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Communication

Nontraditional Fragment Couplings of Alcohols and Carboxylic Acids: C(sp^3)–C(sp^3) Cross-Coupling via Radical Sorting

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ABSTRACT: Alcohols and carboxylic acids are among the most commercially abundant, synthetically versatile, and operationally convenient functional groups in organic chemistry. Under visible light photoredox catalysis, these native synthetic handles readily undergo radical activation, and the resulting open-shell intermediates can subsequently participate in transition metal catalysis. In this report, we describe the C(sp^3)–C(sp^3) cross-coupling of alcohols and carboxylic acids through the dual combination of *N*-heterocyclic carbene (NHC)-mediated deoxygenation and hypervalent iodine-mediated decarboxylation. This mild and practical Ni-catalyzed radical-coupling protocol was employed to prepare a wide array of alkyl–alkyl cross-coupled products, including highly congested quaternary carbon centers from the corresponding tertiary alcohols or tertiary carboxylic acids. We demonstrate the synthetic applications of this methodology to alcohol C_1-alkylation and formal homologation, as well as to the late-stage functionalization of drugs, natural products, and biomolecules.

Alcohols and carboxylic acids are ubiquitous, native functional groups with unparalleled structural diversity, wide-ranging synthetic applicability, and broad representation among both natural and commercial sources.[1,2] These two structural motifs are most commonly coupled via the venerable esterification reaction, reported in its first iteration by Fischer and Speier over 125 years ago.[3] The widespread adoption of this disconnection can be attributed at least in part to the desirability of alcohols and carboxylic acids as highly abundant organic fragments. By contrast, the direct coupling of alcohols and carboxylic acids to forge new C(sp^3)–C(sp^3) bonds has remained an appealing yet elusive goal.[4] Recently, our group has harnessed both carboxylic acids and alcohols as alkylating agents in visible-light-driven processes.[5] We questioned whether these activation modes could be combined in a unified metallaphotoredox strategy that could achieve the longstanding goal of alcohol–carboxylic acid C(sp^3)–C(sp^3) cross-coupling.[6] This technology would leverage the versatility, stability, and convenience of alcohols and carboxylic acids, thus offering a modern, orthogonal approach to well-known esterification protocols.

In recent years, metallaphotoredox catalysis has transformed organic synthesis by enabling the activation and subsequent cross-coupling of previously inert alkyl fragments, such as alcohols, carboxylic acids, and C(sp^3)–H bonds.[7] In particular, alkyl carboxylic acids are highly amenable to light-induced redox activation, participating in a diverse array of transformations, including arylation, alkylation, and amination, among others.[5a,8] In a similar fashion, the radical deoxygenative functionalization of alcohols has been achieved through a variety of mechanisms.[9−13] These approaches often entail preactivation of the alcohol substrate, requiring additional chemical steps and purifications.[14,15] Moreover, the homolytic cleavage event can liberate byproducts that are incompatible with transition metal catalysis.[16] To overcome these challenges, our group recently disclosed an alternative technology that leverages an *N*-heterocyclic carbene (NHC)-based reagent to achieve the deoxyarylation of an extensive array of complex, structurally distinct alcohols.[5b] The NHC reagent reacts with the alcohol substrate to generate an electron-rich intermediate that is poised to undergo in situ oxidative fragmentation, ejecting an alkyl radical that can be subsequently captured by a metal catalyst.[5b]

While reports of decarboxylation and deoxygenation have been described in separate contexts, the main challenge for a nontraditional C(sp^3)–C(sp^3) fragment coupling is ensuring the cross-compatibility of activation modes in combination with a suitable transition metal catalyst. We sought to merge NHC-promoted oxidative radical formation with a reductive strategy for decarboxylation[8d] to enable a redox-neutral coupling protocol. However, the proposed transformation involves transient generation of two alkyl radicals that must be differentiated in order to achieve efficient cross-coupling.[17] As a design principle, we recognized that the relative instability of more highly substituted metal–alkyl species should favor formation of the desired product via catalyst-controlled radical sorting mechanisms.[18] Nickel,[19] with its well-established ability to efficiently capture and stabilize alkyl radicals, was selected to mediate bond formation. We hypothesized that the nickel catalyst would preferentially bind and stabilize the less-substituted alkyl species in the form of a more persistent metal–alkyl complex,[20] directing its cross-coupling with the

