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Communication

Expedient Access to Underexplored Chemical Space: Deoxygenative C(sp^3)–C(sp^3) Cross-Coupling

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ABSTRACT: Alcohols are commercially abundant and structurally diverse reservoirs of sp^3-hybridized chemical space. However, the direct utilization of alcohols in C–C bond-forming cross-couplings remains underexplored. Herein we report an N-heterocyclic carbene (NHC)-mediated deoxygenative alkylation of alcohols and alkyl bromides via nickel–metallaphotoredox catalysis. This C(sp^3)–C(sp^3) cross-coupling exhibits a broad scope and is capable of forming bonds between two secondary carbon centers, a longstanding challenge in the field. Highly strained three-dimensional systems such as spirocycles, bicycles, and fused rings were excellent substrates, enabling the synthesis of new molecular frameworks. Linkages between pharmacophoric saturated ring systems were readily forged, representing a three-dimensional alternative to traditional biaryl formation. The utility of this cross-coupling technology is highlighted with the expedited synthesis of bioactive molecules.

The clinical success of a drug candidate is directly correlated to its degree of saturation.[1] Such sp^3-rich molecules possess desirable attributes, including improved solubility, lower melting point, and reduced off-target promiscuity, resulting in increased drug absorption and improved toxicological profiles.[1−3] Despite the medicinal value of these types of saturated architectures, the vast majority of standard cross-coupling reactions forge C(sp^2)–C(sp^2) bonds, while less than 5% of all cross-couplings deliver C(sp^3)–C(sp^3) bonds (Figure 1a). While significant contributions have been made to the field of C(sp^3)–C(sp^3) cross-coupling, modern methods typically necessitate large excesses of one coupling partner and often require nonabundant starting materials, such as air- and moisture-sensitive alkyl organometallics, thereby limiting the reaction scope and practicality.[4,5] To address this challenge, we sought to develop a robust C(sp^3)–C(sp^3) cross-coupling platform that utilizes two commercially abundant alkyl feedstocks: alcohols and alkyl bromides. Alcohols are among the most ubiquitous and structurally diverse alkyl fragments,[6] yet they are seldom employed in cross-coupling reactions. Conversely, alkyl bromides are the most utilized alkyl fragments in cross-coupling reactions due to their advantageous balance of reactivity and stability (Figure 1b). Conventionally, alcohols and alkyl bromides react to form C–O bonds via the Williamson ether synthesis.[7] We envisioned instead harnessing these substrates in a novel direct C(sp^3)–C(sp^3) cross-coupling (Figure 1c). This reaction would leverage the unmatched commercial availability of alcohols with the synthetic prowess of alkyl bromides to unlock a vast area of underexplored chemical space.

Historically, cross-coupling has centered around noble metals like palladium, whose properties promote facile oxidative addition and reductive elimination of sp^2-hybridized species.[8] However, in the context of sp^3-hybridized species, noble metals readily undergo deleterious β-hydride elimination over product-forming reductive elimination pathways.[5] Work in our lab and others has shown the promise of nickel catalysis in overcoming this longstanding problem.[9−11] This earth-abundant first-row transition metal is excellent at oxidatively capturing radicals[12] and is significantly less prone to β-hydride elimination compared to noble metals.[9,13] Nickel has been utilized extensively in the development of metallaphotoredox catalysis, which has opened a new realm of chemical space by enabling open-shell pathways to form complex, sp^3-rich molecules from abundant precursors, such as halides, carboxylic acids, and even C–H bonds.[12] In contrast, native alcohols remain underexplored as cross-coupling partners. Functionalized alcohols, such as alkyl tosylates,[14,15] mesylates,[15] benzylic ethers,[16] and benzylic esters,[17] have shown promise in a variety of C(sp^3)–C(sp^3) cross-coupling reactions. However, the direct use of native alcohols as cross-coupling partners is an unrealized goal. Recent work from our group has uncovered a solution to this problem: we have introduced an N-heterocyclic carbene (NHC)-derived reagent capable of activating alcohols *in situ* and transforming them into alkyl radicals through photoredox catalysis.[18−21] We envisioned utilizing this novel activation mode to unlock unprecedented sp^3-rich chemical space by coupling ubiquitous alcohols with bench-stable, commercially abundant alkyl bromides through nickel metallaphotoredox catalysis (Figure 1d). A key goal of this work is to forge bonds between two secondary sp^3 centers. These scaffolds are especially relevant to medicinal chemistry, being found in seven of the top 30

