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Efficient copper-catalyzed amination of DNA-conjugated aryl iodides under mild aqueous conditions

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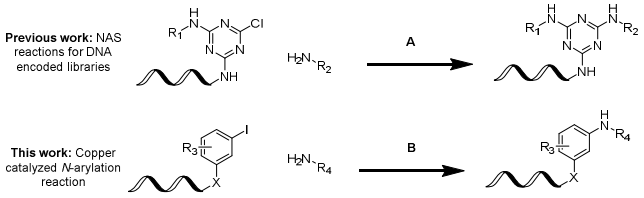
Abstract. Herein, we describe the development of a copper-catalyzed cross-coupling of DNA-conjugated aryl iodides with aliphatic amines. This protocol leverages a novel ligand, 2-((2,6-dimethoxyphenyl)amino)-2-oxoacetic acid, to effect the transformation in aqueous DMSO, under mild conditions, in air, making it an ideal candidate for the synthesis of DNA-encoded libraries.

DNA-Encoded Libraries (DELs) consist in collections of hundreds of millions to billions synthetic small molecules each conjugated to a unique DNA sequence, or DNA tag[1, 2]. These vast collections of synthetic compounds are screened in mixtures by affinity selection processes, making them a powerful tool for the discovery of ligands to biological targets.[1, 3-5] To build these libraries, synthetic small molecules are constructed directly on DNA using split-and-mix combinatorial chemistry protocols often involving several hundreds if not thousands of building blocks.[1, 6] Therefore, DEL synthesis rests on the development of methodologies for the formation of covalent bonds under conditions compatible with the solubility and stability of the nucleic acid tags,[1, 7-10] tolerant of a wide substrate scope and practical enough to facilitate miniaturization and parallelization. Thus, "nitrogen-capping" reactions such as acylation, urethanation, sulfonylation and reductive amination have been applied to the synthesis of millions to trillions of DNA-encoded compounds[1, 7] among which numerous potent protein ligands have been identified.[5] The formation of *N*-aryl bonds is another nitrogen-derivatization transformation commonly deployed in medicinal chemistry for the generation of bioactive molecules.[11, 12-14] It is therefore not surprising that several DNA-encoded library chemistry groups sought to identify amine arylation conditions compatible with the generation of DNA-encoded libraries. One approach to construct *N*-aryl bonds in the presence of oligonucleotides consists in performing nucleophilic aromatic substitution (NAS) using heteroaromatic systems (Scheme 1). While successfully used in DEL synthesis[15-19], it is limited in practice to strongly-activated heteroaromatic systems such as triazine[15, 16, 19] and pyrimidine[8] chlorides, or nitro-substituted aromatic fluorides.[20]



Scheme 1. Current and proposed *N*-arylation approaches for DELs synthesis. **A** 46 equiv. R_2-NH2 (200mM DMA stock), 80°C, 6h. **B** CuI or $Cu(OAc)_2$ (25mM), Ligand (50-200mM), Na Ascorbate (50mM), base K_3PO_4 (500mM), R_4-NH_2 (500mM) DMSO/Water 1/1, 5/3 or 1/3, 40°C.

In order to extend the scope of this transformation to less-activated aromatic cores, we and others[21] chose to investigate the copper catalyzed Ullmann *N*-arylation of amines with aryl halides[22-24] (Scheme 1). Indeed, while this manuscript was in preparation, Lu *et al.* reported their efforts to optimize palladium- and copper-based *N*-arylations of DNA-conjugated aryl iodides with primary aliphatic and aromatic amines. While a wide range of such amines were shown to be competent under the reported conditions, cross-coupling reactions involving secondary amines still appeared to pose a significant challenge.[21] Spurred by the large numbers of ligands reported to enable such cross-couplings under mild reaction conditions in polar solvents[25-27] and, in some cases, in the presence of air[28] and water,[29] we surmised that a systematic survey of catalytic systems might unlock previously unreachable portions of chemical space.

We started with investigating the model on-DNA coupling reaction between DNA-conjugated aryl iodide **1a** and a set of amine substrates **2a-f** mediated by ligands **L1-10**[26, 28-34] under reaction conditions compatible with DNA-encoded library

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synthesis.[7, 8] Namely, we desired to manipulate building block stock solutions in water-miscible organic co-solvents and in plate format (Figure **1A**).