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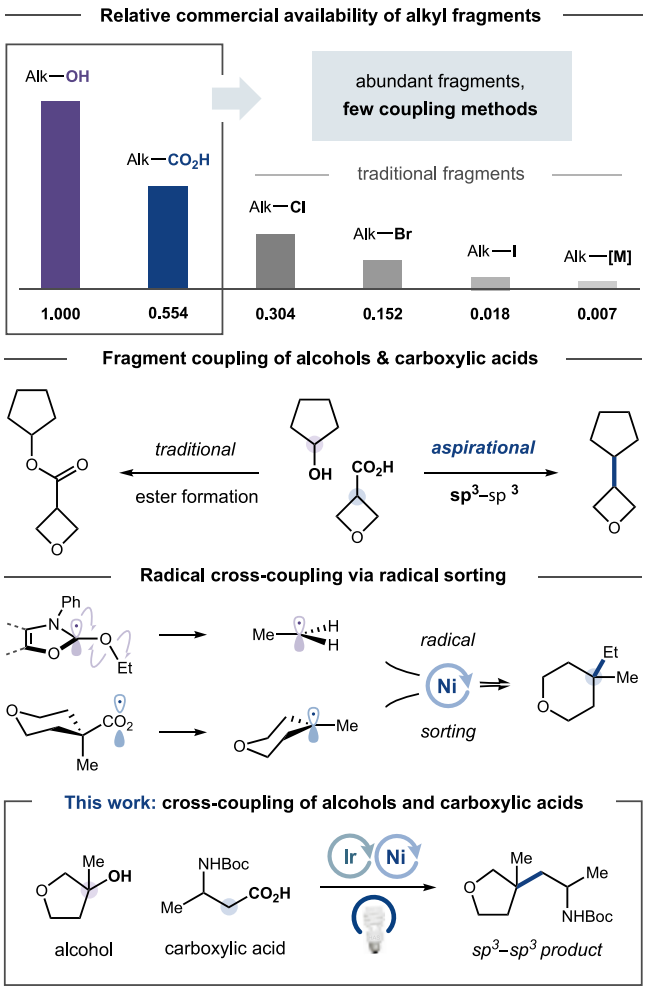

Figure 1. Cross-coupling of alcohols and carboxylic acids.

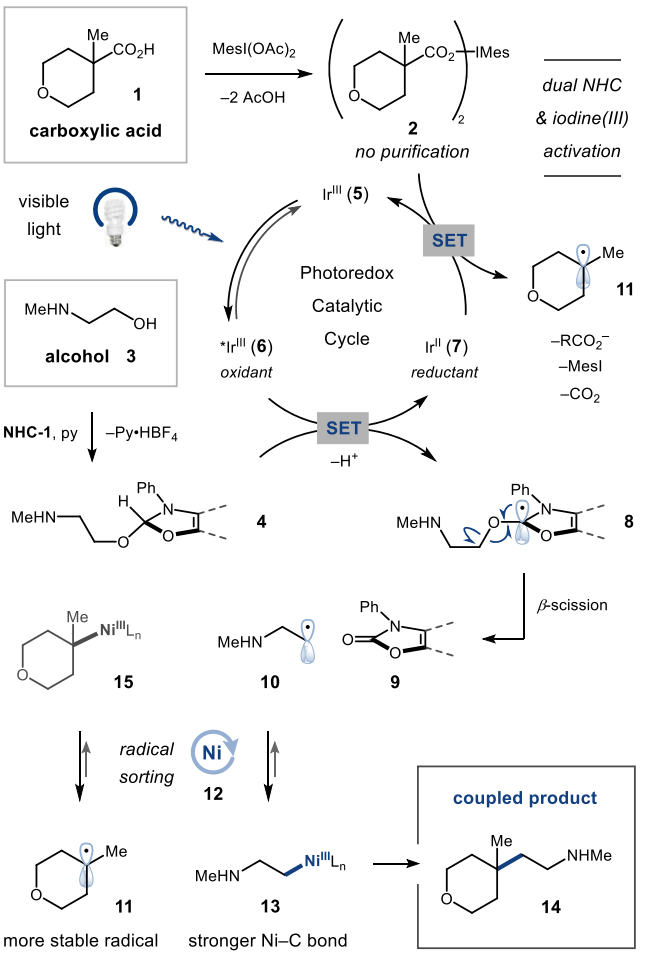

Figure 2. Proposed reaction design.

