Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2023, **14**, 2713

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 10th January 2023
Accepted 8th February 2023

DOI: 10.1039/d3sc00144j

rsc.li/chemical-science

Dearomative intermolecular [2 + 2] photocycloaddition for construction of C(sp^3)-rich heterospirocycles on-DNA†

Longbo Li,[a] Bianca Matsuo,[a] Guillaume Levitre,[a] Edward J. McClain,‡[bd] Eric A. Voight,[b] Erika A. Crane‡*[c] and Gary A. Molander*[a]

DNA-encoded library (DEL) screens have significantly impacted new lead compound identification efforts within drug discovery. An advantage of DELs compared to traditional screening methods is that an exponentially broader chemical space can be effectively screened using only nmol quantities of billions of DNA-tagged, drug-like molecules. The synthesis of DELs containing diverse, sp^3-rich spirocycles, an important class of molecules in drug discovery, has not been previously reported. Herein, we demonstrate the synthesis of complex and novel spirocyclic cores *via* an on-DNA, visible light-mediated intermolecular [2 + 2] cycloaddition of olefins with heterocycles, including indoles, azaindoles, benzofurans, and coumarins. The DNA-tagged *exo*-methylenecyclobutane substrates were prepared from easily accessible alkyl iodides and styrene derivatives. Broad reactivity with many other DNA-conjugated alkene substrates was observed, including unactivated and activated alkenes, and the process is tolerant of various heterocycles. The cycloaddition was successfully scaled from 10 to 100 nmol without diminished yield, indicative of this reaction's suitability for DNA-encoded library production. Evaluation of DNA compatibility with the developed reaction in a mock-library format showed that the DNA barcode was maintained with high fidelity, with <1% mutated sequences and >99% amplifiable DNA from quantitative polymerase chain reaction (PCR) and next generation sequencing (NGS).

Introduction

Spirocycles are important structural motifs in drug discovery, as their three-dimensionality provides an opportunity to orient functional groups in different spatial directions, avoiding the restrictions of planarity that are commonly encountered with highly unsaturated, sp^2-rich arene cores.[1–3] In particular, spiro[3.3]heptanes represent a unique class of spirocyclic compounds with two cyclobutane rings that project functional groups into non-coplanar space (Fig. 1a).[4] Because of their novel 3D properties, spiro[3.3]heptanes have become a point of interest for medicinal chemists.[5–9] Syntheses of spiro[3.3]heptanes have been mostly achieved *via* photochemical [2 + 2] cycloaddition.[10–12] However, to our knowledge, a general method for the preparation of diverse spiro[3.3]heptanes on-DNA has yet to be reported.

DNA-encoded library (DEL) technology has emerged as a powerful tool for hit identification in modern drug discovery.[13–21] DELs can be readily assembled to afford exceptionally large combinational libraries that can be efficiently screened in a cost-efficient manner, as only nanomolar quantities of both drug-like molecules and the biomolecular targets are required.[21] Furthermore, prior successes in the identification of valuable hits for challenging therapeutic targets *via* DEL chemistry have attracted increasing attention in academia and industry.[22,23] Solution-based chemical syntheses on-DNA must be carried out within strict reaction parameters, as the transformations must be tolerant of aqueous conditions and the basic DNA backbone.[24,25] To this end, visible light-mediated transformations have attracted significant attention in DEL chemistry for the ability to generate novel C–C bonds[26–41] while expanding chemical space under extremely mild conditions.[42–44] For example, Kölmel and coworkers demonstrated that this mild reactivity paradigm could be utilized for the synthesis of strained cyclobutane scaffolds on-DNA *via* visible light-mediated [2 + 2] photocycloaddition between cinnamate substrates and styrene derivatives (Fig. 1b).[41] Additional

[a]Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, USA. E-mail: gmolandr@sas.upenn.edu

[b]Drug Discovery Science & Technology, Discovery Research & Development, AbbVie, Inc., 1 North Waukegan Rd, North Chicago, Illinois 60064-1802, USA

[c]Drug Hunter, Inc., 13203 SE 172nd Ave, Suite 166 PMB 2019, Happy Valley, Oregon, 97086, USA. E-mail: erika@drughunter.com

[d]Department of Chemistry, University of Wisconsin–Madison, Madison, Wisconsin 53706, USA

† Electronic supplementary information (ESI) available: Experimental procedures and characterization. CCDC 2215502. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc00144j

‡ EAC and EJM are former employees of AbbVie.