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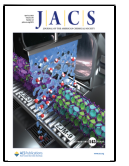

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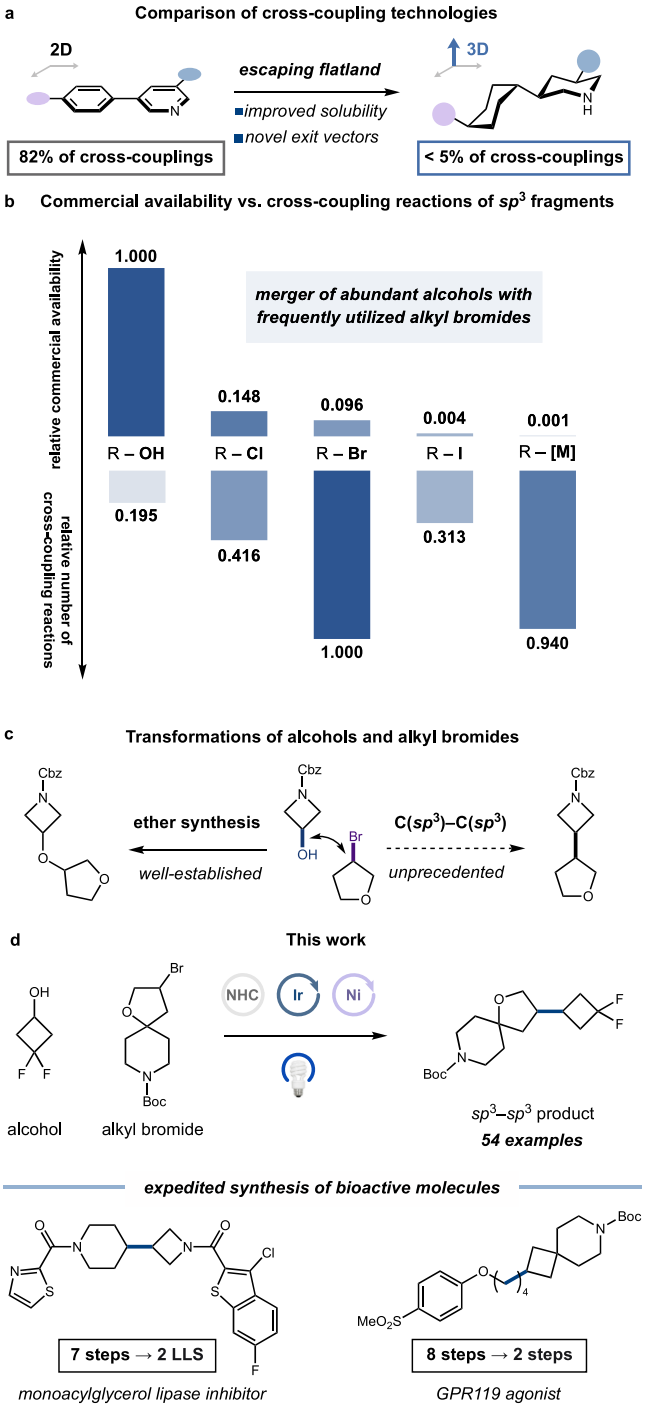


Figure 1. Cross-coupling of alcohols and alkyl bromides.

