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On-DNA Hydroalkylation to Introduce Diverse Bicyclo[1.1.1]pentanes and Abundant Alkyls via Halogen Atom Transfer

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Abstract

DNA-encoded libraries have proven their tremendous value in the identification of new lead compounds for drug discovery. To access libraries in new chemical space, many methods have emerged to transpose traditional mol-scale reactivity to nmol-scale, on-DNA chemistry. However, procedures to access libraries with a greater fraction of C(sp^3) content are still limited, and the need to “escape from flatland” more readily on-DNA remains. Herein, we report a Giese addition to install highly functionalized bicyclo[1.1.1]pentanes (BCPs) using tricyclo[1.1.1.$0^{1,3}$]pentane (TCP) as a radical linchpin, as well as other diverse alkyl groups, on-DNA from the corresponding organohalides as non-stabilized radical precursors. Telescoped procedures allow extension of the substrate pool by at least an order of magnitude to ubiquitous alcohols and carboxylic acids, allowing us to “upcycle” these abundant feedstocks to afford non-traditional libraries with different physicochemical properties for the small-molecule products (i.e., non-peptide libraries with acids). This approach is amenable to library production, as a DNA damage assessment revealed good PCR amplifiability and only 6% mutated sequences for a full-length DNA tag.

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Author Contributions

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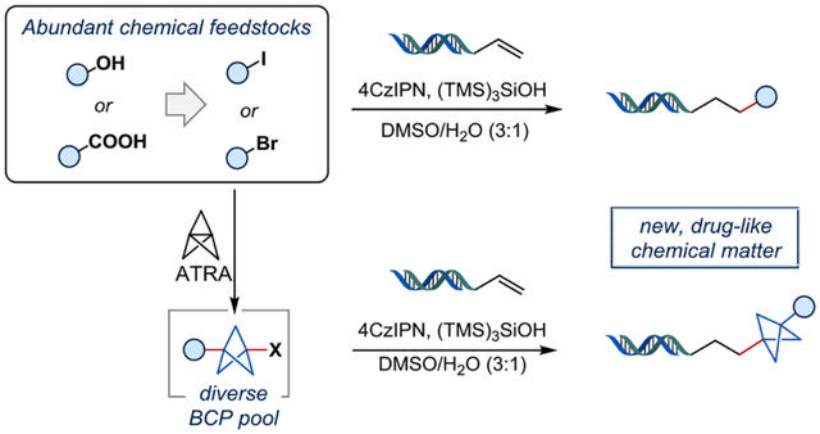
Supporting Information. Preparation of on-DNA substrates, synthesis of alkyl halides and BCP-halides, general procedure for photoinduced transformations on-DNA, NMR spectra of small molecules prepared, UPLC/MS of on-DNA reactions, results of DNA damage assessment.

Graphical Abstract



INTRODUCTION

DNA-encoded library (DEL) platforms have emerged as powerful tools for drug discovery.[1–10] They offer the advantage of requiring extremely small quantities of both the libraries and protein targets to reveal selective and potent small molecule binders, resulting in diminished costs for research and discovery efforts.[5] In creating these libraries, standard organic reactions have been adapted to fit the constraints of this noncanonical and demanding discovery platform. Executing small molecule transformations in the presence of a DNA tag introduces several method limitations. Reaction requirements include chemoselectivity for the desired transformation, functional group compatibility with the encoding DNA, and being amenable to aqueous conditions at low concentrations.[11] Furthermore, the DNA sequences must be conserved to be able to identify the attached small molecule binders following a DEL screen. The development of methods that operate within these allowances and also install the broadest diversity of scaffolds is of high interest to the DEL community.[9]

Within the DNA chemistry tool set, photoredox chemistry has demonstrated its usefulness to expand chemical space under extremely mild conditions,[12–14] creating both carbon–carbon and carbon–heteroatom bonds. Among these, C(sp^3)-C(sp^3) bond formation has been of specific interest.[7,14–19] Along these lines, Flanagan and coworkers developed a decarboxylative Giese-addition to introduce stabilized α-amino- or α-oxy radicals on-DNA (Figure 1).[20,21]

Following this report, Liu[22] and Lu[23] independently reported methods for α-amino radical addition to on-DNA alkenes, providing amino-alkylated products. Although accessing new, sp^3-rich chemical space on-DNA, these methods and others[24,25] are limited to stabilized radicals, while non-stabilized radical precursors react with low efficiency.

