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Homogeneous Liquid-Phase Oxidation of Ethylbenzene to Acetophenone in Continuous Flow Mode

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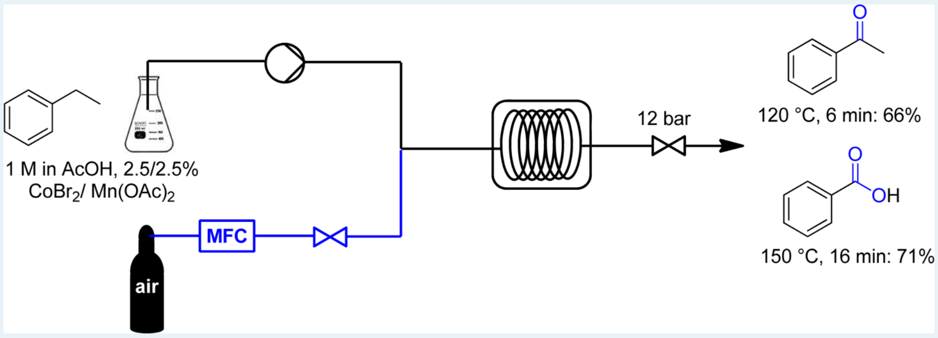
Supporting Information



ABSTRACT: The oxidation of ethylbenzene with hydrogen peroxide and molecular oxygen catalyzed by cobalt and bromide ions in acetic acid as solvent was studied. The oxidation of ethylbenzene with hydrogen peroxide provided a mixture of ethylbenzene hydroperoxide, acetophenone, 1-phenylethanol, and 1-phenylethyl acetate. After rapid initial oxidation, the reaction rate decreased steadily so that full conversion of ethylbenzene and reaction intermediates to acetophenone could not be achieved. In contrast, no catalyst deactivation was observed for oxidations using atmospheric oxygen. Ethylbenzene was oxidized to acetophenone in 74% selectivity after a reaction time of 150 min at 80 °C. The reaction conditions were translated to a continuous flow process using a tubular gas−liquid reactor. At temperatures of 110 to 120 °C and an oxygen pressure of ~12 bar, the reaction time necessary for complete oxidation of ethylbenzene was reduced to 6 to 7 min. The acetophenone was formed in 80 to 84% selectivity, and virtually pure acetophenone was isolated in 66% product yield without the need for chromatography. Increasing the reaction time to 16 min at a reaction temperature of 150 °C led to benzoic acid as the final product in 71% yield.

KEYWORDS: *acetophenone, autoxidation, benzylic oxidation, cobalt bromide, continuous flow, novel process windows*

INTRODUCTION

Traditionally, phenyl ketones were produced primarily by Friedel−Crafts acylation employing acid halides or acid anhydrides as reagents utilizing stoichiometric amounts of $AlCl_3$ as catalyst.[1] The need for stoichiometric amounts of catalyst and the large quantities of generated waste make this process undesirable on large scale. Therefore, current industrial processes for the synthesis of phenyl ketones are mainly based on the oxidation of alkylbenzenes.[2−7] Stoichiometric oxidants such as permanganate, chromic acid, potassium dichromate, or nitric acid are often used for these transformations.[2c] However, oxidizing agents such as hydrogen peroxide or molecular oxygen (O_2) are clearly advantageous from an economical and environmental perspective.[4−7] In the chemical manufacturing industry oxidations utilizing molecular oxygen as terminal oxidant are becoming increasingly popular because of their low cost and negligible environmental impact. In the past decades, highly efficient reaction systems have been developed for liquid phase oxidations with gaseous oxygen, and several bulk chemicals, such as cyclohexanol/cyclohexanone (KA oil), cumene hydroperoxide, *tert*-butyl hydroperoxide/*tert*-butyl alcohol, or terephthalic acid, are manufactured on a massive scale by this method.[4] One of the most active and selective catalysts for aerobic, homogeneous liquid phase oxidations is a mixture of cobalt, manganese and bromide salts in acetic acid as solvent (MC-system).[5−7] This reaction system was originally developed for the production of terephthalic acid from *p*-xylene in the 1950s.[5] The method proves to be quite general and hundreds of different carboxylic acids and ketones have been successfully synthesized by this catalytic protocol since then.[5−7]