Bemis–Murcko frameworks.[22] Moreover, secondary-carbon-rich saturated heterocycles, such as piperidine, pyrrolidine, and tetrahydropyran, are among the 10 most common ring structures in approved pharmaceuticals,[23] yet few methods can accomplish the C(sp^3)–C(sp^3) cross-coupling of these motifs. In contrast, there are myriad methods available for the diversification of common unsaturated heterocycles, such as pyridine and benzene.[24] A method capable of linking saturated heterocycles would thus be expected to find broad synthetic application. Herein we report a catalytic C(sp^3)–C(sp^3) cross-coupling of alcohols and alkyl bromides that forms secondary–secondary bonds between all permutations of saturated rings,

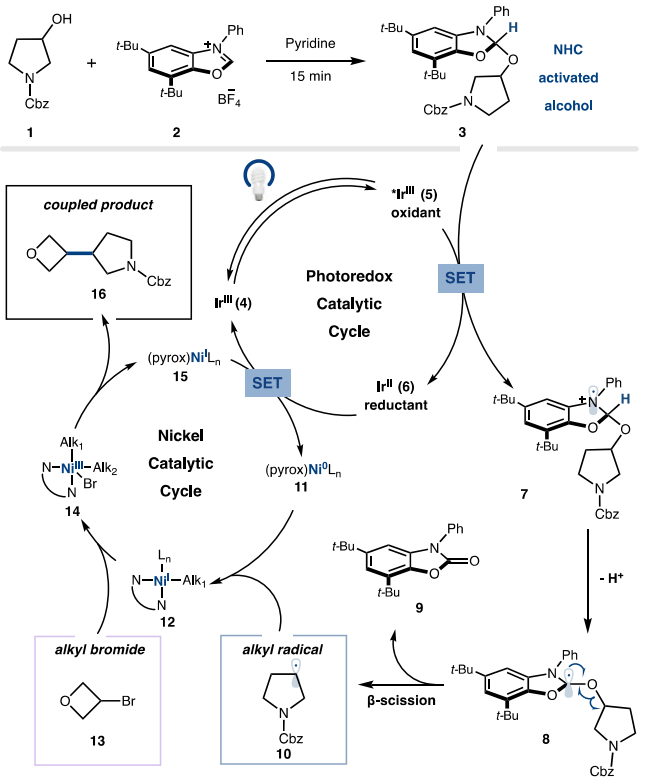
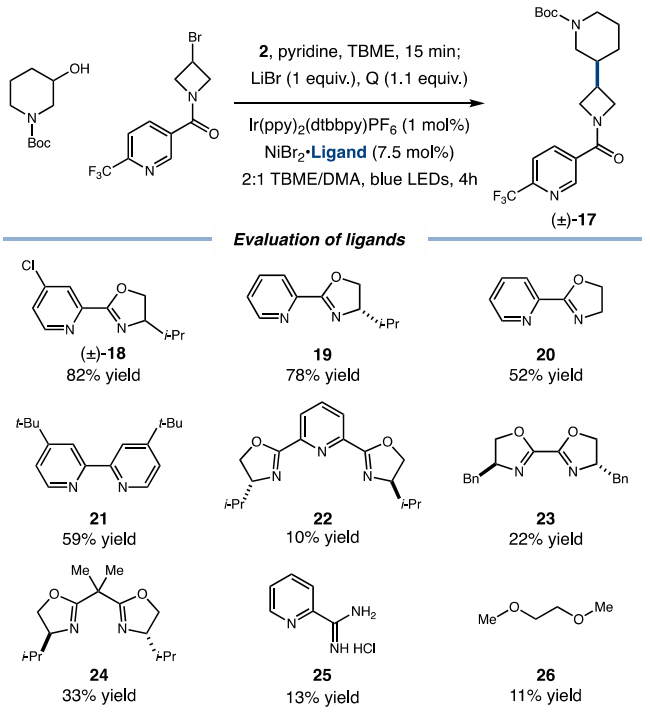


Figure 2. Proposed mechanism.

