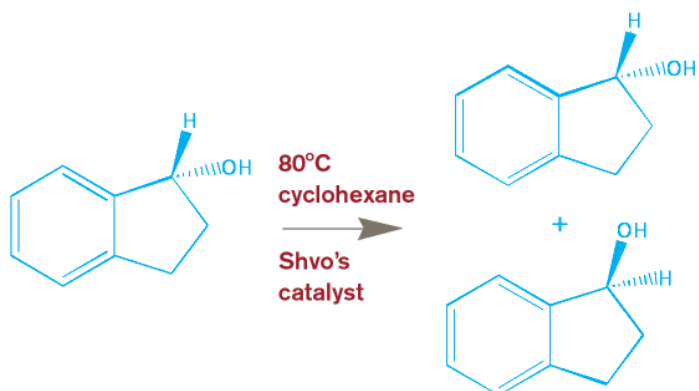


real-time monitoring of a chiral reaction by Microflow™ liquid chromatography

Enantiomeric conversion in process scale reaction can now be monitored in real-time using the Microflow ExpressRT™-100 LC system from Eksigent.



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introduction

Chemical process development and optimization require quality analytical data taken over the course of a reaction. Traditionally, this sampling is done manually and the samples are then submitted for analysis. Existing on-line reaction monitoring techniques, like IR, can not distinguish between enantiomers. The racemization of an enantiomerically pure indanol can be accomplished using Shvo's catalyst, a diruthenium complex. This is an important step in dynamic kinetic resolutions, and is required to increase theoretical yield from 50 to 100% for the product of a highly enantioselective catalytic reaction. Monitoring the racemization of indanol requires a chiral analysis. With integrated reaction sampling and chiral chromatography, the ExpressRT-100 system allows for continuous unattended monitoring and chiral analysis of this process.

method

To begin, 420 mg of R-indanol was dissolved into 210 mL of cyclohexane. Then 2% molar ratio of Shvo's catalyst was added (140mg). This reaction mixture was refluxed for 22 hours. Eighteen microliters of sample were drawn directly from the reaction vessel and diluted 3-fold with isopropanol. This dilution was delivered to the chromatography module's sample loop where 40 nL was then injected. Chromatography was performed on Chiral Technology's 150 x 0.3mm Chiralcel OD-H from with an isocratic mobile phase composition of 5:95 isopropanol:heptane. The indanol enantiomers were detected @ 212 nm. Retention times for S-indanol and R-indanol were 4.7 and 5.2 minutes respectively.

Figure 1. Chromatogram showing racemic indanol standard.

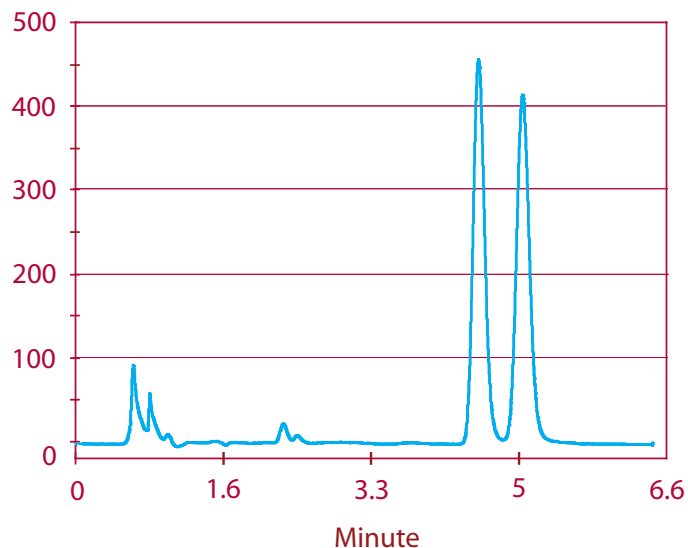
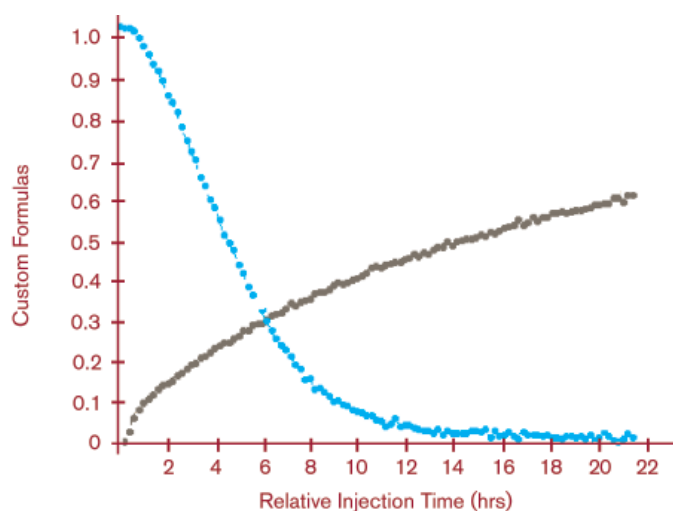


Figure 2. Enantiomeric excess and percent impurity expressed as fractions.

