

Photochemistry Csp³-Csp² Cross-Coupling via Metallaphotoredox

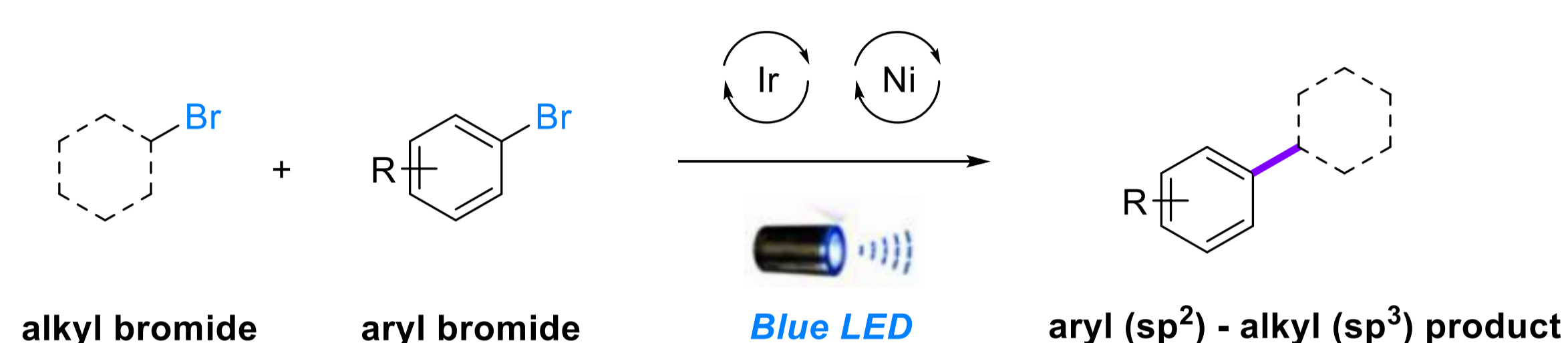
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Abstract

In 2016, MacMillan and co-workers reported that a photocatalytically-generated silyl radical species could perform a halogen-atom abstraction to activate an alkyl halide as a nucleophilic cross-coupling partner.^[1]

At Charnwood Discovery, we investigated the application of MacMillan's chemistry in the synthesis of drug-like molecules, allowing us to expand both the repertoire and reach of the synthetic capabilities available to our chemists in support of our clients' projects.