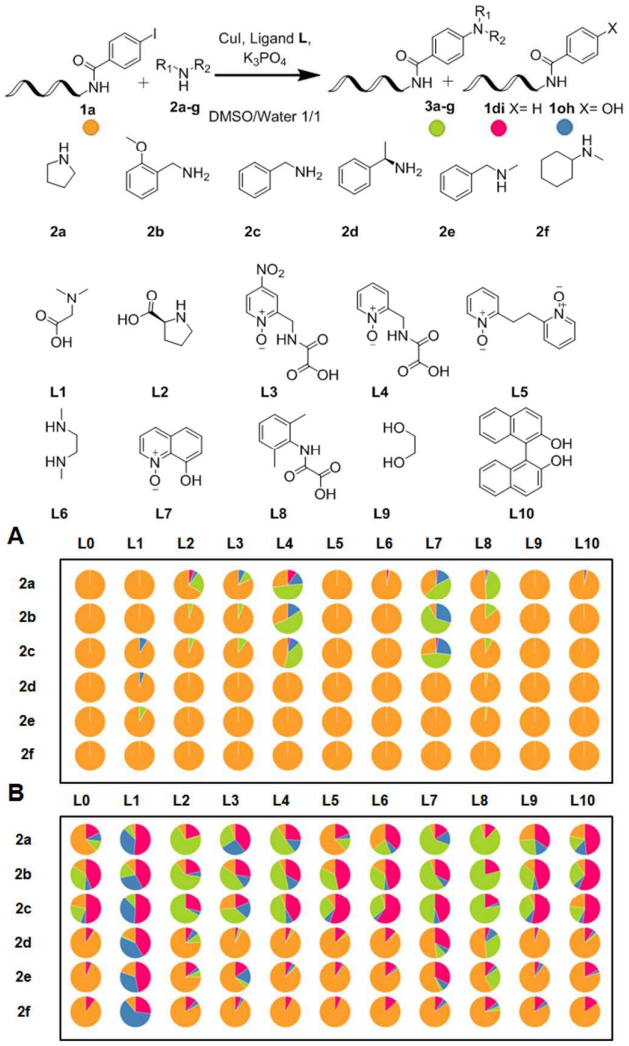

Figure 1. Initial screening of known ligands for the Copper-catalyzed coupling of representative amines and model DNA-conjugated aryl iodide **1a**. **Reaction conditions: A: 1a** (1nmol), **2a-f** (500mM), CuI (25mM), ligand **L** (50mM), K_3PO_4 (500mM), DMSO (8µl), water (8µl), 40°C, 3h; **B: 1a** (1nmol), **2a-f** (500mM), CuI (25mM), ligand **L** (50mM), sodium ascorbate (50mM), K_3PO_4 (500mM), DMSO (8µl), water (8µl), 40°C, 3h. Reactions performed in air. Pie chart areas represent conversion to **3a-f** (%) as determined by UPLC-TOF.

Among the ligands reported for the *N*-arylation of aliphatic amines, **L7**[33] (8-hydroxyquinoline 1-oxide) and **L8**[35] (DMPAO: 2-(2,6-dimethylphenylamino)- 2-oxoacetic acid) showed moderate to good conversion of **1a** with amines **2a**, **2b** and **2c** to the respective products **3a**[36]**, 3b** and **3c** under aerobic aqueous conditions at 40°C. Notably, **L8** provided the cleanest reaction profile and lowest proportion of side products **1di** and **1oh** while only limited amounts of DNA degradation could be observed by LC-MS.[37] Satisfied with these early, positive results, we did not further investigate oligonucleotide damage at this stage and proceeded with reaction optimization.

