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Prilezhaev Dihydroxylation of Olefins in a Continuous Flow Process

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Epoxidation of both terminal and non-terminal olefins with peroxy acids is a well-established and powerful tool in a wide variety of chemical processes. In an additional step, the epoxide can be readily converted into the corresponding *trans*-diol. Batch-wise scale-up, however, is often troublesome because of the thermal instability and explosive character of the peroxy acids involved. This article describes the design and semi-automated optimization of a continuous flow process and subsequent scale-up to preparative production volumes in an intrinsically safe manner.

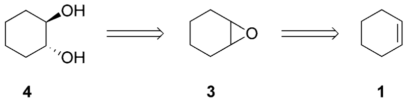
Introduction

The Prilezhaev dihydroxylation is a transformation often used in organic synthesis for the epoxidation of olefins and subsequent hydrolysis into the corresponding *trans*-diol.[1] In this reaction, a peroxy acid is formed in situ by mixing the carboxylic acid with hydrogen peroxide and sulfuric acid.[2] After addition of the olefin, basic hydrolysis to the diol is performed by addition of sodium hydroxide. This method, however, is laborious, and the thermal instability and explosive character of the peroxides, especially in a basic environment, render the scale-up difficult. Since its first publication in 1909, several attempts have been made to simplify the oxidation, and several alternative oxidizing agents, such as *meta*-chloroperoxybenzoic acid (*m*-CPBA), have become commercially available.[3–10] In addition to oxidation with peroxy acids, selective epoxidation of olefins by alkyl hydroperoxidases catalyzed by d^0-metal complexes (Mo^{VI}, V^{V}, and Ti^{IV}) has been developed for the manufacture of propylene oxide.[11] Both types of oxidizing agents and catalysts are rather expensive, and many of these oxidation processes suffer from the same thermal instability,[12] making them unsuitable for most industrial applications. Continuous-flow microreactors can circumvent the aforementioned problems. In a microreactor, reactions take place on a microliter scale so that only small amounts of peroxy acid are present during the process.[13] We envisioned that a flow-chemistry approach would eventually enable us to perform the Prilezhaev dihydroxylation on an industrial scale with enhanced safety because the actual active reaction volume remains within several milliliters.

In 2007, Hartung, Keane, and Kraft demonstrated the feasibility of the oxidation of cyclohexene with in situ-prepared peroxy formic acid in a qualitative continuous flow set up using HPLC-tubing. In an additional step, the epoxide was converted into *trans*-cyclohexane-1,2-diol.[14] Based on these results, we decided to develop a more widely applicable method for the oxidation of olefins in flow by using the commercially available peroxy acetic acid. This quantitative method involves full optimization of reaction parameters including temperature, reaction time, molar ratio (MR), and solvent. Secondly, a flow method for epoxide hydrolysis has been investigated. The combined process has also been successfully applied to a variety of substrates.

Results and Discussion

We chose to investigate the dihydroxylation of cyclohexene (**1**) (Scheme 1) as a generally applicable procedure for the dihydroxylation of olefins using peroxy acetic acid (**2**) as the oxidant. In a later stage, the resulting epoxide **3** was then converted into *trans*-cyclohexane-1,2-diol (**4**).



Scheme 1. Prilezhaev dihydroxylation of cyclohexene (**1**).

In the batch procedure, peroxy acetic acid and cyclohexene (MR = 1:1) were stirred at 60 °C (Scheme 2); after 4 h, the reaction was quenched by using an aqueous solution of sodium sulfite (1 M). A quantitative conversion of cyclohexene was observed resulting in epoxide **3** (54%) and *trans*-diol **4** (36%), as analyzed by using GC. In addition, diester **5** and monoester **6**

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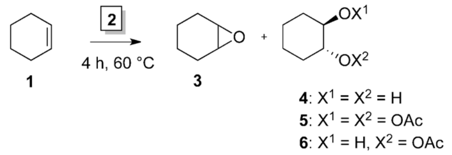


Scheme 2. Epoxidation of cyclohexene in-flow.

were obtained as minor side-products. The large amount of diol observed was probably caused by acid hydrolysis during the reaction. In flow, a similar yield of the epoxide (67%) was obtained, but because of effective heat transfer in the reactor, the reaction time could be significantly decreased to 5 min when heated to 60 °C. Moreover, only 10% of the diol together with traceable amounts of **5** and **6** was observed under these conditions.