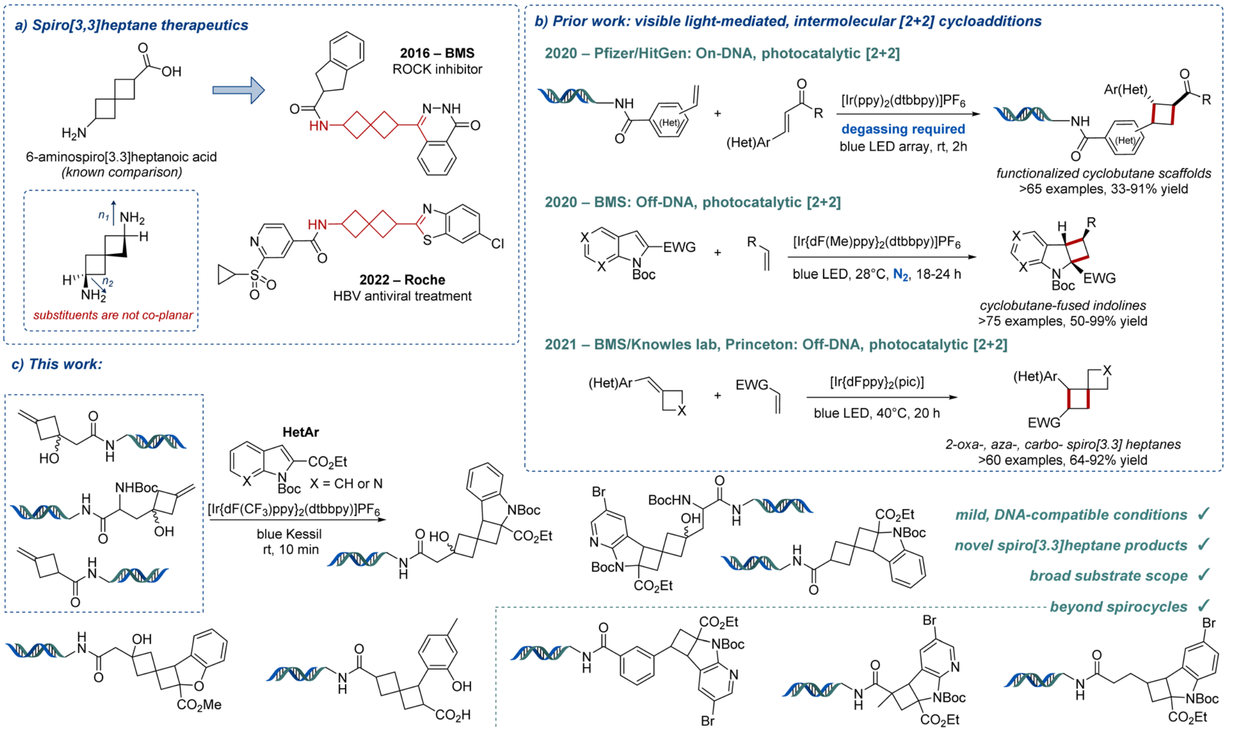


Fig. 1 Background and motivation for this work.

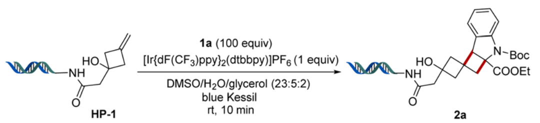
relevant transformations have been performed off-DNA, including a highly diastereoselective dearomative [2 + 2] photocycloaddition of indoles and diverse alkenes to afford cyclobutene-fused indolines, also requiring inert conditions.[45] New heteroarene dearomative functionalization strategies have recently demonstrated great value, particularly those enabled by visible light, enhancing the molecular complexity and three-dimensionality of these venerable products.[46] Additionally, BMS in collaboration with the Knowles laboratory reported a different [2 + 2] photocycloaddition to access polysubstituted (hetero)spiro[3.3]heptane products.[12]

A recent collaborative study from our groups focused on unlocking the radical reactivity of 1,3-disubstituted [1.1.1]bicyclopentyl (BCP) halides for on-DNA reactions.[33] Enabled by visible-light photochemistry, the method allowed the preparation of diverse, sp^3-rich chemical matter on-DNA. As part of our continued study of BCP reactivity, we sought to develop a method that utilized the *exo*-methylenecyclobutanol products derived from the strain-driven hydrolytic ring opening of DNA-conjugated BCP halides (Fig. 1c).[47,48] With well-documented, mild, DNA-compatible reactivity, we envisioned that visible-light photochemistry could be leveraged to engage these and other olefins in a triplet-sensitized [2 + 2]-cycloaddition with indoles and other heterocycles, providing access to novel spirocyclic substructures on-DNA.[12,45,49] As an extension of this chemistry, we also explored additional DNA-conjugated olefin substrates, including *exo*-methylenespiro[2.3]hexanes,[50] unactivated alkenes, styrene derivatives, and acrylamides. The latter three have revealed significant reactivity toward indoles and other heterocycles to form fused ring systems.[45] Finally, we focused on important and abundant scaffolds in drug discovery as the [2 + 2] coupling partners, including indoles, azaindoles, benzofurans, and coumarins, generating complex spiro- and fused polycyclic ring systems.

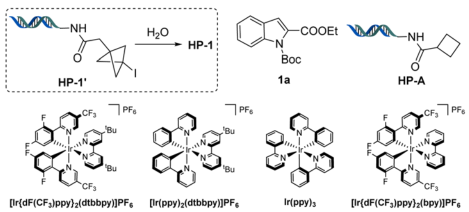
Results and discussion

The initial *exo*-methylene cyclobutanol **HP-1** was prepared by solvolysis of 1-iodo-bicyclo[1.1.1]pentane (BCP-I) on-DNA (**HP-1′**, Table 1). **HP-1′** and other derivatives were prepared by reaction of [1.1.1]propellane with abundant alkyl- or aryl iodides *via* atom transfer radical addition (ATRA).[33,51] The reaction of **HP-1** and ethyl indole-2-carboxylate (**1a**) was investigated to determine suitable reaction parameters (Table 1). Quantitative conversion was observed when using one equivalent of photosensitizer $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ and a small amount of glycerol as cosolvent in under 10 minutes of blue Kessil lamp irradiation at room temperature (>95%, entry 1, Table 1). Control experiments demonstrated that the reaction requires photosensitizer (entry 2), light (entry 3), and glycerol (entry 4), which likely acts as radical scavenger.[41] Other results indicated that the reaction is not complete after 5 min (entry 5), and fewer equivalents (25 and 50 equivalents, respectively) of indole **1a** result in slightly lower yields (entries 6 and 7). Interestingly, by increasing the number of equivalents of indole to 200, a lower reaction yield was also observed (67%) with recovery of starting material (entry 8). We expect this to be caused by the dimerization of indole **1a**,[45] as the probability of self-reaction increases with indole concentration under the fixed catalyst concentration, illumination conditions, and reaction duration.