To improve the three-dimensionality and physicochemical properties of lead compounds, drug discovery chemists have long endeavored to replace the venerable arene ring in an effort to “escape from flatland”.[26,27] Thus, arene bioisosteres such as bicyclo[1.1.1]pentanes

(BCPs), bicyclo[2.2.2]octanes, or cubanes have been of interest to the synthesis community.[28,29] Recent advances include efficient preparations of diversely substituted BCPs, or the Giese-type additions of non-stabilized BCP radical intermediates to alkene coupling partners, delivering sp^3-rich products.[30] Likewise, the ability to install arene bioisosteres on-DNA is of significant interest to the DEL field, but there exist only a few examples under DNA-compatible reaction conditions.[31–33] In 2018, Baran and coworkers[34] applied a bicyclo[2.2.2]octane *N*-hydroxyphthalimide (NHPI) redox active ester in an on-DNA Giese reaction with zinc nanopowder as a reductant, but BCP or cubane examples were not included. To the best of our knowledge, there has only been one example of a BCP radical addition on-DNA, likely because of the difficulty of generating the corresponding non-stabilized radical intermediate.[30] Thus, there exists a gap of general methods to introduce diversely substituted arene bioisosteres on-DNA.

Inspired by the work of the Anderson group,[30] we sought to develop radical couplings via halogen atom transfer (XAT) to access diverse on-DNA chemical matter (Figure 1). Furthermore, by using [1.1.1]propellane as an optional radical linchpin, two completely different products can be obtained from the same organic halide. We envisioned utilizing what has been historically viewed as limitations of DEL chemistry (low substrate concentration, excess of reagents, etc.) to our advantage to achieve desired reactivity and incorporate previously unprecedented substrates. As such, readily available and diverse alkyl- and (hetero)aryl halide feedstocks would be enabled for library preparation. Even further, we sought to upcycle carboxylic acid and alcohol feedstocks by using well-known methods for functional group interconversions (FG → I), which could then be telescoped into the on-DNA hydroalkylation chemistry. As an additional advantage, on-DNA photoredox methods have proven to be relatively less damaging to the DNA tag than typical DEL chemistry workhorses, such as Suzuki-Miyaura couplings or CuAAC.[11,35] Toward this end, this approach offers access to more drug-like DEL libraries of higher fidelity with superior Fsp^3 content.

RESULTS AND DISCUSSION

To initiate our investigation, *p*-styrene DNA headpiece **HP-1** was used as a substrate because of its anticipated effectiveness as a radical acceptor (Table 1). The bicyclo[1.1.1]pentane derivative **1a** was prepared from commercially available 3-iodoalanine in an excellent yield *via* atom transfer radical addition (ATRA).[36]

The conditions were made amenable to on-DNA synthesis by using: 0.5 equivalent of 4CzIPN (1 mM in DMSO), 25 equivalents of BCP-I **1a** (25 mM in DMSO), 50 equivalents of tris(trimethylsilyl)silanol [$(TMS)_3SiOH$] (50 mM in DMSO), and 100 equivalents of Na_2CO_3 (400 mM in H_2O), to afford the expected product after 5 min of irradiation using an H-150 blue Kessil lamp at room temperature, affording product **2a** in a 91% yield (entry 1, Table 1). The developed on-DNA reaction requires a photosensitizer (entry 2), a radical mediator (entry 3), and light (entry 4) for reactivity. The use of a base led to increased reactivity (entry 5). In Anderson's work, the use of a mediator was reported as being crucial to generate the BCP radical.[30] Either tris(trimethylsilyl)silane [$(TMS)_3SiH$] or $(TMS)_3SiOH$ led to the desired product, albeit the two mediators were proposed to

function through two distinct mechanistic pathways. In the present case, when $(TMS)_3SiH$ was used instead of $(TMS)_3SiOH$, the yield dropped to 40% (entry 6). In alignment with studies from the MacMillan group, we believe that the observed increased reactivity when $(TMS)_3SiOH$ is employed as the radical mediator is because of an efficient halogen atom transfer reaction (XAT) to generate the requisite BCP radical intermediate.[37,38] The use of other photocatalysts such as $Ir(ppy)_3$ or $[Ir\{dF(CF_3)_2ppy\}_2(dtbbpy)]PF_6$ led to DNA degradation and a decrease in yield, respectively (entries 7 and 8), in contrast to the off-DNA precedent, which proceeded most effectively with an iridium photocatalyst. Employing a weaker base gave a 68% yield (entry 9). Interestingly, although the off-DNA reaction occurred in a $MeOH/H_2O$ mixture,[30] the on-DNA reaction gave a much lower yield (33%) (entry 10). Overall, this protocol is particularly noteworthy because of the ability to perform this reaction within minutes under air without degassing.

We then sought to evaluate the scope of this transformation with **HP-1** using a set of BCP halides. Among them, a wide range of substrates served as competent partners, including those containing bifunctional handles (**2a**, **2j**), a free alcohol (**2d**), *N*-Boc-protected amines (**2f**, **2h**, **2i**), a sugar (**2g**), and methyl esters (**2e**, **2o**, **2l**, **2r**), all with moderate to excellent yield. The amino-substituted BCP[30] (**2n**) performed well under the developed conditions.

