

Rapid and Modular Access to Quaternary Carbons from Tertiary Alcohols via Bimolecular Homolytic Substitution

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ABSTRACT: Quaternary carbons are ubiquitous in bioactive molecules; however, synthetic methods for the construction of this motif remain underdeveloped. Here, we report the synthesis of quaternary carbons from tertiary alcohols, a class of structurally diverse, bench-stable feedstocks, via the merger of photoredox catalysis and iron-mediated S_{H2} bond formation. This alcohol–bromide cross-coupling is enabled by a novel halogen-atom transfer (XAT) reagent, which is the first reductively activated XAT reagent to be reported. A wide variety of sterically congested quaternary products can be accessed through this mild and practical protocol including products derived from both alkylation and benzylation of tertiary fragments. We further demonstrate the synthetic utility of this method through the expedited synthesis of a liver receptor agonist and through a two-step conversion of ketones and esters to quaternary products, which enables the modular control of up to three of the four substituents on a quaternary center.

Quaternary carbons impart favorable properties to bioactive molecules including metabolic stability, conformation rigidity, and binding selectivity,^{1,2} however, synthetic methods for the construction of this valuable motif remain limited.^{3–5} By contrast, tertiary alcohols are widely available, structurally diverse synthons that can be readily accessed from a variety of precursors including ketones, esters, alkenes, and epoxides. Given this disparity in accessibility, a synthetic method for the direct conversion of tertiary alcohols to quaternary carbons would be highly enabling (Figure 1). Such a transformation could be particularly impactful in the pharmaceutical industry, where most top-selling small-molecule therapeutics that contain quaternary carbons are currently synthesized from starting materials in which this motif is preinstalled.^{3,6} Nevertheless, a general method for the synthesis of quaternary carbons from tertiary alcohols remains elusive.⁷

Recently, our lab and others have demonstrated that metallaphotoredox catalysis can enable facile quaternary carbon synthesis via iron- and nickel-mediated radical sorting mechanisms.^{8–11} In these methods, a photocatalyst induces the mild, simultaneous generation of primary and tertiary alkyl radicals, while a transition metal catalyst selectively binds the primary radical due to the greater strength of the M–C bond. Formation of the key C–C bond then proceeds via bimolecular homolytic substitution (S_{H2}) between a tertiary radical and the primary metal–alkyl species. This S_{H2} mechanism, a single-electron analog of the classic S_{N2} mechanism,¹² obviates the need for the tertiary radical to interact directly with the metal catalyst, avoiding deleterious side reactions that impede quaternary carbon synthesis via traditional cross-coupling methodologies.^{13–16}

We recognized that this radical sorting strategy could provide a method for the synthesis of quaternary carbons from tertiary alcohols. In particular, we sought to develop a cross-coupling of tertiary alcohols and primary alkyl bromides. Alkyl

bromides are widely commercially available, inexpensive feedstock chemicals, and thus, they represent an optimal source of primary alkyl fragments for this transformation.

To facilitate radical deoxygenation of the tertiary alcohol substrate in the proposed cross-coupling reaction, we turned to a benzoxazolium-based reagent, termed “deoxazole” or “NHC”, recently disclosed by our lab.¹⁷ NHC activation of alcohols proceeds *in situ* under mild conditions, avoiding the additional purification steps required for other radical deoxygenation protocols.¹⁸ The NHC reagent has been leveraged in synthetic methods for arylation,¹⁷ alkylation,^{7b,10,19} and trifluoromethylation,²⁰ although the scope of these transformations for quaternary products is typically limited due to reliance on inner-sphere reductive elimination mechanisms.^{17–20} We hypothesized that the merger of NHC activation and S_{H2} catalysis could facilitate a robust and general method for quaternary carbon synthesis.

