Communication

Cross-Electrophile Coupling of Unactivated Alkyl Chlorides

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Cross-Electrophile Coupling of Unactivated Alkyl Chlorides

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Supporting Information Placeholder

ABSTRACT: Alkyl chlorides are bench-stable chemical feedstocks that remain among the most underutilized electrophile classes in transition metal catalysis. Overcoming intrinsic limitations of C(sp^3)–Cl bond activation, we report the development of a novel organosilane reagent that can participate in chlorine atom abstraction under mild photocatalytic conditions. In particular, we describe the application of this mechanism to a dual nickel/photoredox catalytic protocol that enables the first cross-electrophile coupling of unactivated alkyl chlorides and aryl chlorides. Employing these low toxicity, abundant, and commercially available organochloride building blocks, this methodology allows access to a broad array of highly functionalized C(sp^2)–C(sp^3) coupled adducts, including numerous drug analogs.

Nickel-catalyzed cross-electrophile coupling has become a well-accepted and powerful strategy for the rapid assembly of C(sp^3)-rich drug-like molecules, permitting convergent access to novel chemical space while introducing desirable physicochemical and pharmacokinetic properties.[1] Seminal studies by Weix, Gong, Reisman, and others have established the viability and synthetic utility of this approach, wherein a metal reductant such as Zn or Mn obviates the requirement for prefunctionalized, and in many cases air-sensitive, organometallic reagents.[2,3] In 2016, our laboratory disclosed an alternative strategy for the cross-electrophile coupling of aryl bromides and alkyl bromides via the use of silane-mediated bromine atom abstraction in combination with dual nickel/photoredox catalysis.[4,5] Under these robust and mild conditions, a broad collection of C(sp^2)–C(sp^3) coupled products can be prepared in high efficiency, and this methodology has witnessed widespread application throughout the pharmaceutical sector, driven primarily by its degree of success with drug-like substrates.[6] Following these initial reports, a number of cross-electrophile protocols have leveraged silane-mediated halogen atom abstraction[7] in a series of novel transformations that include alkyl–alkyl coupling, trifluoromethylation, alkyl fluorination, as well as alkene hydrosulfamoylation.[8,9]

Given the impact and widespread application of cross-electrophile coupling technologies, it is remarkable to consider that simple alkyl chlorides remain effectively unknown as viable reaction partners,[10] with the vast majority of systems utilizing C(sp^3)–bromides,[11] iodides,[12]