BCP-iodides containing aryl substituents were also accessible under these conditions. Notably, arenes could be brought in through either functionalization at the benzylic position (**2k**, **2l**, **2m**) or through direct substitution of electron-deficient aryl iodides, generating $C(sp^2)$-$C(sp^3)$ bonds prior to halo-BCP coupling (**2p-v**). In addition, by increasing the number of equivalents, BCP-bromides can also be used, affording products **2e** and **2o** in 63% and 46% yields, respectively. To the best of our knowledge, this represents the first time that BCP bromides could be leveraged for a Giese-type reaction on- or off-DNA. We believe that this result indicates a unique advantage that is available to on-DNA reactivity, as the small scale of reactions (nmol scale) and large excess of reagents (20–100 equivs), unlock challenging reactivity paradigms that would be prohibitive to investigate with canonical mol-scale reaction development conditions. Beyond BCP-containing substrates, we also demonstrated the generality of the developed on-DNA reactivity as applied to primary-, secondary-, and tertiary alkyl halides (Figure 2).

The reaction accommodates both alkyl bromides and -iodides, albeit using a slightly decreased amount of alkyl halides and mediator than for the BCP halides (20 equivalents and 40 equivalents, respectively). This adjustment prevented the formation of byproducts corresponding to double addition by mass analysis of the alkyl radical (see SI, p S57 – S61). The unprotected pyrazole **3d** afforded the desired product with **HP-1** in 85% yield. Interestingly, the *N*-Fmoc-protected substrate **3m** demonstrated excellent reactivity, with no observed deprotection despite the presence of sodium carbonate base. The tertiary adamantyl radical obtained from the brominated substrate gave product **3n** in >95% yield. The [2.2.2]bicyclooctane **3o** performed well in the reaction, with a 56% yield starting from the bromide derivative.

Exploration of the scope for on-DNA alkene acceptors (Figure 3) demonstrated that the meta-substituted **HP-2** delivered the desired products in excellent yields with a secondary

radical (**4a**) and a tertiary radical (**4b**). However, the addition of BCP-iodide (**4c**) with **HP-2** failed to produce the product. *ortho*-Substituted styrene **HP-3** provided moderate yields when reacted with substituted BCP-iodide substrates. As 3-alkyl-substituted BCP radicals are considered to be electron rich,[39–41] they should react preferentially with electron-poor alkenes. This hypothesis is in line with our observation of the lack of reactivity of **HP-2** with the BCP-iodide, as it does not benefit from the electron-withdrawing effect of the carboxamide. However, electron-deficient vinyl pyridines **HP-4**, **HP-5** and **HP-6** reacted smoothly with several BCP-iodides under the developed protocol. *meta*-Functionalization can be achieved with **HP-5**, and it is compatible with a variety of substrates: a deprotected piperidine **4j**, quinoline- and pyrazole-containing BCPs (**4o, 4p**), and aryl BCPs possessing two useful handles for further post-functionalization (**4m-n**) were obtained in moderate to good yields. The substituted styrene **HP-7** behaves as an excellent radical acceptor and offers the possibility to achieve further post-functionalization using the aryl halide. Methylacrylamide **HP-8** required a more concentrated solution but was a very accommodating substrate. This activated alkene was of high interest because it allowed access to arene-free products (**4y**, **4z**) and demonstrated the potency of the method to provide a further increase in Fsp^3 in good yields. With the trifluoromethyl-substituted styrene (**HP-9**), the gem-difluoroalkene adduct was observed instead of the Giese-type addition product (**4aa-ad**) (Figure 4). This observed defluorinative alkylation mechanism provides access to interesting ketone isosteres on-DNA.[42]

We then sought to explore whether the scope could be expanded beyond alkyl- and (Het)Ar-halides to other abundant chemical feedstocks. Toward that end, “telescoped” processes for three substrate classes were pursued: activated esters, carboxylic acids, and alcohols. ‘Telescoped’ refers to performing two or more reactions without further purification in between (e.g., no chromatography, distillation, or crystallization), thereby streamlining the workflow and reducing resource waste. First, the redox active esters were used to form alkyl iodides,[43] which were then reacted directly with the styrene headpiece. Secondary- (**3i**) and tertiary (**3p**) alkyl systems provided products in more than 90% yield, while the BCP substrate yielded the desired product **2o** with only 28% yield under these conditions (Figure 5). A control experiment using redox active ester (**S2a**) directly as a radical precursor also provided product **3i** in a low yield (< 25%), as it is known that a stoichiometric metal reducing agent is required for this purpose (see SI for details). The second strategy employed carboxylic acids. Previous photo-induced decarboxylative alkylations have been reported as shown in Figure 1[20], by our group[44] in 2019. However, the present methods (from activated esters and carboxylic acids) allow non-stabilized secondary- and tertiary carboxylic acids to be used as precursors for the Giese addition to the less reactive DNA styrene, which has not been previously reported. Using this method,[45] primary carboxylic acids performed smoothly and gave products **3q** in 67% yield and **3r** in 90% yield. A secondary carboxylic acid provided **3i** in 76% yield. Iodocubane was generated from the corresponding carboxylic acid and reacted with **HP-1** to give **3s** in 84% yield, enabling the introduction of yet another interesting arene bioisostere (Figure 5).