We envisioned that the proposed alcohol–bromide cross-coupling could be achieved according to the design plan shown in Figure 2. First, tertiary alcohol substrate 1 condenses with benzoxazolium salt (NHC) under mildly basic conditions to form the activated NHC alcohol adduct 2.¹⁷ Visible-light excitation of the photocatalyst (PC) 2,4,5,6-tetrakis(9H-carbazol-9-yl) isophthalonitrile (4CzIPN, 3) generates a long-lived, triplet excited state 4 ($\tau = 5.1$ s, $E_{1/2} = +1.35$ V vs saturated calomel electrode (SCE) in MeCN).²¹ Excited-state complex 4 can engage in reductive quenching by NHC-

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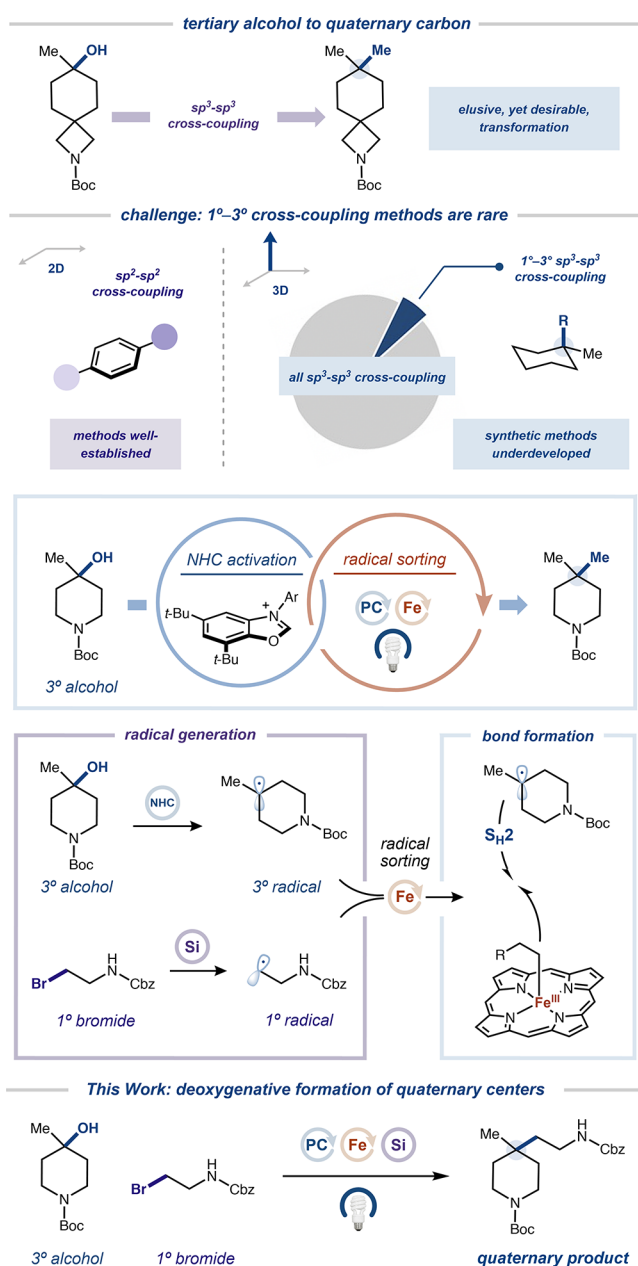


Figure 1. Synthesis of quaternary carbons from tertiary alcohols via bimolecular homolytic substitution (S_{H2}).

alcohol adduct **2** ($E_{pa} = +1.17$ V)¹⁰ to generate reduced photocatalyst **5** ($E_{1/2} = -1.21$ V)²¹ and a transient amine radical cation, which undergoes rapid deprotonation and subsequent β -scission to furnish an aromatized byproduct **6** and tertiary alkyl radical **7**. Concurrently, reduced photocatalyst **5** must activate the primary alkyl bromide **8** to furnish the primary alkyl radical **9** and regenerate photocatalyst **3**. Capture of alkyl radical **9** by iron(II) catalyst **10** yields the key iron(III)-alkyl intermediate **11**, which is poised for S_{H2} substitution by tertiary alkyl radical **7** to form the desired quaternary product **12** and reconstitute the iron catalyst **10**.⁸

