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A Metallaphotoredox Strategy for the Cross-Electrophile Coupling of α-Chloro Carbonyls with Aryl Halides

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Abstract: *Here, we demonstrate that a metallaphotoredox-catalyzed cross-electrophile coupling mechanism provides a unified method for the α-arylation of diverse activated alkyl chlorides, including α-chloroketones, α-chloroesters, α-chloroamides, α-chlorocarboxylic acids, and benzylic chlorides. This strategy, which is effective for a wide variety of aryl bromide coupling partners, is predicated upon a halogen atom abstraction/nickel radical-capture mechanism that is generically successful across an extensive range of carbonyl substrates. The construction and use of arylacetic acid products have further enabled two-step protocols for the delivery of valuable building blocks for medicinal chemistry, such as aryldifluoromethyl and diarylmethane motifs.*

Alpha-aryl carbonyl groups—including α-aryl-esters, amides, and ketones—are important structural motifs found widely among medicinal agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and naturally occurring alkaloids.[1] Canonical methods to access these α-aryl carbonyl motifs traditionally rely on the formation and coupling of nucleophilic enolates with electrophilic metal-aryl salts derived from numerous aryl halide/metal catalyst combinations.[2,3] More recently, palladium- and nickel-catalyzed cross-couplings of α-halocarbonyl electrophiles with aryl nucleophiles, such as boronic acids or organozinc reagents, have also been introduced.[4,5] Not surprisingly, these powerful methodologies employ a wide array of divergent reaction conditions based on the nature of the nucleophile/electrophile coupling partners involved. For example, with enolate couplings, the pK_a of the α-C–H bond varies significantly depending on the nature of the carbonyl motif (e.g., 22–27 for ketones versus 30–35 for amides in DMSO),[6] often requiring a change in the ligand/base combination for each C=O class employed. On this basis, we recognized an opportunity to design a complementary and unifying method for the direct α-arylation of carbonyls using a photo-mediated cross-electrophile coupling pathway. Herein, we describe an α-arylation protocol that employs α-halocarbonyls in a halogen atom abstraction/nickel radical-capture mechanism that is generically successful across an extensive range of carbonyl substrates.

