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Open-Air Alkylation Reactions in Photoredox-Catalyzed DNA-Encoded Library Synthesis

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Abstract

DNA-encoded library (DEL) technology is a powerful tool commonly used by the pharmaceutical industry for the identification of compounds with affinity to biomolecular targets. Success in this endeavor lies in sampling diverse chemical libraries. However, current DELs tend to be deficient in C(sp)³ carbon counts. We report unique solutions to the challenge of both increasing the chemical diversity of these libraries and their C(sp)³ carbon counts by merging Ni/photoredox dual catalytic C(sp²)–C(sp³) cross-coupling as well as photoredox catalyzed radical/polar crossover alkylation protocols with DELs. The successful integration of multiple classes of radical sources enables the rapid incorporation of a diverse set of alkyl fragments.

Graphical Abstract

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Supporting Information

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

Experimental details and spectral data (PDF)

The authors declare no competing financial interest.

INTRODUCTION

DNA encoded library (DEL) technology has emerged as a valuable platform for generating and screening libraries of small molecules that has been adopted and validated by academic¹ and the pharmaceutical industry.² DELs, originally envisioned by Brenner and Lerner,³ combine the robust techniques for DNA synthesis, amplification, and sequencing with organic synthesis to facilitate the assembly of large combinatorial libraries ($>10^6$ discrete compounds) on miniaturized scales (~ 3 nmol).⁴ Consequently, this platform enables the sampling of vast amounts of chemical space and reduces material costs, both in terms of library production, library screening, and target protein requirements.⁵

The backbone of DEL technology is the use of a unique DNA sequence associated with every building block that acts as a molecular barcode for each incorporated subunit.⁶ Through split-and-pool synthesis, the DNA identifier of each newly appended building block is encoded by elongation of the DNA tag (Figure 1A). In this way, the chemical history, and by extension molecular identity, of each library member is recorded by the DNA tag. Combinatorial libraries comprising millions^{2g,5b,7} or billions⁸ of DNA-tagged small molecules can be made using this approach and subsequently screened against immobilized biomolecular targets of interest in a single pooled assay (Figure 1B).⁹ Once non- and low affinity binders are washed away, the DNA sequence of the remaining ligands, frequently present in only a few copies per compound and in sub-attomolar concentrations, can be amplified using PCR and translated through DNA sequencing to infer molecular identity.¹⁰

The DEL platform has resulted in the generation of multiple hits that have led to clinical candidates.^{3b,3c,11} Essential to the continued success of DEL technology is the synthesis of high-quality libraries, which in turn depends upon the development of new DNA-compatible reactions.¹²

As a highly functionalized organic substrate, DNA presents many inherent challenges for selective synthetic transformations. Consequently, any reaction to be considered for use in DEL synthesis must satisfy several stringent requirements. For example, on-DNA reactions must operate at high dilution (1 mM), with 20% water as co-solvent, under mild conditions (pH 4–14, 25–90 °C), on small scales (~ 25 nmol), and have high specificity for modification of the small molecule in preference to the DNA tag.¹³ Although several reaction classes have been adapted to DEL conditions,¹⁴ there is still a paucity of DNA-compatible reactions compared to commonly utilized organic methods, especially when surveying recent advances in synthetic methods development that allow practitioners to forge new C–C bonds at tetrahedral carbon centers.^{10a}

An increased fraction of C(sp³) centers has been correlated with enhanced solubility, greater specificity, and diminished toxicity, which ultimately improve the likelihood of clinical success.^{15,16} However, given the requirements for on-DNA reactivity, many methods for alkylation would be challenging, if not unfeasible, to implement. Frequently, alkylation reactions rely on anionic (e.g., conjugate addition, nucleophilic substitution) or organometallic (e.g., alkyl-magnesium, alkyllithium, alkylzinc) species that are incompatible with the aqueous on-DNA reaction environment.