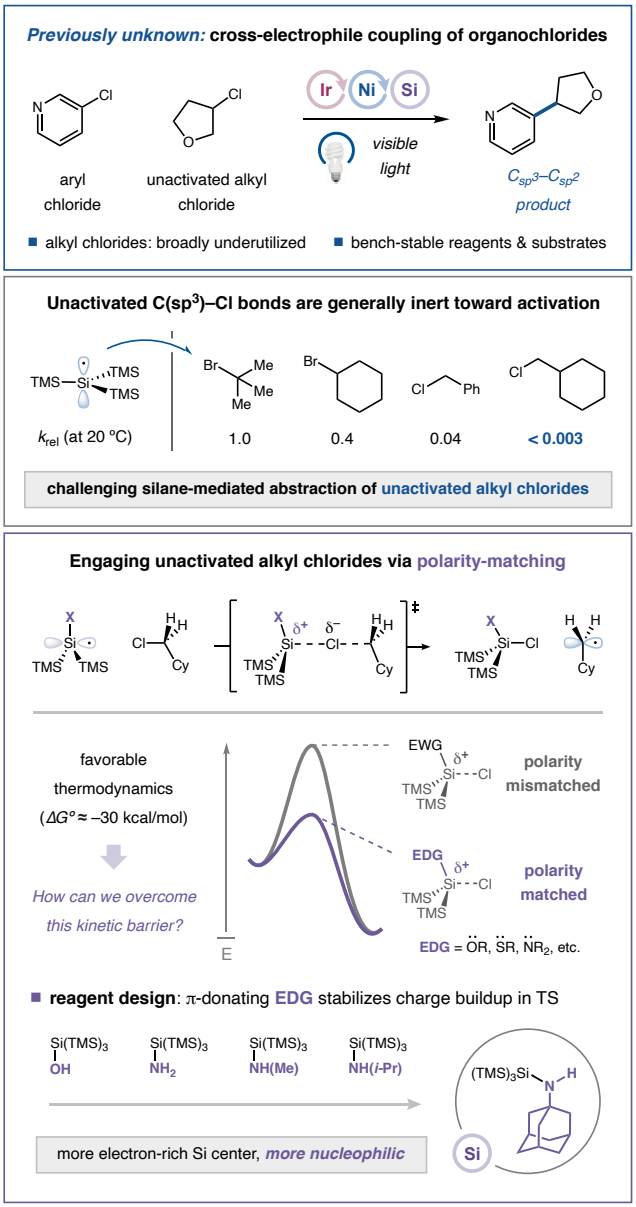


Figure 1. Cross-electrophile coupling of organic chlorides

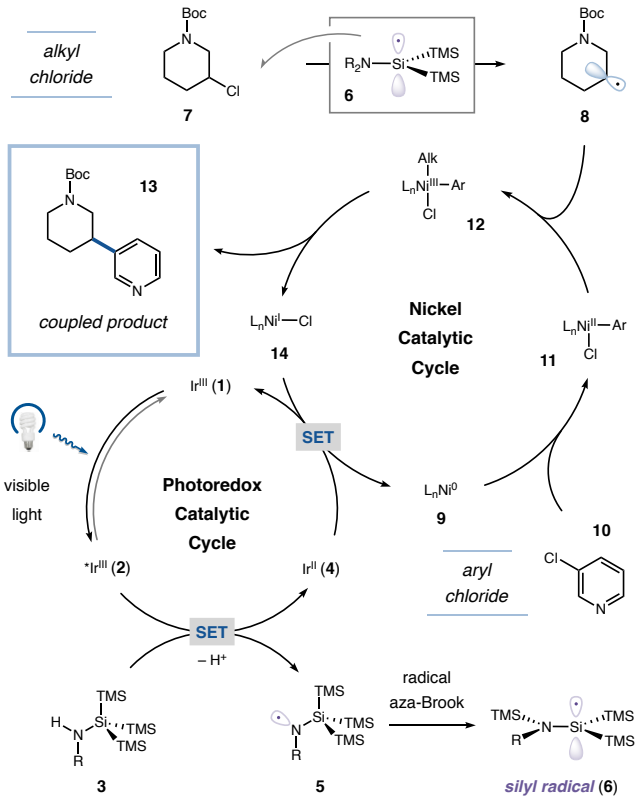


Figure 2. Design plan for cross-electrophile coupling

and sulfonates.[13] In comparison, the use of organochlorides offers a host of chemical, safety, and economic advantages that include: (i) abundant and diverse structural representation across both commercial and natural sources;[14] (ii) reduced toxicity (e.g., as carcinogens) in comparison to most available electrophiles;[15] (iii) chemical stability, with respect to handling, and tolerance in multistep sequences;[16] and (iv) low sourcing and production costs on scale.[17] In practice, however, the benefits arising from the intrinsic chemical stability of alkyl chlorides have prohibited their implementation in nickel-catalyzed cross-electrophile couplings.[18] Within the realm of metal reductant-mediated nickel catalysis, strong C(sp^3)–Cl bonds prevent the necessary oxidative addition steps, while the accompanying reduction potentials preclude outer-sphere electron-transfer.[19] Moreover, within photoredox pathways, the low polarizability of the C–Cl bond kinetically retards chlorine atom transfer in the silyl abstraction event (a step that would otherwise be highly exergonic).[7c] For example, an aliphatic bromide will typically undergo halogen atom abstraction by supersilyl radical with a rate that is several orders of magnitude faster than the corresponding alkyl chloride (Figure 1). To overcome these limitations, we recently sought to employ polarity matching as a design element for the development of new silane reagents in an effort to significantly lower the kinetic barrier to chlorine atom transfer.[20] Herein, we report the successful implementation of these ideals and present the first examples of nickel cross-electrophile coupling using abundant, less toxic, and inexpensive alkyl chlorides.

