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Communication

Aryl Acid-Alcohol Cross-Coupling: $C(sp^3)-C(sp^2)$ Bond Formation from Nontraditional Precursors

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ABSTRACT: Alcohols and aryl carboxylic acids are among the most commercially abundant, synthetically versatile, and operationally convenient building blocks in organic chemistry. Despite their widespread availability, the direct formation of $C(sp^3)-C(sp^2)$ bonds from these functional groups remains a challenge. Recently, our group developed robust protocols to harness alcohols as alkyl radical precursors, but the activation of aryl acids remains relatively unexplored. Herein, we describe the merger of N-heterocyclic carbene (NHC)-mediated deoxygenation and nickel-mediated decarbonylation of aryl acids toward $C(sp^3)-C(sp^2)$ bond formation. The utility of this method is demonstrated through the synthesis of a diverse range of aryl−alkyl cross-coupled products and the late-stage functionalization of complex molecules, including drugs, natural products, and biomolecules.

The development of new methods to form carbon−carbon bonds has the potential to greatly expand access to a valuable chemical space. Of particular importance is the $C(sp^3)-C(sp^2)$ substructure, which plays a critical role in drug discovery and design by imparting three-dimensional complexity through $C(sp^3)$−rich scaffolds. These scaffolds confer improved solubility, bioavailability, and pharmacokinetic profiles and are thus highly desirable in pharmaceuticals.[1] The growing interest in incorporating sp^3-rich fragments has led to a major focus on efficient methods for constructing these linkages.[2] While sp^2 moieties remain essential for interactions such as $\pi-\pi$ and π−cationic binding,[3] the increasing demand for $C(sp^3)$−rich architectures is driving synthetic innovation. Despite the importance of these scaffolds, few methods exist for their construction.[4] Methods that forge $C(sp^3)-C(sp^2)$ bonds from readily accessible starting materials offer a powerful platform for expanding the chemical diversity and driving new discoveries.

Traditionally, the synthesis of $C(sp^3)-C(sp^2)$ bonds has relied on cross-coupling methods involving transition metals such as palladium[5−9] paired with alkyl and aryl organometallic reagents and halides.[10−12] While these strategies have proven invaluable,[13−18] their dependence on costly or less accessible starting materials and catalysts limits their broader applications. Recent developments in nickel catalysis have opened new avenues for reductive $C(sp^3)-C(sp^2)$ couplings,[19,20] providing complementary approaches to palladium-catalyzed methods and enabling broader substrate scope under milder conditions.

Despite these advances, existing methods still largely depend on aryl and alkyl halides,[21−26] which can be expensive, difficult to prepare, or limited in functional group compatibility. We sought alternative cross-coupling partners and identified alkyl alcohols and aryl acids as promising candidates due to their commercial availability, structural diversity, and wide-ranging synthetic applicability.[27−30] Notably, aryl acids are an abundant class of reagents, yet their application in $C(sp^3)-C(sp^2)$ coupling remains largely unexplored. While alcohols and aryl acids typically undergo esterification,[31] we sought to investigate whether a metallaphotoredox strategy[32] could facilitate the decarbonylative formation of $C(sp^3)-C(sp^2)$ bonds (Figure 1a). In addition, aryl acids probe chemical space that is generally uncharted by aryl halides.[33] Therefore, this approach would offer complementary reactivity and expand access to a largely unexplored chemical space (Figure 1b).

Our group recently disclosed the use of a benzoxazolium salt (NHC) reagent to achieve the deoxygenation of alcohols under photoredox conditions,[34] enabling their selective activation in cross-coupling reactions.[35−37] In contrast, the metal-mediated activation of aryl acids has proven more challenging, typically requiring harsh reaction conditions and suffering from poor functional group tolerance.[38] The coupling of aryl carboxylic acids with aryl boron[39−43] or aryl halide[44,45] reagents is well-established, yet translating these techniques to the context of $C(sp^2)-C(sp^3)$ bond formation has proven more difficult.

In recent, back-to-back publications, the Weix and Cernak groups have elegantly demonstrated nickel-catalyzed decarbonylation for C−C bond formation, highlighting the potential of aryl carboxylic acids to serve as versatile synthons in cross-coupling reactions.[33,46] Building on their work, we have integrated our group's alcohol deoxygenation strategy with this aryl acid activation approach to develop a system capable of efficiently forming $C(sp^3)-C(sp^2)$ bonds with improved functional group tolerance. This combined method broadens the substrate scope, complementing existing cross-coupling