Table 1 Optimization of the [2 + 2] cycloaddition[a]



Entry	Deviations from standard conditions	Yield (%)
1	None	>95
2	No photocatalyst	n.d. (>95 rsm)
3	No light	n.d. (>95 rsm)
4	No glycerol	Degradation
5	5 min instead of 10 min	75 (25 rsm)
6	25 equiv. of indole	88
7	50 equiv. of indole	93
8	200 equiv. of indole	67 (19 rsm)
9	MeOH instead of DMSO	15 (68 rsm)
10	DMA instead of DMSO	44
11	$Ir(ppy)_2(dtbbpy)]PF_6$	n.d. (71 rsm)
12	$Ir(ppy)_3$	n.d. (70 rsm)
13	$[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$	83
14	**HP-A** instead of **HP-1**	n.d. (71 rsm)



[a] Standard conditions: DNA (2 mM in H_2O, 10 nmol, 1 equiv.), **1a** (100 mM in DMSO, 100 equiv.), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2 mM in DMSO, 1 equiv.), glycerol (2 μL in 8 μL of DMSO), rt, 10 min, blue Kessil. Work-up: ethanol precipitation. n.d. = product not detected. rsm = recovered starting material.

Solvents other than DMSO, such as methanol and DMA were investigated, but gave lower yields (entries 9 and 10). Unsurprisingly, other iridium complexes with lower triplet state energies (EnT) such as $[Ir(ppy)_2(dtbbpy)]PF_6$, which was used in the previous on-DNA photocatalytic [2 + 2] cycloaddition,[41] as well as $Ir(ppy)_3$ did not yield any product (entries 11 and 12). $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ proved to be a viable alternative photosensitizer, providing the desired product in 83% yield (entry 13). A control experiment with **HP-A** (entry 14) demonstrated that the double-stranded DNA tag is not participating in the [2 + 2] photocycloaddition. Overall, quantitative yields were achieved within 10 min without any degassing, providing an expedient and convenient access to a unique class of molecules on-DNA.

To probe the regio- and stereoselectivity of the reaction on-DNA, off-DNA reactions were conducted between **1a** and ethyl 3-methylenecyclobutane-1-carboxylate (see ESI Section 3.1† for details). Only one regioisomer was observed, which is consistent with previous off-DNA reports.[45] However, four stereoisomers (two sets of diastereomeric enantiomers) were generated, in a 1.3 : 1 ratio by chiral supercritical fluid chromatography (SFC). Despite the low stereoselectivity for this cycloaddition, the unprecedented novelty of these products covers uncharted chemical space, and methods to deconvolute DEL hits as stereoisomeric mixtures of comparable complexity are well established.[52]

We evaluated the scope of cycloaddition partners, reacting many diverse indoles and azaindoles with **HP-1** (Fig. 2). Indoles with various functional groups at different positions about the aromatic ring resulted in good to excellent yields (**2b–2i**). Functional groups including halogens (**2b–2c**), a nitrile (**2d**), and CF_3 (**2e**) were well tolerated with yields >80%. Functional handles at the 5-, 6-, 7-, and 8-positions of the indole ring including F and Cl substituents, as well as methyl and ester groups, also performed well under the standard conditions (**2f–2i**). Azaindoles and pyrrolo[2,3-*d*]pyrimidines with additional functional groups (Cl, Br, or ether substituents) gave good to excellent yields (**2j–2p**). Various electron-withdrawing groups at the 2-position of the indole were tolerated in this reaction. Indole-2-carboxamides provided moderate to good yields of cycloaddition products (**2q**, **2r**). A 2-cyano-substituted indole provided a lower yield of 28% (as compared to the corresponding ester **2s**). Even further, *N*-acetyl-protected indoles afforded moderate yields of products (**2t, 2u**).

Commercially available Boc-3-iodo-L-alanine methyl ester was used to prepare methylenecyclobutanol substrate **HP-2** utilizing the same strategy as used with **HP-1**. Diverse indoles **3a–3c** and azaindoles **3d–3f** performed well in reactions with this headpiece, indicating that the cycloaddition is not limited to DNA-conjugated *exo*-methylenecyclobutanol **HP-1**.

We expanded this reaction further to afford dispiro[2.1.3.1] nonane ring systems. The DNA-conjugated *exo*-methylene spiro [2.3]hexane substrates were prepared using a nickel-catalyzed cyclopropanation of [1.1.1]propellane and readily accessible styrenes or acrylates.[50] **HP-3** demonstrated good reactivity with indoles containing various groups at the 2-position, including an ester (**4a**), amide (**4c**), and nitrile (**4d**). Azaindole **4b** and *N*-Ac indole **4e** also worked well with **HP-3**. Related **HP-4**, prepared from the corresponding vinyl pyridine, performed well with indoles **5a–5e** in >90% yield. Indoles with 2-substituted amides gave moderate to excellent yields (**5f**, **5g**, and **5h**). 2-Cyano and *N*-Ac indoles afforded products **5i** and **5j** in 70% and 90% yields, respectively. **HP-5** was prepared from commercially available 3-*exo*-methylenecyclobutanecarboxylic acid and performed well with various indoles (**6a**, **6c–6f**) and azaindoles (**6b**). Even further, we successfully scaled this reaction from 10 nmol (**6b**) to 100 nmol (**6b′**) with no loss in yield, revealing excellent promise for subsequent functionalization and implementation in DNA-encoded library production.