Recently, Ni/photoredox dual catalysis has emerged as a remarkably mild method for C(sp²)-C(sp³) cross-coupling within complex molecular settings.¹⁷ Forging these linkages has represented a longstanding challenge for cross-coupling chemistries. Historically, either harsh, forcing conditions or reactive organometallic reagents have been required to obtain any measure of desired reactivity in such couplings.¹⁸ The Ni/photoredox system circumvents these limitations by employing a room temperature, single-electron reaction pathway where photocatalytically-generated alkyl radicals can be readily funneled into a Ni cross-coupling cycle (Figure 2). By proceeding via odd-electron intermediates, these couplings have remarkable functional group compatibility, performing equally well in the presence of acidic and basic moieties, and even tolerating small biomolecules (e.g., peptides and coenzyme A).¹⁹

The success of Ni/photoredox dual catalysis with small biomolecules supported its application to DEL environments. Indeed, success here would effectively overcome the inherent challenges posed with utilizing established methods for C(sp²)-C(sp³) cross-coupling (e.g., Negishi and²⁰ Kumada couplings²¹). Although recent publications from both the Baran laboratory^{14h} and Pfizer^{14g} have reported the radical alkylation of acrylates in the presence of DNA, we envisioned the development of alkyl-aryl cross-coupling and radical/polar crossover reactions, which present their own specific challenges and advantages. The modularity of the Ni/photoredox manifold, both in terms of compatible radical precursors [e.g., dihydropyridines, carboxylic acids, bis(catecholato)silicates] and available (hetero)aryl halides, would enable the preparation of diverse, sp³-enriched DELs while retaining aromatic functional groups common to clinical drug candidates.^{14k} In addition, DEL-compatible conditions would push the boundaries of Ni/photoredox technology by not only accommodating large, functional group-rich biomolecules, but also impressively high dilution factors and water content. Herein, the successful merger of on-DNA radical cross-coupling via Ni/photoredox dual catalysis is reported. In addition, we also report the first example of a photoredox-mediated radical/polar crossover reaction on-DNA. Importantly, in contrast to previous reports concerning photocatalytic transformations,^{14g,h} *these reactions can be carried out under ambient reaction conditions within minutes, and the viability of these elaborated DNA fragments has been demonstrated in PCR amplification.*

DISCUSSION

From the outset of our investigations we sought to develop robust, user-friendly chemistries that would be easily employed by chemists utilizing encoded library technologies (ELT). Specifically, our goal was to develop conditions that would allow these photoredox-catalyzed reactions to be *performed rapidly on the bench-top, open to air, and under ambient conditions with minimal effort by the chemist in terms of set-up complexity and timing.*

C(sp²)-C(sp³) Cross-Coupling

Numerous classes of Ni/photoredox-catalyzed reactions have been developed to access varied alkyl-aryl linkages.¹⁷ Mechanistically, coupling is proposed to proceed by excitation of the photocatalyst to access excited state species **B** that generates an alkyl radical **D** via single electron transfer (SET) oxidation of the radical precursor **2** (Figure 2).²² The alkyl

radical is captured by a Ni⁰ species **E**, yielding a Ni^I-alkyl species **F**. This new Ni complex engages in oxidative addition with the aryl halide. The resulting Ni^{III} intermediate **G** undergoes reductive elimination to furnish the cross-coupled product **3** and a Ni^I-X species **H**. Both catalytic cycles are simultaneously closed by SET from the reduced state of the photocatalyst **C** to regenerate Ni⁰ complex **E** and the ground state of the photocatalyst **A**.

DNA-appended molecules are poorly soluble in conventional organic solvents and are prone to precipitation, necessitating the use of dilute reaction conditions from an organic reactivity perspective (~1 mM). To overcome the low substrate concentrations, large excesses of reagents (40–1000 equiv) and catalyst are employed to shorten reaction times.¹³ Thus, our focus when optimizing on-DNA chemistry was the fate of the DNA-tagged substrates. Aside from cross-coupling, the major DNA-containing side products observed were protodehalogenation product **4** and C–O bond formation to generate phenol **5** (Figure 3).²³ Both the choice of nickel pre-catalyst and additives were important reaction parameters that influenced product distributions. We determined that 250 equivalents of radical precursor and a 4:1 nickel precatalyst-to-photocatalyst ratio were suitable for reactivity and to synchronize the nickel and photoredox catalytic cycles. Although such equivalencies would be untenable from the standpoint of traditional synthesis, when performing reactions on the scales associated with DELs (25 nmol), this translates to only 6.25 μmol of the radical precursor, 1.25×10^{-2} μmol of the photocatalyst, and 5.0×10^{-2} μmol of the Ni catalyst.²⁴ Additionally, an important factor for maximizing the utility of this chemistry for DEL is developing a single set of conditions for the widest range of substrates so as to increase throughput. With these considerations in mind, both 4-alkyl-1,4-dihydropyridines (DHPs) and amino acids were investigated as radical progenitors for the on-DNA cross-coupling.

