2$ (7.5 mol %), ligand (8.3 mol %), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1.0 mol %), phthalimide (1.0 equiv), quinuclidine (2.0 equiv), MTBE/MeOH (1:1, 0.05 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity), 30 min. Legend: (a) 0.05 mmol scale; (b) Assay yield determined by UPLC-MS analysis.

different ancillary ligands to promote the challenging $C(sp^3)-N(sp^3)$ reductive elimination. Notably, no product formation was observed with di-*tert*-butylbipyridine (dtbbpy), a common ligand in nickel metallaphotoredox catalysis. However, increasing steric bulk at the 2,2'-positions of the bipyridine scaffold resulted in markedly higher yields. Guided by this trend, we evaluated a series of sterically demanding 6,6'-bisalkylated dtbbpy derivatives (Figure 2). Among these, 6,6'-bis(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-2,2'-bipyridine emerged as the optimal ligand. To our knowledge, this work represents the first application of this ligand in cross-coupling.²¹ With the addition of stoichiometric phthalimide

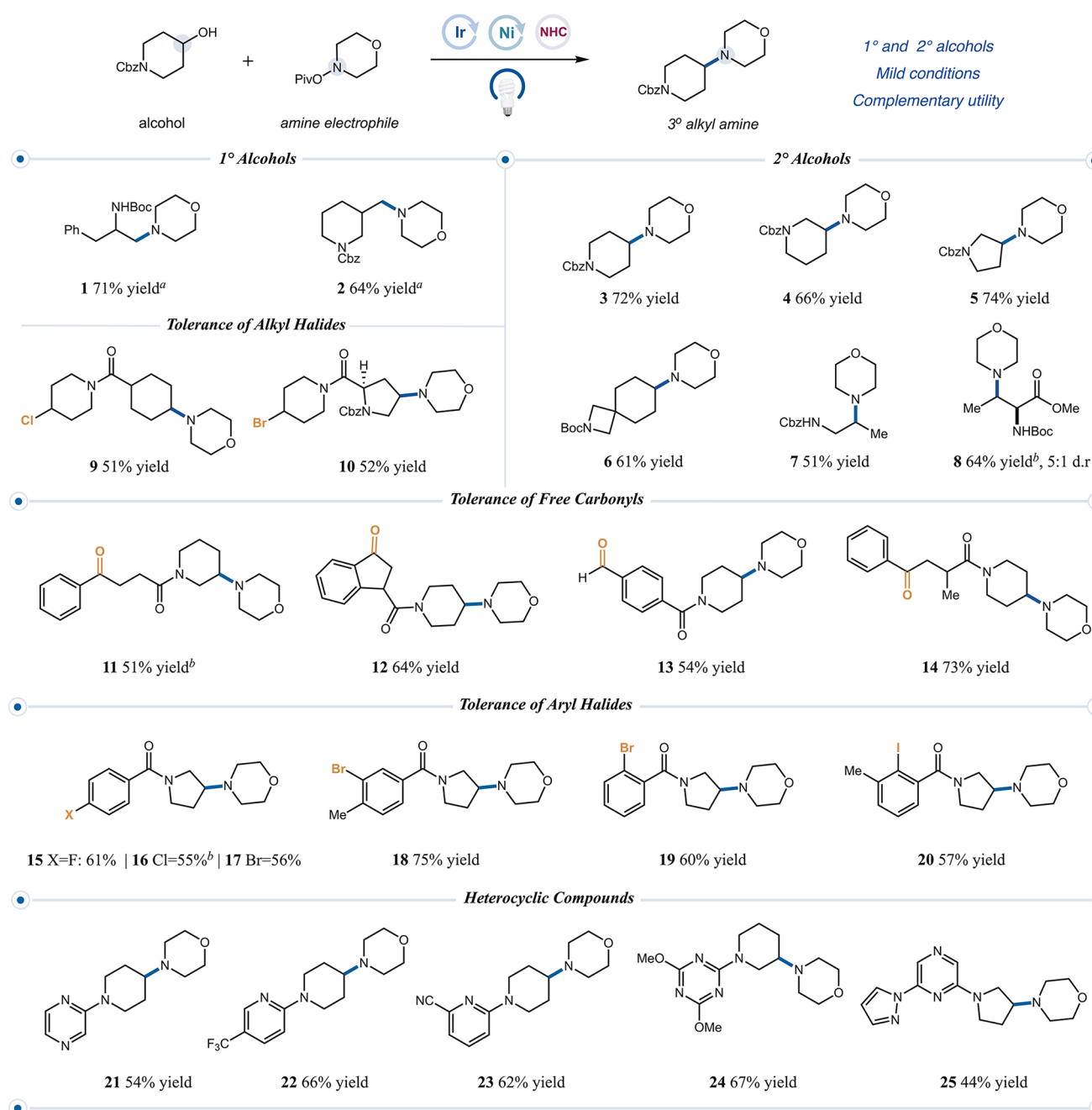


Figure 3. Alcohol scope for deoxygenative $C(sp^3)-N(sp^3)$ cross-coupling. Reactions performed with alcohol (1.0 equiv), *N*-hydroxylamine ester (2.0 equiv), NHC-1 (1.2 equiv), pyridine (1.2 equiv), $NiCl_2$ (7.5 mol %), ligand (8.3 mol %), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1.0 mol %), phthalimide (1.0 equiv), quinuclidine (2.0 equiv), MTBE/MeOH (1:1, 0.05 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity), 2.5 h. Yields are isolated unless specified. Legend: (a) 0.50 equiv. phthalimide used; (b) assay yields determined by UPLC-MS. See [Supporting Information](#) for experimental details.

to prevent decomposition of the nickel oxidative addition complex,²² the desired coupling product was obtained in excellent yield (78%).

Application of these conditions to electronically unbiased $N(sp^3)$ coupling partners proved less successful. For example, the corresponding piperidine product was obtained in only 26% yield (Figure 2, entry 7). Further investigation revealed that competitive product oxidation is particularly problematic for amine substrates lacking an inductive effect (see [Mechanistic Studies](#) and [Supporting Information](#) for further discussion). Upon modifying the reaction conditions—

including the use of NHC-2 as the alcohol activator, *n*-propanol as cosolvent, and succinimide as an additive—the desired product was obtained in significantly improved yield (68%). Employing these conditions for electron-deficient substrates resulted in a slightly reduced yield compared to the original conditions (78% vs 73% for morpholine).

With two sets of optimized conditions—Conditions A for electron-deficient amines and Conditions B for electronically unbiased amines—we next evaluated the scope of the transformation. We began by exploring the alcohol coupling partner. As shown in Figure 3, both primary (1 and 2, 71% and