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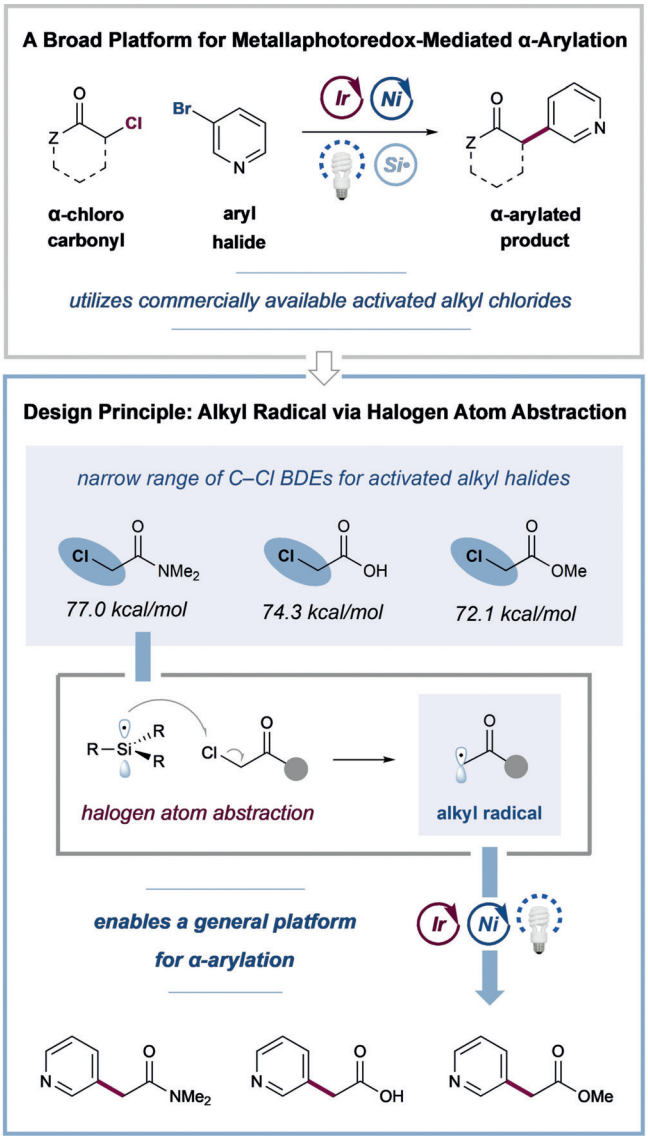
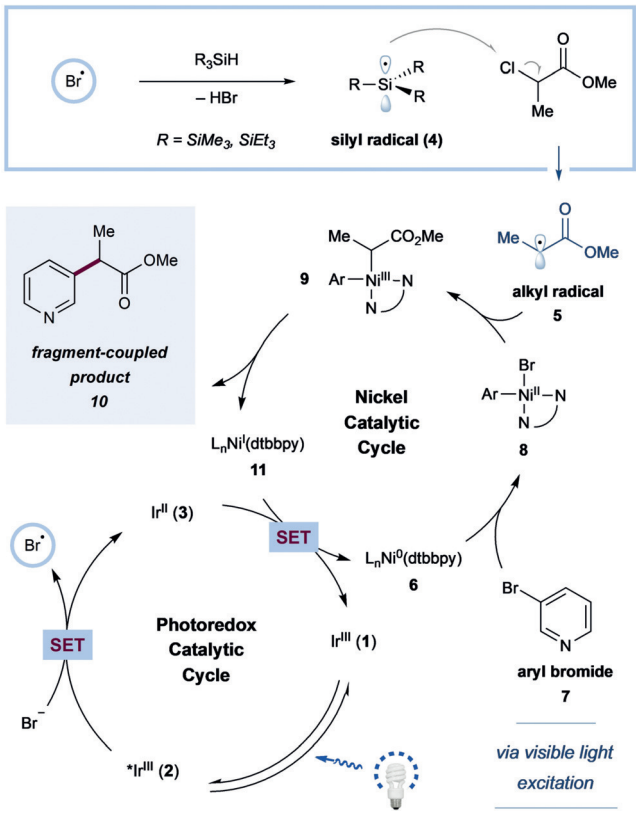
As highlighted in Scheme 1, our unifying strategy is founded upon the knowledge that carbon-chlorine bond dissociation energies (BDEs) for a wide range of α-chloro carbonyls fall within a narrow range (e.g., 74 kcal mol^{-1} for chloroacetic acid to 77 kcal mol^{-1} for chloroacetamides).[7] In addition, these C–Cl systems are expected to have bond polarization characteristics that are similar with respect to their influence on the kinetics of chlorine atom transfer pathways using silyl radicals. As such, we hypothesized that α-carbonyl radical formation via irreversible halogen atom



Scheme 1. Cross-electrophile coupling of α-chloro carbonyls.

abstraction using a silyl radical[8,9] should exhibit similar rates for a broad range of α-chloro C=O substrates. Furthermore, the resulting α-acyl radicals should readily combine with Ni^{II}(aryl) salts (derived from aryl halide oxidative addition) to enable α-arylation cross-coupling across a wide array of carbonyls, providing a generically useful reaction platform.

A proposed mechanism for this α-acyl cross-coupling is detailed in Scheme 2. Excitation of photoredox catalyst $[Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ (**1**) using visible light, followed

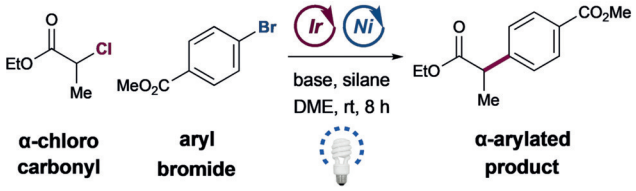


Scheme 2. Plausible mechanism for α-carbonyl arylation.

