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Ionic-liquid supported oxidation reactions in a silicon-based microreactor

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Abstract—The combination of microfabrication and reaction engineering techniques has the potential to produce powerful microreactors. In a microreactor, aqueous buffers provide high electroosmatic mobility and no external pumping is required. While numerous reactions have been demonstrated to be highly efficient in microreactors, so far there has been no report on the epoxidation of cyclohexene in a microreactor. This is mainly due to the reduced solubility of cyclohexene in aqueous media. The greater volatility of cyclohexene leading to long reaction times is another reason. To improve the solubility of cyclohexene in the reaction buffer, a water soluble ionic-liquid 1-butyl-3-methylimidazolium tetrafluoroborate was used, also for the first time in microreactor work. In this letter, four different catalysts (i.e., manganese(II) and copper(II) complexes of Schiff and reduced Schiff bases) were synthesized and used for the oxidation reactions considered. The reactions were monitored by gas chromatography/mass spectrometry. The microreactor performance was evaluated by comparing with a conventional (batch scale) reaction. Catalytic activities and yields were found to be relatively high for the copper(II) complexes as compared with the conventional route.

1. Introduction

Simple microfluidic analytical systems offer many fundamental and practical advantages in organic synthesis and a range of applications have been developed in many different areas.[1,2] The motivation for using micro-analytical devices includes low sample consumption, fast analysis times and high-throughput. These environmentally friendly methods are ideal for screening catalytic efficiency and also to quantify intermediate products.[3–5]

Electrochemical synthesis in microreactors provides an attractive approach to organic synthesis, avoiding toxic, expensive organic solvents, and often providing unique pathways to control the reactant and product distribution.[1,6] Catalytic oxidation of hydrocarbons is an important process.[7] Organometallic complexes are considered to be very effective catalysts for the epoxidation of olefins.[8–10] The development of simple and efficient procedures for selective oxidation of olefins is still a subject of practical and theoretical interest.

Ionic liquids have been employed as solvents or catalysts in many such catalytic processes.[11] Additionally, ionic liquids provide an ideal medium for reactions that involve reactive ionic intermediates. Due to the stabilization of charged intermediates by ionic liquids, they can promote enhanced selectivities and reaction rates and are finding increasing applications in organic synthesis.[12,13] Moreover, ionic liquids uniquely integrate many valuable properties including high polarity, low viscosity, high liquid temperature range, high thermal stability, wide tunability, immiscibility with certain organic solvents and no effective vapour pressure. The main advantages of ionic liquid catalysis are greatly enhanced reaction rates, higher activity at lower temperature and higher selectivity. It is believed that the non-volatile characteristic of ionic liquids allows product separation from the catalyst without the formation of azeotropes, therefore reducing contamination of the product.[14,15]

In this study, silicon-based microreactors were fabricated using standard photolithographic procedures and

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utilized to perform the epoxidation of cyclohexene for the first time in microfluidic work using the ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate [bmim]-[BF_4]). The performance of various types of catalysts such as Schiff-base and reduced Schiff-base complexes of Cu(II) and Mn(II) complexes were investigated. Reactions were monitored using gas chromatography/mass spectrometry (GC/MS) and the yields were compared with those from bulk scale epoxidation. To the best of our knowledge, this is also the first report of the epoxidation of cyclohexene in a silicon-based microreactor.

2. Experimental

2.1. Fabrication of the microreactor

A silicon-based T-shape microreactor (Fig. 1) was fabricated using standard photolithographic techniques, based on Pattekar and Korthare's work.[16]

2.2. Synthesis of ligand and complexes

2.2.1. Synthesis of copper(II) and manganese(II) complexes of L1. The synthesis of the ligand, **L1** and its complexes of both copper and manganese are reported elsewhere.[17]