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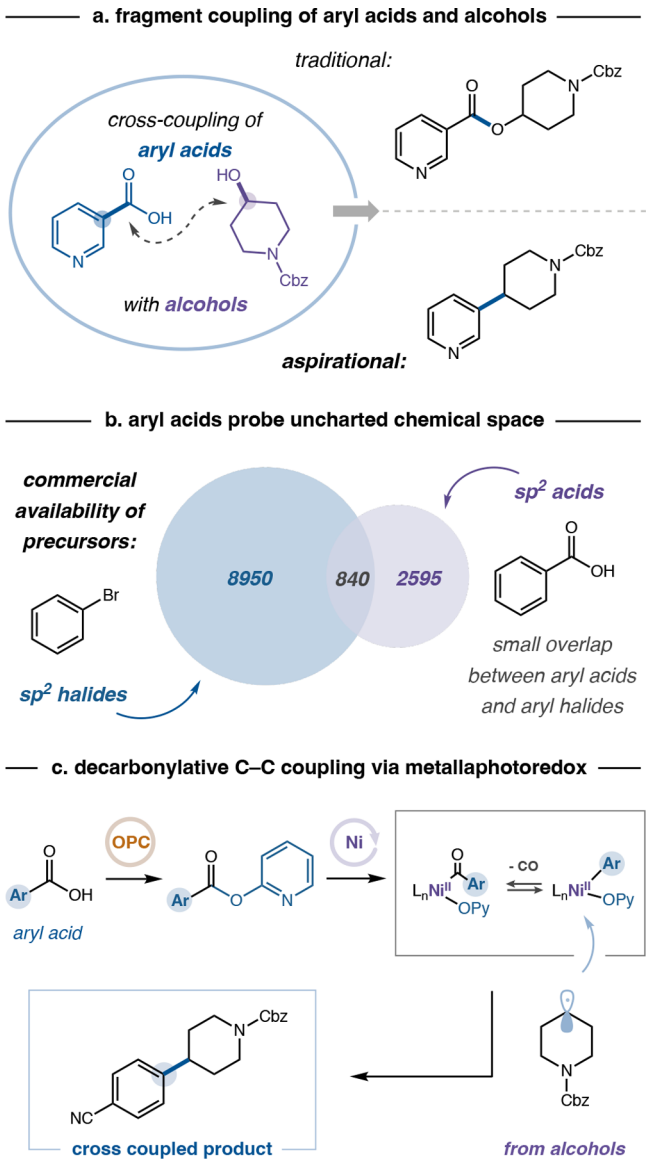


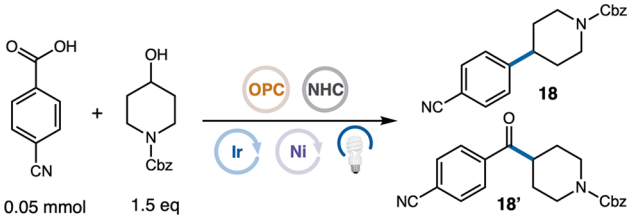
Figure 1. Cross-coupling of aryl acids and alkyl alcohols.

techniques and extending the reach of decarbonylative cross-coupling to new classes of compounds. Furthermore, this transformation provides an orthogonal strategy to traditional esterification, offering a novel pathway for the synthesis of complex molecular architectures (Figure 1c).

Herein, we demonstrate the broad applicability of our method across a wide array of alcohol and aryl acid coupling partners. Notably, the method operates fully at room temperature and exhibits excellent functional group tolerance, making it suitable for late-stage modification of pharmaceuticals and natural products. The versatility of this protocol, combined with its operational simplicity, makes it a valuable tool for synthetic chemists seeking to construct $C(sp^3)-C(sp^2)$ bonds from readily available starting materials.

We envisioned achieving dual nickel/photoredox-catalyzed cross-coupling of alcohols and aryl carboxylic acids according to the design plan depicted in Figure 2. Initially, aryl carboxylic acid **1** is premixed with dipyridin-2-yl carbonate (DPC) **2** and a catalytic amount of DMAP, resulting in the *in situ* formation of the activated acid **3** without purification.[47] In a separate reaction vessel, the alcohol substrate **4** reacts with NHC salt **5** to generate

Table 1. Optimized Conditions and Control Reactions[a]



entry	deviation	yield[b] 18	yield[b] 18'
1	none	68%	12%
2	Cu^{I}-MFU-4l as CO scavenger	62%	8%
3	continuously sparge with N_2	67%	8%
4	no CO scavenger	39%	11%
5	no phthalimide	41%	33%
6	highest fan settings	43%	14%
7	0.05 M	36%	12%
8	5 mol% Ni, no phthalimide, no KOAc, no sieves	25%	62%
9	no photocatalyst	0%	0%
10	no Ni catalyst	0%	0%
11	isolated OPy ester	64%	10%

