DNA-Encoded Library Chemistry: Amplification of Chemical Reaction Diversity for the Exploration of Chemical Space


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Keywords. DNA-encoding; DNA-compatible chemistry; chemical diversity; hit generation; affinity selection; building blocks; commercial availability; drug-like properties; library design.

Abstract. The use of DNA for encoding and decoding in small-molecule synthesis for lead identification continues to gain widespread attention and application—more than a quarter century after its first disclosure. Successful execution of a diverse, drug-like library usually requires hundreds to thousands of commonly functionalized building blocks of relatively similar reactivity profiles. Aqueous and DNA-compatible organic reactions that utilize a large number of functionalized building blocks are perhaps among the most obvious and often discussed aspects of the successful application of this chemistry. This review highlights recent (since ~2015), relevant, new, and potentially highly useful such chemical transformations. Thereafter follows a discussion of the properties, requirements, costs, and diversity of building blocks that are currently available and may be useful for the construction of DNA-encoded libraries.

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1. What Is DELT and Why Does It Continue to Be Important?

DNA-Encoded Library Technology (DELT) is a combination of several technologies for the creation of large mixtures of small molecules that are then used in affinity selection methods for the identification of small molecules having high binding affinity for a particular biological target, usually proteinaceous. In a DEL, each small molecule is covalently attached to a strand

of single- or double-strand DNA as a means of encoding its synthetic history. Population enrichment of high affinity binders, followed by amplification of the encoding DNA with a polymerase chain reaction (PCR) and subsequent sequencing of the resulting amplicons by next generation sequencing (NGS) make possible the identification of such higher affinity hit molecules. The chemistry for creating DELs has been useful for developing mixtures of hundreds of millions to billions of small molecules on a small scale. The concept for this innovation was first proposed in 1992 by Brenner and Lerner,[1] and was promptly followed by its exemplification.[2] During the intervening quarter century, DELT has grown from an interesting concept for the encoding of short peptides synthesized on a solid phase, to a well-established method for small-molecule hit identification, increasingly commonplace in pharma, biotech, and academic drug discovery research. This approach has been thoroughly reviewed.[3] It has also been described in multiple publications that are focused on synthetic chemistry as applied to this technology and hit identification[4] for biological targets of interest as well as clinical drug candidates.[5] Innovation in DELT is appealing to many scientists given its multidisciplinary nature that includes small-molecule organic chemistry, oligonucleotide chemistry, affinity chromatography, informatics, high-throughput (HT) DNA sequencing, and process design.

This review highlights newly disclosed DNA-compatible synthetic organic reactions that have been employed in the preparation of DELs or have the potential of being used for this purpose. Since a critical component for success in DELT is ready access to hundreds to thousands of building blocks (BBs), their availability, cost, chemical classification, and properties may seem obvious and simplistic. However, upon further examination, and given the number of BBs in question, it becomes clear that rigorous attention to these BB aspects is critical for implementing a successful DELT process. To this end, key BB aspects are explored in this review, thereby providing readers with, not only an update of the latest organic chemistry that might be applied in a DELT, but also an understanding of the general availability of BBs needed to demonstrate new molecular designs.

2. General DEL Design Principles: Balancing Diversity, Size, and Drug-Like Properties against the Requirements of DNA-Compatible Reactions

Whereas aspects of cost and feasibility of HTS decks limit screening campaigns to 10^6–10^7 compounds,[6,7] the advent of DELT now allows libraries to comprise typically 10^7–10^{10} compounds.[8,9] While this remains a tiny sampling of the theoretically accessible chemical space (10^{18}–10^{200} molecules, depending on the method of calculation),[10] DELT remains an attractive choice for hit generation. This is because DEL compound libraries result from split-and-pool synthesis, which has been known for many years,[11] even though the details of encoding and decoding millions of small molecules have come about only with the advent of NGS and the perfection of DELT.[1] The power of DELT's combinatorial synthesis to produce large numbers of compounds is strikingly demonstrated in Table 1.

However, well known to drug discovery scientists is Lipinski's "rule of 5"[12] that guides the design of small molecules with respect to oral bioavailability according to upper limits on molecular weight (MW), CLogP, and the count of hydrogen bond donors and acceptors (i.e., 500 Da, 5, 5, and 10, respectively). Without proper and rigorous attention to building block selection, multicycle combinatorial libraries often create molecules that surpass these limits. High affinity hits may be found, but their transformations to useful, orally bioavailable, drug-like substances may be challenging or impossible. Vividly illustrating this obvious point, is a seminal DELT paper by Clark et al. which describes the synthesis of 3- and 4-cycle DELs that are based on the triazine scaffold.[13] The DELs were then probed by affinity selection against p38α, resulting in the identification of high-affinity, off-DNA inhibitors of p38 MAP kinase (**Figure 1**).[13] In Table 2, entries 2 and 5 show the final molecular weights that would result from fairly low-molecular-weight building blocks, whereas entries 3 and 6 show the same from heavier building blocks. The highest molecular weight building blocks in these libraries are in excess of 275 Da for several of the inputs. It thus becomes clear that for 3-cycle DEL-A, the building block and core MWs cannot exceed 125 Da in order to produce molecules of less than 500 Da; for DEL-B the limit is 105 Da. Based on this simple analysis, it should be obvious that building block selection for DELs is quite constrained by molecular weight. As a rule of thumb, DEL building blocks and cores of molecular weights of 125 Da or less are generally the most useful if one expects all members of a DEL library to have less than 500 Da molecular weights. Often DELT chemists design libraries with building blocks that are available to them at the time and thus can end up with final compounds having MWs far in excess of 500 Da. The thinking then is that the DEL library will have some representation of molecular weights less than 500 Da, while larger MWs can be useful for structure–activity relationship (SAR) studies. Indeed, while diversity exploration of higher-molecular-weight products is useful for selection, their potential utility as starting points for small-molecule hit-to-lead drug discovery is invariably negatively assessed against these stringent, hard-wrought design criteria.

Before optimizing the drug-like properties of a DEL for use in hit generation, two key aspects need to be considered: (i) a good understanding of new and established chemical reactions that are compatible with a DNA encoding format, and (ii) the

Table 1. The Number of Compounds That May Result from 3- and 4-Cycle Combinatorial Libraries

No. of Cycles	Input Count for				No. of Library Members
	Cycle I	Cycle II	Cycle III	Cycle IV	
3	96	96	96	–	884,736
3	96	96	96	96	84,934,656
4	1,000	1,000	1,000	–	1×10^9
4	1,000	1,000	1,000	1,000	1×10^{12}

availability of suitable building blocks for the modeling of such reactions. Large pharmaceutical companies, having thousands of small-molecule building blocks in their compound inventories, have a significant advantage in terms of availability of small, diverse, and novel molecular inputs at already sunk costs. For DELT chemists who do not have access to such "hidden treasure", commercially available BBs are the next best option. To this end, the analysis in Section 5 of commercially available BB sets is presented as a means to understand the numbers of commonly used building blocks that are readily commercially available. Whereas an exhaustive analysis of relevant BBs may be more meaningful to a particular design and the preforming organization, it is still useful to the practicing DELT chemist to have an overview of what is available.

3. Recently Developed Reactions That Have Been Applied on DNA or Have the Potential to Be Applied on DNA

3.1. Photochemical and Radical Reactions

Liu and co-workers reported in 2011 the first visible-light-induced photoredox reaction performed on DNA, which was run in pH 7.4 aqueous buffer without precautions against air or oxygen (**eq 1**).[14] The substrate scope expansion and functional group compatibility of the azide reduction reaction were demonstrated with small molecules in organic solvents. A variety of protic functional groups; including free indoles, acids, and alcohols; were compatible with the reaction. Functional groups that are sensitive to hydrogenation; including alkenes, alkynes, and aryl halides; were not affected. In addition, functional groups that are sensitive to nucleophiles; including alkyl halides, alkyl mesylates, and aldehydes; were stable under the reaction conditions. An alkyl azide was also reduced in 24 hours under modified conditions, giving rise to the corresponding amine in 72% yield.