In contrast to oxidations for the production of bulk chemicals, the synthesis of pharmaceuticals and fine chemicals still relies heavily on stoichiometric oxidants such as permanganate and dichromate, while oxygen or hydrogen peroxide is rarely used.[8] Partly, this is because process-scale syntheses of fine chemicals are typically performed in

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multipurpose stirred tank reactors that are poorly equipped to address safety risks and process challenges associated with reactions using molecular oxygen or hydrogen peroxide. Oxidation reactions with these oxidants are generally strongly exothermic and proceed via highly reactive species such as free radicals. The heat of the reaction can be difficult to dissipate, and the consequential nonisothermal conditions in the reactor lower reaction selectivity and product quality and pose serious safety hazards. Dangers of thermal runaways are very real, and, depending upon the composition, temperature, and pressure, the reaction mixture can ignite spontaneously.[4] On the other hand, even though the oxidation is thermodynamically highly favorable, the reaction is hindered kinetically so that the oxidations often have to be performed at fairly high temperatures (175−225 °C are not unusual for MC-type oxidations).[5] The need to maintain a liquid phase under these conditions demands high-pressure operation, and the often corrosive nature of the reaction mixture at elevated temperatures necessitates the use of equipment lined with titanium or other expensive materials.

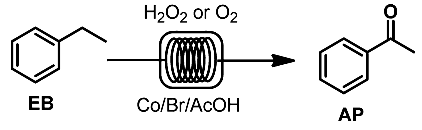
Continuous processing, long established for the production of commodity chemicals, is increasingly implemented for the laboratory and industrial synthesis of pharmaceuticals and fine chemicals. In particular, continuous flow processing in microreactors (channel or capillary diameters of <1000 μm) have become increasingly popular in synthetic organic chemistry, and the advantages of this technology have been extensively utilized in organic synthesis and are discussed in several recent books and review articles.[9,10] Heat and mass transfer can be orders of magnitude higher in microreactors compared to batch reactors, and the improved mass transfer rates can dramatically improve liquid−liquid, gas−liquid, and gas−liquid−solid reactions.[9−11] Importantly, in microreactors rapid mixing and excellent heat transfer can be maintained up to high production rates. Furthermore, combustion and explosion hazards are reduced in microreactors and, consequently, unusually harsh process conditions, for example, reactions in the explosive or thermal runaway regime, can be exploited in a safe and controllable manner. Processing in novel process windows (i.e., high temperature/pressure) reduces reaction times and increases volume productivity, thus allowing smaller plants with smaller capital investment.[12]

The present study was aimed at developing a continuous flow liquid-phase modification of the MC catalytic protocol for benzylic oxidations using the oxidation of ethylbenzene to acetophenone as a model reaction (Scheme 1).[7,13,14] Mechanistic details and differences of the oxidation employing H_2O_2 and O_2 as oxidizing agents under MC-type reaction conditions are discussed.

■ RESULTS AND DISCUSSION

Batch Oxidations with H_2O_2. Initial oxidation reactions were performed on a 0.5 mmol scale with ethylbenzene (**EB**) as the model substrate and with hydrogen peroxide as oxidizing agent in conventional batch equipment (Supporting Information, Figure S1). The redox potential of hydrogen peroxide for the half-reaction H_2O_2/H_2O is ~1.8 V and, thus, one would expect this peroxide to be a very powerful oxidant.[15] However, hydrogen peroxide is, in fact, a relatively mild oxidizing agent and requires activation for oxidations to occur. In the present study, $CoBr_2$ was used to catalyze the oxidation, and acetic acid was used as the solvent. Although $CoBr_2$ in acetic acid is primarily used for C−H oxidations with molecular oxygen (MC system),[5,6] the catalytic ability of the Co/Br/acetic acid system has been demonstrated also for oxidations using H_2O_2 as the oxidant.[16] The bromide ion is thereby essential for the oxidation and almost no reaction was observed in the absence of bromide (see Supporting Information, Table S1). In fact, the oxidation proceeds also in the presence of other bromide sources,[17,18] but, in our hands, by far the fastest reaction was obtained with $CoBr_2$ as the catalyst (see Supporting Information, Table S1). The reaction of **EB** at 80 °C with 2.9 equiv of 35% aqueous H_2O_2 in the presence of 10 mol % $CoBr_2$ in AcOH as solvent gave conversions of **EB** of 87% after a reaction time of 45 min (HPLC peak area integration at 215 nm). Indeed, conversions of around 60% were obtained already after 3 min, but the reaction slowed down dramatically after the first minutes (Figure 1). The reaction proceeded via an intermediate, which was tentatively assigned to the (1-hydroperoxyethyl)benzene (**HPEB**), and provided mainly acetophenone (**AP**), 1-phenylethanol (**PE**), and the acetic ester of 1-phenylethanol (**PEA**) as the products (Figure 1). (1-Bromoethyl)benzene, proposed as the key intermediate for H_2O_2 oxidations catalyzed by cerium salts, was not detected in these reactions.[18] As already hypothesized by van de Water and Maschmeyer[16b] for the H_2O_2 oxidation of 4-*tert*-butyltoluene,