[a]**Acid activation:** acid (1.0 equiv), DMAP (1.0 mol %), dipyridin-2-yl carbonate (DPC) **2** (1.0 equiv). **Alcohol activation:** Alcohol (1.5 equiv), benzoxazolium salt (NHC-1) **5** (1.5 equiv), pyridine (1.5 equiv). **Reaction conditions**: $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.0 mol %), Ni(4,4′-dMe-2,2′-bipyridine)Br_2 (15 mol %), quinuclidine "Q" (1.5 equiv), phthalimide (2.0 equiv), KOAc (2.0 equiv), 4 Å mol sieves (see the Supporting Information), 1:3 MTBE:t-Amyl OH (0.025 M), integrated photoreactor (450 nm, M2 plate, 50% light intensity), 16 h. [b]Yields determined by uHPLC analysis with mesitylene as standard.

the activated NHC–alcohol adduct **6** *in situ* under mildly basic conditions, also without further purification.[34] Upon visible-light excitation[48] of the photocatalyst $Ir[dF(CF_3)-ppy]_2(dtbbpy)PF_6$ (**7**), a long-lived oxidizing triplet excited state is generated (τ = 2.3 μs; $E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +1.21 V vs saturated calomel electrode (SCE) in MeCN).[49] This excited state complex **8** can undergo reductive quenching by the NHC–alcohol adduct **6** through single-electron transfer (SET), resulting in the formation of reduced Ir(II) photocatalyst **9**. Rapid deprotonation and subsequent β-scission of **10** leads to the liberation of an inert aromatized byproduct **12** and the generation of an alkyl radical **11**.[34] Concurrently, we hypothesized that the oxidative addition of Ni(0) species **13** into the activated acid would yield Ni(II) complex **14** which then undergoes decarbonylation to produce **15**. The alkyl radical can be quickly trapped by the nickel catalyst to form Ni(III)–alkyl intermediate **16**, which subsequently undergoes reductive elimination to form the desired cross-coupled product **18** while expelling Ni(I) intermediate **17**. Finally, SET between the Ir(II) species **9** and the Ni(I) complex **17** reduces Ni(I) to Ni(0) ($E_{1/2}^{red}$ [Ni^{II}/Ni^{0}] = −1.2 V versus SCE in DMF) and oxidizes Ir(II) ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = −1.37 V versus SCE in MeCN), thus simultaneously completing both the photoredox and nickel catalytic cycles.[50]

During our optimization campaign, a major challenge was minimizing the formation of the undesired ketone byproduct, which arises when the alcohol-derived alkyl radical is captured by the Ni(II) intermediate before productive decarbonylation. Initially, the ketone byproduct **18′** was formed in 62% yield

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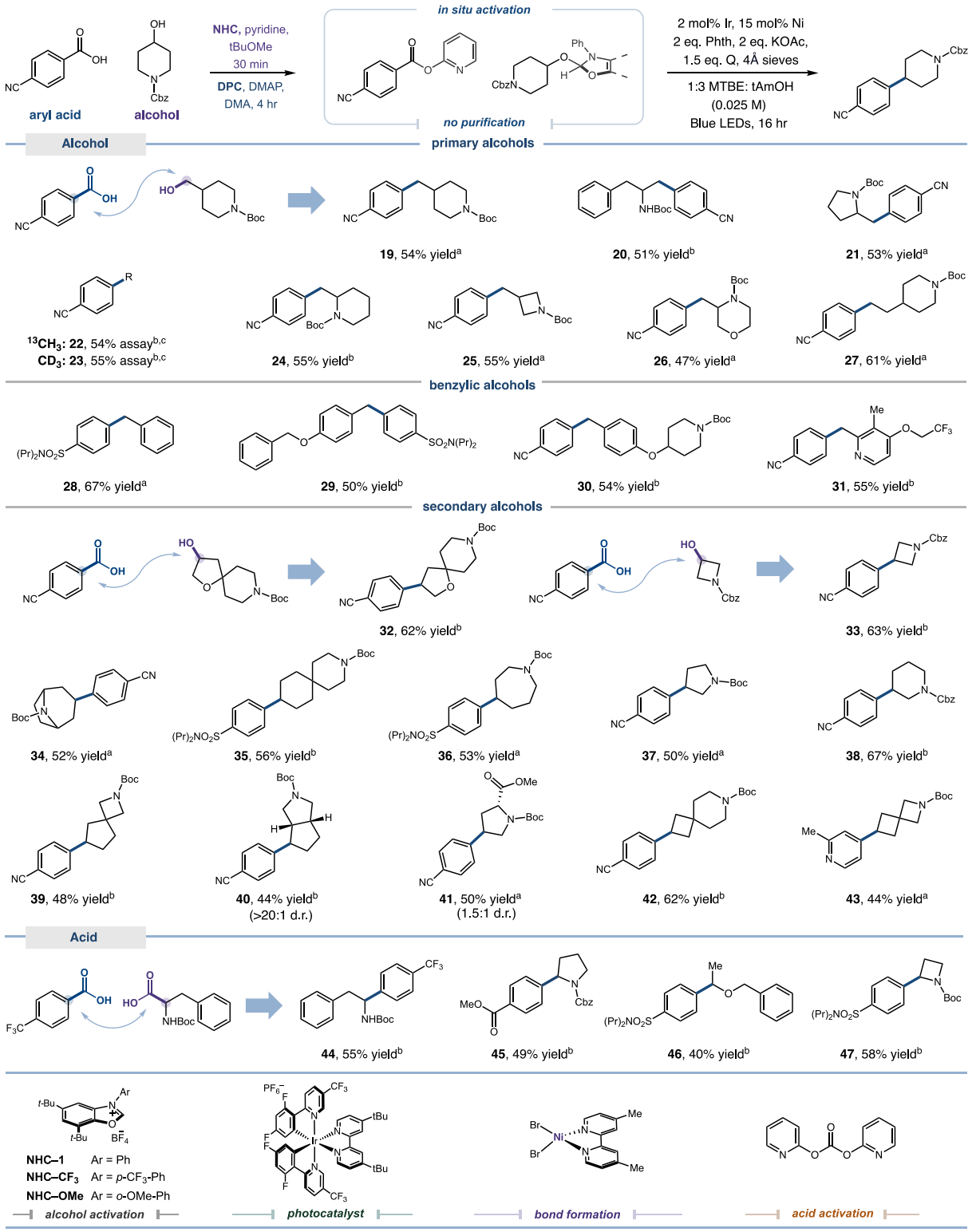
Table 2. Alkyl Alcohol and Alkyl Acid Scope[d]