A "photoclick" cycloaddition between a diaryltetrazole tethered to a single-strand or a double-strand DNA, **3**, and the electron-deficient maleimide double bond in sulfo-Cy3 dye **4** was induced by UV irradiation at 365 nm in a temperature-controlled device (**eq 2**).[15] It was observed that the yield of the purified product DNA, **5**, was higher (34%) on the double-strand DNA relative to the single-strand one (8%). Remarkably, the measured rate constant was found to be high relative to those of other copper-free bioorthogonal transformations and was similar to those of the traditional copper-catalyzed "click" reaction. Two other alkene dipolarophiles, *N*-methylmaleimide and methylmethacrylate, were also reacted with **3** to evaluate the scope of the reaction and they led to 42% and 23% yield, respectively, of the corresponding product DNA.

The first visible-light-induced oxidative coupling reaction with the potential for DNA modification and DNA-encoded library synthesis was disclosed by Chen and co-workers (**eq 3**).[16] The reaction worked well with readily available primary, secondary, and tertiary alkylboronic acids or trifluoroborates to generate aryl-, silyl-, and alkyl-substituted alkynes. Various functional groups including alkenes, alkynes, aldehydes, ketones, esters, nitriles, azides, aryl halides, alkyl halides, alcohols, and indoles were tolerated in this deboronative alkynylation in organic solvents. In addition, compatibility of the reaction with amino acids, oligosaccharides, proteins, and cell lysates was demonstrated. The reaction could be run in pH 7.4 aqueous buffer without excluding air or oxygen.

The same laboratory has also reported the first visible-light-induced reductive coupling reactions with DNA-compatibility, and the reaction conditions did not affect the enzyme activity of a protein enzyme (**eq 4**).[17] This C_{sp3}–C_{sp} bond coupling reaction worked with primary, secondary, tertiary, and α-heteroatom-substituted alkyl *N*-acyloxyphthalimides to construct aryl-, alkyl-,

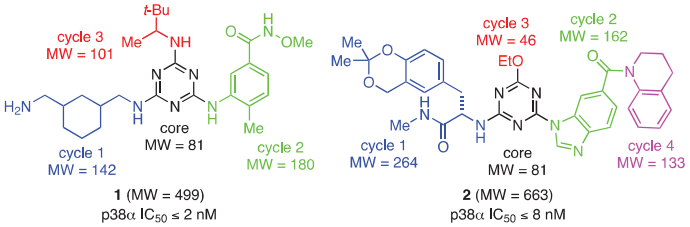
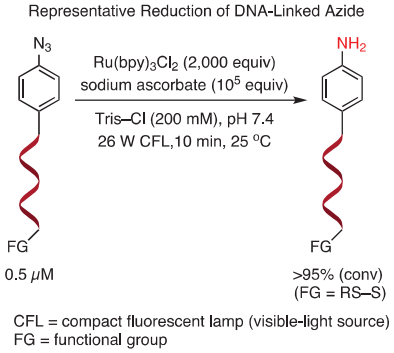


Figure 1. DEL-A and DEL-B, 3- and 4-Cycle DNA-Encoded Libraries Were Employed to Identify High-Affinity Hits against p38α. *(Ref. 13)*

Table 2. Final Product Molecular Weight (MW) That Results from Building Block Inputs for 3- and 4-Cycle DELs[a]

Entry	Building Block MW Input for				Final Product	MW of Final Product
	Cycle I	Cycle II	Cycle III	Cycle IV		
1	142	180	101	–	DEL-A hit **1**	499
2	75	75	75	–	DEL-A low	301
3	200	200	200	–	DEL-A high	676
4	264	162	46	133	DEL-B hit **2**	663
5	75	75	75	75	DEL-B low	357
6	200	200	200	200	DEL-B high	875

[a] Core MW = 81

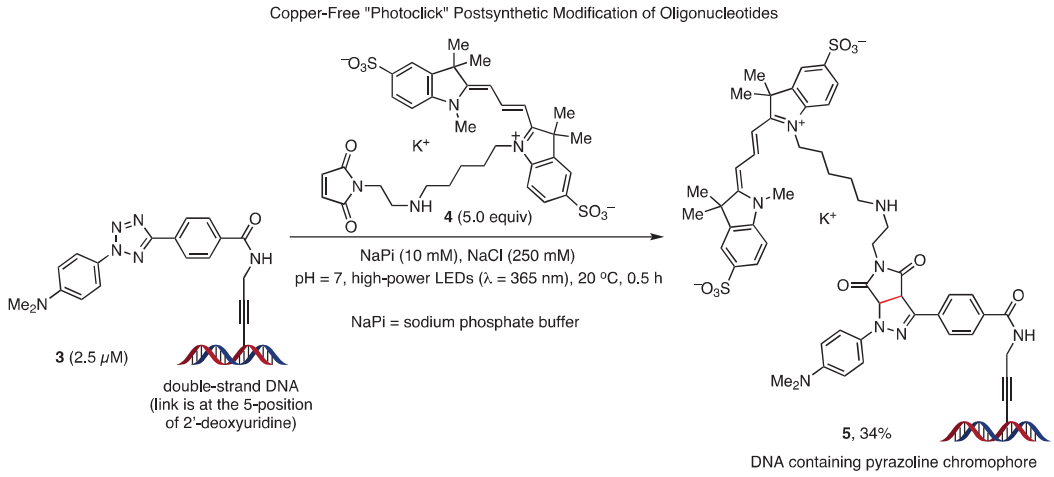


eq 1 *(Ref. 14)*

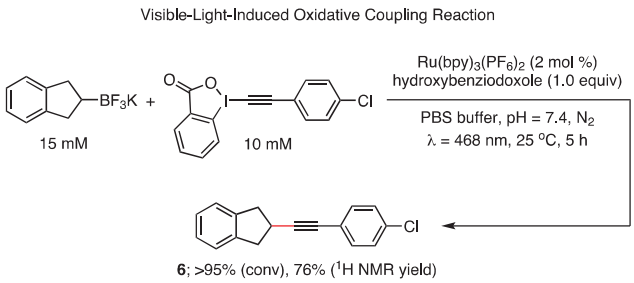
and silyl-substituted alkynes. The reaction was chemoselective when substrates were used that contained sensitive functional groups such as alkenes, alkynes, aldehydes, ketones, esters, amides, azides, aryl/alkyl halides, alcohols, phenols, carboxylic acids, and indoles. This rapid and mild reaction is compatible with biomolecules and thus has the potential to be applied to DNA modification and DNA-encoded library synthesis.

Flanagan and co-workers have reported a first proof of concept that a photoredox-mediated, 1,4-radical-addition reaction can take place under mild, aqueous conditions that are suitable for the preparation of DELs of around 75 million compounds (**eq 5**).[18] This C_{sp3}–C_{sp3} coupling reaction is compatible with a range of structurally diverse radical precursors a well as Michael acceptors and styrene derivatives. Moreover, to achieve high coupling yields, 1,000 equivalents of the protected α-amino acids need to be used. Alcohol, carboxylic acid, carboxamide, and guanidine functional groups are tolerated; however, unprotected aliphatic α-amines, such as H-Pro-OH, afford the coupling product in significantly diminished yield. Unlike the other transformations presented thus far in this review, oxygen has a detrimental effect on the reaction necessitating that the glass reaction vial be degassed with nitrogen for 5 minutes before irradiation with blue LED light.