In a continuous flow process (Figure 1), cyclohexene and toluene (internal standard; syringe A) were mixed (**M**) with a peroxy acetic acid solution (syringe B) for the oxidation reaction to proceed. The reaction was quenched by using an aqueous solution of sodium sulfite (syringe Q), and the reaction mixture was collected in a mixture of acetone/H_2O (1:1, *v*/*v*). The reactor had an internal volume of 92 μL, a channel width of 600 μm, a channel depth of 500 μm, and an effective channel length of 360 mm. The channel layout contained two mixing units (**M**) of the folding-flow type.[15] The reactor temperature was controlled by using Peltier elements and sensed by using a Pt1000 temperature sensor.

A full optimization study was performed based on a reaction time range ($t_r = 60$, 108, 180, 300 s), temperature range ($T = 25$, 36, 48, 60 °C), and molar ratios of peroxy acetic acid to cyclohexene (MR = 0.6, 1.4, 2.2) spread across the optimization region.[16,17] From these ranges, 50 data points (including duplicates and triplicates) were selected using a D-optimal algorithm. All experiments were performed in random order, and the collected samples were analyzed at-line by using GC. The GC results were normalized and fitted to a third-order polynomial model. In house-developed FlowFit software[18] was used to calculate the best possible model fit to provide a set of optimal values for the reaction parameters. The results are visualized in 2D-contour plots (Figure 2). The optimal reaction conditions according to the model fit led to full conversion of cyclohexene in a reaction time of 300 s, a temperature of 60 °C, and a molar ratio of 1.2. However, from this model, various optimal parameter sets can be selected, depending on the demands that have to be satisfied.

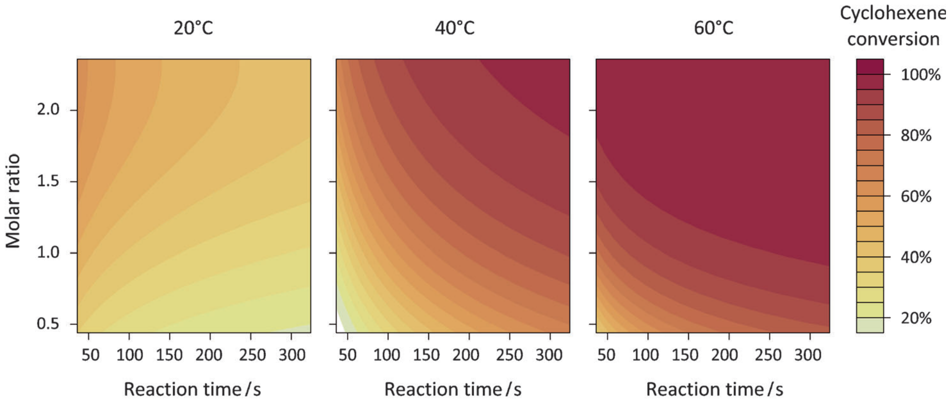


Figure 2. Contour plots of reaction-optimization model fit.

An in-line flow approach for epoxide hydrolysis and ester saponification was investigated (Figure 3). Quenching was not required as the reaction was driven to full completion; the quench inlet was used to add an aqueous solution of sodium hydroxide (5 equiv, 3.5 M) to the crude reaction mixture to hydrolyze the epoxide along with saponification of the mono- and diesters. Although hydrolysis proceeded quantitatively, the large amount of salts formed in the second reaction led to repetitive clogging of the reactor. Therefore, it was decided to collect the epoxide in a solution of sodium hydroxide (3.5 M) (Figure 3). A fast hydrolysis to a nearly quantitative conversion of *trans*-cyclohexane-1,2-diol (**4**) was observed when starting from cyclohexene (**1**). Traceable amounts of mono- and diester were also obtained, but a full conversion to the diol was accomplished after standing for an additional 2 h (Scheme 3).

Scale-up of batch processes generally poses a variety of problems, as heat conduction and mixing greatly differ with reactor size. In batch chemistry, small-scale reactions are usually

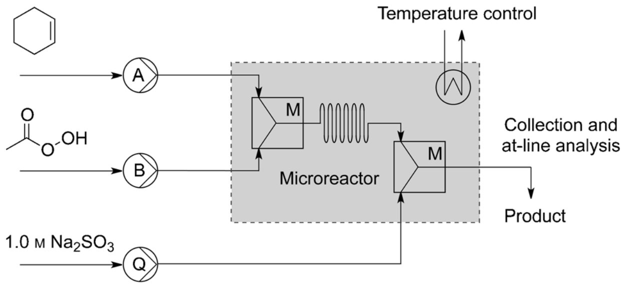


Figure 1. Microreactor design for epoxide optimization.

