7
Liquid- and Liquid–Liquid-phase Reactions – Oxidations and Reduction

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Oxidation and reduction are fundamental processes in the synthesis of organic and inorganic compounds. Some oxidation and reduction reactions are difficult to control in macro-scale batch reactors and in such cases microflow reactors serve as powerful tools for accomplishing the reactions in a highly controlled manner. This is especially true for many oxidation reactions because of their exothermic nature. It should also be noted that the danger of unexpected explosions can be avoided by the use of microflow reactors because of the small volume and highly efficient heat transfer ability of microflow systems. This chapter provides an overview of oxidation and reduction reactions using chemical, electrochemical and biochemical methods in microflow reactors.

7.1
Oxidation

7.1.1
Chemical Oxidation

Microflow systems serve as effective environments to perform various oxidation reactions using chemical reagents. The oxidation using dimethyl sulfoxide (DMSO), which is known as Moffatt–Swern type oxidation, is one of the most versatile and reliable methods for the oxidation of alcohols into carbonyl compounds in laboratory synthesis [1, 2]. However, it is well known that activation of DMSO leads to an inevitable side-reaction, Pummerer rearrangement, at temperatures above $-30\,^{\circ}C$ (Scheme 7.1). Therefore, the reaction is usually carried out at low temperatures ($-50\,^{\circ}C$ or below), where such a side-reaction is very slow [3, 4]. However, the requirement for such low temperatures causes severe limitations in the industrial use of this highly useful reaction. The use of microflow systems solves the problem. For example, the oxidation of cyclohexanol can be accomplished using a microflow

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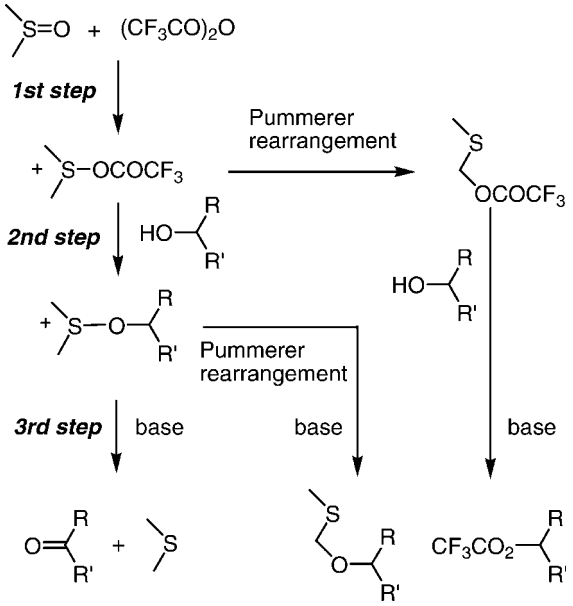


Scheme 7.1 Mechanism of the Swern oxidation using TFAA.

system consisting of micromixers and microtube reactors at room temperature (Figure 7.1) [5].

Oxidation of primary, secondary, cyclic and benzylic alcohols and cyclohexanol also takes place smoothly to give the corresponding carbonyl compounds in good yields and selectivities (Table 7.1). A dramatic effect of the microflow system seems to be attributable to precise temperature control and extremely fast mixing by virtue of a short diffusion path. A short residence time by fast transfer of the reactive intermediate to the next reactor also seems to be essential for the success of the

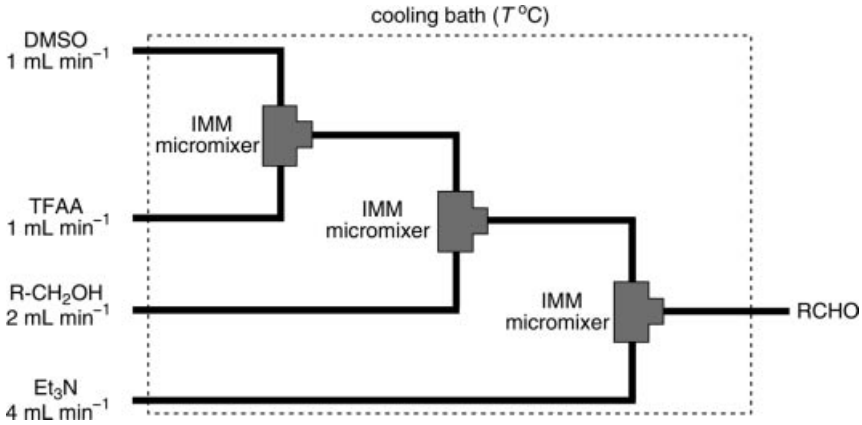
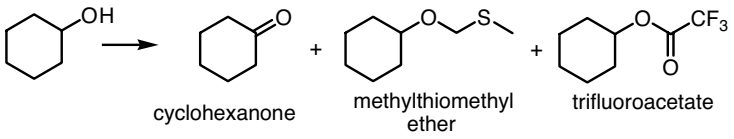


Figure 7.1 Schematic diagram of the microflow system for Swern oxidation.

Table 7.1 Swern oxidation of alcohols by using the microflow system and macrobatch system.

