Eliminating Cryogenic Constraints in Ipsenol Synthesis through Real-Time Reaction Landscape Mapping

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Ipsenol and ipsdienol are pine beetle pheromones isolated from the genus *Ips* and are interesting bioactive molecules, particularly in the context of Canadian forestry, which continues to face significant bark beetle infestations.[1] Despite their utility, synthetic access to these compounds remains difficult as most syntheses remain low yield or require large numbers of steps. The direct transformation of isoprene into ips(di)enol using super base chemistry is an attractive alternative requiring a single step using commodity chemicals. [2] However, strict cryogenic conditions are required to avoid solvent degradation and isoprene oligomerization significantly hampering the scalability of this route.

Herein, we report the design of a scalable synthetic strategy for pilot-scale to allow for efficient production of 1 kg of product from a single reaction. To address challenges in reaction control and monitoring, automated process analytical technologies (PAT) are employed to facilitate high-throughput, data-driven reaction optimisation.

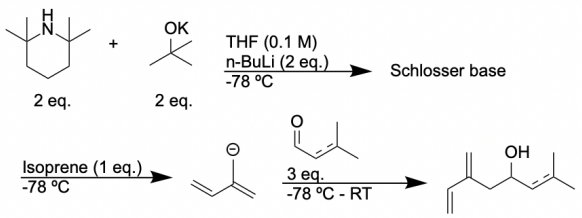

Figure 1: Batch synthetic route to ipsenol inspired by the Schlosser base-mediated strategy reported by Brown and Randad. [2]

Flow chemistry provides an enabling platform to address the thermal challenges associated with LiNK (Schlosser-type mixed metal amide) base formation, as the significant exotherm can be efficiently dissipated through small-diameter tubing into a temperature-controlled bath. In contrast to batch operation, where increasing reaction scale makes low-temperature control increasingly difficult, flow enables precise thermal management independent of reaction volume. This allows the reaction to be operated under cryogenic or sub-ambient conditions without the practical limitations associated with large-volume batch reactors.

The initial objective of this work is to optimise the reaction on small scale, where multiple interacting parameters including base stoichiometry, residence time, and temperature influence reaction performance. To efficiently explore this space, a closed-loop flow optimisation strategy leveraging Bayesian optimisation is employed. Preliminary experimentation indicated that deprotonation of isoprene by the LiNK base formed *in situ* was the most problematic step in the reaction sequence. [3-4] While deprotonation is accompanied by a characteristic colour change from colourless to cherry red, this qualitative observation does not provide quantitative insight into reaction efficiency, motivating the use of process analytical technology and data-driven optimisation. A Bayesian optimisation framework will therefore be employed to evaluate the formation and performance of LiNK bases generated from combinations of n-BuLi, KOtBu, and secondary amine bases such as TMP or DIPA. This approach will enable identification of the most effective base composition for isoprene deprotonation, which is expected to deviate from simple 1:1:1 stoichiometries.

A tiered analytical strategy has been adopted in which in situ IR spectroscopy is used for continuous monitoring and steady-state assessment under flow conditions, while on-line LC is employed to track changes in reaction composition. Once steady state is established, automated on-line LC sampling delivers material for analysis. Off-line NMR analysis using an internal standard is employed for absolute quantitative determination of product formation and to feed data into the Bayesian optimisation of the reaction system.

By using a combination of syringe pumps, flow tubing submerged in a temperature-controlled bath, and mixing chips, temperature control and mixing can be achieved. Furthermore, in-line IR readings can be used to monitor steady state and trigger automated LC sampling, enabling semi-autonomous exploration of the reaction landscape. From this data, reaction conditions can be easily changed to achieve high-throughput optimisation of the reaction landscape.

From these insights, a scalable synthetic strategy for superbase-mediated chemistry can be developed. The online analytical tools described above are used to monitor reaction performance in real time, enabling systematic evaluation of reaction pathways under conditions relevant to large-scale operation. This workflow is designed to make challenging superbase chemistry more tractable, reproducible, and scalable.

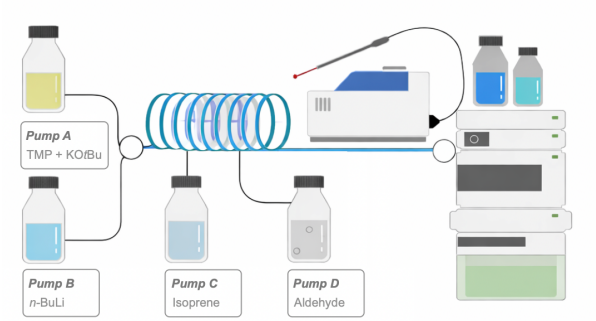

Fig. 2: Automated flow chemistry platform for optimisation of ipsenol and ipsdienol synthesis.

References

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