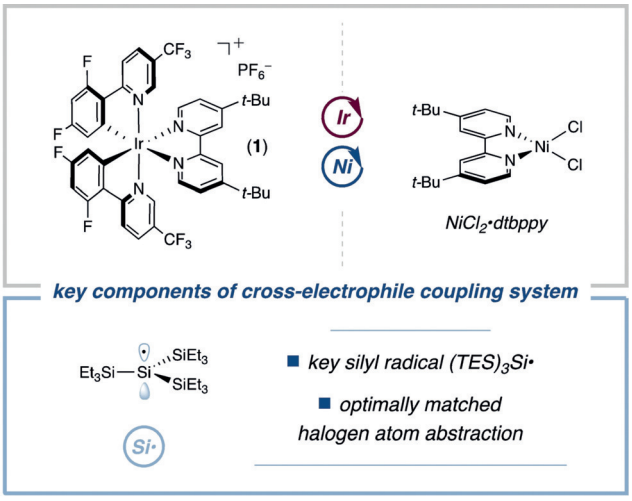
by intersystem crossing, leads to the strongly oxidizing triplet excited state (**2**) ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}] = +1.21$ V vs. saturated calomel electrode (SCE) in CH_3CN)[10] This photocatalyst excited state (**2**) should engage bromide anion (derived from the aryl bromide substrate) in an oxidation event ($E_{pa} = +0.80$ V vs. SCE in CH_3CN)[9] to deliver an electrophilic bromine radical, which is known to rapidly abstract a hydrogen atom from the silane Si–H moiety.[11] The resulting silyl radical **4** should rapidly participate in chlorine atom abstraction from the activated α-carbonyl chloride to generate electrophilic alkyl radical species **5**. Simultaneously, Ni^0 complex **6** is expected to undergo oxidative addition into aryl bromide **7** to generate the aryl–Ni^{II} intermediate **8**. Oxidative capture of α-acyl radical **5** would then deliver an (alkyl)(aryl)–Ni^{III} species (**9**) with the enolate being either the carbon- or oxygen-bound nickel adduct.[12] Subsequent reductive elimination from the carbon-bound form would then furnish the $C(sp^3)$–$C(sp^2)$ coupled product (**10**) and Ni^I species **11**. Finally, electron transfer between reduced Ir^{II} photocatalyst **3** ($E_{1/2}^{red}[Ir^{III}/Ir^{II}] = -1.37$ V vs. SCE in CH_3CN)[9] and the Ni^I salt (**11**) would reconstitute the Ni^0 complex **6** and the ground-state photocatalyst **1**, completing both catalytic cycles at the same time.

Initial studies into the new α-chloro carbonyl cross-electrophile coupling were performed with ethyl 2-chloropropionate, methyl 4-bromobenzoate, $[Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ **1** (1 mol%), $NiCl_2$·dtbbpy (5 mol%), and $(TMS)_3SiH$, with exposure to a 40 W blue LED light source in DME (Table 1, entry 1, 33% yield). Increasing the reaction concentration, photocatalyst loading, and changing the base to 2,6-lutidine proved to further benefit the overall reaction efficiency (entries 2–4). In contrast, initial investigations using 2-bromopropionate in lieu of the 2-chloro analog led to quantitative dehalogenation of the α-carbonyl substrate, with no desired product formation. Given that the rate of chlorine atom abstraction from an activated $C(sp^3)$–Cl bond via a $(TMS)_3Si^{\bullet}$ radical is two orders of magnitude slower than

Table 1: Cross-electrophile coupling optimization studies.[a]

