Autonomous Optimisation for Multistep Chemical Synthesis

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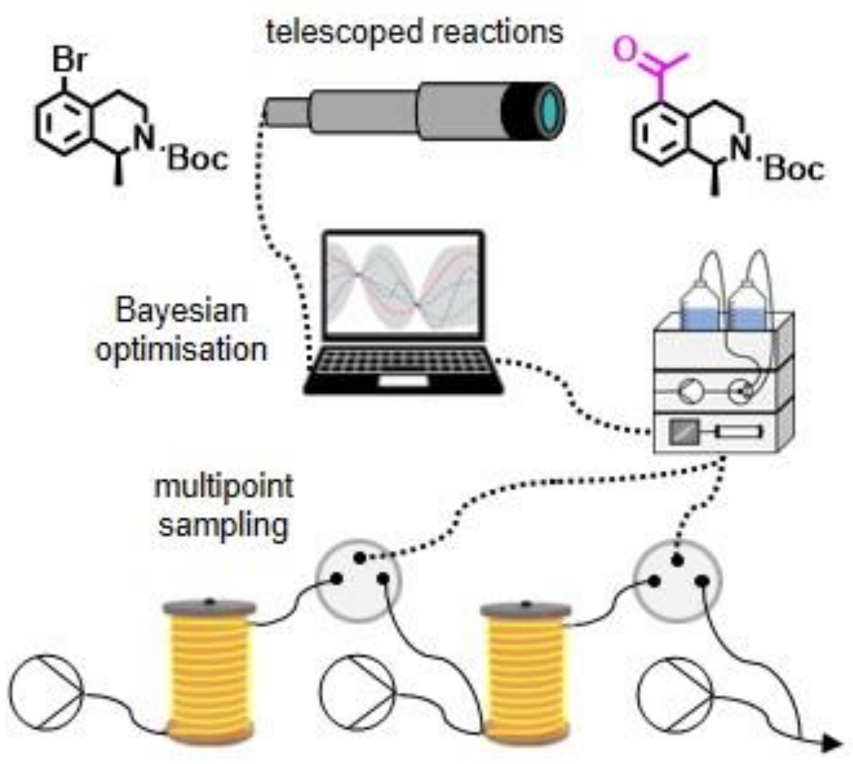
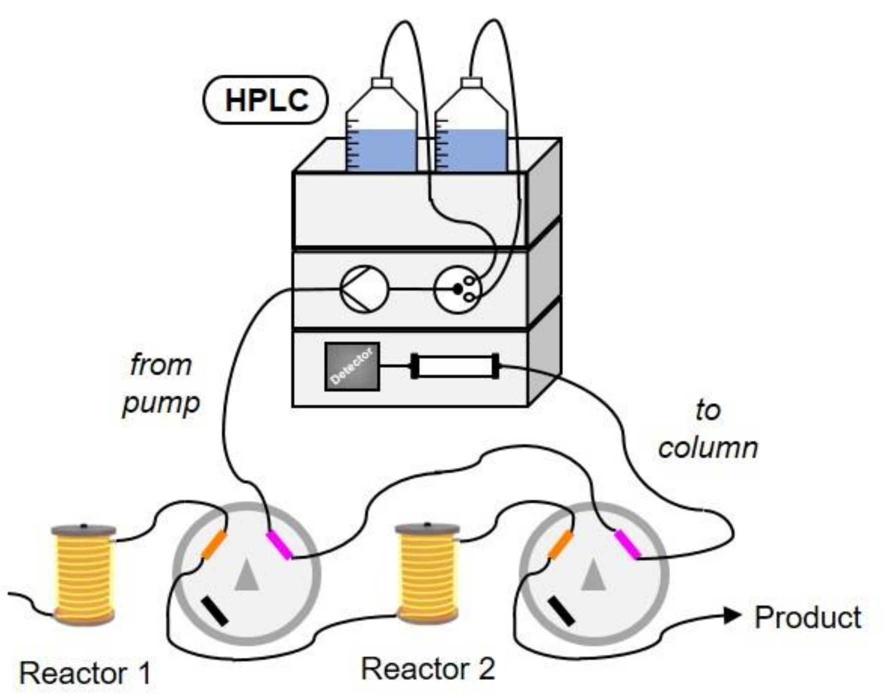
1 Introduction