[a]Alcohol (1.5 equiv), aryl acid (1.0 equiv), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.0 mol %), Ni(4,4′-dMe-2,2′-bpy)Br$_2$ (15 mol %), NHC-1 **5** (1.5 equiv), pyridine (1.5 equiv), quinuclidine "Q" (1.5 equiv), phthalimide (2.0 equiv), KOAc (2.0 equiv), DMAP (1.0 mol %), DPC **2** (1.0 equiv), 4Å mol sieves (see the Supporting Information), 1:3 MTBE:t-Amyl OH (0.025 M), integrated photoreactor (450 nm, M2 plate), 16 h. [b]See the Supporting Information for experimental details. [c]Yield determined by uHPLC analysis. [d]Run at a 0.5 mmol scale. Yields are isolated unless specified.

(Table 1, entry 8). Mechanistic insights from the Weix lab indicate that both decarbonylation and oxidative addition are

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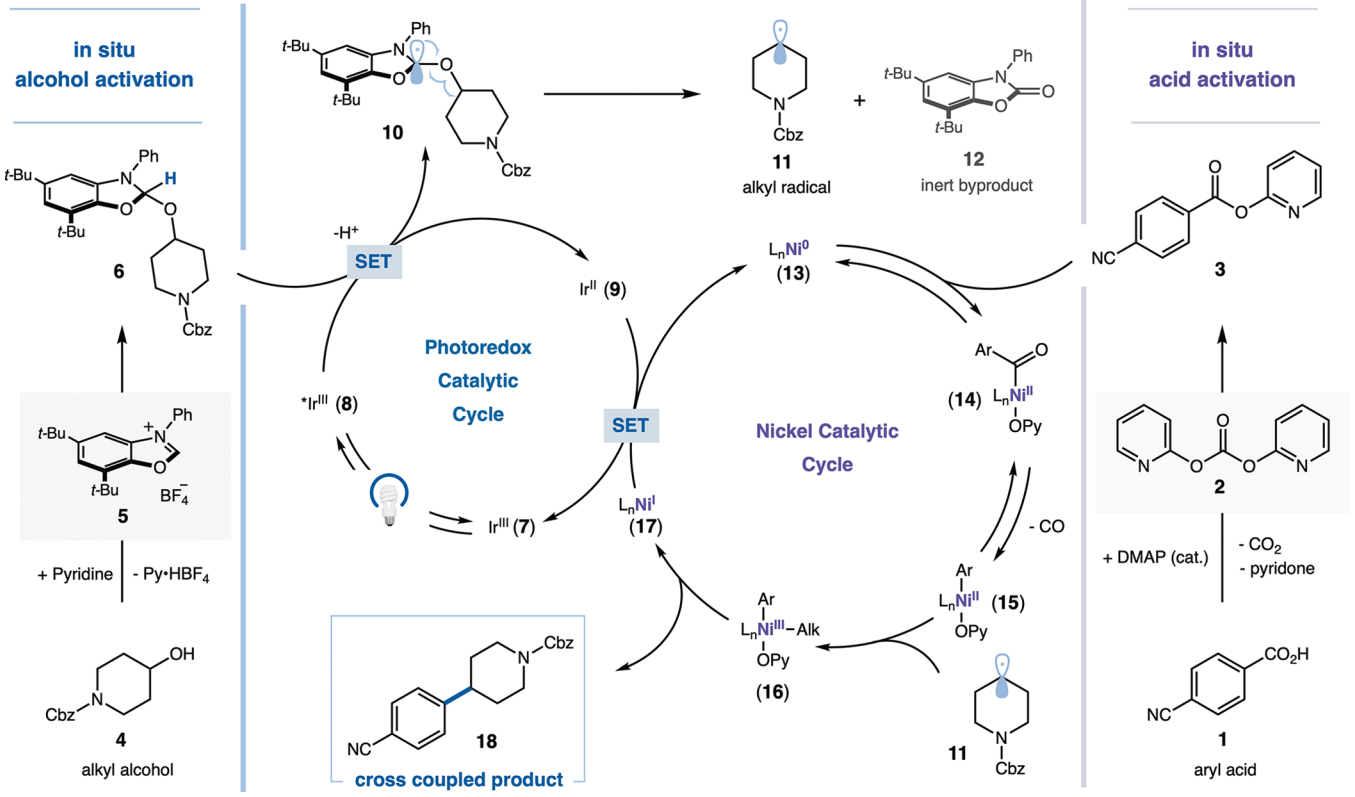

