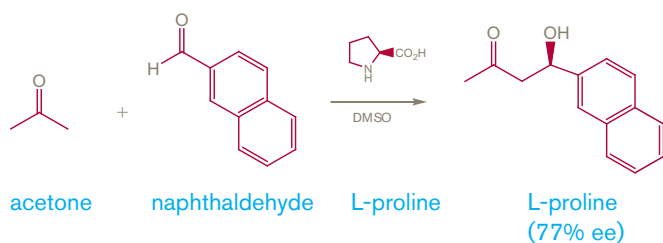


## Real-time monitoring of a chiral reaction with HPLC analysis software

The ExpressRT-100 system software analyzes each time point and updates results graphically in real-time.



expressRT•100

## Introduction

Chemical process development and optimization require quality analytical data taken over the course of the reaction. Traditionally this sampling is done manually and the samples then submitted for analysis. Peak area data is then collated and processed off-line.

With integrated reaction sampling, chromatography, and data analysis, peak area data is generated and graphed automatically with the ExpressRT-100 system. Custom formulas for parameters such as conversion, percent impurity and enantiomeric excess over time are graphed automatically and updated with each new time-point. Data does not need to be transferred in a specific format to third-party graphing software in order for the results to be visualized.

After establishing peak identification settings and beginning the reaction, progress of the reaction is displayed graphically in real-time, eliminating any manual data analysis steps. This application for the ExpressRT-100 system creates a chiral aldol product from naphthaldehyde in an excess of acetone.

## Method

Initially, 1.5mg of naphthaldehyde was dissolved into 100 ml of a 4:1 DMSO:acetone mixture and then 0.35g of proline catalyst was added. This reaction reaches completion in 5-6 hours at room temperature. Sample was drawn and diluted 100 fold with ACN by the ExpressRT sampling module. This dilution was delivered to the

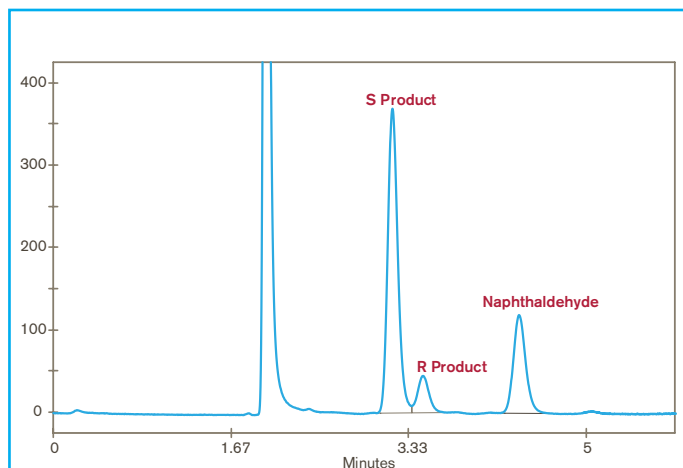


Figure 1.

Chromatogram from reaction timepoint @ 2.1 hours. Large peak at 2 minutes is DMSO, the reaction solvent.

chromatography module's sample loop where 40 nL was then injected. Chromatography was performed on a 150 x 0.3mm Chiralcel AD-RH with an isocratic mobile phase composition of 65:35 ACN:H<sub>2</sub>O. All peaks were detected @ 226 nm. Retention times for S-aldol, R-aldol, and naphthaldehyde starting material were 3.2, 3.5 and 4.4 minutes respectively (figure 1).

