Application Note 15.1

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 translated from batch to continuous flow in the *Flow*Start microreactor platform, providing a viable alternative to the conventional batch process.

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.

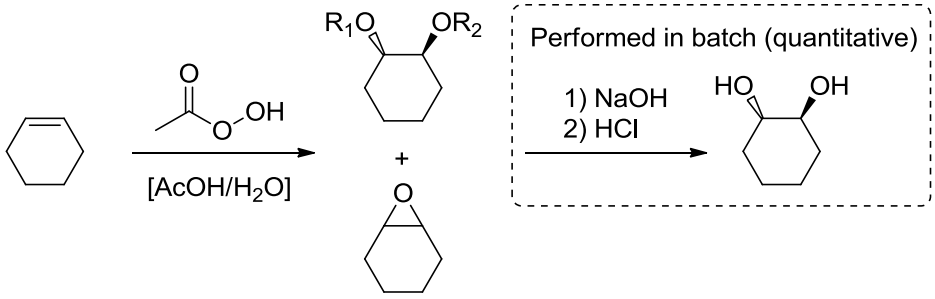


Figure 1: Epoxidation and hydrolysis of model substrate (R_1 = H, acetyl; R_2 = H, acetyl).

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:
   a) Stock solutions approach, yielding a homogeneous reaction mixture.
   b) Quenching solution to follow the reaction in time.
   c) Flow markers approach to accurately assess reaction parameters.
2) Automated reaction optimisation.
3) Out scaling to preparative synthesis.

This *application note* describes the translation of the batch process to the continuous flow process using the *Flow*Start B-200.

Batch to flow conversion

In contrast to batch chemistry, reactions in continuous flow are conducted from stock solutions. These solutions should remain inactive after preparation, but react when combined. In the alkene epoxidation, solution A contains the alkene substrate and solution B contains the peracetic acid reagent. The used flow setup is depicted in Figure 2.

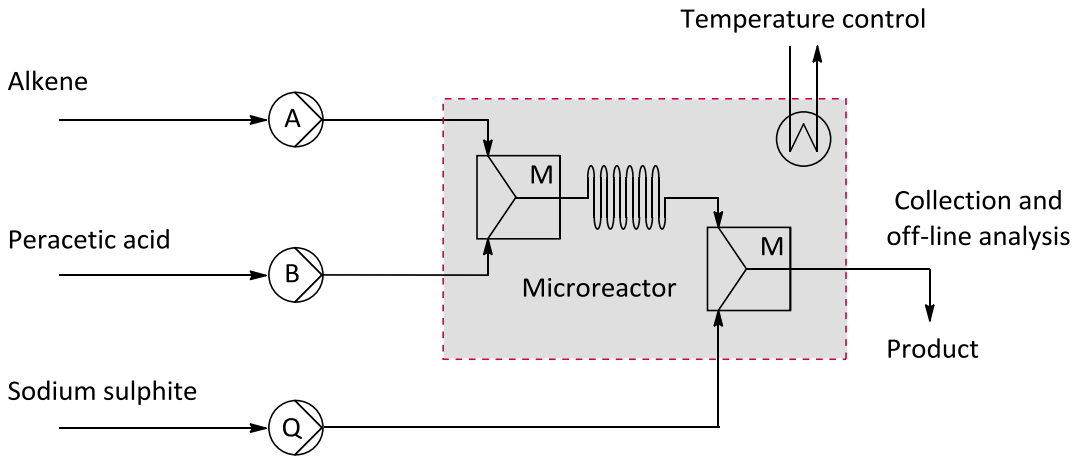


Figure 2: *Flow*Start setup

To stop the reaction at a certain point in time a quenching agent is needed, which reacts with the reagent many times faster than the synthesis reaction itself. In the epoxidation reaction, sodium sulphite is used to remove all leftover peracetic acid by being oxidised to the sulphate species.

