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Multifunctional Building Blocks Compatible with Photoredox-Mediated Alkylation for DNA-Encoded Library Synthesis

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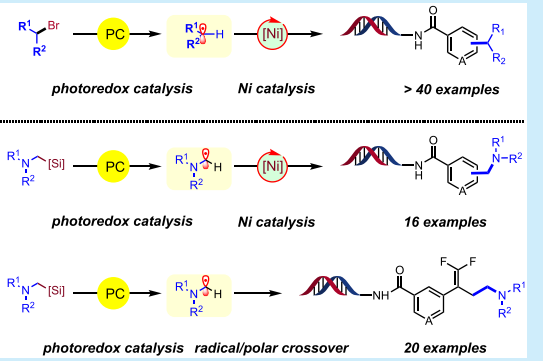
ABSTRACT: DNA-encoded library (DEL) technology has emerged as a novel interrogation modality for ligand discovery in the pharmaceutical industry. Given the increasing demand for a higher proportion of C(sp^3)-hybridized centers in DEL platforms, a photoredox-mediated cross-coupling and defluorinative alkylation process is introduced using commercially available alkyl bromides and structurally diverse α-silylamines. Notably, no protecting group strategies for amines are necessary for the incorporation of a variety of amino-acid-based organosilanes, providing crucial branching points for further derivatization.



The discovery of small organic ligands with high-affinity binding to proteins is a central theme of biomedical research in both academic and industrial settings.[1] Robust chemical probes are key to validating the tractability and translatability of a therapeutic target in drug discovery programs, and they provide a critical starting point for the development of new therapeutic chemical entities.[2] Consequently, considerable attention has been devoted to the development of novel screening methods that diminish clinical attrition and to identify chemical matter with superior specificity more rapidly.

In the search for novel therapeutic compound classes, a strategy has evolved to cast a wide net to capture as many potential hit compounds as possible across a broad range of substructures. Owing to the need for individual synthesis and screening of small molecules that make up a conventional high-throughput screening library, campaigns of a few million compounds against a complex biological target have proven to be cost- and time-intensive, with an estimated price tag of $1000 per library member.[1,3] In recent years, DNA-encoded library (DEL) technology[4] has emerged as an innovative platform to enable the assembly and sampling of combinatorial libraries of unprecedented magnitude (>10^6 to 10^{12} drug-like candidates).[5] Originally conceived by Brenner and Lerner in 1992, DELs are composed of small molecules covalently conjugated with a DNA tag, which functions as a molecular identifier or barcode for each subunit.[6] By harnessing split-and-pool routines, an entire library can be made in a few months by 1−2 chemists and, in a single experiment, screened against immobilized biomolecular targets (Figure 1).[7] Once nonbinders are washed away, the desired ligands are released under denaturing conditions, and subsequently the chemical structures are decoded via PCR amplification and DNA sequencing.[8] In this vein, DEL screens provide a time- and cost-effective format for exploration of uncharted chemical space.

A wide array of medicinal candidates has been identified from DEL platforms.[9] The inherent nature of the DNA barcode, however, renders the implementation of such synthetic transformations challenging. On-DNA reactions must be compatible with water, must be performed at high dilutions, must be high-yielding with the ability to identify any major byproducts, should be user-friendly, and must avoid the use of strong bases and harsh oxidizing or reducing agents.[10] Recent work by the Baran and Dawson groups[11] to increase the solubility of DNA tags in organic solvents utilizing cationic resins has been demonstrated, but this protocol presents its own obstacles when merged with photoredox-mediated alkylation processes. Therefore, myriad structural gaps persist in DEL paradigms, with an increasing need to incorporate functional groups amenable to sequential derivatization.