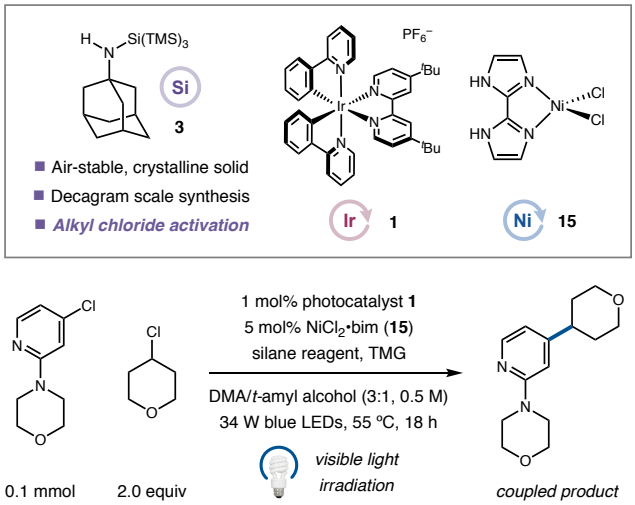
Design plan. Given the inherent kinetic challenges associated with radical-mediated C(sp^3)–Cl activation, we questioned whether we could induce an increased polarity-matching effect between an unactivated C–Cl bond and the silyl abstraction reagent via judicious selection of substituents that would impose increased electron density on an open-shell silicon species. Recognizing that π-donors are well-established to increase the nucleophilic character of adjacent spin-centers, we hypothesized that the incorporation of a heteroatom (i.e., nitrogen)[21] into the silane reagent might significantly improve its polarity complementarity with C–Cl bonds and thereby dramatically lower the barrier to chlorine atom abstraction. Moreover, we envisioned that a bulky *N*-alkyl substituent could significantly improve the electron-releasing capacity of the nitrogen donor via induction while simultaneously conferring hydrolytic stability to the labile Si–N bond.[22] To this end, we disclose the discovery and development of novel organosilicon reagents that fulfill these design criteria, and we highlight the value of silane **3**, a 1-adamantylamine-substituted supersilyl agent that is benchstable, inexpensive, and broadly useful for photocatalytic alkyl chloride activation (Table 1).

A proposed mechanism for this new cross-chloride coupling is described in Figure 2.[23] Upon irradiation with visible light, the photocatalyst [Ir(ppy)$_2$(dtbbpy)](PF$_6$) (**1**) is known to access the long-lived triplet excited state **2**.[24] Central to our reaction design, we envisioned that this mildly-oxidizing species ($E_{1/2}^{red}$ [$^*Ir^{III}/Ir^{II}$] = +0.76 V vs saturated calomel electrode (SCE) in DMA/*t*-amyl alcohol; see Supporting Information (SI)) should engage a suitable silane reagent (**3**) in single-electron transfer (SET) to furnish the reduced Ir^{II} complex **4** and *N*-centered radical **5**. Subsequent radical aza-Brook rearrangement[25] would unveil the electron-rich α-amino silicon-centered radical **6**, which is poised to readily abstract a chlorine atom from an aliphatic chloride **7** to furnish the corresponding alkyl radical **8**. At the same time, low-valent Ni^0 catalyst **9** is expected to undergo oxidative addition into aryl chloride **10** to afford Ni^{II}-aryl intermediate **11**. Oxidative radical capture of the open-shell alkyl species **8** would deliver Ni^{III}-(alkyl)(aryl) complex **12**, which upon reductive elimination should release the desired C(sp^2)–C(sp^3) product **13**. Finally, single-electron reduction of the resulting Ni^I intermediate **14** by the Ir^{II} species **4** ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = –1.38 V vs SCE in DMA/*t*-amyl alcohol) closes both catalytic cycles, simultaneously regenerating the ground-state photocatalyst **1** and the Ni^0 catalyst **9**.

Optimization and reaction scope. Following an extensive survey of various supersilane derivatives,

