Organocatalyzed Epoxidation of Alkenes in Continuous Flow using a Multi-Jet Oscillating Disk Reactor

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Several epoxidation reactions and methods have been reported in the literature,[1] and the majority of these are based on transition metal catalysis. Examples include the Mukaiyama epoxidation,[2, 3] Sharpless epoxidation,[4] and Jacobsen–Katsuki epoxidation.[5] Even though such transition metal-catalyzed processes offer several advantages, a serious disadvantage exists if the epoxide is to be used in the preparation of pharmaceuticals, nutraceuticals, or other food and feed additives: the need for an extensive purification of the synthesized target product. Guidelines from The European Medicines Agency[6] state that the oral permitted exposure to, for example, palladium in the literature,[1] and the majority of these are based on transition metal catalysis. Examples include the Mukaiyama epoxidation,[2, 3] Sharpless epoxidation,[4] and Jacobsen–Katsuki epoxidation.[5] Even though such transition metal-catalyzed processes offer several advantages, a serious disadvantage exists if the epoxide is to be used in the preparation of pharmaceuticals, nutraceuticals, or other food and feed additives: the need for an extensive purification of the synthesized target product. Guidelines from The European Medicines Agency[6] state that the oral permitted exposure to, for example, palladium in the presence of NHPI (1) and 20 μg·kg−1·day−1 respectively. Developing protocols that meet these requirements can be a challenging task, but this can usually be solved by means of classical purification methods. These often involve several consecutive purification steps and/or a combination of several methods. A new, emerging technology known as organic solvent nanofiltration can also be applied,[7] without the need of several repeating steps. However, processing in this manner increases costs and decreases throughput and yield. Competitive organic processes that do not require the use of any transition metals in order to operate exist, but from an industrial point of view these also suffer from a drawback, namely the need for long reactor residence times to reach suitable product yields. This of course limits the efficiency and throughput of the process.

The epoxidation of alkenes via aerobic oxidation with an aldehyde as a co-reagent has been reported by Kaneda and collaborators,[8a] Lassila and collaborators,[8b] and Beak and Jarboe.[8c] The Shi epoxidation gives access to epoxides starting from various alkenes using a fructose-derived organocatalyst with Oxone as the terminal oxidant.[9] Minisci and co-workers disclosed an organocatalyzed epoxidation (Scheme 1) in which N-acetylhydroxyphthalimide (NHPI) serves as catalyst, to obtain epoxides in good to excellent yields.[10] The Minisci epoxidation was demonstrated to operate superbly with α-olefins and cyclic olefins, producing the corresponding epoxides in excellent yields and selectivities, while internal acyclic olefins were proven to be unreactive.

Even though the Minisci epoxidation can be said to be a green and economical process, it also suffers from a disadvantage from an industrial point of view: its low relative efficiency owing to long batch reactor residence times (24–48 h). To overcome this major drawback, we initialized a project for technology transfer, development, and optimization to realize an aerobic epoxidation catalyzed by NHPI (3) under continuous-flow conditions by means of a new technology: the multi-jet oscillating disk (MJOD) reactor.[11] During recent years, we have in our laboratories at the University of Bergen and at Fluens Synthesis designed, manufactured, developed, and investigated an approach for flow organic synthesis that has resulted in this novel reactor platform. A detailed account of the MJOD reactor technology was recently disclosed by us,[11b] but a short description of the MJOD reactor technology follows here.

A 3D drawing of the MJOD reactor that includes the input section, reactor body, output section, and oscillator section is shown in Figure 1. A process flowchart for the experiments disclosed herein is given in Figure 2. The right-hand side of Figure 1 shows a transparent top-down view of the input section, together with a small section of the reactor zone. The MJOD unit is placed in the center of the reactor tube. The outer shell of the reactor body forms a ring-shaped room that encapsulates the whole length of the reactor tube. This room is used for circulating a heating or cooling fluid. Due to the advantages, the reactor net volume versus the heating/cooling surface area ratio of the reactor tube, an exceptionally good heat transfer capacity is achieved. A variable-frequency and variable-amplitude oscillator is used for the vertical “piston movement” of the MJOD unit. An electric motor connected to a cam mechanism is used to power the up–down movement of the MJOD assembly. In addition, the cam assembly provides control of the amplitude by linear translation of the cam assembly to a predefined position (i.e., the distance to the motor shaft). Frequencies in the range of f = 1–10 Hz and amplitudes in the range of A = 0.5–15 mm can be achieved by adjusting the motor speed and the cam assembly. Various types of feeding

Scheme 1. The Minisci epoxidation process.[10]
pumps can be used to feed the substrate, reagents, catalysts, and solvents into the MJOD reactor through the feeding channels of the input section, which is located at the bottom of the vertically placed reactor body. The various reagents and substrates are continuously pumped into the reactor tube via the input section, which implies that the reaction mixture is pushed upwards in the reactor tube (in a plug flow fashion). The reaction mixture successively passes upwards through the jets of the MJOD disks, from one reaction cavity to the next cavity. Together with the up-down movements of the disks, the tightening of the cross section (the small jets in the disks) leads to changes in the rate of liquid flow, which creates an extremely good mixing of the components is achieved by the oscillation of the disks. This study reveals that this is also the case for a two-phase systems, such as a gas/liquid one. The heating and temperature are controlled by a circulation pump connected to the heating/cooling circuit of the MJOD reactor body.