To ensure a versatile chemical foundation, careful selection of building blocks (BBs) is instrumental in constructing libraries. A comprehensive set of BBs encompassing structural motifs that resemble bioactive molecules in combination with those bearing an additional handle for diversification is ideal.[12] Although

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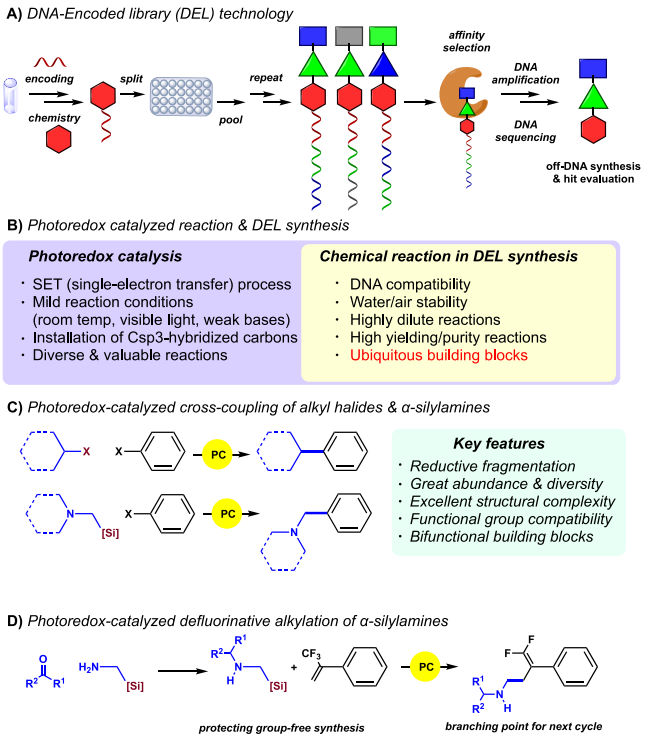

Figure 1. Schematic presentation of DNA-encoded library technology.

monofunctional BBs suitable for existing DEL chemistries are widely accessible, a recent survey estimates that the number of available bifunctional BBs, serving as crucial linkers, encompasses only ~3500 scaffolds.[12] In light of these considerations, we sought to expand the BBs amenable for photoredox-catalyzed DEL synthesis to incorporate two complementary families of radical precursors, namely, aliphatic bromides[13] and α-silylamines.[14]

In recent years, metallaphotoredox catalysis has emerged as a valuable tool for providing unique and alternative C−C bond disconnections, especially in the context of complex biomolecular design.[15] Because of the impact of C(sp^3)-hybridized centers on the enhancement of solubility and specificity in druggable molecules, single-electron transfer (SET) processes have found extensive use in the medicinal chemistry community.[16,17]

Recently, our group and others have validated Ni/photoredox dual catalysis in DNA-encoded synthesis using carboxylic acids and 1,4-dihydropyridines (DHPs) as radical precursors.[18,19] Although this advance presented a milestone in its own right, the scope of these transformations was restricted to α-amino acids, which generate stabilized α-heterosubstituted radicals.[18,19] In the case of DHPs, the cross-coupling was limited to benzylic, secondary, or α-alkoxy structural motifs.[18] The use of other electrophiles was restricted to DNA-conjugated aryl iodides.[19]

To address these limitations, we sought to develop three photoredox approaches to expand chemical space in the DEL platform. In the first, a photoredox/nickel-mediated reductive coupling on DNA was developed, employing primary and secondary alkyl bromides as reaction partners using triethylamine as a mild reductant. Such cross-electrophile couplings furnish several advantages over traditional catalytic cycles.[20] For example, the need for preformed carbon nucleophiles, including harsh organometallic reagents prepared from the corresponding halides, severely limits functional group compatibility and renders such anionic alkylation processes unusable in DEL environments.[21] By contrast, electrophilic reagents such as aliphatic halides have greater abundance and offer excellent structural complexity, with over 2 million building blocks commercially available. Bypassing the need for stoichiometric zinc or manganese reductants, we disclose a versatile cross-coupling with excellent functional group tolerance on DNA.