Scheme 1. General Strategy for the Continuous Flow Oxidation of Ethylbenzene



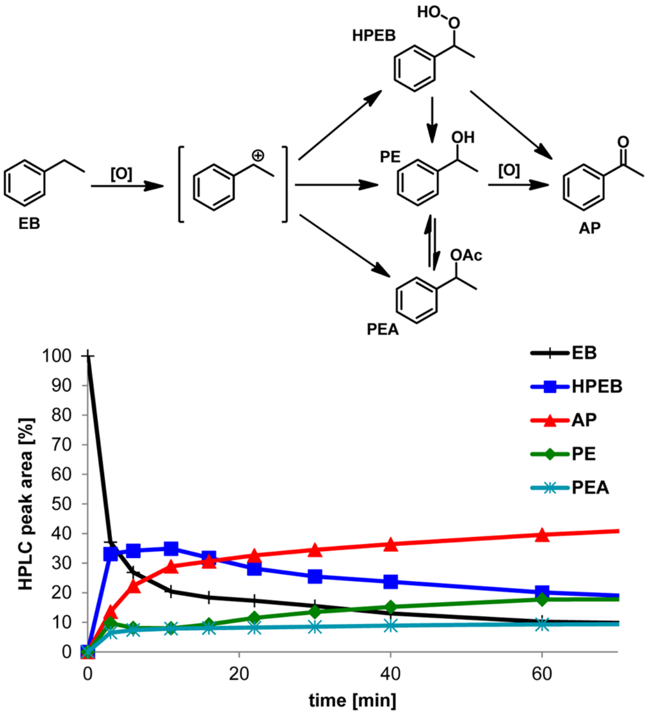


Figure 1. Batch oxidation of ethylbenzene (**EB**) with 35% aq. H_2O_2 (2.9 equiv), 10% $CoBr_2$ in AcOH at 80 °C (HPLC peak area integration at 215 nm); **HPEB** = (1-hydroperoxyethyl)benzene, **AP** = acetophenone, **PE** = phenylethanol, **PEA** = 1-phenylethyl acetate.

the bromide ion is probably oxidized first to the bromine radical in a cobalt catalyzed reaction. This radical abstracts the benzyl hydrogen atom of the substrate and forms a benzylic radical. The benzylic radical is then further oxidized to a cationic species, which subsequently reacts with any of the nucleophiles present in the reaction mixture (i.e., H_2O_2, H_2O, AcOH). The hydroperoxide decomposes to either phenylethanol (**PE**) or acetophenone (**AP**), and phenylethanol is either oxidized to the ketone **AP** or acetylated to the ester **PEA** (Figure 1). Indeed, phenylethanol (**PE**) reacts rapidly to acetophenone (**AP**) under the reaction conditions (Supporting Information, Figure S2). After extended reaction times, acetophenone (**AP**) was further oxidized to 2-bromoacetophenone **BrAP** (e.g., ~5% bromoacetophenone after 250 min; HPLC 215 nm).

The fastest reaction was obtained with 10 mol % of $CoBr_2$, and lower or higher catalyst loadings decreased the reaction rate of the ethylbenzene oxidation (see Table 1 and Supporting Information, Figure S2). On the other hand, the decomposition rate of the intermediate hydroperoxide **HPEB** increased with increasing amounts of $CoBr_2$, and phenylethanol (**PE**) along with phenylethyl acetate (**PEA**) became the main products (Table 1). This indicates that $CoBr_2$ is involved not only in initiating the oxidation of **EB** but also in decomposing the hydroperoxide to phenylethanol. The reaction was somewhat faster in formic acid as the solvent with conversions of 98% after 45 min at 80 °C using 2.9 equiv of 35% H_2O_2 and 10 mol % of $CoBr_2$ as catalyst. However, significant amounts of benzoic acid (24%) were formed as a side product. In trifluoroacetic acid, on the other hand, no acetophenone was formed at all, and only ring-brominated products were detected along with unconsumed starting material.