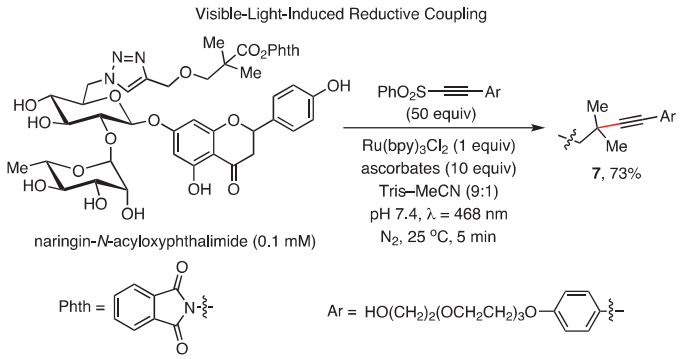
A fast, chemoselective, and general *anti*-Markovnikov hydrothiolation of alkenes and alkynes under mild conditions has been disclosed by Glorius, Guldi, and co-workers (**eq 6**).[19] The transformation relies on a biocompatible disulfide–ene reaction that proceeds by triplet–triplet energy transfer (TTEnT) sensitization of disulfides by the visible-light photocatalyst, and tolerates a wide range of functional groups including amides, sulfonamides, nitriles, alcohols, epoxides, aldehydes, ketones, esters, and heterocycles. The electron-rich, sterically



eq 2 *(Ref. 15)*



eq 3 *(Ref. 16)*



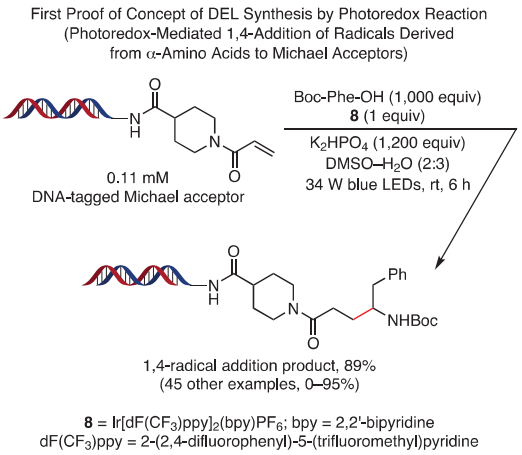
eq 4 *(Ref. 17)*

accessible alkene functionality reacts exclusively, while sterically demanding disulfides such as *tert*-butyl disulfide are unreactive. In aqueous buffer (pH 7.4), the yield of the reaction of carvone with dimethyl disulfide was not affected by the presence of 20 biomolecules such as saccharides, amino acids, nucleosides, nucleic acids, and human cell lysates. A minor modification of the reaction conditions permitted diaryl disulfides to be utilized for the synthesis of arylthioethers.

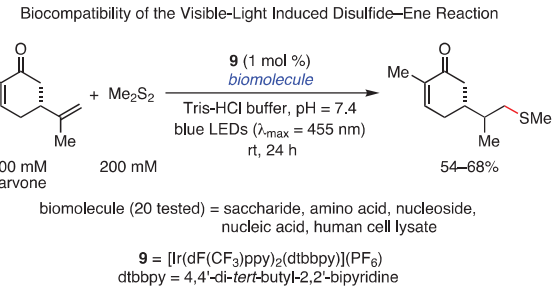
A team of researchers from Scripps, Pfizer, and Asymchem led by Baran and Blackmond have reported the first decarboxylative one-electron alkylation of a DNA-bound molecule using zinc nanopowder as the reductant (**eq 7**).[20] The reaction works with amino-containing alkyl carboxylic acids and even a dipeptide, and tolerates functional groups, such as thioethers and aryl iodides, that are potentially sensitive to reductive conditions or nonphysiological pH. Highly hindered C_{sp3}–C_{sp3} bond linkages, such as those forming quaternary carbons, could also be constructed on DNA through this cross-coupling reaction with electron-deficient alkenes.

The direct, visible-light photoredox-catalyzed deoxygenative ketone synthesis has also been achieved under mild conditions in aqueous medium.[21] This formal hydroacylation of alkenes is compatible with a broad range of alkenes and para-substituted aromatic carboxylic acids and is achieved in moderate-to-good yields. It is proposed to occur via an acyl radical species [RC(O)•] that adds to the alkene with Ph_3P acting as an oxygen-transfer agent and water supplying a proton in the final step of the reaction. Both pyridyl-substituted alkenes and styrene derivatives were good alkene partners, and the reaction was not affected by the presence of biomolecules such as amino acids, oligosaccharides, nucleosides, nucleic acids, and proteins.

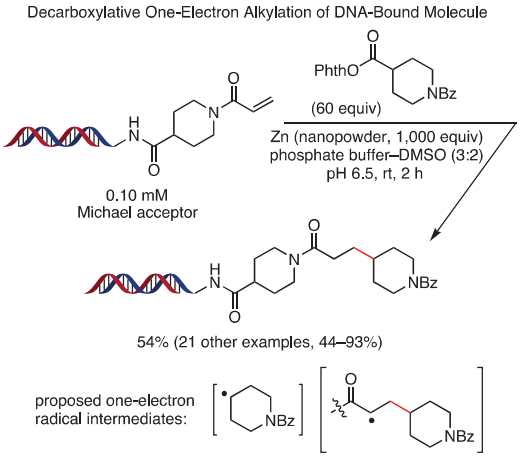
Very recently, two open-air, on-DNA synthetic protocols have been developed by Molander and co-workers (**Scheme 1**).[22] The first involves a Ni/photoredox dual catalytic C_{sp2}–C_{sp3} cross-coupling between a halogenated arene and an alkane. The



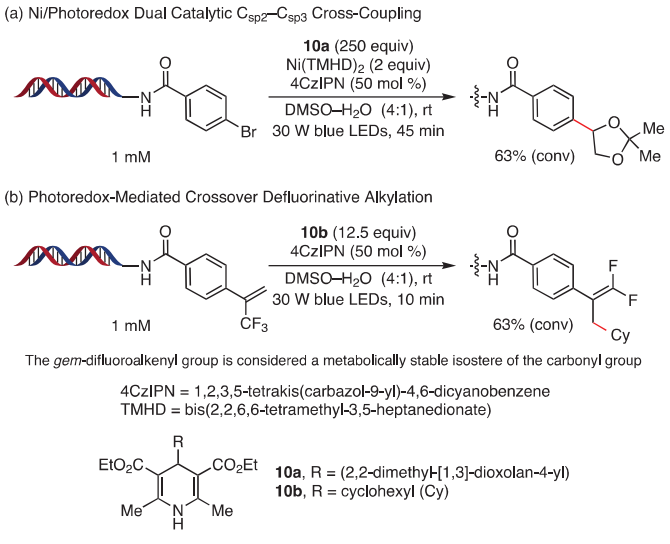
eq 5 *(Ref. 18)*



eq 6 *(Ref. 19)*



eq 7 *(Ref. 20)*



Scheme 1. Photoredox-Mediated, on-DNA Alkylations in Ambient Air and Aqueous Media under Mild Conditions. *(Ref. 22)*

second is the first example of a photoredox-mediated crossover defluorinative alkylation of a trifluoromethylalkene to generate a *gem*-difluoroalkene, which is proposed as a metabolically stable isostere of the carbonyl group. In the dual catalytic process, the water-compatible alkyl radical precursors included alkyl silicates, alkyl dihydropyridines, and amino acids which reacted well with variously substituted aryl iodides and with heteroaryl bromides bearing electron-deficient substituents. Functional groups that could be further elaborated in later cycles of DEL synthesis—e.g., epoxides, esters, alkenes, and *N*-Boc amines—were compatible with the reaction conditions. In the second protocol, the defluoroalkylation of trifluoromethyl alkenes, a DNA compatibility test was done by DNA misreads frequency sequencing, which was meaningful for the DEL synthesis, and such assessment of DNA integrity had often been overlooked before.

