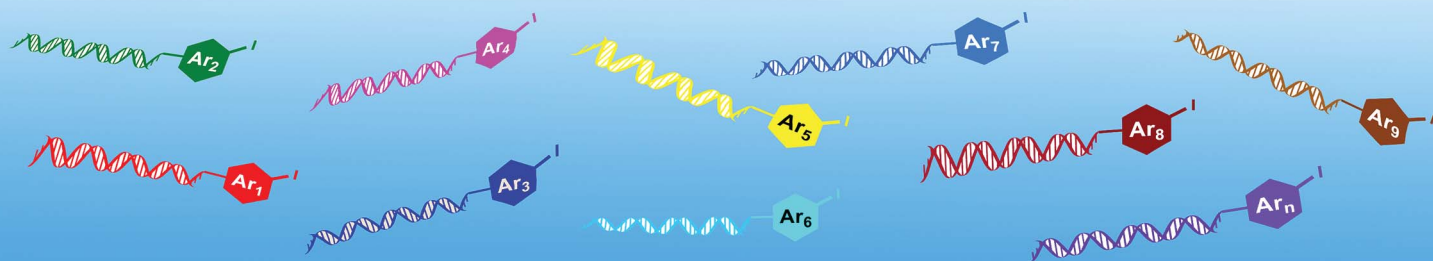
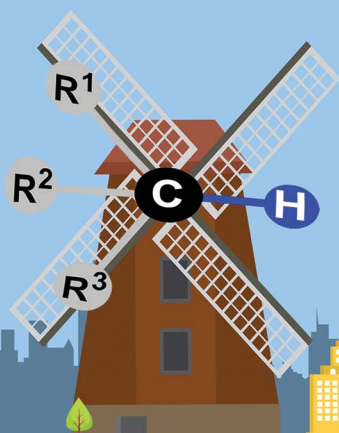
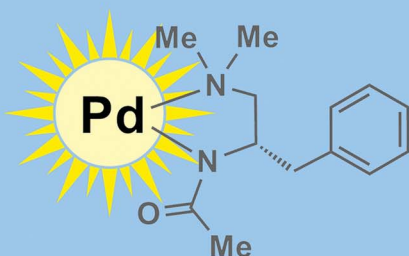


Chemical Science

Volume 11
Number 45
7 December 2020
Pages 12225–12374

rsc.li/chemical-science



ISSN 2041-6539

Cite this: *Chem. Sci.*, 2020, **11**, 12282

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

Merging C(sp³)-H activation with DNA-encoding†

Zhoulong Fan,^{‡a} Shuai Zhao,^{‡a} Tao Liu,^a Peng-Xiang Shen,^{‡a} Zi-Ning Cui,^a Zhe Zhuang,^{‡a} Qian Shao,^a Jason S. Chen,^b Anokha S. Ratnayake,^c Mark E. Flanagan,^c Dominik K. Kölmel,^{‡c} David W. Piotrowski,^{‡c} Paul Richardson^d and Jin-Quan Yu^{‡*a}

DNA-encoded library (DEL) technology has the potential to dramatically expedite hit identification in drug discovery owing to its ability to perform protein affinity selection with millions or billions of molecules in a few experiments. To expand the molecular diversity of DEL, it is critical to develop different types of DNA-encoded transformations that produce billions of molecules with distinct molecular scaffolds. Sequential functionalization of multiple C-H bonds provides a unique avenue for creating diversity and complexity from simple starting materials. However, the use of water as solvent, the presence of DNA, and the extremely low concentration of DNA-encoded coupling partners (0.001 M) have hampered the development of DNA-encoded C(sp³)-H activation reactions. Herein, we report the realization of palladium-catalyzed C(sp³)-H arylation of aliphatic carboxylic acids, amides and ketones with DNA-encoded aryl iodides in water. Notably, the present method enables the use of alternative sets of monofunctional building blocks, providing a linchpin to facilitate further setup for DELs. Furthermore, the C-H arylation chemistry enabled the on-DNA synthesis of structurally-diverse scaffolds containing enriched C(sp³) character, chiral centers, cyclopropane, cyclobutane, and heterocycles.

Received 18th July 2020
Accepted 6th September 2020

DOI: 10.1039/d0sc03935g

rsc.li/chemical-science

Introduction

The concept of using DNA sequences to encode each single reagent in every reaction step during the split-pool synthesis was originally proposed by Brenner and Lerner.¹ DNA-encoded library (DEL) affinity selection against target proteins can now be performed at the benchtop, with millions or billions of DEL molecules incubated with the immobilized target protein in few experiments.² The application of DEL technology has led to rapid identification of lead compounds for drug discovery.³ Currently, increasing the hit rate as well as improving the drug-like properties of the lead compounds is a primary concern for constructing superior DELs. In this context, establishing diverse types of organic transformations compatible with DEL technology (water as solvent, presence of DNA, 1 mM concentration of DNA substrate) is of pivotal importance.⁴ Development of on-DNA reactions faces a number of distinct challenges. DNA backbone degradation could occur under conventional reaction

conditions; metal catalysts could be poisoned by oligonucleotides; at least 20% water is required as co-solvent for dissolving DNA-tagged substrates. Over the past decade, advances in DNA-compatible reactions focused on nucleophilic aromatic substitution (S_NAr), cross-coupling, cycloaddition, and click chemistry to construct C(sp²)-C(sp²),⁵ C-N,⁶ C-O,⁷ S-X bonds,⁸ and heterocycles.⁹ Considering the well-known trends for incorporating C(sp³) carbon centers to build C(sp²)-C(sp³) bond¹⁰ and avoiding high molecular mass and lipophilicity, coupling C(sp³)-H bonds of simple aliphatic acids and ketones with DNA-encoded heteroaryls will be highly desirable. The availability of multiple C-H bonds of a wide range of carboxylic acids and ketones offers a unique opportunity to expand the accessible chemical space for DELs.