catalysts, and solvents, we determined that under optimal conditions (photocatalyst **1** (1 mol%), $NiCl_2$•bim[26] **15** (5 mol%), and TMG as base), the 1-adamantyl aminosilane reagent **3** facilitates a cross-electrophile coupling mechanism that provides the desired product in excellent yield (Table 1, entry 1, 73% yield). The highly crystalline aminosilane reagent **3** can now be purchased (MilliporeSigma, #915319) or be easily prepared in a single step from commercial materials on a decagram scale (see SI), and all other reagents and catalysts are commercially available. Importantly, reagent **3** was found to have a relatively low oxidation potential (E_{pa} = +0.86 V vs SCE in DMA/*t*-amyl alcohol), which permits activation by excited photocatalyst **2** via SET under mild conditions, consistent with excited-state potentials and Stern-Volmer quenching experiments (see Figure S8). Subsequent rearrangement pathways[27] were interrogated through a series of computational studies using density functional theory, which established the feasibility of our proposed aza-Brook rearrangement (see Figure S9 and accompanying discussion). The *t*-butylamine-derived supersilane performs comparably (entry 2), but due to operational difficulties in handling this waxy solid, the crystalline 1-adamantylamine derivative (see Figure S2 for X-ray structure) was selected as the reagent of choice. Consistent with our design hypothesis, the introduction of less electron-rich amines resulted in substantially diminished reaction efficiencies (entries 3 and 4), while silane reagents previously used in photoredox cross-electrophile coupling (i.e., supersilanol and supersilane) were ineffective at alkyl chloride activation under all conditions employed (entries 5 and 6). Decreased yields were also observed when DMA was used without a co-solvent (entry 7) or when $NiCl_2$•dtbbpy was used in lieu of **15** (entry 8). Control experiments established that the iridium photocatalyst, light, aminosilane reagent, and nickel catalyst were all necessary for product formation (entries 9–12).

Table 1. Control Reactions of Optimized Conditions[a]



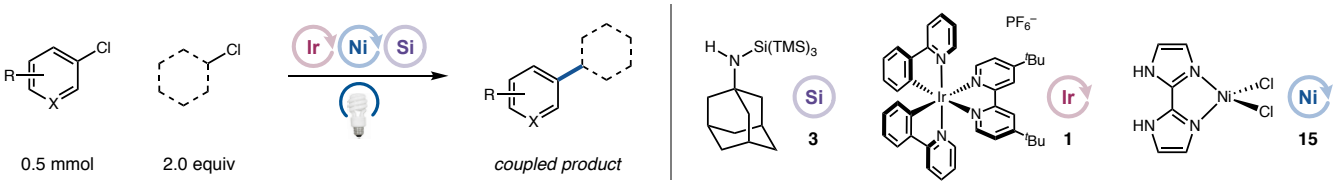
entry	conditions	silane	yield[b]
1	as above	**3**	73%
2	as above	$TMS_3SiNH(^tBu)$	72%
3	as above	$TMS_3SiNH(^iPr)$	45%
4	as above	$TMS_3SiNH(^nBu)$	30%
5	as above	TMS_3SiOH	0% (100%)[c]
6	as above	TMS_3SiH	0% (77%)[c]
7	DMA as solvent	**3**	60%
8	4,4′-dtbbpy as ligand	**3**	20%
9	no photocatalyst	**3**	0%
10	no nickel catalyst	**3**	0%
11	no silane	none	0%
12	no light	**3**	0%

[a]Performed with silane reagent (1.2 equiv), TMG (3.0 equiv), aryl chloride (0.1 mmol), and alkyl chloride (2.0 equiv) in DMA/*t*-amyl alcohol (3:1, 0.5 M) without fans. [b]Yields determined by ^{1}H NMR using mesitylene as internal standard. See SI for experimental details. [c]Recovery of alkyl chloride in parenthesis. bim, 2,2′-biimidazole; TMG, 1,1,3,3-tetramethylguanidine. DMA, *N,N*-dimethylacetamide.

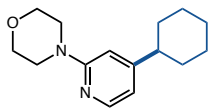
With these optimized conditions in hand, we directed our studies toward exploring the scope of this organochloride cross-electrophile coupling. As summarized in Table 2, we were delighted to find that our silyl-radical activation approach served as a broadly applicable platform for coupling a wide array of alkyl chlorides and aryl chlorides. With respect to the alkyl chloride coupling partner, a variety of five-, six-, and seven-membered cyclic systems performed well (**16**–**20**, 66–77% yield). Secondary acyclic alkyl chlorides, as well as hindered bridged bicyclic and neopentyl substrates, were also found to be competent electrophiles (**21**–**23**, 66–77% yield). While halogen atom abstraction from primary alkyl chlorides was anticipated to be kinetically challenging based on literature precedent,[7c] we were pleased to find that a number of functionalized primary substrates could be successfully engaged in our coupling methodology. In particular, alkyl chloride partners containing cyclic and acyclic ethers can be employed to access the desired $C(sp^2)$–$C(sp^3)$ adducts in good yield (**24** and **25**, 72% and 57% yield, respectively). Gratifyingly, electrophilic moieties, such as esters, nitriles, and ketones, were also well-tolerated under our standard protocol (**26–28**, 58–62% yield). Moreover, alkyl fragments incorporating protected functional groups were successfully introduced, including primary alcohols, aldehydes, and vicinal diols (**29–31**, 61–74% yield). Notably, aliphatic substrates containing nitrogen heteroarenes can also be coupled with useful efficiencies (e.g., **32**, 64% yield).