Table 1. Ligand Evaluation[a]



[a]Yields were determined by uHPLC analysis. See the Supporting Information (SI) for experimental details. Q = quinuclidine.

from four- to seven-membered. A broad scope of alcohols and alkyl bromides has been demonstrated, bearing a variety of medicinally relevant bicyclic, heterocyclic, and spirocyclic cores. To demonstrate the utility of our method, we have

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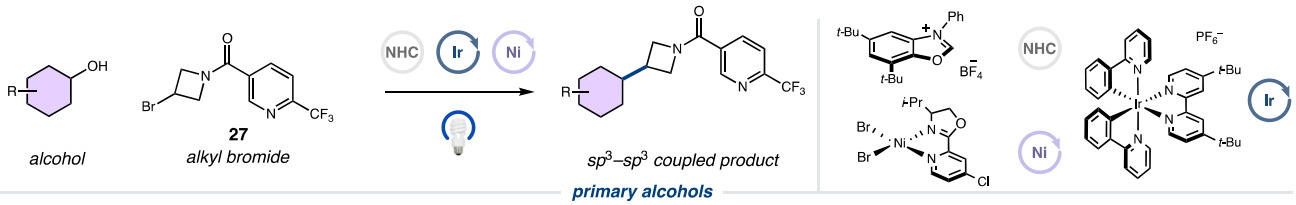
Table 2. Alcohol Substrate Scope[a]



[a]Reactions were performed on a 0.5 mmol scale with alcohol (1.55 equiv), NHC (1.4 equiv), pyridine (1.4 equiv), TBME (0.10 M), 15 min; alkyl bromide (1.0 equiv), quinuclidine (1.1 equiv), **4** (1 mol %), $NiBr_2$·DME (7.5 mol %), (±)-**18** (8 mol %), LiBr (1.0 equiv), 2:1 TBME/DMA (0.067 M), blue LEDs, 4 h. Isolated yields are reported, unless otherwise noted. [b]>99% ee. [c]The reaction was performed with alcohol (1.75 equiv), NHC (1.6 equiv), pyridine (1.6 equiv), (±)-**19** (8 mol %), K_2CO_3 instead of LiBr (1.0 equiv); all other conditions were unchanged. [d]2.6:1 d.r. [e]>20:1 d.r. [f]Dioxane was used instead of TBME. [g]9.5:1 d.r. [h]2.1:1 d.r. [i]1.8:1 d.r. [j]17.4:1 d.r. [k]See the SI for experimental details. [l]The yield was determined by uHPLC analysis. [m]15.8:1 r.r. [n]>20:1 r.r., 5.1:1 d.r.