Our recent development of a wide range of transformations of β-C(sp³)-H bonds demonstrates the potential for creating unprecedented diversity from simplicity (Fig. 1A).¹¹ The attractiveness of using C-H arylation of carboxylic acid derived substrates to build DNA-encoded libraries is evident from a recent study where C-H activation reactions were performed in organic solvent and the DNA tags were subsequently attached individually. However, this approach does not allow encoding each single reagent in every reaction step during the split-pool synthesis, thus limiting the number of available building blocks and thereby the size of the library (Fig. 1B).¹² In contrast, using C-H activation as a coupling step on DNA would allow much larger libraries to be constructed. Notably, despite the use of a very powerful directing group, C(sp³)-H activation reactions

^aDepartment of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: yu200@scripps.edu

^bAutomated Synthesis Facility, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

^cPfizer Medicinal Chemistry, Eastern Point Road, Groton, Connecticut 06340, USA

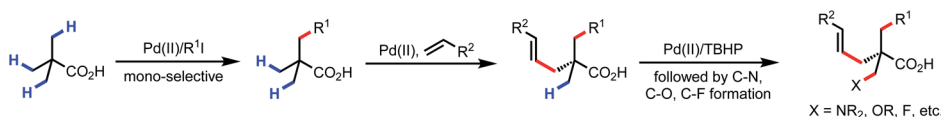
^dPfizer Medicinal Chemistry, 10578 Science Center Drive, San Diego, CA 09121, USA

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc03935g

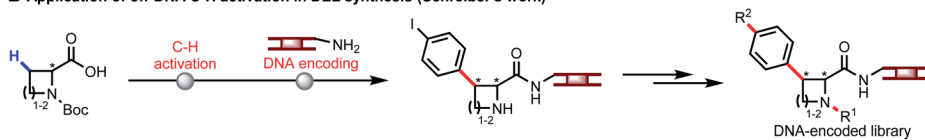
‡ These authors contributed equally to this work.



A Combinatorial chemical libraries through sequential C-H activation



B Application of off-DNA C-H activation in DEL synthesis (Schreiber's work)



C Establishment of on-DNA C-H activation for DEL synthesis (This work)

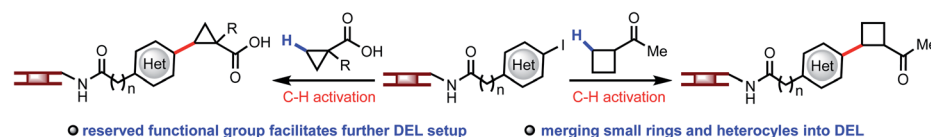


Fig. 1 Exploiting diversity of C–H activation in DELs.

have not been successful in the presence of DNA thus far.¹³ We envision the development of on-DNA C(sp³)–H activation of different classes of monofunctional building blocks to participate in the key cycle for DEL buildup with enriched C(sp³) character, chiral centers, small rings and heterocycles. The reserved functional group could also be directly employed for further setup in DEL synthesis (Fig. 1C).

Results and discussion

Since carboxylic acids and (hetero)aryl iodides are ubiquitous building blocks for DNA-encoded libraries, we first studied the coupling of a DNA-tethered aryl iodide with a free carboxylic acid through Pd-catalyzed β -C–H arylation. This presented formidable challenges beyond the need to adapt the chemistry to aqueous conditions, notably the limited stability of the DNA towards low pH and heat, the potential for interfering reactivity of the DNA bases, and the high dilution of the DNA-tethered component. Nonetheless, we decided to develop this chemistry around free carboxylic acids. Guided by our previous C–H arylation efforts,¹⁴ we screened palladium source, ligand, silver source, base, and co-solvent. The optimized conditions gave product **1** in 78% yield with no di- or tri-arylation of pivalic acid (entry 1, Fig. 2). Palladium, silver, and heat were mandatory (entries 2 to 4). No ligand was required (entry 5), but amino-acid derived ligands improved the yield (see ESI†) and **L1** was found to be optimal. The main side reaction, protodeiodination (see **S1b**), was always present to a small extent due to the use of excess silver salt and palladium. Compound **S1b** containing no iodide was subjected to the reaction conditions and recovered intact, confirming that coupling occurs at the aryl iodide and not at some undetermined location on the DNA tag. Dithiocarbamate releases DNA from the DNA–palladium complex as a result of its stronger coordination with palladium leading to an insoluble complex. After each reaction, the mixture was incubated with sodium diethyldithiocarbamate trihydrate in order to scavenge palladium. The level of DNA recovery was

significantly influenced by the loading of the dithiocarbamate scavenger (see ESI†).

