Application Note

Acid Catalyzed Transfer Hydrogenation

Optimizing the Kinetics

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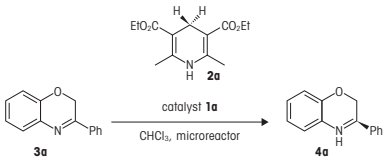
M. Rueping, B. Teerawut, S. Erli, Bilstein J. Org. Chem. 2012, 8, 300-307

Continuous-flow Catalytic Asymmetric Hydrogenations: Reaction Optimization Using FTIR Inline Analysis

The majority of enantioselective reductions depend on various transition-metal-catalyzed high-pressure hydrogenations. However, the drawbacks of these method conditions are often tolerated due to the excellent enantio selectivities and activity they obtain.

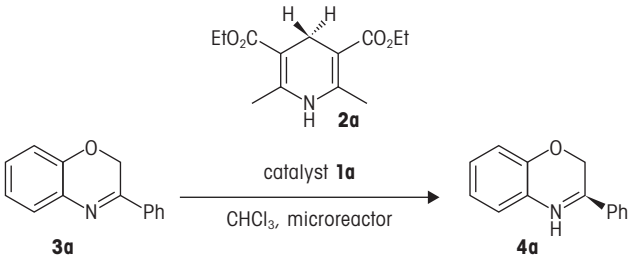
Rueping et. al studied the asymmetric organocatalytic hydrogenation of benzoxazines in continuous-flow microreactors as a metal-free alternative. Coupling inline mid-infrared spectroscopy for real-time reaction monitoring enabled the group to quickly, optimize the reaction for duration (kinetics) and yield (product quality) while minimizing the volume of material needed.



Entry	1a [mol %]	Residence Time [min]	Flow Rate [mL min^{-1}]	Yield [%][b]
1	2	20	0.1	50%
2	2	40	0.1	87%
3	2	60	0.1	98%

Figure 1. Optimization of the Bronsted acid catalyzed reduction of benzoamines. Reaction Conditions: **3a**, **2a** (1.2 equiv), **1a** in $CHCl_3$ (0.05M) at 60 °C. [b]Isolated yields after column chromatography.

By studying the effects of a select set of parameters (temperature, flow rate, and residence time) the optimum set of conditions were determined as based on overall product yield (Figure 1). Inline mid-infrared provided the instantaneous feedback as each of these parameters were examined for their beneficial or negative contribution to the chemistry.



METTLER TOLEDO

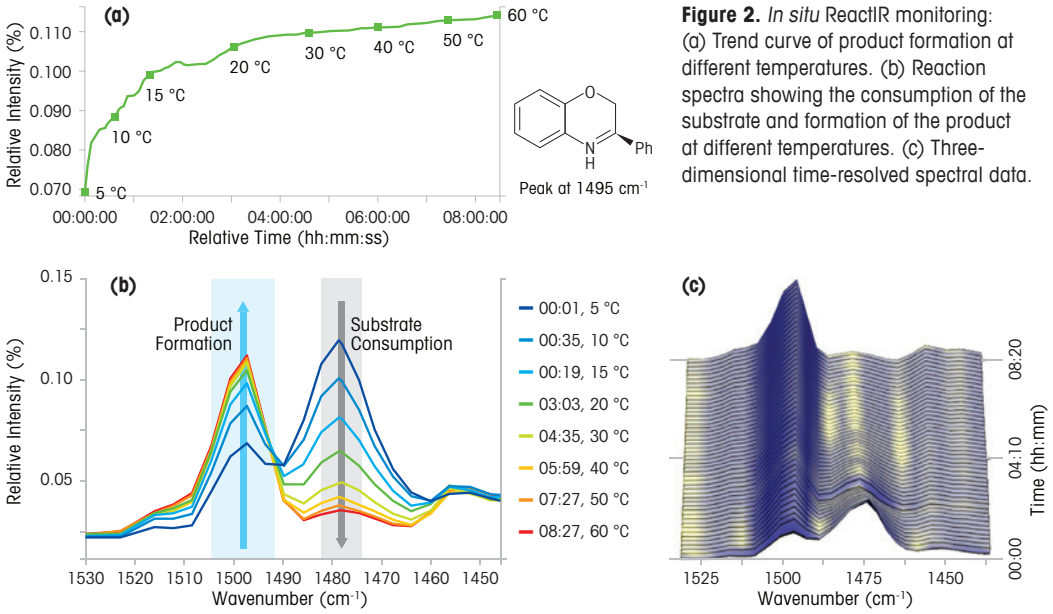


Figure 2. *In situ* ReactIR monitoring: (a) Trend curve of product formation at different temperatures. (b) Reaction spectra showing the consumption of the substrate and formation of the product at different temperatures. (c) Three-dimensional time-resolved spectral data.

Results

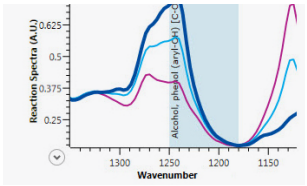
In situ conversion, as measured by ReactIR, tracks changes to the substrate and product over the course of the experiment. This allows researchers to determine key parameters for control and optimization. For example, by varying the temperature from 5 °C to 60 °C (5 °C increments), the ideal reaction temperature was identified to be 60 °C in a single eight-hour reaction. Additionally, ReactIR trends provided time-resolved reaction conversion data measuring the relative concentration of both product and substrate.

Conclusions

In this study, ReactIR demonstrated the ability to detect and monitor the substrate and product kinetic behavior leading to the optimized reactions conditions: temperature 60 °C, flow rate 0.1 mL/min, and 98 % yield (confirmed by column chromatography).

ReactIR: Real-Time Reaction Mechanisms

Monitor Chemistry *In Situ*
Monitor chemistry as it takes place (in flow) to achieve optimal reaction mechanics for a greener, safer process in the shortest time frame possible.



Comprehensive Reaction Information in Real Time
Detect and monitor instantaneous changes (initiation, steady state, process deviation, and endpoint) that are otherwise difficult or impossible to detect via offline methods.

Reaction Kinetics, Pathway and Mechanism
In-depth understanding of reaction mechanism for process efficiency, robustness and safety.

Applications of ReactIR include:

- Reaction Kinetics
- Flow Chemistry
- High Pressure Reactions
- Polymer Synthesis
- Energetic Reactions

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