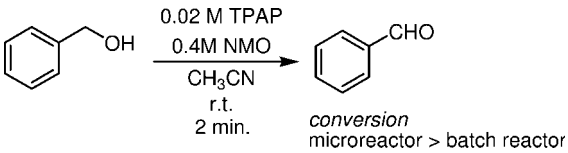


	Temperature (°C)	Residence time (s)	Yield (%)		
			Cyclohexanone	Methylthiomethyl ether	Trifluoroacetate
Batch	−70	–	83	10	5
	−20	–	19	2	70
Microreactor	−20	2.4	88	6	5
	0	2.4	64	6	14
	0	0.01	89	7	1
	20	0.01	88	5	2

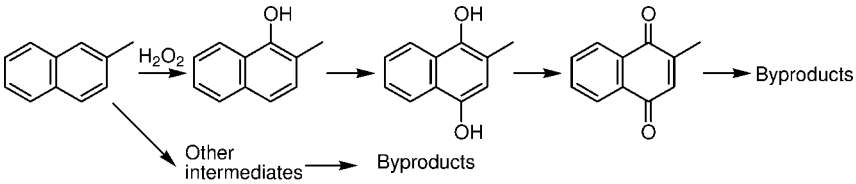
transformation at much higher temperatures that those for the conventional route. Microsystems also serve as a quick means for scale-up, because the quality of the product did not change during the course of scale-up (numbering-up), although batch methods suffer from such a problem.

Microflow systems are also effective for the oxidation of benzyl alcohol to benzaldehyde using a catalytic amount of tetrapropylammmonium perruthenate (TPAP) and a stoichiometric amount of *N*-methylmorpholine-*N*-oxide (NMO) [6]. At a reaction time of 2 min, the conversion of benzyl alcohol in the microreactor is higher than that in the flask (Scheme 7.2).

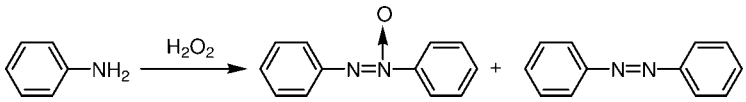
Hydrogen peroxide is one of the best oxidizing agents from viewpoints of environment and economy [7]. Hydrogen peroxide oxidation of 2-methylnaphthalene to 2-methyl-1,4-naphthoquinone, known as antihemorrhagic vitamin, can be carried out using a microflow system, where the oxidation with a high concentration of peroxide at 100 °C can be performed by virtue of precise temperature control [8]. The conversion of 2-methylnaphthalene and the yield of 2-methyl-1,4-naphthoquinone increased in comparison with those for batch system (Scheme 7.3). The reaction time is significantly short (30 s) compared with that in the batch system (15 min). It is noteworthy that the selectivity of the desired product, 2-methyl-1,4-naphthoquinone, is as high as 50% because of the suppression of consecutive side-reactions by virtue of a short residence time.



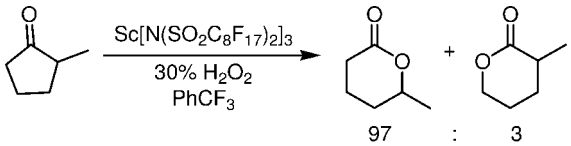
Scheme 7.2 Oxidation of benzyl alcohol by tetrapropylammonium perruthenate.



Scheme 7.3 Oxidation of 2-methylnaphthalene.



Scheme 7.4 Titanium silicalite-1 (TS-1)-catalyzed oxidation of aniline.



Scheme 7.5 Baeyer–Villiger oxidation.

Titanium silicalite-1 (TS-1)-catalyzed H_2O_2 oxidation of aniline gives several important oxygen-containing compounds, including hydroxylamines [9–11]. A multichannel membrane microreactor can be used for the continuous selective oxidation of aniline with hydrogen peroxide on TS-1 nanoparticles (Scheme 7.4) [12]. The product yield and selectivity of azoxybenzene can be improved, although the microreactor operation suffers from bubble formation and hydrogen peroxide decomposition. Titanium silicalite-1 catalyzed epoxidation of 1-pentene with hydrogen peroxides was also carried out in a continuous microfabricated reactor [13–15].

The Baeyer–Villiger reaction catalyzed by scandium bis(perfluorooctanesulfonyl) amide leads to higher yields and regioselectivities than those for analogous batch reactions [16, 17]. For example, the oxidation of 2-methylcyclopentanone gives the corresponding lactones in essentially quantitative yield with high regioselectivity (97:3) (Scheme 7.5).

7.1.2
Electrochemical Oxidation

Electrochemical reactions serve as a powerful method for the oxidation and reduction of organic compounds [18–20], and various redox transformations can be achieved without using chemical reagents. The conventional electrochemical method, however, suffers from several disadvantages such as difficulty in mass transfer on the surface of the electrodes and high ohmic drop between the electrodes [21]. Microflow systems serve as solutions to these problems, by virtue of the inherent advantages of microstructures such as large surface-to-volume ratio. Various types of

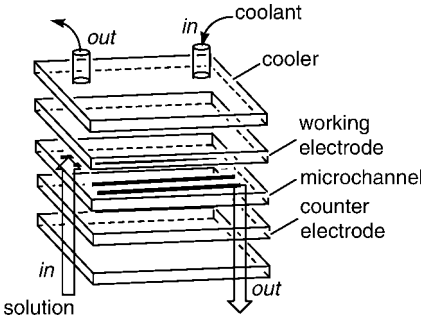
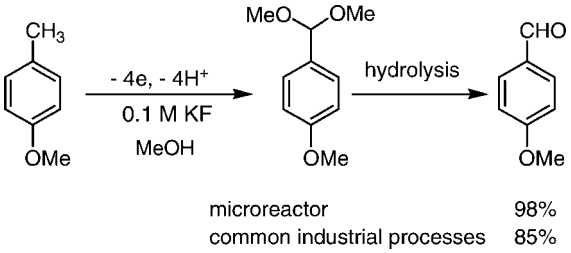


Figure 7.2 Schematic diagram of microreactor for electrochemical synthesis.

