Automated Chemical Reaction Optimisation using Multi-Task Learning

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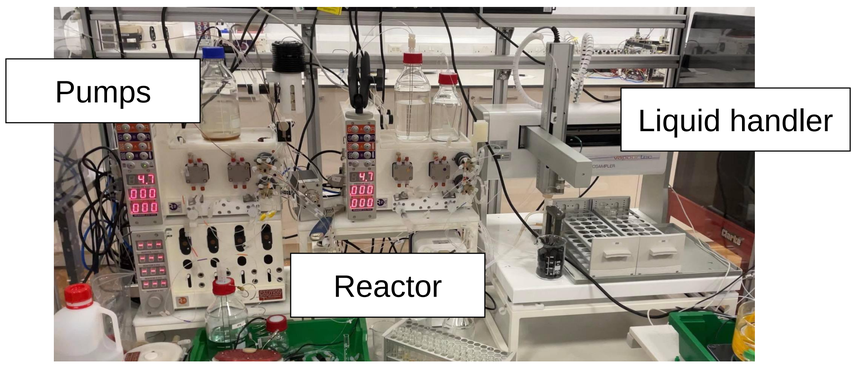
1. Background

Reaction Optimisation for FBDD

- Astex is interested in enabling difficult chemistry on fragments to access secondary binding pockets, but the required functionalisations are often challenging and provide low yields. In particular, carbon atom functionalisations have proven to be very desirable but are ultimately challenging in the presence of polar groups.[1]
- One way to address these challenges is by deploying continuous-flow platforms for the self-optimisation of these processes. These workflows exploit automated reactors and machine-learning algorithms to learn from previous experiments, thereby maximising yields whilst consuming very little starting materials - our reactor setup is shown below.



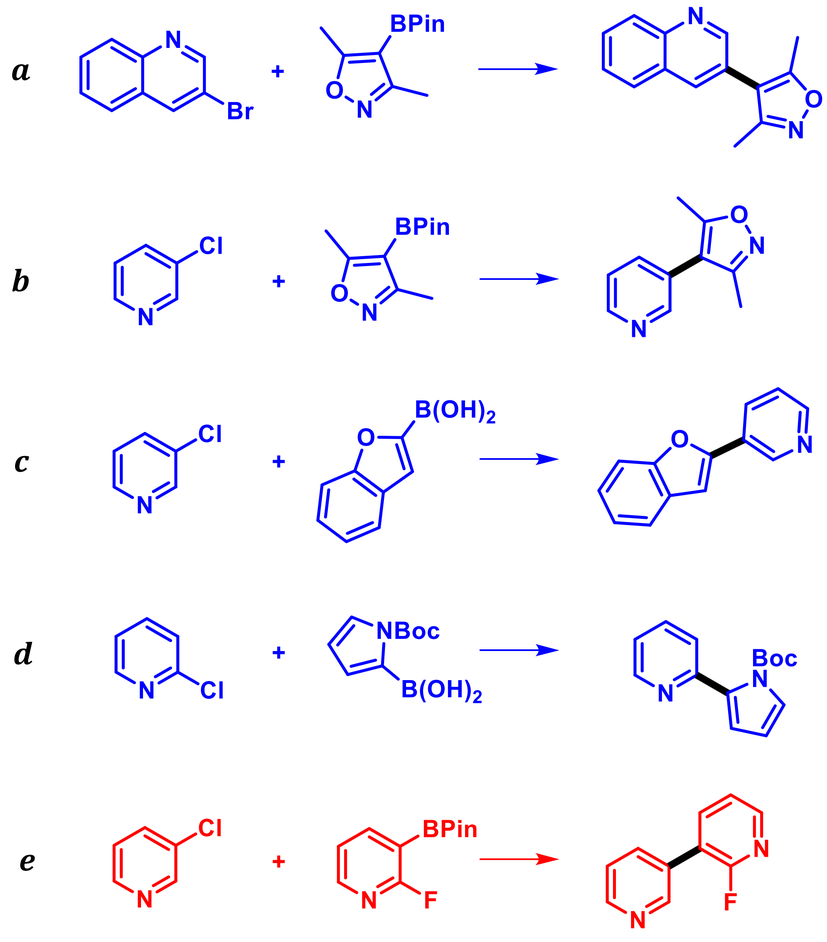
Multi-Task Bayesian Optimisation (MTBO)[2]

- A new, 'multi-task' approach to a well-established technique (Bayesian optimisation) represents the first examples where previous chemical reaction data can be leveraged to further enhance optimisation efficiency.