This data is collected, calculated and displayed in real-time.



discussion

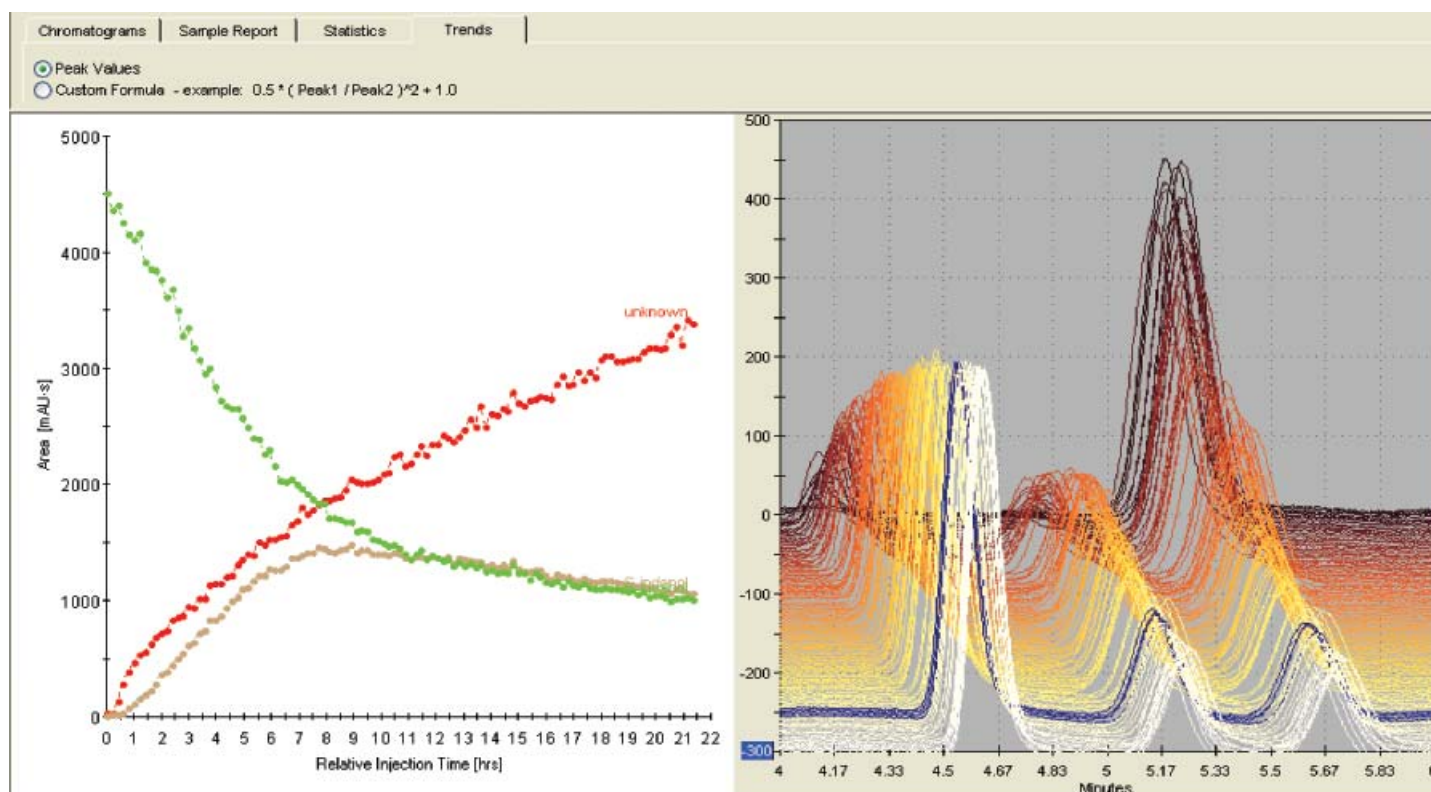
Continuous monitoring of a chiral reaction was achieved with automated sampling, dilution, and chiral chromatography. Real-time reaction data was generated and saved over 22 hours. The three-fold dilution performed by the sampler allowed direct injection of diluted sample from the reaction vessel onto the column. High performance Microflow chromatography allowed for a chiral analysis to be performed continuously and in real-time. Total sample volume used for analysis was less than 2 μL of the reaction mixture volume ($< 1\%$).

Continuous monitoring of the reaction shows a steep and consistent initial reaction rate until about 10% enantiomeric excess. The generation of a side-product can be seen and is constantly increasing during the course of the reaction. Even after a racemic mixture of indanol is achieved, the peak areas of the two enantiomers continue to decrease as the unknown peak increases, suggesting the side-product is generated from indanol and is not enantiospecific.

conclusion

The ability to do real-time monitoring of chiral components during a reaction has been achieved with the ExpressRT-100. Spectroscopic monitoring of this reaction would not be able to differentiate the two enantiomers. If the side-product is closely related to the indanol compound, spectroscopic data might also be unable to differentiate this unknown from the indanol racemate.

Figure 3. Peak Viewer software displays peak area vs. reaction time plot (left) and overlaid chromatograms (right).





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