Figure 2. Proposed reaction mechanism.

rapid and reversible at room temperature.[46] Consequently, the efficient removal of CO from the system is critical, as the high affinity of Ni(0) for CO leads to undesired ketone formation.

Multiple strategies were deployed to address this challenge, which led to a reduction of ketone formation from 62% to 12% yield. These included the use of phthalimide, dilute reaction conditions, low fan settings on the integrated photoreactor, and CO scavengers such as 4 Å powdered molecular sieves or MOF CuI-MFU-4l.[51] Dilute reaction conditions and low fan settings helped to lower the CO concentration in the reaction mixture while increasing the reaction temperature, enhancing CO liberation from the nickel catalyst. Phthalimide likely discourages recarbonylation and stabilizes the Ni(II) complex through ligation, preventing unproductive Ni oligomerization or the formation of off-cycle Ni species.[52]

We found using 4 Å molecular sieves as a CO scavenger[53] as effective as nitrogen sparging (Table 1, entry 1 and 3), offering a more robust and user-friendly setup. Single-component CO adsorption isotherms for 4 Å molecular sieves reveal a modest isosteric enthalpy of adsorption of −25.6(1) kJ/mol (Figures S6 and S7). We hypothesize that during catalytic runs, CO is selectively sequestered via physisorption. Additionally, we observed that $Cu_{2.4}$-MFU-4l[51] ($Cu_{2.4}Zn_{2.6}Cl_{1.6}(btdd)_3$; H_2btdd = bis(1H-1,2,3-triazolo[4,5-*b*],[4′,5′-i])dibenzo[1,4]dioxin), a MOF containing trigonal pyramidal copper(I) sites that irreversibly scavenge CO at low partial pressures,[54] exhibits comparable performance to molecular sieves.

We were pleased to observe that under optimized conditions a broad range of primary and secondary alcohols were readily cross-coupled under the reaction conditions (Table 2; see the Supporting Information for optimization details). A variety of primary alcohols could be employed in this protocol in synthetically useful yields (**19**−**27**, 47−61% yield). The utility of this method is further demonstrated by the facile introduction of hydrogen- and carbon-enriched isotope units from commercial forms of methanol, obviating the need for lengthy de novo synthesis (**22** and **23**, 54% and 55% yield). Additionally, our studies revealed that primary benzylic alcohols were competent substrates, generating the desired products in good yield (**28**−**31**, 50−67% yield).

Secondary aliphatic alcohols were similarly effective in our protocol. Four-membered cyclic alcohols, such as azetidines (**33**, 63% yield) and strained azaspirocycles (**42** and **43**, 62% and 44% yield), performed well in this transformation. Five-membered cyclic alcohols containing saturated scaffolds of pharmaceutical relevance[55] were competent substrates, affording cross-coupled products incorporating pyrrolidine (**37**, 50% yield) and hydroxyproline (**41**, 50% yield). Additionally, five-membered spirocyclic and bicyclic ring systems bearing secondary alcohols could also be cross-coupled in good yield (**32**, **39**, and **40**, 44−62% yields). The method was extended to six-membered rings such as spirocyclic undecane systems (**35**, 56% yield) and piperidines (**38**, 67% yield). Azepanes were also efficiently coupled (**34** and **36**, 52% and 53% yields), showcasing the broad capability of this reaction to accommodate larger ring systems.

To further highlight the versatility of the method, we next extended our protocol beyond alcohols to include carboxylic acids as alkyl radical precursors.[56] Alkyl radicals were oxidatively generated from abundant feedstock α-amino acids—such as phenylalanine (**44**, 55% yield) and proline (**45**, 49% yield)—alongside an α-oxy acid (**46**, 40% yield) and noncanonical α-amino acid azetidine (**47**, 58% yield) en route to $C(sp^3)-C(sp^2)$ products.