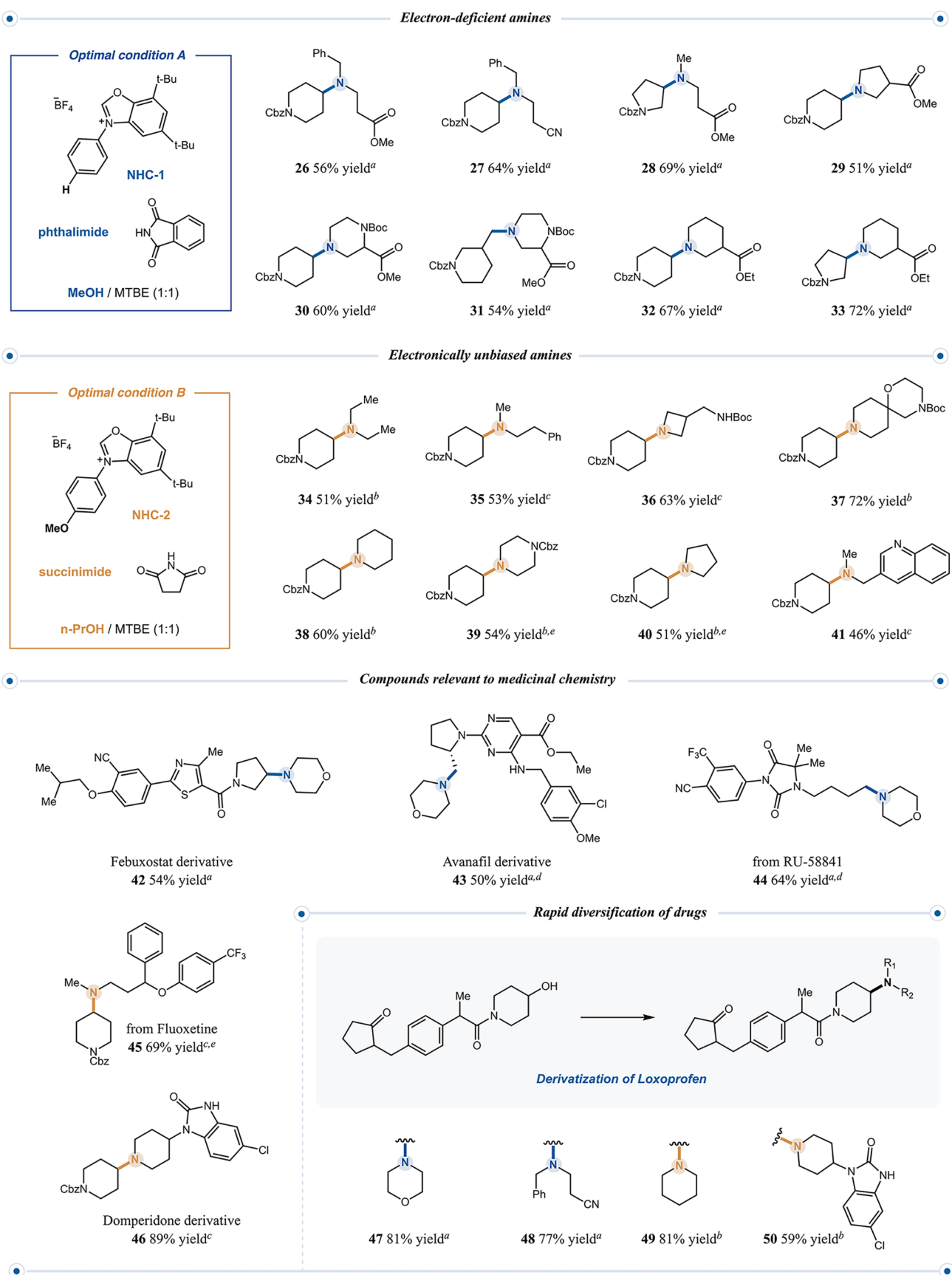


Figure 4. Amine scope and medicinally relevant compounds for deoxygenative C(sp^3)-N(sp^3) cross-coupling. Reactions performed with alcohol (1.0 equiv), *N*-hydroxylamine ester (2.0 equiv), NHC (1.2 equiv), pyridine (1.2 equiv), NiCl₂ (7.5 mol %), ligand (8.3 mol %), [Ir(ppy)₂(dtbbpy)]PF₆ (1.0 mol %), imide (1.0 equiv), quinuclidine (2.0 equiv), solvent (0.05 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity). Yields are isolated unless specified. Irradiation time was adjusted proportionally to reaction scale where applicable. Legend:

Figure 4. continued

(a) run for 2.5 h; 0.50 to 0.40 mmol scale (Conditions A); (b) run for 45 min; 0.50 to 0.45 mmol scale (Conditions B); (c) run for 30 min; 0.30 mmol scale (Conditions B); (d) 0.50 equiv. phthalimide used; (e) assay yields determined by UPLC-MS, see [Supporting Information](#) for experimental details.