Table 1. Oxidation of Ethylbenzene (EB) with 35% aq. H_2O_2 (2.9 equiv) in AcOH at 80 °C after 45 min Reaction Time (Figure 2)[a]

$CoBr_2$ [mol %]	EB [%]	PE [%]	HPEB [%]	AP [%]	PEA [%]	BrAP [%]
2.5	26	9	41	22	2	2
5	18	13	29	34	4	2
10	13	15	24	36	9	3
20	17	19	13	34	13	4
40	24	23	5	25	17	6
80	34[b]	17	0	15	24	4

[a] HPLC peak area integration at 215 nm. [b] Further unidentified side-products were detected; **PE** = phenylethanol, **HPEB** = (1-hydroperoxyethyl)benzene, **AP** = acetophenone, **PEA** = 1-phenylethyl acetate, **BrAP** = 2-bromoacetophenone.

As shown in Figure 1, the oxidation rate decreased significantly after the first few minutes and ultimately the reaction stopped completely. The gradual deactivation of the $CoBr_2$ catalyzed benzylic oxidation with hydrogen peroxide has been reported in previous studies.[16] According to Amin and Beattie, the oxidation of 4-*tert*-butyltoluene stopped at approximately 25 to 30% conversion after a fast initial oxidation of 4-*tert*-butyltoluene to *tert*-butylbenzaldehyde.[16a] It was hypothesized that the water formed during the oxidation reaction inhibits the reaction. However, the addition of 3 equiv of H_2O to the reaction mixture did not inhibit the reaction and, further, the oxidation of EB gave virtually identical results with 35% and 50% H_2O_2 (see Supporting Information, Figure S3). It was further suggested that phenols, formed in small amounts as side-products, or the aldehyde product itself may poison the reaction.[16a] In addition, bromide may be depleted from the reaction mixture by the formation of brominated side products. However, in our hands it was not possible to reinitiate the reaction by the addition of an additional bromide source (e.g., LiBr) or by addition of further $CoBr_2$. The addition of more H_2O_2 also did not increase the obtainable yields of acetophenone appreciably (see Supporting Information, Table S2).

Unfortunately, inhibition of the reaction could not be mitigated by heating the reaction mixture to higher temperatures (sealed vessel microwave heating on a 0.5 mmol scale). For example, the conversions achieved after 20 min (2.5 or 5 mol % $CoBr_2$) were virtually identical, independent of the used reaction temperature in a temperature range of 80 to 140 °C (Figure 2a and 2b). The peroxide intermediate **HPEB** was not observed at temperatures above around 120 °C, but small amounts of benzaldehyde and benzoic acid started to form at these temperatures (up to 5 and 3%, respectively, at 140 °C with 2.5% $CoBr_2$).