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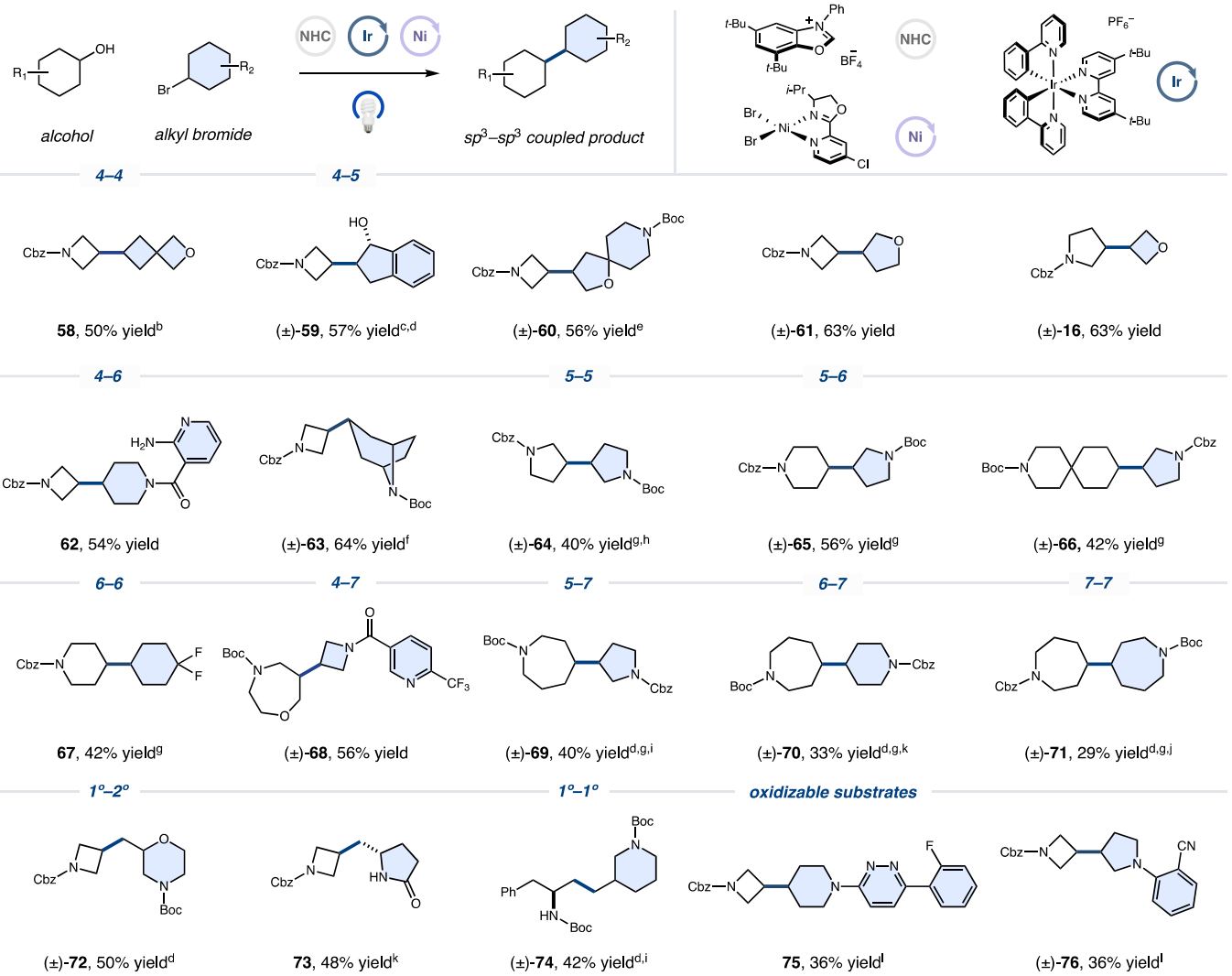
Table 3. Molecular Framework Scope[a]



[a]Reactions were performed on a 0.5 mmol scale with alcohol (1.55 equiv), NHC (1.4 equiv), pyridine (1.4 equiv), TBME (0.10 M), 15 min; alkyl bromide (1.0 equiv), quinuclidine (1.1 equiv), **4** (1 mol %), $NiBr_2$·DME (7.5 mol %), (±)-**18** (8 mol %), LiBr (1.0 equiv), 2:1 TBME/DMA (0.067 M), blue LEDs, 4 h. Isolated yields are reported, unless otherwise noted. [b]**20** was used instead of (±)-**18**. [c]3.7:1 d.r. [d](±)-**19** was used instead of (±)-**18**. [e]The reaction was peformed twice on a 0.25 mmol scale. [f]>20:1 d.r. [g]K_2CO_3 (1.0 equiv) was used instead of LiBr. [h]1.2:1 d.r. [i]1:1 d.r. [j]1.1:1 d.r. [k]The yield was determined by ^{1}H NMR analysis. [l]See the SI for experimental details.

accomplished rapid syntheses of bioactive molecules through the direct construction of key C(sp^3)−C(sp^3) bonds.

