

Catalytic Oxidation of *o*-Chlorotoluene with Oxygen to *o*-Chlorobenzaldehyde in a Microchannel Reactor

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ABSTRACT: Liquid-phase selective oxidation of *o*-chlorotoluene (OCT) to *o*-chlorobenzaldehyde (OCBD) with oxygen as the oxidant catalyzed by a cobalt acetate/manganese acetate/potassium bromide ($\text{Co}(\text{OAc})_2/\text{Mn}(\text{OAc})_2/\text{KBr}$) system was studied in a microchannel reactor using acetic acid doped with a small amount of water as the reaction medium. The reaction parameters were easily controlled by performing the reaction in a microchannel reactor. A selectivity as high as 71.8% for OCBD was achieved by maintaining the conversion of OCT at 10.3% under the optimal reaction conditions.

KEYWORDS: *o*-chlorotoluene, *o*-chlorobenzaldehyde, oxidation, oxygen, microchannel reactor

1. INTRODUCTION

o-Chlorobenzaldehyde (OCBD) is an important intermediate for the synthesis of drugs, dyes, and pesticides.^{1–3} There are several methods to synthesize OCBD, which include hydrolysis of *o*-chlorobenzal chloride,⁴ electrochemical oxidation,¹ and direct oxidation of *o*-chlorotoluene (OCT) with hydrogen peroxide or molecular oxygen.^{2,3,5,6} Very recently, it was reported that OCBD could also be synthesized by iron-catalyzed oxidation of OCT with $\text{K}_2\text{S}_2\text{O}_8$ as the oxidant in the presence of excess polymethylhydrosiloxane or molecular oxygen over a CdS-ZnS photocatalyst.^{7,8} Until now, however, OCBD has mainly been produced in industry through side-chain chlorination of OCT to form *o*-chlorobenzal chloride followed by hydrolysis, which suffers from the disadvantages of a complicated process and serious environmental pollution. It is better to synthesize OCBD via aerobic oxidation of OCT because of the low cost, ready availability, environmental friendliness, and atom economy of molecular oxygen as an oxidant. In the past decades, the direct aerobic oxidation of substituted toluenes to their benzaldehydes and benzoic acids over various catalysts has received much attention.^{3,9–17} Among the catalytic systems, the MC catalysts (combinations of Co, Mn, and Br compounds that were discovered by Mid-Century Corporation) have been successfully applied to the production of both benzoic acids and benzaldehydes in batch reactors in industry.^{3,10} However, there is an explosion risk when aerobic oxidations are performed in batch reactors with MC catalysts. Meanwhile, the selective catalytic oxidation of chlorotoluenes to chlorobenzaldehydes with high selectivity remains a big challenge because of the further oxidation of chlorobenzaldehydes to acids.^{10,16} Many of the safety and process challenges involved in performing gas–liquid aerobic oxidations in batch reactors can be overcome by employing continuous flow microchannel reactor technology, which provides the possibility of minimizing safety hazards while allowing the use of high-temperature and -pressure conditions to obtain an efficient oxidation process.

In recent years, considerable achievements have been made in microchannel reactor technology in the chemical field because of the advancement of science and technology.^{18–20} Compared with traditional batch reactors, continuous flow microchannel reactors show the inherent characteristics of a large specific surface area and high heat and mass transfer efficiencies, which allow fine control of the reaction conditions, good operability, high safety, less degradation and side products, and an easier path to scale-up.^{18,21–23} To date, microchannel reactors have been successfully applied in various organic reactions, such as aldol condensation,^{24a,b} Michael addition,^{24c,25} nucleophilic addition with organometallic reagents,²⁶ the Wittig reaction,²⁷ Suzuki–Miyaura coupling,²⁸ Diels–Alder addition,²⁹ Wolff–Kishner reduction of carbonyls,³⁰ and especially aerobic oxidation of various substrates.^{31–41} For the applications of flow microchannel reactor technology to aerobic oxidations, Stahl,^{31,32} Gavrilidis,³³ and Vanoye³⁴ conducted aerobic oxidation reactions on alcohols and aldehydes through microchannel reactor technology and achieved good results. In addition, Gemoets,³⁵ Willms,³⁶ and Kappe^{37–41} also reported many successful results on the use of continuous flow microchannel reactor technology for aerobic oxidations.

