Communication

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Metallaphotoredox-Catalyzed Cross-Electrophile C_{sp}^3–C_{sp}^3 Coupling of Aliphatic Bromides

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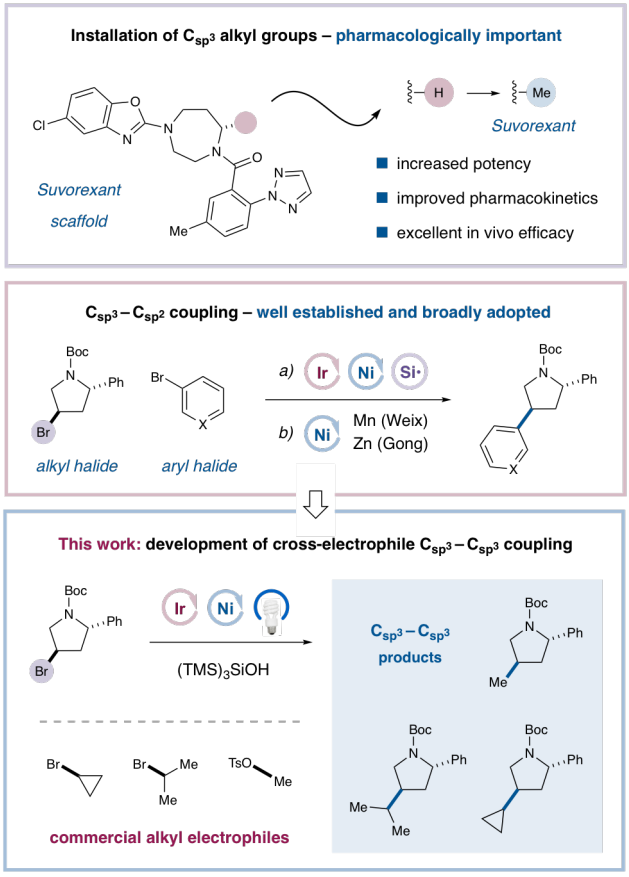
Supporting Information Placeholder

ABSTRACT: A strategy for the installation of small alkyl fragments onto pharmaceutically relevant aliphatic structures has been established via metallaphotoredox catalysis. Herein, we report that tris(trimethylsilyl)silanol can be employed as an effective halogen abstraction reagent that, in combination with photoredox and nickel catalysis, allows a generic approach to C_{sp}^3–C_{sp}^3 cross-electrophile coupling. In this study, we demonstrate that a variety of aliphatic drug-like groups can be successfully coupled with a number of commercially available small alkyl electrophiles, including methyl tosylate and strained cyclic alkyl bromides. Moreover, the union of two secondary aliphatic carbon centers, a long-standing challenge for organic molecule construction, has been accomplished with a wide array of structural formats. Last, this technology can be selectively merged with C_{sp}^2–C_{sp}^3 aryl-alkyl couplings to build drug-like systems in a highly modular fashion.

Recently, it has been reported that the clinical success of small molecule therapeutics can be correlated with increasing levels of C_{sp}^3 incorporation within the carbon framework of medicinal agents.[1] In this regard, small alkyl moieties, and in particular methyl groups, have proven to be of significant value in medicinal chemistry due to their capacity to induce conformational constraints on aliphatic ring systems while decreasing the available sites for P450 metabolism.[2] This was demonstrated in the case of the drug Suvorexant, in which installation of the aliphatic C-7 methyl group led to improved potency and pharmacokinetic properties (Scheme 1).[3] As such, new methods for the modular installation of small alkyl groups are highly desirable, and the pioneering work of Knochel,[4] Fu,[5] and others[6,7] has established that the heterocoupling of C_{sp}^3 centers can be accomplished using organometallic alkyl nucleophiles. However, strategies for the reductive cross-coupling of two alkyl electrophiles have been slower to develop,[8,9] and general methods for the pairing of two secondary alkyl centers remain extremely rare.[10,11]

