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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(sp³)-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.

Graphical Abstract

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Supporting Information

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

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INTRODUCTION

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 HTS 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 \$1,000 per library member.^{1,3} In recent years, DNA-encoded library (DEL) technology⁴ 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 non-binders 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 groups¹¹ 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 mono-functional 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 ~3,500 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 bromides¹³ 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(sp³)-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 advancement 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

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

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 extremely small scale (~25 nmol).¹⁸ To clarify this perspective further, the use of 250 equivalents of radical precursor only equates to 6.25 μ mol 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.

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]₂PF₆ ($E_{1/2}$ = -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 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 assessing a variety of parameters, a loading of 250 equiv of alkyl bromide, coupled with a 4:1 ratio of the NiBr₂•bpy precomplex-to-photocatalyst, was determined to afford the desired product in suitable yield. The addition of magnesium chloride (MgCl₂) 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, not viable under previous reports,^{38,39} 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 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{dFCF₃ppy}(bpy)]PF₆. 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. Aryl iodides bearing *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 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 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 -CF₃ 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 (ELT) 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). Neri D; Lerner RA DNA-Encoded Chemical Libraries: A Selection System Based on Endowing Organic Compounds with Amplifiable Information. *Annu. Rev. Biochem* 2018, 87, 479–502. [PubMed: 29328784]
- (2). Garbaccio RM; Parmee ER The Impact of Chemical Probes in Drug Discovery: A Pharmaceutical Industry Perspective. *Cell Chem. Biol* 2016, 23, 10–17. [PubMed: 26933732]
- (3). For selected examples, see:(a)Erlanson DA; Fesik SW; Hubbard RE; Jahnke W; Jhoti H Twenty years on: the impact of fragments on drug discovery. *Nat. Rev. Drug. Discov* 2016, 15, 605–619. [PubMed: 27417849] (b)Folmer RHA Integrating biophysics with HTS-driven drug discovery projects. *Drug Discov. Today Technol* 2016, 21, 491–498.(c)Halai R; Cooper MA Using label-free screening technology to improve efficiency in drug discovery. *Expert Opin Drug Dis.* 2012, 7, 123–131.(d)Nielsen TE; Schreiber SL Diversity-oriented synthesis - Towards the optimal screening collection: A synthesis strategy. *Angew. Chem., Int. Ed* 2008, 47, 48–56.
- (4). Dickson P; Kodadek T Chemical composition of DNA-encoded libraries, past present and future. *Org. Biomol. Chem* 2019, 17, 4676–4688. [PubMed: 31017595]
- (5). For selected examples, see:(a)Clark MA; Acharya RA; Arico-Muendel CC; Belyanskaya SL; Benjamin DR; Carlson NR; Centrella PA; Chiu CH; Creaser SP; Cuzzo JW; Davie CP; Ding Y; Franklin GJ; Franzen KD; Gefter ML; Hale SP; Hansen NJV; Israel DI; Jiang JW; Kavarana MJ; Kelley MS; Kollmann CS; Li F; Lind K; Mataruse S; Medeiros PF; Messer JA; Myers P; O’Keefe H; Oliff MC; Rise CE; Satz AL; Skinner SR; Svendsen JL; Tang LJ; van Vloten K; Wagner RW; Yao G; Zhao BG; Morgan BA Design, synthesis and selection of DNA-encoded small-molecule libraries. *Nat. Chem. Biol* 2009, 5, 647–654. [PubMed: 19648931] (b)Litovchick A; Dumelin CE; Habeshian S; Gikunju D; Guie MA; Centrella P; Zhang Y; Sigel EA; Cuzzo JW; Keefe AD; Clark MA Encoded Library Synthesis Using Chemical Ligation and the Discovery of sEH Inhibitors from a 334-Million Member Library. *Sci. Rep* 2015, 5, 10916. [PubMed: 26061191] (c)Harris PA; King BW; Bandyopadhyay D; Berger SB; Campobasso N; Capriotti CA; Cox JA; Dare L; Dong XY; Finger JN; Grady LC; Hoffmann SJ; Jeong JU; Kang J; Kasparcova V; Lakdawala AS; Lehr R; McNulty DE; Nagilla R; Ouellette MT; Pao CS; Rendina AR; Schaeffer MC; Summerfield JD; Swift BA; Totoritis RD; Ward P; Zhang AM; Zhang DH; Marquis RW; Bertin J; Gough PJ DNA-Encoded Library Screening Identifies Benzo[b][1,4]oxazepin-4-ones as Highly Potent and Monoselective Receptor Interacting Protein 1 Kinase Inhibitors. *J. Med. Chem* 2016, 59, 2163–2178. [PubMed: 26854747] (d)Mullard A, DNA Tags Help the Hunt for Drugs. *Nature* 2016, 530, 367–369. [PubMed: 26887498]
- (6). Brenner S; Lerner RA Encoded combinatorial chemistry. *Proc. Natl. Acad. Sci. U. S. A* 1992, 89, 5381–5383. [PubMed: 1608946]
- (7). Ottl J; Leder L; Schaefer JV; Dumelin CE Encoded Library Technologies as Integrated Lead Finding Platforms for Drug Discovery. *Molecules* 2019, 24, 1629.
- (8). For selected examples, see:(a)Buller F; Mannocci L; Scheuermann J; Nerit D Drug Discovery with DNA-Encoded Chemical Libraries. *Bioconjugate Chem.* 2010, 21, 1571–1580.(b)Kleiner RE; Dumelin CE; Liu DR Small-molecule discovery from DNA-encoded chemical libraries. *Chem. Soc. Rev* 2011, 40, 5707–5717. [PubMed: 21674077] (c)Ding Y; Franklin GJ; DeLorey JL; Centrella PA; Mataruse S; Clark MA; Skinner SR; Belyanskaya S Design and Synthesis of Biaryl DNA-Encoded Libraries. *ACS Comb. Sci* 2016, 18, 625–629. [PubMed: 27571034]
- (9). For selected examples, see:(a)Maiani JP; McFedries A; Foda ZH; Kleiner RE; Du XQ; Leissring MA; Tang WJ; Charron MJ; Seeliger MA; Saghatelian A; Liu DR Anti-diabetic activity of insulin-degrading enzyme inhibitors mediated by multiple hormones. *Nature* 2014, 511, 94–98. [PubMed: 24847884] (b)Ding Y; O’Keefe H; DeLorey JL; Israelt DI; Messer JA; Chiu CH; Skinner SR; Matico RE; Murray-Thompson MF; Li F; Clark MA; Cuzzo JW; Arico-Muendel