2.2.2. Synthesis of *N*,*N′*-bis(2-pyridyl methyl)benzene-1,2-diamine, L2. 2-Pyridylcarbaldehyde (3.8 mL, 40.0 mmol) was added to a solution of 1,2-phenylenediamine (2.16 g, 20.0 mmol) in isopropanol (40 mL) (Scheme 1). The stirred solution began to deposit a yellow precipitate after 15 min. Stirring was continued for 1 h at room temperature and the precipitate was collected by filtration, washed with cold isopropanol followed by diethyl ether and dried in air for 30 min. The crude Schiff base was recrystallized from ethanol, filtered and dissolved in methanol (50 mL). Sodium borohydride (0.85 g, 22.6 mmol) was added slowly in portions. After refluxing for 2 h, the reaction mixture was cooled and quenched with water (20 mL). Methanol was removed and the reduced ligand was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with water; the organic layer was dried over anhydrous sodium sulfate and concentrated to yield a brown, oily liquid of the pure ligand.

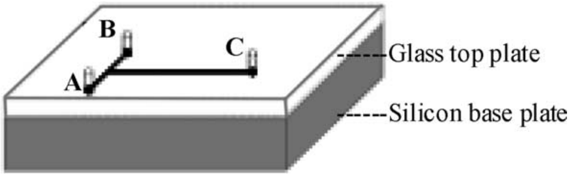
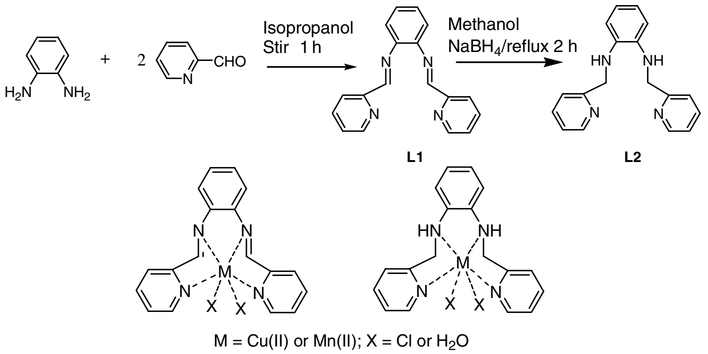


Figure 1. Schematic diagram of microreactor. A, B and C are reservoirs. Length of the channel is 3 cm, width 200 μm and 50 μm depth. The channel was sealed with a glass plate.

Ligand **L2**: Yield = 1.89 g (45%). ^1H NMR (300 MHz, $CDCl_3$), δ: 8.62 (d, pyridyl, 2H, *J* = 6 Hz), 8.45 (d, pyridyl, 2H, *J* = 7.6 Hz), 7.91 (t, pyridyl, 2H, *J* = 7.6 Hz), 7.70–7.60 (m, aromatic, 2H), 7.32 (m, pyridyl, 2H), 7.30–7.10 (m, aromatic, 2H), 4.50 (s, $–H_2C–$, 4H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.8, 149.0, 136.8, 136.7, 122.0, 121.7, 119.3, 112.2 (aromatic), 49.8 ($–H_2C–$). IR (NaCl plates), υ cm^{-1}: 3342 (amine N–H stretch), 3056, 3011 (aromatic C–H stretch), 2926, 2853 (alkane C–H stretch), 1987, 1889, 1851, 1778 (aromatic overtones and combination bands), 1594, 1570 (aromatic C=C stretch), 1511 (amine N–H bend), 1274 (C–N stretch). EI-MS (*m*/*z*) 290.1 (M^+, calculated formula weight 290.37).

2.2.3. Synthesis of copper(II) and manganese(II) complexes of L2. The metal salts $MnCl_2$ and $CuCl_2{\cdot}2H_2O$ were used as starting materials. Both complexes were prepared similarly. 0.7 mmol of each metal chloride was dissolved in methanol (5 mL) and added dropwise to a solution of reduced Schiff base ligand (**L2**) in dichloromethane. The resulting solutions were stirred overnight at room temperature. The solid products deposited were collected by filtration and dried in air. The manganese(II) complex was a brown precipitate and the copper(II) complex, a green solid.

