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# Metallaphotoredox-Catalyzed Cross-Electrophile $C_{sp^3}$—$C_{sp^3}$ Coupling of Aliphatic Bromides

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## 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]

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Supporting Information

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Experimental details and characterization data (PDF)

The authors declare no competing financial interest.

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 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 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.

On the basis of 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 ($\tau = 2.3\ \mu s$)[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 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-acylpyridinyl 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 tetrabuty-lammonium 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 excellent 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-acylpyridinyl 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 crosselectrophile coupling of two secondary aliphatic carbon centers.

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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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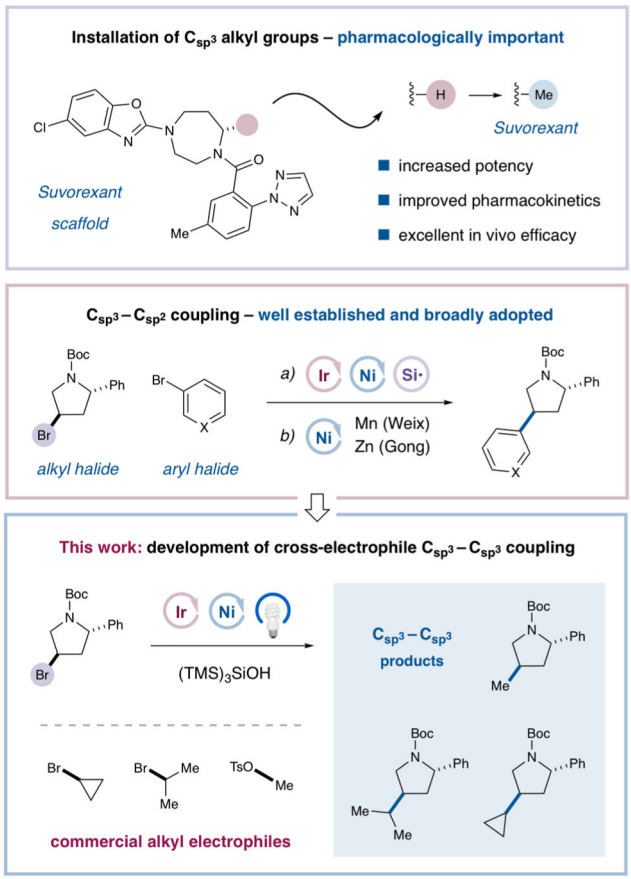
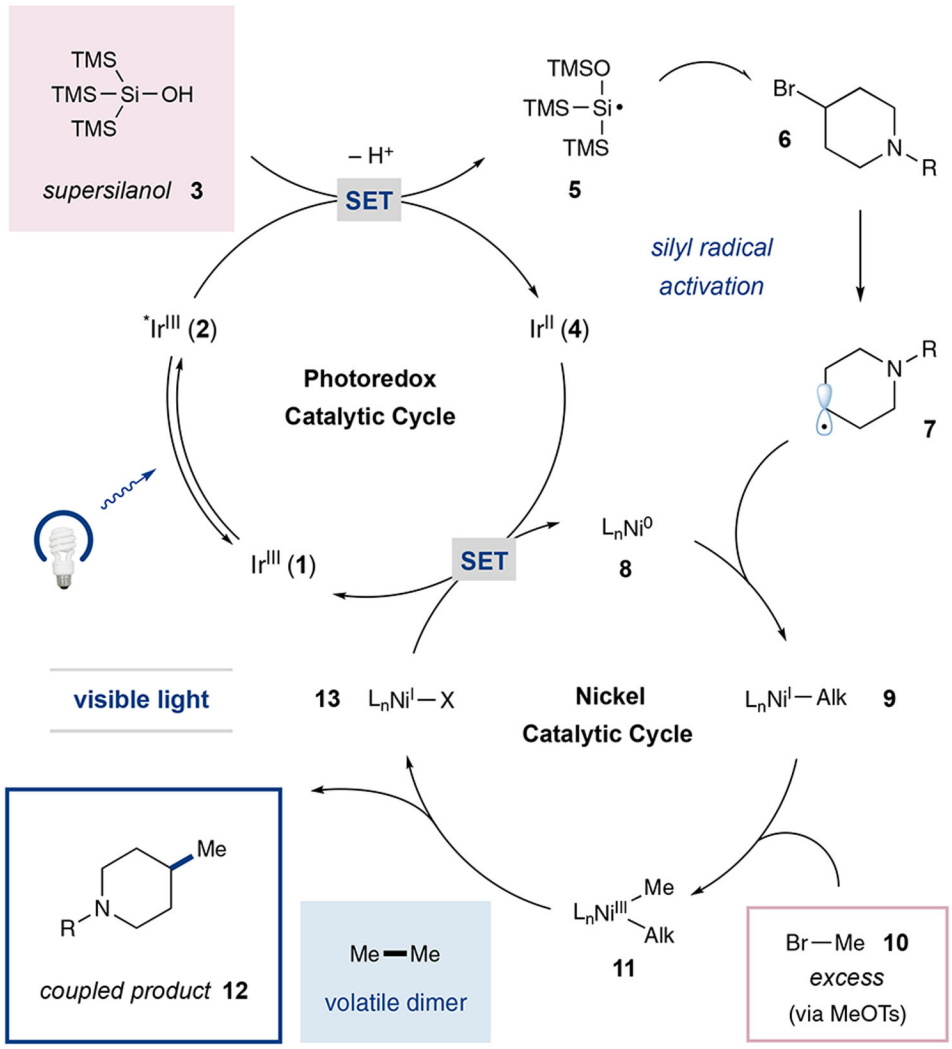
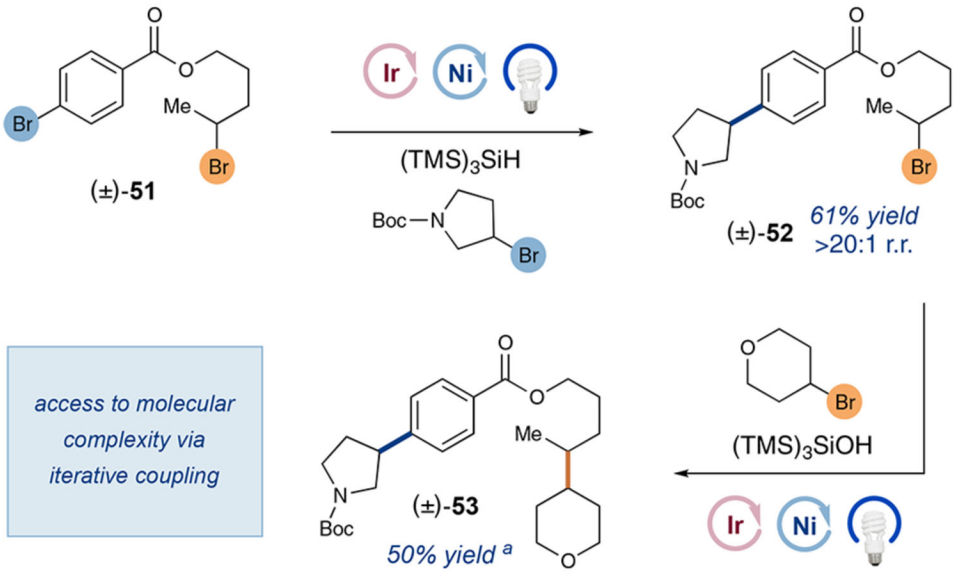



