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Photoredox-catalysed Hydroaminoalkylation of on-DNA *N*-Arylamines

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An efficient approach to the photoredox-catalysed hydroaminoalkylation between on-DNA secondary *N*-substituted (hetero)arylamines and vinylarenes has been developed and explored. The methodology was examined with a broad scope of vinylarenes and secondary arylamines to establish a preferred building block profile for the process. Compatible substrates furnished the desired derivitised amine products in modest to excellent yields and with minimial or no detectable by-products.

Introduction

To meet the need of novel small-molecule lead candidates, many researchers have relied upon high-throughput screening (HTS) methods.[1] Notwithstanding the success of traditional HTS methods, the burden of operation costs, labour, infrastructure, and access to high quality diverse chemical libraries has prompted the development of more accessible drug discovery platforms. Originally conceptualised by Brenner and Lerner,[2] DNA-encoded libraries (DELs) have gained considerable traction as a cornerstone of contemporary drug discovery campaigns.[3] DELs comprise large libraries of small molecules, routinely >10^6 members, that are individually barcoded with a unique DNA sequence. Hits from an encoded library are enriched by affinity pulldown (*i.e.*, selection) with the desired biomolecular target and identified *via* high-throughput DNA sequencing and post-sequencing analysis. DEL technology has been successful in identifying new drug leads, with several candidates already undergoing phase trials in the US.[3] However, due to the chemical restrictions imposed by the DNA barcode and conventional aqueous solvents,[4] DELs continue to be limited by their chemical space and molecular properties, particularly when compared against traditional screening libraries.[5]

Chemists have sought to develop new DEL-compatible chemistries to facilitate the generation of more diverse chemical libraries with drug-like properties. To this end, the last decade has witnessed an explosive growth in available DEL chemistry,[6] including medicinal chemistry staples, such as Suzuki-Miyaura coupling[7] and Buchwald-Hartwig amination.[8] More recently, advances in photoredox-catalysed reactions have been ported into DEL-compatible processes.[9] Of particular note, photoredox catalysis has enabled broader access to new bond-formation reactions to generate complex amine-containing DELs. An evaluation of marketed drugs in the US demonstrates the prevalence of alkyl-substituted aromatic amines, which comprise approximately 20% of the top 100 drugs by sales.[10] Not surprisingly, the synthesis of this class of molecules within the context of DEL synthesis has been extensively explored, particularly via metal-catalysed C-N cross-coupling reactions.[8,11-16] Due to the combinatorial nature of DEL synthesis, chemistries that can derivatise upon installed building blocks can expand the chemical space of the encoded library.

We were initially attracted to the photoredox-catalysed hydroaminoalkylation,[17] as it could combinatorially stack with well-established aryl C-N coupling chemistry. Hydroaminoalkylation via Giese reaction in a DEL context has been previously demonstrated using photoredox chemistry;[18-25] however, given its potential for library development, several aspects of this chemistry remain underexplored. First, α-aminoalkyl radicals are invariably generated as the off-DNA reactant, which then adds to the DNA-tagged alkene. This limits the accessible library architectures and building blocks. Second, and of particular note, generation of the α-aminoalkyl proceeds *via* decarboxylation of α-aminoacids or their corresponding activated esters,[18-19,21,24] α-silylamines,[20] or using readily oxidisable symmetrical tertiary amines.[22-23] These substrate

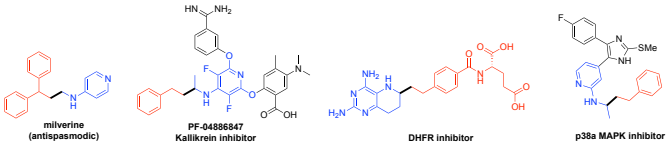

Figure 1. Examples of biologically active molecules synthetically accessible through hydroaminoalkylation with an alkene.