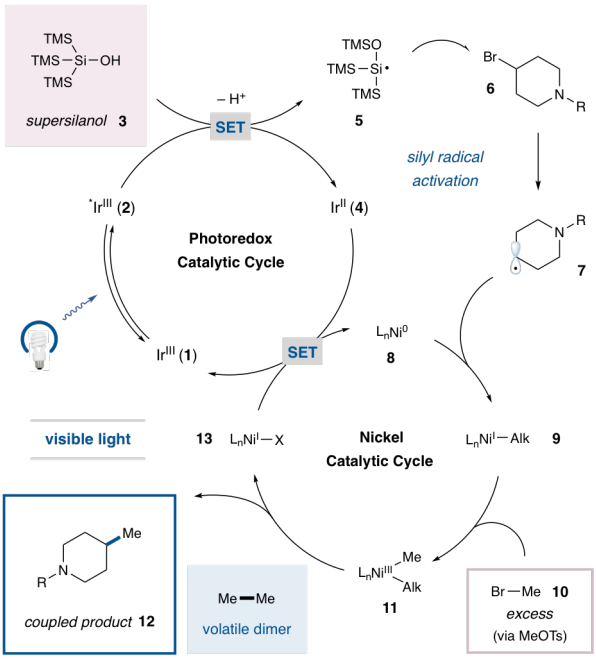
Metallaphotoredox catalysis has become a prominent synthetic strategy in medicinal chemistry for the coupling of complex molecular fragments via C–C, C–N, C–S, and C–O bond



Scheme 1: Small alkyl group installation via halide coupling

formation.[12,13] In 2016, our laboratory reported a novel metallaphotoredox pathway to achieve the reductive cross-coupling of aromatic C_{sp}^2–halides with aliphatic C_{sp}^3–bromides via the catalytic production and application of silyl radicals in combination with nickel catalysis.[14] We recently questioned whether it would be possible to employ the same halogen abstraction mechanism to achieve selective C_{sp}^3–C_{sp}^3 cross-coupling between two discrete alkyl bromides, a pathway that might allow the modular installation of small alkyl groups onto complex drug-like architectures. Among a number of objectives, we hoped to achieve the union of two secondary aliphatic carbon

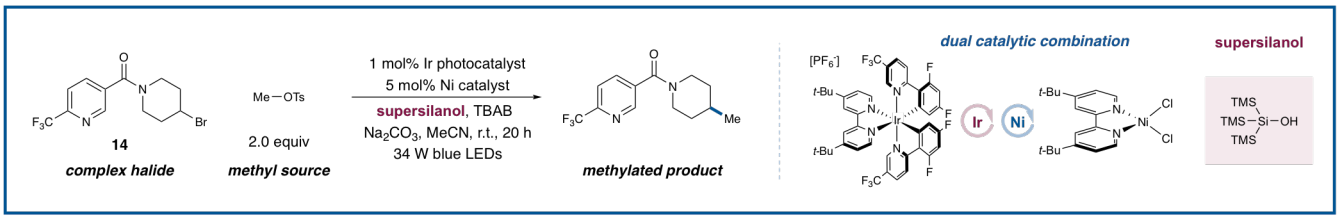
Scheme 2: Plausible mechanism for reductive methylation