Investigations of the MJOD reactor system in our laboratory have demonstrated an excellent heat and mass transfer capacity for the system, usually concomitant with a substantially increased reaction rate. With these results in hand, we supposed that the reactor system could substantially improve the efficiency of the Minisci epoxidation, and set out to reinvestigate the epoxidation protocol under MJOD continuous-flow conditions.

An MJOD millireactor with a net volume of ca. 51 mL (\(L=1500\) mm, i.d. 10 mm) furnished with \(N=80\) four-jet disks (\(d_{\text{jet}}=2\) mm), forming 79 inter-disk cavities (\(V_{\text{cavity}}\approx0.65\) mL) was used for all experiments described herein. The cross section of the four-jet disk corresponds to the cross section of the tubular reactor, similar to the piston head of an engine (see Figure 1). Four reagent inlet lines were used, three of which were connected to precision piston- or syringe-feeding pumps. The fourth input line was connected to a pressurized gas tank containing molecular oxygen. The \(O_2\) flow was adjusted to a pressure slightly above atmospheric pressure. A process flowchart for the set-up is shown in Figure 2. The ring-room encapsulating the reactor tube was used to circulate water that was heated and regulated by a thermostat (temperatures were selected in the range \(T=20–60\) °C). The oscillator (i.e., the cam mechanism) was tuned to provide oscillations with an amplitude \(A=5\) mm and a frequency \(f=1–3\) Hz.

A series of olefins were investigated in the MJOD reactor system described above. The results are summarized in Table 1. It is evident that the epoxidation process runs with high conversions and yields. Moreover, the process is substantially accelerated, shortening the residence time from 24–48 h (batch process) to only 1–4 h. Using continuous-flow conditions it appears that NHPI plays a key role for both the initiation and propagation steps of the radical chain (Scheme 2). Initially we explored three different olefins: octene, decene, and dodecene, in the presence of 10 mol% NHPI at a reaction temperature \(T=60\) °C and a residence time \(t=1\) h. Subsequently we reduced the quantity of the organocatalyst NHPI to 5 mol% and 2.5 mol%. Figure 3 is a summary of these initial experiments. The results obtained under continuous-flow conditions showed different reactivity and selectivity compared to the results achieved using batch conditions.\(^{[10]}\) In particular, while internal acrylic olefins were unreactive under the reported batch conditions, the corresponding epoxides were achieved in high yields and selectivities when the MJOD reactor technology was used (Table 1, entry 9).

In the specific case of limonene, the stereochemistry for the NHPI-catalyzed aerobic epoxidation was also different, that is, the batch mode provided a cis/trans ratio of 67:33, while the
Continuous-flow mode provided the opposite stereochemistry, with a cis/trans ratio of 40:60, and an additional diepoxide in a yield of 25% (Table 1, entry 4). These results suggest that two different mechanisms operate for the epoxidation: one for the batch mode and another for the continuous flow mode. The proposed mechanism for the batch-mode procedure is outlined in Figure 4. In the initiation step, NHPI undergoes molecule-induced homolysis by the presence of the in situ generated peracetic acid, leading to the formation of the corresponding pthalimido-N-oxyl (PINO) radical. PINO plays a key role in the promotion of the free radical process as it performs a fast hydrogen abstraction from acetaldehyde. The corresponding acyl radical adds to molecular oxygen, affording the acyl peroxyl radical that appears to be the actual operating epoxidizing reagent. The acyl peroxyl radical adds directly to the olefin double bond, which subsequently decomposes to produce the epoxide and carbon dioxide and the methyl radical. The reported mechanism is supported by the observed selectivity under batch conditions, which excludes the involvement of peracetic acid in the epoxidation step.

The peracetic acid must be produced in situ, in competition with the addition of the olefin, by fast acyl peroxyl hydrogen abstraction from NHPI (Scheme 2). In fact, even though we could not determine $k_2$ for this reaction, we expect a value higher than $10^4 \text{M}^{-1} \text{s}^{-1}$, as we have measured a value of $7.2 \times 10^3 \text{M}^{-1} \text{s}^{-1}$ for the hydrogen abstraction from NHPI by tBuOO· radical, and the reaction in Scheme 2 is about 5 kcal mol$^{-1}$ more exothermic ($1 \text{cal} = 4.184 \text{J}$). Nevertheless, according to the observed selectivity under batch conditions, reaction of peracetic acid with NHPI has to be faster than the epoxidation of alkenes. The absence of reactivity for internal olefins can most probably be attributed to a simple steric effect, which inhibits the insertion of the acyl peroxyl radical on the double bond. In fact, although peracetic acid is actually formed in situ by fast acyl peroxyl hydrogen abstraction from NHPI ($k_2 > 10^4$, Scheme 2), it undergoes mole-