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[c] *Electronic Supplementary Information (ESI) available: synthetic methods, molecular characterisation, supporting data.*

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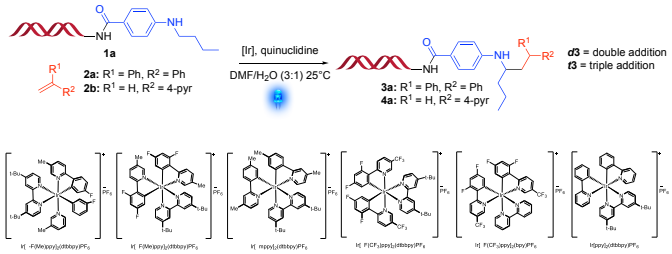
restrictions considerably limit the supply of available amine-containing building blocks. To address these issues and expand upon the scope of this chemistry, we evaluated photoredox-catalysed hydroaminoalkylation of vinylarenes using DNA-tagged secondary *N*-alkylaniline and arylamine derivatives. While secondary aniline substrates are known to be challenging substrates[26] for Giese-type chemistry, the products of such processes are highly represented in bioactive molecules (Figure 1) and will open the scope of complex amines libraries for DELs.

Results and Discussion

We first evaluated the reaction between DNA-tagged *n*-butylaniline **1a** and 1,1-diphenylethylene **2a** (**Table 1**). Using the photoredox catalyst Ir[*p*-F(Me)ppy]$_2$(dtbbpy) (**PC1**) in the presence of hydrogen atom transfer catalyst (HAT) quinuclidine and blue light, resulted in 75% yield of **3a** as determined by LC-MS. Various photocatalysts (**PC1**–**PC6**) were evaluated; however, no increase in yield was observed (**Table 1**, entries 1-6). Extending the reaction time to 3 h using **PC1** resulted in quantitative yield of the desired product (**Table 1**, entry 8). As anticipated, the inclusion of quinuclidine as a HAT catalyst was necessary and significantly improved the yield of the reaction (**Table 1**, entry 9). Since the rate of α-alkylamino radical addition to alkene substrates will be governed by the electronics of the alkene, we evaluated the process on electron poor alkene **2b**. As expected, reactions rates increased, with quantitative yield observed after 1 h (**Table 1**, entry 10). When reactions were left for extended periods, double (***d3***) and triple (***t3***) addition

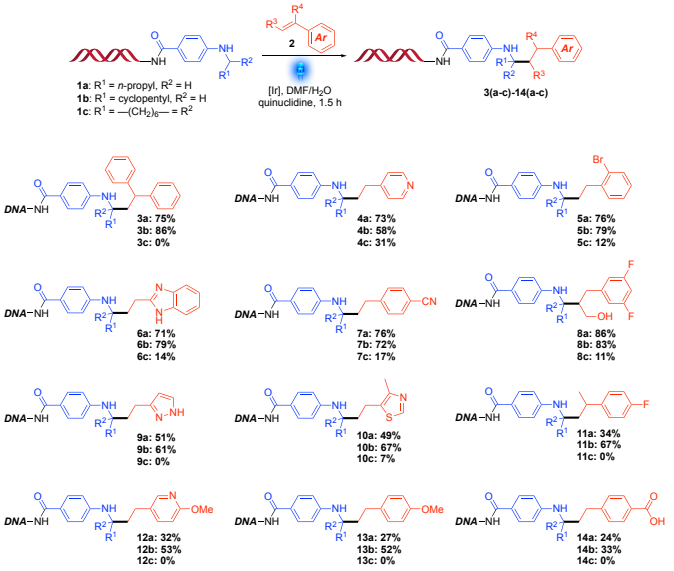
Table 1. Optimisation of on-DNA hydroaminoalkylation[a]



entry	alkene	cat.	time (h)	3 (%)	*d3*[b] (%)	*t3*[c] (%)
1	2a	PC1	1.5	75	0	0
2	2a	PC2	1.5	58	0	0
3	2a	PC3	1.5	17	0	0
4	2a	PC4	1.5	49	0	0
5	2a	PC5	1.5	39	0	0
6	2a	PC6	1.5	75	0	0
7	2a	PC1	2	80	0	0
8	2a	PC1	3	100	0	0
9[d]	2a	PC1	1.5	59	0	0
10	2b	PC1	1	100	0	0
11	2b	PC1	1.5	73	27	0
12	2b	PC1	2	55	32	13
13[d]	2b	PC1	1.5	77	10	0