Next, we turned our attention to the scope of the aryl chloride coupling partner. Our investigations revealed

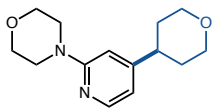
Table 2. Scope of Silane-Mediated Cross-Electrophile Coupling of Unactivated Alkyl Chlorides and Aryl Chlorides[a]



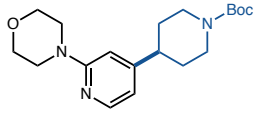
alkyl chloride scope



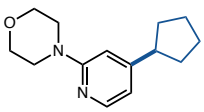
16, 68% yield[b]



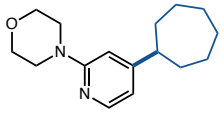
17, 73% yield[b]



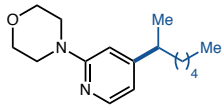
18, 77% yield[b]



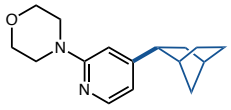
19, 69% yield[b,c]



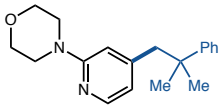
20, 66% yield[b,c]



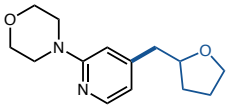
(±)-21, 77% yield



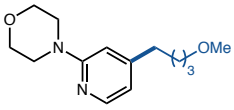
(±)-22, 76% yield[d]



23, 66% yield

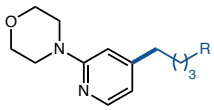


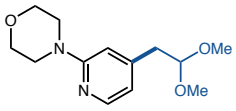
(±)-24, 72% yield[b]



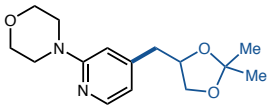
25, 57% yield[b]

R = CO_2Me, **26**, 62% yield[b]
CN, **27**, 61% yield[b]
C(O)Me, **28**, 58% yield[b,c]
OAc, **29**, 61% yield[b]

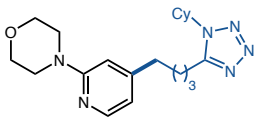




30, 71% yield[b]



(±)-31, 74% yield[b,c]

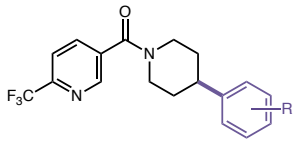


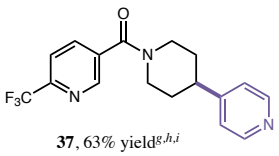
32, 64% yield[e]

(hetero)aryl chloride scope

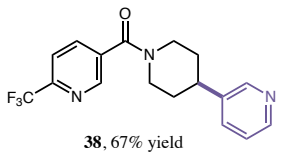
★ not available as aryl bromide

R = *p*-*t*-Bu, **33**, 73% yield[f–i]
p-OMe, **34**, 62% yield[f–i]
m-CO_2Me, **35**, 73% yield[g,h]
p-C(O)NH(*t*-Bu), **36**, 75% yield[g,h]

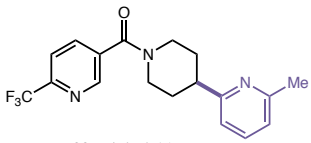




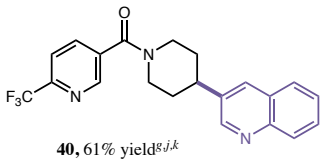
37, 63% yield[g,h,i]