2.2.4. Manganese(II) complex-(L2Mn). Yield = 35%. IR (KBr pellet), υ: 3432 (amine N–H stretch), 3067, 3017 (aromatic C–H stretch), 2983, 2917 (alkane C–H stretch), 1594 (aromatic C=C stretch), 1304 (C–N stretch). UV (MeOH), λ_{max}: 241, 306.5 nm. ESI-MS (*m*/*z*): 999.1 (M^+, calculated formula weight 994.3). Elemental analysis for [$(Mn_3L_2Cl_6){\cdot}2(H_2O)$], found: C, 43.1; H, 3.5; N, 11.1. Calcd: C, 43.5; H, 4.1; N, 11.3.



M = Cu(II) or Mn(II); X = Cl or H_2O

Scheme 1. Synthetic scheme for the ligands, **L1** and **L2**.

2.2.5. Copper(II) complex-(L2Cu). Yield = 48%. IR (KBr pellet), υ: 3426 (amine N–H stretch), 3073, 3041 (aromatic C–H stretch), 2975 (alkane C–H stretch), 1596 (aromatic C=C stretch), 1298 (C–N stretch). UV (MeOH), λ_{max}: 241, 325 nm. ESI-MS (*m*/*z*): 669.9 (M^+, calculated formula weight 662.2). Elemental analysis for $[(Cu_2LCl_4)\cdot(H_2O)(CH_2Cl_2)]$, found: C, 34.4; H, 3.0; N, 9.1. Calcd: C, 34.5; H, 3.4; N, 8.5.

2.3. Epoxidation of cyclohexene in the microreactor

The basic arrangement of the T-shaped microreactor with reservoirs A, B and C, is depicted in Figure 1. The reaction is shown in Scheme 2. Initially, the T-shaped microfluidic channel was filled with 50 mM of phosphate buffer solution (with 0.5% (v/v) of ionic liquid) and 5% (w/v) of the Schiff catalyst.

Extreme care was taken to ensure that air bubbles were absent inside the microfluidic channel. This was checked by measuring a constant current. The reactant (10 μL) was introduced to reservoir A. The conditions included a potential of 4 kV, (+) 200 μA to reservoir A and (−) 200 μA to reservoir C. Platinum wires were used as electrodes. The reaction was monitored for 25 min at room temperature.

2.4. Epoxidation of cyclohexene in bulk scale

The manganese(II) or copper(II) complex (4.4 mg) was added to cyclohexene (0.11 mL, 1 mmol) in 50 mM phosphate buffer containing 0.5% of [bmim][BF_4] with 5% of the respective catalyst under a nitrogen atmosphere at room temperature. The reaction was started by the dropwise addition of 30% aqueous hydrogen peroxide (0.06 mL, 2 mmol) dissolved in acetonitrile (0.5 mL). A control experiment was set up without any metal complex. Epoxidation of cyclohexene was monitored at different intervals (i.e., 1, 2, 3 and 5 h). After completion of the reaction, the analytes were extracted with diethyl ether and filtered, and reconstituted to 1 mL.

2.5. Product mixture analysis

Analysis of the reaction mixture was performed on a Shimadzu (Tokyo, Japan) QP2010 GC/MS system. The GC was fitted with a DB-5 column (30 m × 0.32 mm i.d., 0.25 μm) from J&W Scientific (Folsom, CA, USA). The detector was scanned over the *m*/*z* range 50–500 to confirm the retention times of the analytes. For determination of the reactants and products, selected ion monitoring (SIM) was performed. GC conditions were optimized initially and separate quantitative calibration curves were plotted for individual reactant and products using standards. Based on the calibration, reaction yields were calculated. Additionally, controlled experiments were performed to check the efficiency of the catalyst. Figure 2 shows the optimized chromatograms of reactant and products.