Driven by the stabilization of becoming aromatic, DHPs readily undergo photocatalyst-mediated oxidative fragmentation [$E_{\text{red}} = +1.10$ vs saturated calomel electrode (SCE)] to generate alkyl radicals and pyridinium salts.²⁵ Of further advantage, the DHPs can be easily prepared in a single step from the corresponding aldehydes and other commodity chemicals, and they most often exist as readily handled, storable, crystalline solids. The combination of the organic dye 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)²⁶ as photocatalyst and nickel(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate) [Ni(TMHD)₂] enabled the on-DNA coupling of alkyl DHP **2a** and aryl bromide **1a** (Table 1). Control reactions showed that the nickel precatalyst, photocatalyst, and light were all required for cross-coupling (Table 1, Entries 7–9). Generally, protodehalogenation of the aryl halide was the major byproduct observed. Attempts to modulate the pK_a of the reaction media through use of aqueous buffers (Table 1, entry 6) or other additives (bases, magnesium salts) proved detrimental to reactivity. Additionally, at least 20% water was needed to solubilize the DNA substrate sufficiently, but increasing the fraction of water significantly slowed the rate of reaction (see Supporting Information for additional details).²⁷

An important consideration during our reaction development was what threshold constitutes a viable level of reactivity for application to DEL. The percent conversion to product that dictates whether a building block makes it into a DEL can vary based on the group, library under consideration, and cycle of chemistry. Although 70% conversion in a validation setting is often cited as a threshold for inclusion,^{5a,10b,28} significantly lower thresholds have

also been reported with conversions down to 30% being demonstrably useful.²⁹ In the case of GSK's NK3 antagonist, the compound with the highest copy count (which later demonstrated low nanomolar potency) contained a cycle 3 building block that achieved only 33% conversion to product.^{29b} Additionally, inclusion of a building block is often only determined based on its reactivity with a standard, well-behaved coupling partner,^{5b} which may provide an optimistic view of a building block's reactivity. The results outlined herein demonstrate reactions against a variety of substrate combinations to depict the range of yields that may be experienced in a library setting instead of just those under validation-like conditions.^{14h} The chemistry described is thus anticipated to be synthetically useful in a "real-world" setting, allowing inclusion of building blocks into future libraries under the reported conditions.

We initiated our scope exploration of the cross-coupling of alkyl-DHPs with a variety of (hetero)aryl bromides and iodides, from which some major reactivity trends were observed (Table 2A). Electron deficient aryl bromides coupled efficiently with 2° alkyl, 3° alkyl, benzyl, and α -alkoxy DHP partners (**3a-3e**, **3g-3k**). Electron-neutral aryl bromides showed very low conversion to product. However, by switching to the aryl iodide substrates, moderate conversion to the corresponding cross-coupled product was observed (**3l-3p**). Even aryl iodides containing electron donating substituents and functional group handles for further functionalization coupled well with the cyclohexyl DHP (**3z-3ac**). In addition to benzene-derived aryl halides, bromopyridines were also efficient coupling partners that afforded alkylated heteroaryl products (**3q-3y**) in moderate to good conversion (See Supporting Information for additional details).

The large numbers of structurally diverse, commercially available amino acids make them a particularly attractive radical feedstock for utilization in DEL. They are also appealing building blocks because the amine functional group can serve as a point of diversification for library synthesis. Oxidative decarboxylation to form alkyl radicals from these species occurs via their anionic carboxylate form ($E_{\text{red}} = +1.26\text{--}1.47$ vs SCE).³⁰ Practically, this necessitates the use of basic aqueous media. On the benchtop under ambient conditions, Ni(TMHD)₂, [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**Ir-1**), and tetramethylguanidine (TMG) proved to be the most general set of conditions for efficient decarboxylative cross-coupling of *N*-Boc amino acids with DNA-tagged aryl halides. Attempts to utilize the organic photocatalyst 4CzIPN resulted in decreased conversion to product. Control reactions showed that the base, Ni catalyst, photocatalyst, and light were all required for cross-coupling. After extensive screening of buffers and other additives (e.g., magnesium salts to stabilize the DNA¹⁴ⁱ), 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer proved optimal for minimizing the formation of protodehalogenation and phenol side products.

