



Enabling Safe and Scalable Cryogenic Organometallic Chemistry through Continuous Flow Processing

Case study

Enabling Safe and Scalable Cryogenic Organometallic Chemistry through Continuous Flow Processing

Background

The development of chiral amines often involves organometallic transformations under cryogenic conditions, where precise control of reactivity and temperature is critical to ensuring product quality and process safety.

In this case, the client's supplied process presented significant challenges typical of such chemistries, including impurity formation, limited scalability, and restrictive operating conditions, hindering efficient transition to manufacturing.

Challenge

The initial process developed using a batch-inspired approach, was constrained by several key issues:

- Use of an ethyl ester reagent, resulting in uncontrolled over reaction and formation of a persistent impurity that could not be purged
- Cryogenic operating conditions below – 60 °C, creating complexity in scale-up and plant operability
- Moderate conversion (70–80%), limiting overall yield efficiency
- Extended residence times (35 seconds and 3 minutes), reducing throughput
- Poor robustness and scalability, posing challenges for reliable commercial manufacturing.

Collectively, these limitations increased development timelines, operational risk, and cost of goods, and required a

fundamentally different approach to achieve a scalable solution.

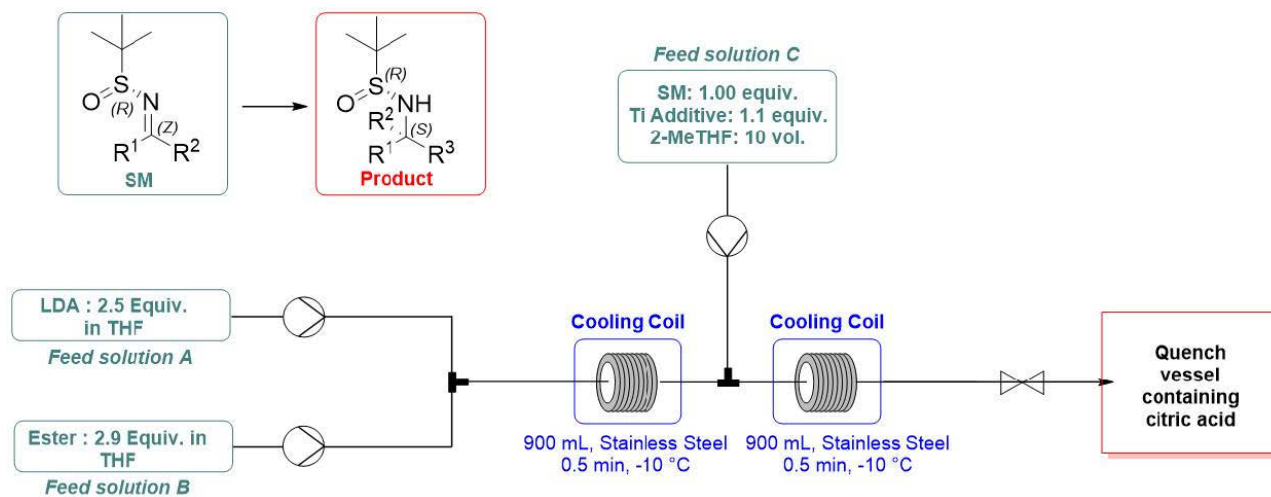
Solution

Leveraging its digitally enabled continuous flow platform, Almac Sciences re-engineered the process to improve control, selectivity, and manufacturability.

The breakthrough centred on a combination of chemistry optimisation and flow processing advantages:

- Introduction of a sterically hindered acetate reagent, suppressing over reaction pathways
- Application of continuous flow conditions, enabling precise control over reaction parameters (temperature, residence time, mixing)
- Use of tightly controlled processing environments to enhance reproducibility and minimise impurity formation.

This integrated approach allowed the process to be redesigned for performance, safety, and scalability from the outset.



Results

The optimised process delivered substantial and measurable improvements across performance, operability, and manufacturing readiness:

- Impurity reduction: decreased to ~0.4%, enabling a clean and controllable process
- Temperature optimisation: increased from < -60 °C to -10 °C, significantly improving operability and safety
- Conversion improvement: increased to 94–97%
- Isolated yield: achieved 95%
- Residence time reduction: reduced to 40 seconds and 30 seconds, increasing throughput
- Successful scale-up and transfer: process implemented in manufacturing, delivering >120 kg of product.

Impact

This case study demonstrates how continuous flow technology can transform highly challenging cryogenic chemistries into robust, scalable manufacturing processes.

Key outcomes include:

- Enhanced safety through reduced reliance on extreme cryogenic conditions
- Improved process robustness and reproducibility via precise control and reduced variability
- Accelerated development-to-manufacture transition, enabled by a scalable flow platform
- Higher productivity and reduced cost of goods, driven by improved yields and shorter processing times.

Importantly, the successful commercialisation of this process reinforces the value of integrating chemistry innovation with digitalised continuous manufacturing infrastructure.



Why This Matters

This case study highlights a broader industry shift:

- The combination of continuous flow processing, digital control, and targeted chemistry optimisation enables the safe and efficient execution of chemistries that are traditionally constrained in batch.
- By overcoming key barriers in low-temperature organometallic transformations, this approach sets a precedent for handling increasingly complex and hazardous reactions in modern pharmaceutical manufacturing.

Contact us:

Global HQ

+44 (0) 28 3833 2200

US HQ

+1 (215) 660 8500

Ireland

+353 90 646 0200