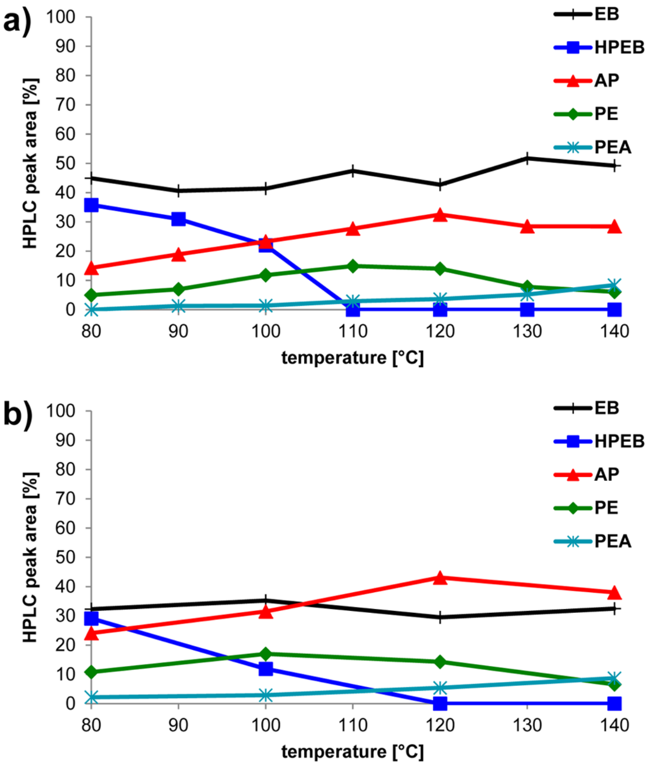


Figure 2. Oxidation of ethylbenzene (**EB**) at different temperatures (sealed vessel microwave heating, HPLC peak area integration at 215 nm). Conditions: 1 M **EB** in 35% aq. H_2O_2 (2.9 equiv) and AcOH; 20 min reaction time; (a) 2.5 mol % $CoBr_2$; (b) 5 mol % $CoBr_2$; **HPEB** = (1-hydroperoxyethyl)benzene, **AP** = acetophenone, **PE** = phenylethanol, **PEA** = 1-phenylethyl acetate.

Continuous Flow Oxidations with H_2O_2. For continuous flow oxidations with H_2O_2, the reaction mixture was pumped by two HPLC pumps through a 6.4 m stainless steel tube reactor heated to 130 °C (1.0 mm i.d., 5 mL reactor volume). The processed reaction mixture was cooled in a plate heat exchanger and left the flow system through a 500 psi back pressure regulator (see Supporting Information, Figure S4).[19] All flow reactions were performed on a 20 mmol scale with 5

Table 2. Oxidation of Ethylbenzene EB with H_2O_2 under Continuous Flow Conditions[a]

flow rate [mL min^{-1}]	RT [s]	**EB** [%]	**BA** [%]	**PE** [%]	**BAL** [%]	**HPEB** [%]	**AP** [%]	**PEA** [%]	**BrAP** [%]
16	19	28	0	17	4	5	37	4	1
12	25	30	0	17	4	5	35	4	1
8	38	29	0	18	5	0	38	5	1
4	75	28	0	18	5	0	39	6	2
2	150	27	2	17	6	0	39	5	3
1	300	34	3	16	6	0	33	5	3

[a] HPLC peak area integration at 215 nm. Conditions: 20 mmol ethylbenzene (**EB**), 5 mol % $CoBr_2$, 2.5 equiv of 50% H_2O_2 in AcOH (15 mL) were pumped through a 5 mL stainless steel tube reactor at 130 °C. **BA** = benzoic acid, **PE** = phenylethanol, **BAL** = benzaldehyde, **HPEB** = (1-hydroperoxyethyl)benzene, **AP** = acetophenone, **PEA** = 1-phenylethyl acetate, **BrAP** = 2-bromoacetophenone; RT = residence time.

Table 3. Aerobic Oxidation of Ethylbenzene (EB) in AcOH at 80 °C (90 min)[a]

catalyst [mol %]	cocatalyst [mol %]	**EB** [%]	**BA** [%]	**PE** [%]	**AP** [%]	**PEA** [%]	**BrAP**[b] [%]
2.5/$CoBr_2$		42	0	18	30	8	3
5/$CoBr_2$		9	0	10	59	17	5
10/$CoBr_2$		29	0	10	15	40	5
20/$CoBr_2$		48[c]	0	4	4	41	3
2.5/$CoBr_2$	2.5/$Co(OAc)_2$	19	1	13	56	5	6
2.5/$CoBr_2$	2.5/$Mn(acac)_2$	10	2	14	64	8	2
2.5/$CoBr_2$	2.5/$Mn(OAc)_2$	12	2	18	60	6	2
2.5/$CoBr_2$	2.5/$Mn(OAc)_3 \cdot 2H_2O$	9	2	13	69	6	2
2.5/$CoBr_2$	2.5/$MnBr_2$	3	1	6	65	18	6
2.5/$Co(OAc)_2$	2.5/$MnBr_2$	7	2	12	67	8	3