A broad range of carboxylic acids adjacent to quaternary carbon atoms are suitable for this chemistry, including those containing ethers or fluorine (**2** to **14**). However, acids adjacent to a secondary or tertiary carbon react with 26–28% yields (**15** to **16**). Importantly, cyclopropane- and cyclobutanecarboxylic acids (desirable as alkene isosteres) are competent coupling partners (**17** to **21**). The mechanism of the Pd-catalyzed β -C–H arylation is well known to give the *cis* stereoisomer for cyclic carboxylic acid exclusively. Importantly, these *cis* products are resistant to epimerization in the presence of strong bases.^{14b} Our LCMS analysis was unable to determine whether chiral ligand **L1** gave any absolute stereoselection. Though we screened different silvers for achieving best yields for all of carboxylic acid substrates (see ESI†), silver trifluoroacetate gave acceptable yields in most of cases and can be used in split-pool synthesis for a DEL buildup.

The aryl iodide substitution pattern is flexible (**22** to **28**, **39** to **41**). Although our previously-published reaction conditions in organic solvent could not couple heteroaryl iodides,¹⁴ we were optimistic that conditions that tolerate DNA—the bases of which contain nitrogen heterocycles—should allow coupling of heteroaryl iodides (*e.g.*, pyridines and pyrazoles). This was indeed the case; heteroaryl iodides successfully reacted with carboxylic acids under the same reaction conditions (**29** to **38**, **42** to **44**). Since aryl and heteroaryl iodides react under the same conditions, they can both be present in a split-pool synthesis of a DEL. In addition, the β -C(sp³)–H arylated product attached to DNA can undergo the second carboxylate-directed C(sp³)–H arylation to obtain the DNA-tagged product **1'**. Furthermore, we selected product **24** to proceed off-DNA synthesis and demonstrate the reliability of the present on-DNA C–H reaction.

The carboxylic acids in the products from the above chemistry can be further derivatized (*vide infra*). One interesting possibility is coupling to chiral amino acids in order to enhance the chiral recognition potential of the resultant DNA-encoded



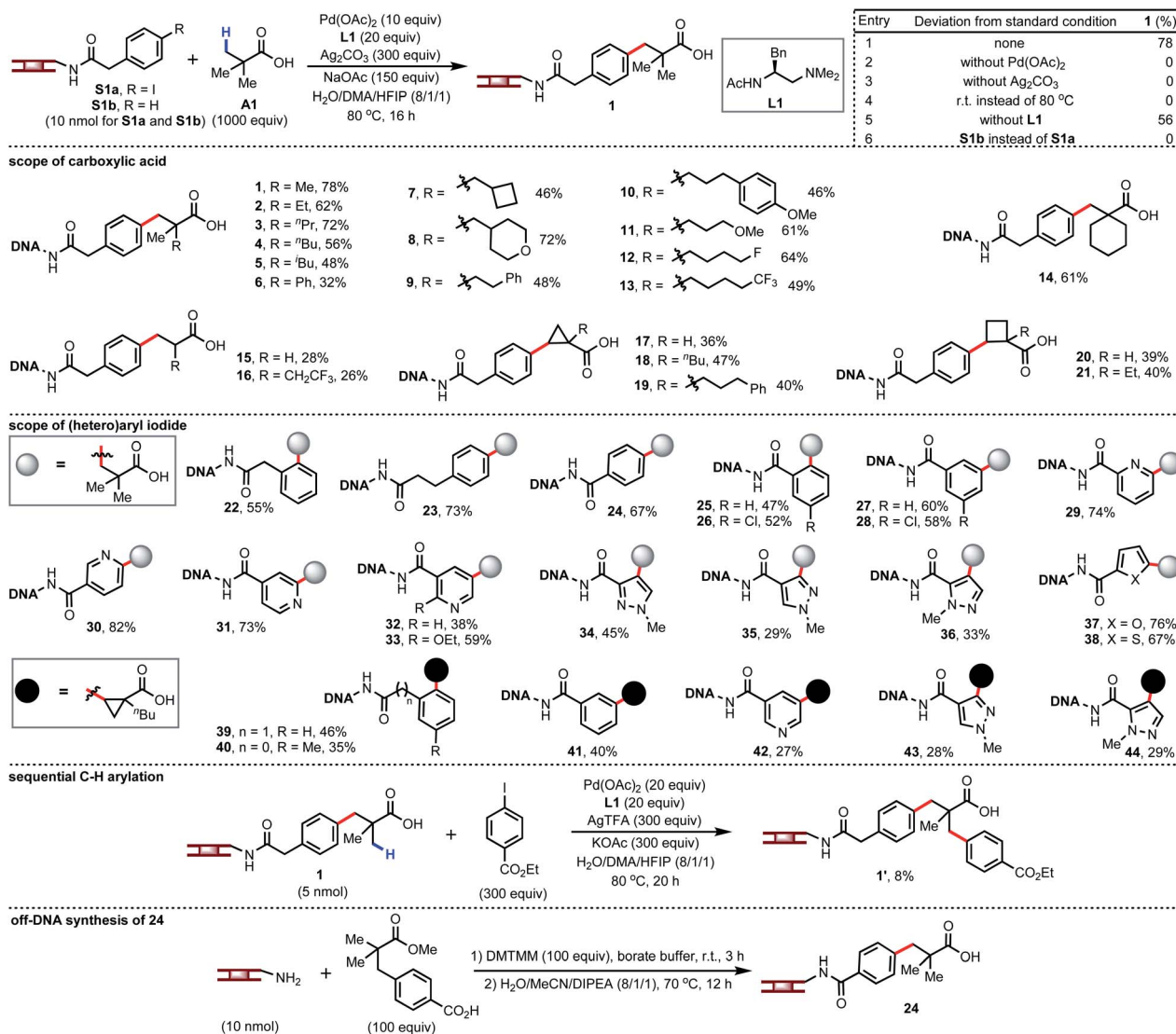


Fig. 2 Ligand-promoted on-DNA C–H arylation of free carboxylic acids. Unless otherwise noted, condition of entry 1 was used as the standard condition. For 2: corresponding A, 500 equiv. For 3–14, 18, 19, and 39–44: AgTFA, 300 equiv.; corresponding A, 300 equiv.; 36 h. For 15: Ag₃PO₄, 200 equiv.; corresponding A, 300 equiv.; 36 h. For 21: corresponding A, 300 equiv.; 36 h. For 16: AgOTf, 300 equiv.; corresponding A, 300 equiv.; 36 h. For 17: H₂O/DMA (6/1).