In this paper, we report the selective aerobic oxidation of OCT in acetic acid doped with a small amount of water catalyzed by an MC catalyst system in a chip-based microchannel reactor. Generally, chip-based reactors offer good heat transfer capacity due to their exceedingly high surface-to-volume ratios. Thermal reactions such as aerobic oxidations can be regulated with otherwise unreachable accuracy, which makes this kind of reactor an ideal tool for scale-up of the process.²³

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Various reaction conditions were investigated, including the composition of the catalyst system, the oxygen/OCT molar ratio, the reaction temperature and pressure, and the residence time, to get an optimal process for the aerobic oxidation of OCT to give OCBD.

2. EXPERIMENTAL SECTION

2.1. Instruments and Reagents. Analytical grade *o*-chlorotoluene, cobalt(II) acetate tetrahydrate ($\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$), manganese(II) acetate tetrahydrate ($\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$), potassium bromide (KBr), glacial acetic acid, and industrial-grade pure oxygen were obtained from commercial sources and used as received. Distilled water was prepared in our laboratory.

The oxidation was performed in a Protrix-type continuous flow microchannel reactor from Chemtrix B.V. (Echt, The Netherlands) with a LOW- ΔP -FLOW gas mass flow meter and controller from Bronkhorst (Ruurlo, The Netherlands). An Agilent 1260 Infinity high-performance liquid chromatograph equipped with a Shim-pack VP-ODS C_{18} column was used to analyze the reaction mixture.

2.2. Oxidation of OCT with Molecular Oxygen. Predetermined amounts of $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, and KBr were added successively to a conical flask, and the mixture was dissolved with a mixture of glacial acetic acid and water with a predetermined weight ratio. A certain amount of OCT was added to this solution to form a clear and transparent homogeneous solution under stirring. The solution was fed into the microreactor at a given temperature and pressure by a 10 mL liquid feed pump, where it was mixed with the oxygen flux controlled by a LOW- ΔP -FLOW-type gas mass flow controller.

The amount of oxygen used can be obtained from the ideal gas law (eq 1),^{42,43}

$$n = \frac{PV}{RT} \quad (1)$$

in which P is the reaction pressure (in Pa), T is the room temperature (in K), V is the gas volume (in m^3) obtained from the gas mass flow controller, and R is the universal gas constant ($8.314 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$).

After the reaction, the process stream was analyzed by HPLC, and quantification was achieved using the external standard method. The conversion of OCT and the selectivities for OCBD and *o*-chlorobenzoic acid (OCBA) (in mol %) were calculated according to the following equations:

$$\text{OCT conversion} = \frac{n_{\text{OCT,converted}}}{n_{\text{OCT,initial}}} \times 100\% \quad (2)$$

$$\text{OCBD selectivity} = \frac{n_{\text{OCBD}}}{n_{\text{OCT,converted}}} \times 100\% \quad (3)$$