The last strategy employed alcohols in the telescoped reaction, another class of abundant and easily accessible building blocks. Using methyltriphenoxyphosphonium iodide to generate

the iodide *in situ*[46] allowed the introduction of primary- and secondary radicals with >90% yield (**3t**, **3u, 3i**) (Figure 5). Of special note, the *N*-Fmoc-threonine-iodide derivative was successfully generated and added to **HP-1** to give **3m** in >95% yield.

A critical metric for any new on-DNA chemistry is to ensure that the integrity of the encoding tag is maintained well enough to be employed in actual library production, an important aspect that is often not fully reported.[11,35] It is essential that the encoding DNA is able to be amplified and sequenced following a DEL screen such that the corresponding small molecule and potential target binder can be revealed. If the dsDNA is significantly damaged, then the molecule cannot be identified, contributing to a false negative result.

Toward this end, the *p*-styrene substrate was prepared on an elongated DNA tag and then subjected to the reaction or other control conditions. Upon isolation of the single constructs by ethanol precipitation and filtration, a series of ligations were performed, mimicking the library production process, followed by quantitative polymerase chain reaction (qPCR) and next-generation sequencing (NGS) analysis of the full-length tag (see SI for details). Several controls were prepared in the same way. The ligations for all four samples proceeded with excellent efficiencies (97 –100%), as confirmed by LC-MS and/or gel. Amplification efficiency of the full-length sequence by qPCR was comparable for all four samples (90 – 92%) and the reaction maintained 63% amplifiable DNA, as compared to the no light, no reagents control (entry 1, Table 2). In contrast, some of the most often used, non-photonic on-DNA chemistries have only 30 – 50% amplifiable DNA remaining.[35] Finally, NGS analysis revealed that the reaction sample had only 6% mutated sequences. Notably, the no light with reagents control had 7% mutated sequences, while the complementary control (light, but no reagents) had 0%. The observation that the reagents and not the irradiation were the cause of sequence mutations for the current method supports the hypothesis that photonic on-DNA chemistries offer a significant advantage over other protocols, particularly those methods that require high temperatures, longer reaction times, and metal-catalysis.

CONCLUSION

In conclusion, we have capitalized upon what have been considered limitations to on-DNA chemistry to develop a convenient, fast, general, and robust method to increase the Fsp^3 content of DNA-encoded libraries with abundant chemical feedstocks. We successfully introduced a diverse set of arene bioisosteres, such as BCPs and cubanes, to radical acceptors on-DNA. Free alcohol, free amine, *N*-Fmoc-protected amine, ketone, bromide, and chloride functional groups are tolerated, introducing a possibility of further post-functionalization. A variety of DNA-conjugated olefin substrates are compatible with this transformation. Furthermore, the integrity of the DNA tag was preserved under these mild photonic reaction conditions, such that this method can be successfully employed to produce DNA-encoded libraries that cover previously inaccessible chemical space utilizing a larger subset of compatible and diverse building blocks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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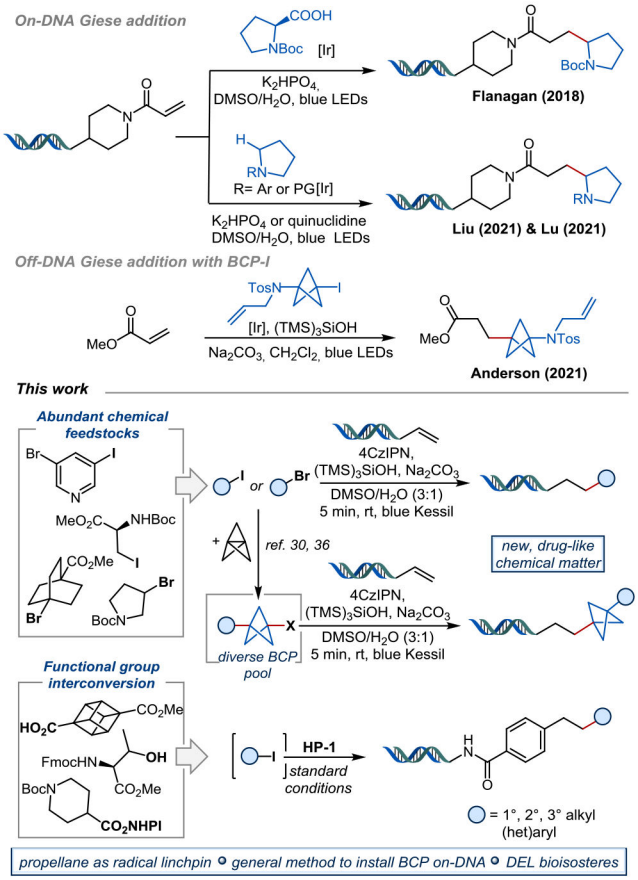