We then explored the substrate scope of the reaction with respect to the aryl acid fragment (Table 3). A wide range of

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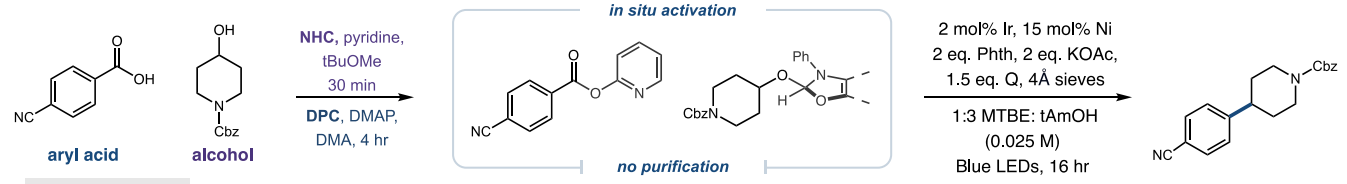
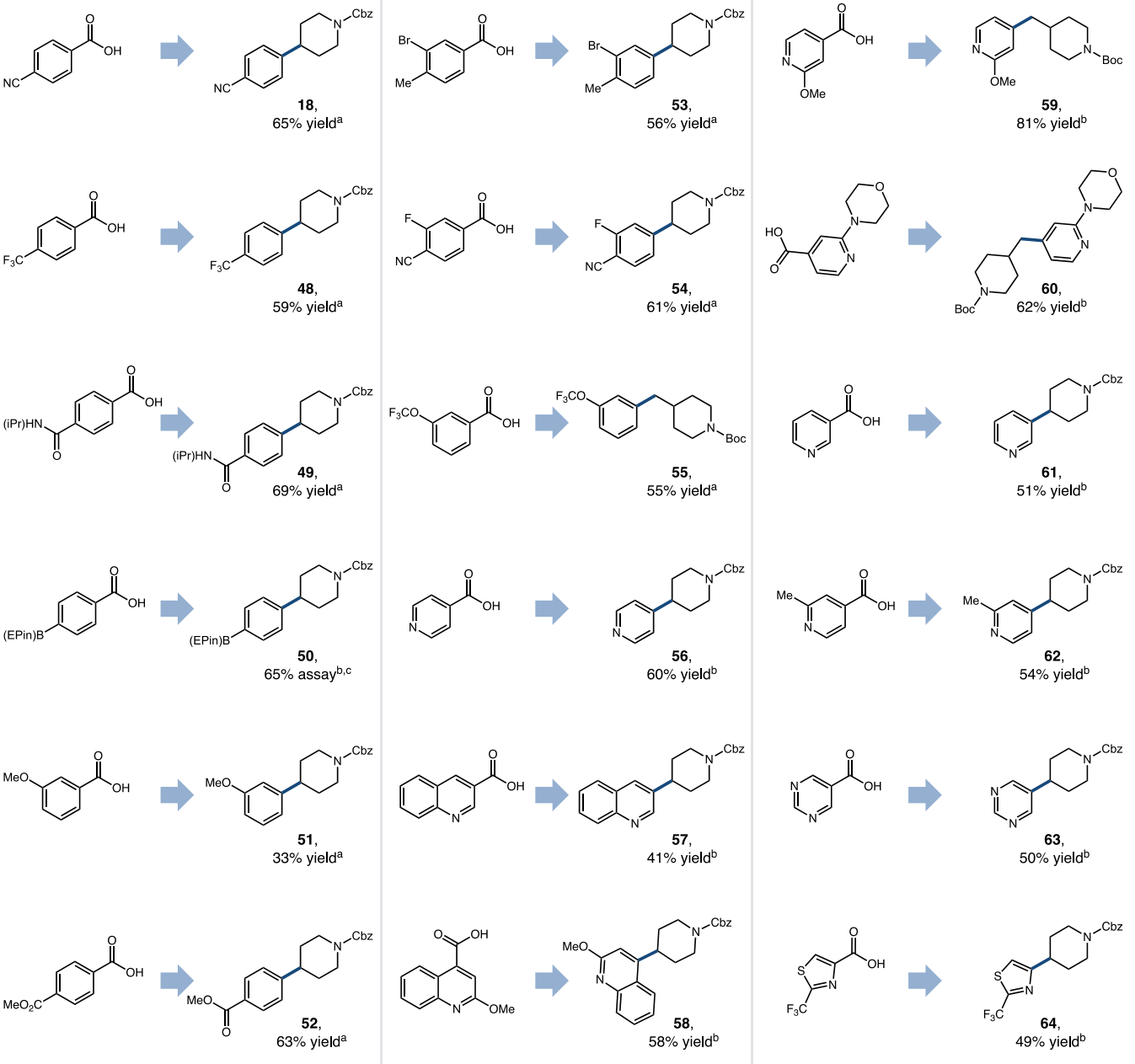
Table 3. Aryl Acid Scope[d]