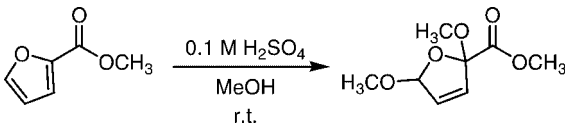
electrochemical micro devices have been developed, including electrochemical detection devices for electrophoresis [22, 23], electrochemical analytical studies [24] and electrogenerated chemiluminescence [25, 26]. Microflow systems for electrochemical synthesis have also been developed and the following part outlines the state of art of electrochemical oxidation using microflow systems. A microreactor for electrochemical synthesis consisted of a plate-to-plate electrode configuration mounted in a non-conducting housing has been developed. The working electrode and the counter electrode are separated using a 75 µm thick polyimide foil between them, as shown in Figure 7.2 [27, 28].

The electrochemical microreactor is fairly effective for the oxidation of *p*-methoxytoluene and 4-methoxybenzaldehyde is obtained after hydrolysis. The efficiency of the microreactor reaction (98%) is higher than that of the common industrial processes (85%) (Scheme 7.6) [29].

Oxidation of furans can be also carried out using a ceramic microflow electrochemical reactor (CEM) using H_2SO_4 as the supporting electrolyte [30]. Scheme 7.7 shows the oxidative methoxylation of methyl 2-furoate.



Scheme 7.6 Electrochemical oxidation of *p*-methoxytoluene followed by hydrolysis.



Scheme 7.7 Electrochemical dimethoxylation of methyl 2-furoate.

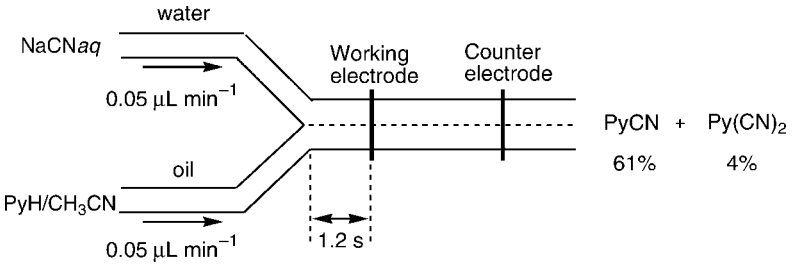


Figure 7.3 Cyanation reaction of PyH in a microchannel.

Oxidation of pyrene (PyH) in the presence of NaCN can be accomplished [31, 32] using polymeric microchannel chips (100 μm wide × 20 μm deep) integrated with the electrode [33–35]. An acetonitrile solution of PyH containing tetrabutylammonium perchlorate and an aqueous NaCN solution are introduced into the chip by pressure-driven flow (Figure 7.3). PyH is then oxidized at the working band electrode in the channel. Under the optimum conditions, 1-cyanopyrene (PyCN) is produced very efficiently (61% yield). The PyCN:$Py(CN)_2$ ratio is 15.3 in the microchannel chip, whereas it is 2.9 in the bulk.

PyCN can be obtained as the sole product by using the electrochemical microreactor shown in Figure 7.4.

The electrochemical method is also effective for the oxidation of heteroatom compounds. For example, oxidation of carbamates using a microflow electrochemical cell leads to the formation of *N*-acyliminium ion, which is allowed to react with various carbon nucleophiles such as allylsilanes in the flow system (Figure 7.5). This is a microflow version of the "cation pool" method, in which highly reactive organic cations are generated and accumulated in the absence of nucleophile and are allowed to react with nucleophiles in the next step [36–47]. The microflow version is called the "cation flow" method [48, 49]. The "cation flow" method can be applied, in principle, to more reactive and unstable organic cations, which are difficult to accumulate in a macro-scale batch system.

The generation of the cation can be monitored using an FTIR spectrometer (ATR method) equipped with a low-temperature flow cell attached to the outlet of the electrochemical microflow reactor. The absorption at 1814 cm^{-1}, which is assigned as the C=O vibration, increases with increase in the electric current. An interesting application of the "cation flow" method is continuous sequential combinatorial

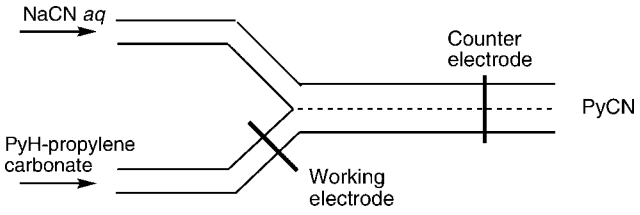


Figure 7.4 Cyanation reaction of PyH in a microchannel with a different configuration.

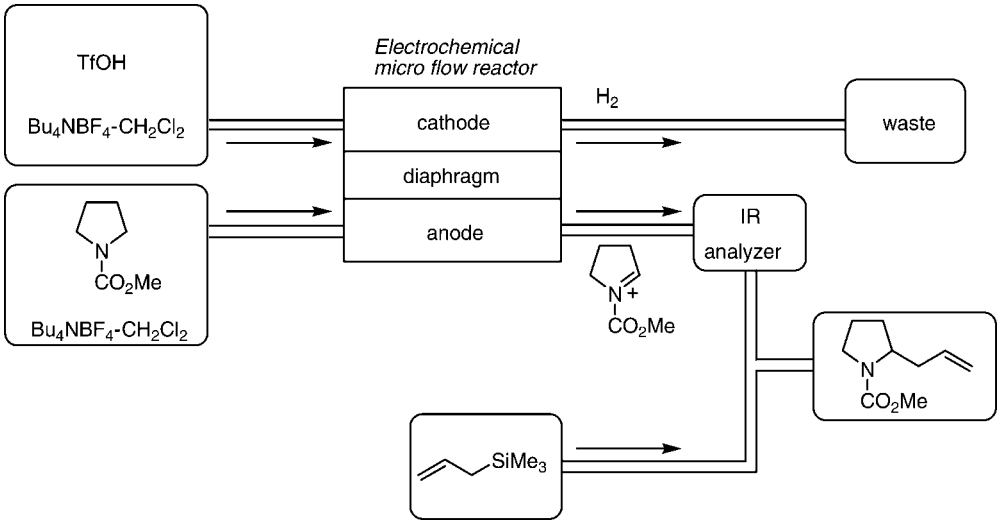


Figure 7.5 Schematic diagram of the "cation flow" system.

synthesis based on simple flow switching as shown in Figure 7.6 [50]. In the first step, the cation flow generated from a carbamate is allowed to react with nucleophiles in a sequential fashion. In the next step, the precursor of the cation is switched to a different carbamate and the cation flow generated is allowed to react with nucleophiles sequentially. Then the precursor of the cation is switched to a different one and the cation flow is allowed to react with nucleophiles sequentially. Hence 3×3 combinatorial synthesis can be accomplished with one flow system.