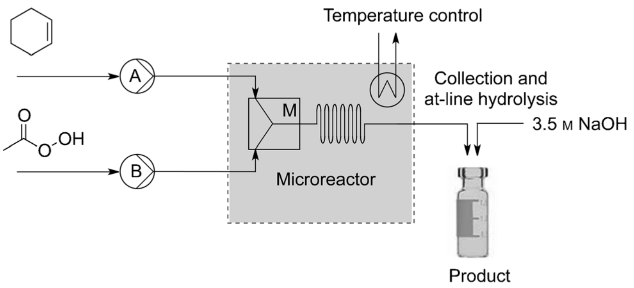
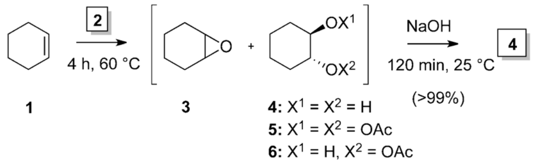


Figure 3. Microreactor design for olefin dihydroxylation.



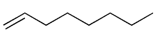
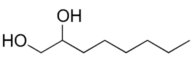
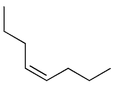
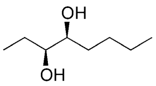
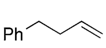
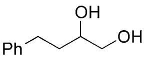
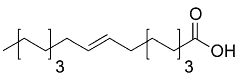
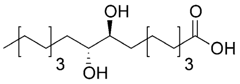
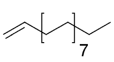
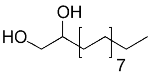
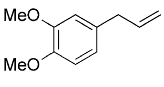
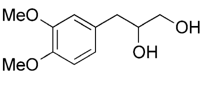
Scheme 3. Epoxide hydrolysis in-flow.

conducted by organic chemists, whereas large-scale reactions are performed by chemical engineers. By using flow chemistry, scale-up is a one-to-one process in most cases, eliminating the need for a different viewpoint on reaction conditions and practical concerns between small- and large-scale.

By using the optimal conditions obtained from the optimization data, a preparative synthesis of the target compound (*trans*-cyclohexane-1,2-diol) resulted in continuous production at a 2.46 g h^{-1} rate when using Uniqsis FlowSyn with a reactor having an internal volume of 650 µL. If required, the production can readily be scaled-up to higher rates by using parallel reactors.

Based on the optimal conditions obtained in the dihydroxylation of cyclohexene (**1**), a range of different substrates were screened, containing both terminal and internal olefins (Table 1). Initially, substrates **7**, **9**, and **11** were oxidized by using the previously found optimal conditions. The latter substrates, however, appeared to be less reactive than cyclohexene, which results in low to moderate yields ranging from 5–64 %. Extended reaction times and slightly higher temperatures were used for the preparative-scale experiments. Dihydroxylation of the terminal olefin 4-phenyl-1-butene (**11**, entry 3) on a 100 mg scale resulted in a satisfactory isolated yield of 74 %. Conversely, the terminal olefins 1-octene (**7**, entry 1) and methyl eugenol (**17**, entry 6) appeared slightly less reactive, resulting in somewhat lower yields of 25 and 31 %, respectively, together with a substantial amount of starting material. Oxidation of 1-octadecene (**15**, entry 5) gave only trace amounts of the product, which can be probably attributed to a low solubility of the lipophilic olefin in the aqueous solvent mixture. The internal olefins (*Z*)-4-octene (**9**, entry 2) and oleic acid (**13**, entry 4) were readily dihydroxylated in good to high isolated yields of 65 and 99 %, respectively.

Table 1. Screening of terminal and non-terminal olefins.

Entry	Substrate	Product	Isolated yield
1			25 % $t = 10$ min $T = 65$ °C MR = 1.2
2			65 % $t = 10$ min $T = 65$ °C MR = 1.2
3			74 % $t = 5$ min $T = 75$ °C MR = 1.2
4			> 99 % $t = 5$ min $T = 60$ °C MR = 1.2
5			< 5 % $t = 5$ min $T = 60$ °C MR = 1.2
6			31 % $t = 5$ min $T = 60$ °C MR = 1.2

Conclusions

It has been demonstrated that the Prilezhaev dihydroxylation can be performed on a large scale in a continuous-flow microreactor system for the oxidation of both terminal and internal olefins. A full optimization study for the epoxidation of cyclohexene was performed by using a D-optimal algorithm for the parametric optimization of reaction time (t_r), temperature (T), and MR. Optimal conditions were reached in a reaction time of 300 s at 60 °C with a molar ratio of 1.2. With the optimal conditions found, an at-line procedure was developed to convert the epoxide in the *trans*-diol. The newly developed method was used to successfully scale-up the dihydroxylation of cyclohexene to continuously produce 2.46 g h^{-1} of *trans*-cyclohexane-1,2-diol (**4**). The overall yield of 82 % showed that the continuous process performs similar to the conventional batch procedure. The major benefits, however, of performing this flow process are better control and therefore less safety risks and a faster overall process, leading to a significantly higher throughput. The process also shows good applicability to a wider range of substituted olefins.