The scope of the coupling using amino-acid radical precursors was then evaluated (Table 2B). Couplings employing aryl bromides provided limited success for the standard benzamide substrate (**3ad**). However, by employing more electron-deficient heteroaryl bromides, synthetically useful levels of conversion could be achieved to prepare pyrrolidine and indole containing products (**3am**, **3an**). Gratifyingly, by switching to more reactive aryl iodide substrates reactivity was recovered, allowing the incorporation of pyrrolidine (**3ad**, **3ae**), 5–6 fused-ring (**3af**, **3ag**), piperidine (**3ah**), and an unprotected indole (**3ai**) both *para*-

and *meta*- to the amide linker. Unfortunately, sterically hindered ortho-substituted aryl iodides provided only trace product. Electron-neutral (**3aj**-**3al**) and electron-rich aryl iodides were also competent substrates that provided access to more complex coupling products containing basic amines (**3ao**, **3ap**, **3aq**). (See Supporting Information for additional details).

Defluorinative Alkylation

Having explored Ni/photoredox for DEL we sought to demonstrate further the amenability of photoredox catalysis for DEL synthesis by exploring the radical/polar crossover defluorinative alkylation of trifluoromethyl alkenes to form *gem*-difluoroalkenes (Figure 4A).³¹ We were interested in not only pushing the limits of radical/polar crossover chemistry, but *gem*-difluoroalkenes would constitute a valuable addition to an encoded library. The motif has been proposed to act as a more metabolically stable carbonyl isostere and has been explored on leads within pharmaceutical drug discovery.³²

Radical/polar crossover defluorinative alkylation is proposed to proceed via single-electron oxidation of the alkyl radical precursor **2** by the photoexcited state of the catalyst **B** (Figure 4A). Radical addition to trifluoromethyl alkene **6** followed by single electron reduction by the reduced state of the photocatalyst **C** furnishes carbanion **J**, which undergoes rapid anionic fluoride elimination to form *gem*-difluoroalkene **7**. Side products that we were concerned would form under the partially aqueous DEL compatible conditions included alkylated trifluoromethyl alkanes (Figure 4B, **8**), which could arise via either hydrogen atom transfer to **I** or protonation of carbanion **J**. Encouragingly, prior studies have demonstrated that fluoride elimination occurs faster than protonation of carbanion **J**, even in the presence of carboxylic acids.³³ We were also concerned about secondary alkylation of the *gem*-difluoroalkene product in the presence of excess radical precursor (Figure 4B, **9**).³⁴

In considering these aspects, we revised our reaction conditions rather than simply extrapolating the conditions used for Ni/photo-redox cross-coupling. Three classes of commonly employed,¹⁷ water compatible, radical precursors that would provide differentiated alkyl fragments were selected for exploration: alkyl bis(catecholato)silicates, DHPs, and amino acids (Figure 4C). Depending on the radical structure, full consumption of starting material and minimal secondary alkylation was observed when using between 5 and 50 equivalents of the radical precursors. Photocatalyst 4CzIPN proved best for both the silicate and DHP radical precursors, while **Ir-1** was optimal for acids. Decreased loading of **Ir-1** was employed for some acids to provide better selectivity for the desired monoalkylation product. However, dropping the loading of 4CzIPN for silicates and DHPs resulted in poor reactivity. Control experiments confirmed that the transformation did not proceed in the absence of either photocatalyst or light. It is worth noting that despite the reaction being conducted in an aqueous environment and in the presence of acidic functional groups, only minor amounts of trifluoromethyl alkane side product **8** were observed.³³

With a general set of conditions established, the scope of the transformation was first explored using alkyl bis(catecholato)silicates as radical precursors (Table 3A).³⁵ These radical precursors have uniformly low oxidation potentials ($E_{\text{red}} = +0.75$ V versus SCE),