[a] Reaction conditions: degassed mixture of DNA tagged **1a** (10 nmol), quinuclidine (500 eq.), alkene **2a** or **2b** (250 eq.), Iridium photocatalyst PC1–PC6 (1 eq.), DMF/H_2O (3:1), blue light (10 cm, max intensity, Kessil A160WE), fan cooled. [b] double addition product. [c] triple addition product. [d] no quinuclidine.

Table 2. Hydroaminoalkylation of various vinylarenes with variably substituted DNA-tagged secondary *N*-alkyl anilines[a]



[a]Reaction conditions: degassed mixture of DNA tagged **1a**-**1c** (10 nmol), quinuclidine (500 eq.), alkene **2** (250 eq.), Iridium photocatalyst PC1 (1 eq.), DMF/H_2O (3:1), blue light (10 cm, max intensity, Kessil A160WE), fan cooled. The yield was determined by LC-MS analysis.

adducts were observed with a concomitant decrease in desired product (**Table 1**, entries 11-12). To enable broad access to alkene substrates with variable electronics, we opted for a 1.5 h reaction, which yielded 75% and 73% for **2a** and **2b** substrates respectively. Importantly, reactions were found to require rigorous degassing under an inert atmosphere to minimise undesired *N*-dealkylation. We also tested the stability of DNA under the photoredox conditions and found that the DNA tag was left intact after the reaction (**Figure S13**).

We subsequently applied our optimised hydroaminoalkylation process to a more diverse substrate scope of vinylarenes (**Table 2**). Using DNA-tagged aniline **1a**, vinylarenes with diverse electronics were surveyed to afford products **3a**-**14a**. Disubstituted alkenes were compatible with the reaction and resulted in products (**3a**, **8a**, **11a**) in good to excellent yields. As expected, electron rich vinylarenes were less tolerated, resulting in products in modest yields (**12a**, **13a**, **14a**). Importantly, vinylheteroarenes were within the scope of the process (**6a**, **9a**, **10a**, **12a**) and did not result in the detection of unknown by-products. Other substituents on the aniline nitrogen were explored, including more sterically encumbered alkyl substrates (**1b**, **1c**). We observed that having a trisubstituted α-carbon for the DNA-tagged amine, **1c**, severely hampered the reaction, resulting in low yield and produced products only for a handful of substrates. This is likely due to a sterically inhibited attack of the α-alkylamino radical on the vinylarene substrates.

N-benzyl substituted aniline **1d** was also explored with the optimised hydroaminoalkylation process (**Table 3**). Due to the lower oxidation potential of *N*-benzyl anilines compared with

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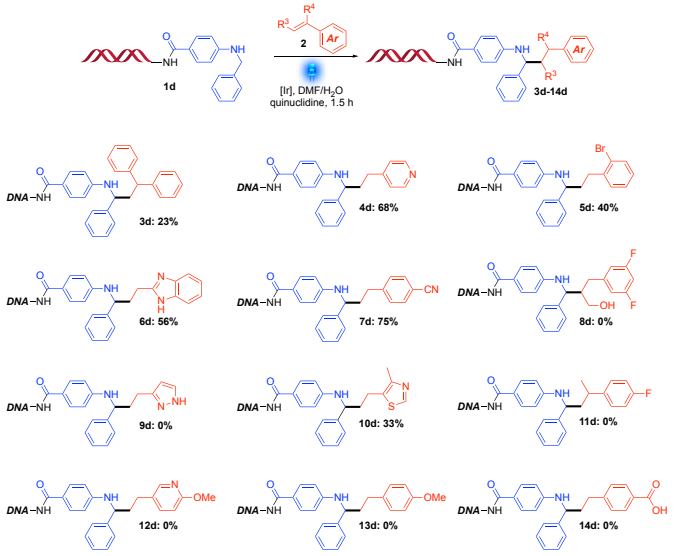
Table 3. Hydroaminoalkylation of various vinylarenes with DNA-tagged secondary *N*-benzyl aniline[a]