Figure 1.
State-of-the-art and this work

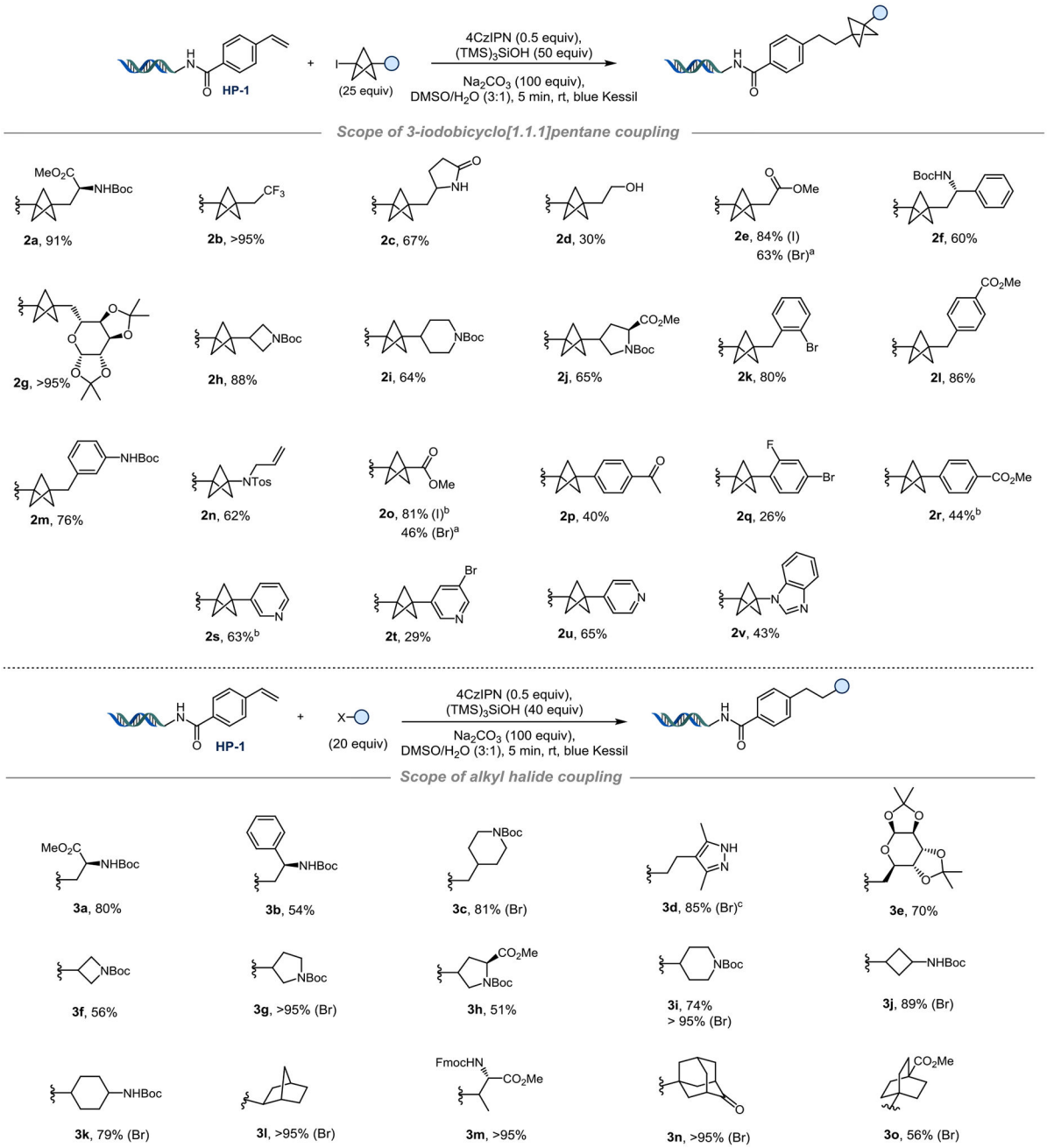


Figure 2.