libraries. We recognized an opportunity in these cases to develop a ligandless Pd-catalyzed β-C–H arylation. Rather than couple the free carboxylic acid and then amide couple, one could pre-synthesize amides derived from carboxylic acids and amino acids and take advantage of the presence of a bidentate directing group to run a more facile Pd-catalyzed arylation.¹⁵ Re-evaluation of the silver source, base, and co-solvent in the absence of ligand led to optimized conditions that afforded compound **45** in 69% yield (entry 1, Fig. 3). Palladium is essential for this transformation (entry 2). Silver salts and bases are not strictly required but have a significant impact on yield (entries 3 to 9). Surprisingly, we found this reaction also worked well at room temperature (entry 10).

Amides derived from cyclopropane- or cyclobutanecarboxylic acid and a broad range of α-amino acids reacted smoothly both

heated and at room temperatures (45 to 56). Pd-catalyzed arylation proceeds only at the β-C–H bond from the amide; attempted coupling of Ac-*t*-Val-OH gave none of arylation product **59** indicating that α-arylation did not occur. Two LC peaks having same mass were due to the generation of diastereomers after the C–H arylation. To demonstrate this, we ran a representative off-DNA reaction to synthesize product **51**. As expected, a mixture of diastereomers was observed, although the ratio is slightly lower due to the different reaction temperature. Although we focused on amides derived from α-amino acids and containing cyclopropyl or cyclobutyl rings, the chemistry can be extended to other alkyl carboxylic acids (57 and 58) and to β-amino acids (60). Diverse arene substitution patterns on the DNA-tethered aryl iodide were tolerated (61 to 65). As was the case for β-C–H arylation of carboxylic acids, the