64% yield, respectively) and secondary (3 to 8, 51–74% yield) alcohols underwent efficient cross coupling. Alcohols bearing alkyl halides—functional groups that often challenge S_N2 and dehalogenative amination strategies—were well tolerated under our conditions (9 and 10, 51% and 52% yield). Furthermore, a series of aldehyde- and ketone-containing substrates were smoothly converted to the deoxyaminated products without detectable side reactions at the carbonyl positions (11 to 14, 51–73% yield), highlighting orthogonality with reductive amination and hydrogen borrowing protocols.¹¹ Notably, multiple aryl halide-containing alcohols participated in the transformation in good to excellent yields (15 to 20, 55–75% yield), with no evidence of oxidative addition into the Ar–X bond, suggesting attenuated nucleophilicity of the catalyst and a preference for oxidative addition into the weaker N–O bond.^{23,24} Finally, we examined alcohols bearing medicinally relevant heterocycles. To this end, pyrazine (21, 54% yield), pyridine (22 and 23, 66% and 62% yield, respectively), and triazine 24 (67% yield) all coupled successfully. Furthermore, an alcohol containing a pyrazine-pyrazole biheterocyclic scaffold was converted to the corresponding tertiary amine in synthetically useful yield (25, 44% yield).

We next turned our attention to the amine coupling partner. As illustrated in [Figure 4](#), a broad range of *N*-hydroxylamine esters underwent efficient cross-coupling. Open-chain secondary *N*-hydroxylamines (26 to 28, 34, 35, 51–69% yield) reacted smoothly, along with amines derived from azetidine (36, 63% yield), pyrrolidine (29 and 40, both 51% yield), piperazine (30, 31, 39, 54–60% yield), piperidine (32, 33, 38, 60–72% yield), and spirocyclic amine (37, 72% yield). Notably, this scope includes all saturated ring systems from the ten most abundant *N*-heterocycles in recently FDA-approved drugs.⁴ Additionally, a quinoline-derived amine (41) afforded the desired product in synthetically useful yield (46% yield).

To showcase the mildness and functional group tolerance of this transformation, we applied our methodology to a range of pharmaceutical compounds and their derivatives. Cross-coupling delivered aminated analogues of Febuxostat (42, 54% yield), Avanafil (43, 50% yield), and RU-58841 (44, 64% yield) in good yields. Moreover, complex *N*-hydroxylamine esters derived from Fluoxetine (45, 69% yield) and Domperidone precursor (46, 89% yield) furnished the desired products in excellent yields. Finally, a one-step derivatization of the ketone-bearing Loxoprofen derivative enabled efficient synthesis of a small library of aminated analogues (47 to 50, 59–81% yield).

Mechanistic Studies. A plausible mechanism for the deoxygenative C–N cross-coupling is proposed in [Figure 5A](#). The alcohol first reacts with the NHC salt to form the corresponding adduct, 52. Upon blue light irradiation, the excited-state iridium photocatalyst 55 undergoes selective reductive quenching by 52, generating reduced photocatalyst 56 and an NHC–alcohol radical cation. This intermediate is subsequently deprotonated to give radical 53, which undergoes facile β -scission to generate a carbon-centered radical (60).

Concurrently, the Ni(0) species (57) engages in oxidative addition to the N–O bond of the *N*-hydroxylamine ester (58), affording a Ni(II) complex 59. This complex intercepts radical 60 to form Ni(III) species 61, which undergoes reductive elimination to furnish the C–N cross-coupled product 63 and reduced Ni(I) complex 62. Both catalytic cycles are closed by single-electron reduction of 62 to Ni(0), mediated by reduced iridium photocatalyst 56.

To gain preliminary support for the proposed mechanism and to better understand the observed tolerance of easily oxidizable tertiary amine products, we conducted a series of experiments, including stoichiometric studies, Stern–Volmer/electrochemical analysis, and computational investigations ([Figures S09–S19](#)). First, the proposed Ni(II) oxidative addition complex was independently synthesized from Ni(COD)₂ and characterized by NMR spectroscopy ([Figure 5B](#)). Subjecting this complex to stoichiometric reaction conditions yielded the expected C–N coupled product, supporting the involvement of a Ni(II) intermediate in the catalytic cycle.

To probe the origin of selectivity for oxidation of the NHC–adduct over undesired oxidative decomposition of the tertiary amine product, we performed cyclic voltammetry studies. Only a modest difference in oxidation potentials was observed between the NHC–alcohol adducts and the C–N coupled products ([Figure 5D](#)), indicating that oxidation by the excited-state photocatalyst is thermodynamically favorable for both species. These results suggest that selectivity arises from kinetic, rather than thermodynamic, control—a conclusion that is further supported by reaction time-course studies ([Scheme S08](#)), which demonstrate that prolonged irradiation leads to eventual product consumption.