From the outset, we recognized that the proposed reductive bromide activation step presented a significant obstacle to our desired transformation. Indeed, direct alkyl bromide reduction occurs at extreme potentials ($E_{1/2} \approx -2.5$ V vs SCE)²² that are inaccessible to conventional photocatalysts.²³ Prior work has

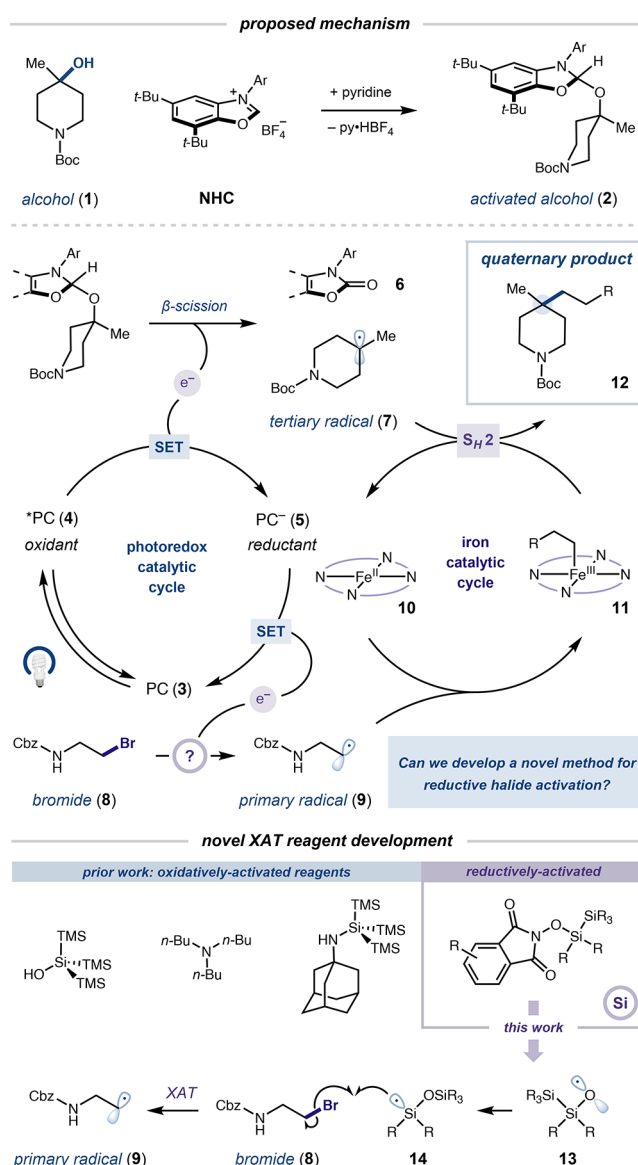
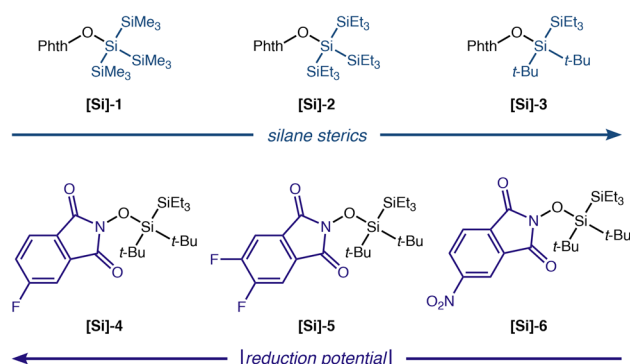
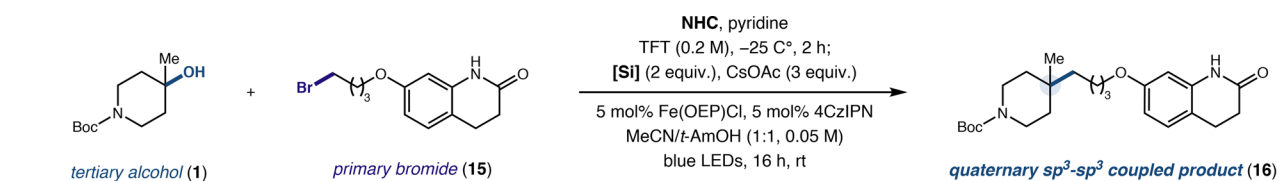


Figure 2. Proposed reaction design (top) and design of a reductively activated halogen atom transfer (XAT) reagent (bottom).