The reactivity of unactivated alkene headpieces was also investigated (Fig. 2). For **HP-6**, 50 equivalents of indole gave higher yields (*e.g.*, **7a**, 79% yield) than 100 equivalents (*e.g.*, **7a′**, 46% yield + 39% starting material) after irradiation for 10 min. This is likely caused by the lower reactivity of **HP-6** compared to *exo*-methylenecyclobutane headpieces **HP-1–HP-4**. The indole at a higher concentration competes with DNA-conjugated alkenes and reacts with the excited triplet 1,2-diradical indole species to form a dimer, which leads to a lower yield of product in the same reaction time. Similar products have been observed in analogous off-DNA [2 + 2] photocycloaddition studies.[45] Various indoles (**7a–7d**) and azaindoles (**7e** and **7f**) performed

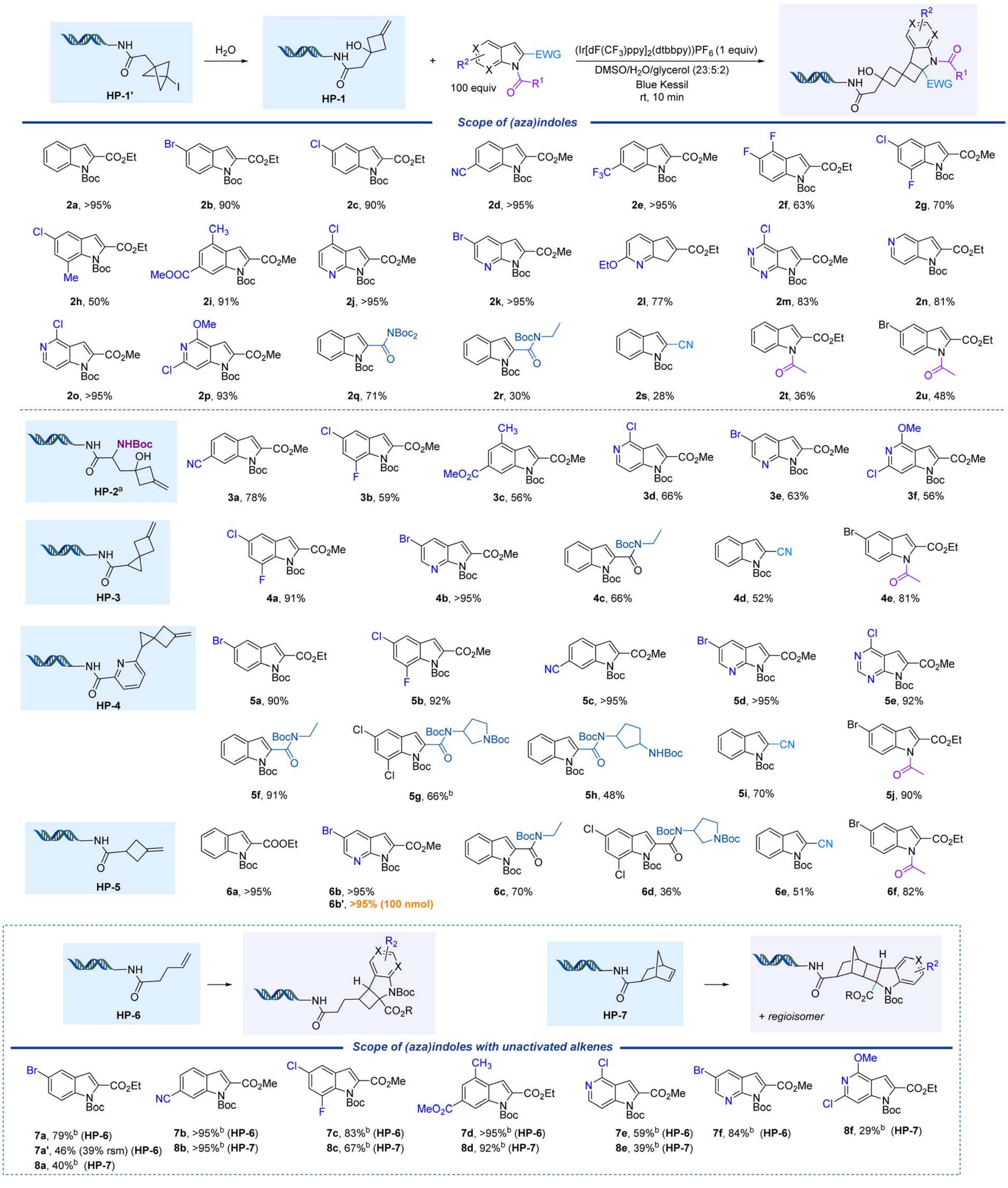


Fig. 2 Scope of (aza)indoles with DNA-tagged *exo*-methylenecyclobutanes and unactivated alkenes. DNA substrate (2 mM in H_2O, 10 nmol, 1 equiv.), (aza)indole (100 mM in DMSO, 100 equiv.), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2 mM in DMSO, 1 equiv.), glycerol (2 μL in 8 μL of DMSO), rt, 10 min, blue Kessil. Work-up: ethanol precipitation. [a] **HP-2** purity was 88%. [b] (Aza)indole (50 mM in DMSO, 50 equiv.).

well under this set of conditions. We expect high regioselectivity of **7a–7f** as indicated by a similar reaction off-DNA.[45] Another headpiece, **HP-7**, was also investigated with indoles (**8a–8d**) and azaindoles (**8e** and **8f**) (Fig. 2). The complex polycycles obtained are unique, with no reported precedent in the literature.