It is noteworthy that both anodic and cathodic reactions can be used for desired transformations in some cases. For example, the anodic oxidation of silyl-substituted carbamates can be combined with the cathodic reduction of allylic halides in the presence of chlorotrimethylsilane (paired electrolysis) [51]. The products of both reactions, i.e. *N*-acyliminium ion and the allylic silane, are then allowed to react with each other to obtain a final coupling product (Table 7.2).

Let us briefly consider electrochemical synthesis without an added electrolyte. The use of supporting electrolytes is one of the major problems in electrochemical synthesis. Although various electrolyte-free electrochemical systems have been developed [52–61], an approach based on microchemical systems is attractive [62]. A high electrode surface area to reactor volume and a short distance between electrodes are advantageous from the viewpoints of conductivity and reaction efficiency. One of the most typical microflow electrochemical cells has a parallel electrode configuration. Two electrodes are placed facing each other at a distance of the order of micrometers and the substrate solution flows through the chamber between them (Figure 7.7). Therefore, the liquid flow and the current flow are perpendicular. By using this microflow electrochemical cell, one-electron oxidation of ferrocene and the two-electron–two-proton reduction of tetraethyl ethylenetetracarboxylate in ethanol can be achieved without intentionally added electrolyte [63].

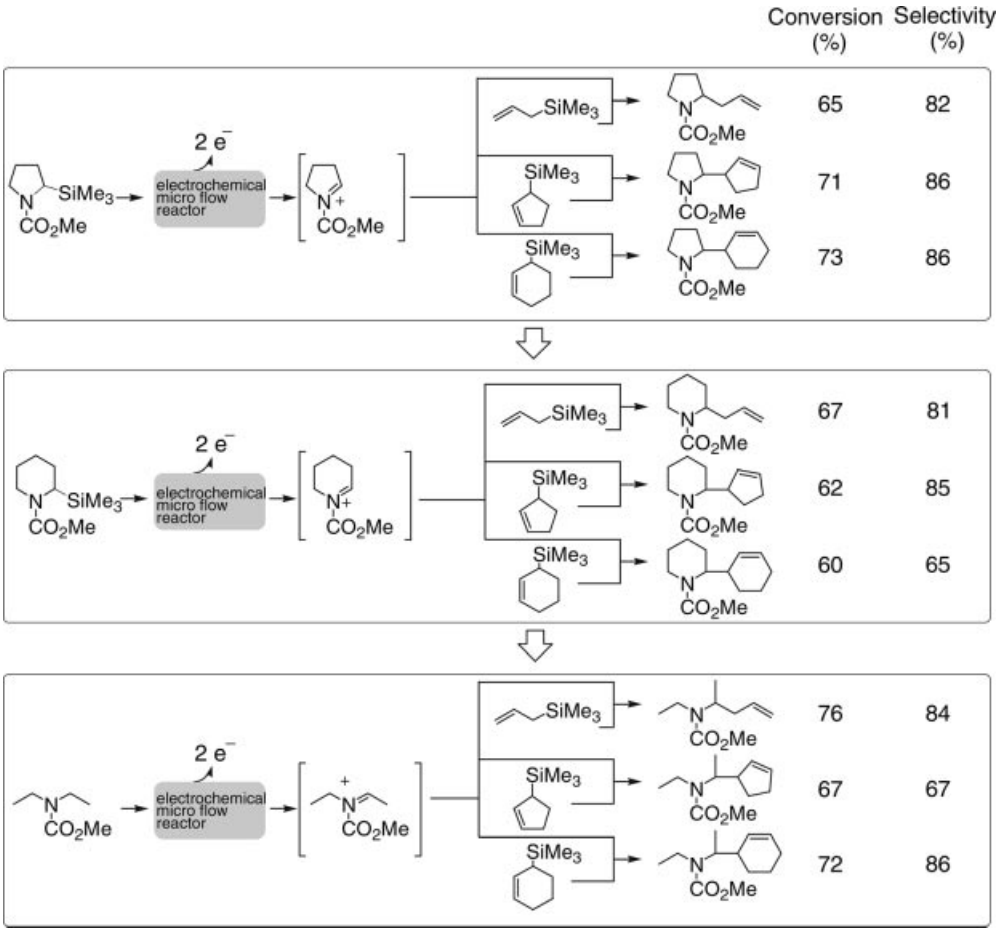
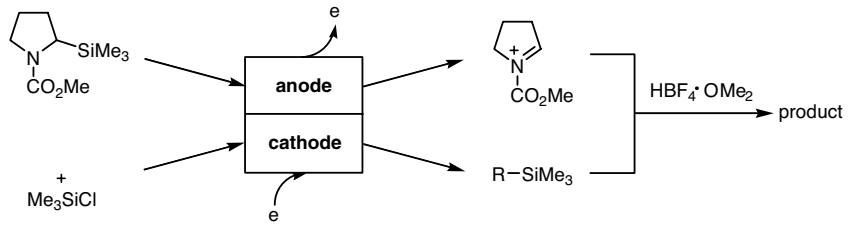
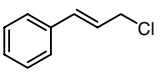
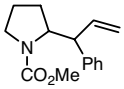
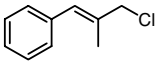
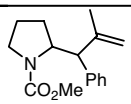
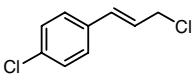
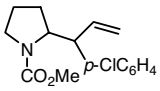
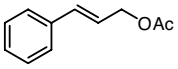
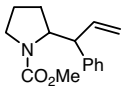
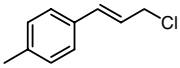
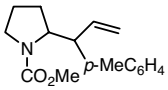


Figure 7.6 Continuous serial combinatorial synthesis using the "cation flow" system.