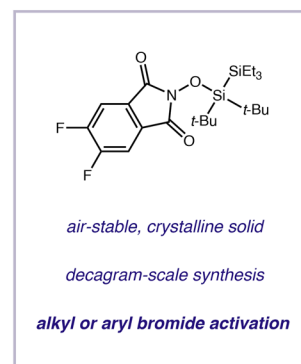
demonstrated that alkyl bromides can be converted to the corresponding alkyl radical via halogen-atom transfer (XAT) to nucleophilic silicon or α -amino radicals;²⁴ however, such XAT reagents are typically activated through single-electron oxidation.^{25–27} No reductively activated analogue has yet been reported.

To this end, we designed a class of *N*-silyoxyphthalimide reagents, [**Si**] (Figure 2, bottom; Table 1). One-electron reduction of the [**Si**] reagent initiates N–O bond scission, leading to concurrent formation of phthalimide anion and an oxygen-centered radical **13**.²⁸ Subsequent radical Brook rearrangement reveals a silicon-centered radical **14**,²⁹ which can engage in rapid XAT ($k \approx 10^9$ M⁻¹ s⁻¹) with an alkyl bromide substrate **8** to form the corresponding alkyl radical **9**.³⁰ Gratifyingly, initial studies revealed that the [**Si**] reagents are capable of activating both alkyl and aryl bromides upon photocatalytic single-electron reduction (Figure S5).

We next applied our reductively activated XAT reagents to the proposed cross-coupling reaction using tertiary alcohol **1** and primary bromide **15** (Table 1). Following extensive

Table 1. Optimization of Reductively-Activated Halogen-Atom Transfer Reagent^a

entry	silane reagent	yield
1	none	6%
2	[Si]-1	17%
3	[Si]-2	12%
4	[Si]-3	60%
5	[Si]-4	67%
6	[Si]-5	71%
7	[Si]-6	0%



^aPerformed with bromide (0.05 mmol, 1.0 equiv), alcohol (2.5 equiv), NHC (2.8 equiv), pyridine (2.8 equiv), silane reagent ([Si], 2.0 equiv), and CsOAc (3.0 equiv). Yields determined by HPLC analysis with 1,3,5-trimethoxybenzene as an internal standard. See Supporting Information for experimental details.

optimization (Supporting Information, Section 4; Table 1), we found that alcohol 1 (2.5 equiv) underwent condensation with NHC (2.8 equiv) and pyridine (2.8 equiv) in α,α,α -trifluorotoluene (TFFT, 0.2 M), followed by cross-coupling with primary bromide 15 in the presence of CsOAc (3.0 equiv), reductively activated XAT reagent ([Si]-5, 2.0 equiv), 4CzIPN (5 mol %), Fe(OEP)Cl (5 mol %; OEP = 2,3,7,8,12,13,17,18-octaethyl-21H,23H-porphine) in acetonitrile/*tert*-amyl alcohol (1:1, 0.05 M) to afford the desired quaternary product 16 in good yield (71% yield) after 16 h of irradiation (450 nm) in an integrated photoreactor.³¹ Control reactions revealed all reaction components to be necessary for optimal yield of product 16 (Figure S7). Notably, no reaction is observed in the absence of light, and the reaction yield decreases substantially in the absence of XAT reagent [Si] (6% yield).

The structure of XAT reagent [Si] has a substantial impact on the yield of product 16 (Table 1). In particular, we found that increasing the steric bulk at the central silicon atom from R-Si(SiMe₃)₃ ([Si]-1) to R-Si(*t*-Bu)₂(SiEt₃) ([Si]-3) resulted in an increase in the yield of product 16 from 17% to 60%. We attribute this effect to the enhanced stability of [Si]-3 with respect to base-mediated decomposition (Figure S6).

