Utilising Enabling Technologies for the Synthesis of Drug-like Bicyclic Species

[a],[b]Diarmuid O'Hanlon, [a]Brian Glennon, [b]Marcus Baumann
[a]APC Ltd., Dublin, Ireland, [b]UCD School of Chemistry, Dublin, Ireland

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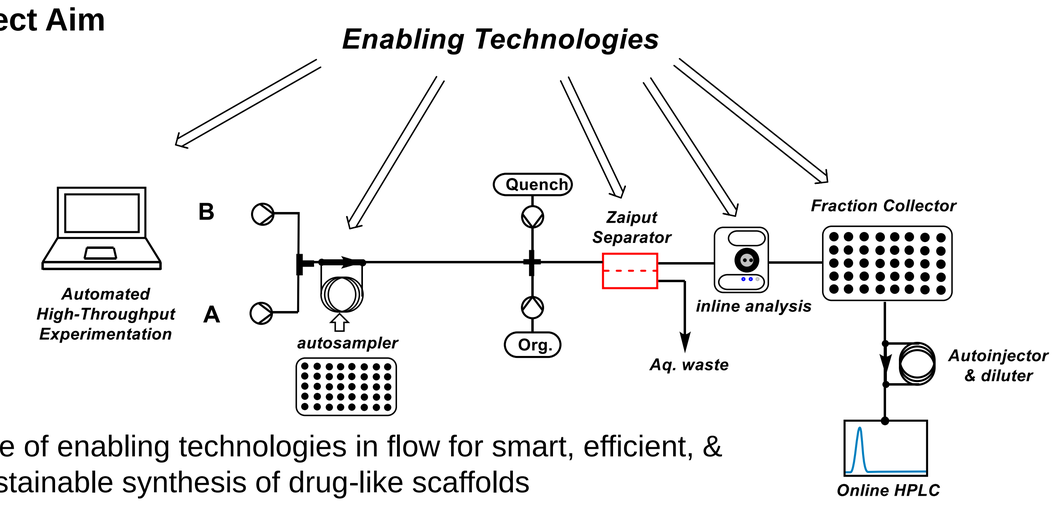
Introduction

Over the past few decades, flow chemistry emerged as a powerful tool for enhancing synthetic procedures, drug designs, and reaction discovery due to its advantages over traditional batch methods.[1] While standard flow setups consist of a pump, tubing, and collection vial, additional technologies such as inline analytics, inline workup devices, and high-throughput tools offer further optimisation potential but remain underutilised.

This research presents a clear contribution to this field, where the proven advantages of flow chemistry and these enabling technologies have been exploited to show how flow chemistry can improve upon known reactions from batch. Using the advantages of photoflow chemistry and inline workup tools, the aqueous-based Kochi-Salomon[2] reaction developed by the Burns group[3] has been exploited to show that the [2+2] cycloaddition of unactivated olefins can be done in the absence of any Cu(I) catalyst.[4] Similarly, automation, high-throughput experimentation, and inline IR have been utilised to present further how flow chemistry can be built upon for data-driven synthesis of desirable bicyclic species.

