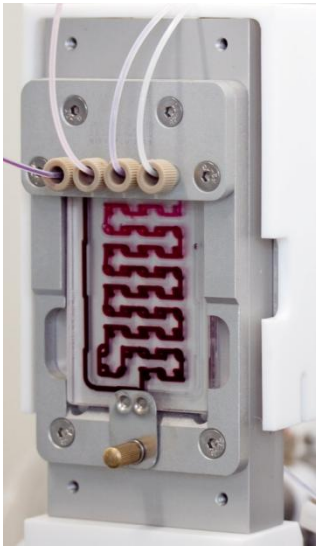
Application Note 15.3

Prilezhaev epoxidation reaction of alkenes and formation of trans-diols



Epoxidation of alkenes is a useful reaction in organic chemistry, but can be performed in a microreactor for added safety and reaction control. The reaction was successfully scaled out to a preparative scale in the *Flow*Syn microreactor platform, thereby continuously producing 2.46 g/hr of the desired product.

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.

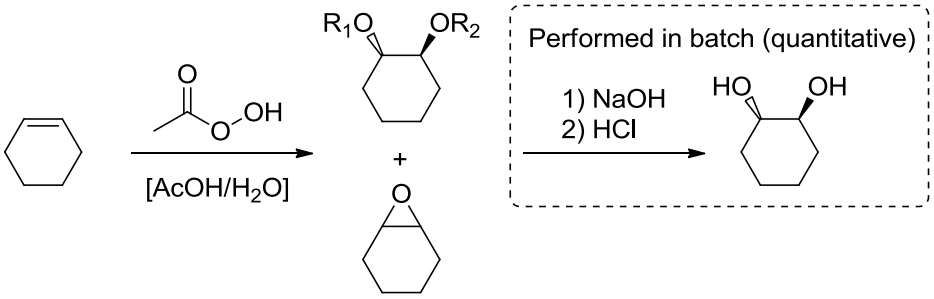


Figure 1: Epoxidation and hydrolysis of model substrate (R_1 = H, acetyl; R_2 = H, acetyl).

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.
3) Out scaling to preparative synthesis:
   a) Validate previously found optimum.
   b) Scale out to preparative synthesis.

This *application note* describes the out scaling of the continuous flow process using the *Flow*Syn.

Reaction out scaling

Up scaling of batch processes traditionally poses a variety of problems, since heat conduction and mixing greatly differs with reactor size. In batch chemistry, small-scale reactions are usually conducted by organic chemists while large-scale reactions are performed by chemical engineers. Using flow chemistry, out scaling is a one-to-one process in most cases, eliminating the need for a different viewpoint on reaction conditions and practical concerns between small-scale and large-scale.

Optimal conditions were determined using the model obtained from the *Flow*Screen optimisation data (see: *Application note 15.2*), yielding an optimum at a **temperature of 60°C, peracetic acid molar excess ratio of 1.1 and reaction time of 5 minutes**.

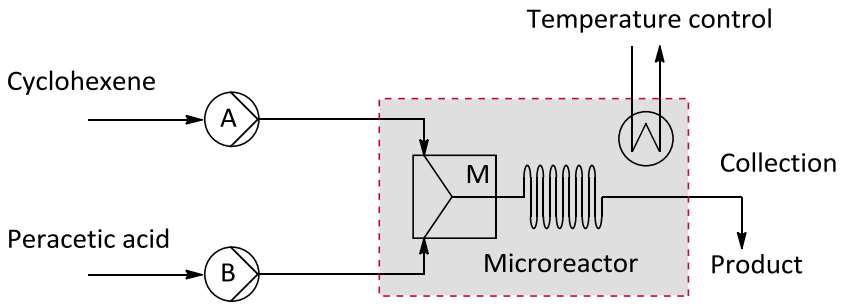


Figure 2: *Flow*Syn setup.

Preparative synthesis of the target compound (*trans*-1,2-cyclohexadiol) with the setup depicted in Figure 2 resulted in the **continuous production** at a **2.46 g/hr** rate, which can easily be scaled out to higher rates by using a larger reactor. Quenching was not needed, since the reaction was driven to full completion.

Method

All experiments were conducted in a standard FutureChemistry *Flow*Syn setup, using the *Flow*Syn Quench Microreactor with an internal volume of 0.65 mL. No flow markers were used in the preparative run. Quenching was not needed, since the reaction was driven to full completion.

Solution A (9.9 M): Cyclohexene

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

Two bottles were filled with solutions A and B. Pump rates were set to 39.2 µL/min and 90.8 µL/min respectively. The experiment was run for 142 min at a reactor temperature of 60°C. Solvent and excess reagent from the collected reaction mixture was removed under reduced pressure, the residue treated with 20 mL 5 M NaOH at 60°C for 45 minutes and neutralised with aqueous HCl. Solvent was removed under reduced pressure, the product extracted from the residue with ethyl acetate (4 x 30 mL), dried, filtered and solvent removed to yield 5.81 g *trans*-1,2-cyclohexadiol in a 91% yield.