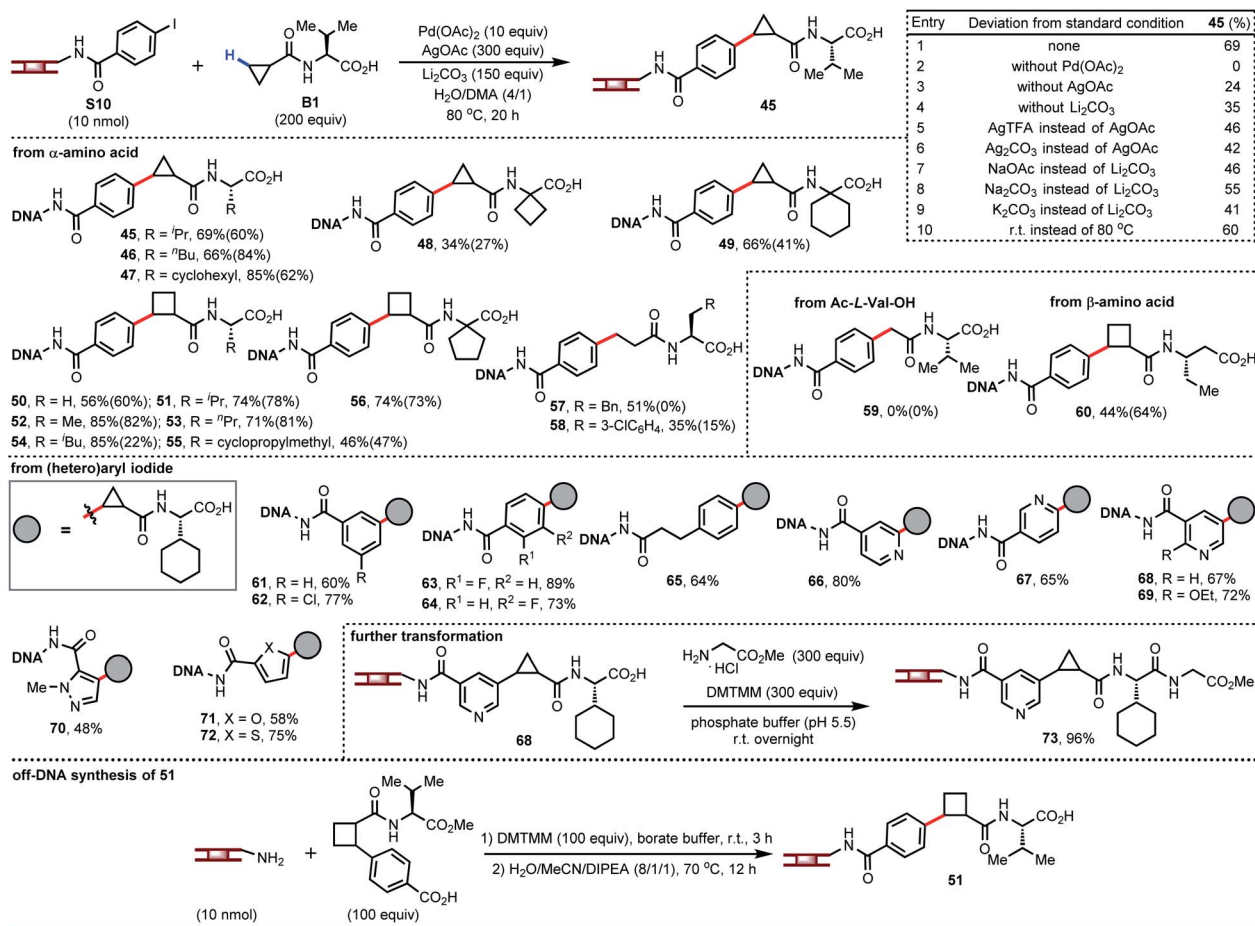


Fig. 3 On-DNA C–H arylation of amides. Unless otherwise noted, condition of entry 1 was used as the standard condition. Yields at room temperature are listed in parentheses. DMTMM, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.

DNA-tolerant conditions for amide arylation can also be employed for coupling DNA-tethered heteroaryl iodides such as pyridines and pyrazoles (66 to 72). If desired, the carboxylic acid of the product can be further modified (73).

Having developed DNA-compatible C(sp³)-H arylations for carboxylic acids and amides, we turned our attention to ketones. Ketones are useful monomers for building DELs since they can be further elaborated *via* reductive amination. Guided by our previous work using aminooxyacetic acids as removable directing groups to recruit palladium to activate the β-C–H bond of ketones,¹⁶ we optimized a DNA-tolerant version of this reaction. The optimized reaction gave arylation product **83** in 62% yield (entry 1, Fig. 4). This reaction requires palladium and heat (entries 2 and 3) and is strongly influenced by the silver salt (entries 4–6); ligand and base play a lesser role (entries 7 and 8). We also found **L8** could decrease the degradation of DNA and provide clean LC traces. Although a large excess of palladium is often associated with degradation of the DNA tag, this chemistry gives higher yield at 40 equiv. Pd/L (entry 1) than at 30 equiv. (entry 9).

The above conditions affect β-C–H arylation in diverse settings, including on acyclic ketone derivatives (74 to 77, **84** to **89**), at positions next to simple or complex rings (78 to **82**, **90**,

91), and on simple or complex rings (**83**, **92**). A broad range of functional groups are tolerated, including esters, ethers, acetals, and amides. Ketone derivatives bearing β-quaternary centers can be γ-arylated (**93**). The DNA-tethered aryl iodide accepts different substitution patterns (**94** to **97**) and heteroaryl iodides can react under the same conditions (**98** to **102**). We also noticed that *cis* and *trans*-isomers of directing group were separated in the LC traces.

The ability to convert the oxime ethers back into ketones is critical for implementing this chemistry in a DEL buildup. We discovered that these oxime ethers readily hydrolyze in the presence of aniline and acetone (**103**), likely through equilibrium transimination with aniline and trapping of the free aminooxyacetic acid with acetone.¹⁷

Each of these C(sp³)-H activation reactions, as new disconnections for DEL synthesis, can incorporate unique structural motifs. The combination of multiple C(sp³)-H activations in DEL synthesis can further enhance the diversity. Hence, we embarked on a multi-step synthesis on DNA consisting of β-C–H arylation of a carboxylic acid, amide formation, β-C–H arylation of a masked ketone, and ketone deprotection (Fig. 5A) in order to demonstrate how these C–H activation chemistries can be combined to develop large DELs of diverse, drug-like compounds. A

