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Design and Synthesis of Biaryl DNA-Encoded Libraries

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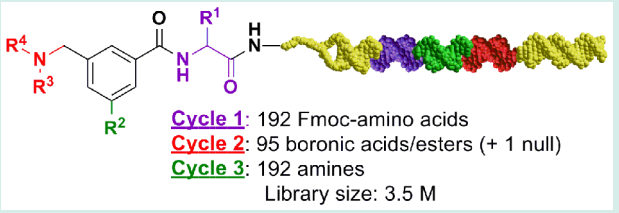
Supporting Information

ABSTRACT: DNA-encoded library technology (ELT) is a powerful tool for the discovery of new small-molecule ligands to various protein targets. Here we report the design and synthesis of biaryl DNA-encoded libraries based on the scaffold of 5-formyl 3-iodobenzoic acid. Three reactions on DNA template, acylation, Suzuki–Miyaura coupling and reductive amination, were applied in the library synthesis. The three cycle library of 3.5 million diversity has delivered potent hits for phosphoinositide 3-kinase α (PI3Kα).

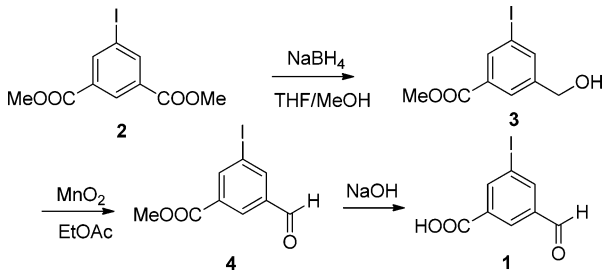


KEYWORDS: *Suzuki–Miyaura cross-coupling, DNA-encoded library technology*

The DNA-encoded library (DEL) technology has been developed over decades and now is widely used both in the pharmaceutical industry and in academia.[1−4] DNA encoding allows simultaneous interrogation of millions to billions of small molecules through affinity selection. Using high-throughput sequencing technologies,[5] the output sequences can be amplified and characterized to yield the structures of potential hits. As reported earlier,[6−10] we and others have discovered potent inhibitors for various targets using this approach.

A key to the success of DEL technology is the diversity of possible library structures, which depends on the repertoire of chemical reactions that are compatible with "on-DNA" synthesis. We have spent considerable effort to develop and utilize useful organic transformations that can be performed under DEL-compatible conditions. Recently various groups have reported the DNA-templated synthetic transformations.[11−13] Here, we describe the application of two common synthetic reactions, Suzuki–Miyaura cross-coupling and reductive amination, to DEL synthesis. Before designing a library synthetic scheme, we initially sought to confirm that the desired reactions were feasible, using simple substrates on-DNA (vide infra). With these preliminary results in hand, we then needed to choose a library scaffold that would be the substrate for further optimization of the chemistry, and ultimately the basis for library synthesis. To this purpose, we designed the trifunctional scaffold, 5-formyl 3-iodobenzoic acid **1**. We reasoned that the meta-disposition of the functional groups would minimize the possibility of steric or neighboring-group interference of the key reactions. We planned to link the scaffold to DNA through acylation with the carboxylate group. Boronic acids/esters and amines could then be introduced through Suzuki–Miyaura coupling and reductive amination, respectively. The synthesis of 5-formyl 3-iodobenzoic acid is described in Scheme 1. 5-Iodoisophthalate was selectively reduced with $NaBH_4$/MeOH to give methyl 3-(hydroxymethyl)-5-iodobenzoate. The alcohol was oxidized to an aldehyde using MnO_2. Finally, the methyl ester was hydrolyzed to carboxylic acid with 1 equiv of NaOH.

Scheme 1



Chemistry Development: Suzuki–Miyaura Coupling. Suzuki–Miyaura cross coupling is widely used in medicinal chemistry for the synthesis of biaryls. Recently we reported that $Pd(PPh_3)_4$ can effectively catalyze the Suzuki–Miyaura cross coupling on DNA-linked aryl iodides/bromides with various boronic acids/esters.[14] The scope and robustness of on-DNA Suzuki–Miyaura coupling with **HP-1** was well demonstrated (Scheme 2). For purposes of our planned library, we sought to validate a large number of boronic acids/esters against a representative model substrate.

