Application Note 15.2

Prilezhaev epoxidation reaction of alkenes and formation of trans-diols

Alkene epoxidation is a useful reaction in organic chemistry, but can be performed in a microreactor for added safety and reaction control. The reaction was successfully optimised in the *Flow*Screen microreactor platform, providing a method to obtain the *trans*-diol in a 100% yield. A reaction model was fitted using the optimisation data.

Future Chemistry

Introduction

The synthesis of epoxides is a useful reaction in organic chemistry, as it provides a good pathway towards trans-diols through alkaline hydrolysis. Traditionally, this reaction is difficult to control due to its fast reaction rate and exothermic character. In batch, temperature runaway is largely overcome by controlled reagent addition and the use of milder epoxidation reagents such as *meta*-chloroperoxybenzoic acid (mCPBA), whose synthesis again requires the use of a peroxy compound and are less atom-efficient. Epoxidation with peracetic acid poses its limits to batch scale-up, but has been shown to be possible in continuous flow. The latter has the added advantage of handling all toxic and corrosive reagents inside a closed system.

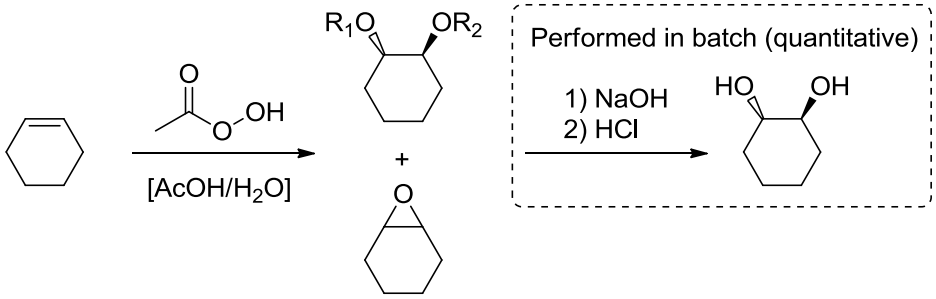

Figure 1: Epoxidation and hydrolysis of model substrate (R_1 = H, acetyl; R_2 = H, acetyl).

To avoid the use of expensive epoxidation reagents (e.g. mCPBA) while keeping a high throughput at the same time, FutureChemistry has translated this reaction from a batch process to a continuous flow process. FutureChemistry's typical three-tier approach led to a protocol which can be adapted to any viable alkene substrate:

1) Translation of batch process to continuous flow process.
2) Automated reaction optimisation:
   a) Univariate screening of reaction parameters.
   b) Selection of parameter range and optimisation points.
   c) Multivariate optimisation experiment.
   d) Analysis and modeling.
3) Out scaling to preparative synthesis.

This *application note* describes the optimisation of the continuous flow process using the *Flow*Screen C-300.

Reaction optimisation

In contrast to batch-wise optimisation of chemical reactions, optimisation in continuous flow offers some significant advantages. Firstly, each experiment can be carried out using material in the microgram or nanogram scale, thereby minimising waste and costs. Secondly, automated optimisation is a lot less time-consuming and more precisely controlled, especially when optimising fast reactions.

To obtain accurate concentration measurements of the reaction mixtures, a flow markers approach is used. To the cyclohexene stock solution an internal standard is added. Accurate concentration measurements follow from calibration of the cyclohexene substrate onto the internal standards.

Table 1: Reaction parameter ranges

Parameter	Range
Temperature [°C]	25 to 60
Stoichiometry (reagent/substrate)	0.6 to 2.2
Reaction time [s]	60 to 300

To select a useful region for performing the optimisation experiment, three univariate optimisation experiments were conducted in the *Flow*Screen to show parameter influences. From this it followed that all three parameters – temperature, peracetic acid molar excess ratio and reaction time – had a pronounced effect on substrate conversion, with increasing conversion as parameter values increased. The found parameter ranges are given in Table 1.