**Scheme 1.**
Small Alkyl Group Installation via Halide Coupling




**Scheme 2.**
Plausible Mechanism for Reductive Methylation




**Scheme 3.**

Iterative Coupling Sequence

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

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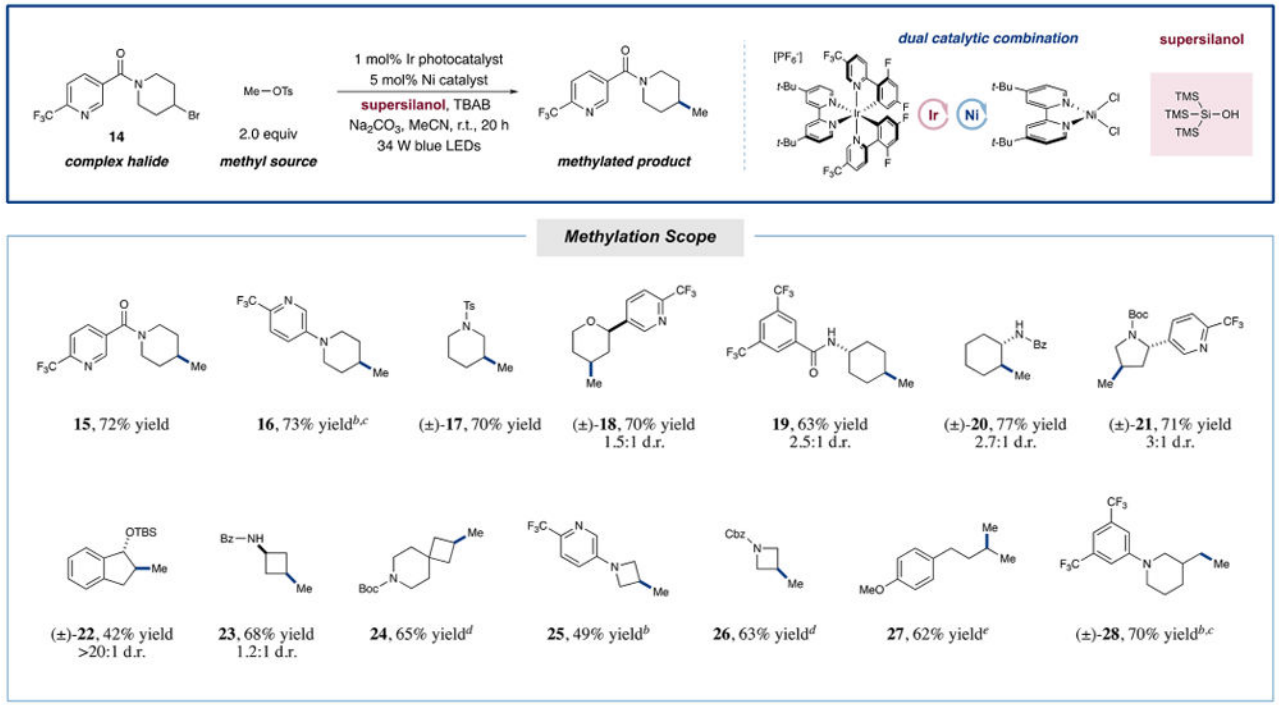
**Table 1.**

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 equiv $Na_2CO_3$ used.

[d]$K_3PO_4$ as base.

[e]GC yield.

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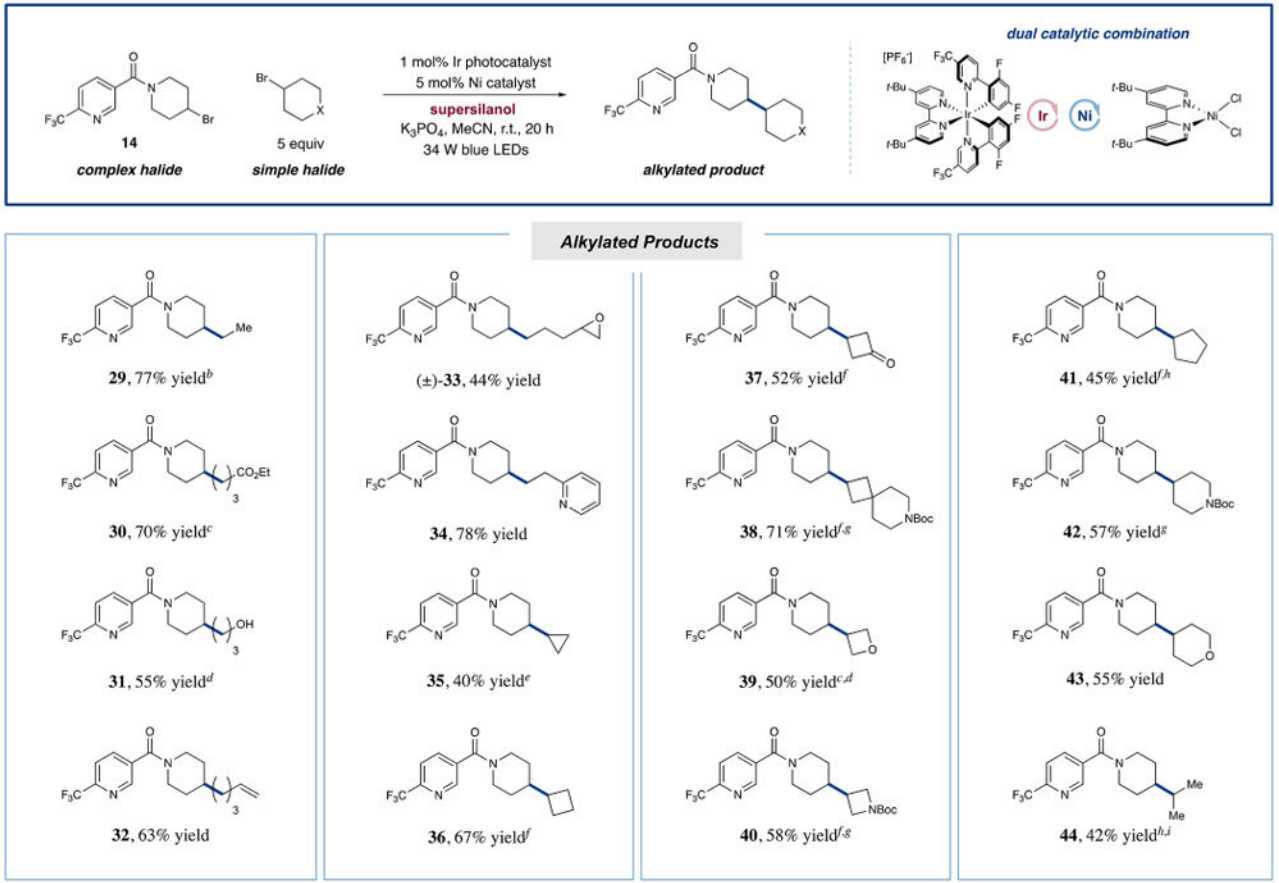
**Table 2.**