[a] HPLC peak area integration at 215 nm (corrected for response factors, see Supporting Information, Figure S5). Conditions: 1.33 M solution of ethylbenzene **EB** in AcOH was stirred in an open vial for 90 min at 80 °C. [b] Response factor of **BrAP** was assumed to be the same as for **AP**. [c] Further unidentified side-products were detected; **BA** = benzoic acid, **PE** = phenylethanol, **AP** = acetophenone, **PEA** = 1-phenylethyl acetate, **BrAP** = 2-bromoacetophenone; acac = acetylacetonate.

mol % of $CoBr_2$ as catalyst and 2.5 equiv of 50% aq. H_2O_2 in AcOH as solvent. The continuous flow reaction revealed that conversions of ethylbenzene of about 70% were, in fact, attained already after reaction times of just ~19 s at 130 °C. Unfortunately, however, analogous to the experiments performed in the microwave batch reactor under comparable conditions, the reaction then stopped and did not proceed any further (Table 2).

Batch Oxidations with Air. In contrast to oxidations with H_2O_2, the aerobic oxidation of **EB** with $CoBr_2$ in AcOH as solvent was not complicated by deactivation of the reaction system during the course of the reaction. The aerobic oxidation catalyzed by combinations of cobalt and bromide salts is used for the commercial batch production of terephthalic acid and a variety of other carboxylic acids, and the relevant chemistry has been comprehensively reviewed by Partenheimer.[5] The most challenging step for the oxidation of alkylbenzenes is the introduction of the initial oxygen while subsequent oxidations generally proceed with ease. Therefore, the selective aerobic oxidation of alkylbenzenes to ketones is relatively difficult to perform. Reaction times are usually long (many hours), and conversions of the alkylbenzene are often limited (e.g., ~25% for a commercial process for the production of acetophenone)[3] to minimize the formation of benzoic acid as a byproduct.

In our hands, the oxidation with atmospheric oxygen gave conversions of ethylbenzene of around 90% with around 60 to 70% selectivity for acteophenone after 90 min at 80 °C with 5 mol % of $CoBr_2$. Similar to what was observed for reactions with H_2O_2 as oxidizing agent, the reaction rate (and also the purity of the reaction) decreased with large amounts of $CoBr_2$ and phenylethanol **PE** together with phenylethyl acetate **PA** became the main products at high catalyst loadings (Table 3). The best results were obtained with 5 mol % of $CoBr_2$. Basically identical results were obtained with several combinations of cobalt and manganese catalysts (e.g., $CoBr_2$ and $Mn(OAc)_2$ or $Co(OAc)_2$ and $MnBr_2$; see Table 3). Several other metals, however, inhibit the reaction strongly (e.g., Fe^{2+}, Zn^{2+}, see Supporting Information, Table S3).

It is generally accepted that the $CoBr_2$-catalyzed aerobic oxidation proceeds through a free radical process.[5,20] The initial formation of the organic radical is mediated by a bromine radical. The organic radical is highly reactive and reacts quickly with dioxygen to form a peroxy radical. The peroxyl radical in turn, forms the hydroperoxide or decomposes into the ketone. According to Partenheimer, the former reaction is much slower and can be neglected, so that the majority of the alkylbenzene is directly oxidized to the ketone.[5,20] The metal ions are involved in the oxidation of bromide ions to bromine radicals and in the decomposition of the peroxy radical.[20]

The aerobic oxidation of ethylbenzene appears to proceed via the alcohol **PE** as intermediate which is subsequently oxidized to the ketone **AP**. Acetophenone is then gradually further oxidized to 2-bromoacetophenone and benzoic acid. Ethylbenzene hydroperoxide was not detected as an intermediate in these reactions. Even though exact reaction mechanisms of aerobic oxidations are generally exceedingly complex and the rate laws notoriously nonlinear,[4] the experimental data obtained under batch conditions could be nicely described with the simple kinetic model shown in Figure 3, with each oxidation step assumed to be of zero-order with respect to O_2 (see Supporting Information, Figure S6 for details). A least-squares fit revealed rate constants for this simple model of $k_1 = 0.36 \times 10^{-3}$, $k_2 = 0.61 \times 10^{-3}$, and $k_3 = 0.018 \times 10^{-3}$ s^{-1} for the oxidation of ethylbenzene, phenylethanol, and acetophenone,

