Photochemistry

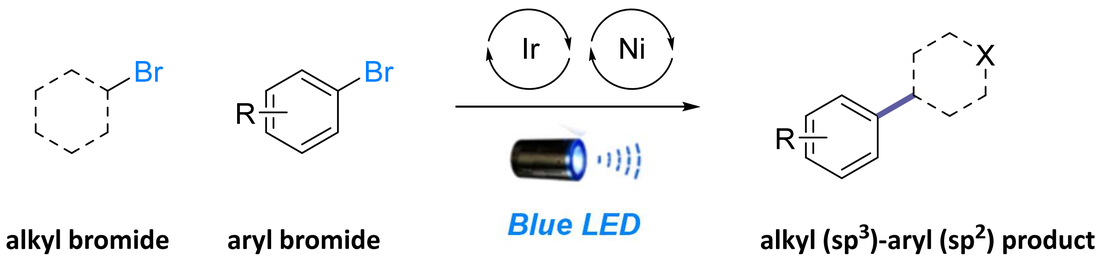
Csp^3–Csp^2 Cross-Coupling via Metallaphotoredox

charnwood molecular
for the discovery

Authors: Aurélie Chabrun, Chloe Donnart and Jenny Stockwell

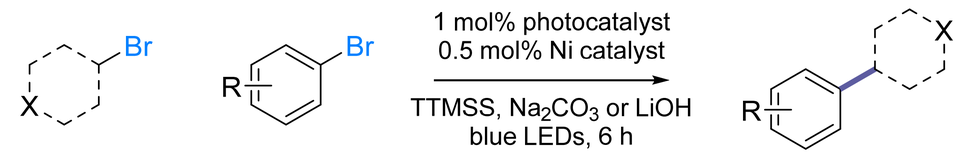
Abstract

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 Molecular, we investigated the application of MacMillian'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.



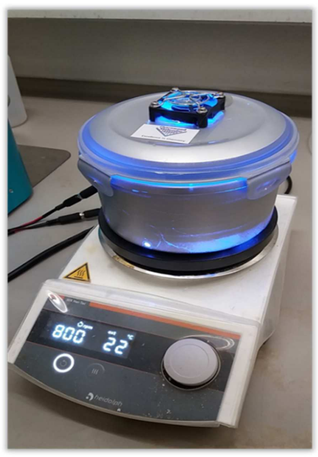
alkyl bromide **aryl bromide** **alkyl (sp^3)-aryl (sp^2) product**

Background and Aims



alkyl bromide **aryl bromide** **alkyl-aryl product**

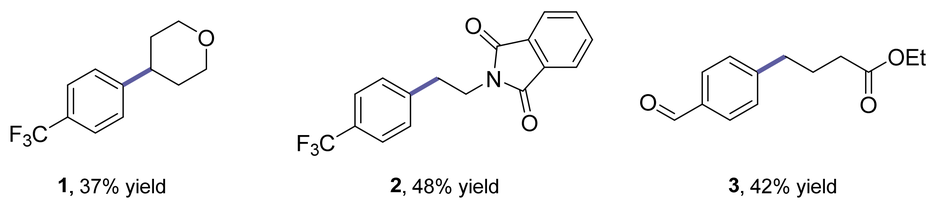
Our aim was to exploit the versatility and broad substrate scope of MacMillan's work to provide facile access to a range of traditional solubilising functional groups (e.g., morpholine, piperazine), which would be otherwise difficult to introduce *via* 'classical' conditions.



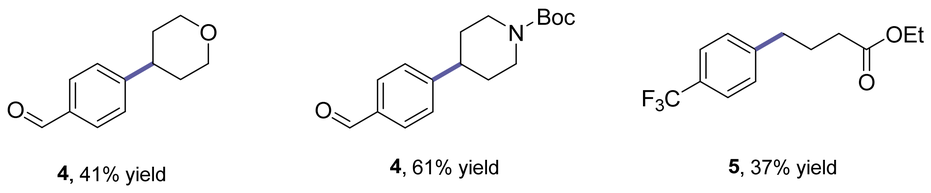
To transfer this technology to Charnwood Molecular, we constructed a blue LED reactor using MacMillan's photoreactor as a model system.[2] With our newly constructed photoreactor in hand, we designed a library of fragment-like compounds incorporating a range of different functionalities with which to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

Scope

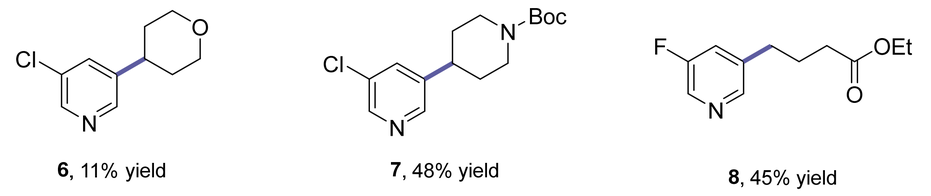
- In the majority of cases evaluated as part of this study, we observed moderate yields.
- Notably, we observed better conversions for aryl bromides bearing an electron-withdrawing group at the 4 position of their phenyl ring, as exemplified by compounds **1-6.**
- General*ly ortho*-substituted isomers did not afford any of the desired products (results no shown), most likely because of steric hinderance.