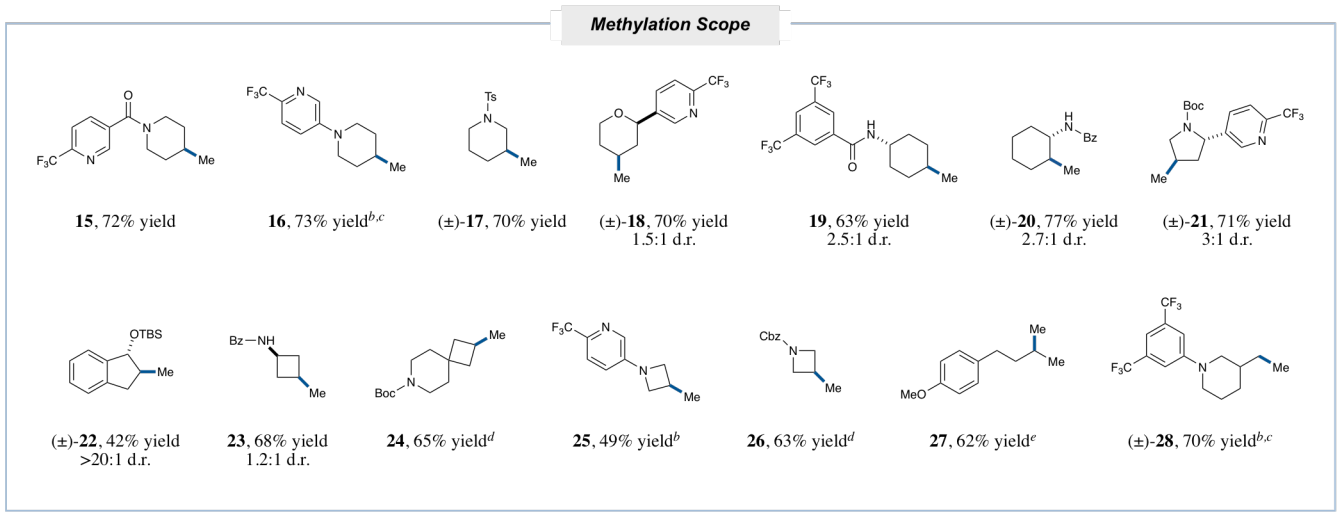


centers, a long-standing challenge for all areas of organic molecule construction (total synthesis, medicinal, process chemistry, etc.),[10] given the associated issues involving oxidative addition of hindered alkyl–nickel or alkyl–palladium species into secondary aliphatic C_{sp}^3–halide bonds. In particular, we hoped that a halogen abstraction/radical-nickel recombination mechanism might bypass this oxidative addition problem, thereby rendering a novel cross-coupling pathway for the construction of C_{sp}^3–C_{sp}^3 architectures. As an important design criterion, we recognized that the use of alkyl halides for both reaction partners would remove the requirement for substrate prefunctionalization (e.g., as Grignard, organozinc, or borate salts), thereby reducing operational complexity while expanding the scope of available structural fragments. Furthermore, the reduction in step count would allow for streamlined synthetic sequences and decreased costs.

Based on recent work from our lab involving (i) nickel catalyzed aryl-alkylation[14] and (ii) copper-catalyzed trifluoromethylation,[15] we were confident that reductive coupling of two alkyl halide partners should be possible using tris(trimethylsilyl)silane or the corresponding silanol in combination with nickel and photoredox catalysis. As shown in Scheme 2, we envisioned that visible-light excitation of the Ir(III) photocatalyst Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (**1**) would generate the long-lived (τ = 2.3 μs)[16] excited-state *Ir^{III} complex **2**. This species is a powerful single-electron oxidant ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.21 V vs. SCE in CH_3CN),[16] and we presumed it would undergo reduction by the silanolate resulting from deprotonation of supersilanol **3** to furnish the reduced Ir(II) catalyst **4**.[15] The resultant silyloxy-centered radical is known to undergo bond isomerization to produce silyl radical **5**,[15] which can rapidly[17] participate in halogen atom abstraction with alkyl bromides such as **6** to furnish the aliphatic radical **7**. At the same time, we anticipated that single-electron reduction of (dtbbpy)Ni(II)Cl_2 by the electron-rich Ir(II) form of the photocatalyst **4** would lead to the requisite dtbbpy-ligated Ni(0) complex **8** ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = –1.37 V vs. SCE in CH_3CN, $E_{1/2}^{red}$ [Ni^{II}/Ni^0] = –1.2 V vs. SCE in