Activated alkenes, including styrene derivatives **HP-8–HP-15** and acrylamides **HP-16** and **HP-17**, reacted smoothly with azaindole **1k** with yields >50% (Fig. 3). The regioselectivity of a similar product off-DNA (indole **1a** and styrene) has been reported in the literature.[45] *para*-(**HP-8**), *meta*-(**HP-9**), and *ortho*-substituted styrenes (**HP-10**) performed well with bromoindole **1k** in 77%, 91%, and >95% yields, respectively. Chloro-substituted **HP-11**, primed for post-functionalization, provided a 57% yield of product. Fluoride-substituted **HP-12** reacted well

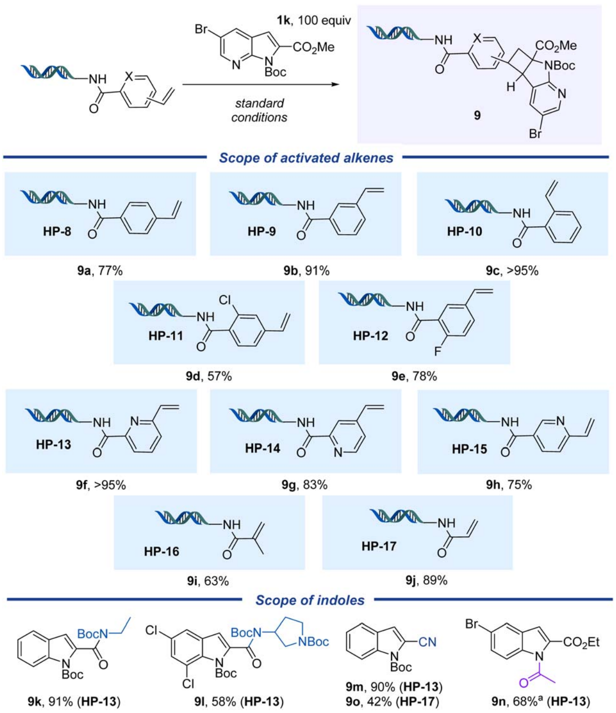


Fig. 3 Scope of DNA-tagged, activated alkenes. DNA substrate (2 mM in H_2O, 10 nmol, 1 equiv.), indole **1k** (100 mM in DMSO, 100 equiv.), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (2 mM in DMSO, 1 equiv.), glycerol (2 μL in 8 μL of DMSO), rt, 10 min, blue Kessil. Work-up: ethanol precipitation. ^{a} Indole (50 mM in DMSO, 50 equiv.).

in 78% yield, and vinyl pyridine headpieces (**HP-13–HP-15**) provided polycyclic products in yields >70%. Acrylamide **HP-17** showed higher reactivity than methyl acrylamide **HP-16**, providing the desired cycloaddition products in 89% and 63% yields, respectively. We explored the reactivity of other indoles toward the vinyl pyridine-derived substrates further. Vinyl pyridine **HP-13** performed well with Boc-protected indole-2-carboxamides (**9k** and **9l**) and indole-2-carbonitrile (**9m**), as well as *N*-acylindole-2-carboxy ester (**9n**), with yields >50%. Acrylamide **HP-17** reacted with indole-2-carbonitrile to afford **9o** in a moderate 42% yield.

Given the prevalence of diverse heterocyclic compounds in the medicinal chemistry field, additional heterocyclic coupling partners were also explored, including benzofuran and coumarin derivatives. Methyl benzofuran-2-carboxylate (**1y**) reacted smoothly with olefin headpieces **10a–10h** to afford products in good yield (Fig. 4). The off-DNA reaction of benzofuran and *exo*-methylenecyclobutanol proceeds in a ∼1 : 1 dr and ∼3 : 1 regioisomeric ratio (see ESI Section 3.2† for details). This regioisomeric ratio is consistent with what has been reported off-DNA.[45] A variety of benzofurans were reacted with **HP-5**. The 2-carboxamide afforded **10i** in a moderate 46% yield and, surprisingly, 3-methylbenzofuran-2-carboxylate afforded **10j** in a good 70% yield of the cycloaddition product. This substrate showed good reactivity with other DNA-conjugated olefin substrates, including *exo*-methylenecyclobutanes **HP-1** (**10k**) and **HP-3** (**10l**), as well as vinyl pyridine **HP-13** (**10m**) to give

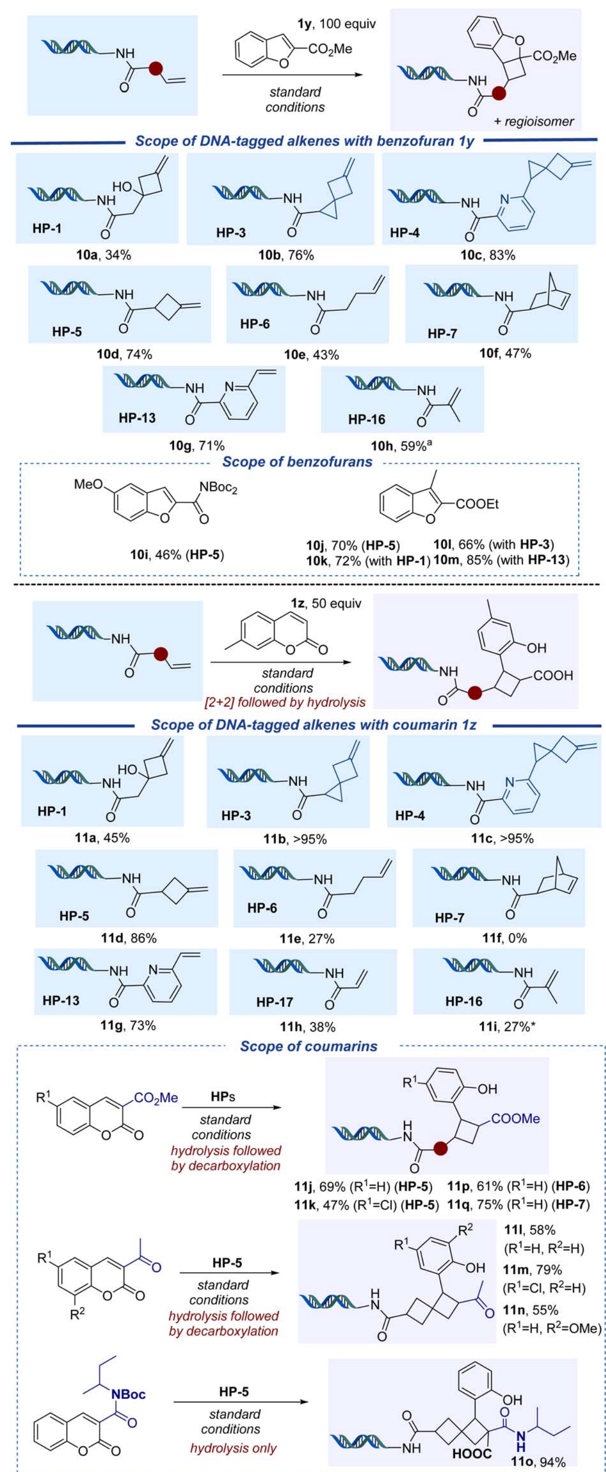
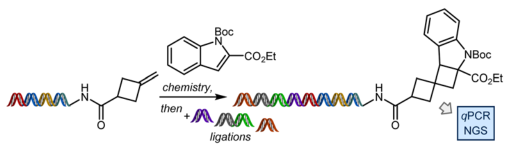