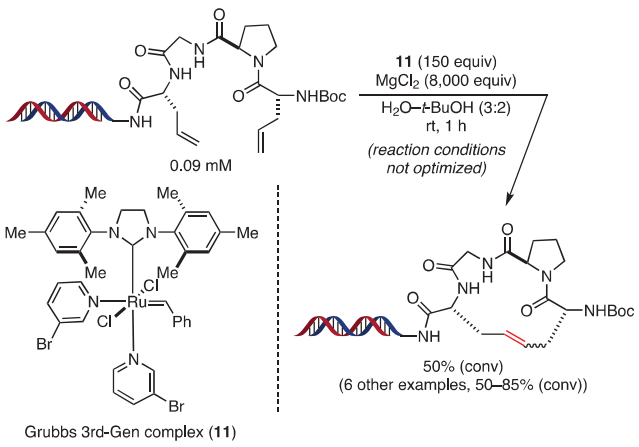
3.2. Transition-Metal-Catalyzed Reactions

The first on-DNA ring-closing metathesis (RCM) and cross-metathesis (CM) were achieved on a double-strand DNA in water–*tert*-butyl alcohol solvent system by Lu et al. (**eq 8**).[23] The unoptimized RCM was promoted by Grubbs third-generation ruthenium complex **11** (150 equivalents), and required a large excess of $MgCl_2$ (8,000 equivalents) to be utilized to protect the DNA backbone from ruthenium-induced decomposition. The substrate scope for the on-DNA RCM was investigated with the purpose of forming saturated small (5-, 6-, 7-, and 8-membered) and large (14- and 16-membered) rings in synthetically useful conversions. The on-DNA CM was tested with a representative on-DNA alkene and allyl alcohol as the other olefin under similar reaction conditions; here, too, $MgCl_2$ was required to achieve a 50% conversion.

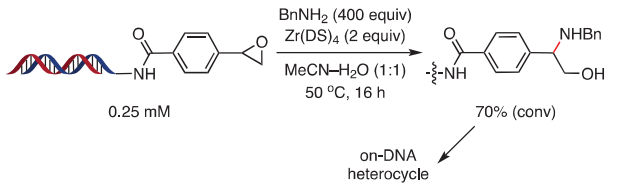
Fan and Davie reported in 2017 the first water-compatible, Zr(IV)-catalyzed aminolysis of epoxides on DNA to afford β-amino alcohols (**eq 9**).[24] Both aliphatic and aromatic primary amines gave moderate-to-excellent yields of the amino alcohols, while sterically hindered amines reacted more sluggishly to form mostly diols. The researchers took advantage of this protocol to build a library of 136.6 million on-DNA β-amino alcohols and their cyclization products, which led to the identification of multiple hits for a number of targets.

The acid- and gold-mediated on-DNA syntheses of hexathymidine-DNA-heterocycle chimeras have been disclosed by a team of researchers from Dortmund University (**Scheme 2**).[25] Diversely substituted β-carbolines—core scaffolds of drugs and pharmacologically active natural products—were accessed by a Brønsted acid catalyzed Pictet–Spengler reaction, while hexathymidine-DNA (hexT) conjugates of highly substituted pyrazolines and pyrazoles were prepared by a Au(I)-mediated cascade reaction. The hexT-heterocycle conjugates could then be ligated to the coding DNA sequences by T4 DNA ligation to produce encoded screening libraries that were informed by drug structures.

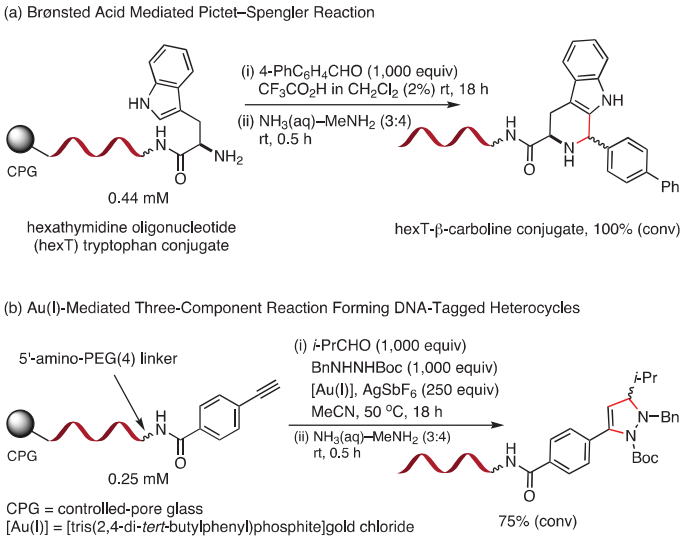
The same laboratory has also reported a similar Au(I)-mediated three-component reaction between alternately DNA-tethered aldehydes, hydrazides, and alkynols.[26] The reaction was compatible with thymine-, cytosine-, and adenine-



eq 8 *(Ref. 23)*



eq 9 *(Ref. 24)*



Scheme 2. TFA- and Au(I)-Mediated on-DNA Syntheses of Substituted β-Carbolines, Pyrazolines, and Pyrazoles. *(Ref. 25)*

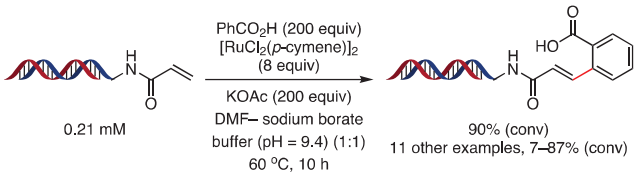
containing DNA, while guanine-containing DNA strands were degraded under the reaction conditions. The DNA-coupled aldehyde starting material resulted in the best yields of DNA-tagged substituted spiroheterocycles, whereas the alkynol- and hydrazide DNA-conjugates gave complex product mixtures, which precludes their use for parallel synthesis.

The first Pd- or Cu-promoted C–N cross-coupling between DNA-conjugated aryl iodides and primary amines has been achieved (**Scheme 3**).[27] The reaction works well for primary aromatic amines, aliphatic amines, and amino acids, which included over five hundred amino acids. The amino acids not only serve as Cu(I) ligands to promote the C–N coupling, but also prevent DNA decomposition as a result of DNA coordination to Cu(I). Using this technology, the authors succeeded in generating DNA-encoded libraries of 30.4 and 177 million compounds, of which a number of small-molecule hits were identified for biological targets of interest. An analogous copper-promoted amination of DNA-conjugated aryl iodides was reported by Ruff and Berst.[28] In this variant, the novel ligand 2-((2,6-dimethoxyphenyl)amino)-2-oxoacetic acid was found to improve conversions, and both primary and secondary amines—even some sterically congested secondary amines—were competent coupling partners. It is worth noting that this protocol could be carried out in air at low temperature, worked well for a large number of amine building blocks, and was compatible with DMSO as a water-miscible organic cosolvent.