$$\frac{n}{n}$$

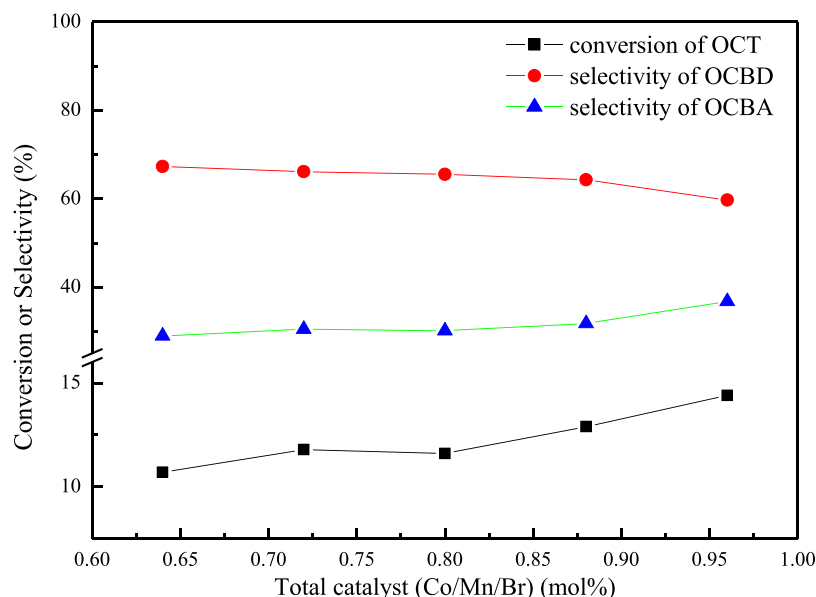


Figure 2. Effect of the the amount of catalyst on the oxidation of OCT. Reaction conditions: 0.158 mol of OCT; 47.3 mL of acetic acid; 1.65 wt % water; Co/Mn/Br molar ratio = 0.3/0.3/1; liquid flow rate = 0.5 mL/min; oxygen flux = 58 mL/min; residence time = 9.4 s; reaction pressure = 0.8 MPa; reaction temperature = 423 K.

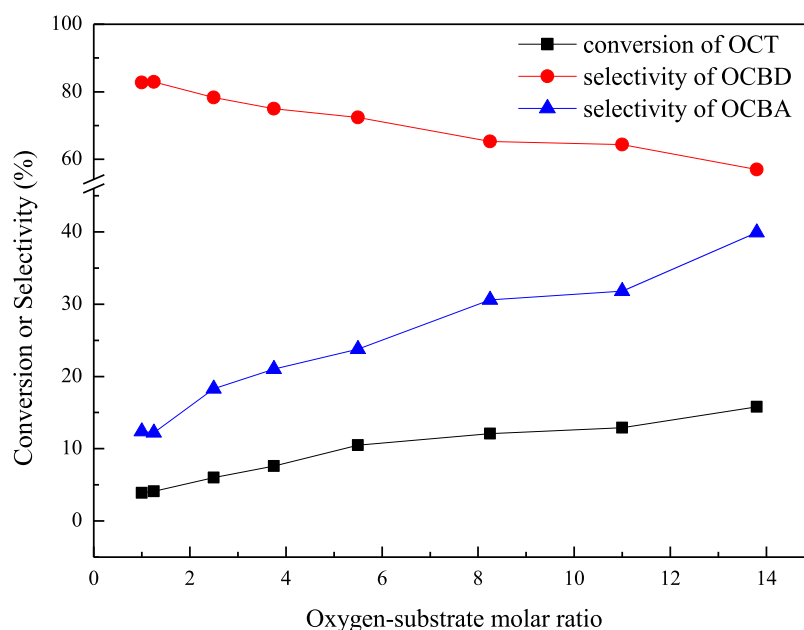


Figure 3. Effect of the oxygen/substrate molar ratio on the oxidation of OCT. Reaction conditions: 0.158 mol of OCT; 0.88 mol % catalyst; Co/Mn/Br molar ratio = 0.3/0.3/1; 47.3 mL of acetic acid; 1.65 wt % water; oxygen flux = 58 mL/min; residence time = 9.4 s; reaction pressure = 0.8 MPa; reaction temperature = 423 K.

67.4%. When bromide was employed in the range of 0.35–0.5 mol %, the rate of conversion of OCT decreased, and the selectivities for both OCBD and OCBA changed only slightly. The conversion of OCT reached a maximum of 11.6% when 0.5 mol % bromide was employed, with OCBD and OCBA selectivities of 65.5% and 30.1%, respectively, and the highest yield (7.6%) of OCBD was achieved. On the basis of this result, further experiments utilized 0.5 mol % bromide. In this case, the Co/Mn/Br molar ratio was 0.3/0.3/1.