Fig. 4 Scope of benzofurans and coumarins. (1) Substrate DNA (2 mM in H_2O, 10 nmol, 1 equiv.), benzofuran (100 mM in DMSO, 100 equiv.) or coumarin (50 mM in DMSO, 50 equiv.), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (2 mM in DMSO, 1 equiv.), glycerol (2 μL in 8 μL of DMSO), rt, 10 min, blue Kessil. (2) H_2O, 70 °C, 20 min [coumarins only]. Work-up: ethanol precipitation. ^{a}Benzofuran (50 mM in DMSO, 50 equiv.). * With 37% non-hydrolyzed product.

Table 2 DNA damage assessment



Entry	Conditions	Amplifiable DNA (%)	Mutated sequences (%)
1	Standard reaction conditions	99	0.5
2	Standard conditions under N_2	100	0.1
3	Reagents with no irradiation control	100	0.2
4	Irradiation with no reagents control	99	0.4
5	Standard conditions, no BCP-I	100	0.2
6	No irradiation, no reagents control	100	0

>60% yield in each case. Benzofurans with a Cl and/or methyl ether substitution both proceeded in low yields (see ESI Section 7, Fig. S4†), as did the corresponding 2-nitrile substrate.

We investigated the reactivities of coumarin derivatives with different DNA-conjugated alkenes, including *exo*-methylenecyclobutanes, unactivated alkenes, styrene derivatives, and acrylamides (Fig. 4). Visible light-mediated intermolecular [2 + 2] cycloadditions of coumarin-3-carboxylates and acrylamide analogs off-DNA have been previously reported.[53] We conducted these analogous off-DNA reactions to confirm the regio- and diastereoselectivity of the [2 + 2] cycloaddition products (see ESI Section 3.3† for details). Initial on-DNA experiments revealed that a small percentage of lactone hydrolysis product was observed under standard conditions, along with the expected [2 + 2] cycloaddition adduct as the major product. We found that the [2 + 2] product could be funneled to hydrolyzed product in aqueous solution by heating at 70 °C for 20 min. Overall, 7-methylcoumarin (**1z**) showed good reactivity with methylenecyclobutanes **HP-1**, **HP-3**, **HP-4**, and **HP-5**, affording spiro[3.3]heptanes **11a–11d** in good to excellent yields. Unactivated alkene substrate **HP-6** resulted in a low 27% yield (**11e**), while **HP-7** did not afford any desired product. For the activated alkene substrates, vinyl pyridine **HP-13** and acrylamide **HP-17** reacted to provide **11g** and **11h** in 73% and 38% yields, respectively. The reactivity of coumarin derivatives containing an ester, ketone, or amide was evaluated with *exo*-methylenecyclobutane **HP-5**. For coumarin-containing esters and ketones, hydrolysis followed by decarboxylation yielded spiro[3.3]heptane products **11j–11n** in >45% yield. For a coumarin-containing amide, only the hydrolysis product without decarboxylation was observed, affording **11o** in 94% yield. Furthermore, unactivated alkenes **HP-6** and **HP-7** reacted to provide **11p** and **11q** in good yields. Control experiments with a headpiece that lacked an alkene functional group were conducted under the standard reaction conditions with benzofuran and coumarin (**HP-A**, see Table 1 and ESI Section 6† for details). We observed benzofuran and coumarin adducts in 10% and 7% yields, respectively, which indicates the potential addition of benzofuran and coumarin to the DNA tag. Therefore, actual yields for **10a–10m** and **11a–11n** are slightly lower than reported.

To ensure that this method would be compatible with DNA-encoded library production, *exo*-methylenecyclobutane substrate **HP-5** was prepared on an elongated DNA tag and then subjected to the reaction with indole **1a** or other control conditions (Table 2). 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) of the full-length tag (see ESI Section 8† for details). The ligations for all six samples proceeded with good efficiencies (80–100%), as confirmed by gel electrophoresis. Amplification efficiency of the full-length sequence by qPCR was comparable for all six samples (93–98%) and the reaction maintained 99% amplifiable DNA, as compared to the no light, no reagents control (entry 6, Table 2). In contrast, some of the most often used non-photonic on-DNA chemistries often have only 30–50% amplifiable DNA remaining.[54] Finally, NGS analysis revealed that all samples as compared to the control had <1% mutated sequences.