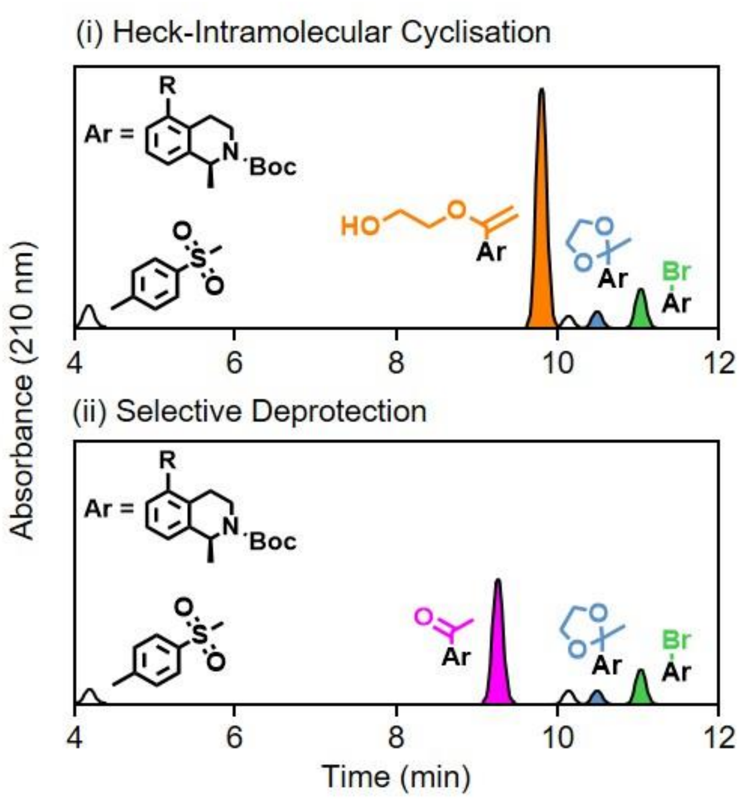
- Multistep syntheses and reaction telescoping have the potential to greatly reduce the carbon footprint of chemical manufacturing.[1]
- Concatenating steps introduces complex interactions which must be optimised simultaneously.[2]
- Self-optimisation can accelerate the development of single step reactions.[3]
- Aim: develop an autonomous method for optimisation of telescoped reactions.