In two further protocols, α-silylamines have been incorporated as surrogates of structural motifs embedded within natural products.[12,22] We have thus engaged several members of this class of substrates in both Ni/photoredox dual cross-coupling and defluorinative alkylation processes. *Importantly, all of the protocols developed are completed within minutes and do not require an inert atmosphere, providing an exceedingly low barrier to practical implementation.*

A fundamental challenge facing cross-electrophile couplings is *selectivity*.[20] Because of the labile nature of both electrophilic starting materials toward oxidative addition in the presence of a nickel catalyst, careful design of reaction parameters must be implemented to synchronize the nickel and photoredox catalytic cycles (Figure 2A).[13]

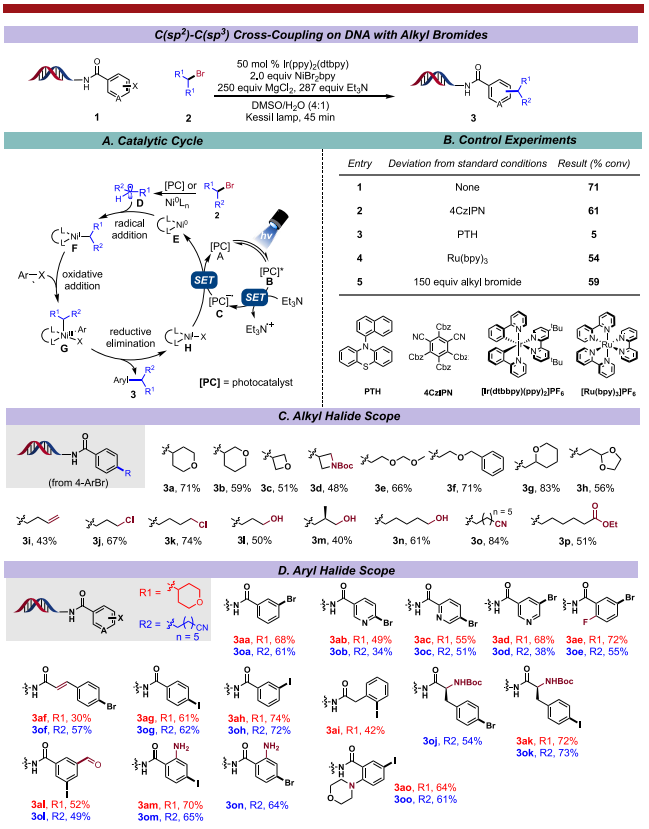

Figure 2. Plausible catalytic cycle, key optimization parameters, and scope of this transformation.

To induce selectivity in substrates with inherently equal or similar reactivities, excess amounts of one reagent over the other can be leveraged.[20,23] This strategy is particularly powerful in the context of DEL chemistries, which are carried out on an extremely small scale (~25 nmol).[18] To clarify this perspective further, the use of 250 equiv of radical precursor equates to only 6.25 μmol of starting material. Notably, the ease of separation of homodimers from DNA-alkylated products further highlights the potential of implementing cross-electrophile couplings in DEL strategies.

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We initiated our studies using a DNA-tagged *para*-substituted aryl bromide (**1**) and 4-bromotetrahydropyran as the model substrates under 20% aqueous conditions (Figure 2). Given the reductive nature of this transformation, a variety of photocatalysts were screened (Figure 2B). Although product formation was observed in the case of the organic dye 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN),[24] the iridium-based photoreductant $[Ir(dtbbpy)(ppy)_2]PF_6$ ($E_{1/2}$ = −0.96 V vs SCE) proved superior.[25,26] Of particular note, minimal product was generated using 10-phenylphenothiazine (PTH). With a drastically higher reduction potential ($E_{1/2}$ = −2.1 V vs SCE) compared to that of $Ir(ppy)_3$ ($E_{1/2}$ = −1.7 V vs SCE),[27] this photoreductant presumably engages the aryl halide on DNA in protodehalogenation via reductive fragmentation of the corresponding C−X bond. After a variety of parameters was assessed, a loading of 250 equiv of alkyl bromide, coupled with a 4:1 ratio of the $NiBr_2$·bpy precomplex-to-photocatalyst, was determined to afford the desired product in suitable yield. The addition of magnesium chloride ($MgCl_2$) was utilized to enhance stabilization of the DNA backbone.[28] *Of note, the reactions were complete in <45 min and did not require an inert atmosphere.*

We subsequently evaluated the scope of this reductive coupling (Figure 2C). A wide range of primary and secondary alkyl bromides served as competent substrates, including those with bifunctional handles such as *N*-Boc-protected amine **3d**, unactivated alkene **3i**, alkyl chlorides **3j** and **3k**, and nitrile **3o**. Because of the mild base utilized, free alcohols **3l**−**n**, stemming from a primary alkyl bromide, were effectively coupled in acceptable yields. The scope of this method was further extended to cyclic systems, including oxetane **3c**, azetidine **3d**, and pyran **3g**.