Conclusions

In conclusion, a versatile and operationally simple dearomative [2 + 2] cycloaddition is described that provides access to diverse DNA-encoded libraries of novel and compact hetero-spirocycles with high Fsp^3 content. This protocol utilizes abundant heterocycles including indoles, azaindoles, benzofurans, and coumarins, which readily react with various easily accessible DNA-conjugated *exo*-methylenecyclobutanes. In addition, we demonstrated the versatility of this method for building diverse cyclobutane-fused scaffolds from unactivated and activated DNA-tagged alkenes. In most cases, the reaction of the various alkene headpieces and indoles proceeded in high yields. The reaction could be scaled up ten-fold while maintaining >95% yield, which will render it useful in library production, allowing further functionalization in subsequent chemistry cycles. Through the developed method, vast new DEL chemical space can be accessed. The prepared compounds possess unique chemical structures bearing different functional groups and reactive handles, which is key for further functionalization strategies aimed at the construction of structurally diversified libraries. Furthermore, the integrity of the DNA tag was maintained under the mild reaction conditions, indicating that this method could be applied to DNA-encoded library production to afford libraries with previously inaccessible hetero-spirocycles, utilizing abundant and diverse indoles, azaindoles, benzofurans, or coumarins.

Data availability

General considerations, preparation of indoles, headpieces, general procedure for the cycloadditions, limitations of the reaction, and characterization of all compounds synthesized are available in the ESI.†

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are thankful for financial support provided by NIGMS (R35 GM 131680 to GAM) and the National Science Foundation (CHE-1952583 to GAM). Financial support for this research was also provided in part by AbbVie. The NSF Major Research Instrumentation Program (award NSF CHE-1827457), the NIH supplements awards 3R01GM118510-03S1 and 3R01GM087605-06S1, as well as the Vagelos Institute for Energy Science and Technology supported the purchase of the NMRs used in this study. We thank Dr Charles W. Ross, III (UPenn) for mass spectral data and Kessil for donation of LED lamps. We thank Gary O'Donovan (AbbVie) for his participation in the AbbVie-Molander collaboration. We thank Dr Gaonan Wang and the WuXi AppTec HitS Unit for experimental execution of ligations, qPCR, NGS, and analysis for the DNA damage assessment.

Notes and references

1 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
2 F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515–519.
3 K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150–183.
4 D. S. Radchenko, S. O. Pavlenko, O. O. Grygorenko, D. M. Volochnyuk, S. V. Shishkina, O. V. Shishkin and I. V. Komarov, *J. Org. Chem.*, 2010, **75**, 5941–5952.
5 X. Lin, H. Yun, B. Zhang and X. Zheng, WO2022112207, 2022.
6 X. Lin, J. Wang, H. Yun and X. Zheng, WO2022112188, 2022.
7 X. Lin, H. Yun, B. Zhang and X. Zheng, WO2022112140, 2022.
8 V. Ladziata, P. W. Glunz, Z. Hu and Y. Wang, US20160016914A1, 2016.
9 M. Hagihara, Y. Tsuzaki, K. Komori, H. Nishida, K. Kido, T. Fujimoto, T. Matsugi and A. Shimazaki, WO2007142323, 2007.
10 O. P. Demchuk, O. V. Hryshchuk, B. V. Vashchenko, A. V. Kozytskiy, A. V. Tymtsunik, I. V. Komarov and O. O. Grygorenko, *J. Org. Chem.*, 2020, **85**, 5927–5940.
11 X. Gu, Y. Wei and M. Shi, *Org. Chem. Front.*, 2021, **8**, 6823–6829.
12 P. R. D. Murray, W. M. M. Bussink, G. H. M. Davies, F. W. van der Mei, A. H. Antropow, J. T. Edwards, L. A. D'Agostino, J. M. Ellis, L. G. Hamann, F. Romanov-Michailidis and R. R. Knowles, *J. Am. Chem. Soc.*, 2021, **143**, 4055–4063.
13 S. Brenner and R. A. Lerner, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 5381–5383.
14 M. W. Kanan, M. M. Rozenman, K. Sakurai, T. M. Snyder and D. R. Liu, *Nature*, 2004, **431**, 545–549.
15 W. Decurtins, M. Wichert, R. M. Franzini, F. Buller, M. A. Stravs, Y. Zhang, D. Neri and J. Scheuermann, *Nat. Protoc.*, 2016, **11**, 764–780.
16 J. Ottl, L. Leder, J. V. Schaefer and C. E. Dumelin, *Molecules*, 2019, **24**, 1629.
17 F. V. Reddavide, M. Cui, W. Lin, N. Fu, S. Heiden, H. Andrade, M. Thompson and Y. Zhang, *Chem. Commun.*, 2019, **55**, 3753–3756.
18 M. Song and G. T. Hwang, *J. Med. Chem.*, 2020, **63**, 6578–6599.
19 N. Favalli, G. Bassi, C. Pellegrino, J. Millul, R. De Luca, S. Cazzamalli, S. Yang, A. Trenner, N. L. Mozaffari, R. Myburgh, M. Moroglu, S. J. Conway, A. A. Sartori, M. G. Manz, R. A. Lerner, P. K. Vogt, J. Scheuermann and D. Neri, *Nat. Chem.*, 2021, **13**, 540–548.
20 A. L. Satz, A. Brunschweiger, M. E. Flanagan, A. Gloger, N. J. V. Hansen, L. Kuai, V. B. K. Kunig, X. Lu, D. Madsen, L. A. Marcaurelle, C. Mulrooney, G. O'Donovan, S. Sakata and J. Scheuermann, *Nat. Rev. Methods Primers*, 2022, **2**, 3.
21 R. A. Goodnow, C. E. Dumelin and A. D. Keefe, *Nat. Rev. Drug Discovery*, 2017, **16**, 131–147.
22 D. T. Flood, C. Kingston, J. C. Vantourout, P. E. Dawson and P. S. Baran, *Isr. J. Chem.*, 2020, **60**, 268–280.
23 Y. Shi, Y. Wu, J. Yu, W. Zhang and C. Zhuang, *RSC Adv.*, 2021, **11**, 2359–2376.
24 M. L. Malone and B. M. Paegel, *ACS Comb. Sci.*, 2016, **18**, 182–187.
25 P. R. Fitzgerald and B. M. Paegel, *Chem. Rev.*, 2021, **121**, 7155–7177.
26 D. K. Kölmel, R. P. Loach, T. Knauber and M. E. Flanagan, *ChemMedChem*, 2018, **13**, 2159–2165.
27 R. Chowdhury, Z. Yu, M. L. Tong, S. V. Kohlhepp, X. Yin and A. Mendoza, *J. Am. Chem. Soc.*, 2020, **142**, 20143–20151.