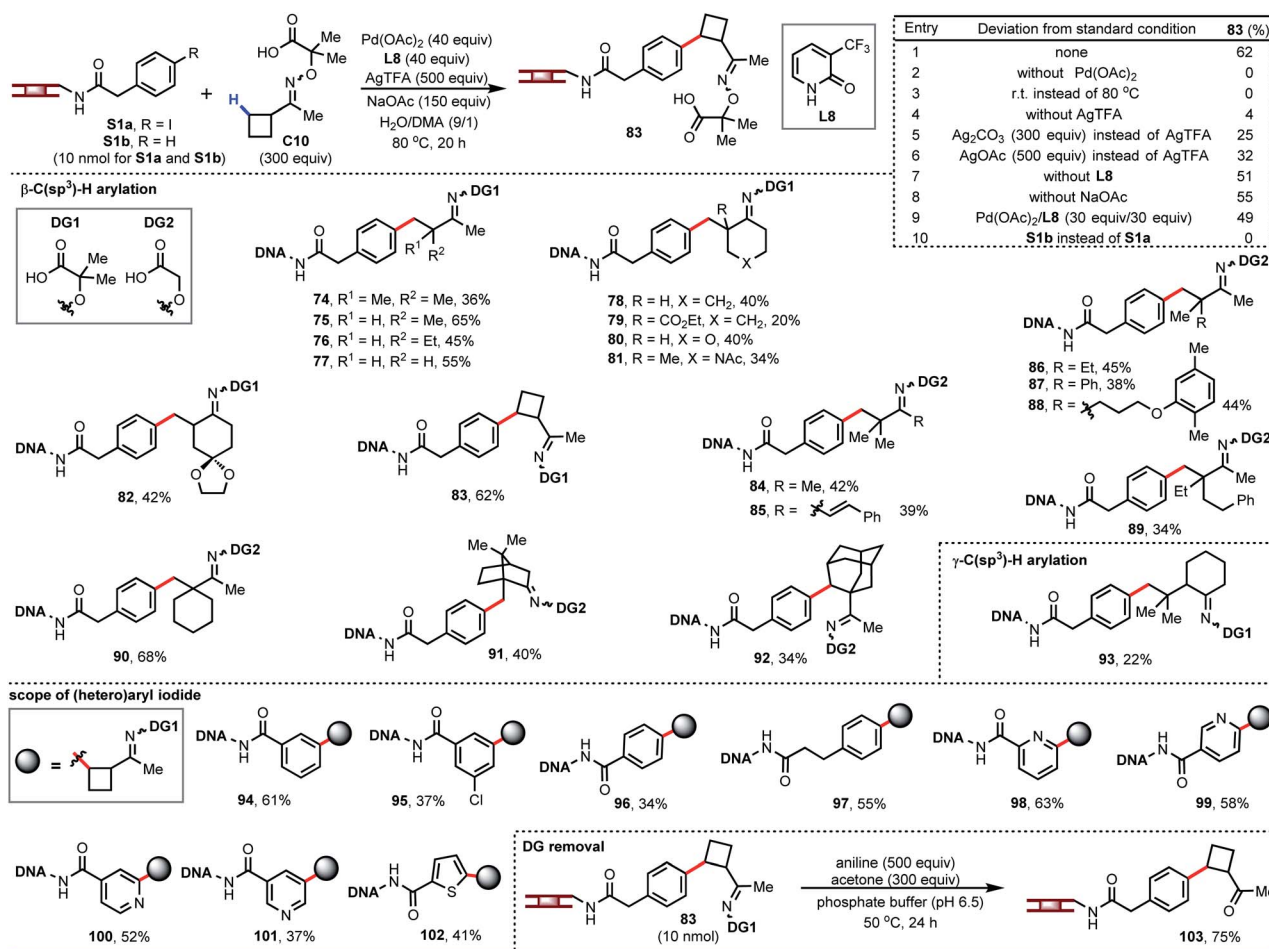


Fig. 4 DNA-compatible C–H arylation of ketones. Unless otherwise noted, condition of entry 1 was used as the standard condition. For 89 and 90: Pd(OAc)₂, 30 equiv.; L8, 30 equiv.; H₂O/DMA (2/1).

representative analog synthesis is shown in Fig. 5B. Thus, pyridyl iodide **S18** and pivalic acid were coupled to form intermediate **31**, and amide coupling with *p*-iodobenzyl amine then set up

a second C–H arylation event. Coupling with a masked cyclobutyl ketone gave oxime ether **105**. The above is only one of many sequences that one could design by using sequential multiple

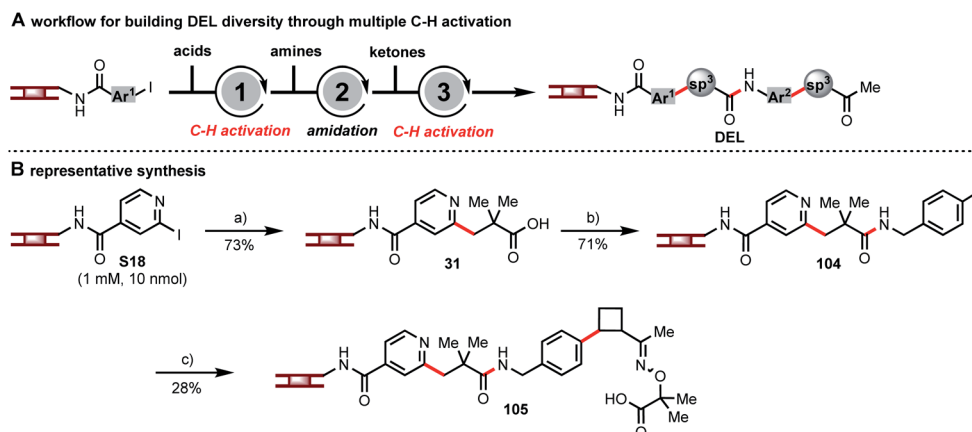


Fig. 5 The utility of multiple C–H activation in DEL synthesis. (A) Workflow for building DEL diversity through multiple C–H activation; (B) representative synthesis. Conditions: (a) **A1** (1000 equiv.), Pd(OAc)₂ (10 equiv.), **L1** (20 equiv.), Ag₂CO₃ (300 equiv.), NaOAc (150 equiv.), H₂O/DMA/HFIP (8/1/1), 80 °C, 16 h. (b) 4-Iodobenzylamine (300 equiv.), DMTMM (300 equiv.), phosphate buffer (pH 5.5), r.t. 16 h. (c) **C10** (300 equiv.), Pd(OAc)₂ (40 equiv.), **L8** (40 equiv.), AgTFA (500 equiv.), NaOAc (150 equiv.), H₂O/DMA (9/1), 80 °C, 20 h.

C–H arylation steps in combination with common DNA-encoded library-building steps such as amide formation or reductive amination. The use of multiple C–H activation reactions connects commonly used building blocks at different carbon centers hence providing complementary diversity of chemical space.