Background and Aims

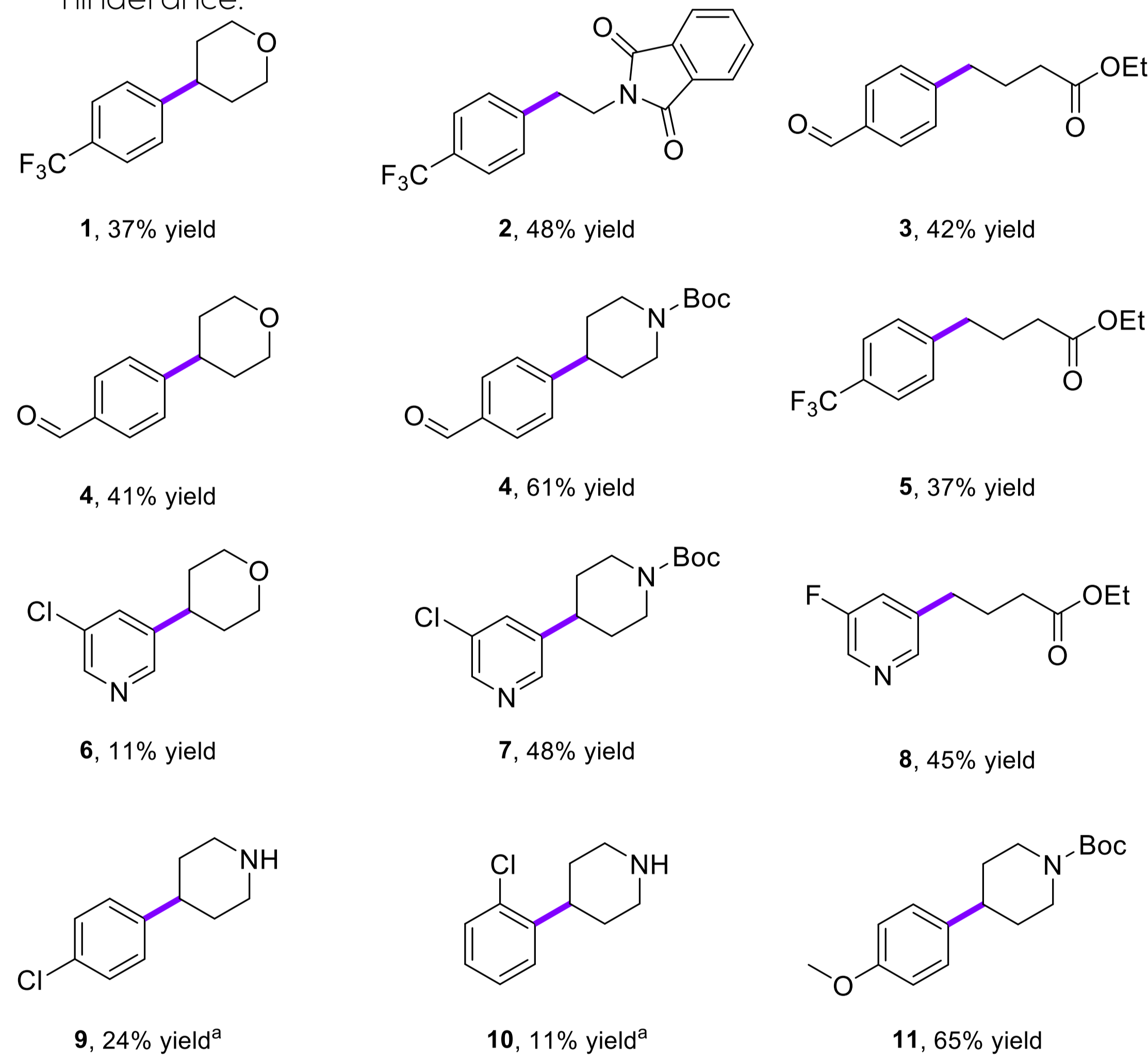


Our aim was to exploit the versatility and broad substrate scope of MacMillan's work to provide facile access to a range of traditional solubilizing functional groups (e.g., morpholine, piperazine), which would be otherwise difficult to introduce *via* 'classical' conditions.

To transfer this technology to Charnwood Discovery, we constructed a blue LED reactor using MacMillan's photoreactor as a model system.^[2] We designed a library of fragment-like compounds incorporating a range of different functionalities, to develop our understanding of this chemistry.

Scope

- In the majority of cases evaluated as part of this study, we observed moderate yields.
- Notably, we observed better conversions for aryl bromides bearing an electron-withdrawing group at the 4 position of their phenyl ring, as exemplified by compounds 1-6.
- Generally *ortho*-substituted isomers failed to afford any of the desired products (results not shown), most likely because of steric hindrance.