28 S. O. Badir, J. Sim, K. Billings, A. Csakai, X. Zhang, W. Dong and G. A. Molander, *Org. Lett.*, 2020, **22**, 1046–1051.

29 H. Wen, R. Ge, Y. Qu, J. Sun, X. Shi, W. Cui, H. Yan, Q. Zhang, Y. An, W. Su, H. Yang, L. Kuai, A. L. Satz and X. Peng, *Org. Lett.*, 2020, **22**, 9484–9489.

30 R. Wu, T. Du, W. Sun, A. Shaginian, S. Gao, J. Li, J. Wan and G. Liu, *Org. Lett.*, 2021, **23**, 3486–3490.

31 J. Shan, X. Ling, J. Liu, X. Wang and X. Lu, *Bioorg. Med. Chem.*, 2021, **42**, 116234.

32 S. O. Badir, A. Lipp, M. Krumb, M. J. Cabrera-Afonso, L. M. Kammer, V. E. Wu, M. Huang, A. Csakai, L. A. Marcaurelle and G. A. Molander, *Chem. Sci.*, 2021, **12**, 12036–12045.

33 E. Yen-Pon, L. Li, G. Levitre, J. Majhi, E. J. McClain, E. A. Voight, E. A. Crane and G. A. Molander, *J. Am. Chem. Soc.*, 2022, **144**, 12184–12191.

34 J. P. Phelan, S. B. Lang, J. Sim, S. Berritt, A. J. Peat, K. Billings, L. Fan and G. A. Molander, *J. Am. Chem. Soc.*, 2019, **141**, 3723–3732.

35 D. K. Kölmel, J. Meng, M.-H. Tsai, J. Que, R. P. Loach, T. Knauber, J. Wan and M. E. Flanagan, *ACS Comb. Sci.*, 2019, **21**, 588–597.

36 D. K. Kölmel, A. S. Ratnayake and M. E. Flanagan, *Biochem. Biophys. Res. Commun.*, 2020, **533**, 201–208.

37 Y. Zhang, H. Luo, H. Ma, J. Wan, Y. Ji, A. Shaginian, J. Li, Y. Deng and G. Liu, *Bioconjugate Chem.*, 2021, **32**, 1576–1580.

38 M. Krumb, L. M. Kammer, S. O. Badir, M. J. Cabrera-Afonso, V. E. Wu, M. Huang, A. Csakai, L. A. Marcaurelle and G. A. Molander, *Chem. Sci.*, 2022, **13**, 1023–1029.

39 Y. Shen, G. Yang, W. Huang, A. Shaginian, Q. Lin, J. Wan, J. Li, Y. Deng and G. Liu, *Org. Lett.*, 2022, **24**, 2650–2654.

40 S. R. N. Kolusu and M. Nappi, *Chem. Sci.*, 2022, **13**, 6982–6989.

41 D. K. Kölmel, A. S. Ratnayake, M. E. Flanagan, M.-H. Tsai, C. Duan and C. Song, *Org. Lett.*, 2020, **22**, 2908–2913.

42 S. Patel, S. O. Badir and G. A. Molander, *Trends Chem.*, 2021, **3**, 161–175.

43 V. M. Lechner, M. Nappi, P. J. Deneny, S. Folliet, J. C. K. Chu and M. J. Gaunt, *Chem. Rev.*, 2022, **122**, 1752–1829.

44 R. J. Fair, R. T. Walsh and C. D. Hupp, *Bioorg. Med. Chem. Lett.*, 2021, **51**, 128339.

45 M. S. Oderinde, A. Ramirez, T. G. M. Dhar, L. A. M. Cornelius, C. Jorge, D. Aulakh, B. Sandhu, J. Pawluczyk, A. A. Sarjeant, N. A. Meanwell, A. Mathur and J. Kempson, *J. Org. Chem.*, 2021, **86**, 1730–1747.

46 N. Kratena, B. Marinic and T. J. Donohoe, *Chem. Sci.*, 2022, **13**, 14213–14225.

47 K. B. Wiberg and V. Z. Williams, *J. Am. Chem. Soc.*, 1967, **89**, 3373–3374.

48 E. Della and D. Taylor, *Aust. J. Chem.*, 1990, **43**, 945–948.

49 M. R. Becker, E. R. Wearing and C. S. Schindler, *Nat. Chem.*, 2020, **12**, 898–905.

50 S. Yu, A. Noble, R. B. Bedford and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2019, **141**, 20325–20334.

51 J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte and E. A. Anderson, *ACS Catal.*, 2019, **9**, 9568–9574.

52 M. V. Westphal, L. Hudson, J. W. Mason, J. A. Pradeilles, F. J. Zécri, K. Briner and S. L. Schreiber, *J. Am. Chem. Soc.*, 2020, **142**, 7776–7782.

53 Q. Liu, F.-P. Zhu, X.-L. Jin, X.-J. Wang, H. Chen and L.-Z. Wu, *Chem.–Eur. J.*, 2015, **21**, 10326–10329.

54 B. Sauter, L. Schneider, C. Stress and D. Gillingham, *Bioorg. Med. Chem.*, 2021, **52**, 116508.