There is another type of microflow cell that is used for electrolyte-free electrolysis [64]. Two carbon fiber electrodes are separated by a spacer (porous PTFE membrane, pore size 3 μm, thickness 75 μm) at a distance of the order of micrometers. A substrate solution is fed into the anodic chamber where the oxidation takes place. The anodic solution flows through the spacer membrane into the cathodic chamber where the reduction takes place. The product solution leaves the cell from the cathodic chamber. In this cell, the electric current flow and the liquid flow are parallel. The effectiveness of the cell is shown by the oxidation of *p*-methoxytoluene. A solution of *p*-methoxytoluene in methanol is fed into the electrochemical microflow system and the reaction is carried out under constant current conditions to obtain the desired product in more than 90% yield based on consumed starting material (Figure 7.8). The microflow system can also be used for the oxidative methoxylation of *N*-methoxycarbonylpyrrolidine and acenaphthylene.

Table 7.2 Coupling of an *N*-acyliminium ion and an allylic silane generated by using a paired electrochemical microsystem.



R–X	Product	Yield (%)	R–X	Product	Yield (%)
		79			49
		53			43
		47			

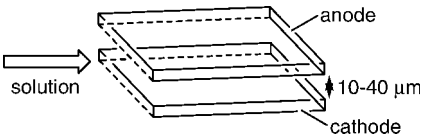


Figure 7.7 Electrochemical microflow process without adding supporting electrolyte.

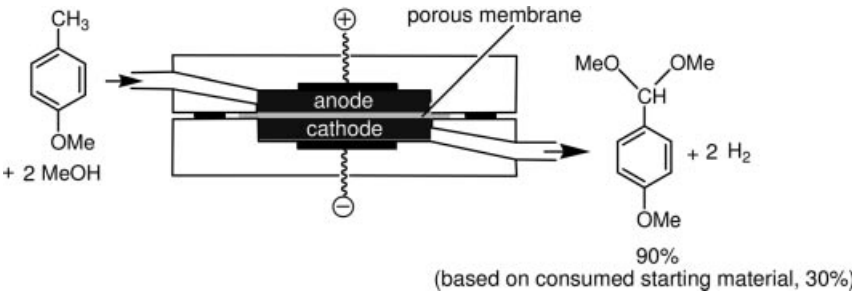


Figure 7.8 Methoxylation of *N*-methoxycarbonyl pyrrolidine.

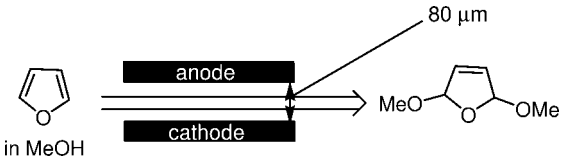


Figure 7.9 Electrochemical oxidation of furans.

Electrochemical oxidation of furans can also been carried out without intentionally added electrolyte using a microflow system. In this case, an electrochemical thin-layer flow cell, which has a simple geometry with a glassy carbon anode and a platinum cathode directly facing each other at a distance of 80 μm apart is used (Figure 7.9) [65, 66]. 2,5-Dimethoxy-2,5-dihydrofuran is obtained in 98% yield by the oxidation of furan in methanol solvent. Similar electrochemical methoxylation and acetoxylation of various organic molecules can also be carried out using this system.

7.1.3 Biochemical Oxidation

Enzymatic reactions have attracted significant research interest because of their environmentally friendly nature. Microflow systems can serve as efficient tools for the development of enzyme processes [67].

The peroxidase-catalyzed reaction of 3,3′-diaminobenzidine tetrahydrochloride (DAB) with sodium *N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-3-methylaniline, 4-aminoantipyrine and H_2O_2 can be achieved in a stopped-flow microreactor using photothermal temperature control and equipped with an IR diode laser (Figure 7.10) [68, 69]. The time to reach the end of the reaction in the microchip is half of that in a batch process.

Oxidation of xanthine with H_2O_2 is achieved using microreactors with immobilized xanthine oxidase (Scheme 7.8). The reactors can be used for the detection of xanthine using chemiluminescence [70].

Oxidation reaction of glucose is achieved with microfluidic channels fabricated from poly(dimethylsiloxane) (PDMS) using immobilized microbead-supported

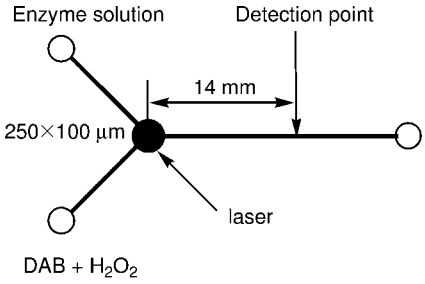
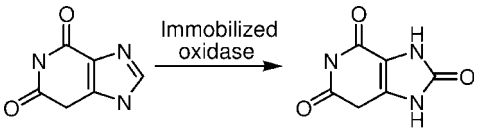


Figure 7.10 Peroxidase-catalyzed reaction of 3,3′-diaminobenzidine tetrahydrochloride (DAB) with H_2O_2.



Scheme 7.8 Oxidative reaction of xanthine using microreactors with immobilized xanthine oxidase.