C; Morgan BA Discovery of Potent and Selective Inhibitors for ADAMTS-4 through DNA-Encoded Library Technology (ELT). *ACS Med. Chem. Lett* 2015, 6, 888–893. [PubMed: 26288689] (c)Samain F; Ekblad T; Mikutis G; Zhong N; Zimmermann M; Nauer A; Bajic D; Decurtins W; Scheuermann J; Brown PJ; Hall J; Graslund S; Schuler H; Neri D; Franzini RM Tankyrase 1 Inhibitors with Drug-like Properties Identified by Screening a DNA-Encoded Chemical Library. *J. Med. Chem* 2015, 58, 5143–5149. [PubMed: 26061013] (d)Li YZ; De Luca R; Cazzamalli S; Pretto F; Bajic D; Scheuermann J; Neri D Versatile protein recognition by the encoded display of multiple chemical elements on a constant macrocyclic scaffold. *Nat. Chem* 2018, 10, 441–448. [PubMed: 29556050] (e)Cuzzo JW; Centrella PA; Gikunju D; Habeshian S; Hupp CD; Keefe AD; Sigel EA; Soutter HH; Thomson HA; Zhang Y; Clark MA Discovery of a Potent BTK Inhibitor with a Novel Binding Mode by Using Parallel Selections with a DNA-Encoded Chemical Library (vol 18). *Chembiochem*. 2017, 18, 2441–2441. [PubMed: 29239533] (f)Brown DG; Brown GA; Centrella P; Certel K; Cooke RM; Cuzzo JW; Dekker N; Dumelin CE; Ferguson A; Fiez-Vandal C; Geschwindner S; Guie MA; Habeshian S; Keefe AD; Schlenker O; Sigel EA; Snijder A; Soutter HT; Sundstrom L; Troast DM; Wiggan G; Zhang J; Zhang Y; Clark MA Agonists and Antagonists of Protease-Activated Receptor 2 Discovered within a DNA-Encoded Chemical Library Using Mutational Stabilization of the Target. *SLAS Discov*. 2018, 23, 429–436. [PubMed: 29316408] (g)Petersen LK; Blakskjaer P; Chaikwad A; Christensen AB; Dietvorst J; Holmkvist J; Knapp S; Korinek M; Larsen LK; Pedersen AE; Rohm S; Slok FA; Hansen NJV Novel p38 alpha MAP kinase inhibitors identified from yoctoReactor DNA-encoded small molecule library. *Medchemcomm*. 2016, 7, 1332–1339.(h)Ahn S; Kahsai AW; Pani B; Wang QT; Zhao S; Wall AL; Strachan RT; Staus DP; Wingler LM; Sun LD; Sinnave J; Choi MJ; Cho T; Xu TT; Hansen GM; Burnett MB; Lamerdin JE; Bassoni DL; Gavino BJ; Husemoen G; Olsen EK; Franch T; Costanzi S; Chen X; Lefkowitz RJ Allosteric “beta-blocker” isolated from a DNA-encoded small molecule library. *PNAS USA* 2017, 114, 1708–1713. [PubMed: 28130548]