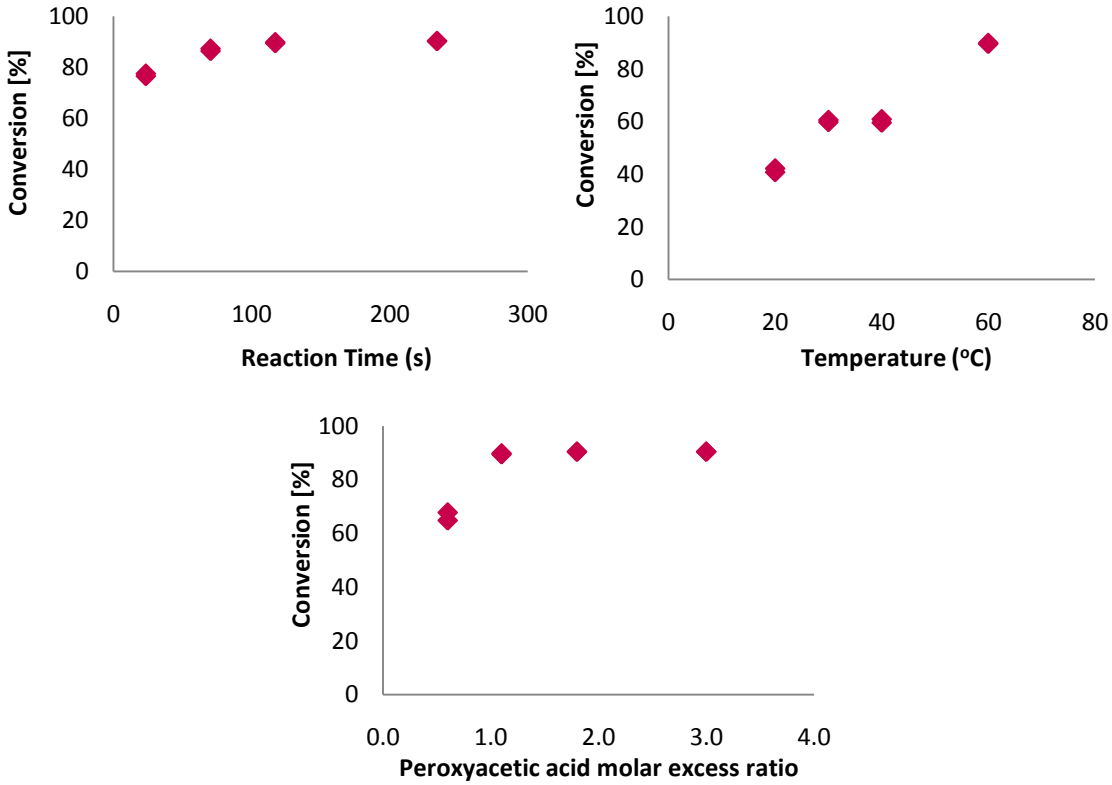


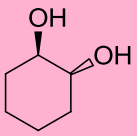
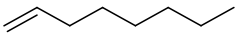
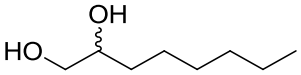
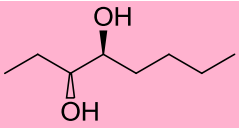
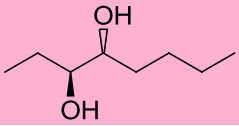
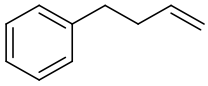
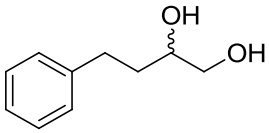
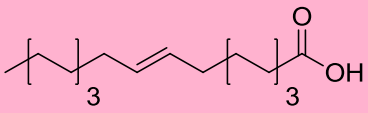
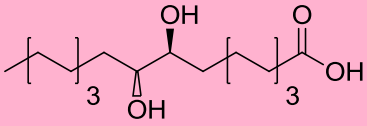
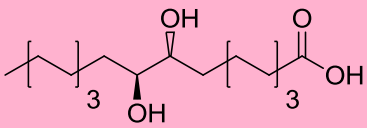
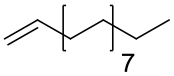
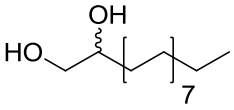
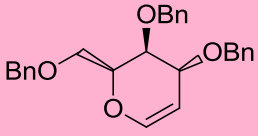
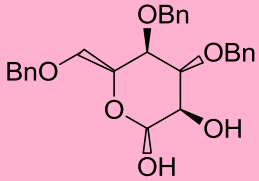
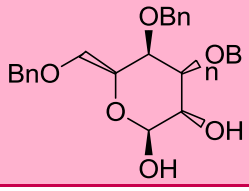
Figure 3: Cyclohexene conversion *vs.* reaction time, temperature and peracetic acid molar excess ratio. Each parameter was varied while keeping the other two at fixed values, which are a reaction time of 117 sec, temperature of 60°C and a peracetic acid molar excess ratio of 1.1. All experiments were conducted in duplicate.

In the *Flow*Start experiments, temperature, peracetic acid molar excess ratio and reaction time were varied. With the above parameter values, alkene conversions up to 90% were observed (Figure 3), and alkene epoxidation was successfully converted from batch to flow.

Other substrates

A variety of terminal and non-terminal alkenes were subjected to the epoxidation reaction. The results are presented in Table 1.

Table 1: Epoxidation of a variety of alkene substrates at reaction time t_R, temperature T and molar excess ratio S.

Substrate	*Product(s)*	*Results*
Cyclohexene 		90% alkene conversion, 82% isolated yield after batch hydrolysis @ t_R = 2.0 min, T = 60°C, S = 1.1
1-Octene 		46% alkene conversion @ t_R = 10 min, T = 65°C, S = 1.1
***trans*-3-Octene** 	 and 	100% alkene conversion @ t_R = 10 min, T = 65°C, S = 1.1
4-Phenyl-1-butene 		100% alkene conversion @ t_R = 5 min, T = 75°C, S = 1.1
Oleic acid 	 and 	'almost complete' alkene conversion @ t_R = 5 min, T = 80°C, S = 1.1
1-Octadecene 		substrate partially converted (not quantified) @ t_R = 10 min, T = 85°C, S = 1.1
Tri-O-benzyl-D-glucal 	 and 	100% alkene conversion @ t_R = 5 min, T = 65°C, S = 1.6

Method

All experiments were conducted in a standard FutureChemistry B-200 *Flow*Start setup, using the Basic Quench Microreactor with internal volume of 92 µL. Cyclohexene was used as model substrate.

Solution A (9.9 M): Cyclohexene

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, the desired flow rates were calculated according to the following equations:

Total flow = microreactor volume / reaction time

Flow A = total flow / (1 + peracetic acid molar excess ratio)

Flow B = Flow Q / quench molar excess ratio = Flow A * peracetic acid molar excess ratio

Cyclohexene conversion was determined by collecting the microreactor outflow into a GC vial containing dichloromethane and sampling the organic layer.

Conversion of the reaction mixture to the corresponding trans-diol was obtained by evaporating excess (per)acetic acid and water, and subsequent treatment of the residue with a 5 M NaOH solution (2 equivalents). After neutralisation with aqueous HCl and evaporation to dryness, the diol was extracted from the residue with ethyl acetate, dried, filtered, and evaporated to dryness to yield the diol in a quantitative yield.

All product mixtures were analysed with GC, with retention times according to Table 2. 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 2: GC analysis retention times

Compound	Function	Retention time [min]
cyclohexene	substrate	0.59
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