3.2. Effect of the Amount of Catalyst. First, several blank experiments were performed, including catalysis by neat $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ or $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, by $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$

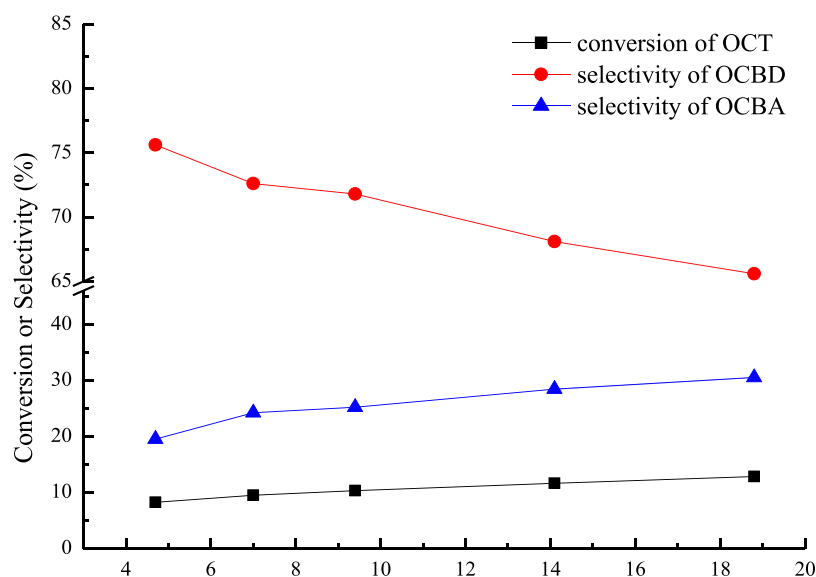
and KBr without $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, or by $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ and KBr without $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$. As shown in Tables S1–S4 in the Supporting Information (SI), very low conversion of OCT was observed in all of these cases, which indicated the necessity of each component in the catalyst system.

The effect of the total amount of catalyst on the oxidation of OCT was subsequently investigated in the range of 0.64–0.96 mol % with respect to the substrate, retaining a Co/Mn/Br molar ratio of 0.3/0.3/1. As shown in Figure 2, the conversion of OCT increased from 10.7% to 14.4% when the catalyst loading was increased from 0.64 mol % to 0.96 mol %. Meanwhile, the selectivity for OCBD decreased as a result of further oxidation of

OCBD to OCBA, resulting in an increase in the selectivity for OCBA. In order to increase the selectivity for OCBD, a catalyst loading of 0.88 mol % was selected. In this case, the conversion of OCT was 12.9% with OCBD and OCBA selectivities of 64.3% and 31.8%, respectively.

3.3. Effect of the Oxygen/Substrate Molar Ratio. The effect of the oxygen/substrate molar ratio (O/S) was investigated next. In this experiment, the oxygen flux per unit time and the concentration of the substrate in the reaction solution remained constant. Changing the feeding ratio changed the amount of substrate fed per unit time, thereby changing O/S. As shown in [Figure 3](#), both the conversion of OCT and the

selectivity for OCBA increased with increasing O/S, but as expected, the selectivity for OCBD decreased. When O/S was 1:1, the conversion of OCT was only 3.9%, while the selectivity for OCBD was as high as 82.7%. When O/S increased to 13.8:1, the conversion of OCT and the selectivity for OCBA reached 15.8% and 39.9%, respectively, but the selectivity for OCBD decreased to 57.0%. With the aim of obtaining an increased amount of OCBD per unit time, the optimal O/S was determined to be 5.5:1. In this case, the conversion of OCT was 10.5%, and OCBD and OCBA were obtained with selectivities of 72.4% and 23.8%, respectively.



3.4. Effect of the Reaction Temperature. Since the aerobic oxidation of OCT is an autocatalytic exothermic reaction, the effect of the reaction temperature is an important parameter to be investigated. Figure 4 shows the effect of the temperature on the reaction in the range of 393–433 K. The conversion of OCT and the selectivity for OCBA increased with increasing reaction temperature, but the selectivity for OCBD decreased. At a reaction temperature of 393 K, the conversion of OCT was only 1.7%, but the selectivity for OCBD was as high as 88.2%. When the reaction temperature was increased to 433 K, the conversion of OCT increased to 13.3%, but the selectivity for OCBD decreased to 66.2%. After comprehensive consideration, the optimal reaction temperature was determined to be 423 K. In this case, the yield of OCBD reached 7.6%.