more highly substituted free radical (vide infra). If successful, the ability to directly couple two of the most abundant and versatile alkyl sources—alcohols and carboxylic acids—would permit broad combinatorial access to sp^3-rich products in a single-step process,[21] thereby facilitating a practical synthesis of aliphatic motifs encompassing an expansive region of chemical space (Figure 1).[22]

We envisioned achieving dual nickel/photoredox-catalyzed cross-coupling of alcohols and carboxylic acids via the design plan depicted in Figure 2. First, carboxylic acid **1** is premixed with iodomesitylene diacetate to afford the activated iodonium dicarboxylate **2**, which can be prepared directly on a rotary evaporator without additional purification.[8d,23] The alcohol substrate **3** condenses with benzoxazolium salt **NHC-1** to form the activated NHC–alcohol adduct (**4**) under mildly basic conditions.[24] Visible-light excitation of the photocatalyst $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ (**5**) [dF(Me)ppy = 2-(2,4-difluorophenyl)-5-(methyl)-pyridinyl; dtbbpy = 4,4′-bis(*tert*-butyl)-2,2′-bipyridine] generates a long-lived, oxidizing triplet excited state (**6**, τ = 1.2 μs, $E_{1/2}^{red}$ [*Ir(III)/Ir(II)] = +0.77 V vs saturated calomel electrode (SCE) in MeCN).[25] The excited state complex **6** can readily undergo reductive quenching by **4** (in preference to oxidative quenching by **2**; see Figures S8 and S15 for emission quenching studies) via single-electron transfer (SET) to provide the reduced Ir(II) photocatalyst **7**. Rapid deprotonation of the transient amine radical cation[26] generates a carbon-centered radical adjacent to three heteroatoms (**8**). At this stage, subsequent β-scission[27,28] ($\Delta G^{\ddagger}$ < 12 kcal/mol by density functional theory; see Table S17) liberates an aromatized byproduct[29] (**9**) and alkyl radical **10**, which can be rapidly trapped by the nickel catalyst **12** to form Ni–alkyl intermediate **13**. Concurrently, reduction of the preformed iodonium dicarboxylate (**2**, E_{pc} = −1.00 V vs SCE in 1:1 DMSO/MTBE) by **7** ($E_{1/2}^{red}$ [Ir(III)/Ir(II)] = −1.25 V vs SCE in 1:1 DMSO/MTBE) should afford, upon fragmentation and CO_2 extrusion, the acid-derived radical **11** along with the regenerated Ir(III) photocatalyst (**5**). Finally, nickel-catalyzed bond formation[30,31] would deliver the desired $C(sp^3)$–$C(sp^3)$ coupled product (**14**) and reconstitute the nickel catalyst **12**.

Although alternative sequences of radical capture and bond formation are possible, we postulated that the nickel catalyst should effectively distinguish between the two radical species and direct their productive cross-coupling as a combined consequence of (i) the differing relative stabilities of alkyl radicals,[17] (ii) differences in nickel–carbon bond strengths,[20] and (iii) the reversibility of radical capture for hindered alkyl radicals.[32] Literature precedent and preliminary computational studies suggest that nickel catalyst **12** should preferentially bind and sequester the less-substituted alkyl radical, **10** (ΔG = −12.4 kcal/mol by DFT; Figure S23), thereby promoting the buildup of the more-substituted radical, **11**, in solution. Under steady-state reaction conditions, we postulated that this "radical sorting" mechanism should favor the accumulation