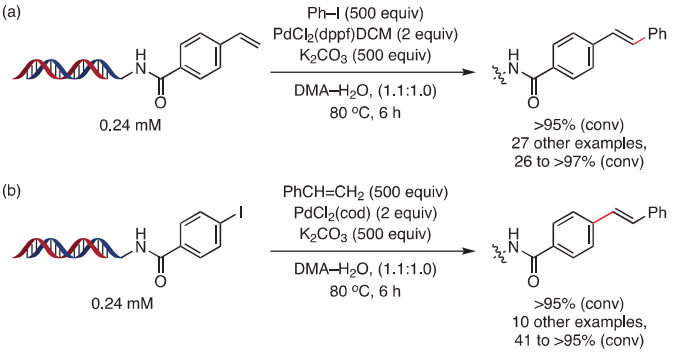
More recently, a palladium-mediated C–N cross-coupling between DNA-conjugated aryl bromides and aromatic amines was disclosed by Torrado and collaborators.[29] The reaction worked for diverse heteroaromatic amines such as thiazoles, pyrazoles, pyrazines, pyridines, benzoxazoles, benzimidazoles, and oxadiazoles as well as anilines containing aliphatic alcohols, sulfonamides, and ester functional groups. Not surprisingly, the coupling of the aryl bromides required a higher temperature (60 °C) to achieve useful conversions than the coupling of the aryl iodides (30 °C).

Lu, Zhong, and co-workers have disclosed the first ruthenium-promoted, on-DNA C_{sp2}–C_{sp2} coupling between acrylamides and aromatic carboxylic acids via a C–H activation reaction (**eq 10**).[30] Under the optimized conditions, good-to-excellent conversions were obtained regardless of whether the acrylamide or the carboxylic acid was conjugated to the DNA. Because aromatic carboxylic acids are more readily commercially available, the reaction scope was investigated with respect to the acid partner. The reaction tolerated bromo, iodo, chloro, amino, hydroxyl, and carboxyl substituents in the carboxylic acid partner, whereas aldehydo, vinyl, and alkoxycarbonyl substituents resulted in low conversions. The value of this approach is that the aromatic carboxylic acid partner serves as a bifunctional building block, whereby the carboxylic acid group can, after the coupling step, be further elaborated to introduce more diversity in a DEL that could range in size from millions to billions after three cycles.

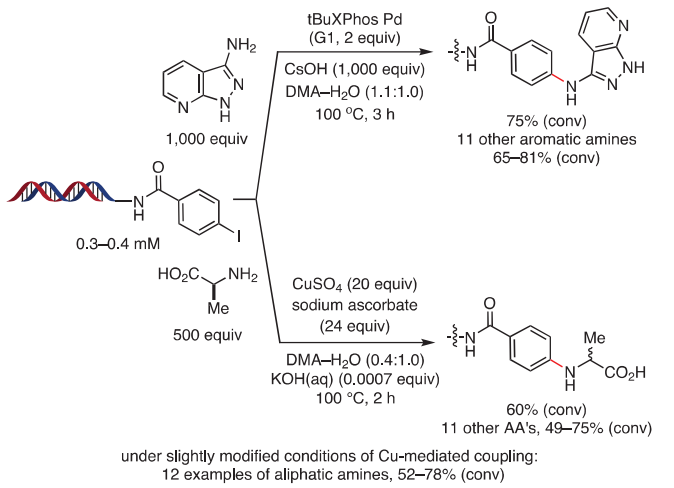
The palladium-promoted Heck coupling has been successfully extended to the reaction of double-strand and single-strand DNA-conjugated acrylamides, styrenes, and aryl iodides with aryl iodides and bromides, aromatic borates, and styrenes (**Scheme 4**).[31] Moderate-to-excellent conversions were observed, and the reaction was compatible with cyano, hydroxyl, amino, and halide functional groups, which could conceivably be elaborated further. The applicability of this method to library diversification was demonstrated with the on-DNA Heck reaction as the cycle 2 step in a three-cycle DEL synthesis.



eq 10 *(Ref. 30)*



Scheme 4. Palladium-Promoted Heck Reaction on the DNA. *(Ref. 31)*



Scheme 3. Pd- or Cu-Promoted C–N Cross-Coupling between DNA-Conjugated Aryl Iodides and Primary Amines or Amino Acids. *(Ref. 27)*

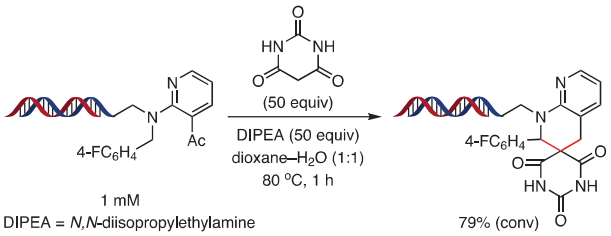
3.3. Nucleophilic Reactions

One of very few examples of an on-DNA reaction sequence that forms two carbon–carbon bonds was reported by Tian et al. (**eq 11**).[32] In this process, termed "T-reaction" for "tertiary amino effect reaction", *ortho*-dialkylaminoaryl aldehydes undergo a reaction cascade consisting of a Knoevenagel condensation, a 1,5-hydride shift, and a Mannich cyclization to form diversely substituted spirocycles. Various benzylic amines were applicable, less activated alkyl amines were tolerated, and differentially substituted secondary amines were also tolerated. Heterocyclic and structurally complex substrates performed equally well as simple piperidines and pyrrolidines. The reaction worked for activated cyclic ketones, amides and esters, which gave higher yields than their acyclic counterparts. Various remote functional groups such as thiocarbonyls and esters did not hinder the reaction.

Neri and co-workers employed an on-DNA Diels–Alder cycloaddition protocol to generate a 4,000-compound DEL in good purities and yields. The DNA fragments functioned as amplifiable bar codes for identification purposes, and the DEL was compatible with decoding strategies that are based on ultra-HTS techniques,[33] In a similar vein, Dai and co-workers demonstrated the utility and versatility of the inverse-electron-demand Diels–Alder reaction for the synthesis of DNA-tagged pyridazines (**eq 12**).[34] The authors reported two complementary protocols for reacting DNA-conjugated 1,2,4,5-tetrazines with olefins and alkene surrogates such as cyclic ketones to yield the desired pyridazines with moderate-to-excellent conversions. Select functionalized pyridazines were shown to undergo Suzuki–Miyaura coupling, acylation, and S_NAr substitution, respectively, underscoring the potential utility of the pyridine scaffold for future DEL syntheses.

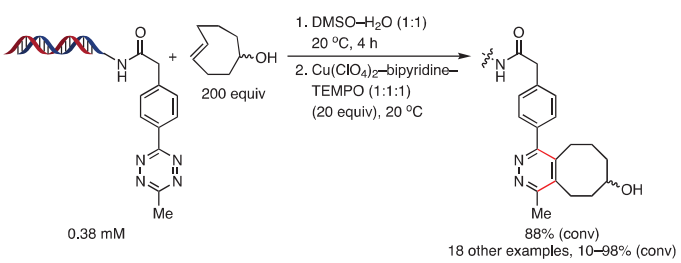
In a series of papers,[35–37] Kodadek and his research teams have reported the development of DNA-compatible variants of the asymmetric aldol reaction (**Scheme 5**, Part (a)), the asymmetric Mannich reaction, and the Knoevenagel condensation (Scheme 5, Part (b)) all on solid support. In the aldol variant, proline promoted the asymmetric synthesis of β-hydroxy ketones from immobilized aldehydes and soluble ketones. Heteroaromatic aldehydes were compatible with the reaction and the reaction conditions did not adversely affect the polymerase chain amplification of DNA; however, the enantioselectivities observed were generally modest (ee = 54%–79%). Similarly, the same laboratory disclosed a DNA-compatible, solid-phase synthesis of β-amino ketones through a proline-mediated asymmetric Mannich reaction, again between immobilized aldehydes and soluble ketones.[36] Anilines substituted at the meta or para position worked well, in contrast to ortho-substituted anilines which did not form the desired products. Moreover, the syn product was favored, and the ee of the syn product varied from 54% to 96%. Extending the applicability of the DNA-compatible, combinatorial synthesis on solid support approach, another of Kodadek's teams reported the synthesis of β-cyanoacrylamides by a Knoevenagel condensation between immobilized α-cyano amides and soluble aldehydes.[37] The cyanoacrylamides underwent Michael additions with thiol and phosphine nucleophiles, and thus could serve as a source of reversibly covalent protein ligands that are cysteine-reactive. The Knoevenagel reaction worked well for aliphatic and aromatic aldehydes including those with branched alkyl groups; however ketones were unreactive.