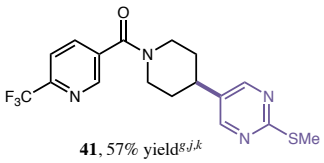
38, 67% yield



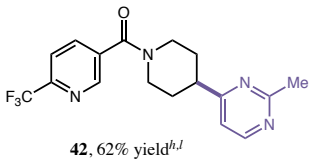
39, 74% yield



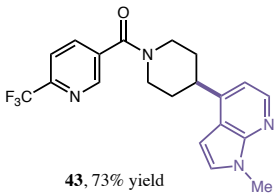
40, 61% yield[g,j,k]



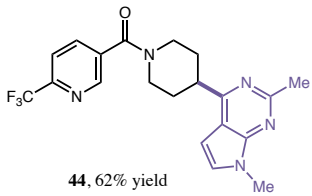
41, 57% yield[g,j,k]



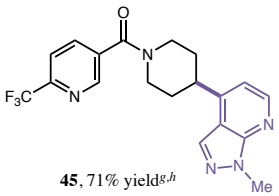
42, 62% yield[h,l]



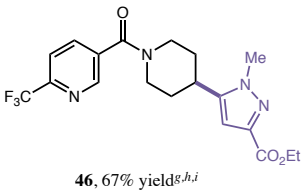
43, 73% yield



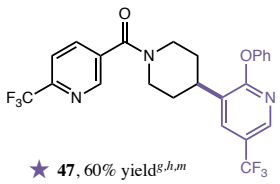
44, 62% yield



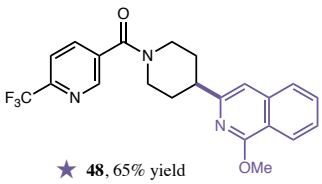
45, 71% yield[g,h]



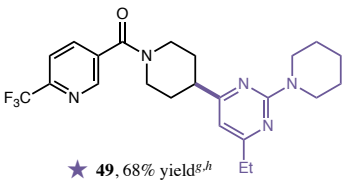
46, 67% yield[g,h,i]



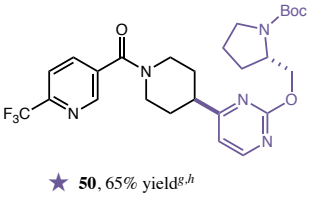
★ **47**, 60% yield[g,h,m]



★ **48**, 65% yield



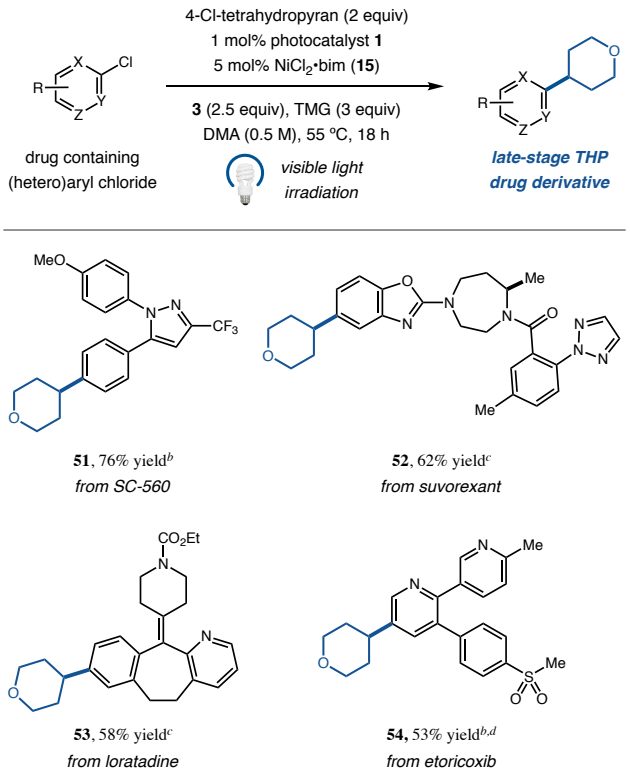
★ **49**, 68% yield[g,h]



★ **50**, 65% yield[g,h]