To better understand the selective oxidation of NHC–alcohol adducts over tertiary amine products, we performed Stern–Volmer quenching studies to compare the relative rates of photocatalyst-mediated oxidation under the solvent mixtures used in Conditions A (1:1 MeOH:MTBE) and Conditions B (1:1 *n*-PrOH:MTBE) ([Figure 5E](#)).

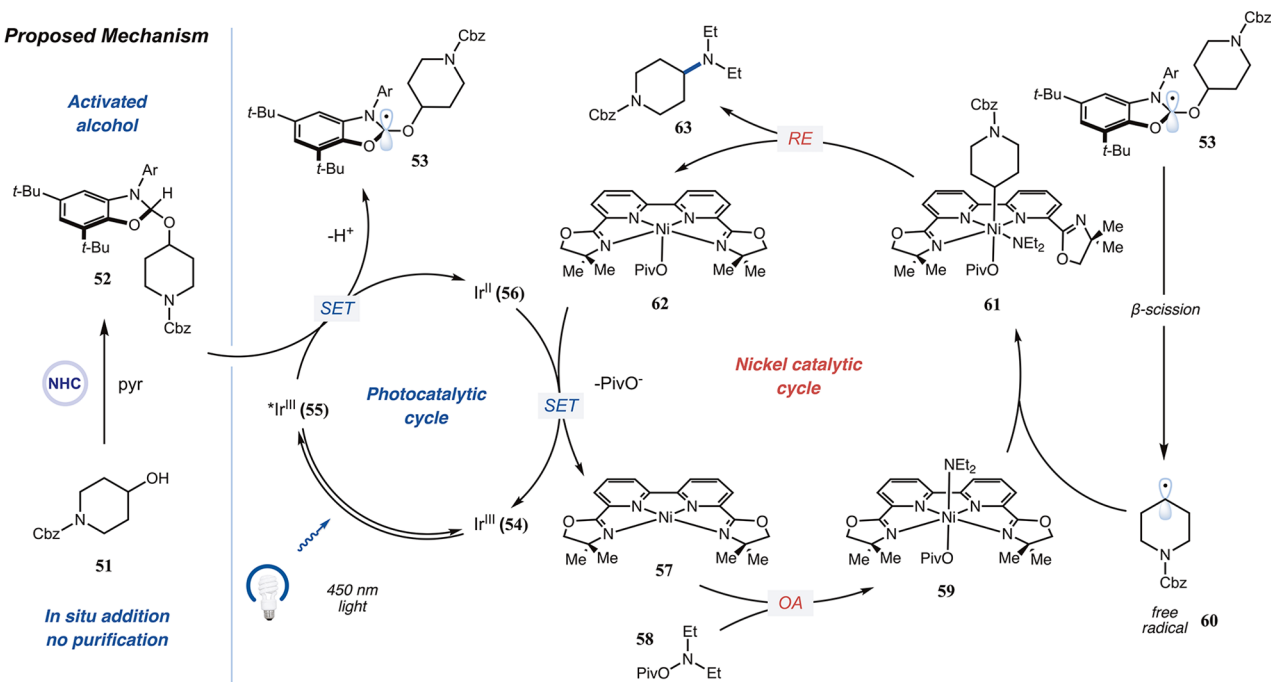
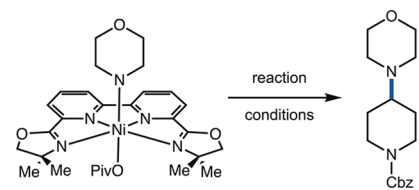
Under Conditions A, the electronically unbiased amine underwent electron transfer at a rate comparable with the NHC–alcohol adduct, consistent with the poor efficiency observed for this substrate under Conditions A. In contrast, the electron-deficient amine underwent slower electron transfer compared to the NHC–alcohol adduct, enabling coupling to outcompete product oxidation.