3.5. Effect of the Oxygen Pressure. The oxidation of OCT is a gas–liquid-phase reaction, and increasing the oxygen pressure can enhance the dissolution of oxygen in the liquid phase. In a microchannel reactor, the application of pressure can change the flow regime and influence the reaction yield and selectivity. To evaluate this, the effect of the oxygen pressure on the reaction was investigated in the range of 0.3–1.0 MPa. At all of the investigated pressures, the amount of oxygen was kept in excess with regard to OCT. As shown in Figure 5, the conversion of OCT almost remained constant at about 10%, but the selectivities of OCBD and OCBA changed in the low oxygen pressure range of 0.3–0.6 MPa. The highest selectivity for OCBD and the lowest selectivity for OCBA were obtained at the oxygen pressure of 0.6 MPa and remained constant with further increases in the oxygen pressure. We concluded that this catalytic system prefers a low oxygen pressure to conduct the reaction while the liquid phase of OCT is maintained at the reaction temperature; the optimal reaction pressure was determined to be 0.5 MPa. In this case, the selectivity for OCBD reached 71.8%, corresponding to a yield of 7.4%.

The reaction was also carried out using air instead of oxygen as the oxidant at a pressure of 0.3 MPa. As shown in Figure 5, the conversion of OCT was only 0.2%, which is much smaller than the value of 10% with oxygen as the oxidant under the same reaction conditions. This can be ascribed to the low

concentration of oxygen in the liquid phase due to dilution by the nitrogen in the air.

3.6. Effect of the Residence Time. For a continuous reaction conducted in a microchannel reactor, the residence time of reactants is a key factor to influence the reaction. Therefore, the effect of residence time on the reaction was finally investigated. As shown in Figure 6, the conversion of OCT increased with extension of the residence time, so did the selectivity of OCBA. However, the selectivity of OCBD decreased with the increase of the residence time. When the residence time was greater than 9.4 s, the selectivity of OCBD was less than 70%. For the aim to obtain OCBD as much as possible, the residence time is selected to be 9.4 s. In this case, the conversion of OCT reached 10.3%, and the selectivities toward OCBD and OCBA were 71.8% and 25.2%, respectively.

3.7. Optimized Conditions. On the basis of the experimental investigation, the optimum reaction conditions for the aerobic oxidation of OCT to synthesize OCBD in a microchannel reactor were concluded to be the following: acetic acid/H₂O as the solvent (aq, 1.65 wt %), 0.88 mol % catalyst with a Co/Mn/Br molar ratio of 0.3:0.3:1, an oxygen/OCT molar ratio of 5.5:1, a residence time of 9.4 s, a reaction temperature of 423 K, and an oxygen pressure of 0.5 MPa. Under these conditions, the conversion of OCT was 10.3% with a selectivity for OCBD of 71.8%, corresponding to an OCBD yield of 7.4%, which is higher than that in the literature.^{3,4,6,7}

4. ORTHOGONAL EXPERIMENTS

To confirm the reliability of the single-factor-optimization experimental results, orthogonal experiments were carried out. A four-factor, three-level (3^4) orthogonal experiment table was established (Table 1), retaining the Co/Mn/Br molar ratio of 0.3:0.3:1 and the reaction pressure of 0.5 MPa. The conversion of OCT and the selectivity for OCBD were used as criteria. The orthogonal test data and analysis are given in Tables S5 and S6.