We chose to validate our boronic acids/esters against the simple iodobenzamide **HP-1**. The validation reactions were run in 96-well plates and analyzed by LCMS. Product, starting material, and any other major byproducts were quantitated and tabulated. The results of the validation are shown in Figure 1. 153 boronic acids/esters were validated and 107 were designed as passing with a yield of 70% or greater. The passing boronic

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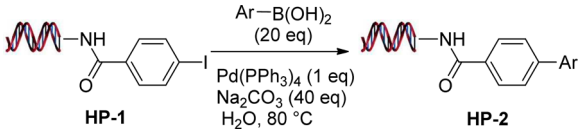
Scheme 2



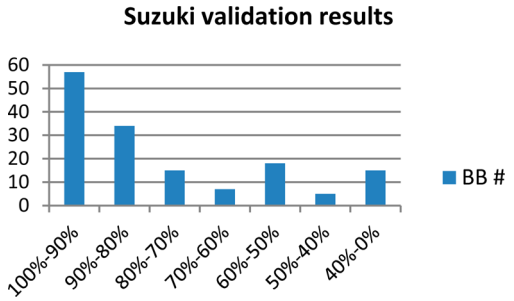
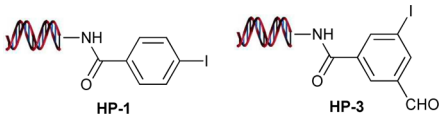


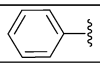
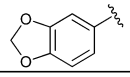
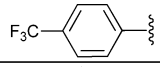
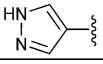
Figure 1. Validation results of Suzuki–Miyaura coupling.

acids/esters spanned several structural classes, including electron-rich and electron-poor phenyls, 1,2- and 1,3-azoles, furans, pyridines, and aliphatic boronic acids/esters. Of the failing boronic acids/esters, a similarly broad diversity of structures was observed, with no strong structural trend predicting pass/fail easily observable. A full tabulation of the validation results can be found in the Supporting Information.

While this boronic acid/ester set was validated against **HP-1** as a model, we were interested in their reactivity with respect to **HP-3**.[15] To confirm the validation results for **HP-1** would hold true for **HP-3**, we ran a small set of boronic acids/esters which included electron-rich (Table 1, entry 2), electron-poor (Table 1, entry 3) phenyl boronic acid and heterocyclic boronic ester (Table 1, entry 4) against **HP-3** as well. This data gave us confidence that the validation data would be suitable relevant to the library substrate.

Table 1. Comparison of Suzuki–Miyaura Coupling with HP-1[a] and HP-3[b]

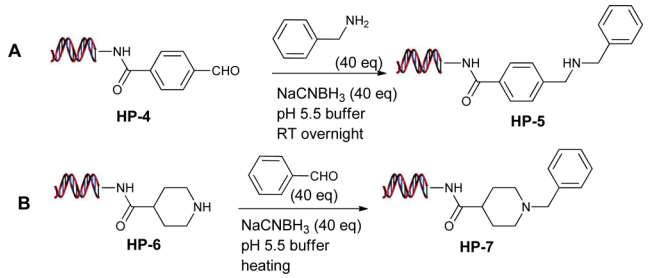


Entry	Ar	**HP-1** Yield	**HP-3** Yield
1		~100%	95%
2		~100%	95%
3		56% (92%[c])	90%
4		~100%[d]	95%

[a]Reaction conditions: 1 equiv of **HP-1** (1 mM in H_2O), 20 equiv of Boronic acid or ester (600 mM in CH_3CN/H_2O (1/1)), 1 equiv of $Pd(PPh_3)_4$, 40 equiv of Na_2CO_3 (400 mM in H_2O), 80 °C for 90 min. [b]Reaction conditions: 1 equiv of **HP-3** solution (1 mM in H_2O), 40 equiv of Boronic acid (800 mM in DMA), 1 equiv of $Pd(PPh_3)_4$ (3 mM in CH_3CN, degassed), 80 equiv of Na_2CO_3 (1.2 M in H_2O), 80 °C for 4 h. [c]80 °C for 17 h. [d]Pyrazole boronate was in pinacol ester form.

Chemistry Development: Reductive Amination/Alkylation. Next we sought to demonstrate that reductive amination would be a useful reaction for library synthesis. Reductive amination has been applied to attach peptides or proteins to DNA.[16] When we started the development of reductive amination with on-DNA substrates, the transformation of small molecules to DNA-conjugates has not been reported. Recently the group of Neri published the reductive amination with $NaCNBH_3$ in great details.[17] We used the same reducing reagent but with different conditions. We treated benzaldehyde-modified DNA headpiece (**HP-4**)[18] (1 mM in pH5.5 sodium phosphate buffer (200 mM)) with 40 equiv of benzylamine (400 mM in CH_3CN) and 40 equiv of $NaCNBH_3$ (400 mM in CH_3CN) (Scheme 3A). After reacting

Scheme 3



at room temperature overnight, all the starting aldehyde converted to the desired amination product. When **HP-6**[19] (1 mM in pH5.5 sodium phosphate buffer (250 mM)) was treated with benzaldehyde (40 equiv, 200 mM in CH_3CN) and $NaCNBH_3$ (40 equiv, 400 mM in CH_3CN), the complete conversion required heating at either 80 °C for 4 h or 60 °C overnight (Scheme 3B).