Tuning the reduction potential of reagent [Si] via functionalization of the *N*-hydroxyphthalimide fragment also impacts the product yield. As shown in Table 1, reagents with either one ([Si]-4, $E_{pc} = -1.33\text{ V}$ vs SCE in MeCN) or two ([Si]-5, $E_{pc} = -1.30\text{ V}$) fluoride substituents outperformed the unsubstituted analogue ([Si]-3, $E_{pc} = -1.39\text{ V}$). This is likely due to competition between the reduction of the XAT reagent and the Fe^{II}(OEP) catalyst ($E_{1/2}(\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}) = -1.28\text{ V}$), which becomes less favorable as the reagent becomes easier to reduce. Interestingly, reagents with more strongly electron withdrawing substituents such as a nitro group ([Si]-6, $E_{pc} = -0.75, -1.18\text{ V}$) were significantly less effective (0% yield). We attribute this phenomenon to a decrease in the rate of N-

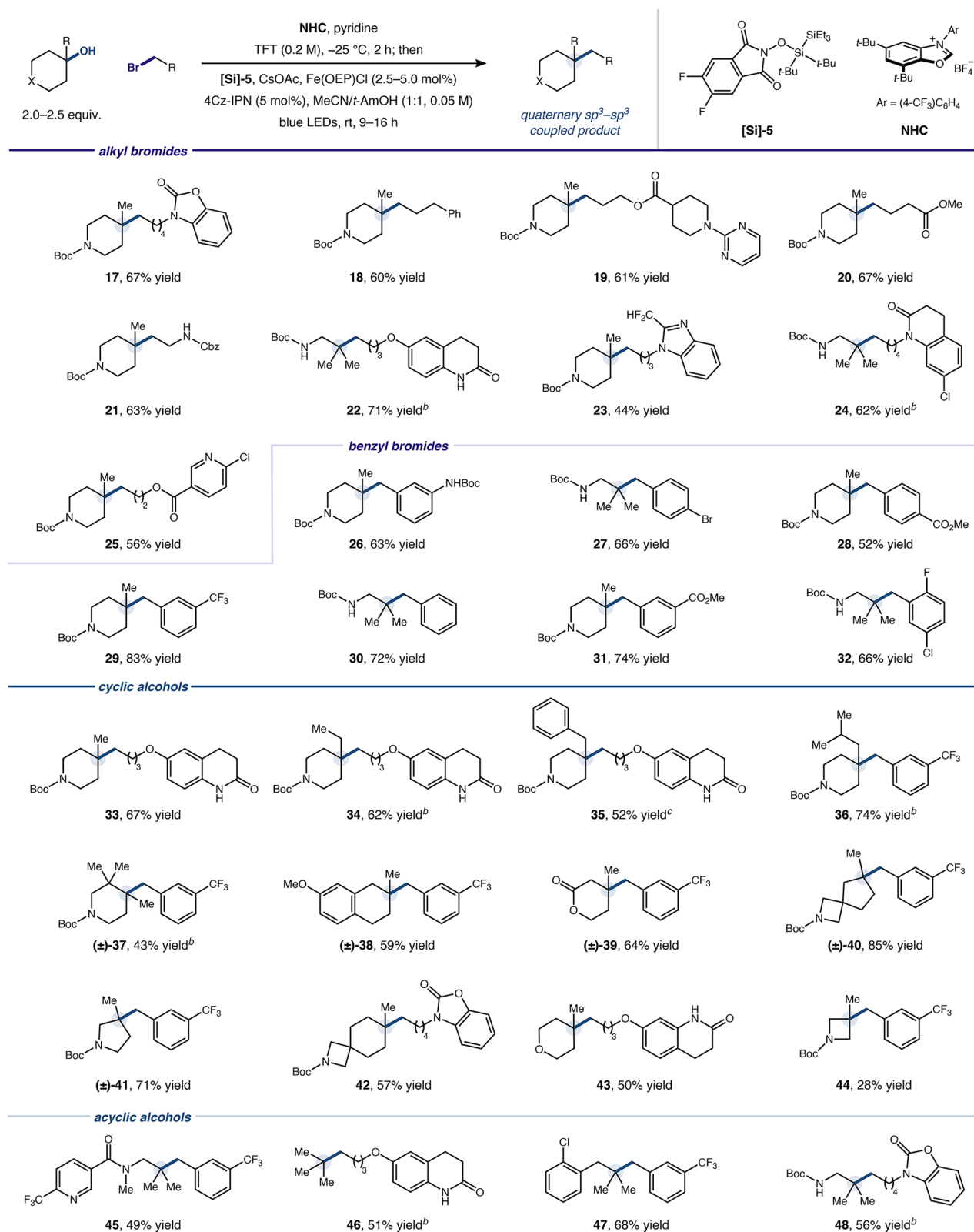
O bond scission for [Si]-6, as indicated by an increase in the reversibility of cyclic voltammetry measurements (Figure S4).