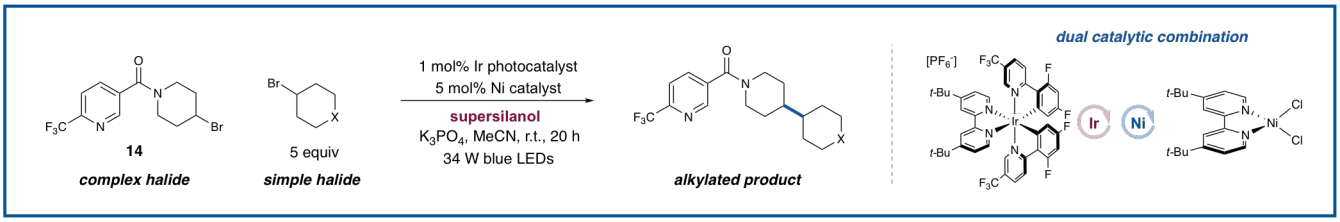
Table 1: Methylation scope for the metallaphotoredox-catalyzed coupling of aliphatic halides[a]

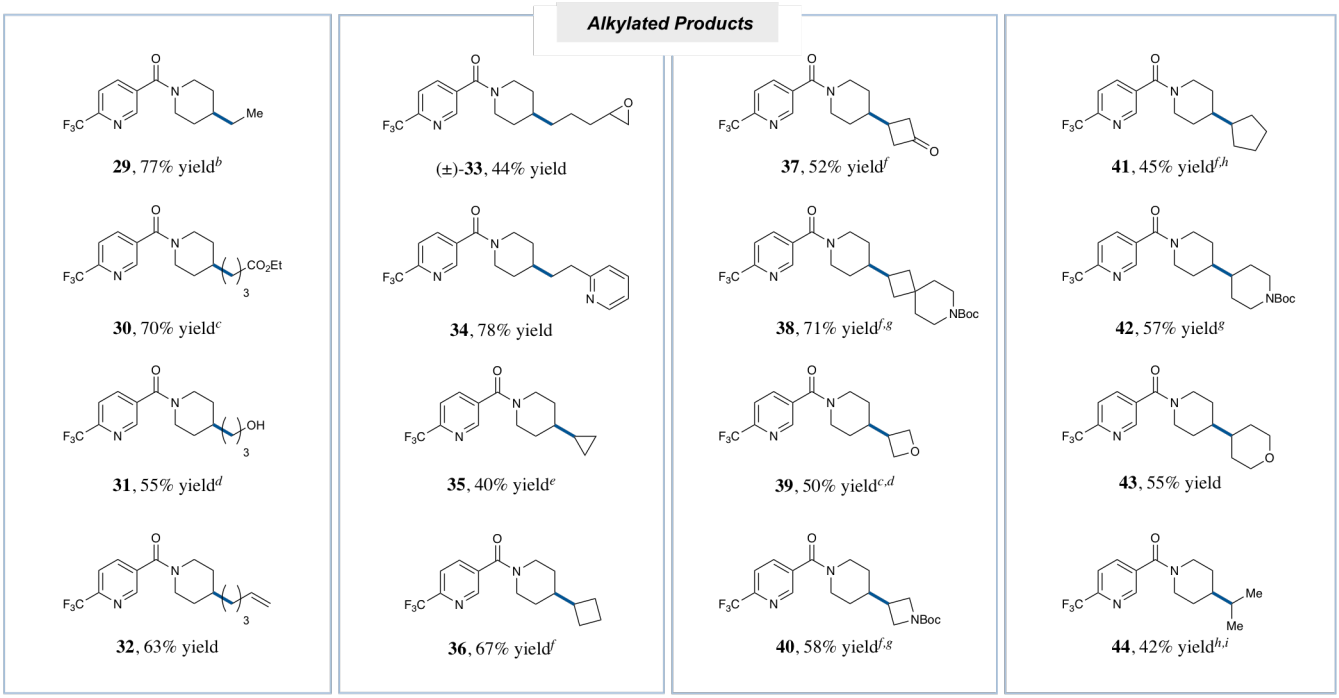




[a]Reactions performed with 1.5 equiv supersilanol, 2 equiv Na_2CO_3, and 2.5 equiv TBAB. Yields isolated unless otherwise noted. Only a small amount (<5%) of homodimerization of the limiting reagent **14** was observed. See SI for experimental details. [b]Using Ir[dF(Me)ppy]$_2$(dtbbpy)PF_6 as photocatalyst. [c]3 euiv Na_2CO_3 used. [d]K_3PO_4 as base. [e]GC yield.