Figure 7 shows the relationships of the conversion and selectivity with the four factors and levels, according to the average diameters m_i of the T_i values in Tables S5 and S6. It is obvious that the four factors monotonically increase or decrease

Table 1. Factors of Orthogonal Experiment $L_9(3^4)^a$

level	A (mol %)	B	C (K)	D (s)
1	0.8	3.75	413	7.0
2	0.88	5.5	423	9.4
3	0.96	8.25	433	14.1

^aThe four factors are defined as follows: A is the total amount of catalyst; B is the oxygen/OCT molar ratio; C is the reaction temperature; and D is the residence time.

with the increase in level and share a similar tendency. Moreover, when it comes to factors B and C, their range of variation is relatively large with the increase in level. However, it is noteworthy that the conversion and selectivity of factor C increased or decreased much more drastically with the growth in the reaction temperature, leading to the highest *R* values in Table 2. Hence, the factor with the greatest effect on the conversion and selectivity is the reaction temperature, which is consistent with the results of range *R*.

The results of the comprehensive balance analysis from Tables S5 and S6 are listed in Table 2. For factor A, the highest conversion of OCT and selectivity for OCBD were obtained at the A_3 and A_1 levels, respectively. To the end of obtaining as much OCBD as possible, it is better to select A_2 as the preferred level. Similarly, B_2 , C_2 , and D_2 are the preferred levels for factors B, C, and D.

On the basis of the above analysis, the optimum process for the reaction in the microchannel reactor is $A_2B_2C_2D_2$, in which the Co/Mn/Br molar ratio is 0.3:0.3:1, the total amount of catalyst is 0.88 mol %, the reaction temperature is 423 K, the oxygen/OCT molar ratio is 5.5, the reaction pressure is 0.5 MPa, and the residence time is 9.4 s. The orthogonal test results are consistent with the results of single-factor-optimization experiments.

5. PRACTICALITY EXPERIMENTS

To confirm the practice of this process, about 1000 mL of reaction solution under the optimal reaction conditions was collected, and OCBD was separated as follows. First, the collected reaction solution was distilled at 50 °C under −0.1 MPa to distill off acetic acid and water, and then the temperature

was increased to 80 °C under the same pressure to remove OCT. The residue was then distilled at 90 °C under −0.1 MPa to collect OCBD. The crude product was transferred into a small flask and distilled again to give OCBD with a purity of 98.5% and a yield of 70% compared with the amount determined by GC.

As shown in Table 3, the results in this work were compared with those in literature. Compared with the reaction over the solid catalyst $(\text{Co,Mn})_2\text{O}_4$ in combination with KBr in a batch reactor,³ a slightly lower yield of OCBD was obtained. However, the aerobic oxidation in a batch reactor suffers from the disadvantage of potential safety hazards, which were resolved by performing the reaction in a microchannel reactor in this work. To our delight, the results are better than those over other catalyst systems in view of the comprehensive results of the conversion of OCT and the selectivity for OCBD. For instance, although the selectivity for OCBD was as high as 99%, the conversion was smaller than 1.7% over a CdS–ZnS photocatalyst.⁸

Finally, the catalytic system and optimal conditions were applied to the aerobic oxidation of other methyl aromatics, including 2-methylpyridine, to the corresponding aldehydes. The results are presented in Table 4. Compared with those for OCT, higher conversions but lower aldehyde selectivities were obtained in the oxidations of toluene and 4-*tert*-butyltoluene, which are more electronegative than OCT (Table 4, entries 1 and 2). Similar results were obtained in the cases of OCT, *p*-chlorotoluene, and *m*-chlorotoluene as substrates, with aldehyde selectivities in the range of 70–72% (Table 4, entries 3–5). Both the conversion and the aldehyde selectivity were lower in the oxidation of 2-methylpyridine than in that of OCT, indicating that this catalytic system and optimal conditions were not compatible with the methyl heteroaromatics (Table 4, entry 6).