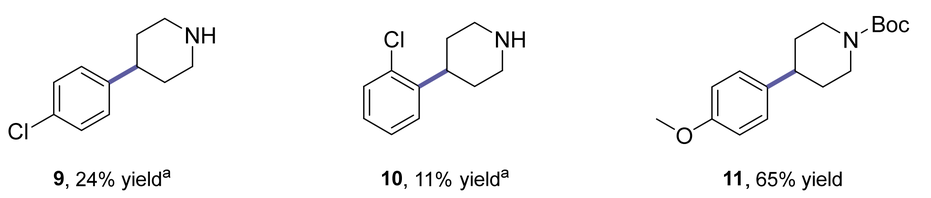
1, 37% yield **2**, 48% yield **3**, 42% yield



4, 41% yield **4**, 61% yield **5**, 37% yield



6, 11% yield **7**, 48% yield **8**, 45% yield



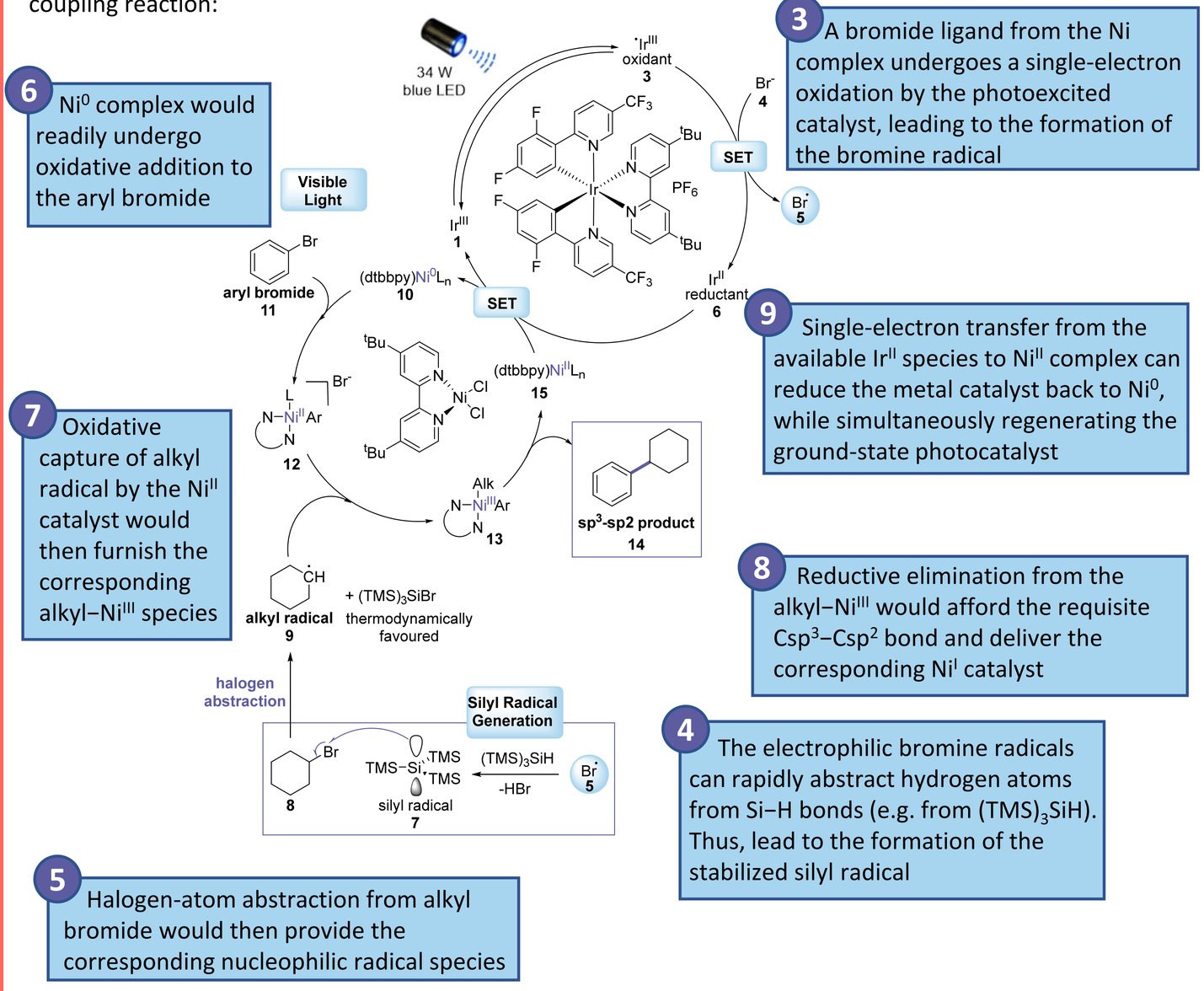
9, 24% yield[a] **10**, 11% yield[a] **11**, 65% yield

[a]Yield 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.
- 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:



1 The photocatalyst readily absorbs photons from the blue LED light

2 The photocatalyst undergoes excitation to the strongly oxidizing Ir^{III} complex

3 A bromide ligand from the Ni complex undergoes a single-electron oxidation by the photoexcited catalyst, leading to the formation of the bromine radical

4 The electrophilic bromine radicals can rapidly abstract hydrogen atoms from Si–H bonds (e.g. from $(TMS)_3SiH$). Thus, lead to the formation of the stabilized silyl radical

5 Halogen-atom abstraction from alkyl bromide would then provide the corresponding nucleophilic radical species

6 Ni^0 complex would readily undergo oxidative addition to the aryl bromide

7 Oxidative capture of alkyl radical by the Ni^{II} catalyst would then furnish the corresponding alkyl–Ni^{III} species

8 Reductive elimination from the alkyl–Ni^{III} would afford the requisite Csp^3–Csp^2 bond and deliver the corresponding Ni^{I} catalyst

9 Single-electron transfer from the available Ir^{II} species to Ni^{II} complex can reduce the metal catalyst back to Ni^0, while simultaneously regenerating the ground-state photocatalyst

Summary

Access to metallaphotocatalysis has given Charnwood Molecular the capability to synthesise 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.

References: [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/,