Table 2: Scope of simple aliphatic electrophiles in the metallaphotoredox-catalyzed coupling of aliphatic halides[a]





[a]Reactions typically performed with 3 equiv supersilanol and 3 equiv K_3PO_4. See SI for experimental details. Yields isolated unless otherwise noted. Homodimerization of limiting reagent **14** typically between 5 and 10%. [b]7 equiv small halide. [c]4 equiv small halide. [d]UPLC yield. [e]8 equiv small halide. [f]Na_2CO_3 as base. [g]3 equiv small halide. [h]Using PyBOX **L1** (*vide infra*) as ligand. [i]6 equiv small halide.

DMF),[16,18] a Ni(0) complex that can readily intercept radical **7**.[19] Subsequent oxidative addition of this alkyl–Ni(I) species **9** into methyl bromide (**10**), generated in situ from methyl tosylate, would then lead to the putative dialkyl-organometallic-Ni(III) species **11**, which upon reductive elimination would generate the C_{sp}^3–C_{sp}^3 bond within the desired fragment-coupled adduct **12**.[20,21] At this stage both catalytic cycles would converge via SET between the resulting Ni(I) species **13** and the reduced iridium photocatalyst **4** to reestablish both Ir(III) complex **1** and Ni(0) complex **8**.[16, 22] As a key design element, we recognized that the use of excess quantities of the small aliphatic coupling partner (e.g., methyl tosylate) would be operationally viable given that a competitive homodimerization pathway would lead mainly to volatile byproducts (e.g., ethane), thereby allowing facile removal from the desired adduct.

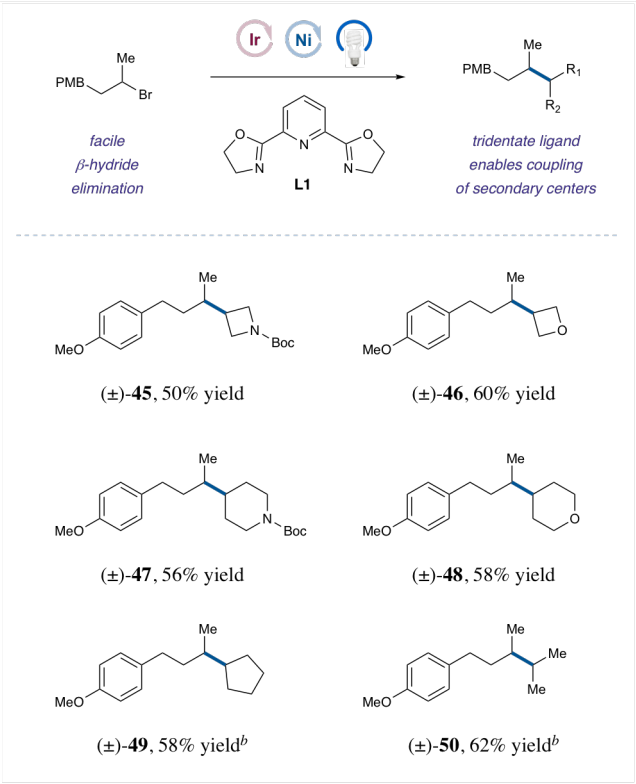
The feasibility of this new approach to C_{sp}^3–C_{sp}^3 cross-electrophile coupling was first investigated using a drug-like 3-acyl pyridinyl piperidine bromide **14** and methyl tosylate in a variety of reaction conditions (see Supporting Information for details). While supersilane was found to be optimal in our previous alkyl-arylation studies,[14] we observed that this halogen abstraction agent was generally ineffective in this new C_{sp}^3–C_{sp}^3 coupling protocol, mainly due to predominant formation of the dehalogenated alkane byproduct. To overcome this halide-reduction problem, we recognized that the use of supersilanol would allow the formation of silyl radicals via a photocatalytic silanolate oxidation/silyl migration sequence, thereby avoiding the use of a Si–H based reagent that can participate in a deleterious hydrogen atom transfer step with alkyl radical intermediates. During the course of reaction optimization, we also found that use of tetrabutylammonium bromide as an additive provided superior yields of the desired methylation adduct. We attribute this observation to the importance of rapidly converting methyl tosylate to methyl bromide in situ. Control experiments revealed that excluding light, nickel, or photocatalyst resulted in no product formation (see Supporting Information for details).