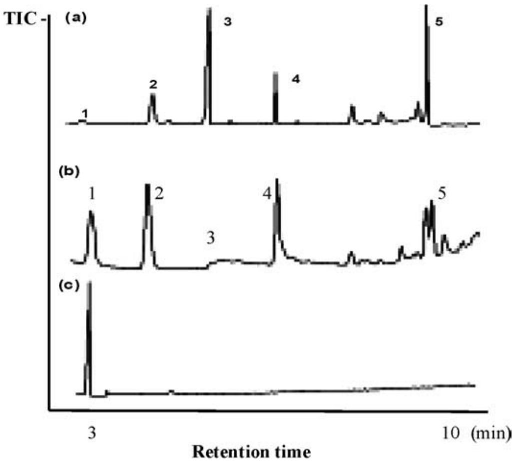


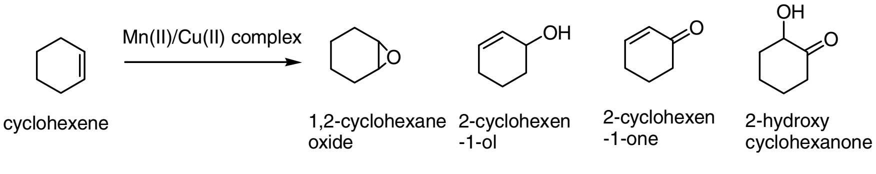
Figure 2. GC/MS-SIM chromatograms generated by the epoxidation of cyclohexene under optimized conditions in the microreactor (a); bulk scale epoxidation in the presence of hydrogen peroxide (b); and a blank experiment (without catalyst) (c). Peak identifications: [1]. cyclohexene, [2]. 1,2-cyclohexene-oxide, [3]. 2-cyclohexen-1-ol, [4]. 2-cyclohexen-1-one, [5]. 2-hydroxy-cyclohexanone.

3. Results and discussion

3.1. Optimization of the epoxidation of cyclohexene in the microreactor

The nature and relative yields of the products formed by the catalytic oxidation of cyclohexene using a Schiff base catalyst vary considerably depending on the conditions and catalyst used. In order to optimize the reaction conditions in the microreactor, analytical factors such as addition of ionic liquid to the reaction medium, the catalyst used (Cu(II) and Mn(II) complexes), applied potential, current and reaction time, that might affect the reaction conditions were studied.

Initially, oxidation of cyclohexene was performed with a phosphate buffer as the reaction medium. Due to the low solubility of cyclohexene in the reaction medium, less precise results and poor reaction yields were obtained. This provided the impetus to perform the reaction in a more favourable medium. Therefore, the ionic liquid [bmim][BF_4] was introduced (0.5% v/v) to the buffer solution. A high concentration of 5% ionic liquid did not give any improvement in the reaction. Since



Scheme 2. Epoxidation of cyclohexene.

the ionic liquid was miscible with the reaction medium and reactant, more reproducible results were obtained.

Reaction time is one of the most important parameters in the epoxidation of cyclohexene. The reaction time was varied between 5 and 30 min at 100 μA current and 5 kV applied potential and the reaction yield with respect to time was monitored. A reaction time of 25 min appeared to be the optimum (Fig. 3).

We evaluated the performance of the reaction with respect to the applied current range from 75 μA to 250 μA at a constant potential of 5 kV for 25 min. The reaction yield (% of conversion) increased with increasing current up to 150 μA. At 200 μA, products were obtained at comparably higher yields than the conventional procedure.

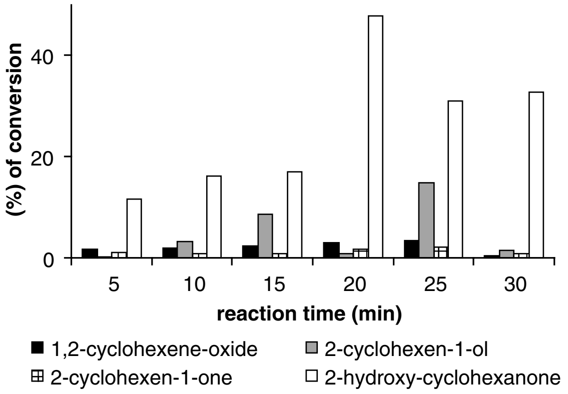


Figure 3. Epoxidation of cyclohexene at various reactions time.

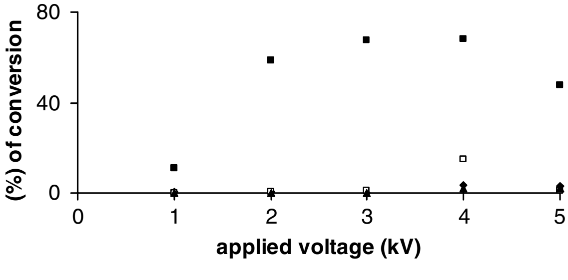


Figure 4. Epoxidation of cyclohexene at various applied potentials under constant current and time (200 μA for 25 min).