We further tested the reductive amination with a scope of amines against **HP-3** and found the yield was improved with 100 equiv of amines and 100 equiv of $NaCNBH_3$. With these data in hand we turned to the validation of a large number of amines for reductive amination against **HP-3**. Using the conditions described above,[20] a total of 831 amines were validated. Of those, 218, or 26%, passed at a yield of greater than 70%. Figure 2 shows the yield breakdown for primary aliphatic, secondary aliphatic, primary aromatic, and secondary aromatic amines. It is apparent that the primary amines had significantly better yields than the secondary amines, and aromatic amines had higher passing rate than aliphatic amines.

Library Development and Mock Library. Now that we had a large set of validated building blocks, we sought to ensure

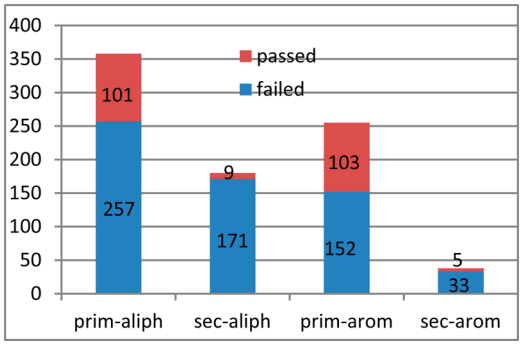


Figure 2. Validation results of reductive amination.

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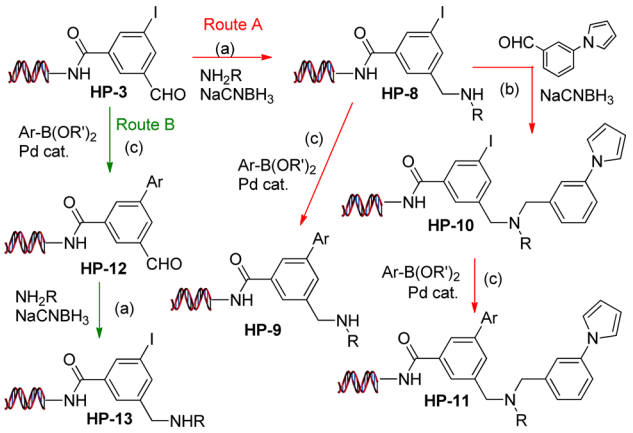
that they would behave as hoped in the setting of library synthesis. Because of high masses and the mixtures of products, it is very difficult to calculate a reaction yield for every reaction in a library step. We, therefore, undertook a series of experiments to explore the following questions: (1) What is the optimal ordering of steps? Or put another way, could the reactivity of the scaffold's aldehyde site be influenced by the substituent at the iodo position, and vice versa? (2) Will the chemistry proceed as expected when the intervening encoding ligation steps are undertaken as well?

To get at the first question we designed two synthetic routes A and B (Scheme 4). Route A would proceed the reductive

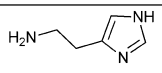
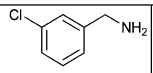
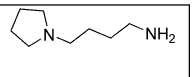
Scheme 4[a]



[a](a) **HP-3** (or **HP-12**) (1 mM in pH5 phosphate buffer (250 mM)), 40 equiv of amine, 40 equiv of $NaCNBH_3$ (200 mM in CH_3CN), RT overnight; (b) **HP-8** (1 mM in pH5 phosphate buffer (250 mM)), 40 equiv of aldehyde (200 mM in CH_3CN), 40 equiv of $NaCNBH_3$ (200 mM in CH_3CN), 80 °C for 4 h; (c) **HP-3**, **8**, or **10** (1 mM in water), 40 equiv of boronate (400 mM in DMA), 80 equiv of Na_2CO_3 (800 mM in water), 1 equiv of $Pd(PPh_3)_4$ (3 mM in CH_3CN, degassed), 80 °C for 2–4 h.