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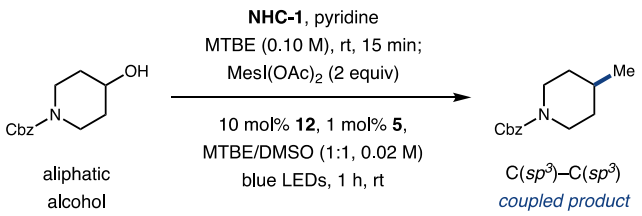
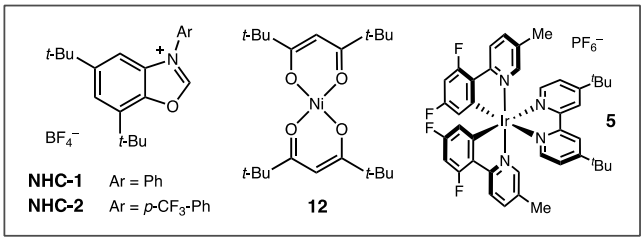
Table 1. Control Reactions of Optimized Conditions[a]



entry	deviation from above	yield[b]
1	none	76%
2	$Ni(acac)_2$ instead of **12**	73%
3	$NiCl_2$·dtbbpy instead of **12**	24%
4	$PhI(OAc)_2$ instead of $MesI(OAc)_2$	71%
5	1 equiv of $MesI(OAc)_2$	67%
6	irradiation for 5 min	67%
7	no Ir catalyst	<5%
8	no Ni catalyst	12%
9	no Ir catalyst, no light	0%
10	no Ir catalyst, no Ni catalyst	0%
11	no light, 50 °C	0%

[a]Performed with alcohol (0.05 mmol, 1.0 equiv), NHC precursor (1.10 equiv), pyridine (1.05 equiv), and iodomesitylene dicarboxylate (2.0 equiv). [b]Yields determined by HPLC analysis with acetanilide as internal standard. See Supporting Information for experimental details.



of species **11** and **13** (over **10** and **15**), from which bond formation would provide the desired cross-coupled product.[18]

We first explored this idea in the context of the model deoxymethylation shown in Table 1. Following an extensive evaluation of reaction conditions (Tables S1−S10), we ultimately found that the alcohol substrate underwent efficient in situ condensation with **NHC-1** (1.10 equiv) and pyridine (1.05 equiv) in MTBE (0.10 M), followed by cross-coupling with iodomesitylene diacetate (2.0 equiv) in the presence of photocatalyst **5** (1 mol %) and nickel catalyst **12** (10 mol %)[30] in MTBE/DMSO (1:1, 0.02 M) to afford the desired product in excellent yield (Table 1, 76% yield) after 1 h of visible light irradiation (450 nm) in an integrated photoreactor.[33] This protocol permits the direct in situ activation of alcohol substrates, representing a highly practical and exceptionally mild procedure for alkyl cross-couplings. Diminished reaction performance was observed with related nickel salts, such as acetylacetonate- or bipyridine-ligated systems (entries 2 and 3, 73% and 24% yield, respectively). While the commercially available carboxylate precursor $MesI(OAc)_2$ remains optimal under these conditions, the related reagent, phenyliodine(III) diacetate (PIDA),[34] can be used with minimal reduction in yield (entry 4, 71% yield). Reduced stoichiometric excess of the carboxylate is well-tolerated (entry 5, 67% yield) and may be desirable for structurally complex or high-value coupling partners. Both the NHC- and iodine(III)-mediated radical generation pathways are exceptionally facile, and the vast majority of product formation occurs in a matter of minutes (entry 6, 67% yield). Control experiments indicate that iridium, light, and nickel are each essential for optimal efficiency of product formation (entries 7−11), although small amounts of cross-coupled product are formed through background radical coupling in the absence of **12** (entry 8).