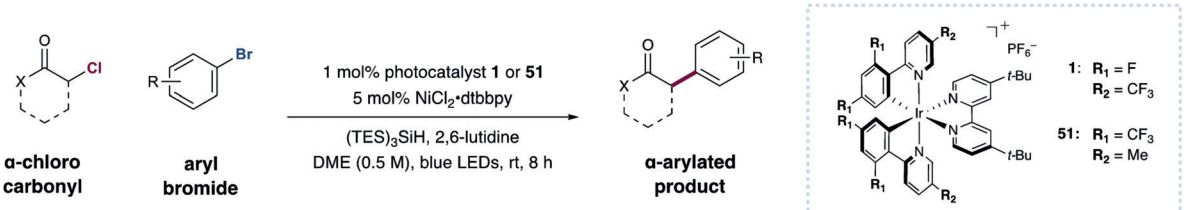


Entry	Conditions	Si source	Base	Yield
1	0.1 M	$(TMS)_3SiH$	LiOH	33%
2	0.1 M	$(TMS)_3SiH$	lutidine	48%
3	0.5 M	$(TMS)_3SiH$	lutidine	56%[b]
4	0.5 M	$(TMS)_3SiH$	lutidine	65%[c]
5	0.5 M	$(TES)_3SiH$	lutidine	80%[b]
6	no photocatalyst	$(TES)_3SiH$	lutidine	0%[b]
7	no light	$(TES)_3SiH$	lutidine	0%[b]
8	no silane	–	lutidine	0%[b]
9	no Ni	$(TES)_3SiH$	lutidine	0%[b]

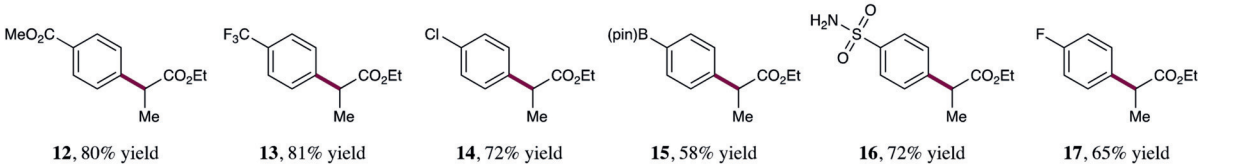


[a] Performed with photocatalyst **1** (1 mol%), $NiCl_2$·dtbbpy (5 mol%), silane (1.5 equiv.), base (1.1 equiv.), and alkyl chloride (1.5 equiv.) on 0.25 mmol scale in DME. Yields determined by ^1H NMR analysis vs. mesitylene. [b] Performed with 2.5 equiv. base. [c] Performed with 2 mol% photocatalyst **1**.

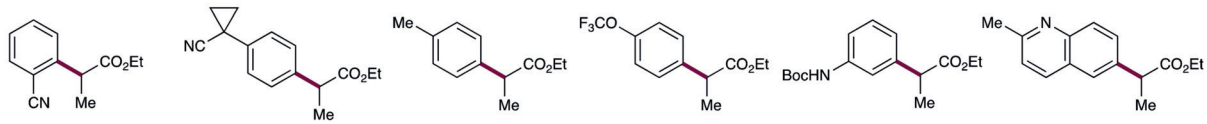
Table 2: Scope for the cross-electrophile coupling of activated α-carbonyl and benzyl chlorides with aryl halides.[a]



aryl bromides

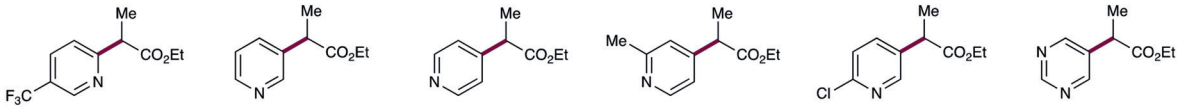


12, 80% yield; **13**, 81% yield; **14**, 72% yield; **15**, 58% yield; **16**, 72% yield; **17**, 65% yield