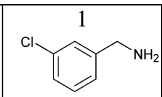
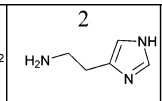
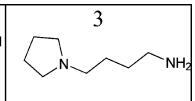
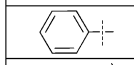
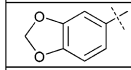
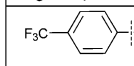
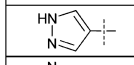
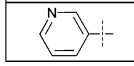
amination before the Suzuki–Miyaura coupling, and Route B would reverse. For Route A, we installed 3 amines which represented normal amines, amines with long side chain and amines containing heterocyclic ring that might chelate with metal onto **HP-3** (Table 2). They all produced mild yields

Table 2. Reductive Amination of HP-3 with Amines

Entry	 1	 2	 3
Product	~60%	~70%	~85%

using the standard condition with unreacted aldehyde starting material left. The reactions were intentionally not further pushed because we'd like to know how the aldehyde starting material would behave in the following coupling step, which would be the Route B strategy. We next performed the Suzuki–Miyaura reaction on these substrates (**HP-8**) using 5 different boronic acids/esters (Table 3). While the cross-couplings proceeded well for the other two substrates (entries 1 and 3), they completely failed for the substrate whose amine was histamine (entry 2). The contaminated aldehyde starting material (**HP-3**) underwent cross-coupling in all cases. Possibly

Table 3. Suzuki–Miyaura Coupling of HP-8 with Ar–$B(OH)_2$[a]

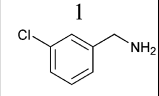
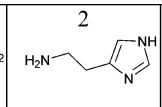
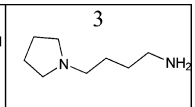
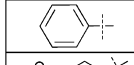
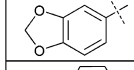
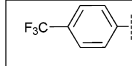
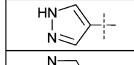
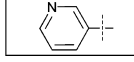
Entry	 1	 2	 3
	95%	0%	85%
	95%	0%	85%
	70%	0%	60%
	95%	0%	75%
	95%	0%	85%

[a]Yield was based on the aminated starting material.

the metal-coordinating imidazole group somehow interfered with the catalysis. In any event, this result showed that the cross-coupling step was indeed sensitive to the structures installed in the amination step. This conclusion was further confirmed with the coupling of 3 **HP-10** substrates, which were obtained through the reductive alkylation of **HP-8** with 3-(*H*-pyrrol-1-yl)benzaldehyde, with the same 5 boronic acids/esters. The compatibility problems with the amine functional groups and cross-coupling led us to investigate the alternative synthetic route (route B).

In Route B, the same five boronic acids/esters were reacted with **HP-3** under the standard conditions. They all proceeded in quantative yield. Without HPLC purification, the coupling product was then reductively aminated with the same three amines as previously shown. As shown in Table 4, the reductive

Table 4. Reductive Amination of HP-12 with Amines[a]

Entry	 1	 2	 3
	89%	80%	79%
	86%	83%	75%
	65%	69%	59%
	100%	87%	73%
	54%	61%	50%

[a]The yield was calculated based on UV and TIC.

aminations proceeded smoothly, including the installation of histamine, yielding a set of products which were unachievable with the different order of steps in Route A.

These data addressed our first question and led us to design a strategy in which cross-coupling preceded reductive amination. We then turned to the effect of library molecular biology steps on the chemistry behavior and the effect of Pd on the ligase/ligation. The best way to ensure that all the steps and operations in a library do not interfere with one another is to

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actually synthesize a library with a number of members small enough that it can be rigorously characterized. We designed a library of 8 compounds (Figure 3), with Fmoc-Phe-OH at cycle

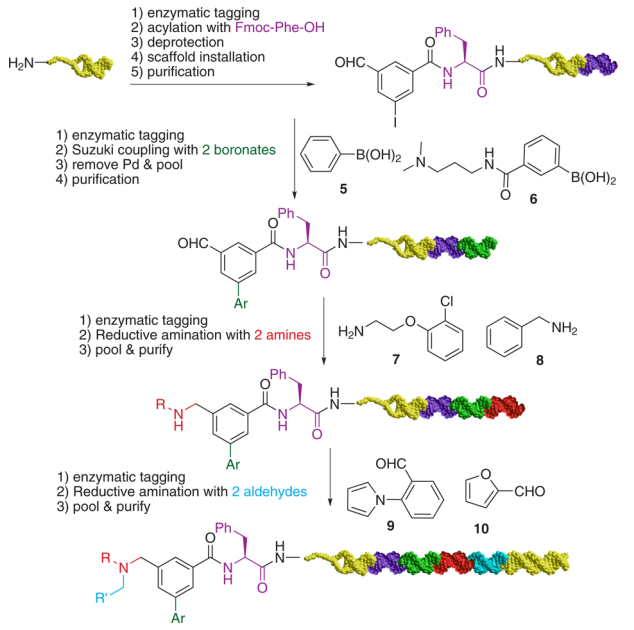


Figure 3. Synthetic scheme for mini library.