With optimized conditions in hand, we set out to explore the scope of our reaction (Table 2). Using a β-alanine derivative (**16**) as the carboxylic acid coupling partner, primary, secondary, and tertiary alcohols could be successfully cross-coupled under the reaction conditions.[35] Secondary aliphatic alcohols containing saturated scaffolds of pharmaceutical relevance were competent substrates in our protocol, affording alkylated products incorporating pyrrolidine (**17**, 51% yield), tetrahydropyran (**18**, 62% yield), piperidine (**19** and **20**, 62% and 63% yield, respectively), dioxane (**21**, 78% yield), and azepane (**22**, 68% yield) motifs.[36] Rotationally unconstrained secondary acyclic substrates could also be successfully utilized to access the desired products in good yield (**23** and **24**, 79% and 73% yield, respectively), and sterically encumbered polycyclic alcohols such as 2-adamantanol and *exo*-norborneol were employed without appreciable decrease in reaction performance (**25** and **26**, 47% and 79% yield, respectively). Significant homocoupling is observed in the cross-coupling of two primary radicals, as the nickel catalyst is less able to effectively differentiate between these two active species. Nonetheless, using 2 equiv of the activated acid component, primary aliphatic alcohols could be employed to provide $C(sp^3)$−$C(sp^3)$ coupled products in synthetically useful yields, demonstrating tolerance of functional groups such as primary alkyl chlorides (**27**, 50% yield), as well as ethers and protected amines (**28**−**30**, 52−75% yield). Notably, tertiary alcohols underwent successful deoxygenative alkylation to afford products with hindered alkyl quaternary carbon centers—a longstanding challenge in the field of alkyl−alkyl cross-coupling.[18,37,38] This protocol was successfully applied to both cyclic and acyclic tertiary alcohols, including *tert*-butanol, illustrating the power of this method to deliver previously elusive products from readily available starting materials (**31**−**35**, 57−75% yield).

With respect to the carboxylic acid coupling partner, we selected phenylalanine-derived alcohol substrate **36** to interrogate the performance of a range of primary, secondary, and tertiary alkyl acids under our reaction conditions. An array of secondary carbocyclic substrates performed well using this technology, affording a host of alkyl coupled products. Small ring systems, such as cyclobutane (**37** and **38**, 57% and 52% yield, respectively), cyclopentane (**39**, 67% yield), pyrrolidine (**40**, 42% yield), and tetrahydrofuran (**41**, 50% yield), were found to be viable coupling partners, as were larger cyclohexane (**42** and **43**, 65% and 69% yield, respectively), tetrahydrofuran (**44**, 66% yield), and cycloheptane (**45**, 66% yield) scaffolds. Commercially available fluoroalkyl moieties could be readily incorporated into these cross-coupled products (**38** and **43**)—an important objective in the synthesis of medicinal agents where the ability of fluorine to modulate physicochemical properties is well-recognized.[39] Secondary acyclic carboxylic acids could be subjected to our reaction conditions, affording alkylated products in good yields (e.g., **46**, 64% yield). A range of acetic and primary carboxylic acids underwent successful cross-coupling, including substrates with α-branching and electrophilic groups, such as carboxylate esters (**47**−**50**, 47−67% yield). Of note, tertiary carboxylic