Experimental Section

Reaction optimization

The *Future*Chemistry *Flow*Screen (C-300) automated reaction optimization platform was used to perform the screening of reaction parameters. The set up was identical to the FlowStart B-200, but equipped with a sample collector and software to run automated reaction parameter sequences. A glass syringe with an internal volume of 5 mL and plastic syringes (NORM-JECT) of 10 mL were used, as indicated in Figure 1. Pumps A and B were loaded with cyclohexene (5 mL) and peroxy acetic acid (10 mL), respectively. Pump Q contained an aqueous solution of sodium sulfite (1 M, 10 mL). The quenching and sampling procedure were left unchanged.

Scale-up reaction

A scale-up experiment was performed by using a Uniqsis *Flow*Syn (UQ-1020) equipped with a glass microreactor (0.65 mL) containing folding flow-type mixing units. The general setup was similar to the one depicted in Figure 1, but the quenching feed was omitted. With a flow rate A (cyclohexene) of 39.1 µL min^{-1} and a flow rate B (peroxy acetic acid, 32 % *w/w* in acetic acid/water) of 90.8 µL min^{-1}, a reaction time of 5 min was set to obtain full cyclohexene conversion. In contrast to the optimization, no in-line quenching was used, because the reaction was driven to completion. The reaction mixture was collected for 157 min. Excess peroxy acetic acid from the collected reaction mixture was removed under reduced pressure, and the residue was treated with NaOH (5 м, 20 mL) at 60 °C for 45 min and neutralized with aqueous HCl. The solvent was removed under reduced pressure, and the product was extracted from the residue by using ethyl acetate (4×30 mL) and concentrated to yield *trans*-cyclohexane-1,2-diol (5.81 g, 50.5 mmol) in a 82 % isolated yield, which was comparable to the yield obtained in the batch process (86 %).

GC-analysis

All product mixtures were analyzed by using GC; the retention times were according to Table 1. Analysis was performed by using a Shimadzu GC2010 using a Quadrex 007 1701 apolar column (length 15.0 m, inner diameter 0.10 mm) and a flame-ionization detector ($T = 325\,^{\circ}$C, hydrogen flow rate 60 mL min^{-1}, air flow rate 400 mL min^{-1}), 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).

Experimental procedures

A typical procedure for the oxidation in batch: Cyclohexene (5.61 mL, 55.0 mmol) was slowly added to peroxy acetic acid (12.83 mL, 61.0 mmol, 32 % *w/w*) at room temperature. The reaction mixture was stirred at 60 °C for 4 h. For a quantitative analysis, the reaction was quenched with an aqueous sodium sulfite solution (1 м). The remaining peroxy acetic acid was evaporated, and the residue was treated with an aqueous solution of sodium hydroxide (5 м, 20 mL) at 60 °C for 45 min. The solution was neutralized using hydrochloric acid (1 N) and concentrated in vacuo. The residue was washed with ethyl acetate (4×30 mL) to extract the diol and recrystallized from cyclohexene. Yield: 86 %; m.p.: 101 °C; ^{1}H NMR: $\delta = 1.10$–1.33 (m, 4 H), 1.60–1.75 (m, 2 H), 1.90–2.05 (m, 2 H), 2.10–2.60 (br s, 2 H), 2.35–2.40 ppm (m, 2 H). ^{1}H NMR data are in agreement with literature.[19]

A typical procedure for the oxidation in flow: Peroxy acetic acid (32 % *w/w*; solution B) and an aqueous solution of sodium sulfite (1 м, solution Q) were filled into a 10 mL syringe. Cyclohexene (3.95 mL, 39.0 mmol) and toluene (803 µL, 7.55 mmol) (internal standard) were mixed together and filled into a 5 mL syringe (solution A). The syringes were connected to the *Flow*Start B-200 system and the flows were actuated. For a quantitative analysis, the reaction mixture (100 µL) was collected in acetone/water (400 µL, 1:1).

Keywords: alkenes · dihydroxylation · flow chemistry · microreactors · oxidation

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