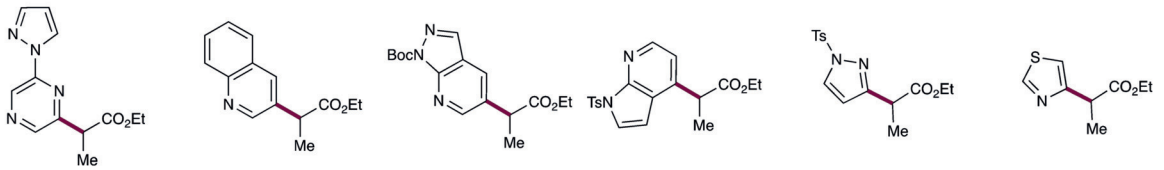


18, 54% yield[b,c]; **19**, 78% yield; **20**, 73% yield[c]; **21**, 71% yield; **22**, 83% yield; **23**, 71% yield

heteroaryl halides

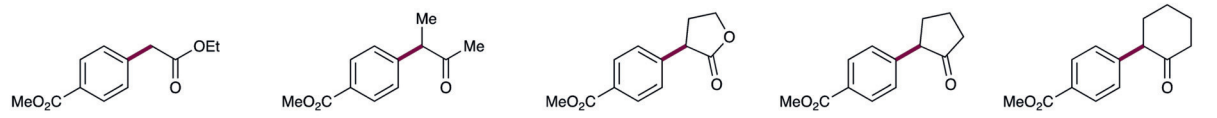


24, 53% yield[c,d]; **25**, 69% yield[c]; **26**, 68% yield[h]; **27**, 70% yield[h]; **28**, 72% yield[e]; **29**, 58% yield[c]

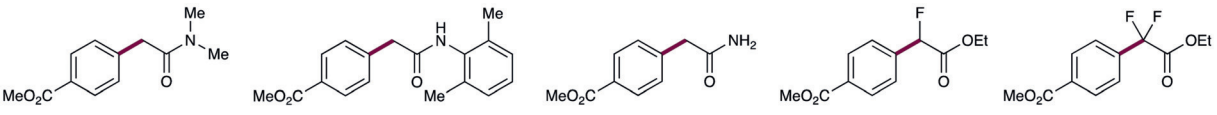


30, 68% yield[c,d]; **31**, 75% yield; **32**, 60% yield[h]; **33**, 58% yield[h]; **34**, 53% yield[h]; **35**, 45% yield[b]

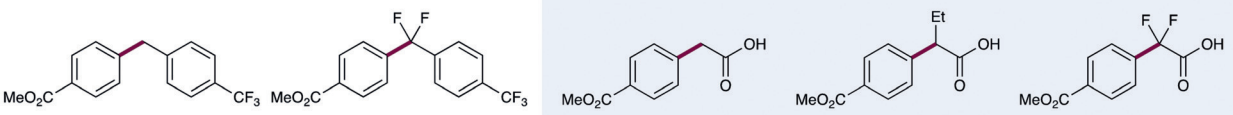
activated alkyl chlorides



36, 78% yield; **37**, 51% yield; **38**, 61% yield[c,f,g]; **39**, 75% yield[c,f,h]; **40**, 63% yield[c,f,h]



41, 55% yield; **42**, 57% yield; **43**, 55% yield; **44**, 71% yield; **45**, 75% yield[c]



46, 73% yield; **47**, 54% yield[c,f,i]; **48**, 65% yield[j]; **49**, 69% yield[c,j]; **50**, 67% yield[j]

[a] Reactions performed with 1.5 equiv. activated alkyl chloride, 1.5 equiv. $(TES)_3SiH$, and 2.5 equiv. 2,6-lutidine on 0.5 mmol scale. Yields isolated unless otherwise noted. [b] 1 mol% nickel catalyst. [c] With 0.25 M reaction concentration. [d] With aryl chloride and tetrabutylammonium bromide (0.05 equiv., see Supporting Information for discussion). [e] 5,5′-d(Me)bpy as ligand. [f] $[Ir[d(CF_3)(Me)ppy]_2(dtbbpy)]PF_6$ as photocatalyst. [g] NaOAc as base. [h] Na_2CO_3 as base. [i] Yield determined using ^{19}F NMR vs. 3,5-bis(trifluoromethyl)bromobenzene. [j] Using an in situ silyl masking protocol. See Supporting Information for additional substrates and for experimental details.