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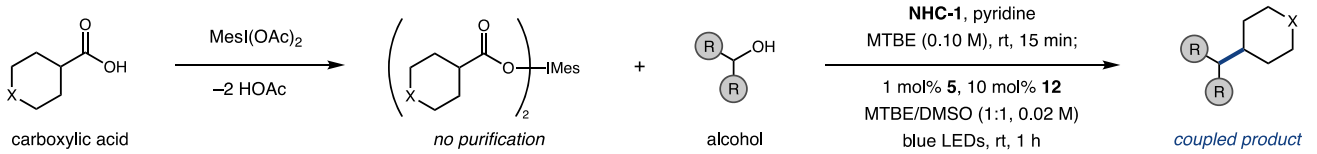
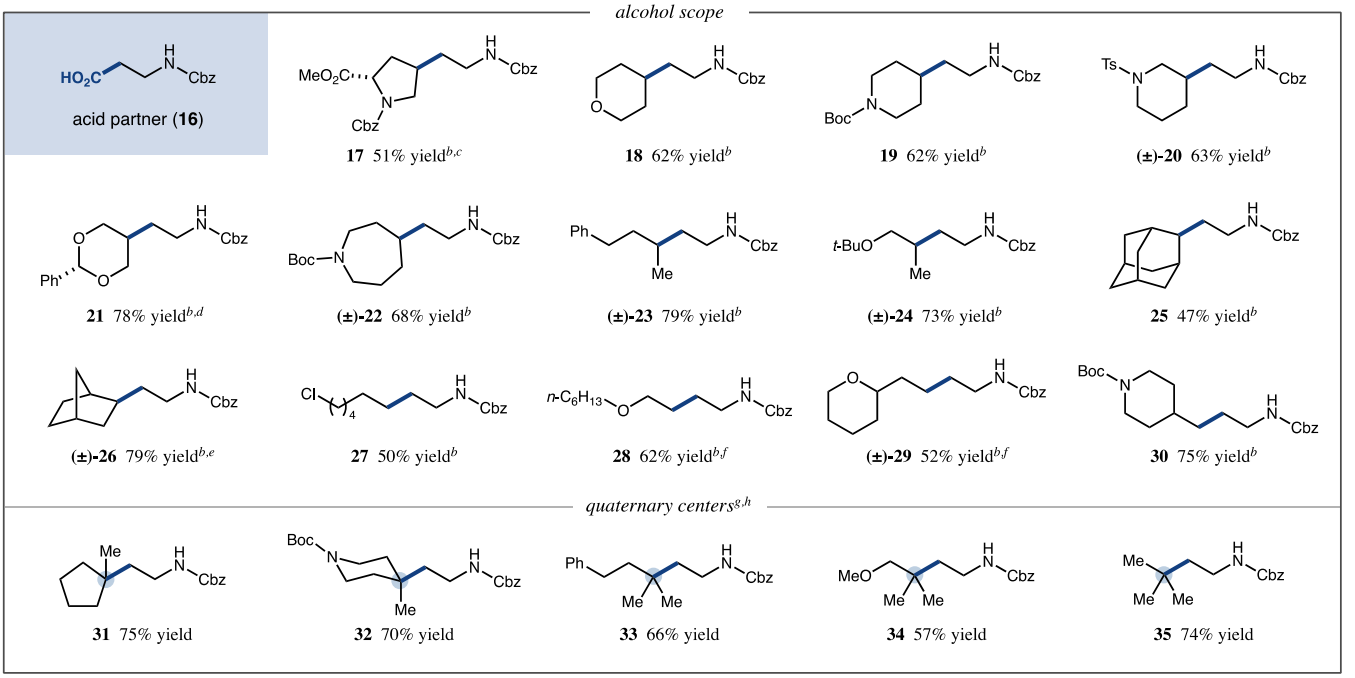
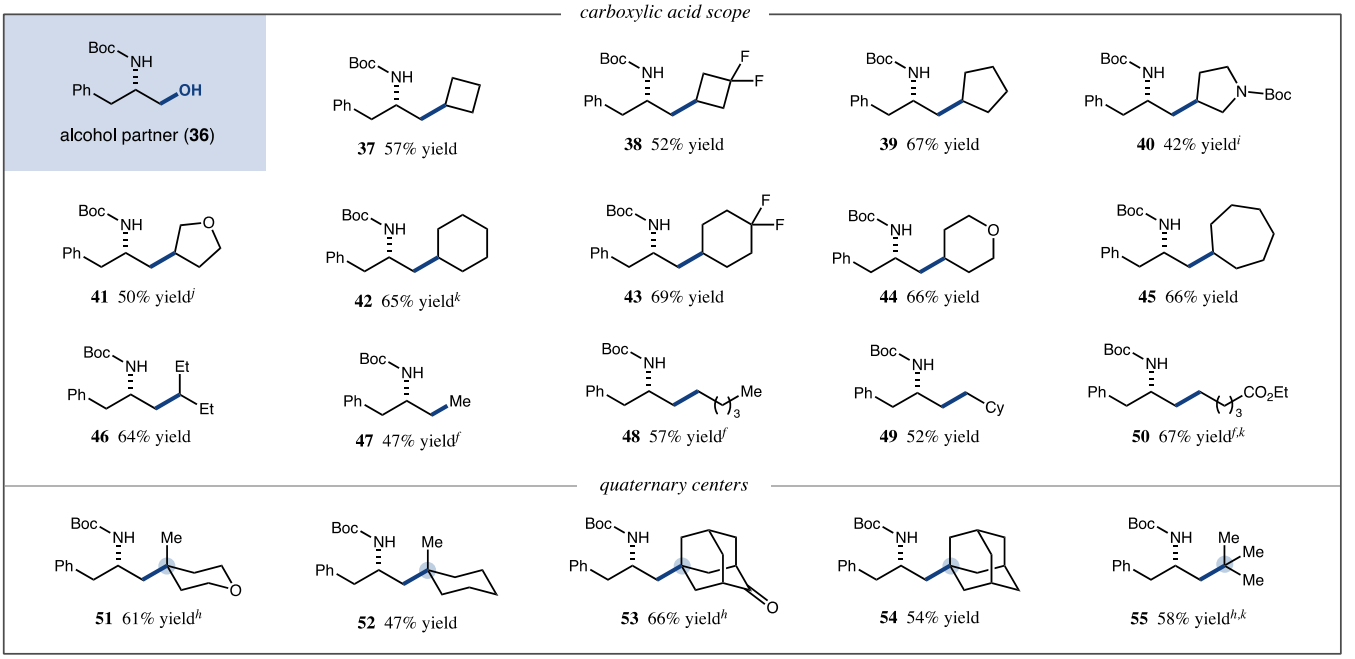
Table 2. Scope of Metallaphotoredox C(sp^3)−C(sp^3) Cross-Coupling of Carboxylic Acids and Alcohols[a]