"Tertiary Amino Effect" (T-) Reaction Cascade for DEL Synthesis Involving a Knoevenagel Condensation, a 1,5-Hydride Shift, and a Mannich Cyclization



eq 11 *(Ref. 32)*

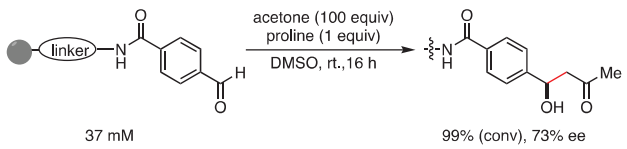
Inverse-Electron-Demand Diels–Alder Reaction for DEL Synthesis



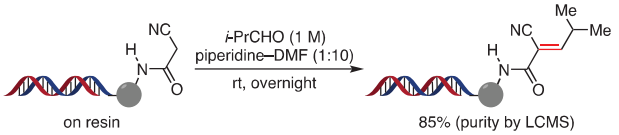
Employing proline as promoter and no oxidation step required, 12 additional examples from reaction with alkene surrogates were reported: 26–87% (conv)

eq 12 *(Ref. 34)*

(a) DNA-Compatible, Proline-Promoted Asymmetric Aldol Reaction on Solid Support



(b) Knoevenagel Condensation for One-Bead, One-Compound β-Cyanoacrylamide DELs



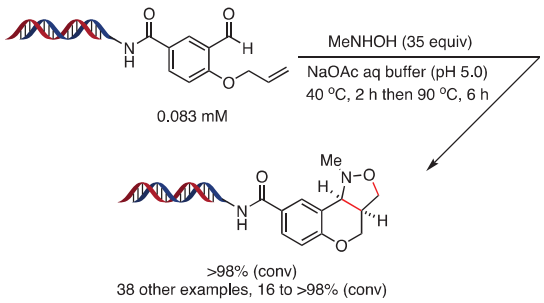
Scheme 5. DNA-Compatible Aldol Reaction and Knoevenagel Condensation on Solid Support. *(Ref. 35,37)*

A method for synthesizing DELs that contain members possessing the less well studied polycyclic isoxazolidine moiety was developed by a team led by Schreiber.[38] The method relies on an intramolecular and DNA-compatible nitrone–alkene [3 + 2] cycloaddition that forms the DNA-linked isoxazolidine, a structural feature found in a number of alkaloids and bioactive compounds (**eq 13**). The nitrone is formed in situ from reaction of the corresponding *N*-alkylhydroxylamine with the carbonyl group of the substrate, and the subsequent intramolecular cycloaddition generates a minimum of two stereogenic centers. The method allows for appendage diversification and does not cause DNA damage or preclude subsequent amplification and ligation steps.

Very recently, Sharpless and co-workers reported the first iminosulfur oxydifluoride (R–N=SOF_2) reaction with primary amines and phenols on single-strand DNA with the aim of demonstrating the usefulness of the SuFEx click chemistry for bioconjugation applications (**Scheme 6**).[39] The off-DNA model reactions took place under mild conditions in aqueous buffer to give sulfamides (from primary amines), sulfuramidimidoyl fluorides (from secondary amines), and sulfurofluoridoimidates (from phenols) in up to 99% isolated yields (29 examples).

3.4. Enzymatic Reactions

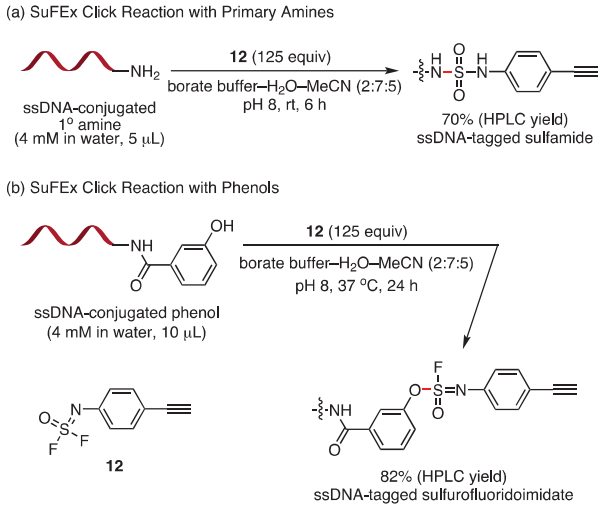
The first on-DNA chemo-enzymatic synthesis of a small, carbohydrate-based library was reported by Thomas et al. (**Scheme 7**).[40] This approach relied on either an enzymatic galactosylation or an enzymatic and site-specific oxidation to generate the DNA-glycoconjugate library members. In the galactosylation protocol, bovine β1,4-galactosyltransferase (β1,4-GalT) catalyzed the selective transfer of Gal-β1,4 from uridine diphosphate galactose (UDP-Gal) to an acceptor GlcNAc in the presence of $MnCl_2$ under mild conditions and leading to excellent conversions. In the site-specific oxidation protocol, galactose oxidase (GOase) variants M_1 and F_2 generated aldehydes from hexoses by a highly selective oxidation of the C6 hydroxyl group in the galactose moiety. The aldehydes were then elaborated further by hydrazone/oxime ligation or reductive amination.



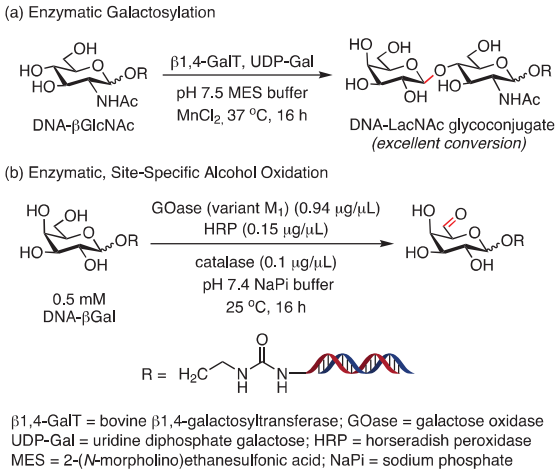
eq 13 *(Ref. 38)*

4. Commonly Employed Reactions in DELT

DEL chemistry is at its core combinatorial chemistry. Accordingly, it should not be a surprise that its practice has evolved to date using chemical transformations that are robust, high yielding, and for which the necessary building blocks are readily available. DELT-compatible chemistries must not only satisfy the three criteria just listed, but must also operate under DNA-compatible conditions: dilute (0.1–1 mM) aqueous media at pH between 4 and 14 and at temperatures between 25 and 90 °C, and the reactions must not alter or degrade the DNA encoding tags. In Section 3, we have presented "recently developed reactions", which we arbitrarily define as those



Scheme 6. First Iminosulfur Oxydifluoride on-DNA Reaction with Primary Amines and Phenols. *(Ref. 39)*



Scheme 7. Carbohydrate DEL Synthesis via Enzymatic Catalysis. *(Ref. 40)*

having been reported since 2015, and which have included many interesting and potentially very useful transformations. For the purposes of this review, we term "commonly employed reactions" in DELT as those already reported and tabulated in various reviews and communications.[41,42] Such reactions include amide formation, reductive aminations, amine capping reactions, Suzuki and Sonogashira couplings, some condensations and some heterocycle-forming cyclizations.