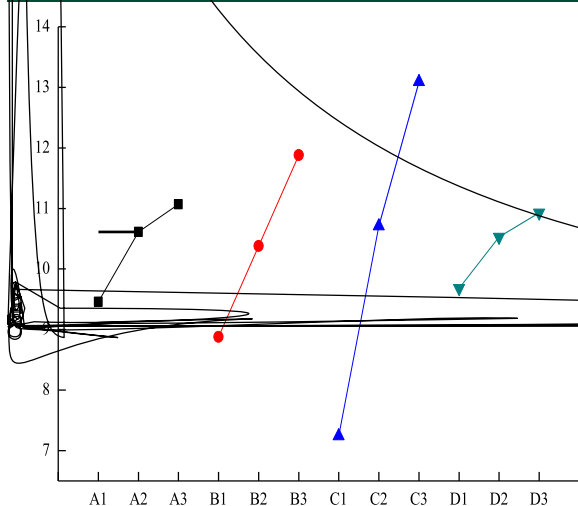
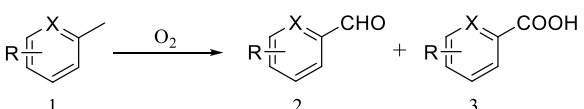


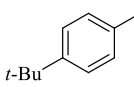
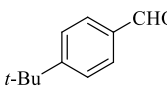
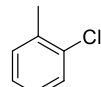
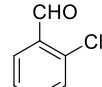
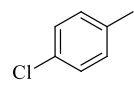
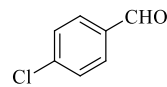
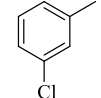
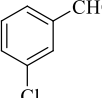

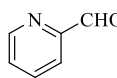


Table 3. Comparison with Literature Results for the Aerobic Oxidation of OCT to OCBD

entry	catalyst	solvent	reaction conditions	conv. (%)	sel. (%)	ref
1	(Co,Mn) ₂ O ₄ /KBr	CH ₃ CO ₂ H	120 °C, 4 h	20.0	48.0	3
2	NHPI/NaNO ₂	TFA/H ₂ O	45 °C, 3 h	46.0	18.0	44
3	CdS–ZnS	–	r.t., <i>hν</i> , 3 h	<1.7	99.0	8
4	NHPI/T(2-CH ₃ O)PPCo	–	O ₂ (1 MPa), 120 °C, 8 h	8.4	21.3	45
5	Co(OAc) ₂ /Mn(OAc) ₂ /KBr	CH ₃ CO ₂ H/H ₂ O	O ₂ (0.5 MPa), 150 °C, 9.4 s	10.3	71.8	this work

Table 4. Aerobic Oxidation of Various Substrates Catalyzed by the Co/Mn/Br Catalytic System in Acetic Acid/Water^a

					
Entry	1	2	Conv. (%)	Sel. (%)	
				2	3
1			15.0	49.0	38.6
2			16.1	55.8	17.8
3			10.3	71.8	25.2
4			11.3	72.3	12.0
5			8.6	70.2	11.0
6			6.79	31.1	66.6

^aReaction conditions: 0.158 mol of substrate; 0.88 mol % catalyst; Co/Mn/Br molar ratio = 0.3/0.3/1; substrate concentration = 2.39 mol/L; 1.65 wt % water; oxygen/substrate molar ratio = 5.5; reaction pressure = 0.5 MPa; reaction temperature = 423 K. The conversion and selectivity were determined by GC.

6. CONCLUSIONS

The selective aerobic oxidation of OCT to OCBD catalyzed by a Co(OAc)₂/Mn(OAc)₂/KBr catalyst system in acetic acid doped with water as the solvent was performed in a microchannel reactor. The effects of the catalyst loading, catalyst composition, oxygen/OCT molar ratio, reaction temperature, reaction pressure, and residence time were thoroughly investigated. Optimal reaction conditions were obtained for the selected catalytic system. The results revealed that maintaining a low conversion of OCT was essential to target OCBD with high selectivity. Under the optimal reaction conditions, the selectivity for OCBD reached 71.8% when the conversion of OCT was controlled at 10.3%. The parameters were easily controlled by performing the oxidation in the microchannel reactor, allowing a thorough evaluation of the various reaction parameters. Further work will focus on the identification of catalytic systems with increased selectivity toward OCBD with higher OCT conversion rates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.0c00135>.

Blank experiments and orthogonal test data and analysis (PDF)

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Author Contributions

^{||}L.Y. and P.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.



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