[a]Alcohol (1.5 equiv), acid (1.0 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.0 mol %), Ni(4,4′-dMe-2,2′-bipyridine)Br_2 (15 mol %), NHC-1 **5** (1.5 equiv), pyridine (1.5 equiv), quinuclidine "Q" (1.5 equiv), phthalimide (2.0 equiv), KOAc (2.0 equiv), DMAP (1.0 mol %), DPC **2** (1.0 equiv), 4Å mol sieves (see the Supporting Information), 1:3 MTBE:t-Amyl OH (0.025 M), integrated photoreactor (450 nm, M2 plate, 50% light intensity), 16 h. [b]See the Supporting Information for experimental details. [c]Yield determined by uHPLC. [d]Run at 0.5 mmol scale, and yields are isolated unless specified.

benzoic acids possessing diverse electronic and steric properties served as viable substrates (**18**, **48**−**55**, 33−69% yield). Excitingly, heteroaryl acids derived from pyridines, quinolines, and pyrimidines were also successfully coupled (**56**−**63**, 41−81% yield) as were five-membered heteroaryl acids such as thiazole (**64**, 49% yield). High functional-group compatibility was observed, with esters, ethers, nitriles, trifluoromethyl groups, aryl fluorides, aryl bromides, amines, benzyloxycarbonyl,

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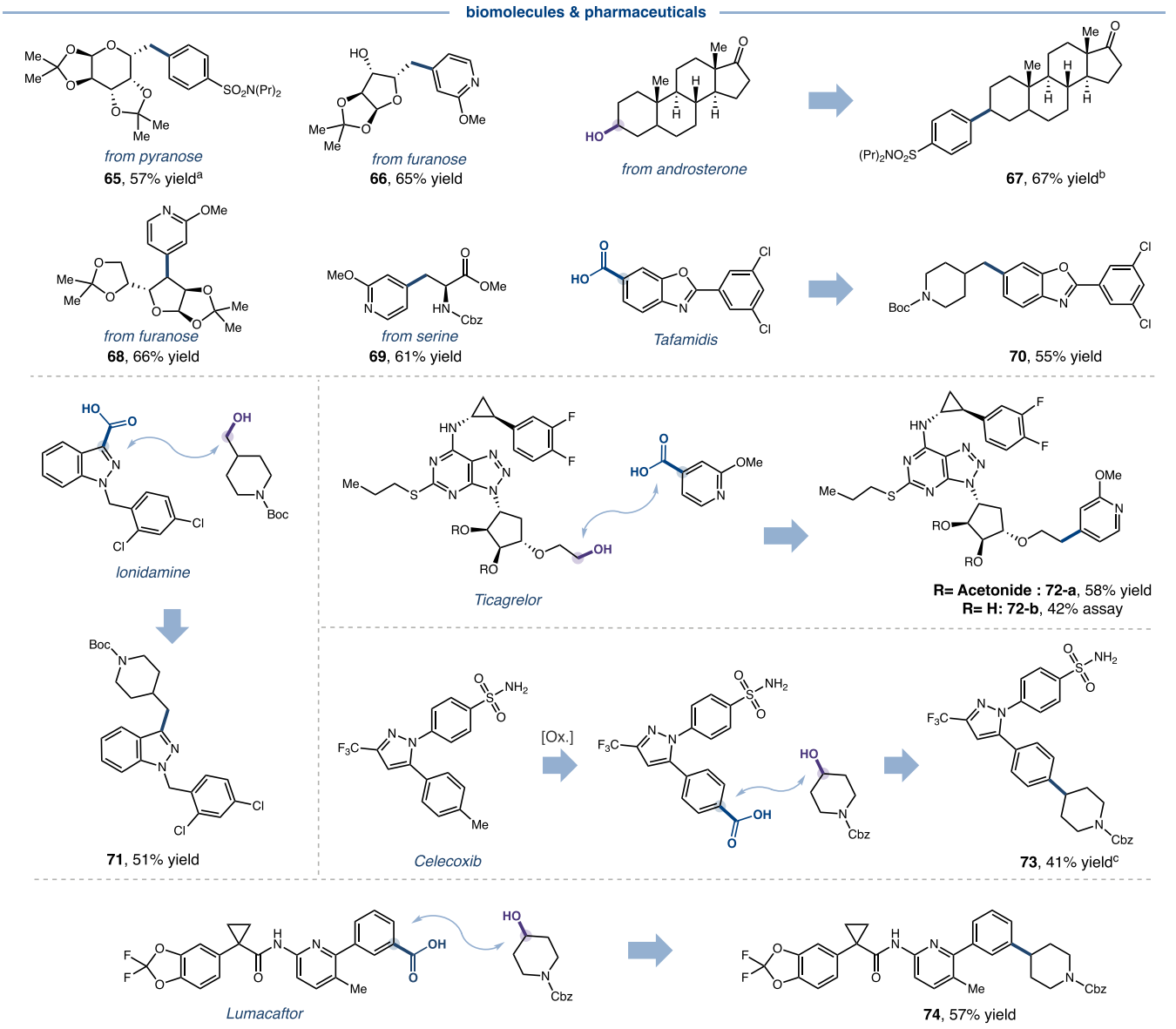
Table 4. Application to Late-Stage Functionalization of Biomolecules and Pharmaceuticals[d]