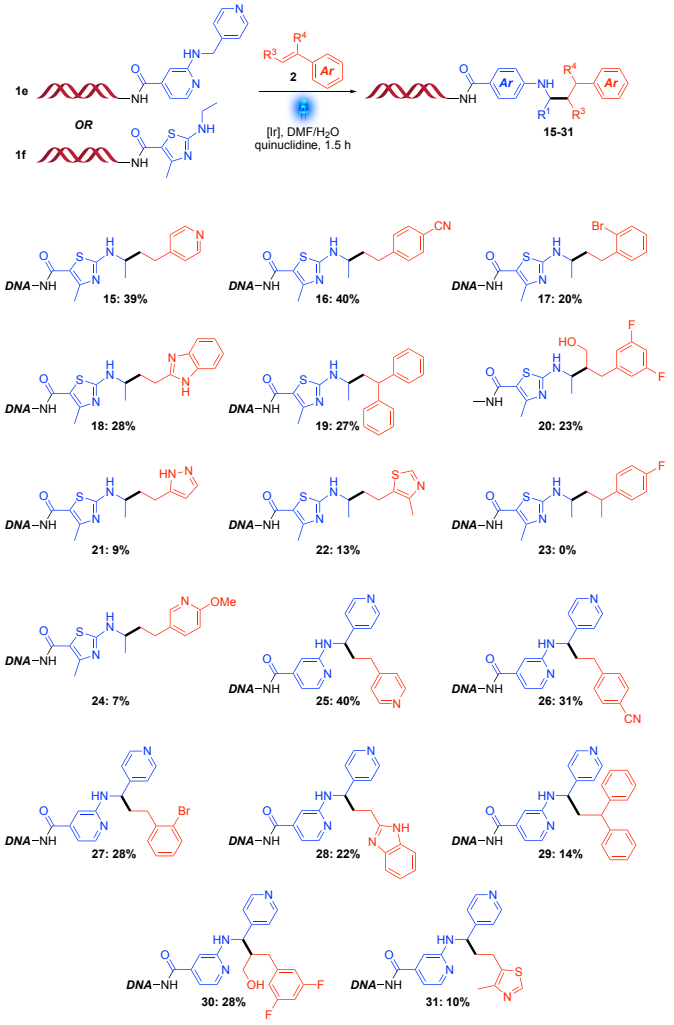


[a]Reaction conditions: degassed mixture of DNA tagged **1d** (10 nmol), quinuclidine (500 eq.), alkene **2** (250 eq.), Iridium photocatalyst PC1 (1 eq.), DMF/H_2O (3:1), blue light (10 cm, max intensity, Kessil A160WE), fan cooled. The yield was determined by LC-MS analysis.

their alkyl counterparts, a HAT catalyst was not necessary, but was found to increase the rate of reaction and minimise reaction by-products including *N*-dealkylation (**Table S1**). This enables the incorporation of such *N*-benzylic substrates during the combinatorial preparation of DELs without the requirements for separate plate conditions. Electron-deficient vinylarenes were well tolerated during hydroaminoalkylation with **1d**, producing the desired products in good to high yield; however, sterically demanding alkenes and electron-rich alkenes resulted in no observable product formation. Curiously, while most failed reactions resulted in quantitative recovery of starting material, reactions for **9d**, **13d**, and **14d**, resulted in 10-20% of the desired product as a covalent adduct with HAT catalyst quinuclidine (**Table S5**).