allowing them to form primary non-stabilized alkyl radicals efficiently, a task that is intractable with other oxidizable carbon radical sources. A loading of 50 equivalents of silicate was needed to ensure complete consumption of the DNA-tagged starting material, likely due to degradation of the radical precursor in aqueous media via hydrolysis. Silicates enabled incorporation of not only aliphatic (**7a**) and fluorinated motifs (**7e**), but also functional groups capable of further derivatization in subsequent cycles of DEL synthesis. Alkenes (**7b**), epoxide (**7c**), esters (**7d**, **7f**), and an *N*-Boc amine (**7g**) were all compatible with the optimized conditions. Variation of the on-DNA trifluoromethyl alkene was also explored, and both an aryl chloride (Table 3D) capable of further functionalization via DEL-compatible Suzuki cross-coupling^{14d} and a nitrogen heterocycle (Table 3G) reacted efficiently with a free urea (**7ac**, **7ah**) (See Supporting Information for additional substrate scope and details). Alkyl DHPs were next explored as radical progenitors (Table 3B). Full consumption of the trifluoromethyl alkene required a much lower loading of this radical precursor (12.5 equivalents), speaking to their improved water stability compared to silicates. Secondary alkyl (**7h**, **7i**), saccharide (**7j**), pendant alkyne (**7k**), and pendant alkene (**7l**) DHPs all readily reacted. The reaction also worked well using both an aryl chloride (Table 3E) and pyridine headpieces (Table 3I) (See Supporting Information for additional substrate scope and details).

Lastly, we investigated amino acids as radical precursors for the defluorinative alkylation of trifluoromethyl-substituted alkenes. A non-nucleophilic base, 2,6-lutidine, was preferred over TMG because amine bases capable of adding to the electrophilic alkene resulted in significant side-product formation. Additionally, when using *N*-Boc amino acids, basic buffers increased formation of the protonation side product **8**. The combination of **Ir-1** and 2,6-lutidine resulted in efficient reaction conversion to the corresponding products.

A wide array of amino acids reacted efficiently, enabling installation of free alcohol (**7p**), pyridyl (**7t**), imidazolyl (**7y**), and benzothienyl (**7w**, **7x**) substructures (Table 3C). Changing the protecting group to a base-sensitive Fmoc required modification of the reaction conditions (32% conversion for *N*-Fmoc proline under *N*-Boc conditions). Switching from 2,6-lutidine to using a basic pH 9 TRIS buffer provided the Fmoc-protected product **7n** in good conversion. The modified conditions also proved general for Fmoc protected amino acids, affording *N*-Fmoc products with aliphatic and aromatic functional units. The reactivity was not limited to amino acids, as stabilized α -oxy acid (**7z**) and pivalic acid (**7ab**) served as efficient substrates. Cyclohexanecarboxylic acid, which furnishes a less stabilized 2° alkyl radical, proceeded with modest conversion (**7aa**). To explore the scope with respect to the alkene, a subset of amino acids was evaluated with both the chloroaryl (Table 3F) and pyridinyl (Table 3I) alkenes (See Supporting Information for additional substrate scope and details). A benzylic radical originating from *N*-Boc-phenyl glycine did not provide detectable product, consistent with results obtained with benzylic radicals generated from silicates and DHPs. The attenuated reactivity of benzylic radicals owing to resonance stabilization has been previously observed.³⁶ These patterns highlight the fact that successful transformations are not solely determined by the radical precursors and their redox potential, but are also critically dependent on the structure, stability, and inherent reactivity of the resulting radicals.

DNA Compatibility

Given the radical nature of these reactions and the potential for radical-induced DNA damage,³⁷ we evaluated whether the products of the defluorinative alkylation chemistry remained competent for PCR amplification and sequencing. In a library setting, the DNA sequence is the only record available to identify which building block and reaction sequence was used to produce a putative binder. If the chemistry developed creates a decreased capacity for amplification and a greater frequency of misreads, the interpretation of selection results could become compromised, leading to incorrect identification of building blocks or misrepresentation of binding affinity. It was satisfying to see that when using a 4-cycle tag elongated head-piece, the conditions developed for the defluorinative alkylation chemistry using three different radical precursor classes led to no significant differences in the ability of the samples to undergo PCR amplification and quantitation. Importantly, there was no difference in the frequency of misreads after sequencing between the product formed under the reaction conditions versus the no-radical precursor control or the no-radical precursor and no-photocatalyst control. Taken together, these results suggest that these reactions could be used in a library setting with high confidence in the fidelity of the corresponding DNA (See Supporting Information for additional details).

CONCLUSIONS

In summary, the development of robust DEL compatible methods for the Ni/photoredox catalyzed cross-coupling and the photo-redox catalyzed radical/polar crossover alkylation has been reported. These protocols present operationally simple methods for the preparation of compound libraries on the bench-top and open to air. Furthermore, both approaches increase molecular complexity and C(sp³) carbon counts and were demonstrated using multiple classes of radical precursors, opening encoded-library synthesis to the entire ecosystem of radical precursors and existing photoredox reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A) Split-and-Pool Library Synthesis: DNA Tag Encodes Chemical History **B) Implementation of DNA Encoded Libraries for Hit Identification**

Figure 1.
Workflow in generating and utilizing DELs.

