

Case study

Cascading imine formation and hydrogenation

Problem

Cascading several reactions into one creates an opportunity to simplify product synthesis and reduce the number of unit-operations. In this regard, we investigated the synthesis of an imine followed by its hydrogenation into amine.

The reaction cascade requires precise control of reaction conditions:

- starting hydrogenation too early results in aldehyde hydrogenation and by-product formation.
- leaving hydrogenation for too long results in impurities such as decomposition, oligomerisation, and aromatic ring hydrogenation.

What's the benefit?

Continuous flow chemistry provides superior heat and mass transfer. Small reactor volume enhances process safety opening new process windows (temperature, pressure) for process intensification and enables rapid optimisation of process conditions.

What did we do?

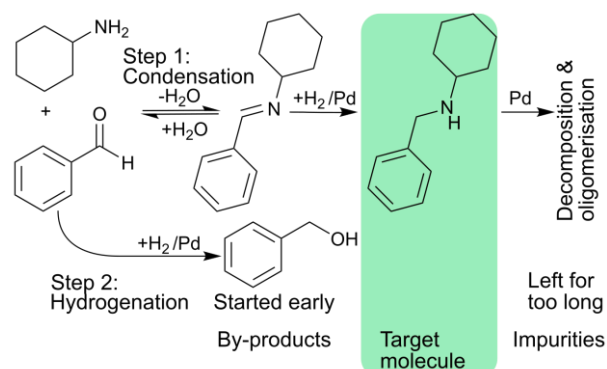
We optimised the solvent, substrate concentration, catalyst, residence time and temperature in the continuous-flow hydrogenation of an imine to an industrially relevant secondary amine used for pharma applications.

Imine reactions are known to cause rapid catalyst deactivation. This is less of an issue in batch processing where catalysts may be replaced after each cycle at high expense. In continuous flow, however, process intensification allowed for evaluation of the optimal reaction temperature (130 °C) to maximise reaction rates while keeping catalyst deactivation to a minimum.

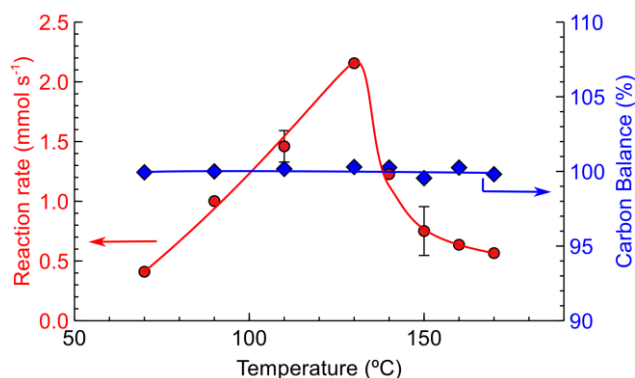
Compared to reported batch values, continuous flow reactors allow for greatly increased catalyst utilisation – by a factor of 10-1,000x higher.

Outcome

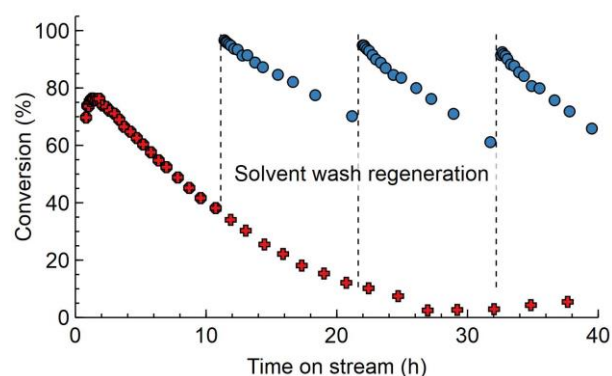
Rapid process development in continuous flow allowed us to develop a detailed process understanding of the imine hydrogenation process including reaction and deactivation rates. We quickly established the optimum solvent (THF) and reaction temperature (110 °C) to maximise the desired product yield and minimise impurity formation. All data is published in [the Industrial & Engineering Chemistry Research journal](#).



Scheme of cascaded imine synthesis and hydrogenation.



Imine hydrogenation rate and total carbon balance as a function of temperature



Time on stream imine conversion without and with solvent washing regeneration (dashed vertical lines).