Top. Scope of radical coupling with 3-iodobicyclo[1.1.1]pentanes. The reaction was performed on 10 nmol scale for **HP-1** (2 mM in H_2O, 1.0 equiv), 4CzIPN (1 mM in DMSO, 0.5 equiv), BCP-I (25 mM in DMSO, 25 equiv), $(TMS)_3SiOH$ (50 mM in DMSO, 50 equiv), Na_2CO_3 (400 mM in H_2O, 100 equiv), rt, 5 min, blue Kessil. *a*) 50 equiv of BCP-I (50 mM in DMSO) and 100 equiv of $(TMS)_3SiOH$ (100 mM in DMSO). *b)* 20 equiv of BCP-I (20 mM in DMSO) and 40 equiv of $(TMS)_3SiOH$ (40 mM in DMSO). *Bottom.* Evaluation of primary, secondary, and tertiary halides. Yields are indicated for alkyl iodides unless otherwise stated. **HP-1** (2 mM in H_2O, 10 nmol, 1 equiv), 4CzIPN (1 mM in DMSO,

0.5 equiv), alkyl halide (20 mM in DMSO, 20 equiv), $(TMS)_3SiOH$ (40 mM in DMSO, 40 equiv), Na_2CO_3 (400 mM in H_2O, 100 equiv), rt, 5 min, blue Kessil. *c)* 40 equiv of alkyl-Br (40 mM in DMSO) and 40 equiv of $(TMS)_3SiOH$ (40 mM in DMSO)

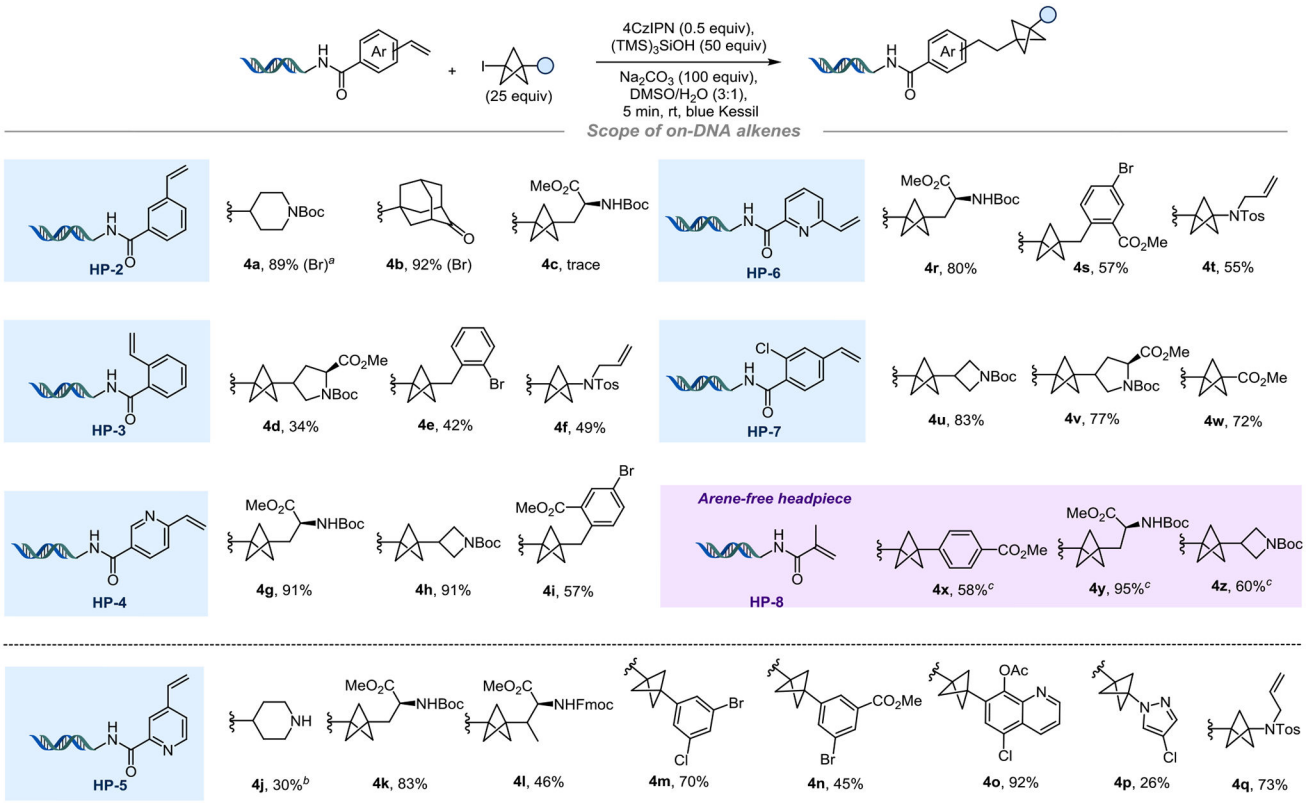


Figure 3.