We envisioned achieving the C(sp^3)−C(sp^3) cross-coupling of alcohols and alkyl bromides via the nickel metallaphotoredox catalysis pathway outlined in Figure 2. Our proposed mechanism starts with the condensation of alcohol substrate **1** onto benzoxazolium salt **2**, affording activated alcohol **3**. Visible-light excitation of the photocatalyst [Ir(ppy)$_2$(dtbbpy)](PF_6) (**4**) (ppy = 2-phenylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) yields an oxidizing, long-lived triplet excited state (**5**, τ = 557 ns,[25] $E^{red}_{1/2}[Ir^{III}*/Ir^{II}]$ = +0.66 V vs saturated calomel electrode (SCE)).[26] This excited-state photocatalyst oxidizes the anilinic nitrogen atom, yielding aminium radical cation **7**, which is readily deprotonated at the α-position, forming carbon-centered radical **8**.[27] Subsequent β-scission is thermodynamically favored,[19] yielding inert by-product **9** and alkyl radical **10**. This radical is then interfaced with the nickel catalytic cycle via radical capture onto low-valent Ni(0) species **11**,[28] itself generated from **15** by single electron transfer (SET) from highly reducing photocatalyst **6** ($E^{red}_{1/2}[Ir^{III}/Ir^{II}]$ = −1.51 V vs SCE).[26] The resulting Ni(I)−alkyl species **12** undergoes oxidative addition with alkyl bromide substrate **13**,[13] forging dialkylnickel(III) species **14**, which undergoes reductive elimination, releasing C(sp^3)−C(sp^3) cross-coupled product **16**.

Initial optimization studies revealed the importance of the ligand identity to the cross-coupling efficiency. Specifically, we found that the pyridine−oxazoline (pyrox) scaffold was adept at promoting this transformation. Notably, the introduction of an isopropyl group on the oxazoline ring and a chloride on the pyridine (**18**) gave optimal results with an 82% yield of product **17** (Table 1). LiBr and K_2CO_3 proved to be important additives for certain substrate classes (see Table S6 for details).

With the optimized conditions in hand, we began to explore the reaction scope (Table 2). We first probed the ability of primary alcohols to cross-couple in our system. Heterocyclic methanol units were viable substrates (**28**−**31**, 67−85% yield). Next, we were delighted to find that a broad range of