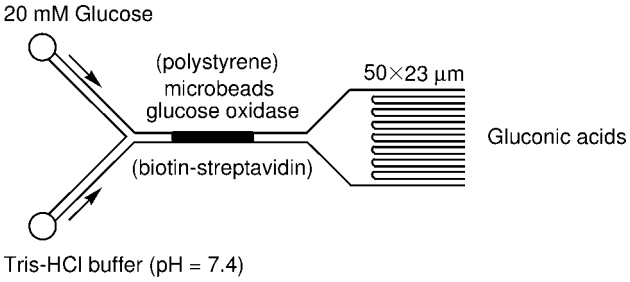


Figure 7.11 Oxidative reaction of glucose.

glucose oxidase and biotin-labeled glucose oxidase (GOX) on microbeads coated with streptavidin (Figure 7.11) [71]. Multistep reactions can be also carried out by connecting multiple reactors having different immobilized microbead-supported enzymes.

P450-catalyzed polyketide hydroxylation is achieved in a microfluidic channel using an enzyme immobilized on Ni–NTA agarose beads (Figure 7.12) [72]. The use

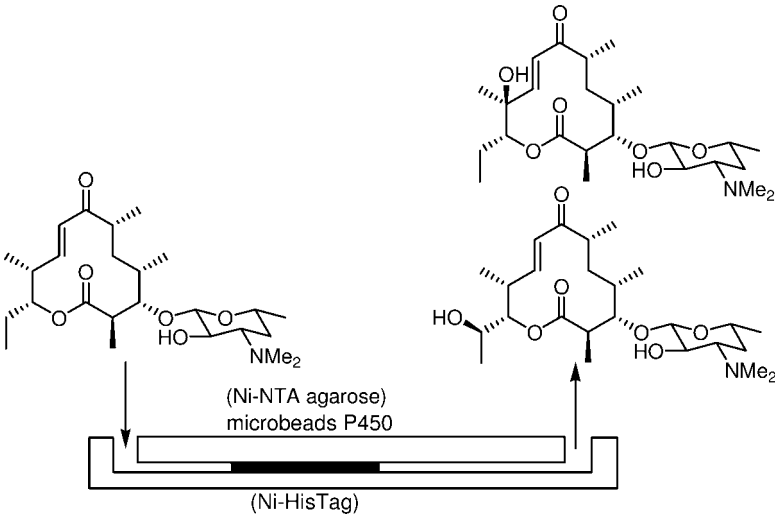


Figure 7.12 P450-catalyzed polyketide hydroxylation in a microfluidic channel using immobilized microbead-supported enzyme.

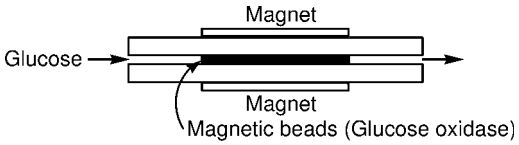


Figure 7.13 Enzyme-immobilized magnetic microparticles.

of the microreactor with the immobilized enzyme permits rapid hydroxylation of the macrolide YC-17 to methymycin and neomethymycin.

Immobilization of enzymes in microchannels can be achieved using magnetic power. Enzyme-immobilized magnetic microparticles (EMMP) are introduced into a microchannel and are retained there by using small permanent magnets as shown in Figure 7.13 [73]. The system can be used for the assay of glucose. The oxidation of glucose with immobilized glucose oxidase (GOx) produces hydrogen peroxide, the amount which is determined by the amperometric analysis.

Oxidative homocoupling of 4-hydroxy-3-methoxyphenylacetic acid using H_2O_2 is achieved using a miniaturized reactor having peroxidase immobilized on alumina surfaces to give 2,2′-dihydroxy-3,3′-dimethoxybiphenyl-5,5′-diacetic acid (Figure 7.14) [74].

Although the use of microbead-supported enzymes is fairly easy for small-scale reactions [75–92], large-scale processing suffers from problems such as increasing pressure. There is another method, i.e. immobilization of enzymes on the surface of the microchannel wall. This method enjoys the advantage of high surface area to volume ratio of microstructures and solves the pressure drop problem. For example, a microreactor having streptavidin-conjugated enzyme linked to biotinylated phospholipid bilayers coated inside poly(dimethylsiloxane) microchannels

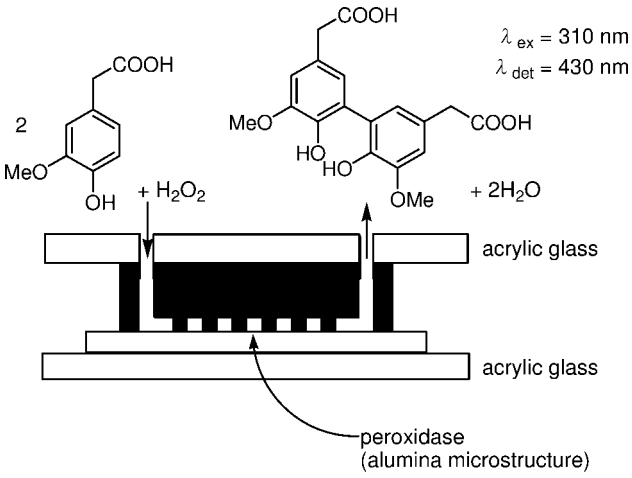


Figure 7.14 Reaction of 4-hydroxy-3-methoxyphenylacetic acid and hydrogen peroxide using a miniaturized peroxidase reactor.