2 Multipoint Sampling

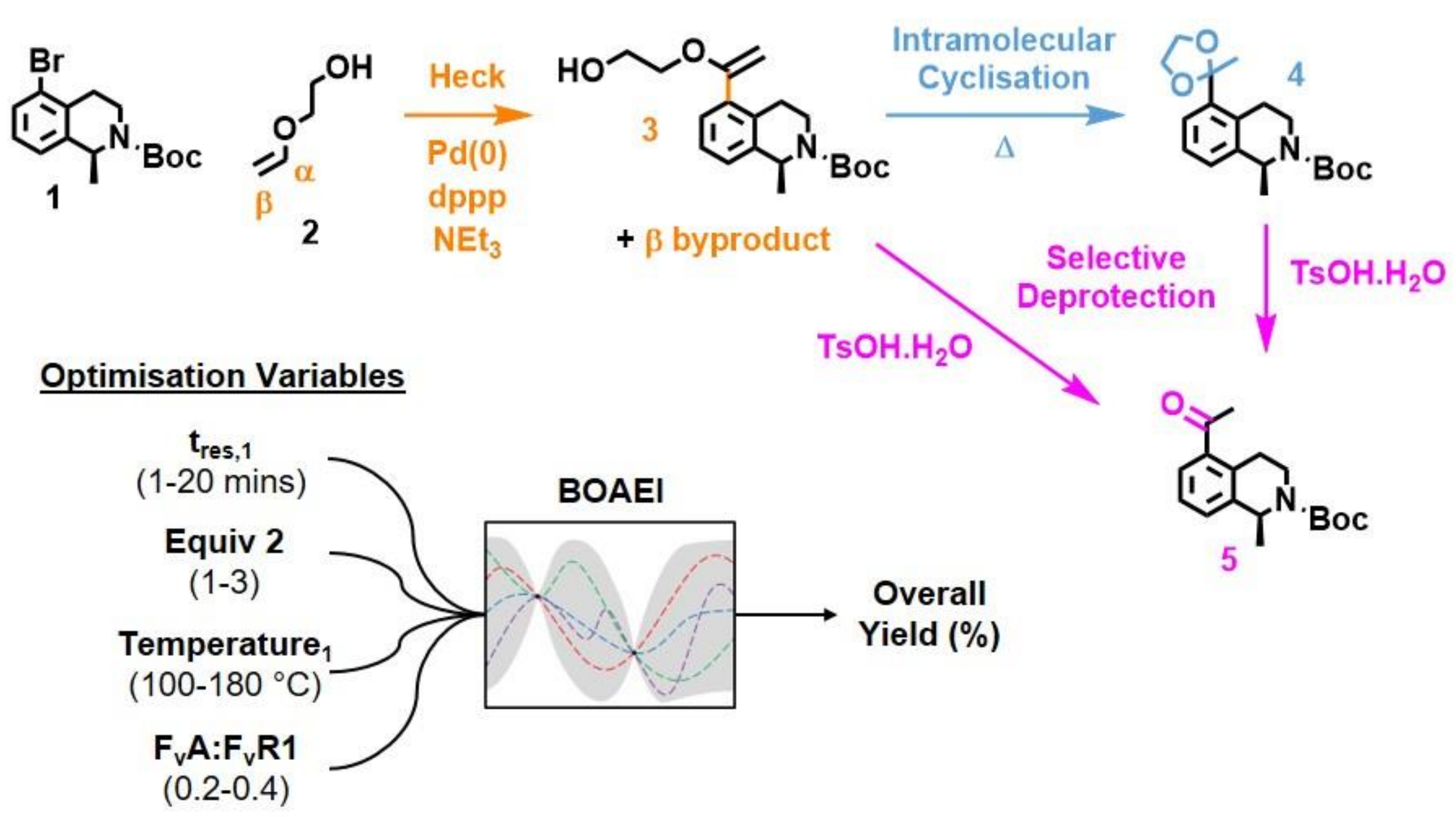
- A single analytical measurement at the outlet of an interconnected process limits the understanding of individual reaction steps.[4]
- Integration of multiple inline/online analytics enables monitoring of different chemical species across the multistep sequence.[5]
- Multipoint sampling with a single HPLC instrument was developed to enable affordable and accurate quantification of complex reaction mixtures:





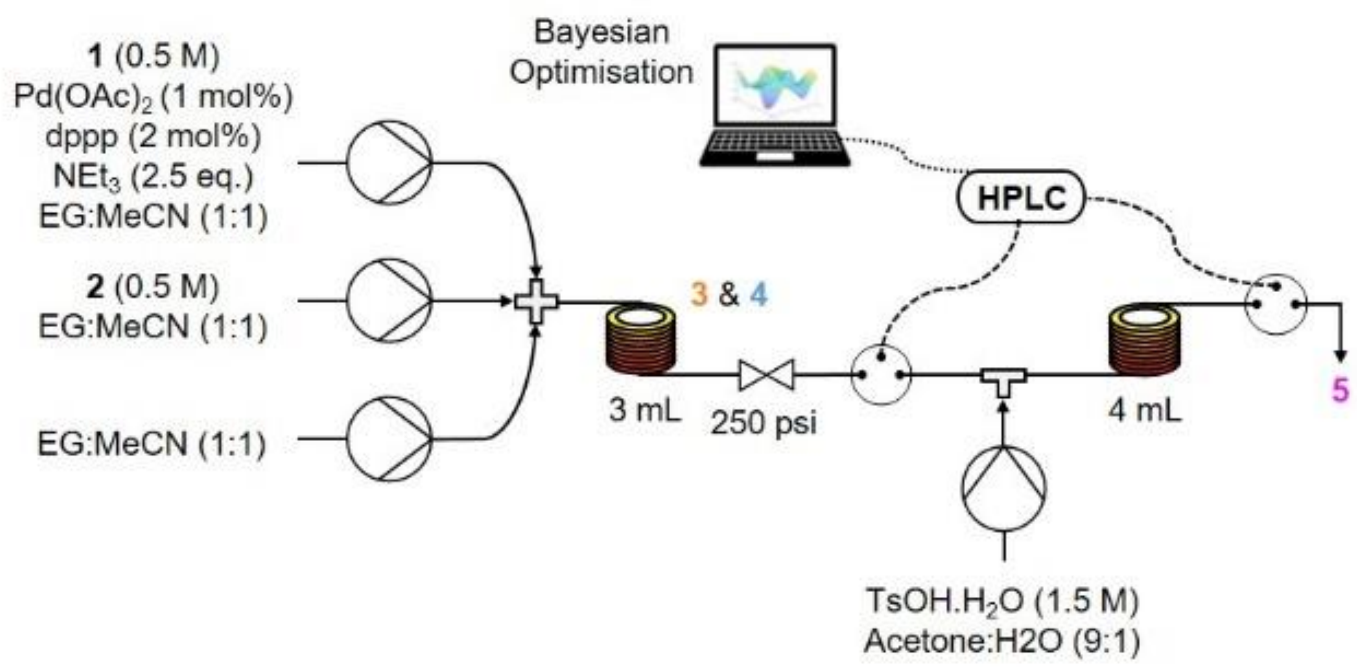
3 Heck-Cyclisation-Deprotection

- Case study: telescoped synthesis of aryl ketone **5**, a potentially versatile precursor for 1-MeTHIQ C-5 functionalisation.
- Proposed synthesis: (i) regioselective Heck arylation of electron-rich olefin **2** with aryl bromide **1**; (ii) intramolecular cyclisation of vinyl ether **3** to ketal **4**; (iii) selective deprotection of *N*-Boc aryl ketal **4** to aryl ketone **5**.
- The multistep synthesis was validated in batch. Notably, TsOH was identified as a suitable acid for the desired selective deprotection.

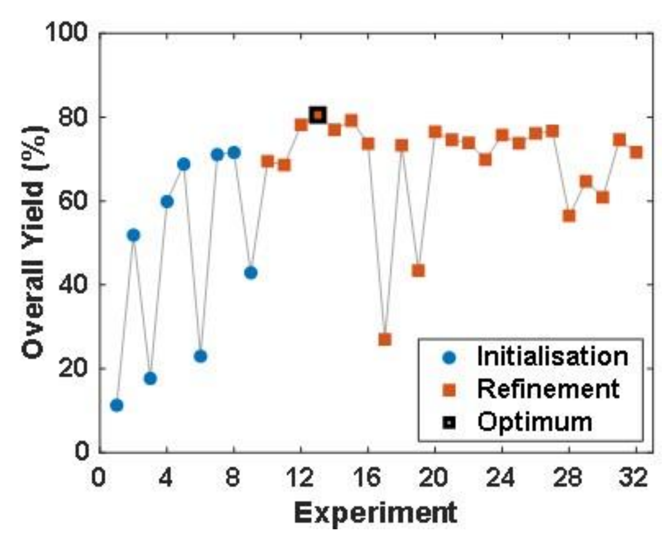


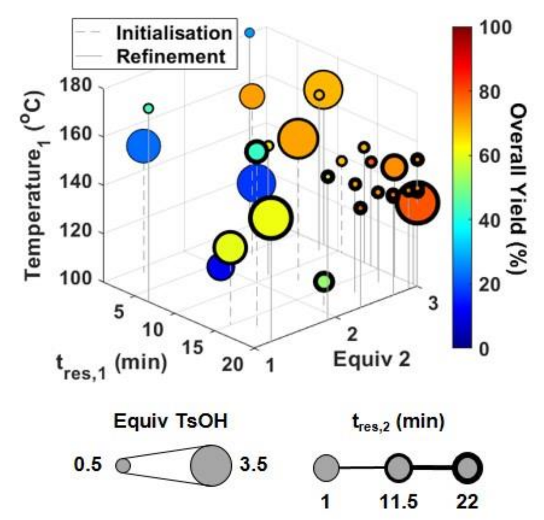
4 Telescoped Optimisation

- Bayesian optimisation with an adaptive expected improvement acquisition function (BOAEI) was selected to dynamically control the explore/exploit trade-off.



- Optimisation: 9 LHC initialisation points → 23 BOAEI refinement points.
- Optimum overall yield of 81% identified after 13 experiments (14 hours).
- Favours long residence times, high equivalents of **2** and moderate temperatures. Equivalents of TsOH has little influence.