To establish robust reactivity, we surveyed these DNA substrates with one primary and one secondary alkyl bromide (Figure 2D). Aryl bromides and iodides bearing electron-withdrawing and electron-donating groups were cross-coupled effectively. Activated heteroaryl systems (**3ab**, **3ac**, **3ad**) reacted in moderate yields because of their delicate nature under reducing photoredox conditions. This limitation, however, complements existing SET-mediated cross-coupling procedures operating under an oxidative fragmentation paradigm.[18,19] By contrast, electron-neutral aryl bromides or those bearing electron-donating substituents, not viable under previous reports,[18,19] furnished the desired alkylated products in moderate yields in this cross-electrophile coupling. A variety of other structural motifs were accommodated, including aryl fluoride **3ae**, styrene **3af**, *N*-Boc-protected amines (**3oj** and **3ok**), aldehyde **3al**, and free primary amines (**3om** and **3on**). Remarkably, aryl halide **3ao**, containing a morpholine residue, did not suffer diminished reactivity, despite its structural resemblance to the triethylamine used as a stoichiometric reducing agent in this reaction.

Having explored the utility of alkyl bromides as electrophilic cross-coupling partners on DNA, we then investigated α-silylamines as radical precursors.[14] An ambitious goal of unbiased DNA-encoded libraries aimed at multiple biological targets is to encompass a large collection of diverse scaffolds.[28] Inspired by the concept of diversity-oriented synthesis (DOS), first championed by Schreiber in 2000,[29] we pursued the aminomethylation of (hetero)aryl bromides to yield skeletal diversity prevalent in natural products (Figure 3). Indeed, the aminomethyl subunit serves as a pivotal linker in bioactive molecules as well as leading pharmaceutical drugs such as

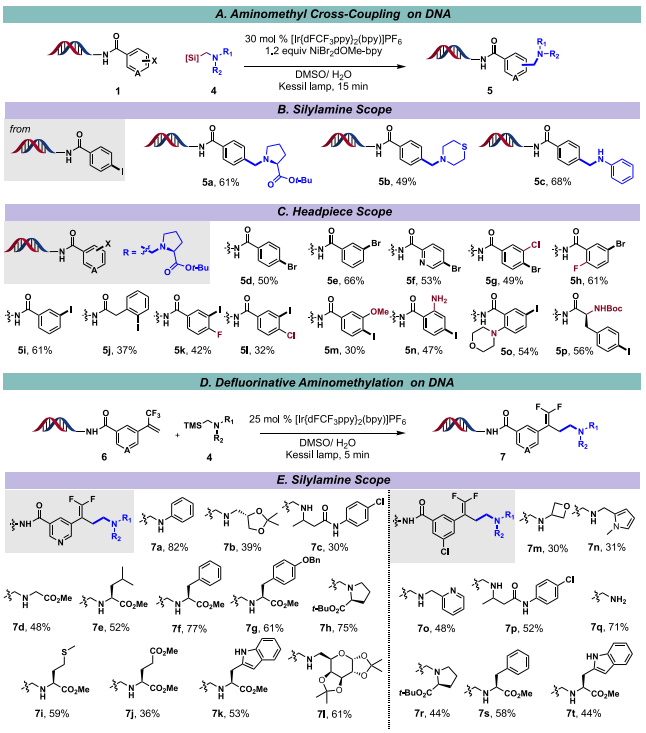

Figure 3. Cross-coupling and radical/polar defluorinative aminomethylation.