Scope of the olefin-functionalized DNA headpiece. *a)* alkyl bromide (20 mM in DMSO, 20 equiv) and $(TMS)_3SiOH$ (40 mM in DMSO, 40 equiv). *b*) 200 equiv of base, starting from the piperidine HBr salt. *c*) BCP-I (30 mM in DMSO, 15 equiv) and $(TMS)_3SiOH$ (60 mM in DMSO, 30 equiv).

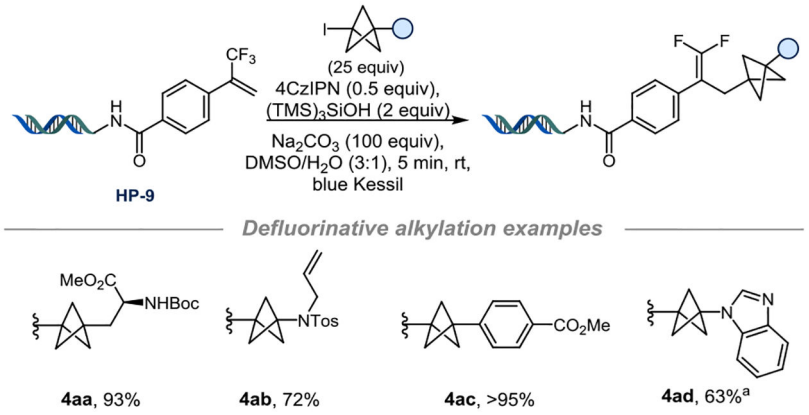


Figure 4.

Defluorinative alkylation of CF_3-alkene-functionalized DNA headpiece **HP-9**. *a)* BCP-I (20 mM in DMSO, 20 equiv), $(TMS)_3SiOH$ (20 mM in DMSO, 20 equiv)

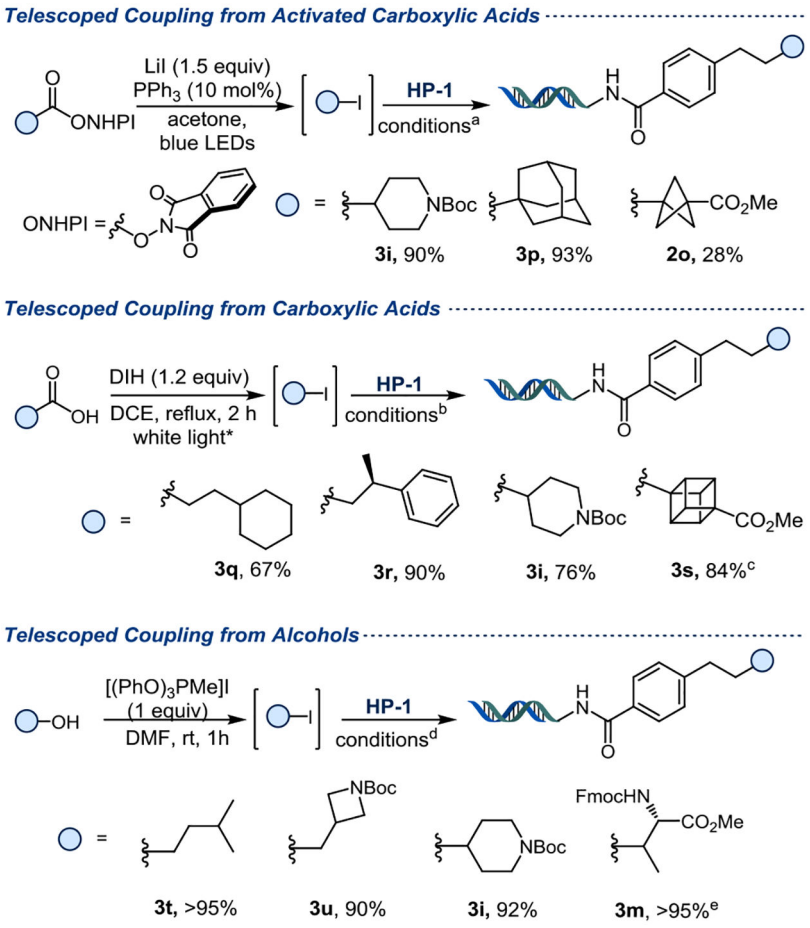
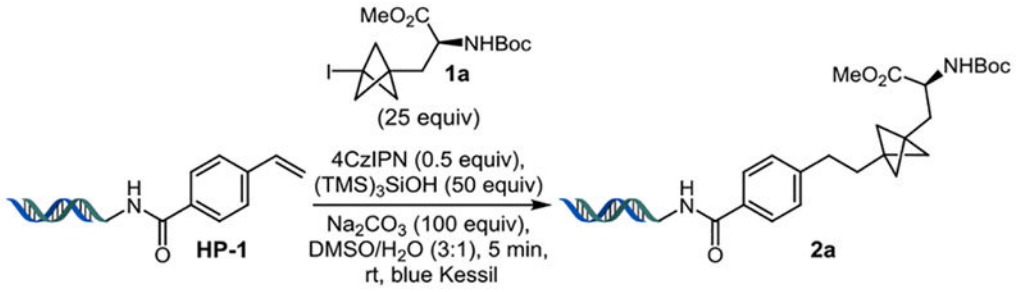


Figure 5.