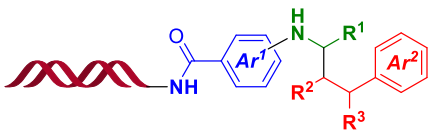
To expand the scope of the chemistry, we also explored the tolerance of the optimised hydroaminoalkylation reaction using *N*-substituted heteroarylamines on DNA (**Table 4**). Consistent with the previous scope, electron-poor alkene substrates performed the best, with most giving modest yields. The yield of strongly electron deficient alkenes, such as those with 4-pyridine and 4-cyanobenzene, suffered from significant double and triple addition adducts (**Tables S6 and S7**). By and large, the modest yields were mostly attributed to low reactivity, as the mass balance of the reactions were starting material, with the exception of **20**, which was partially contaminated with 20% *N*-dealkylated **1f**. A more comprehensive heteroarylamine scope may reveal other limitations or preferences for the chemistry; however, alkyl substituents on the amine paired with electron-deficient alkenes appear to be the best tolerated and highest yielding, while heteroarylamine substrates underperformed compared with substituted anilines.

Table 4. Hydroaminoalkylation of various vinylarenes with DNA-tagged secondary *N*-substituted arylamines[a]



[a]Reaction conditions: degassed mixture of DNA tagged **1e-1f** (10 nmol), quinuclidine (500 eq.), alkene **2** (250 eq.), Iridium photocatalyst PC1 (1 eq.), DMF/H_2O (3:1), blue light (10 cm, max intensity, Kessil A160WE), fan cooled. The yield was determined by LC-MS analysis.

It is envisaged that the optimised hydroaminoalkylation will find use in DEL workflows where secondary *N*-alkyl or *N*-benzyl arylamines are generated on DNA. A hypothetical library synthesis may involve an initial coupling of a library of (hetero)aryl halides for cycle 1, followed by palladium-mediated C-N coupling of a library of primary alkylamines/benzylamines for cycle 2.[16] Both steps would take advantage of large and readily available building block libraries. For cycle 3, the



cycle 1: 384 (hetero)aryl halides bearing carboxylic acid
cycle 2: 384 primary amines with α-CH_2
cycle 3: 100 electron poor/neutral vinylarene
Estimated library size: 15 million

Figure 2. Proposed library design of 15 million members

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photoredox-catalysed hydroaminoalkylation with a library of electron poor/neutral vinylarenes would furnish the resulting derivatised amine library. The envisaged DEL could feasibly provide a library with 15 million encoded members (**Figure 2**).

Conclusions

In conclusion, we have developed a photoredox-catalysed hydroaminoalkylation reaction between on-DNA secondary *N*-alkylated (hetero)arylamines and vinylarenes. Despite secondary arylamines serving as poor surrogates for α-alkylamino radicals, reactions proceeded well with a fairly broad scope of alkene acceptors. The most effective vinylarenes reactants were found to be electron poor to neutral; strongly electron poor substrates were observed to undergo undesired double-addition, while electron-rich substrates resulted in poor yields. Ideal on-DNA secondary *N*-arylamine reactants contained an α-methylene; substrates with α-methines resulted in poor conversions. *N*-alkyl and *N*-benzyl substrates, along with heteroaryl amines were within the scope of the process. As the process can build from a secondary amine molecule on-DNA, products will contain a free NH group, which may serve as a hydrogen-bond donor when conducting selections against proteins, but may also serve a site for further combinatorial elaboration. We anticipate that this process will find application when combinatorially stacked with readily available aryl C-N coupling chemistries.

Author Contributions

R.H. and Y.M-A. conceptualised the project and wrote the manuscript. Y.M-A., N.F. and R.H. carried out experimental work. R.H., Y.M-A., and A.C. directed the research.

Conflicts of interest

There are no conflicts to declare

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