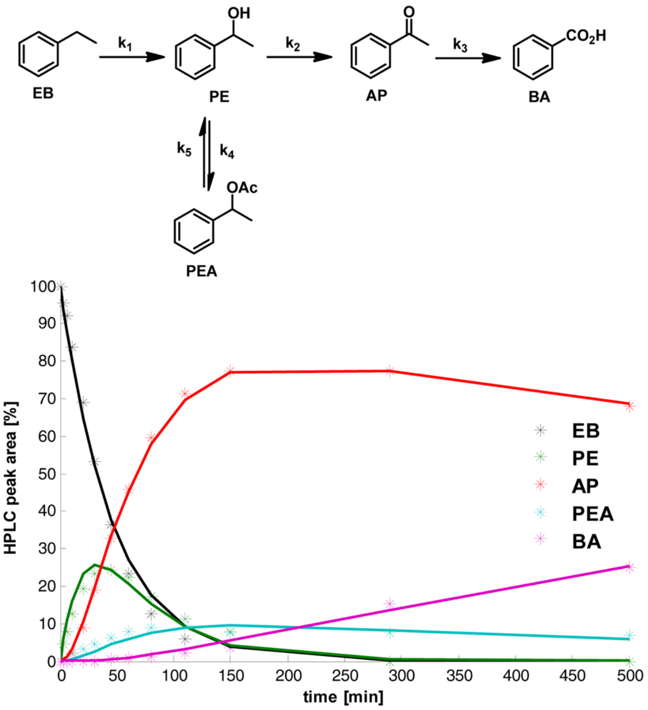


Figure 3. Oxidation of ethylbenzene (**EB**) with air (HPLC peak area integration at 215 nm; corrected for response factors, see Supporting Information, Figure S5). Conditions: 1.3 M **EB** in AcOH, 2.5 mol % $CoBr_2$, 2.5 mol % $Mn(OAc)_2$ stirred in open vial at 80°; points: experimental results; solid lines: kinetic model (see Supporting Information, Figure S6 for details); **BA** = benzoic acid, **AP** = acetophenone, **PE** = phenylethanol, **PEA** = 1-phenylethyl acetate.

respectively, at a reaction temperature of 80 °C (Figure 3). Thus, overoxidation of acetophenone to benzoic acid is about 1 order of magnitude slower than the two preceding oxidations so that acceptable yields of acetophenone can be anticipated. Indeed, with 2.5 mol % $CoBr_2$ and 2.5 mol % $Mn(OAc)_2$, the best selectivity to acetophenone was ~74%, obtained at a conversion of ethylbenzene of ~96% (~150 min reaction time at 80 °C). At higher conversions of ethylbenzene, acetophenone is increasingly oxidized to benzoic acid.

Continuous Flow Oxidations with Air. The kinetics of gas—liquid reactions are, in general, subject to mass-transfer limitations and reaction rate as well as product selectivity can be influenced by gas—liquid mass transport.[4,11] This makes gas—liquid reactions significantly more complicated than single-phase reactions and inherently difficult to scale. Microreactors offer enhanced mass transfer rates which may improve gas—liquid aerobic oxidation and ensure that the reaction operates close to intrinsic kinetics.[11,14]

For continuous flow reactions, the reaction mixture was delivered by a HPLC pump into a T-shaped mixing device where it was combined with synthetic air from a gas cylinder (Figure 4). Because of the zero-order dependence of the oxidation rate on oxygen (as long as the O_2 concentration remains sufficiently high), neither oxidation rate nor selectivity was seriously affected by the choice of gas (see Supporting Information, Table S4). Therefore, synthetic air was chosen as oxygen source rather than pure O_2. The gas flow of the air was controlled using a mass flow controller (MFC). The combined gas—liquid stream passed through a 50 m residence loop (i.d. of 0.8 mm, 25 mL reactor volume) made of perfluoroalkoxy (PFA) heated to the respective reaction temperature in a standard GC oven and left the system through a heat exchanger and an adjustable back pressure regulator (BPR).[21]

With a gas flow rate of 100 mL min^{-1} (gas flow at normal conditions, that is, T_n = 0 °C and p_n = 1 atm), and a flow rate of the liquid stream of 0.7 mL min^{-1}, residence times of 4 to 8 min were obtained in the 50 m PFA coil, depending on the reaction temperature (Table 4). Despite the very short residence times, essentially full conversion of ethylbenzene was achieved at temperatures above 110 °C. Furthermore, with