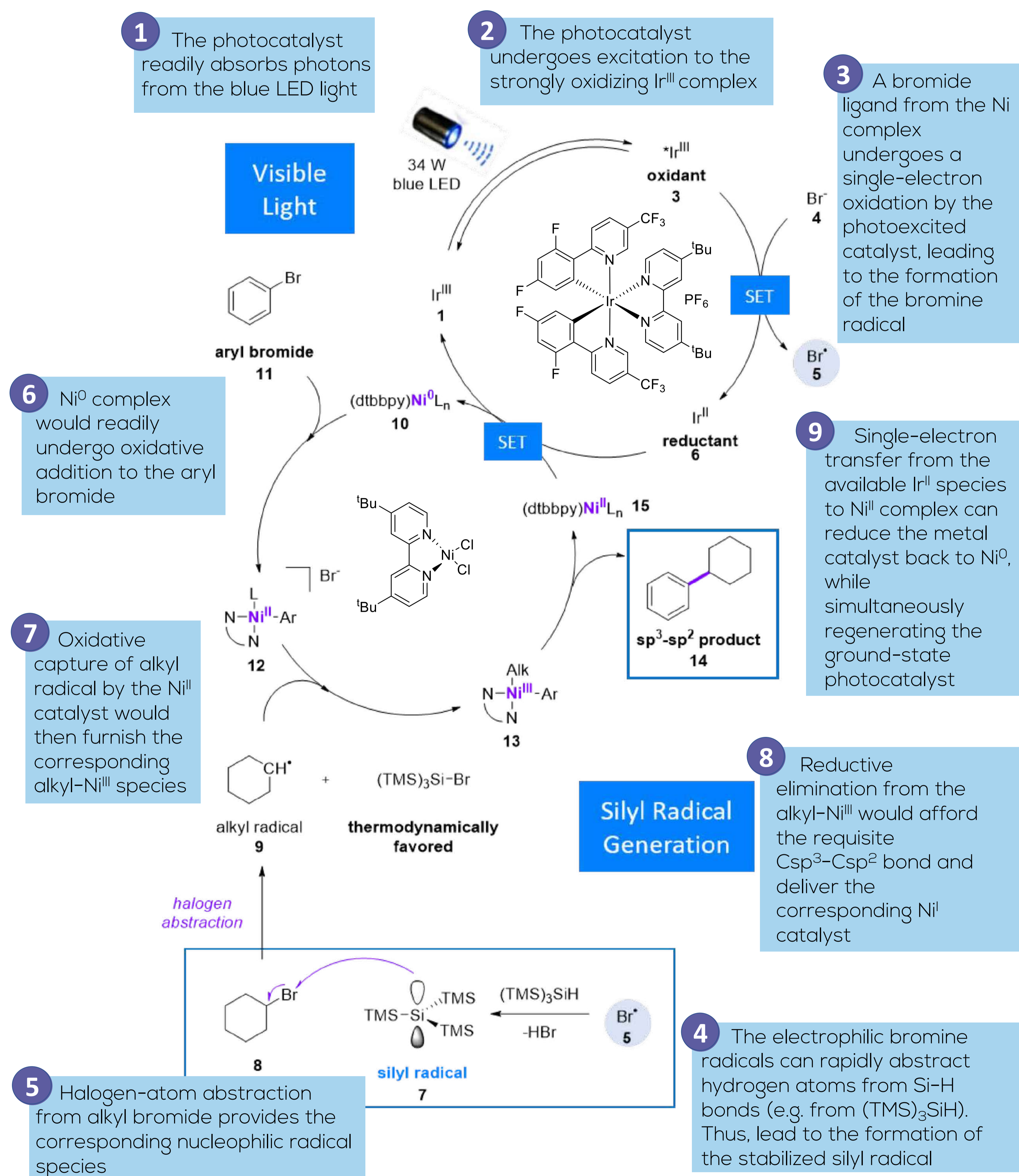


^aYield over 2 steps (i.e., following the cleavage of the *N*-Boc group); all yields have been adjusted according to purity.

- Our results show that this transformation tolerates a broad range of functional groups, as well as a number of suitably protected reactive handles that could be readily unmasked for further derivatisation.
- The tolerance of groups such as esters is potentially useful as these groups can be further manipulated (e.g. reduction, hydrolysis) to afford access to increasingly complex structures

Mechanism

Proposed mechanism for MacMillan's^[1] photoredox coupling reaction:



Summary

Access to metallaphotocatalysis has given Charnwood Discovery the capability to synthesize a diverse set of compounds. The versatility of functional groups permitted by this technique, and accessibility of the in-house blue LED reactor, means that we will now have access to a new range of reactions and products for drug discovery.

[1] Patricia Zhang, Chi "Chip" Le, and David W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, 138, 8084-8087, [2] <https://macmillan.princeton.edu/photoredox/>.