1, phenylboronic acid (**5**) and 3-(3-(dimethylamino)-propylcarbamoyl)phenylboronic acid (**6**) at cycle 2, benzylamine (**7**) and 2-(2-chlorophenoxy)ethanamine (**8**) at cycle 3, and 2-(1*H*-pyrrol-1-yl)benzaldehyde (**9**) and furan-2-carbaldehyde (**10**) at cycle 4. After completion of the test library synthesis, the DNA portion of the library was digested enzymatically. This process left the library products attached to the linker and a single nucleotide. The digested library sample was analyzed by LCMS. All 8 of the expected massed (and their sodium adducts) were observed, as well as the deiodide byproducts which had been observed during the chemistry development and validation and several leftover starting materials in each steps (see Supporting Information). These data gave us confidence that the library scheme was feasible, that the chemical steps did not interfere with ligation or vice versa, that the chemistry was well-behaved on substrates with longer DNA, and that our purification strategy was effective.

Library Synthesis. Confident that we could enter production phase, we designed a library based on the scaffold of 5-formyl 3-iodobenzoic acid (Figure 4). We conducted the

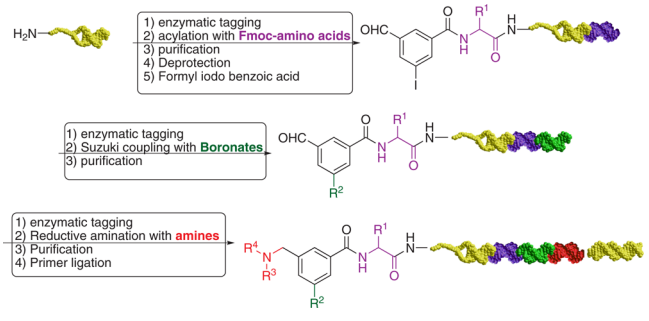
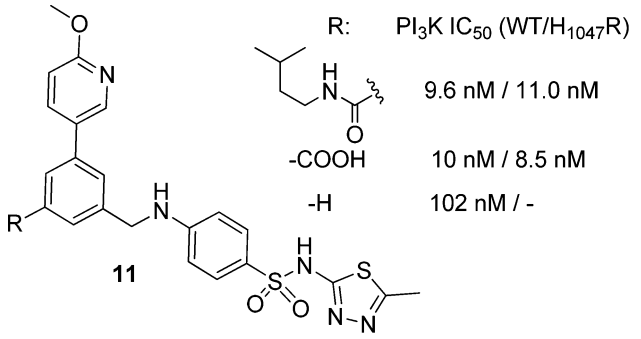


Figure 4. Synthetic scheme for library DEL-A.

library synthesis using a split-and-pool strategy in 96-well plates. At cycle 1, 192 Fmoc amino acids would be acylated onto the headpiece at cycle 1. The same set of amino acids have been used in our earlier reported library.[2] After deprotection, the scaffold was installed via amide bond formation under the activation of DMT-MM. At cycle 2, the iodide was substituted with 95 aryl boronic acids/esters and one null through the Suzuki−Miyaura coupling reaction. At cycle 3, the aldehyde underwent reductive amination with 192 amines which cover 88 primary aliphatic amines, 8 secondary aliphatic amines, 92 primary aromatic amines and 4 secondary aromatic amines. The final library which contained 3502080 components was further ligated with cycle 4 tags and closing primer before handing off for the affinity selection.

DEL-A represents the first DNA-encoded library we have generated with Pd-catalyzed cross-coupling or reductive amination. To date the library has been screened against over 50 biological targets. In retrospect, DEL-A has delivered various active hit series against different targets. For example, in selections against phosphoinositide 3-kinase α (PI3Kα), the potent and selective inhibitors **11** were discovered.[21] The ELT selection for cycle 2 and cycle 3 disynthons allowed for truncation at cycle 1 position which was consistent with the off-DNA compound activity. We also pursued another four cycle library (DEL-B) as described in mini library scheme. In DEL-B, 48 aliphatic primary amines were installed at cycle 3 and 166 aldehydes were reductively alkylated at cycle 4, yielding a four cycle library of 146866176 components. However, the 4-cycle library has not given the same level of success as 3-cycle version.



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00078.

Structure of the headpiece, experimental procedures, analytical methods, and LCMS analysis of the data in the tables (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

DEL, DNA-encoded library; HP, covalently linked DNA duplex—the "headpiece" with a free amine warhead (Figure S1); ELT, DNA-encoded library technology

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