The optimal reagent [Si]-5 is an air-stable, crystalline solid that can be synthesized at the decagram scale in only three steps from commercial materials (Supporting Information, Section 2). Compound [Si]-5 is the first reductively activated XAT reagent that has been developed for conversion of alkyl or aryl bromides to the corresponding radical species. As such, we believe that this reagent will find widespread application in photoredox catalysis and organic methodology development generally.

With the optimized conditions in hand, we next explored the scope of this reaction (Table 2). First, we examined a range of primary alkyl bromides with both cyclic and acyclic tertiary alcohol partners (17–25). We were pleased to find that medically relevant heterocycles were well-tolerated including benzoxazolinone (17, 67% yield), benzimidazole (23, 44% yield), and pyridine (25, 56% yield). Additionally, substrates bearing tertiary anilines (19, 61% yield) and free N-H bonds (21, 63% yield; 22, 71% yield) were converted to quaternary products with good efficiency.

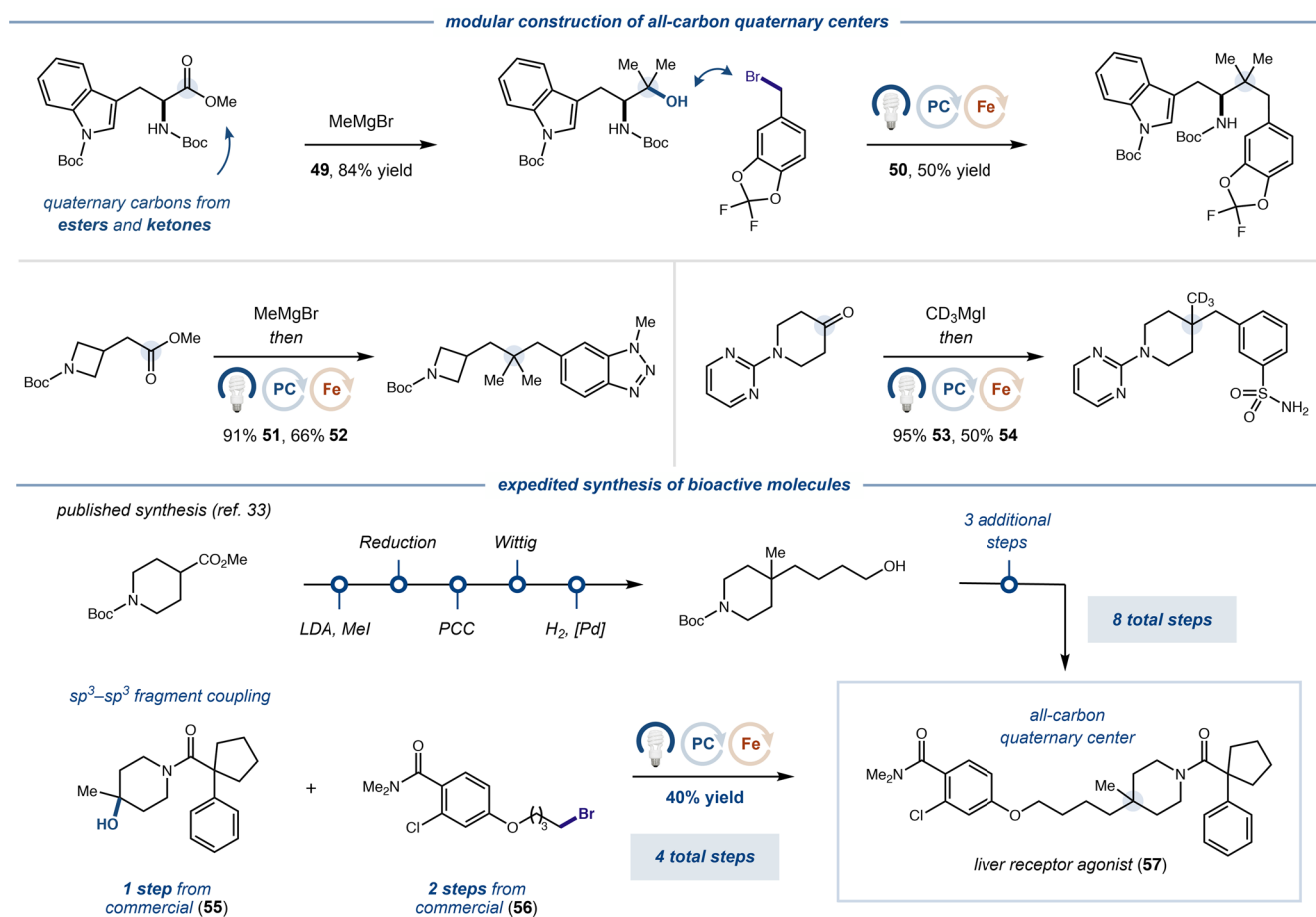
Using this method, a wide variety of benzyl bromides were readily coupled with both cyclic and acyclic tertiary alcohols (26–32). Control reactions revealed that benzyl bromide substrates do not require activation via silane reagent [Si]-5 (Figure S8) and can instead be activated via direct photocatalyst mediated reduction to furnish comparable yields