**Table 1.** Continuous-flow epoxidation of olefins by aerobic oxidation of acetaldehyde, catalyzed by NHPI. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Product epoxide(s)</th>
<th>$t$ [h]</th>
<th>Yield [%]</th>
<th>Conversion [%]</th>
<th>Selectivity [%]</th>
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<tr>
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<td></td>
<td></td>
<td>1</td>
<td>30</td>
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<td>72</td>
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<td></td>
<td>1</td>
<td>81</td>
<td>90</td>
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</table>

[a] General procedure: olefin (5 mmol), acetaldehyde (15 mmol), and NHPI (0.5 mmol, 10%) were mixed in acetonitrile (10 mL) and pumped into the MJOD reactor system at T = 60 °C. was is introduced to the MJOD reactor at normal atmosphere (1 atm; time shown in the Table). The epoxides were isolated and purified by flash chromatography and characterized by NMR and MS. Spectra were compared to those of authentic samples or data previously disclosed in the literature. [b] Isolated yield. [c] Calculated as mmol(epoxide)/mmol(olefin) × 100%. [d] Calculated based on conversion and yield of product.

**Scheme 2.** Acyl peroxyl hydrogen abstraction from NHPI.
In summary, this study reports an improved Minisci epoxidation process suitable for olefins. The improved process is based on the original batch protocol, redesigned and redeveloped for continuous-flow conditions by using the novel multi-jet oscillating disk (MJOD) reactor technology. While the batch protocol requires a residence time of 24–48 h, the continuous-flow process only requires a residence time of 1–4 h for the same substrates. Without any further optimization of the through flow, the flow protocol possesses a capacity of 1 mL min\(^{-1}\) containing 5 mmol substrate. With a yield of 80% and using one MJOD reactor system as described in this report, this corresponds to a production capacity on the order of 80 g day\(^{-1}\). The reaction mechanism in continuous flow appears to be different from the mechanism that operates in reactions carried out according to batch protocols, but both mechanisms seem to involve NHPI as catalyst (Figure 4).

### Experimental Section

Starting materials, reagents, and solvents were purchased commercially and used without further purification. GLC analyses were performed on a capillary gas chromatograph equipped with a fused silica column (\(L = 25 \text{ m}, \text{i.d.} = 0.20 \text{ mm}, \text{film thickness} = 0.33 \text{ mm}\)) at a helium pressure of 200 kPa, splitless/spilt injector, and a flame ionization detector. Mass spectra were acquired on a GC-MS instrument, using a gas chromatograph equipped with fused silica column (\(L = 30 \text{ m}, 0.25 \text{ mm i.d.}, 0.25 \mu \text{m film thickness}\) and helium as carrier gas. Structure control \(^1\)H NMR spectra were recorded on a NMR spectrometer operating at 400 MHz. Chemical shifts were referenced to internal TMS.

Synthetic procedure. The alkene (5 mmol) was dissolved in CH\(_2\)CN (4 mL) and transferred to reservoir \(\#1 (V_{\text{total}} \approx 5 \text{ mL})\). N-Hydroxysuccinimide (1–10 % w/w) was dissolved in CH\(_2\)CN (6 mL) and heated at 60 °C under good stirring until the organocatalyst was dissolved whereof the solution was cooled at room temperature and acetaldehyde (0.85 mL) was added. This mixture was transferred to the reservoir \(\#2 (V_{\text{total}} \approx 7 \text{ mL})\). Reservoir \(\#3\) was filled with pure solvent, acetonitrile. The oxygen gas flow was adjusted carefully using a bubble glass to achieve 1–2 bubbles. Note that a too vigorously bubbling of oxygen results in a flush-off of the organic components, especially the low boiling component such as acetaldehyde. Control of the oxygen flow should be performed on the inlet at the input section of the reactor. The reactor residence times was regulated by adjusting the flow rate of the feeding pumps.

**Residence time of 1 h.** The flow rate of pump \(\#1\) was tuned to provide a rate of 0.46 mL min\(^{-1}\) and the flow rate of pump \(\#2\) was tuned to provide 0.64 mL min\(^{-1}\). The feeding pumps \(\#1\) & \(\#2\) was run until the two reservoirs were emptied, then switched off at the same time as pump \(\#3\) was switched on to feed the pure solvent at a rate of \(1.1 \text{ mL min}^{-1}\) until a volume of \(\approx 10 \text{ mL}\), corresponding to the total volume of the reacting mixture was collected in the receiving reservoir.

**Residence time of 2 h.** The flow rate of pump \(\#1\) was adjusted to a rate of \(0.92 \text{ mL min}^{-1}\) and the flow rate of feeding pump \(\#2\) was adjusted to \(0.54 \text{ mL min}^{-1}\). The pumps \(\#1\) & \(\#2\) were run until the reservoirs were emptied, then the pump \(\#3\) was switched on to feed the pure solvent at a rate of \(0.55 \text{ mL min}^{-1}\) until a volume of \(\approx 10 \text{ mL}\), corresponding to the total volume of the reacting mixture was collected in the receiving reservoir.

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**Figure 4.** Proposed reaction mechanism for the Minisci epoxidation.

**Scheme 3.** Epoxidation of olefins by peracetic acid.
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