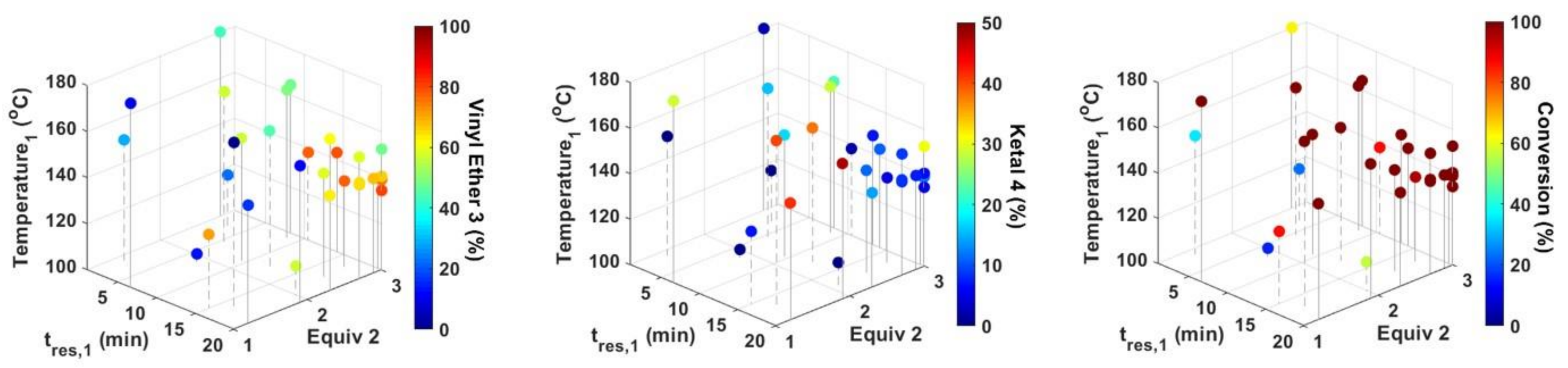




5 Reaction Profiles

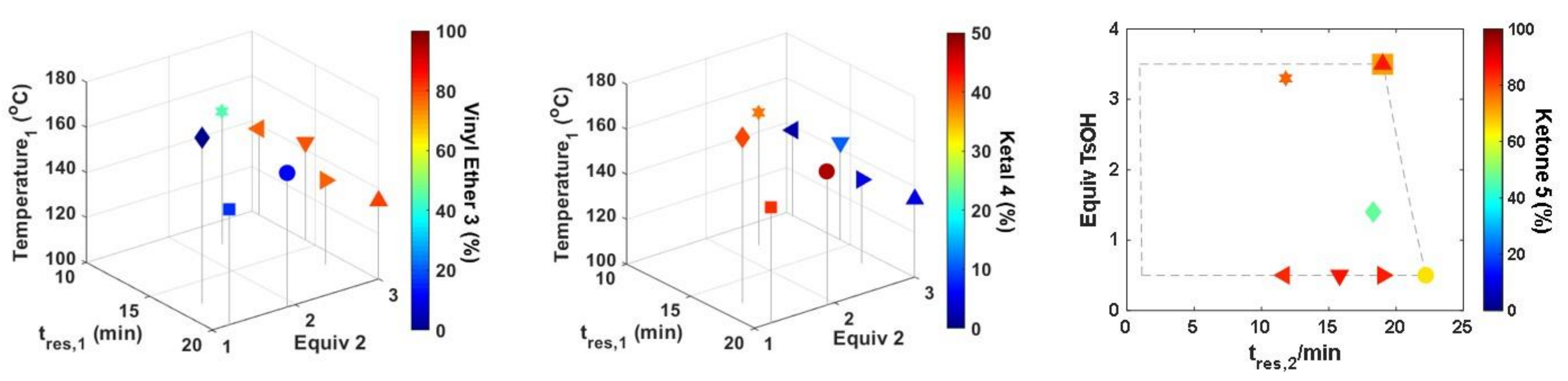
Heck-Cyclisation

- Significant formation of ketal **4** requires temperatures exceeding 140 °C.
- Highest formation of vinyl ether **3** occurs under the overall process optimum conditions, suggesting hydrolysis of **3** is the favourable pathway.



Deprotection

- Hydrolysis of ketal **4** is less favoured and more dependant on higher equivalents of TsOH compared to vinyl ether **3**.



Conclusion

- This approach enabled simultaneous optimisation of telescoped reactions in a practical time frame, whilst providing an in-depth understanding of the multistep reaction pathway.

6 References

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[2] A. M. K. Nambiar, C. P. Breen, T. Hart, T. Kulesza, T. F. Jamison, K. F. Jensen, *ACS Cent. Sci.* **2022**, *8*, 825-836.
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