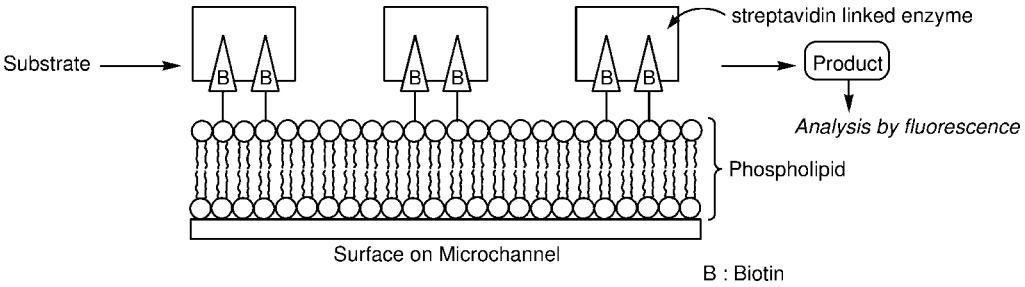
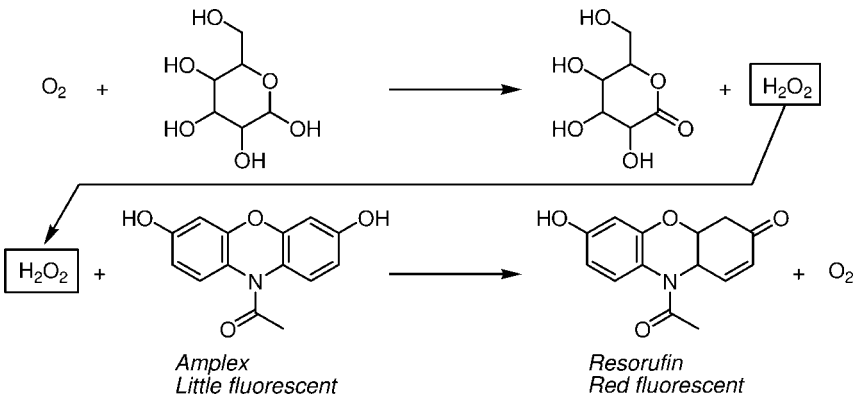


Figure 7.15 Immobilized avidin-conjugated glucose oxidase.

(Figure 7.15) is used for analysis. The presence of glucose can be detected by two coupled steps employing immobilized avidin-conjugated glucose oxidase and streptavidin-conjugated horseradish peroxidase [93, 94]. The process can be operated by employing glucose oxidase in the first step to oxidize glucose to gluconolactone and hydrogen peroxide, which are used in a second step to convert the low-fluorescent Amplex molecule into a highly fluorescent red resorufin molecule (Scheme 7.9).

A membrane inside a microchannel can serve as an effective support for an enzyme. A chemically functionalized polymer membrane can be produced by an interfacial polycondensation reaction using multilayer flow inside a microchannel (Figure 7.16) [95]. Single and parallel dual-membrane structures can be successfully prepared by using organic–aqueous two-layer flow and organic–aqueous–organic three-layer flow inside the microchannel followed by an interfacial polycondensation reaction. By using the inner-channel membrane, horseradish peroxidase can be immobilized on one side of the membrane surface to integrate the chemical transform function on to the inner-channel membrane.

Enzymatic reaction of *N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-*m*-toluidine (TOOS) and 4-aminoantipyrine (4-AAP) with H_2O_2 at the membrane surface can be successfully performed using this system (Figure 7.17).



Scheme 7.9 Oxidation of glucose to gluconolactone.

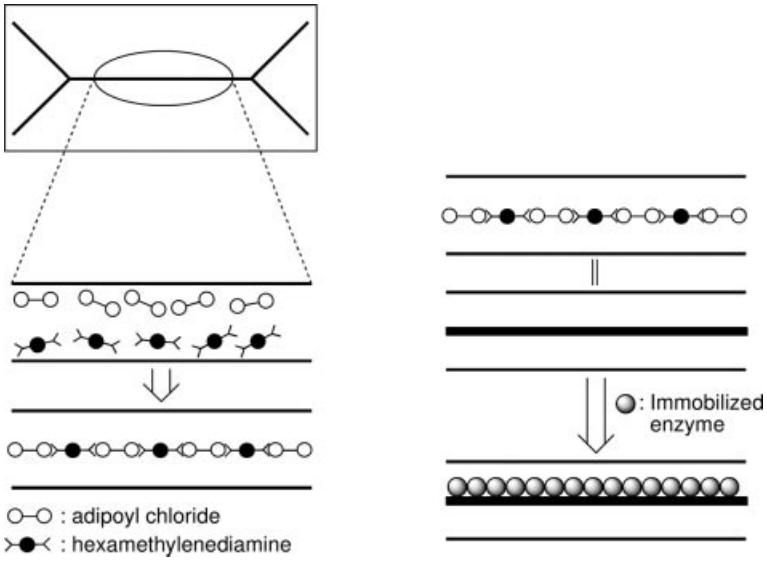


Figure 7.16 Design and synthesis of a chemically functional polymer membrane by an interfacial polycondensation reaction and multilayer flow inside a microchannel.

7.1.4
Miscellaneous Oxidations

Recently, ionic liquids have been employed as solvents in many catalytic processes, because they provide effective media for reactions involving ionic intermediates. Easy separation of organic products from ionic liquids is also advantageous. An efficient and rapid method for the oxidation of cyclohexene in an ionic liquid medium has been developed using a microreactor (length of the channel of the microreactor 3 cm, width 200 μm, depth 50 μm) (Scheme 7.10) [96, 99]. The yield of product is higher than that with conventional batch reactors. The water-soluble ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate is used to improve the solubility of cyclohexene in the reaction buffer.