5. Analysis of Commonly Used, Commercially Available Building Block Sets

Presently, published reports of methods developed specifically for assembling DEL libraries are growing rapidly. However, many newly described DELT-applied reactions are often exotic and lacking sufficient validation with a wide variety of reagents. For some of these reactions, reagents are simply not available in any practical numbers (hundreds) to create a DEL. At the same time, large and diverse DELs reported to date have been synthesized using what one would mostly call classical combinatorial chemistry transformations and producing libraries that have been used in affinity selection campaigns to identify useful hits for drug discovery. While such classical and well-known reactions are modest in number compared to standard organic chemistry in solution, an abundance of building blocks for these reactions (e.g., amines, carboxylic acids, and aryl halides) has enabled the creation of DELs of sufficient size, quantity, and diversity. Therefore, while more advanced approaches will continue to be reported and building blocks for them will become available, the use of commonly applied reactions will likely remain the mainstay of DEL production for the time being. Thus, an understanding of the availability and diversity of building blocks commercially available and applicable to DELT becomes critical to creating the most economical, diverse, drug-like, and ultimately the most useful DELs for drug discovery.

The number of modifiable functional groups in the DELT cores is also limited because of the necessity of orthogonal reactivity. For this analysis, we selected several functional groups that have many readily available reaction partners in well-established and DELT-compatible protocols. The list includes classical functional groups such as amines, aldehydes, and carboxylic acids, as well as more recently introduced ones such as terminal alkynes, azides, aryl halides, and boronic acids/esters.

We have grouped the modifiers in three categories: (1) *Amine Modifiers* (aldehydes, aryl halides, carboxylic acids, and sulfonyl halides but not alkyl halides due to concerns about reaction selectivity); (2) *Carbo Modifiers* (primary and secondary amines), and (3) *Couplers* (alkynes, aryl halides, azides, and boronic acids or esters). Indeed, depending on the library chemistry in question, one might require a different classification of functional groups. Furthermore, the exclusion of various chemical substituents will likely reduce these numbers. Nevertheless, the intent of this analysis is to give an understanding of building blocks that exist physically and fall into acceptable categories of cost and molecular weight.

To analyze the availability of the modifiers, we selected 12 vendors with more than 8,000 "off-the-shelf" compounds.[43] This cut-off identifies vendors that could immediately ship large numbers of building blocks as a single source. As such, this helps to reduce costs, logistical complexity, and lead time, as special formatting is typically required. The distribution of the modifiers from each supplier is shown in **Figure 2**, and the percentages among them of so-called *small* compounds and *inexpensive* compounds are shown in **Table 3**. The criteria used for selecting *small* and *inexpensive* are: (i) A *small* modifier for two-cycle libraries should have a molecular weight (MW) ≤150 Da, while a *small* core building block's MW should not exceed 200 Da. (ii) An *inexpensive* compound is one costing not more

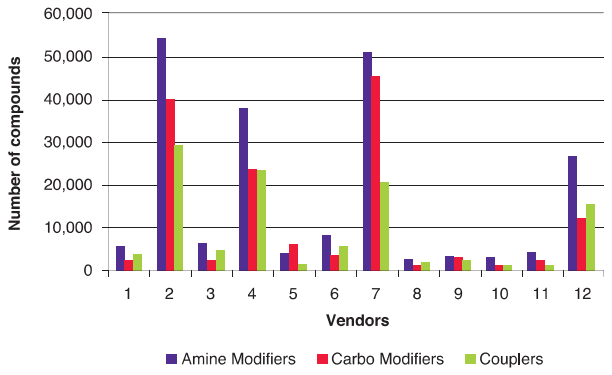


Figure 2. Distribution of Modifiers from the Ten Vendors Selected. *(Ref. 43)*

Table 3. Commercially Available Modifier Compounds: Count and % Small / % Inexpensive. *(Ref. 43)*

Vendor No	1	2	3	4	5	6	7	8	9	10	11	12
Amine Modifiers[a]	**5,665**	**54,083**	**6,328**	**37,892**	**4,169**	**8,200**	**51,163**	**2,476**	**3,409**	**2,897**	**4,300**	**26,571**
	65/42	24/24	60/40	22/29	46/25	60/42	15/22	64/53	32/42	0/22	21/14	34/30
Carbo Modifiers[b]	**2,400**	**40,342**	**2,338**	**23,575**	**5,891**	**3,528**	**45,602**	**1,047**	**2,856**	**1,241**	**2,202**	**12,124**
	55/26	15/14	59/25	14/16	48/14	51/22	10/13	57/34	20/25	0/14	20/11	27/19
Couplers[c]	**3,608**	**29,323**	**4,590**	**23,497**	**1,396**	**5,757**	**20,516**	**1,752**	**2,354**	**1,161**	**1,282**	**15,408**
	67/57	25/37	58/52	22/42	50/46	60/55	18/37	66/67	32/51	0/37	25/25	33/46

[a] Aldehydes, aryl halides, carboxylic acids, and sulfonyl halides. [b] Primary and secondary amines. [c] Alkynes, aryl halides, azides, and boronics.

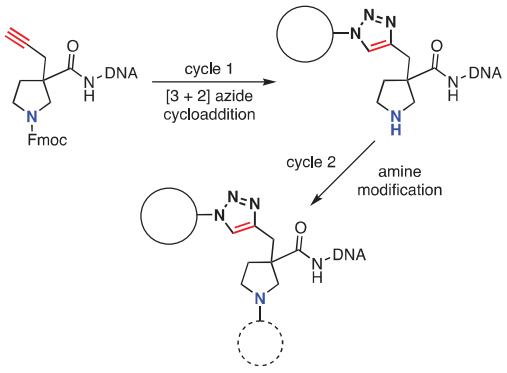
than US $100 per gram. To add flavor to these numbers, we estimate the size of a possible 2-cycle DEL assembled from each vendor's collection. For this simulation, we selected an alkyne-containing N-protected amino acid as the core molecule (**Scheme 8**). The chemistry for decorating these cores appears classical from one side while challenging from the other: *amine modifiers* being the largest group of decorators, while *azides* being the smallest.

The sizes of the resultant libraries are obtained by multiplying the number of decorators by the number of cores (**Table 4**). As the number of cores, we took all available from selected 12 vendors core compounds. Column "All" shows the libraries assembled with all decorators and cores; columns "*Small*" and "*Inexpensive*" show the libraries assembled with small or inexpensive modifiers, respectively. For the "*Inexpensive*" libraries, we took all available numbers of cores, while for "*Small*" libraries, the cores had MW ≤ 200 Da. The number of cores is indicated in the header.

In some cases, modifiers that meet the small or inexpensive criteria do not exist and, thus, the library size is zero. Clearly, it is generally possible to enumerate many compounds. This is a good start from which to exclude compounds according to various design criteria (e.g., size, molecular diversity, undesired functional groups, predicted target affinity, etc.). This simulation also illustrates the numbers of building blocks that will have to be available in order for recently reported DNA-compatible reactions to have the impact for hit identification as the more classical reactions have already had.

6. Conclusion and Outlook

The past decades have witnessed excellent and widely used applications of transition-metal catalysis and nucleophilic addition reactions in the synthesis of DNA-encoded libraries. In the years to come, it is expected that the recently disclosed photochemical, radical, and enzymatic reactions—with their excellent chemoselectivity, functional group compatibility, and mild reaction conditions—will have a profound impact on DNA-encoded library chemistry by enabling greater chemical reaction diversity amplification and more extensive chemical space exploration. At the same time, business drivers will make available ever larger numbers of building blocks to create large DEL sets based on these reactions.