Figure 2.
 Mechanistic view of Ni/photoredox dual catalytic C(sp²)-C(sp³) cross-coupling.

Figure 3.
Major DNA-containing side products from the cross-coupling.

A) Defluorinative Alkylation of Trifluoromethylalkenes

B) Major DNA containing side products

C) Optimal conditions for each radical precursor

Figure 4.

Radical/polar crossover defluorinative alkylation of trifluoromethyl alkenes.

Table 1.Optimization of DHP Coupling Reaction Conditions.^a

Entry	Deviation from initial conditions	8 (% conv ^b)
1	None	63
2	[Ir{dF(CF ₃)ppy}(dtbbpy)]PF ₆	0
3	[Ni(Phen)(H ₂ O) ₄ Cl ₂]	10
4	[Ni(dtbbpy)(H ₂ O) ₄ Cl ₂]	0
5	2:1 Ni/photocatalyst	32
6	100 mM MOPS pH 8 added	4
7	No Ni catalyst	0
8	No 4CzIPN photocatalyst	0
9	No light	0

^aReaction conditions: DHP (250 equiv, 6.25 μmol), 4CzIPN (50 mol %, 12.5 nmol), Ni(TMHD)₂ (2.0 equiv, 50 nmol), aryl halide (25 nmol, 1.0 equiv), 80:20 DMSO/H₂O (1 mM), 45 min, irradiating with blue LED (30 W).

^bConversion to 8 as determined by LC/MS.

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Table 2.

Ni/Photoredox Dual Catalytic C(sp²)-C(sp³) Cross-Coupling on-DNA^a

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^a All values indicate conversion to the indicated product as determined by LC/MS.

^b Reaction conditions: DHP (250 equiv, 6.25 μ mol), **4CzIPN** (50 mol %, 12.5 nmol), Ni(TMHD)₂ (2.0 equiv, 50 nmol), aryl halide (25 nmol, 1.0 equiv), 80:20 DMSO/H₂O (1 mM), 45 min, irradiating with blue LED (30 W).

^c Using 4-(*tert*-butyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile.

^d Reaction conditions: amino acid (250 equiv, 6.25 μ mol), **Ir-1** (50 mol %, 12.5 nmol), Ni(TMHD)₂ (2.0 equiv, 50 nmol), aryl halide (25 nmol, 1.0 equiv), TMG (700 equiv, 17.5 μ mol), MOPS pH 8 buffer (25 mM), 77:23 DMSO/H₂O (1 mM), 10 min, irradiating with blue LED (30 W).

^e Using TMG (990 equiv, 24.75 μ mol) and 30 min reaction time. TMG = 1,1,1,3,3-tetramethylguanidine. MOPS = 3-(*N*-morpholino)propanesulfonic acid. See Supporting Information for additional details.

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Table 3.

Defluorinative Alkylation using Silicates, Dihydropyridines, and Amino Acids^a

^a All values represent conversion to the indicated product as determined by LC/MS. All reactions were run using alkene (1.0 equiv, 25 nmol), 80:20 DMSO/H₂O (1 mM), 10 min, irradiating with blue LED (30 W).

^b Silicate (50 equiv, 1.25 μ mol), 4CzIPN (50 mol %, 12.5 nmol).

^c DHP (12.5 equiv, 312.5 nmol), 4CzIPN (50 mol %, 12.5 nmol).

^d Using 25 equiv of DHP.

^e Acid (5 equiv, 125 nmol), Ir-1 (5 mol %, 1.25 nmol), 2,6-lutidine (150 equiv, 3.75 μ mol).

^f Using 2.5 mol % **Ir-1**.

^g Acid (25 equiv, 625 nmol), **Ir-1** (10 mol %, 12.5 nmol), pH 9 TRIS buffer (100 mM), 60:40 DMSO/H₂O (1 mM).

^h Acid (25 equiv, 625 nmol), **Ir-1** (10 mol %, 12.5 nmol), 2,6-lutidine (150 equiv, 3.75 μ mol).

ⁱ Using 25 equiv of acid, 10 mol % Ir-1.

^j Using 50 equiv of acid, 50 mol % **Ir-1**. See Supporting Information for additional details and substrate scope.