[a]All yields are isolated. Photocatalyst **1** (1 mol%), $NiCl_2$•bim (5 mol%), aminosilane reagent **3** (1.2 equiv), TMG (3.0 equiv), aryl chloride (0.5 mmol), and alkyl chloride (1.0 mmol) were irradiated by blue LEDs in DMA/*t*-amyl alcohol (3:1, 0.5 M) without fans, equilibrating at 50–55 °C. [b]4,4′,5,5′-tetramethyl-2,2′-biimidazole as ligand. [c]3 mol% Ni catalyst and 0.6 mol% photocatalyst. [d]dr > 20:1. [e]10 mol% nickel and 2 mol% photocatalyst. [f]2,2′-bibenzimidazole as ligand. [g]BTMG (3.0 equiv) as base. [h]2.5 equiv **3**. [i]DMA (0.5 M) as solvent. [j]DMA/t-amyl alcohol (3:1, 1.0 M) as solvent. [k][Ir(dF(H)ppy)$_2$(dtbbpy)](PF_6) as photocatalyst. [l]DMA/t-amyl alcohol (1:2, 0.3 M) as solvent. [m][Ir(dF(Me)ppy)$_2$(dtbbpy)](PF_6) as photocatalyst.

Table 3. Application to Late-Stage Functionalization[a]



[a]Isolated yields for reactions performed on 0.5 mmol scale. [b]In DMA/t-amyl alcohol (3:1, 0.5 M). [c]With 2,2′-bi-1H-benzimidazole as ligand. [d]With 3 equiv TMG and 1.25 equiv **3**.

that both electron-rich and electron-deficient chlorobenzene derivatives could be employed to provide the corresponding adducts in good yield (**33**–**36**, 65–75% yield). Given the abundance of heteroarene substructures in pharmaceutical agents,[28] we were delighted to find that 2-, 3-, and 4-chloropyridines, as well as extended aromatic systems such as quinoline, could be readily alkylated with good efficiency (**37–40**, 61–72% yield). Pyrimidines with diverse substitution patterns were also competent aryl electrophiles, enabling access to diazine products (**41** and **42**, 57% and 62% yield, respectively). In addition, we were pleased to find that nitrogen-abundant heteroaryl fragments, such as azaindole, pyrrolopyrimidine, and azaindazole, were combined with the parent alkyl chloride scaffold without difficulty (**43–45**, 62–73% yield). Five-membered heterocycles such as pyrazole could also be coupled with good yield using this new protocol (**46**, 67% yield). Perhaps most notable, a number of heteroaryl chlorides could be readily employed for which the corresponding aryl bromides are not commercially available (designated by ★), illustrating the immediate utility of this approach in preparing value-added products from synthetically accessible precursors (**47–50**, 60–68% yield). Finally, in an effort to demonstrate the applicability of our method to the late-stage elaboration of drug-like molecules, we tested several known medicinal agents and drug candidates containing aryl chlorides in this new transformation. As shown in Table 3, we were delighted to find that the desired C(sp^2)–C(sp^3) adducts could be formed in good yield (**51–54**, 53–76% yield), illustrating the compatibility of our reaction with medicinally relevant functional groups such as triazoles, amides, sulfones, and carbamates. These results further support the generic utility of our method for application in medicinal chemistry settings.[29]

In summary, we have developed the first general cross-electrophile coupling of unactivated alkyl chlorides and aryl chlorides via the merger of nickel and photoredox catalysis. Our reaction conditions enable the formation of a broad range of C(sp^2)–C(sp^3) coupled products from widely abundant and bench-stable organic chlorides, including several drug derivatives. In particular, our approach has employed a novel 1-adamantyl aminosilane **3** that exploits polarity-matching effects to achieve the kinetically challenging halogen atom abstraction from unactivated alkyl chlorides. Mechanistic studies exploring the activation of the reagent and subsequent chlorine atom abstraction are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data (PDF)

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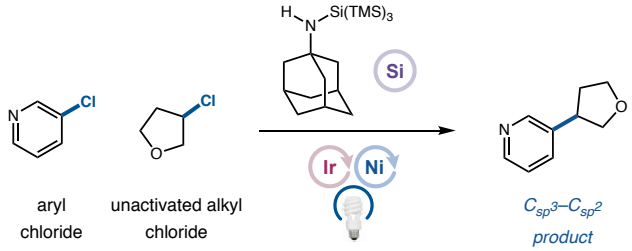
TOC Graphic


H
N
Si(TMS)3
Si
Cl
N
Cl
O
Ir
Ni
N
O
aryl chloride
unactivated alkyl chloride
C_{sp^3}–C_{sp^2} product