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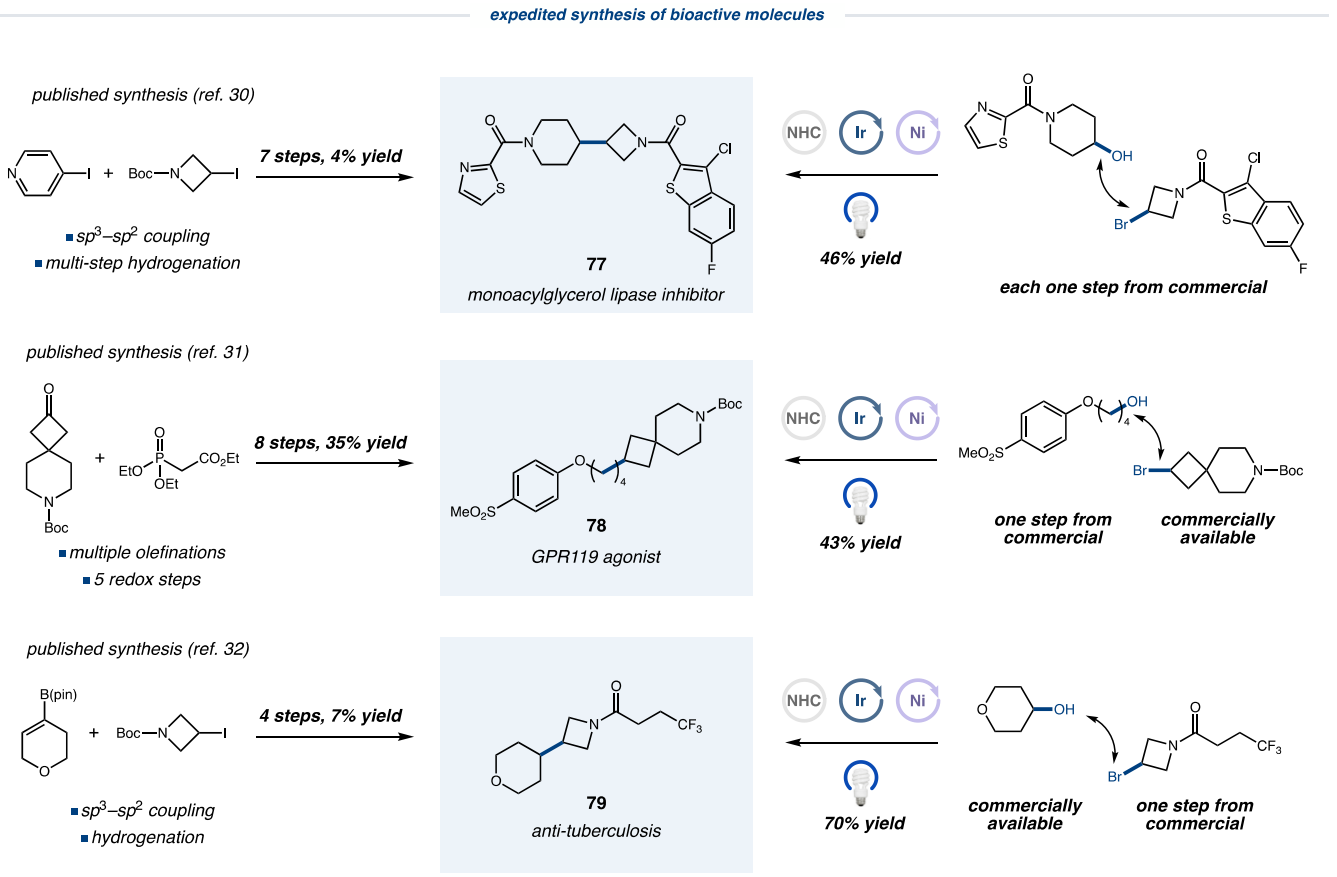
Table 4. Expedited Synthesis of Bioactive Molecules[a]



[a]Isolated yields are reported. See the SI for experimental details.

secondary alcohols readily underwent cross-coupling to form challenging secondary−secondary products. Four-membered-ring alcohols, such as strained azaspirocycles (**37** and **38**, 65% and 68% yield, respectively), performed well in this transformation. A variety of five-membered-ring alcohols provided good to excellent yields, including medicinally relevant scaffolds such as pyrrolidine (**39**, 84% yield) and hydroxyproline (**40**, 86% yield). Pharmacophoric six-membered rings such as piperidine (**17**, 82% yield) and tetrahydropyran (**45**, 79% yield), were successfully coupled. Azepanes were also efficiently coupled (**51**, 85% yield), showing the capability of this reaction to couple seven-membered rings.

We next set out to evaluate the applicability of our method to complex targets, such as drugs and biomolecules. We were pleased to observe that an α-D-mannofuranose-derived product, **55**, was formed in 60% yield with excellent diastereoselectivity. Moreover, Jardiance (empagliflozin), the sixth-highest-selling small-molecule pharmaceutical of 2021,[29] was successfully coupled (**56**, 41% yield), showing exceptional regioselectivity for the primary alcohol moiety in the presence of three secondary alcohols. Estriol, a steroidal hormone, was also a viable substrate in the deoxygenative alkylation (**57**, 48% yield); in this substrate, the least sterically hindered secondary alcohol coupled with full regioselectivity. These examples together show the power of NHC reagent **2** to deliver highly regioselective deoxygenated products based exclusively on steric control of polyol substrates.