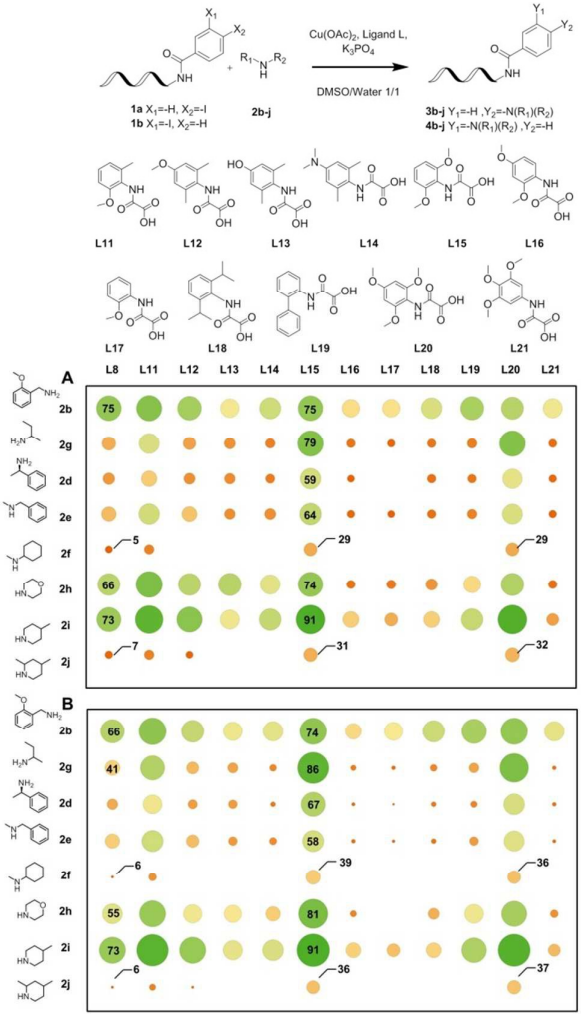

Figure 2. Structural and electronic effect on ligand efficiency: selected screening results. **Reaction conditions: A: 1a** (1nmol), **2b-j** (500mM), $Cu(OAc)_2$ (25mM), ligand L (50mM), sodium ascorbate (50mM), K_3PO_4 (500mM), DMSO (8ul), water (8ul), 40°C, 3h. **B: 1b** (1nmol), **2b-j** (500mM), $Cu(OAc)_2$ (25mM), ligand **L** (50mM), sodium ascorbate (50mM), K_3PO_4 (500mM), DMSO (8ul), water (8ul), 40°C, 3h. The color and diameter of circles correlates with the conversion to **3b-j** (**A**) or **4b-j** (**B**) determined by UPLC-TOF analysis.

Since library synthesis under inert atmosphere or using degassed solvents can prove cumbersome in practice, we repeated the experiment to investigate the effect of an additional reducing agent introduced to circumvent the risk of aerobic oxidation of the copper catalyst (Figure **1B**). The superior conversions of starting DNA-conjugate into product and by-products observed in the presence of ascorbic acid provided circumstantial evidence that copper oxidation was indeed limiting the reactivity of the system. Gratifyingly, when 50 mM aqueous sodium ascorbate solution was added to the reaction (2 eq. compared to CuI), significantly improved conversions to the *N*-arylated products **3a-c** could be

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observed. Again, ligand **L8** led consistently to higher yields of product than any of the other ligands tested **L1-10**.

Ligand **L8** was originally reported as particularly efficient for the *N*-arylation of hindered secondary aliphatic amines.[35] Under our aqueous conditions, it performed better for the *N*-arylation of hindered substrates **2d**, *N*-methylbenzylamine **2e** and *N*-methylcyclohexylamine **2f** (Figure 1B, entry **2d**/**L8**, **2e**/**L8** and **2f**/**L8**) than any of the other candidates. Encouraged by this positive trend, we set out to investigate alternative designs of **L8**.

The group of Ma demonstrated the utility of the two methyl groups in **L8** and the beneficial effect of introducing electron-donating moieties on structurally-related oxalic diamide ligands.[38] Since the steric and electronic properties of the ligand appeared critical to its efficiency in this study, we synthesized 11 analogues of **L8** and evaluated them for competency in the amination of DNA-conjugates **1a** and **1b** with a panel of diverse amines (Figure **2A** and **2B**). We elected to use this particular pair of DNA-conjugates to rule out any electronic effect that could be specific to **1a.** For practical reasons, we also replaced copper (I) iodide with copper (II) acetate, as the latter is not sensitive to oxidation and yields stable stock solutions in either DMSO or water. In a preliminary experiment, this change did not appear to cause any detrimental effect (recapitulated in Figure 1**B**/combination **1a**/**2b**/**L8** 78% compared with Figure 2**A**/combination **1a**/**2b**/**L8** 75% conversion). The results of this screening experiment showed a dramatic influence of the ligand structure on its reactivity. As evidenced by the conversion observed for ligands **L8**, **L12, L13** and **L14**, the addition of electron-donating moieties in *para*- did not provide noticeable advantages. Replacing one of the methyl groups in **L8** with methoxy (**L8** →**L11**) led to an increase in conversion across the panel of tested amines, while increasing the steric bulk around the oxalic amide (**L8**→**L18**) did not provide any noticeable advantage. Ligands lacking two *ortho*-substituents (**L17**, **L19** and **L21**) were generally found to be inferior to **L8** despite attempts to vary the electron density on the aromatic ring. Finally, *di-ortho*- substitution appeared mandatory to get efficient ligands: replacing both methyl groups on **L8** by two methoxy groups led to the strikingly more efficient ligand **L15** and this finding was recapitulated by the matched pair **L12**→**L20**. Notably, using **1b** as substrate, a 6-fold improvement in product yield could be observed for secondary amine **2f** when **L15** was used instead of **L8** (Figure 2**A**: **L8**-**2f**: 6%; **L15**-**2f**: 39%).