Imatinib and Donepezil.[14,30] Strategies based on DOS attest to their success in the discovery of new therapeutic treatments,[31] especially in DNA-encoded library synthesis as described recently by Schreiber et al.[32]

We envisioned that single-electron oxidation of electron-rich alkyl(trimethyl)silanes **4** under photoredox conditions would give rise to silyl radical cations.[14,33] This species would undergo facile desilylation to yield the desired α-aminomethyl radical, which could then be intercepted by the nickel catalytic cycle to furnish the coupled product. We anticipated that nucleophilically assisted desilylation could occur when using water as a (co)solvent. This added benefit could be further leveraged as the free amine handle allows systematic branching sequences in DEL platforms. Driven by low oxidation potentials in protic solvents,[33] we demonstrate for the first time that unprotected aminomethylsilanes are efficiently oxidized by $[Ir\{dFCF_3ppy\}(bpy)]PF_6$. Notably, diverse alkyl(trimethyl)silanes can be accessed in a single step from the corresponding commercially available amines and chlorotrimethylsilane. *Importantly, the reactions require less than 15 min to proceed to completion and are carried out in the absence of an inert atmosphere.*

The bifunctional nature and commercial availability of amino acids make them highly valued building blocks for library synthesis, and we successfully carried out the aminomethylation with a variety of electron-deficient and electron-rich halides with an organosilane stemming from proline to produce synthetically useful levels of product. An aryl iodide bearing an *N*-Boc-protected amine (**5p**) served as a competent substrate. Additionally, aryl iodides bearing a free amine **5n** and tertiary amine **5o** both reacted with ease. We have also successfully demonstrated the cross-coupling with non-amino-acid-derived organosilanes (**5b** and **5c**).

Given the metabolic stability of *gem*-difluoroalkenes as carbonyl mimics,[34] we subjected α-silylamines to radical/polar

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crossover defluorinative alkylation processes (Figure 3D).[18,35] We propose that a single-electron oxidation of the α-silylamine radical precursor by the photoexcited state of the photocatalyst furnishes a nucleophilic primary radical. This species then undergoes addition to the trifluoromethyl alkene to generate an α-CF_3 radical, which is further reduced to the carbanion by the photocatalyst. Subsequent fluoride elimination occurs to yield **7**.[18,35]

After extensive reaction optimization, we assessed the scope of this transformation (Figure 3E). A wide array of amino-acid-based organosilanes proved competent, including leucine **7e**, phenylalanine **7f**, proline **7h**, methionine **7i**, and tryptophan **7k**. Remarkably, nitrogen protecting groups were not necessary in this alkylation platform, providing an additional branching point to be utilized for further building block incorporation.

Numerous other silylamines, derived from commercially available aminomethylsilane and the corresponding ketones/aldehydes via reductive amination, displayed adequate reactivity with a variety of substrates, including aniline **7a**, glycoside **7l**, oxetane **7m**, pyridine **7o**, and amide **7p**. Notably, we subjected aminomethyltrimethylsilane to the reaction conditions and obtained the primary amine **7q** without any loss in reactivity. We foresee that the structural diversity created in these photoredox-mediated processes will be instrumental in providing unique and alternative bond disconnections in DEL libraries.

Finally, maintaining the integrity of the DNA tag during library synthesis is vital to the success of encoded library technology as a drug discovery platform because the DNA barcode is the only record available to decode the synthetic steps used to construct the putative binder following selection. We verified the integrity of the DNA tag when subjected to the photoredox conditions developed herein (see Supporting Information for details). We observed no significant differences in the ability of our samples treated with standard conditions to undergo ligation, PCR amplification, quantification, or sequencing when compared to a no-blue-light-exposed control sample. These results, consistent with historical findings,[18] suggest that the reported transformations are amenable for DEL synthesis without compromising the integrity of the DNA.

In summary, taking advantage of diverse and commercially available alkyl bromides, a selective cross-electrophile coupling on DNA has been devised. A variety of unactivated primary and secondary radical precursors are employed with high functional group tolerance. Of further advantage, photoredox-mediated radical/polar crossover reactions using structurally diverse α-silylamines were employed to generate novel *gem*-difluoroalkene scaffolds without the need for nitrogen protecting groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04568.

Detailed experimental procedures (including workflow and qPCR/sequencing of representative examples), preparation of on-DNA substrates and α-silylmethylamines, characterization data, NMR spectra for new compounds, and UPLC/MS of on-DNA reactions (PDF)

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Notes

The authors declare no competing financial interest.

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