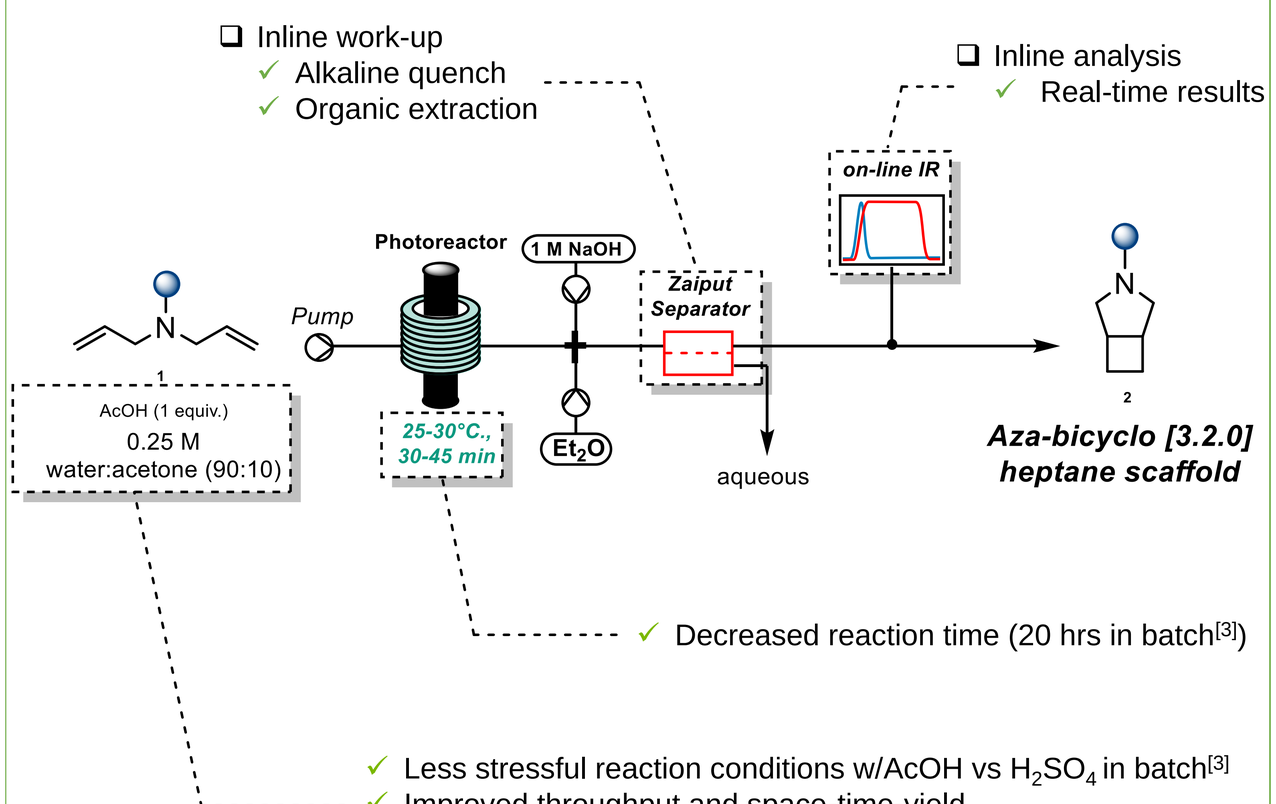
Project Aim



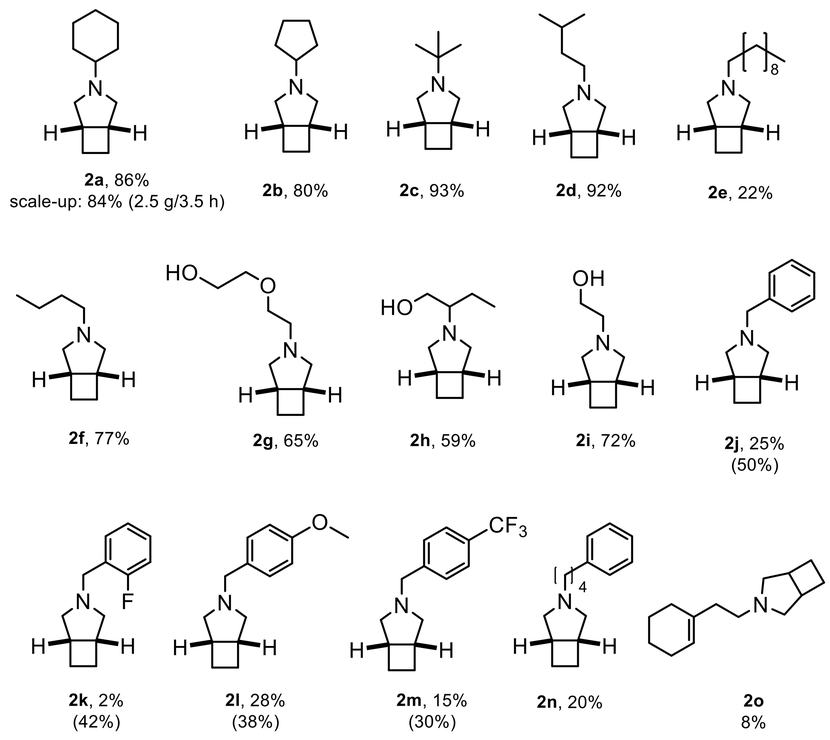
❖ Use of enabling technologies in flow for smart, efficient, & sustainable synthesis of drug-like scaffolds