An efficient oxidation of glucose to gluconic acid in phosphate buffer solution can be performed using a porous gold(0) catalyst in a Pyrex capillary tubing microreactor (Figure 7.18) [98]. The yield increases with increase in reaction time. A pH range of

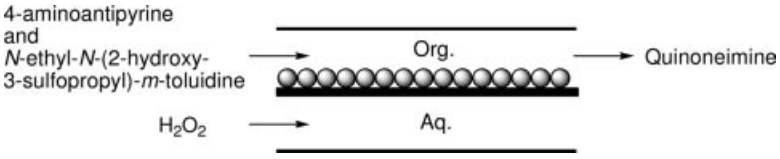
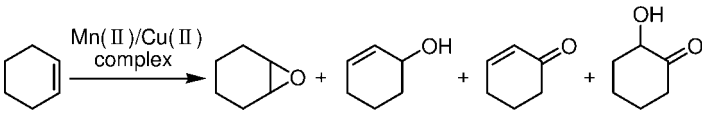


Figure 7.17 Enzyme reaction with *N*-ethyl-*N*-(2-hydroxy-3-sulfopropyl)-*m*-toluidine (TOOS) and 4-aminoantipyrine (4-AAP).



Scheme 7.10 Epoxidation of cyclohexene.

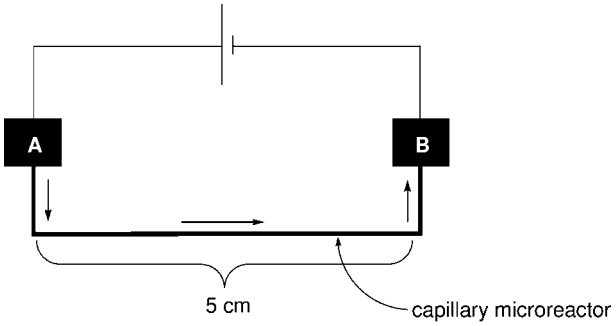
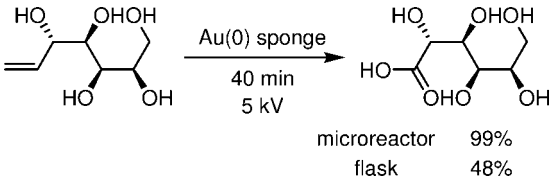


Figure 7.18 Capillary microreactor.



Scheme 7.11 Oxidation of D-glucose to gluconic acid.

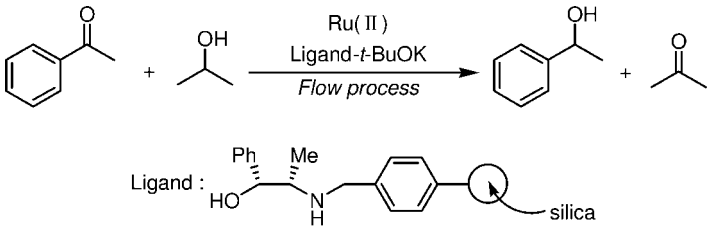
6–10 gives rise to the maximum yield of gluconic acid. The catalytic activity seems to be higher in comparison with that for the conventional procedure. The approach using a capillary microreactor offers a convenient and highly efficient means to optimize the reaction conditions (Scheme 7.11).

7.2 Reduction

In contrast to a large number of reports on oxidation using microflow systems, only a few examples of reduction have been reported in the literature.

An asymmetric transfer hydrogenation reaction between acetophenone and 2-propanol has been carried out using a microflow reactor containing a ruthenium complex of NH-benzyl-(1*R*,2*S*)-(−)-norephedrine covalently tethered to silica (Scheme 7.12) [99].

The electrochemical method also serves as an effective means of reducing organic compounds. For example, the electrochemical reduction of 4-nitrobenzyl bromide in *N*,*N*-dimethylformamide in the presence and absence of intentionally added



Scheme 7.12 Reduction of acetophenone.

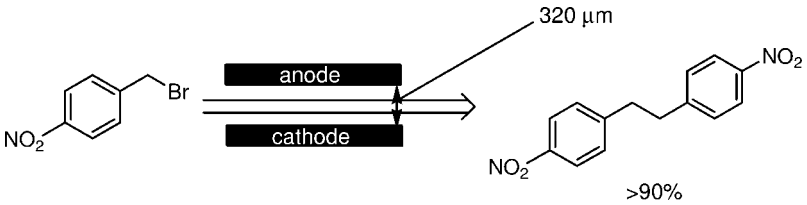


Figure 7.19 Homo-coupling reaction of benzyl bromides.

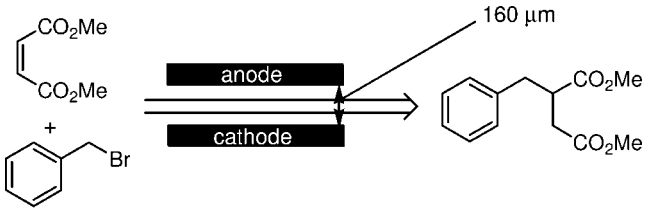


Figure 7.20 Coupling reaction of various alkenes with benzyl bromides.

supporting electrolyte using a microflow electrochemical cell leads to the formation of the homocoupling product (Figure 7.19) [100].

The electrochemical reductive coupling reaction of various alkenes with benzyl bromides can also been achieved in the absence of supporting electrolyte using the microflow cell (Figure 7.20) [101]. When the inter-electrode gap is 160 μm, the desired cross coupling product is obtained effectively, whereas a significant amount of homocoupling product is obtained when the gap is 320 μm.

As mentioned in Section 7.1.2, the electrochemical reduction of allylic halides in the presence of chlorotrimethylsilane can be achieved using a microflow cell and the desired allylic silanes are obtained (Table 7.2).

7.3 Conclusion

Oxidation and reduction using chemical, electrochemical and biochemical methods are attained by virtue of characteristic features of microflow systems. Microflow

reactors serve as powerful tools for accomplishing oxidation and reduction that are difficult to control in conventional macrobatch reactors.

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