- (10). (a)Malone ML; Paegel BM What is a “DNA-Compatible” Reaction?. *ACS Comb. Sci* 2016, 18, 182–187. [PubMed: 26971959] (b)Satz AL; Cai JP; Chen Y; Goodnow R; Gruber F; Kowalczyk A; Petersen A; Naderi-Oboodi G; Orzechowski L; Strebel Q DNA Compatible Multistep Synthesis and Applications to DNA Encoded Libraries. *Bioconjugate Chem.* 2015, 26, 1623–1632.
- (11). Flood DT; Asai S; Zhang XJ; Wang J; Yoon L; Adams ZC; Dillingham BC; Sanchez BB; Vantourout JC; Flanagan ME; Piotrowski DW; Richardson P; Green SA; Shenvi RA; Chen JS; Baran PS; Dawson PE Expanding Reactivity in DNA-Encoded Library Synthesis via Reversible Binding of DNA to an Inert Quaternary Ammonium Support. *J. Am. Chem. Soc* 2019, 141, 9998–10006. [PubMed: 31136164]
- (12). Zhao GX; Huang YR; Zhou Y; Li YZ; Li XY Future challenges with DNA-encoded chemical libraries in the drug discovery domain. *Expert Opin Drug Dis.* 2019, 14, 735–753.
- (13). Duan ZL; Li W; Lei AW Nickel-Catalyzed Reductive Cross-Coupling of Aryl Bromides with Alkyl Bromides: Et₃N as the Terminal Reductant. *Org. Lett* 2016, 18, 4012–4015. [PubMed: 27472556]
- (14). Remeur C; Kelly CB; Patel NR; Molander GA Aminomethylation of Aryl Halides Using alpha-Silylamines Enabled by Ni/Photoredox Dual Catalysis. *ACS Catal.* 2017, 7, 6065–6069. [PubMed: 29354317]
- (15). (a)Tellis JC; Primer DN; Molander GA Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* 2014, 345, 433–436. [PubMed: 24903560] (b)Milligan JA; Phelan JP; Badir SO; Molander GA, Alkyl Carbon-Carbon Bond Formation by Nickel/Photoredox Cross-Coupling. *Angew. Chem., Int. Ed* 2019, 58, 6152–6163.(c)Twilton J; Le C; Zhang P; Shaw MH; Evans RW; MacMillan DWC The merger of transition metal and photocatalysis. *Nat. Rev. Chem* 2017, 1, 0052.
- (16). Brown DG; Bostrom J Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem* 2016, 59, 4443–4458. [PubMed: 26571338]
- (17). Schneider N; Lowe DM; Sayle RA; Tarselli MA; Landrum GA Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists’ Bread and Butter. *J. Med. Chem* 2016, 59, 4385–4402. [PubMed: 27028220]