While excellent conversions were already observed for **L15** in most cases, the yields were still low to moderate for the most hindered substrates *N*-methylcyclohexylamine **2f** and 2,4-dimethylpiperidine **2j**. We therefore went through another round of reaction condition optimization, studying the effect of the concentration of ligand **L15**, base, sodium ascorbate and amine on the yield of the *N*-arylation of **2f** with **1b**. While varying the concentrations of amine, base and ascorbic acid had marginal effects on conversion, increasing the concentration of ligands to 200 mM did cause a noticeable increase in the formation of *N*-arylated **2f** (data not shown, please see supporting information section VII). We therefore sought to validate this observation in the reaction of DNA-conjugated aryliodide **1a** and **1b**[39] with our set of diverse test amines. Suspecting that the proportion of DMSO in water might also affect the yield and formation of side-products during the reaction, we introduced this additional parameter in the experimental design (Figure **3**).

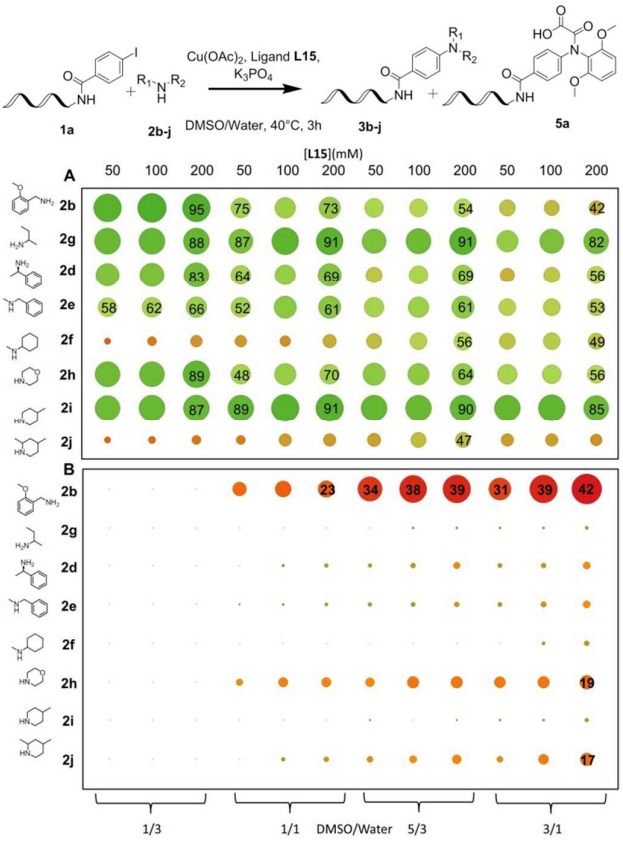

Figure 3: Optimization of the concentration of **L15** and cosolvent proportion in a plate format. **Reaction conditions: A 1a** (1nmol), **2b-j**(500mM), $Cu(OAc)_2$(25mM), ligand **L15** (50-200mM), Sodium Ascorbate (50mM), K_3PO_4 (500mM), DMSO/Water(1/3-3/1 16ul), 40°C, 3h. The color and diameter of circles correlates with the yield of **3b-j** determined by UPLC-TOF analysis. **B 1a** (1nmol), **2b-j**(500mM), $Cu(OAc)_2$(25mM), ligand **L15** (50-200mM), Sodium Ascorbate (50mM), K_3PO_4 (500mM), DMSO/Water(1/3-3/1 16ul), 40°C, 3h. The color and diameter of circles correlates with the yield of **5a** determined by UPLC-TOF analysis.