In order to evaluate DNA compatibility of the C–H activation chemistry with DEL synthesis, a select set of chemically modified on-DNA analogs (C–H arylation products **1**, **45** and **83**), along with their starting aryl iodide analog **S1a** were enzymatically ligated to a 65-mer dsDNA, so that the resulting oligomers were approximately equal in length to an encoding tag of a 3-cycle DEL build. All four ligation reactions proceeded smoothly, indicating that chemistry had no significant impact on encodability. In order to determine the amount of amplifiable DNA remaining after exposure to C–H activation conditions, the ligation products from **1**, **45** and **83** were amplified by PCR and compared with that of **S1a** (untreated control). All three reactions showed satisfactory PCR viability (60–80% amplifiable DNA remaining). Moreover, Sanger sequencing reads also confirmed the integrity of their nucleobase sequence structures (see ESI†).

As purification is an inherently difficult process in split-pool synthesis, the reactivity required for DNA-compatible reactions must be devoid of unidentified byproducts that can complicate analysis. In this case, the main byproducts generated through our reaction platform consists only of starting material or its protodehalogenated derivative. Finally, we were able to obtain all products through our on-DNA C–H arylation platform in moderate and synthetically useful yields; higher than the threshold of 25% deemed practical in DEL synthesis.^{10f} Gratifyingly also, we were able to obtain 60–80% DNA recovery from qPCR experiments, greater than the acceptable 30% threshold deemed practical in these processes.^{4c} Altogether, these promising results further demonstrate the practicality of our DEL-compatible C(sp³)–H activation platform, enabling practitioners to rapidly generate structural complexity and diversity in a modular manner.

Conclusions

In summary, we have developed DNA-compatible C(sp³)–H activation reactions of carboxylic acid, amides, and ketones. The use of universal building blocks and reserved functional group facilitates direct access to next setup for DEL synthesis. These protocols are compatible with the C(sp³)–H bond of small rings and heterocyclic coupling partners that are desirable for improving drug-like properties. These C(sp³)–H activation reactions for DEL synthesis provides a unique tool for constructing chemical diversity containing high C(sp³) character.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge The Scripps Research Institute and Pfizer for their financial support. S. Z. thanks Jiangsu Overseas Research & Training Program for University Prominent Young &

Middle-aged Teachers and Presidents. Chris O'Donnell, Russell Dushin, Bruce Lefker, and Joe Abramite are acknowledged for their suggestions during the early phases of this work. Brian M. Paegel is acknowledged for the evaluation of DNA compatibility with aqueous conditions for C–H activation. Brittany Sanchez and Emily Sturgell are acknowledged for their assistance with LC-MS analysis.

Notes and references

- 1 S. Brenner and R. A. Lerner, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 5381.
- 2 (a) R. A. Goodnow, A Brief History of the Development of Combinatorial Chemistry and the Emerging Need for DNA-Encoded Chemistry, *A handbook for DNA-encoded chemistry*, Wiley-Blackwell, 2014, pp. 19–43; (b) R. M. Franzini, D. Neri and J. Scheuermann, *Acc. Chem. Res.*, 2014, **47**, 1247; (c) G. Zimmermann and D. Neri, *Drug Discovery Today*, 2016, **21**, 1828; (d) R. A. Lerner and S. Brenner, *Angew. Chem., Int. Ed.*, 2017, **56**, 1164; (e) D. Neri, *ChemBioChem*, 2017, **18**, 827; (f) B. Shi, Y. Zhou, Y. Huang, J. Zhang and X. Li, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 361; (g) A. L. Satz, *ACS Med. Chem. Lett.*, 2018, **9**, 408; (h) G. Zhao, Y. Huang, Y. Zhou, Y. Li and X. Li, *Expert Opin. Drug Discovery*, 2019, **14**, 735.
- 3 (a) P. Zhao, Z. Chen, Y. Li, D. Sun, Y. Gao, Y. Huang and X. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 10056; (b) Y. Ding, H. O'Keefe, J. L. DeLorey, D. I. Israel, J. A. Messer, C. H. Chiu, S. R. Skinner, R. E. Matico, M. F. Murray-Thompson, F. Li, M. A. Clark, J. W. Cuzzo, C. Arico-Muendel and B. A. Morgan, *ACS Med. Chem. Lett.*, 2015, **6**, 888; (c) C. C. Arico-Muendel, *Med. Chem. Commun.*, 2016, **7**, 1898; (d) S. L. Belyanskaya, Y. Ding, J. F. Callahan, A. L. Lazaar and D. I. Israel, *ChemBioChem*, 2017, **18**, 837; (e) D. Neri and R. A. Lerner, *Annu. Rev. Biochem.*, 2018, **87**, 479; (f) L. H. Yuen, S. Dana, Y. Liu, S. I. Bloom, A. G. Thorsell, D. Neri, A. J. Donato, D. Kireev, H. Schüler and R. M. Franzini, *J. Am. Chem. Soc.*, 2019, **141**, 5169; (g) B. Cai, D. Kim, S. Akhand, Y. Sun, R. J. Cassell, A. Alpsy, E. C. Dykhuizen, R. M. Van Rijn, M. K. Wendt and C. J. Krusemark, *J. Am. Chem. Soc.*, 2019, **141**, 17057.
- 4 (a) A. L. Satz, J. Cai, Y. Chen, R. Goodnow, F. Gruber, A. Kowalczyk, A. Petersen, G. Naderi-Oboodi, L. Orzechowski and Q. Strebel, *Bioconjugate Chem.*, 2015, **26**, 1623; (b) R. M. Franzini and C. Randolph, *J. Med. Chem.*, 2016, **59**, 6629; (c) M. L. Malone and B. M. Paegel, *ACS Comb. Sci.*, 2016, **18**, 182.
- 5 (a) Y. Ding and M. A. Clark, *ACS Comb. Sci.*, 2015, **17**, 1; (b) Y. Ding, J. L. DeLorey and M. A. Clark, *Bioconjugate Chem.*, 2016, **27**, 2597; (c) X. Lu, L. Fan, C. B. Phelps, C. P. Davie and C. P. Donahue, *Bioconjugate Chem.*, 2017, **28**, 1625.
- 6 (a) X. Lu, S. E. Roberts, G. J. Franklin and C. P. Davie, *Med. Chem. Commun.*, 2017, **8**, 1614; (b) Y. Ruff and F. Berst, *Med. Chem. Commun.*, 2018, **9**, 1188.
- 7 D.-Y. Wang, X. Wen, C.-D. Xiong, J.-N. Zhao, C.-Y. Ding, Q. Meng, H. Zhou, C. Wang, M. Uchiyama, X.-J. Lu and A. Zhang, *iScience*, 2019, **15**, 307.