- (18). Phelan JP; Lang SB; Sim J; Berritt S; Peat AJ; Billings K; Fan LJ; Molander GA, Open-Air Alkylation Reactions in Photoredox-Catalyzed DNA-Encoded Library Synthesis. *J. Am. Chem. Soc* 2019, 141, 3723–3732. [PubMed: 30753065]
- (19). Kolmel DK; Meng J; Tsai MH; Que JM; Loach RP; Knauber T; Wan JQ; Flanagan ME, On-DNA Decarboxylative Arylation: Merging Photoredox with Nickel Catalysis in Water. *ACS Comb Sci* 2019, 21, 588–597. [PubMed: 31283168]
- (20). Everson DA; Weix DJ Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem* 2014, 79, 4793–4798. [PubMed: 24820397]
- (21). Mal D; Jana AK; Mitra P; Ghosh K Benzannulation for the Regiodefined Synthesis of 2-Alkyl/Aryl-1-naphthols: Total Synthesis of Arnottin I. *J. Org. Chem* 2011, 76, 3392–3398. [PubMed: 21405112]
- (22). Gerry CJ; Wawer MJ; Clemons PA; Schreiber SL DNA Barcoding a Complete Matrix of Stereoisomeric Small Molecules. *J. Am. Chem. Soc* 2019, 141, 10225–10235. [PubMed: 31184885]
- (23). Qian Q; Zang ZH; Wang SL; Chen Y; Lin KH; Gong HG Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides (vol 24, pg 619, 2013). *Synlett*. 2013, 24, 1164–1164.
- (24). Cartier A; Levernier E; Corce V; Fukuyama T; Dhiman AL; Ollivier C; Ryu I; Fensterbank L Carbonylation of Alkyl Radicals Derived from Organosilicates through Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed* 2019, 58, 1789–1793.
- (25). Duret G, Quinlan R, Bissleret P, and Blanchard N Boron chemistry in a new light. *Chem. Sci* 2015, 6, 5366–5382. [PubMed: 28717443]
- (26). Klauck FJR; James MJ; Glorius F Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem., Int. Ed* 2017, 56, 12336–12339.
- (27). Discekici EH; Treat NJ; Poelma SO; Mattson KM; Hudson ZM; Luo YD; Hawker CJ; de Alaniz JR A highly reducing metal-free photoredox catalyst: design and application in radical dehalogenations. *Chem. Commun* 2015, 51, 11705–11708.
- (28). Lu XJ; Fan LJ; Phelps CB; Davie CP; Donahue CP, Ruthenium Promoted On-DNA Ring-Closing Metathesis and Cross-Metathesis. *Bioconjugate Chem* 2017, 28, 1625–1629.
- (29). Schreiber SL Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* 2000, 287, 1964–1969. [PubMed: 10720315]
- (30). Bolea I; Juarez-Jimenez J; de los Rios C; Chioua M; Pouplana R; Luque FJ; Unzeta M; Marco-Contelles J; Samadi A Synthesis, Biological Evaluation, and Molecular Modeling of Donepezil and N-[(5-(Benzyloxy)-1-methyl-1H-indol-2-yl)methyl]-N-methylprop-2-yn-1-amine Hybrids as New Multipotent Cholinesterase/Monoamine Oxidase Inhibitors for the Treatment of Alzheimer's Disease. *J. Med. Chem* 2011, 54, 8251–8270. [PubMed: 22023459]
- (31). Kato N; Comer E; Sakata-Kato T; Sharma A; Sharma M; Maetani M; Bastien J; Brancucci NM; Bittker JA; Corey V; Clarke D; Derbyshire ER; Dornan GL; Duffy S; Eckley S; Itoe MA; Koolen KMJ; Lewis TA; Lui PS; Lukens AK; Lund E; March S; Meibalan E; Meier BC; McPhail JA; Mitasev B; Moss EL; Sayes M; Van Gessel Y; Wawer MJ; Yoshinaga T; Zeeman AM; Avery VM; Bhatia SN; Burke JE; Catteruccia F; Clardy JC; Clemons PA; Decherer KJ; Duvall JR; Foley MA; Gusovsky F; Kocken CHM; Marti M; Morningstar ML; Munoz B; Neafsey DE; Sharma A; Winzeler EA; Wirth DF; Scherer CA; Schreiber SL Diversity-oriented synthesis yields novel multistage antimalarial inhibitors. *Nature* 2016, 538, 344–349. [PubMed: 27602946]
- (32). Gerry CJ; Wawer MJ; Clemons PA; Schreiber SL DNA Barcoding a Complete Matrix of Stereoisomeric Small Molecules. *J. Am. Chem. Soc* 2019, 141, 10225–10235. [PubMed: 31184885]
- (33). Cao ZY; Ghosh T; Melchiorre P, Enantioselective radical conjugate additions driven by a photoactive intramolecular iminium-ion-based EDA complex. *Nat. Commun* 2018, 9.
- (34). Magueur G; Crousse B; Ourevitch M; Bonnet-Delpon D; Begue JP Fluoro-artemisinins: When a gem-difluoroethylene replaces a carbonyl group. *J. Fluorine Chem* 2006, 127, 637–642.
- (35). (a) Xiao TB; Li LY; Zhou L Synthesis of Functionalized gem-Difluoroalkenes via a Photocatalytic Decarboxylative/Defluorinative Reaction. *J. Org. Chem* 2016, 81, 7908–7916. [PubMed: 27467781] (b) Lang SB; Wiles RJ; Kelly CB; Molander GA Photoredox Generation of Carbon-

Centered Radicals Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics. *Angew. Chem., Int. Ed* 2017, 56, 15073–15077.

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Figure 1.
Schematic presentation of DNA-encoded library technology

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

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