Experiments were run across a voltage range of 1–5 kV at a constant current of 200 μA to determine the optimum potential at which the highest yield was obtained. Figure 4 shows the influence of the applied voltage. As can be seen, a maximum product yield was obtained at 4 kV.

The optimum experimental conditions, involved a reaction time of 25 min, an applied potential of 4 kV, an applied current of 200 μA and 5% of catalyst in a 50 mM phosphate buffer containing 0.5% of [bmim][BF_4]. Representative results are summarized in Table 1. Compared with the conventional synthesis, the microreactor experiments provided higher reaction yields.

The mechanism of the oxidation of cyclohexene involves its double bond reacting readily with electrophilic radical cations.[18,19] Oxidation is believed to be similar to anodic oxidation of dienes[18,20] and alkenes.[21] Additionally, Schiff complexes of Cu or Mn catalyse the oxidation of cyclohexene to the corresponding ketones and aldehydes.[22] In the microreactor, both radical cations and metal complex play significant roles in the oxidation of cyclohexene.

The products obtained are 1,2-cyclohexene-1-oxide, cyclohexanone; cyclohexen-1-one and 2-hydroxy-cyclohexanone; and cyclohexen-1-ol is the main product in both cases (microreactor and bulk). The transfer of an oxygen atom from the oxometal complex to the allylic radical gave the 2-cyclohexen-1-ol product. Furthermore, 2-cyclohexen-1-ol could be converted to cyclohexen-1-one by loss of a proton. A similar type of oxidation of cyclohexene to the epoxide, cyclohexenol and cyclohexenone using iron phthalocyanines has been reported elsewhere.[23]

Comparing the manganese and copper complexes, the copper complex could be a better catalyst for oxidation of cyclohexene. The yield of oxidation products obtained in the study is comparable with those reported earlier[24] via conventional procedures.

4. Conclusions

In conclusion, the Schiff and reduced Schiff base ligands, **L1** and **L2** and their copper and manganese complexes have been synthesized in good yields. The Schiff base copper and manganese complexes (**L1**Cu and **L1**Mn) and the dimeric copper and trimeric manganese com-

Table 1. Percentage of product conversion in microreactor, bulk scale conversions are shown in parenthesis via Scheme 2

Products	Complex of **L2**		Complex of **L1**	
	Reduced Cu(II) complex	Reduced Mn(II) complex	Cu(II) Schiff	Mn(II) Schiff
1,2-Cyclohexene-oxide	5.5 (15.7)	3.5 (15.9)	24.3 (28.1)	5.2 (16.1)
2-Cyclohexen-1-ol	22.0 (51.7)	14.8 (45.0)	14.5 (6.1)	56.7 (2.6)
2-Cyclohexen-1-one	2.3 (nd)	2.2 (4.5)	43.7 (11.1)	4.0 (3.3)
2-Hydroxy-cyclohexanone	65.5 (10.9)	31.0 (5.3)	9.1 (9.4)	4.3 (nd)
Total conversion	95.3 (78.3)	51.5 (70.7)	91.6 (54.7)	70.2 (22.0)

nd = not detected.

plexes of the reduced Schiff base ligands (**L2**Cu and **L2**Mn) worked fairly as catalysts for the oxidation of cyclohexene and systems. The microfluidic system described here is an efficient and rapid cyclohexene oxidation method. When the oxidation was carried out in an ionic liquid medium, significant (<70%) conversion was achieved. Higher conversions to oxidation products were obtained when reduced Schiff base–Cu(II) and Mn(II) complexes were used, compared to the Schiff base complexes. The major products were 2-cyclohexen-1-ol and 2-hydroxy-cyclohexanone. The activity of cyclohexene oxidation decreases in the series, [reduced Schiff Cu(II)] > [reduced Schiff Mn(II)] > [Schiff Cu(II)] > [Schiff Mn(II)]. In contrast to the bulk scale approach, 2-cyclohexen-1-ol was found to be the major product.

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