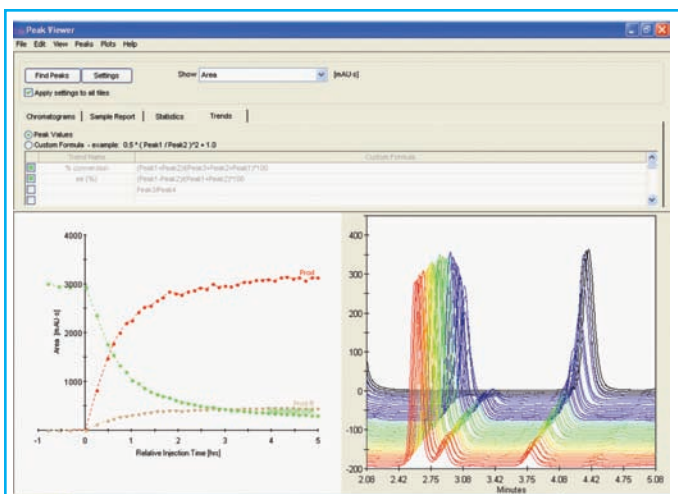


Figure 2.

Peak Viewer software displays peak areas for starting material (naphthaldehyde) and chiral products vs. reaction time (left) and overlaid chromatograms (right). The first time point is at the back of the overlaid set.

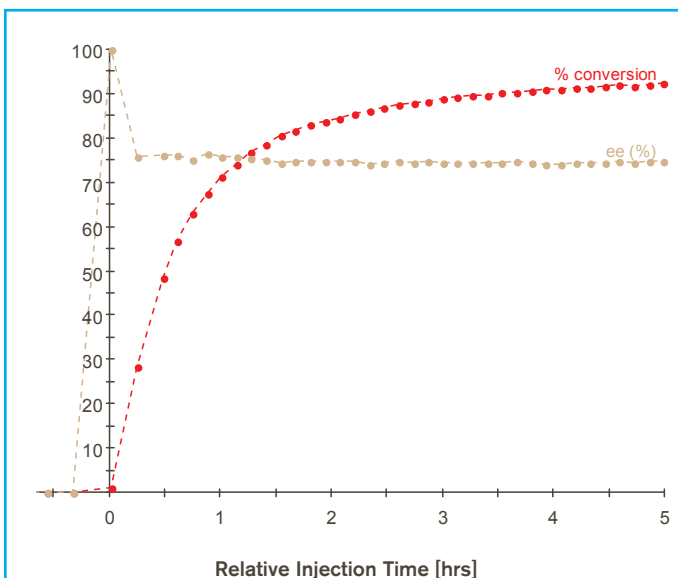


Figure 3.

"Trends" view of reaction results, conversion and enantiomeric excess (ee), updated as each time-point analysis is completed. Offset function allows 0 time point to be set for when reaction is initiated.

## Discussion

Continuous monitoring of chiral product formation was achieved with an integrated sampler, diluter, and chiral chromatography system. Reaction time-points were analyzed and graphed by Eksigent Peak Viewer software. The 100-fold dilution performed by the sampler allowed direct injection of diluted sample from the reaction vessel onto the column. High performance micro-scale chromatography allowed for a chiral analysis to be performed continuously and in real time with minimal solvent usage (1.2 mL over 6 hours).

Once peak analysis settings are determined, peaks are identified by a retention time window, integration parameters, and within window criteria such as largest, nearest to specified RT or best fit. Analytes of interest are named and graphed over time (figure 2). Graphs can represent data from one of 35 peak parameters (including peak area, peak height, or retention time). Custom calculations on the peak areas can be performed automatically and higher order information such as conversion, enantiomeric excess, and % impurity graphed in real-time (figure 3).

## Conclusion

The ExpressRT-100 eliminates the need for manual reaction sampling and extensive data workup. All steps from sampling, dilution, chromatography, peak integration, peak identification, and the plotting of results are all performed automatically in real-time, on one integrated system.

**eksigent**

eksigent technologies

headquarters  
5875 arnold road  
dublin, california 94568  
tel: 925 560 2600  
fax: 925 560 2700

new jersey office & laboratory  
11 deer park, suite 204  
monmouth junction, new jersey 08852  
tel: 732 274 9190  
fax: 732 274 9161

email: [info@eksigent.com](mailto:info@eksigent.com)  
website: [www.eksigent.com](http://www.eksigent.com)

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