of quaternary product. Benzyl bromides bearing electron-donating substituents, such as protected amines (26, 63% yield), and electron-withdrawing substituents, such as trifluoromethyl (29, 83% yield), ester (31, 74% yield), and fluoride (32, 66% yield), all displayed good to excellent yields.

Notably, this method can be used to couple substrates containing aryl bromides (27, 66% yield) and (hetero)aryl chlorides (24, 62% yield; 32, 66% yield), including activated 2-pyridyl chlorides (25, 56% yield), which have the potential to act as vectors for subsequent derivatization. This capability

Table 2. Scope of Alcohol–Bromide Cross-Coupling^a

^aReactions were performed on a 0.5 mmol scale with alcohol (2.0–2.5 equiv), NHC (1.1 equiv. with respect to alcohol), pyridine (1.1 equiv. with respect to alcohol), TFT (0.2 M), 2 h, –25 °C; alkyl bromide (1.0 equiv), [Si]-5 (2.0 equiv. for alkyl bromides; 0.0 equiv. for benzyl bromides), CsOAc (2.5–3.0 equiv), 4CzIPN (5 mol %), Fe(OEP)Cl (2.5–5.0 mol %), 1:1 MeCN/*t*-AmOH (0.05 M), blue LEDs, 9–16 h. All yields are isolated. ^b3.0 equiv. alcohol. ^c3.5 equiv. alcohol. ^d4.0 equiv. alcohol.

Table 3. Modular Access to Quaternary Carbons via Alcohol–Bromide Cross-Coupling and Expedited Synthesis of Bioactive Molecules



highlights an advantage of S_H2-based cross-coupling methods compared to traditional strategies that rely on low-valent metal catalysts, which rapidly react with such aryl electrophiles.

