Accessing 2-Aryl *N*-Heterocycles with Photocatalysis

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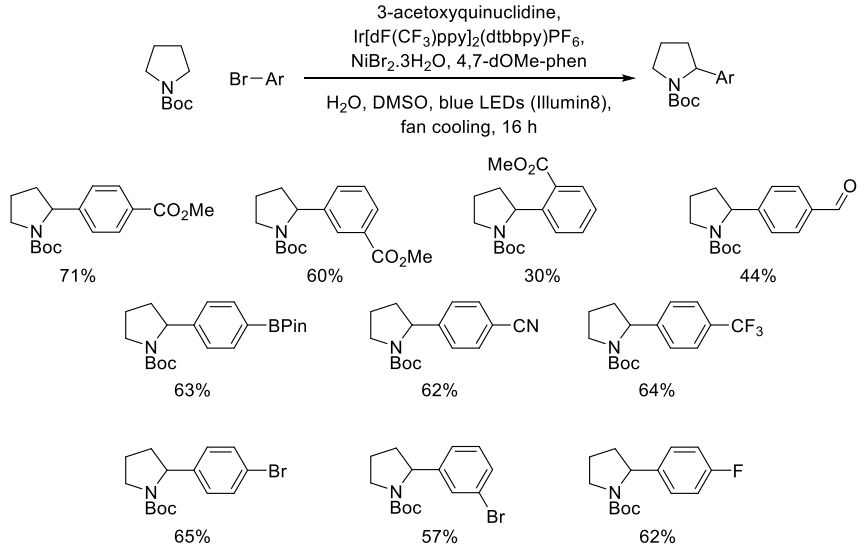
Photocatalysis has seen a lot of attention over the past decade which has led to the development of new methodologies and technologies for the synthetic organic chemist.[1] A range of powerful transformations developed during this time allow for access to compounds of high interest to LCC and our customers.

In particular the combination of photoredox-mediated hydrogen atom transfer (HAT) and nickel catalysis developed by MacMillan *et al.* allows for the C-H activation in the α-position of *N*-heterocycles followed by cross-coupling with an aryl bromide.[2] This methodology was shown to work on a range of *N*-heterocycles and aryl bromides in moderate to good yields. The reaction tolerated many functional groups on both the *N*-heterocycle and the aryl bromide giving access to multi-functionalised products. We envisaged that this simple one-step transformation could allow access to novel, 3D building blocks and fragments which would be of high value for the design of screening libraries for hit-identification.

Figure 1. Asynt's Illumin8 set-up

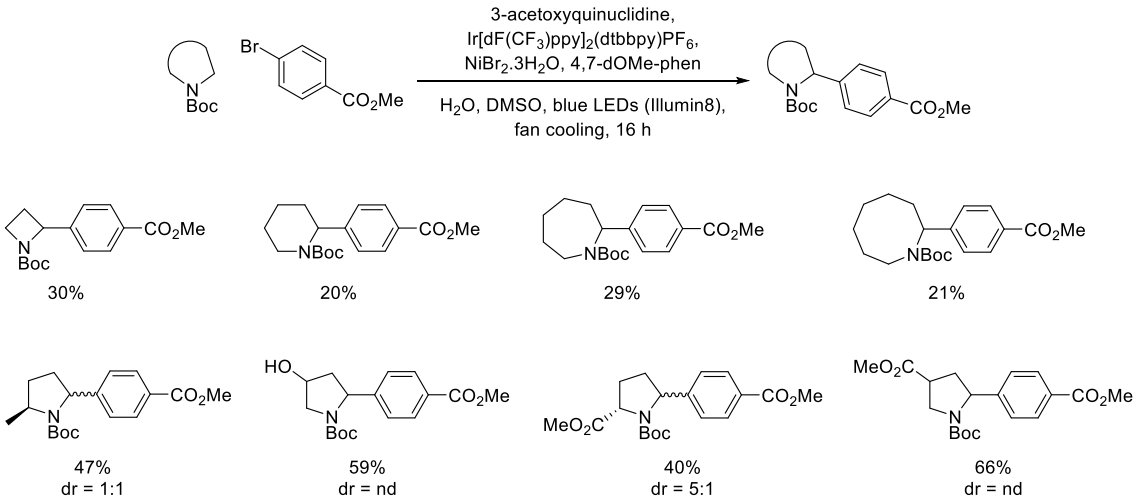
Our initial reaction set-up was similar to that described by MacMillan *et al.* using Kessil 40 W lamps.[2] The introduction of Asynt's Illumin8 drastically improved our efficiency when testing the substrate scope by allowing us to perform eight reactions simultaneously (Figure 1). The yields and selectivities of these reactions were comparable on both set-ups.

Our studies, using similar conditions to those developed by MacMillan *et al.*, were carried out on Boc-*N*-pyrrolidine with a range of aryl bromides of interest to LCC (Scheme 1). This methodology gave access to 2-substituted pyrrolidines with poor to good yields. The reaction was amenable to electron-withdrawing groups (ester, nitrile, aldehyde, trifluoromethyl), halides (bromide, fluoride) and boronic esters. Substitution in the ortho-position was generally less tolerated than substitution in the para- and meta-positions.



Scheme 1. Coupling of Boc-N-pyrrolidine with aryl bromides. Reactions were carried out on Asynt's Illumin8 set-up. Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Various *N*-heterocycles of different size were tested with only pyrrolidine giving acceptable yields (Scheme 2). Substitution on the pyrrolidine ring was tolerated in the 2- and 3-positions giving access to 2,4-disubstituted and 2,5-disubstituted pyrrolidines.



Scheme 2. Coupling of N-heterocycles with methyl 4-bromobenzoate. Reactions were carried out on Asynt's Illumin8 set-up. Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. dr = diastereomeric ratio. nd = not determined.

In summary, we have been able to utilise the methodology developed by MacMillan *et al.* to access di- and tri-functionalised *N*-heterocycles of high interest to the drug discovery community.

References:

(1) For reviews, see: (a) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. *Chem. Rev.* **2020**, *120*, 2613. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035.
(2) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, 352, 1304.

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