Results

Flow-Based [2+2] Cycloaddition of Unactivated Olefins

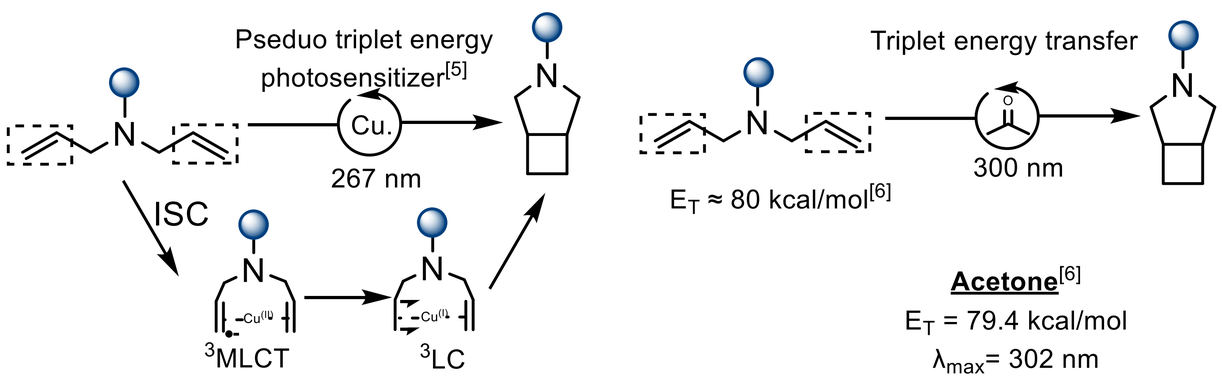


Substrate Scope

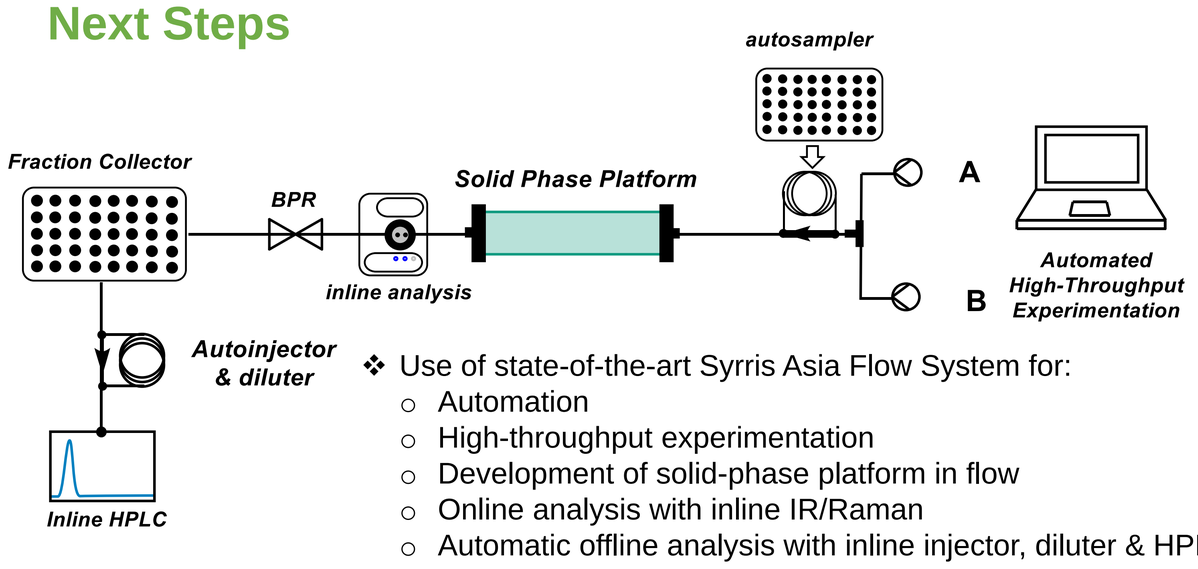


❖ 100% conversion with products yielding mid-to-high yields (**2a – 2i**)
❖ Selective absorption of light of the chromophore in **2j-2n** resulted in decreased yield
❖ Selectivity of azabicyclo structure tested for **2o** with the 1,6-diene intramolecular reaction being observed as the major product over the 1,7-diene reaction (decreased yield due to purification issues)

Metal-Free Reaction Design



Next Steps



❖ Use of state-of-the-art Syrris Asia Flow System for:
- Automation
- High-throughput experimentation
- Development of solid-phase platform in flow
- Online analysis with inline IR/Raman
- Automatic offline analysis with inline injector, diluter & HPLC

Conclusion

Previously, [2+2] cycloadditions have been restricted to using olefins containing activating groups. The Kochi-Salomon reaction[2] has been developed and optimised[3] to allow the generation of drug-like, bicyclic structures from unactivated olefins, but still suffers from various issues and undesirable reaction conditions, making it unsuitable for industrial-scale synthesis.

The introduction of this reaction to continuous flow has enabled the development of a superior process with key features involving the lack of need for the copper catalyst while also showing real-world applications with the use of a Zaiput separator for inline basification & separation, and inline analysis for real-time results and optimisation.

Acknowledgement

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References

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APC Ltd
Building 11 Cherrywood Business Park
Loughlinstown Co. Dublin D18 DH 50 Ireland
info@approcess.com
APC Ltd
@apcinnovate