[a]>20:1 d.r. unassigned. [b]10:1 d.r. unassigned. [c]Yield given for the cross-coupling step only. [d]See the Supporting Information for experimental details. Run at 0.5 mmol scale, and all yields are isolated unless otherwise specified.

tert-butyl carbamate, and aryl boronic 1,1,2,2-tetraethylethylene glycol ester [B(EPin)] groups being well tolerated in the reaction. In line with previous findings,[33,46] electron-deficient acids favored C−C bond formation, likely due to more rapid decarbonylation, while electron-rich acids produced higher amounts of ketone byproducts, consistent with slower decarbonylation. Therefore, the reduced yields for more electron-rich acids (**51**, 33% yield) can be attributed to the slower oxidative addition of the 2-pyridyl ester to the Ni catalyst, along with diminished decarbonylation rates (Table S2).

Lastly, we sought to evaluate more complex alcohols and aryl acids for applications in late-stage functionalization. The wide availability of aryl carboxylic acids and alcohols facilitated the synthesis of products from diverse, complex starting materials. A range of pharmaceuticals were successfully deployed in the reaction, including tafamidis (**70**, 55% yield) and lonidamine (**71**, 51% yield)—both bearing valuable chloride functional groups—as well as lumacaftor (**74**, 57% yield) and ticagrelor (**72a,b**, 58% yield and 42% assay), were successfully employed in the reaction, forming the desired products in good yields. Additionally, saccharides (**65**, **66**, **68**, 57%, 65% and 66% yield), a derivative of canonical α-amino acid serine (**69**, 61% yield), and alcohol-bearing steroidal hormones such as androsterone (**67**, 67% yield) provided useful yields. Notably, in the case of furanose **66** and ticagrelor **72b**, exceptional regioselectivity was observed in which the primary alcohol was selectively targeted in the presence of secondary alcohols.

The utility of benzoic acids extends beyond their ready availability; these motifs offer significant synthetic versatility due to their ability to be masked as a variety of stable and accessible functional groups. For instance, tolyl groups in complex molecules such as celecoxib can be selectively oxidized to reveal aryl carboxylic acids. We envisioned applying this transformation in our cross-coupling protocol, allowing for the

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modification of such intermediates to form a wide array of products.

This demethylative C−C cross-coupling strategy provides an efficient and flexible pathway to rapidly increase molecular complexity. As shown in Table 4, celecoxib-CO_2H, readily obtained upon benzylic oxidation of celecoxib, was subjected to the reaction conditions with benzyl 4-hydroxypiperidine-1-carboxylate to furnish the cross-coupled product in useful yields (**73**, 41% yield).

These results demonstrate the broad applicability of this strategy, particularly its tolerance for complex molecular structures, and the unique utility of aryl carboxylic acids as versatile building blocks in synthetic sequences. This versatility enables the efficient synthesis of valuable compound libraries, which can serve as pharmacophores or be subjected to further functionalization.[57] In addition, a commercial availability search revealed that 70% of the aryl carboxylic acids used in our scope were cheaper than their aryl bromide counterparts, in many cases by over an order of magnitude (Table S9). The approach underscores the potential for constructing complex molecular frameworks from abundant and easily accessible starting materials.

In conclusion, we present a formal cross-coupling of aryl carboxylic acids and alkyl alcohols to form $C(sp^3)$−$C(sp^2)$ bonds, offering not only a complementary strategy to conventional cross-coupling methods but also an orthogonal alternative to traditional esterification protocols. By combining NHC-mediated deoxygenation with nickel-mediated decarbonylative bond formation, we have developed a nickel/photoredox-catalyzed approach applicable to a broad range of aliphatic alcohols and aryl carboxylic acids. A key factor in the success of this transformation was the incorporation of molecular sieves and other scavengers to efficiently remove CO, thereby minimizing undesired ketone formation and enhancing reaction robustness. Using nontraditional cross-coupling partners, such as alcohols and aryl acids, this method enables access to novel $C(sp^3)$-rich chemical space. Overall, this aryl acid−alcohol coupling provides a versatile platform for expanding accessible chemical space.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c15827.

Additional experimental details, optimization, additional substrate tables, characterization, and spectra (PDF)

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Notes

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

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