Scheme 8. Decoration of Alkyne-Containing N-Protected Amino Acid for a Simulated DEL.

7. Acknowledgments

Y. H. and Y. C. contributed to the DNA-compatible reaction analysis. O. S. and Y. M. contributed to the building block analysis. R. A. G. developed the manuscript concept and contributed to the introduction, design principle, and final editing. Financial support to Y. C. was provided by the National Natural Science Foundation of China 91765126, 21622207, 21602242, and the Strategic Priority Research Program of the Chinese Academy of Sciences XDB20020200.

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Table 4. Estimated Size of a Possible 2-Cycle DEL Assembled from each Vendor's Collection.[a]

Vendor No	All Cores & Modifiers	"Small" Cores & Modifiers	All Cores & "Inexpensive" Modifiers
1	291,195	0	0
2	169,523,700	1,789,452	5,453,700
3	1,635,300	732,144	0
4	34,957,725	917,084	836,925
5	908,460	141,470	95,130
6	1,688,400	394,730	52,575
7	715,456,170	2,085,552	35,033,625
8	42,810	0	0
9	17,902,500	1,382,346	4,120,830
10	524,205	0	19,650
11	7,628,310	93,296	54,540
12	31,920,480	2,971,458	854,595

[a] Cores: 15 total, 14 "small".

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(43) (a) Vendor: Accela ChemBio (1), Angene Chemical (2), Apollo Scientific (3), AstaTech (4), ChemBridge (5), ChemScene (6), Enamine (7), Manchester Organics (8), Pharmablock (9), Specs (10), Toronto Research Chemicals (11), and WuXi LabNetwork (12). (b) Analysis of the vendors' catalogs and pricing as well as the classification of compounds and calculation of molecular weights (using RDKit software tools) were performed by Chemspace (chem-space.com).

About the Authors

Ying Huang received her B.S. degree in chemistry in 2015 from Central China Normal University. The same year, she moved to the Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, to pursue a master's degree under the direction of Professor Yiyun Chen. She is currently a doctorate student in Professor Yiyun Chen's group, and is focusing on developing novel and biocompatible light-induced chemical reactions for the post-synthetic modification of nucleic acids.

Olena Savych received her M.Sci. degree in organic chemistry in 2017 from the National Taras Shevchenko University of Kyiv. Her thesis research project focused on developing new

technologies for parallel chemistry applications. She is currently a data curation specialist at Chemspace.

Yurii Moroz received his Ph.D. degree in inorganic chemistry in 2010 from the National Taras Shevchenko University of Kyiv. His doctoral dissertation was on the topic of polymetal coordination compounds. Yurii then did postdoctoral research at Tufts University, working with organometallic compounds, and at Syracuse University, working with peptides and proteins. After returning to the Ukraine, Yurii has focused on approaches to generate synthetically feasible small molecules. He joined Chemspace as CEO in 2017.

Yiyun Chen is a professor at the Shanghai Institute of Organic Chemistry and a joint professor at ShanghaiTech University. Yiyun received his B.S. degree in chemistry with honors in 2002 from Peking University, and earned his Ph.D. degree in organic chemistry in 2007 with Professor Chulbom Lee at Princeton University. During his postdoctoral studies with Professor David R. Liu at Harvard University and Howard Hughes Medical Institute, Yiyun used the DNA-encoded reaction-discovery system to discover a new biocompatible visible-light-induced azide reduction reaction. In 2011, Yiyun was appointed Principal Investigator at the Shanghai Institute of Organic Chemistry, where he is developing novel biocompatible light-induced chemical reactions and new optochemical tools for studying biological systems.

Robert A. Goodnow, Jr. obtained his B.S. degree in chemistry from Georgetown University and his Ph.D. degree (in natural products organic and bioorganic chemistry) from Columbia University. He then carried out research on oligosaccharide synthesis at Princeton University as an NIH Postdoctoral Fellow. Rob began his industrial career at Hoffmann-La Roche, and his research interest has since focused on medicinal chemistry and the implementation of several chemistry platform technologies such as small-molecule targeted delivery of siRNA, analytical chemistry, and DNA-encoded chemistry. In 2013, he joined AstraZeneca as Executive Director of the Discovery Sciences Chemistry Innovation Centre, where he led research projects in chemical biology, fragment-based lead generation, and computational chemistry. Since October 2016, Rob has been Vice President of Chemistry Innovation at Pharmaron, Inc. (Boston, MA), and is responsible for shared risk research programs. He has edited the book, *A Handbook for DNA-Encoded Chemistry: Theory and Applications for Exploring Chemical Space and Drug Discovery* (Wiley, 2014).

product highlight

Enrich Your Chemical Toolbox

The fluoroalkylation toolbox has now been expanded beyond the standard Togni Reagents to include novel hypervalent iodine perfluoroalkylation reagents as well as fluoroalkyl bromides, silanes, carboxylates, and sulfonyl fluorides.

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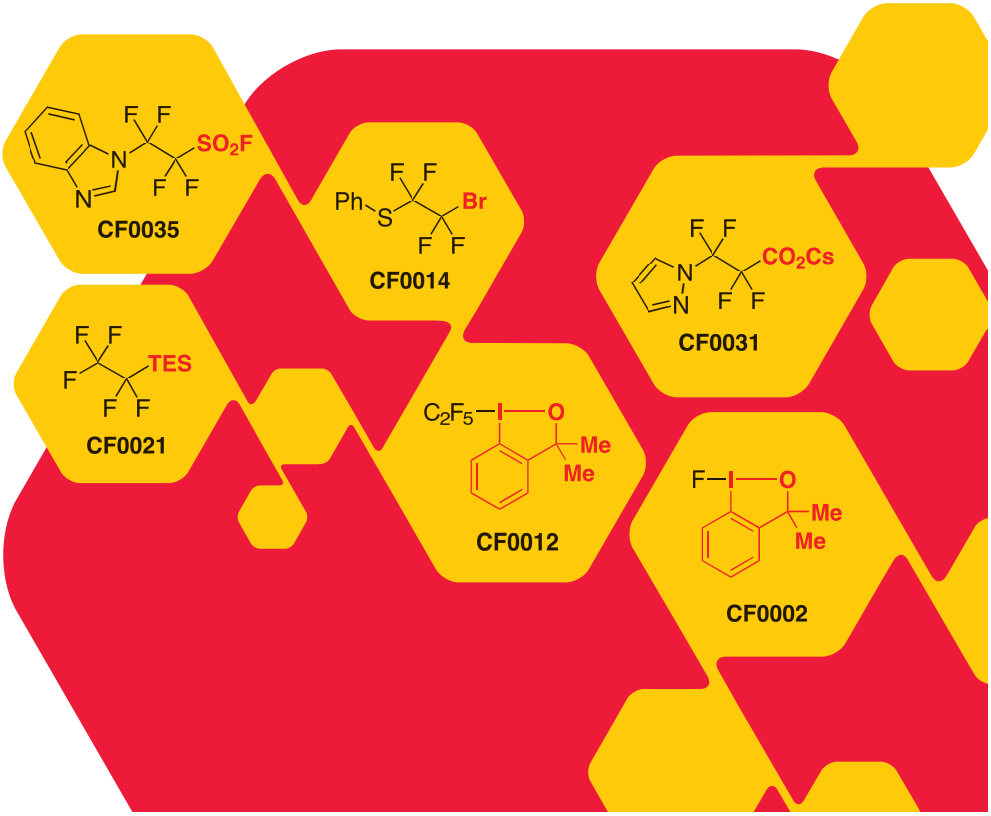

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