With optimal conditions in hand, we next evaluated the scope of this new C_{sp}^3–C_{sp}^3 methylation protocol using a wide array of pharmaceutically relevant aliphatic structures. As shown in Table 1, the transformation is effective for heterocyclic bromides such as substituted piperidine (**15**–**17**, 70–73% yield) and tetrahydropyran (THP) (**18**, 70% yield) ring systems, both of which are common motifs within medicinal chemistry.[23] Furthermore, functionalized cyclohexane rings are also competent in this reaction manifold, providing the corresponding methyl-bearing adducts in good yield (**19** and **20**, 63 and 77% yield respectively). Pyrrolidine, a privileged pharmacophore, can also be alkylated efficiently using this catalytic system (**21**, 71% yield). Notably, in the case of an indane core, an adjacent protected alcohol is readily tolerated, giving the desired product with ex-

cellent diastereoselectivity (**22**, 42% yield, >20:1 d.r.). Examining more strained systems, we were delighted to find that a number of four-membered rings readily undergo methyl coupling in this transformation, including spirocyclic cyclobutanes and azetidine systems (**23**–**26**, 49–68% yield). In the context of acyclic systems, we found that both secondary and primary centers gave the desired products in good yield (**27** and **28**, 62 and 70% yield, respectively). Surprisingly, anilines such as **16**, **25**, and **28** are well-tolerated in this protocol, despite their established capacity for amine oxidation under photocatalytic conditions.[24]

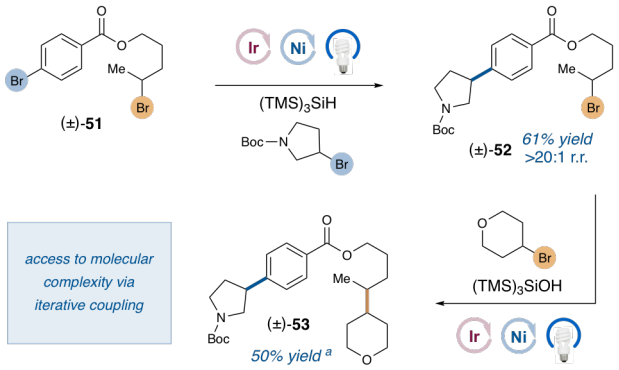
Having examined the scope of C_{sp}^3–methylation, we next turned our attention to the capacity of this protocol to introduce a range of small alkyl groups onto the drug-like 3-acyl pyridinyl piperidine bromide **14** (Table 2). From the outset we were pleased to find that ethyl and other primary long-chain aliphatic bromides that incorporate esters, free alcohols, alkenes, epoxides, and basic pyridine moieties could be readily implemented in good to excellent efficiency (**29**–**34**, 44–78% yield). Given the importance of small cyclic systems in pharmaceutical synthesis, we were delighted to find that strained cyclic alkanes can be readily employed to forge the desired C_{sp}^3–C_{sp}^3 bond between two aliphatic ring systems (**35** and **36**, 40 and 67% yield, respectively). Moreover, functionalized cyclobutanes and four-membered heterocycles can be introduced efficiently, allowing for modular access to a variety of strained C_{sp}^3 rich bicyclic motifs (**37**–**40**, 50–71% yield). Notably, larger ring systems can be readily installed using this new coupling protocol, including cyclopentyl, piperidinyl, and THP fragments (**41**–**43**, 45–57% yield). Perhaps most important, we were able to couple an isopropyl group (**44**, 42% yield) without the formation of isomeric alkyl products. As a critical aspect of this experiment, the use of a tridentate PyBOX (**L1**)-ligated Ni(II) catalyst successfully prevented metal-alkyl bond isomerization, which frequently leads to the predominant formation of *n*-propylated adducts in palladium and nickel catalyzed cross-couplings.[25] Indeed, given the difficulty of coupling two secondary aliphatic centers, we were pleased to observe that this catalytic protocol can be extended to a range of methine-bearing halides of varying structural complexity (**35**–**44**). As further demonstrated in Table 3, the reaction was generically successful for strained ring systems, such as azetidine and oxetane (**45** and **46**, 50 and 60% yield, respectively), as well as for larger six- and five-membered rings (**47**–**49**, 56–58% yield). Remarkably, coupling of two acyclic secondary centers was also possible using this technology (**50**, 62% yield). We believe that these results demonstrate the first broadly general approach to cross-electrophile coupling of two secondary aliphatic carbon centers.