[a]Iodonium dicarboxylate formed with MesI(OAc)$_2$ (2 equiv) and carboxylic acid (4 equiv) in toluene (0.05 M) at 55 °C over 10 min. Coupling performed with alcohol substrate (0.50 mmol, 1.0 equiv), **NHC-1** (1.10 equiv), and pyridine (1.05 equiv) in MTBE (0.10 M) for 15 min at room temperature, then iridium photocatalyst **5** (1.0 mol %), nickel catalyst **12** (10 mol %), and preformed iodomesitylene dicarboxylate (2.0 equiv, added over 5 min) in MTBE/DMSO (1:1, 0.02 M) with blue LED irradiation for 1 h at 23 °C. Homodimerization of the limiting alcohol substrate is typically 5−10%. Yields are isolated unless otherwise noted. See SI for experimental details. [b]1.30 equiv of **NHC-1**, 1.25 equiv of pyridine. [c]2.7:1 dr. [d]8:1 dr. [e]>20:1 dr. [f]Yield by ^{1}H NMR. [g]**NHC-2** in PhCF$_3$, −20 to 0 °C for 4 h; 2 mol % **5**, 20 mol % **12**. [h]1.5 equiv iodomesitylene dicarboxylate. [i]1.1:1 dr. [j]1:1 dr. [k]>99% ee by HPLC.

acids could be effectively utilized for the preparation of fully C(sp^3)-substituted quaternary carbon centers, including those arising from monocyclic (**51** and **52**, 61% and 47% yield, respectively) and polycyclic (**53** and **54**, 66% and 54% yield,

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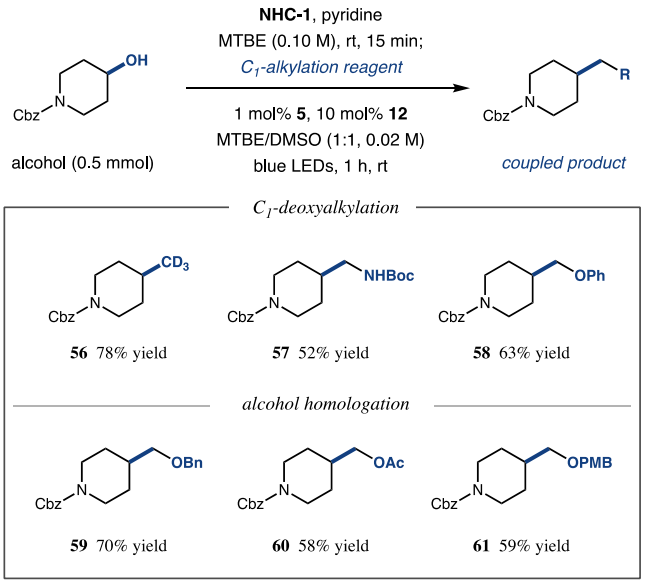
Table 3. Deoxygenative C_1-Alkylation[a]



[a]See SI for experimental details. All yields are isolated.

respectively) tertiary acid substrates. The sterically hindered, planarized *tert*-butyl radical derived from pivalic acid was successfully employed to generate the corresponding product in good yield (**55**, 58% yield).