This experiment confirmed that increasing the concentration of ligand had a beneficial effect on the conversion for reactions with hindered substrates **2f** and **2j** (Figure **3** and **SI VI1**). In addition, increasing the ligand concentration and DMSO proportion worked synergistically to improve the yield of the reaction with a maximal 56% yield of **3f** obtained with a 200mM concentration of **L15** in DMSO/water : 5/3. However, these observations could not be broadly generalized as the proportion of DMSO had a deleterious effect on the conversions observed for primary amines **2b** and **2d** (Figure **3A**). Indeed, altering the DMSO/water ratio from 1/3 to 3/1

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caused a 56% reduction in the yield of *N*-arylation between **1a** and 2-methoxybenzylamine **2b** (Figure 3**A** line **2b**).

We hypothesize that the amine and DMSO compete for coordination of the copper catalyst and as a consequence, an inhibitory effect of this co-solvent is observed for higher ratios. Indeed, using **1a** as substrate in particular, increasing the proportion of DMSO led to the appearance of side-products resulting from unwanted *N*-arylation of the ligand, with up to 42% of the starting material **1a** being converted into **5a** when combined with 2-methoxybenzylamine (Figure 3**B** and **SI VI2**).

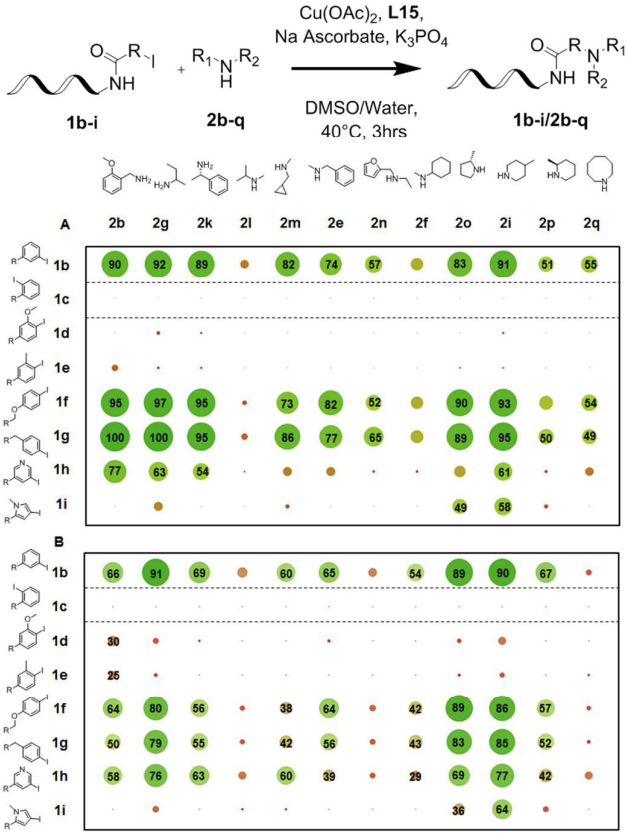

Figure 4: Scope determination of the N-arylation of susbtrates **1b-1i** with amines **2b-2q**. **A Reaction conditions 1: 1b-i** (1nmol), **2b-q**(500mM), $Cu(OAc)_2$(25mM), ligand **L15** (200mM), Sodium Ascorbate (50mM), K_3PO_4 (500mM), DMSO/Water(1/3 16ul), 40°C, 3h. **B Reaction conditions 2: 1b-i** (1nmol), **2b-q**(500mM), $Cu(OAc)_2$(25mM), ligand **L15** (200mM), Sodium Ascorbate (50mM), K_3PO_4 (500mM), DMSO/Water(5/3 16ul), 40°C, 3h.

Therefore, while our initial studies were conducted with an equal proportion of DMSO and water in the reaction medium, we found that lowering the proportion of DMSO to DMSO/Water: 1/3 (**Conditions 1**) led to a more efficient system for the majority of unhindered primary and secondary amines while, at the same concentration of ligand **L15**, more hindered substrates like **2f** or **2j** did benefit from increasing the proportion of co-solvent to a ratio DMSO/Water : 5/3 (**Conditions 2**). All other parameters being kept equal, the perspective of using two different solvent proportions during library synthesis was deemed only a minor annoyance. At this stage of our optimization campaign, we decided to conduct a more thorough analysis of DNA damage caused by **conditions 1**. In a manner analogous to that described by the group of Paegel,[40] model reactions were conducted in the presence of a small amount of amplifiable DNA. Gratifyingly, quantification by qPCR after work-up and comparison with a reference sample indicated that 65% of the amplifiable DNA remained after submission to **conditions 1**. This amount is in line with those observed for reactions we have already deployed in the synthesis of large discovery libraries[40] (a full experimental account is provided in the supporting information, **SI IX**).