2. *In silico* Case Studies

Benchmarking of Suzuki Couplings

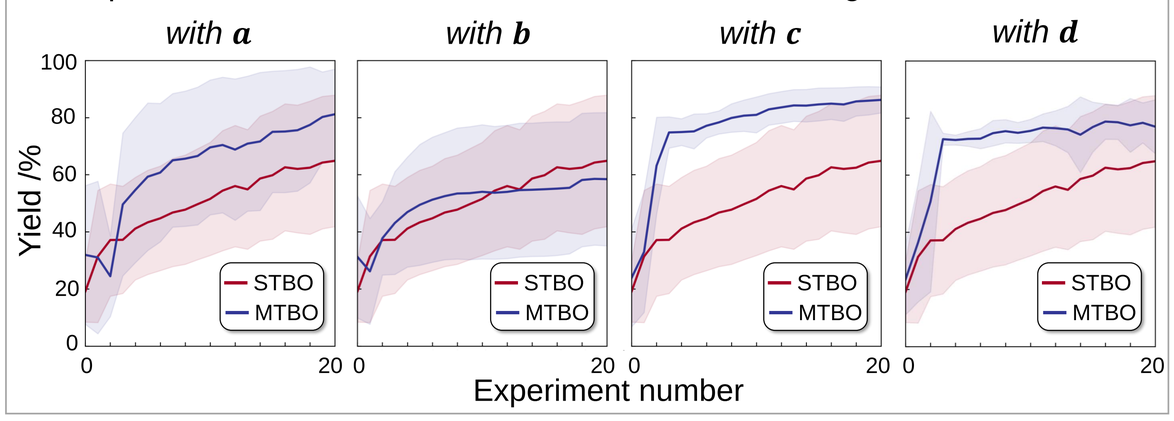
- Prior to real experimentation, we wanted to understand the performance of MTBO in simulated studies. This includes training the MTBO algorithm using reaction data from other similar transformations, then comparing these results with traditional single-task Bayesian optimisation (STBO).
- We examined two literature reports of Suzuki couplings from Reizman[3] (***a*** - ***d***) and Baumgartner[4] (***e***), and predictive models were built for their reaction yields using a single-layer neural network.



- The goal was to compare the speed of optimisation of reaction yield in ***e*** using STBO, with MTBO using prior reaction data from each of ***a*** - ***d***. This was performed 20 times and averaged.

Results

- The results indicate overall increases in optimisation speed, but is dependent on the nature of the 'task' that the MTBO algorithm is trained on:

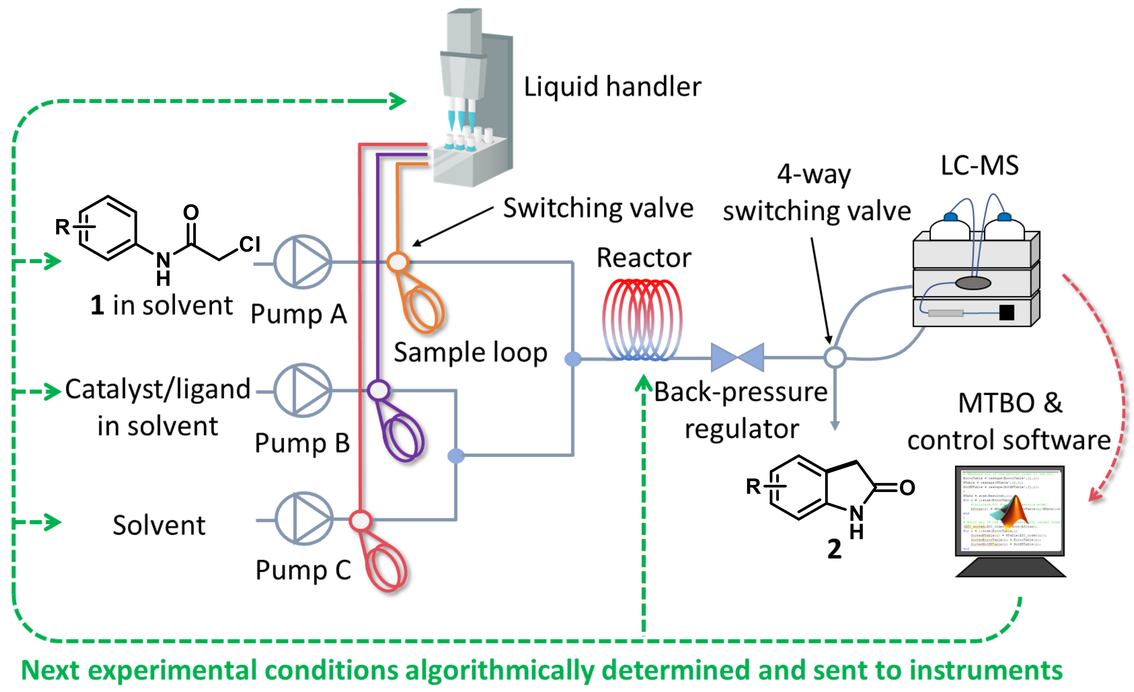


3. Experimental Methods

Self-Optimisation

- Our automated reactor platform utilises liquid handling robots, pumps, switching valves and analytical equipment. The workflow iterates as follows:

1. *Algorithm selects conditions.*
2. *Liquid handler loads sample loops.*
3. *Pumps deliver reagents to reactor.*
4. *Reaction is analysed via LC-MS.*
5. *Steps 1 - 4 repeated until optimal conditions are identified.*

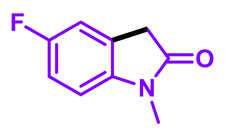
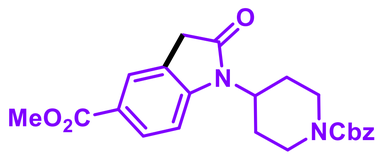
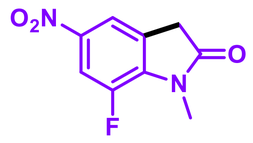
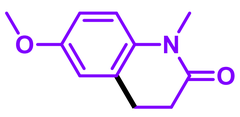


4. Reaction Optimisation

C-H activation

- The reaction class of interest was the palladium-catalysed C-H activation shown below, which yielded several pharmaceutically relevant oxindole products. The optimisation parameters were:
  - Residence time (5 - 60 minutes).
  - Temperature (50 - 150 °C).
  - Catalyst conc. (1 - 10 mol%).
  - Solvent (toluene, DMA, acetonitrile, DMSO, NMP).
  - Ligand (JohnPhos, SPhos, XPhos, DPEPhos).

- The cumulative data from each case study were leveraged by the MTBO algorithm to expediate optimisation:

Product	Yield /%	Experiments required	Starting material consumed /mg
	75	23	930
	85	11	980
	98	5	250
	82	9	450

5. Conclusions

- MTBO has proven successful in quickly optimising *in silico* and real-world case studies. Using this methodology significantly reduces the consumption of valuable FBDD-relevant starting materials and precursors.
- For these C-H activation case studies, utilising this workflow with MTBO to find optimal reaction conditions resulted in a material saving of 132 g (£25k) when compared with kinetic studies and 167 g (£32k) when compared with traditional 'design of experiments' optimisation.

6. References

[1] Chem. Sci., 12.36 (2021): 11976-11985.
[2] ACS. Cent. Sci., 9.5 (2023): 957-968.
[3] React. Chem. Eng., 1.6 (2016): 658-666.
[4] React. Chem. Eng., 3.3 (2018): 301-311.

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Research collaborations, open PhD opportunities.

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