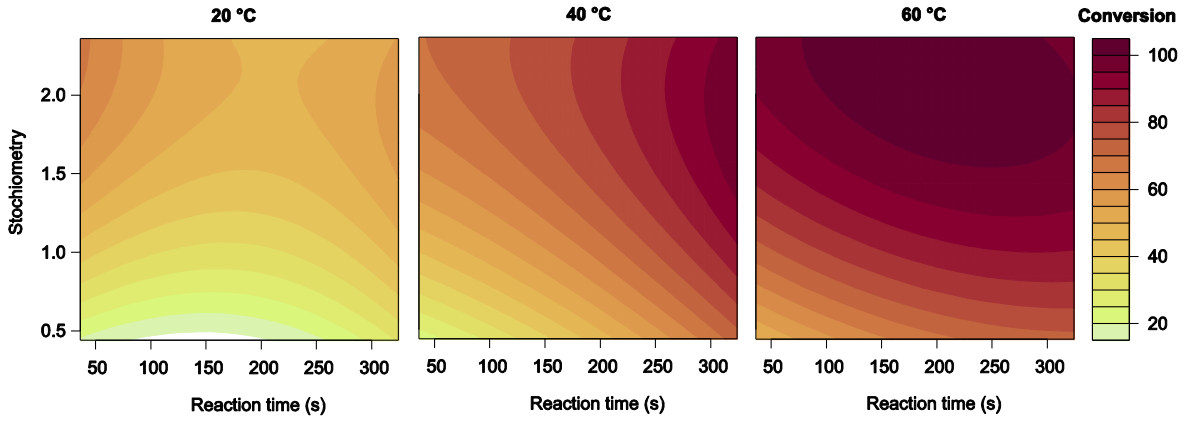

Figure 2: Reaction model fit.

An optimisation experiment was set up with 50 points, spread out across the optimisation region. The experiment was prepared, uploaded to the *Flow*Screen controller and conducted in an automated fashion. Afterwards all samples were analysed, processed and an optimum was found at a **temperature of 60°C, peracetic acid molar excess ratio of 1.1 and reaction time of 300 seconds**. Subsequently, a reaction model was fitted with FutureChemistry's *Flow*Fit software, which is visualised in Figure 2. From this model various optimal parameter sets can be selected, depending on the demands one has to satisfy.

Method

The used setup for the epoxidation reaction is identical to the *Flow*Start setup (see: *Application note 15.1*). The used flow markers are given in Table 2.

Table 2: Used flow markers

Compound	Function	Used in
toluene	internal standard	Solution A

All experiments were conducted in a standard FutureChemistry C-300 *Flow*Screen setup, using the Basic Quench Microreactor with internal volume of 92 µL. Cyclohexene was used as model substrate.

Solution A (8.3 M): Cyclohexene/toluene (5:1)

Solution B (5.4 M): Peracetic acid 35% w/w in acetic acid

Solution Q (1.0 M): Sodium sulfite (1.26 g, 10.0 mmol) dissolved to a total volume of 10 mL with water

Three glass 1.0 mL syringes were loaded with solutions A, B and Q respectively. For each experiment, 200 µL of microreactor outflow was collected directly into a GC vial containing 400 µL dichloromethane and sampling the organic layer. Experiments were conducted in random order. Data modelling was done using FutureChemistry's *Flow*Fit software.

All product mixtures were analysed with GC, with retention times according to Table 3. Analysis was performed on a Shimadzu GC2010 using a Quadrex 007 1701 apolar column (L 15.0 m, ID 0.10 mm) and flame ionization detector (T 325°C, H_2 60 mL/min, Air 400 mL/min), using a temperature program (0-0.8 min 35°C, 0.8-4.9 min 35-200°C, 4.9-5.4 min 200°C) and a 1.0 µL injection with a split ratio of 200 (250°C injection temperature).

Table 3: GC retention times

Compound	Function	Retention time [min]
cyclohexene	substrate	0.59
toluene	internal standard	1.05
cyclohexene oxide	(intermediate) product	1.63
***trans*-1,2-cyclohexadiol**	product	3.15
***trans*-1,2-cyclohexadiol monoacetate (racemic mixture)** *or* ***trans*-1,2-cyclohexadiol diacetate**	(intermediate) product	3.54