Having demonstrated a broad substrate scope, we were interested in expanding the molecular frameworks accessible through this deoxygenative alkylation technology. To realize this goal, we set out to form all possible ring systems from the coupling of four-membered rings to seven-membered rings (Table 3). The four-membered−four-membered (four−four) oxaspiro[3.3]heptane−azetidine system was readily accessed (**58**, 50% yield). A range of four−five scaffolds could also be prepared, including isomeric tetrahydrofuran−azetidine and oxetane−pyrrolidine bisheterocycles (**61** and **16**, 63% and 63% yield, respectively). Five−six products were efficiently formed, including pyrrolidine−piperidine and spirocyclic undecane systems (**65** and **66**, 56% and 42% yield, respectively). As a saturated mimic to traditional biaryl formation, six−six coupling between difluorocyclohexyl and piperidine units proceeded smoothly (**67**, 42% yield). Excitingly, seven-membered rings were also competent substrates, with four- through seven-membered rings readily coupling with seven-membered heterocycles (**68**−**71**, 29−56% yield). Primary bromides performed well in the reaction (**72** and **73**, 50% and 48% yield, respectively). Traditionally challenging anilinic functionality was also tolerated, with pyridazine and electron-deficient aryl groups yielding alkylated products in synthetically useful yields (**75** and **76**, 36% and 36% yield, respectively).

To further demonstrate the applicability of this method toward the formation of complex sp^3-rich molecules from readily accessible starting materials, we undertook the rapid syntheses of several bioactive molecules, with the objective of introducing novel bond disconnections and decreasing the overall step count (Table 4). Monoacylglycerol lipase inhibitor

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77 had previously been synthesized in seven steps in 4% overall yield.[30] To form the key piperidine−azetidine $C(sp^3)-C(sp^3)$ bond, a laborious four-step sequence was required. We reasoned that a direct $C(sp^3)-C(sp^3)$ cross-coupling could offer an expedient alternative to this synthetic route. The required components could be readily accessed through amide couplings of commercially available alcohol and alkyl bromide substrates. Gratifyingly, the cross-coupling proceeded in 46% yield, despite the presence of an activated heteroaryl chloride. This new method also has the potential to improve upon the stepwise olefination−reduction sequence often employed to form primary−secondary $C(sp^3)-C(sp^3)$ bonds. In the case of GPR119 agonist **78**, a seven-step sequence[31] is required to build a four-carbon linker, which is subsequently coupled with an aryl ring. While this sequence provides a synthetically useful 35% yield, the total of eight chemical steps severely limits the ability to make related analogues. We envisioned applying $C(sp^3)-C(sp^3)$ cross-coupling of the commercially available bromoazaspiro[3.5]nonane unit with a primary phenoxybutanol, itself prepared in one step. Excitingly, the cross-coupling proceeded in 43% yield, providing accelerated access to this key tetramethylene−azaspiro[3.5]nonane system in just two chemical steps. Another common approach to formal $C(sp^3)-C(sp^3)$ cross-coupling involves $C(sp^2)-C(sp^3)$ coupling of a vinylboronic ester with an alkyl halide, followed by hydrogenation of the alkene. This type of sequence was used in the patented synthesis of antituberculosis agent **79**.[32] While this route requires only four steps, it has a low efficiency, with only 7% overall yield. As an alternative, we coupled commercially available tetrahydropyran-4-ol with a readily accessible azetidine bromide (prepared in a single step) to deliver **79** in 70% yield, representing a dramatic improvement over the established synthesis.

In summary, we have described herein the deoxygenative $C(sp^3)-C(sp^3)$ cross-coupling of alcohols and alkyl bromides. A broad scope of alcohol and bromide coupling partners has been demonstrated, and the transformation has good functional group tolerance and delivers products in high yields. A specific emphasis was placed on the direct construction of challenging secondary−secondary $C(sp^3)-C(sp^3)$ bonds. All saturated bisheterocycle systems from four−four to seven−seven were formed, and primary substrates were found to be competent reaction partners. Lastly, the merits of this method were demonstrated through expedited syntheses of several bioactive molecules via the direct installation of key $C(sp^3)-C(sp^3)$ bonds. We anticipate that this method will be broadly utilized to rapidly construct challenging sp^3-rich scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c01488.

Additional experimental details, characterization, and spectra (PDF)

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Notes

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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