Switching the cosolvent from methanol to *n*-propanol (Condition B) suppressed oxidation of the electronically unbiased amine relative to the NHC–alcohol. This observation may be rationalized by the greater solvation sensitivity of the amine radical cation, which is less conjugated than the corresponding NHC–alcohol radical cation. Hence, a solvent mixture with a lower dielectric constant favors selective oxidation of the NHC–alcohol adduct.

Finally, the NHC-2-alcohol adduct, bearing an electron-rich *p*-methoxyphenyl group, was more readily oxidized than its NHC-1 counterpart, further enhancing selectivity.

Conclusion. Herein, we present a nickel metallaphotoredox platform for the cross-coupling of aliphatic alcohols and *N*-

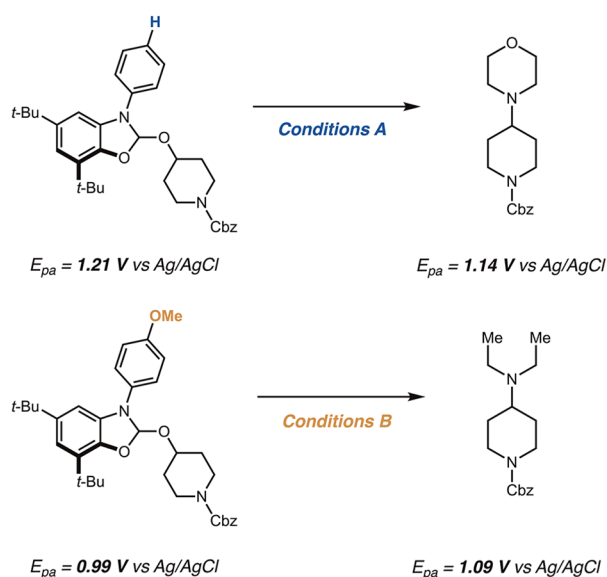
A) Proposed Mechanism

B) Stoichiometric Ni^{II} complex

C) Conditions

Electron-deficient amines	
	Conditions A (NHC-1): 78% AY
	Conditions B (NHC-2): 73% AY
Electronically unbiased amines	
	Conditions A (NHC-1): 11% AY
	Conditions B (NHC-2): 51% AY

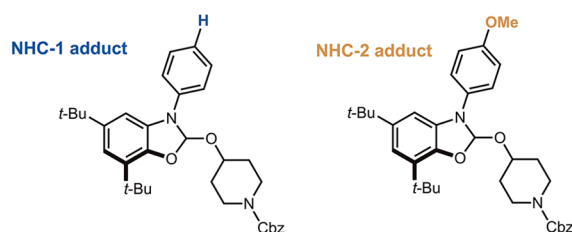
D) Thermodynamics of oxidation (Cyclic Voltammetry)



Potentials are within $\pm 0.1 \text{ V}$ suggesting competitive product oxidation

E) Kinetics of oxidation (Stern-Volmer)

k_{rel} quenching	In MTBE/MeOH	In MTBE/nPrOH
NHC-2 adduct	4.0	3.2
NHC-1 adduct	1.0	1.0
	0.5	<0.1
	<0.1	<0.1



NHC-2 and *n*-PrOH cosolvent are necessary for electronically unbiased amines

Figure 5. Proposed mechanism and mechanistic studies.

hydroxylamine esters. *In situ* activation of alcohols with NHC reagents enables general access to alkyl radicals via kinetically

favorable oxidation of the resulting NHC adducts. Following oxidative addition into the N–O bond and subsequent alkyl

radical capture, the challenging $C(sp^3)-N(sp^3)$ reductive elimination step is facilitated by a specifically designed, sterically demanding nickel bis(oxazolium)bipyridine catalyst. This approach offers broad access to oxidant-sensitive tertiary amines under mild photoredox conditions with excellent functional group tolerance. Mechanistic investigations indicate that reactivity is achieved through kinetic bias, highlighting both the mild conditions for NHC activation and an alternative strategy to circumvent product inhibition—a common challenge in photoredox catalysis with potential relevance to other transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.5c10915>.

Additional experimental details, optimization, additional substrate tables, mechanistic studies, DFT calculation, characterization, and spectra (PDF)

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Author Contributions

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Notes

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

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