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.

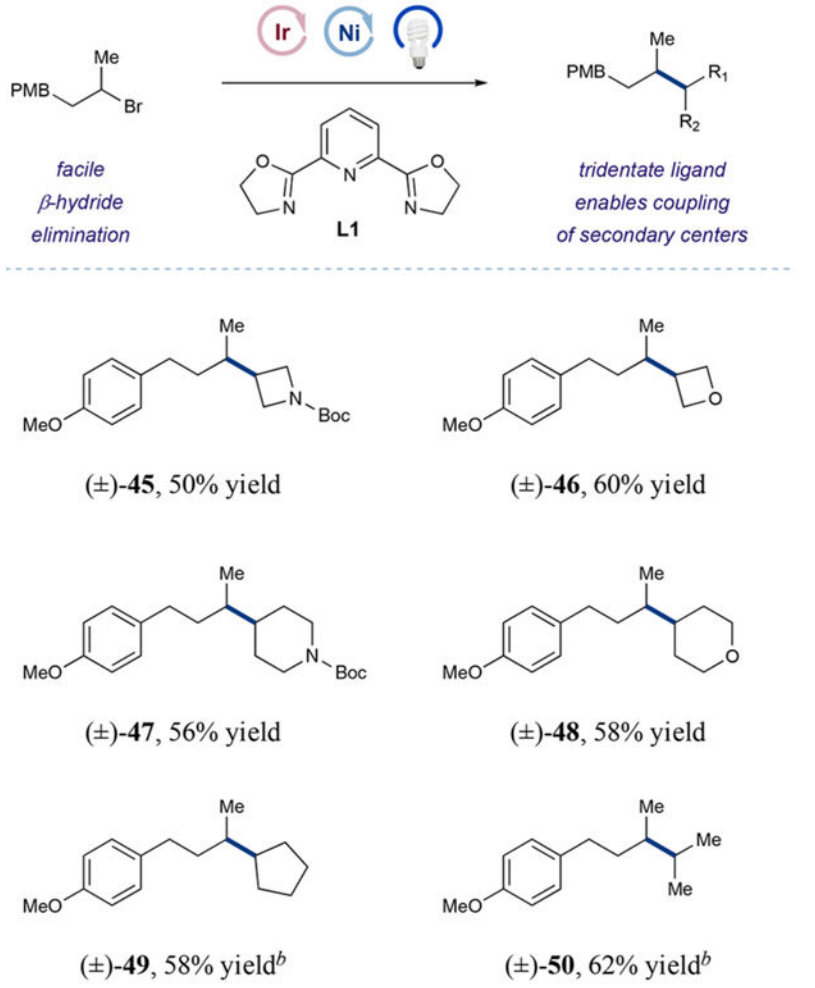
[g] 3 equiv small halide.

[h] Using PyBOX **L1** (*vide infra*) as ligand.

[i] 6 equiv small halide.

**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.