Telescoped reactions with additional chemical feedstocks. DIH = 1,3-diiodo-5,5'-dimethylhydantoin. The on-DNA reaction was performed on 10 nmol scale of **HP-1** (2 mM in H_2O, 1.0 equiv), 4CzIPN (1 mM in DMSO, 0.5 equiv), Na_2CO_3 (400 mM in H_2O, 100 equiv), rt, 5 min, blue Kessil. *a)* 25 equiv of alkyl iodide (25 mM in DMSO) and 40 equiv of $(TMS)_3SiOH$ (40 mM in DMSO); *b)* 20 equiv of alkyl iodide (20 mM in DMSO) and 40 equiv of $(TMS)_3SiOH$ (40 mM in DMSO); *c)* 25 equiv of alkyl iodide (25 mM in DMSO) and 50 equiv of $(TMS)_3SiOH$ (50 mM in DMSO); *d)* 40 equiv of alkyl iodide (40 mM in DMSO) and 40 equiv of $(TMS)_3SiOH$ (40 mM in DMSO); *e) off-DNA*: 3 equiv of $[(PhO)_3PMe]I$, overnight. *On-DNA*: 40 equiv of alkyl iodide (40 mM in DMSO) and 40 equiv of $(TMS)_3SiOH$ (40 mM in DMSO).

Table 1.

Optimization of on-DNA radical coupling.



Entry	Deviations from Standard Conditions	Yield (%)
1	None	91%
2	No photocatalyst	n.d. (71% rsm)
3	No $(TMS)_3SiOH$	decomposition
4	No light	n.d. (89% rsm)
5	No base	21%
6	$(TMS)_3SiH$ instead of $(TMS)_3SiOH$	40%
7	$Ir(ppy)_3$ instead of 4CzIPN	decomposition
8	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ instead of 4CzIPN	17%
9	$NaHCO_3$ instead of Na_2CO_3	68%
10	MeOH instead of DMSO	33%

Standard conditions: DNA-styrene (2 mM in H_2O, 10 nmol, 1 equiv), **1a** (25 mM in DMSO, 25 equiv), 4CzIPN (1 mM in DMSO, 0.5 equiv), $(TMS)_3SiOH$ (50 mM in DMSO, 50 equiv), Na_2CO_3 (400 mM in H_2O, 100 equiv), rt, 5 min, blue Kessil. n.d. = product not detected. rsm = returned starting material

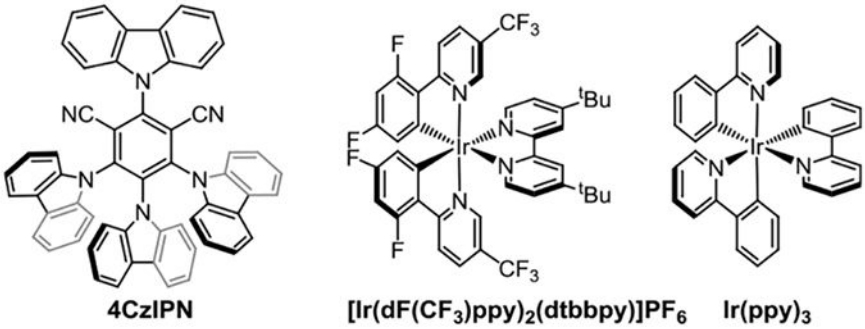
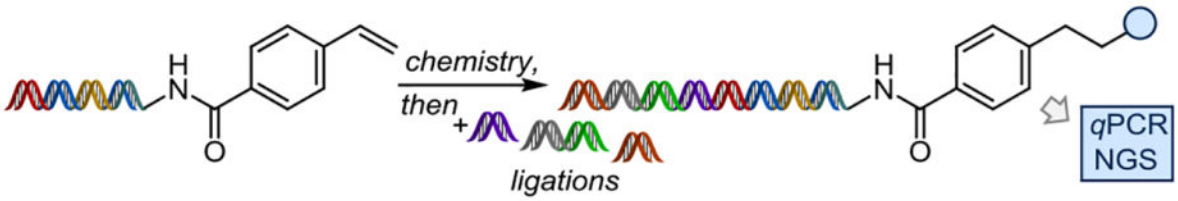


Table 2.

DNA damage assessment.



Entry	Conditions	% amplifiable DNA	% mutated sequences
1	standard reaction conditions	63%	6%
2	reagents with no irradiation control	75%	7%
3	irradiation with no reagents control	71%	0%
4	no irradiation, no reagents control	100%	0%