With these results in hand, we proceeded with investigating the scope of **conditions 1** and **2** on a combinatorial matrix of 8 DNA-conjugated aryl iodides with 12 different amines (Figure **4**). This experiment confirmed that **conditions 1** led to useful yields for the majority of substrate combinations as long as the halogen atom found itself in an unhindered environment. For benzene derivatives, electronic effects on the aromatic ring seemed to have negligible influence on the conversions observed, as most amines gave good to excellent conversions (41%-100%) with substrates **1b, 1f, 1g** and **1h**. Interestingly, the 3-iodopyrrole derived substrate **1i** could only be combined with cyclic secondary amines **2o** and **2i,** giving 49% and 58% conversion respectively, while reactions with simpler amines failed to yield useful amounts of coupling product (Figure 4**A**). The *N*-arylation reaction appeared, however, to be very sensitive to steric hindrance. Indeed, little to no conversion was observed with substrates **1c, 1d** and **1e** having substituents *ortho*- to the reactive halogen (figure 4**A**). In contrast, it was satisfying to observe that unfavourable combinations like **1d**/**2b** or **1e**/**2b** were still formed in moderate yield (30 and 25% respectively) under **conditions 2**, when these products were only formed as traces under **conditions 1** (Figure 4**B**). Interestingly, higher yields were also obtained under **conditions 2** for the reactions involving iodopyridine **1h** as substrate (Figure 4**B**). Taken together, these results highlighted the nuances of reactivity imparted by both coupling partners: a thorough vetting of building blocks prior to library synthesis will be necessary to ensure useful yields of final library products.[41] C**onditions 2** appeared to be most beneficial to very specific substrate combinations, which may warrant their deployment in the synthesis of focused DNA-encoded libraries. In contrast, **conditions 1** appeared to more-generally lead to higher product yields, making them our natural choice for the synthesis of larger discovery libraries.

Conclusions

In conclusion, we have developed a novel ligand and a set of reaction conditions to facilitate the copper-catalyzed cross-coupling of DNA-conjugated aryliodides with a variety of aliphatic amines, most notably relatively hindered secondary amines. Importantly, the catalytic system operates at low temperature, in air, using an organic co-solvent compatible with the generation and storage of a large number of amine building block stock solutions. These features render our reaction conditions highly amenable to the synthesis of DNA-

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encoded libraries based on the formation of Csp^2-N bonds and complement the existing NAS and *N*-arylation protocols.[21]

Conflicts of interest

The authors declare no competing interest.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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41. As a rule of thumb, we estimate that a 40% product yield is sufficient to ensure adequate representation of each members of the library, provided that the presence of unknown by-products is limited.

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A practical and efficient protocol for the amination of DNA-conjugated aryl iodide using a novel ligand was developed.

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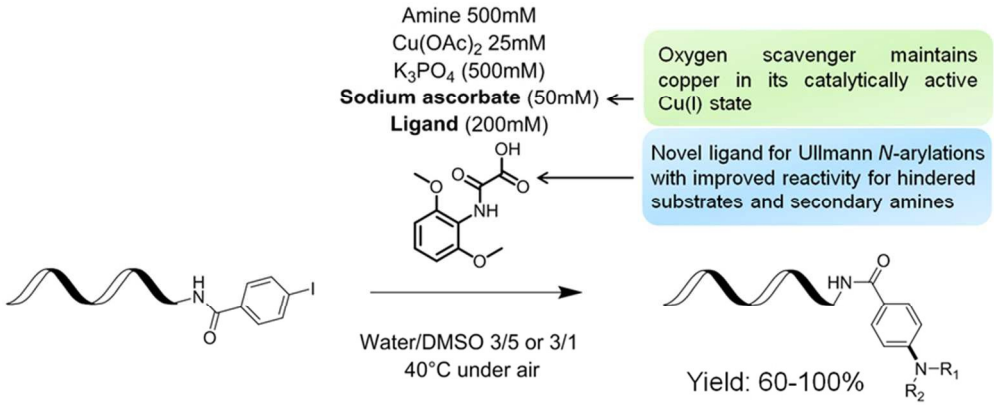

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