- 8 (a) N. Probst, R. Lartia, O. Th  ry, M. Alami, E. Defrancq and S. Messaoudi, *Chem.-Eur. J.*, 2018, **24**, 1795; (b) F. Liu, H. Wang, S. Li, G. A. L. Bare, X. Chen, C. Wang, J. E. Moses, P. Wu and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2019, **58**, 8029; (c) D. T. Flood, X. Zhang, X. Fu, Z. Zhao, S. Asai, B. B. Sanchez, E. J. Sturgell, J. C. Vantourout, P. Richardson, M. E. Flanagan, D. W. Piotrowski, D. K. K  lmel, J. Wan, M.-H. Tsai, J. S. Chen, P. S. Baran and P. E. Dawson, *Angew. Chem., Int. Ed.*, 2020, **59**, 7377.
- 9 (a) H. Li, Z. Sun, W. Wu, X. Wang, M. Zhang, X. Lu, W. Zhong and D. Dai, *Org. Lett.*, 2018, **20**, 7186; (b) C. J. Gerry, Z. Yang, M. Stasi and S. L. Schreiber, *Org. Lett.*, 2019, **21**, 1325; (c) P. Ma, H. Xu, J. Li, F. Lu, F. Ma, S. Wang, H. Xiong, W. Wang, D. Buratto, F. Zonta, N. Wang, K. Liu, T. Hua, Z.-J. Liu, G. Yang and R. A. Lerner, *Angew. Chem., Int. Ed.*, 2019, **58**, 9254; (d) M. K. Škopi  , K. G  tte, C. Gramse, M. Dieter, S. Pospich, S. Raunser, R. Weberskirch and A. Brunschweiler, *J. Am. Chem. Soc.*, 2019, **141**, 10546; (e) M. Potowski, F. Losch, E. Wunnemann, J. K. Dahmen, S. Chines and A. Brunschweiler, *Chem. Sci.*, 2019, **10**, 10481.
- 10 (a) D. K. K  lmel, R. P. Loach, T. Knauber and M. E. Flanagan, *ChemMedChem*, 2018, **13**, 2159; (b) J. Wang, H. Lundberg, S. Asai, P. Mart  n-Acosta, J. S. Chen, S. Brown, W. Farrell, R. G. Dushin, C. J. O'Donnell, A. S. Ratnayake, P. Richardson, Z. Liu, T. Qin, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, E6404; (c) D. T. Flood, S. Asai, X. Zhang, J. Wang, L. Yoon, Z. C. Adams, B. C. Dillingham, B. B. Sanchez, J. C. Vantourout, M. E. Flanagan, D. W. Piotrowski, P. Richardson, S. A. Green, R. A. Shenvi, J. S. Chen, P. S. Baran and P. E. Dawson, *J. Am. Chem. Soc.*, 2019, **141**, 9998; (d) 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; (e) S. O. Badir, J. Sim, K. Billings, A. Csakai, X. Zhang, W. Dong and G. A. Molander, *Org. Lett.*, 2020, **22**, 1046; (f) Y. Ruff, R. Martinez, X. Pell  , P. Nimsgern, P. Fille, M. Ratnikov and F. Berst, *ACS Comb. Sci.*, 2020, **22**, 120.
- 11 (a) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; (b) Z. Zhuang and J.-Q. Yu, *Nature*, 2020, **577**, 656.
- 12 C. J. Gerry, M. J. Wawer, P. A. Clemons and S. L. Schreiber, *J. Am. Chem. Soc.*, 2019, **141**, 10225.
- 13 X. Wang, H. Sun, J. Liu, D. Dai, M. Zhang, H. Zhou, W. Zhong and X. Lu, *Org. Lett.*, 2018, **20**, 4764.
- 14 (a) G. Chen, Z. Zhuang, G.-C. Li, T. G. Saint-Denis, Y. Hsiao, C. L. Joe and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 1506; (b) P.-X. Shen, L. Hu, Q. Shao, K. Hong and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 6545.
- 15 (a) W. Gong, G. Zhang, T. Liu, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 16940; (b) T. Liu, J. X. Qiao, M. A. Poss and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 10924.
- 16 (a) R.-Y. Zhu, L.-Y. Liu, H. S. Park, K. Hong, Y. Wu, C. H. Senanayake and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 16080; (b) R.-Y. Zhu, Z.-Q. Li, H. S. Park, C. H. Senanayake and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 3564.
- 17 D. K. K  lmel and E. T. Kool, *Chem. Rev.*, 2017, **117**, 10358.