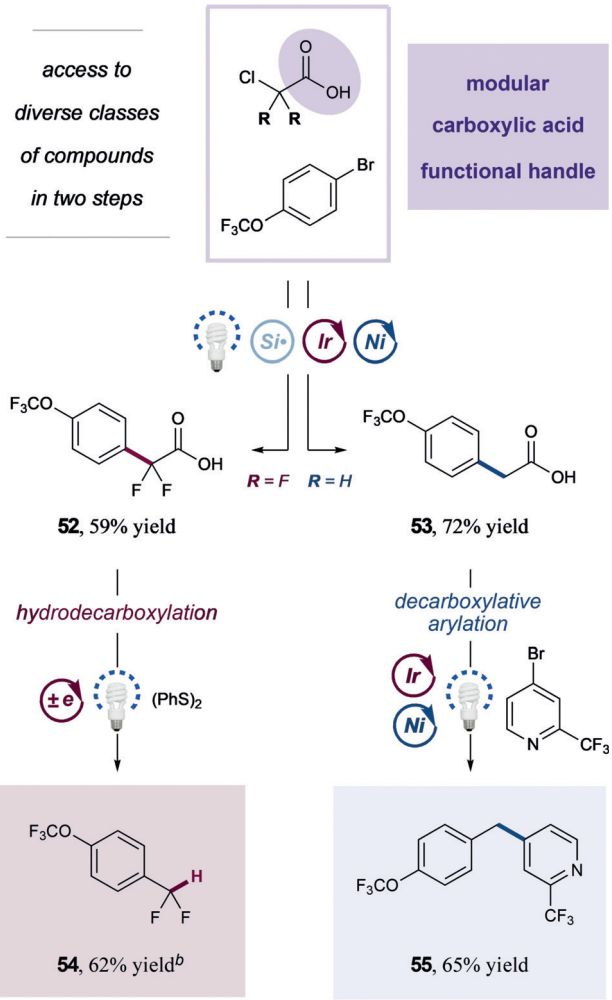
the corresponding bromine atom abstraction (e.g., $k = 2.0 \times 10^7\,M^{-1}s^{-1}$ for benzyl chloride vs. $2.4 \times 10^9\,M^{-1}s^{-1}$ for benzyl bromide silyl radical-mediated halogen atom abstraction),[8b] we presume that the rate of radical formation in the latter case is too rapid to efficiently interface with the slower kinetics of the nickel catalytic cycle. Subsequently, a survey of silyl radical sources revealed that a substantial increase in yield and decrease in alkyl chloride protodehalogenation was possible using the bulkier, commercially available tris(triethylsilyl)silane ($(TES)_3SiH$) in comparison to $(TMS)_3SiH$ (entry 5).[13] Control experiments indicated that the photocatalyst, nickel salt, silane, and light are all necessary for this new cross-coupling to be operative (entries 6–9), and no products of multiple arylation events were observed under any of the utilized conditions.

With these optimized conditions in hand, we next examined the generality of this photomediated cross-electrophile coupling protocol. As summarized in Table 2, we have found that a broad range of α-chloro carbonyls and aryl bromides are suitable coupling partners. For example, bromoarene moieties that incorporate functional handles that can be subsequently elaborated using orthogonal technologies, e.g., chloride and boronic ester substituents (**14** and **15**, 72% and 58% yield, respectively), are well-tolerated. Notably, *ortho*-substitution of the aryl coupling partner can be accommodated (**18**, 54% yield). Heterocyclic bromoarenes—substrates that are of significant utility to medicinal chemists—were also found to be suitable coupling partners, e.g., 2-, 3-, and 4-bromopyridines (**S2**, **25**–**28**, 52–72% yield). As five-membered bromoarenes are traditionally a difficult class of electrophile for fragment-couplings in general,[14] we were pleased to find that a bromopyrazole and 4-bromothiazole were readily incorporated in useful yields (**34** and **35**, 53% and 45% yield, respectively). Moreover, multi-N-bearing heteroarenes were also competent substrates (**29** and **32**, 58% and 60% yield, respectively). Finally, activated aryl chlorides, such as 2-chloropyrazine derivative **30** (68% yield) as well as a 2-chloropyridine (**24**, 53% yield), could be coupled in moderate to good yields using catalytic amounts of tetrabutylammonium bromide as a bromine radical source.