Table 3: Scope for coupling of secondary aliphatic centers[a]



[a]Yields isolated unless otherwise noted. Only a small amount (<5%) of homodimerization of the limiting reagent was observed. Reactions performed with 2-5 equiv small halide, 3 equiv Na_2CO_3 and 2-3 equiv supersilanol. See SI for experimental details. [b]GC yields.

Scheme 3: Iterative coupling sequence



[a]Only a small amount (<5%) of homodimerization of the limiting reagent was observed. 1:1 d.r.

Finally, we sought to investigate the capacity to iteratively build drug-like molecular complexity in a highly expeditious yet modular fashion via the combination of aryl-alkyl and alkyl-alkyl cross-electrophile technologies. To this end, we prepared compound **51**, which contains both an aromatic and an aliphatic bromide moiety (Scheme 3). Using the conditions previously published by our lab for metallaphotocatalytic halogen abstraction C_{sp}^2–C_{sp}^3 coupling,[14] it was possible to selectively and efficiently introduce a pyrrolidine ring onto the aromatic ring (compound **52**, 61% yield), while leaving the aliphatic bromide group intact. Subjection of the resulting alkyl bromide **52** and 4-bromotetrahydropyran to the protocol outlined herein, resulted in selective C_{sp}^3–C_{sp}^3 coupling to give the drug-like adduct **53** in useful yield. These results further demonstrate the exquisite functional group tolerance and chemoselectivity of photocatalytic cross-electrophile coupling as well as its potential for application to complex target synthesis.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: (link to DOI)
Experimental details and characterization data

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Notes

The authors declare no competing financial interests.

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(22) We also recognize that an alternative pathway could be operative wherein Ni(0)-mediated oxidative addition and trapping of the alkyl radical **7** by a Ni(II) species could lead to the desired product via the same Ni(III) intermediate depicted in Scheme 2. Furthermore, in the case of small alkyl electrophiles other than methyl tosylate, it is possible that alternative mechanisms involving radical intermediates from both partners may be operative. Either of these potential pathways would alleviate the need for a challenging second oxidative addition, which might explain the ability of this system to couple secondary centers. Studies to elucidate the mechanism(s) of action are currently underway.

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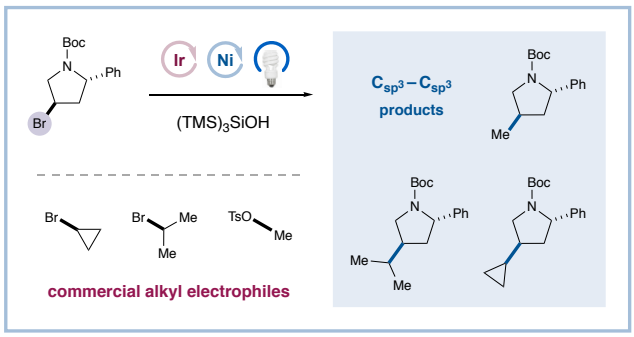
TOC Graphic:


Boc
N
Ph
Br
Ir
Ni
(TMS)3SiOH
Csp3 – Csp3
products
Me
commercial alkyl electrophiles
TsO