We next explored the scope of this transformation with respect to tertiary alcohols using both primary alkyl and benzyl bromide partners (33–48). To investigate steric tolerance, we examined piperidine substrates bearing *ipso* methyl (33, 67% yield), ethyl (34, 62% yield), benzyl (35, 52% yield), and *iso*-propyl (36, 74% yield) substituents and observed good to moderate yields. This compares favorably with alternative cross-coupling methods for quaternary carbon synthesis, which typically require that at least one *ipso* substituent be a methyl group for a substrate to be coupled with synthetically useful yields.^{10,11,15d} Notably, our method can also furnish products bearing contiguous quaternary carbons (37, 43% yield), a motif that presents a significant challenge in bioactive molecule synthesis.³²

Additionally, we found that tetrahydronaphthalene (38, 59% yield), δ -lactone (39, 64% yield), and tetrahydropyran (43, 50% yield) derived substrates coupled in good to moderate yields. Our method can also be used to form quaternary carbons in five-membered ring backbones including cyclopentane (40, 85% yield) and pyrrolidine (41, 71% yield). Acyclic tertiary alcohol substrates also coupled in good to moderate yields (45–48, 49–68% yield) including *tert*-butanol (46, 51% yield), providing a nontraditional approach to the installation of *tert*-butyl groups.

Limitations of this cross-coupling protocol include secondary alkyl or benzyl bromides, which likely perform poorly due to decreased efficiency of the key S_H2 substitution, analogous to trends observed for S_N2 reactions. Nucleophilic moieties, such as pyridines without ortho substituents, also diminish the reaction yield (see Supporting Information, Section 8). In addition, low yields were observed for tertiary azetidins (44, 28% yield), potentially due to the decreased nucleophilicity of the corresponding radical.

To further illustrate the utility of this alcohol–bromide cross-coupling, we subjected ketone- or ester-containing substrates to a two-step alkylation sequence (Table 3). Compounds were first converted to the corresponding tertiary alcohols via Grignard reaction (49, 51, 53; 85–95% yield), then subjected to alcohol–bromide cross-coupling to yield quaternary products (50, 52, 54; 50–66% yield). Notably, this alkylation sequence enables modular control of up to three of the four substituents on a quaternary carbon in only two steps. Furthermore, it provides rapid access to the *gem*-dimethyl motif, common in small-molecule therapeutics,⁵ from ester-containing substrates, an enabling disconnection that allows biomass-derived building blocks to be readily converted to quaternary carbon-containing pharmacores.

Finally, we applied our cross-coupling technology to the expedited synthesis of 57, which is a liver receptor agonist. Compound 57 was previously synthesized in eight linear steps.³³ In the published route, the quaternary center is installed in the first step via enolate methylation, and then four

additional steps are required to convert the methyl group to a primary alkyl chain, representing a significant synthetic burden for analogue exploration. We envisioned that the quaternary center could instead be installed in the final step via alcohol–bromide cross-coupling, thus allowing for a convergent synthesis. Gratifyingly, tertiary alcohol **55** and primary bromide **56** could be prepared in one and two steps from commercial materials, respectively, and these fragments were coupled in moderate yield, furnishing **57** in four total steps.

In summary, we report here a method for the synthesis of quaternary carbons from tertiary alcohols and primary bromides. This cross-coupling reaction is enabled by a novel reagent, [Si]-5, which is the first reductively activated reagent for halogen-atom transfer (XAT). This synthetic methodology enables rapid access to sterically congested quaternary centers from a structurally diverse range of alcohols and bromides. The utility of this transformation is highlighted through the modular synthesis of quaternary products from ketone or ester feedstocks and the expedited synthesis of a liver receptor agonist. Additional studies on $S_{\text{H}}2$ -mediated cross-coupling reactions and applications of reductively activated XAT reagents are ongoing in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c05405>.

Additional experimental details, materials, and methods, including NMR characterization data for all compounds (PDF)

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Notes

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

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