With respect to the alkyl chloride scope, we were delighted to find that various classes of α-chloro carbonyl substrates could be employed in good to excellent yields using this unified manifold. For example, esters performed well using our standard protocol, including primary α-chloroesters (**36**, 78% yield), secondary α-chloroesters (model substrate **12**, 80% yield), as well as α-chloro-γ-butyrolactone (**38**, 61% yield). Additionally, α-chloroacetamide derivatives were also effective coupling partners (**41** and **42**, 55% and 57% yield, respectively), including acetamides that bear N–H moieties (**43**, 55% yield). Cyclic ketones such as α-chlorocyclopentanone and α-chlorocyclohexanone could also be successfully coupled (**39** and **40**, 75% and 63% yield, respectively), via the application of a less-oxidizing photocatalyst (**51**, $E_{1/2}^{red}[*Ir^{III}/Ir^{II}] = +1.03$ V vs. SCE in CH_3CN).[15] Moreover, the implementation of 3-chloro-2-butanone (**37**, 51% yield) allows arylation at the more substituted α-carbonyl position, a variant that demonstrates complementary selectivity to the traditional palladium-catalyzed α-arylation of enolizable ketones wherein the methyl group is favored.[16] Notably, the construction of pharmaceutically valuable α-fluorinated α-aryl motifs[20a] could be readily achieved in good yields (**44** and **45**, 71% and 75% yield, respectively) using mixed 1,1-chlorofluoro- and chlorodifluoro-bearing α-carbonyls.

Intriguingly, we also found that benzylic chlorides are equally effective as activated alkyl chloride substrates in this mechanism (**46** and **47**, 73% and 54% yield, respectively). For example, a diaryldifluoromethane benzylic linkage (**47**) was generated in one step from commercially available materials using this protocol. The capacity to rapidly incorporate fluorine-bearing groups at a metabolically labile benzylic position via a fragment coupling step is likely to be of interest to practitioners of medicinal chemistry.

Finally, we were gratified to find that, by silyl masking the carboxylic acid moiety in situ using bis(trimethylsilyl)acetamide or hexamethyldisilazane,[16] unprotected arylacetic acid products can be directly accessed in one step using this new arylation reaction–a transformation that is traditionally challenging in enolate arylation (**48**–**50**, 65–69% yield).[2]



Scheme 3. Linchpin catalysis sequence via photoredox.[a] [a] Reactions performed on 0.5 mmol scale. Yields isolated unless otherwise noted. [b] Yield determined by ^{19}F NMR vs. 1,3-bis(trifluoromethyl)-5-bromobenzene. See Supporting Information for experimental details.

Leveraging this in situ silyl masking protocol enabled the delivery of reaction efficiencies that were comparable to the corresponding ester substrates, while an aqueous workup allowed for quantitative access to the aryl carboxylic acid product. Given that decarboxylation has emerged in recent years as a useful cross-coupling strategy with nickel catalysis,[18,19] we envisioned that these arylacetic acid products might be directly incorporated into subsequent photoredox steps to rapidly furnish medicinally relevant compounds. To showcase this concept and the modularity of these arylacetic acid products, we developed a series of two-step protocols that employ α-chloroacids as a linchpin catalysis substrate (Scheme 3). More specifically, applying the title cross-electrophile coupling method, arylacetic acids **52** and **53** can be accessed in one step from the corresponding α-chlorocarboxylic acids and aryl bromide (59% and 72% yield, respectively). The resulting carboxylic acid moieties of these products can then undergo further diversification, as shown. Hydrodecarboxylation of **52** (62% analytical yield) and decarboxylative arylation of **53** (65% yield) provide an aryl−CF_2H and a diarylmethane motif,[20,21] respectively, with good efficiencies using photoredox protocols.[19,22]

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Conflict of interest

The authors declare no conflict of interest.

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