To further demonstrate the value of this method, we next sought to deploy our protocol in the context of deoxygenative C_1-alkylation.[40] Acetic acid derived C_1-alkylating reagents bearing isotopic or heteroatom substituents were successfully employed to prepare products with deuteromethyl (**56**, 78% yield), aminomethyl (**57**, 52% yield), and aryloxymethyl (**58**, 63% yield) functionality (Table 3). In addition, using readily available α-hydroxy acids as highly convenient and versatile homologation reagents,[41] we accessed alcohol homologation products bearing benzyl (**59**, 70% yield), acetoxy (**60**, 58% yield), and *p*-methoxybenzyl (**61**, 59% yield) protecting groups. Finally, to illustrate the practical advantages of this technology in the context of late-stage functionalization of drugs and biomolecules, we subjected complex alcohol and acid substrates to our reaction conditions. We were excited to obtain synthetically useful quantities of alkyl coupled products, demonstrating the applicability of this synthetic technology to the late-stage derivatization of drugs, natural products, and biomolecules (Table 4, **62**–**65**, 34–80% yield).

In summary, we introduce here the merger of alcohols and carboxylic acids via $C(sp^3)$–$C(sp^3)$ cross-coupling as an orthogonal fragment coupling to the traditional esterification reaction. By combining NHC-mediated deoxygenation with hypervalent iodine-mediated decarboxylation, we have successfully developed a dual nickel/photoredox-catalyzed technology applicable to a wide range of aliphatic alcohols and carboxylic acids. We demonstrate the utility of this methodology for quaternary carbon center synthesis, alcohol homologation, and late-stage derivatization. Additional studies probing the nature of the bond formation and its application to new synthetic contexts are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c02062.

Additional experimental and computational results, characterization data and spectra (PDF)

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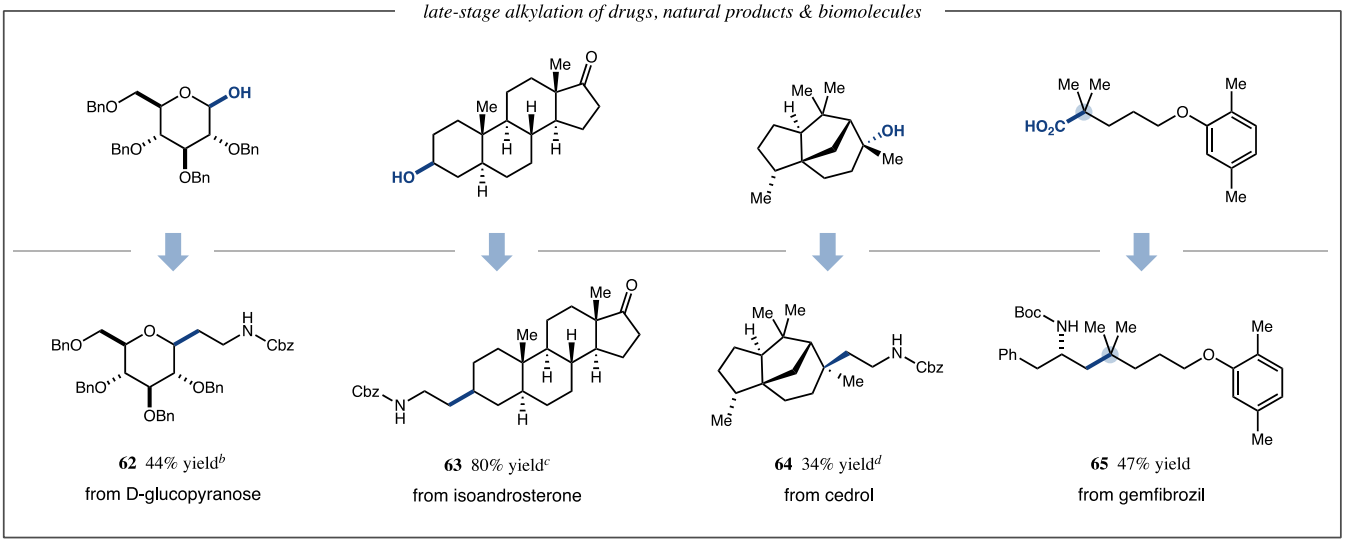
Table 4. Application to Late-Stage Functionalization[a]



[a]See SI for experimental details. All yields are isolated. [b]3:1 dr. [c]4:1 dr. [d]>20:1 dr.

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Notes

The authors declare no competing financial interest.

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