Table 4. Aerobic Oxidation of Ethylbenzene EB under Continuous Flow Conditions in a 50 m PFA Coil (Figure 4)[a]

temp. [°C]	RT [min]	EB [%]	BA [%]	PE [%]	BAL [%]	AP [%]	PEA [%]	BrAP[b] [%]
100	~8	15	2	15	3	61	1	3
110	~7	5	3	2	0	84	2	4
120	~6	0	11	0	1	80(77)[c]	2	7
140	~5	0	38	0	0	54	0	8
150	~4	0	63	0	0	29	0	7

[a]HPLC peak area integration at 215 nm (corrected for response factors, see Supporting Information, Figure S5). Conditions: feed A: 0.7 mL/min, 5 mL of 1 M solution of ethylbenzene **EB** containing 2.5% $CoBr_2$ and 2.5% $Mn(OAc)_2$ in AcOH; feed B: 100 mL/min synthetic air. [b]Response factor of **BrAP** was assumed to be the same as for **AP**. [c]Based on quantitative HPLC analysis; **BA** = benzoic acid, **PE** = phenylethanol, **BAL** = benzaldehyde, **AP** = acetophenone, **PEA** = 1-phenylethyl acetate, **BrAP** = 2-bromoacetophenone; RT = residence time.

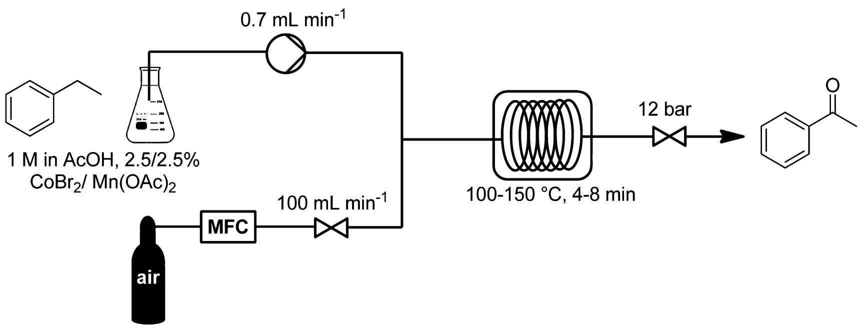


Figure 4. Schematic diagram of the gas—liquid continuous flow reactor. The flow rate of the liquid phase is controlled by an HPLC pump. The gas flow was controlled using a mass flow controller (MFC). The two streams were mixed in a T-shaped mixing device before entering the residence time unit (50 m PFA or 120 m stainless steel, inner diameter 0.8 mm) heated in a GC oven.[21]

Table 5. Aerobic Oxidation of Ethylbenzene EB under Continuous Flow Conditions in 120 m Stainless Steel Coil (Figure 4)[a]

flow rate[b] [mL min^{-1}]	temp. [°C]	RT [min]	**EB** [%]	**BA** [%]	**PE** [%]	**BAL** [%]	**AP** [%]	**PEA** [%]	**BrAP**[c] [%]
0.5	90	26	7	2	8	0	76	2	4
0.4	90	32	3	3	5	1	83	1	4
0.6	100	20	1	5	2	1	84	2	5
0.4	150	16	0	95(89)[d]	0	0	0	2	2

[a] HPLC peak area integration at 215 nm (corrected for response factors, see Supporting Information, Figure S5). Conditions: feed A: 5 mL of 1 M solution of ethylbenzene **EB** containing 2.5% $CoBr_2$ and 2.5% $Mn(OAc)_2$ in AcOH; feed B: 100 mL/min synthetic air. [b] Flow rate of the liquid stream. [c] Response factor of **BrAP** was assumed to be the same as for **AP**. [d] Based on quantitative HPLC analysis; **BA** = benzoic acid, **PE** = phenylethanol, **BAL** = benzaldehyde, **AP** = acetophenone, **PEA** = 1-phenylethyl acetate, **BrAP** = 2-bromoacetophenone; RT = residence time.

a selectivity of 84 and 80% for acetophenone at reaction temperatures of 110 and 120 °C, respectively, the reaction selectivity surpassed the selectivity obtained at 80 °C under batch conditions. Quantitative HPLC revealed an acetophenone content of 77% in the processed mixture recovered from the experiment performed at 120 °C (Table 4). Lower temperatures gave incomplete conversions of ethylbenzene, while higher temperatures increasingly led to overoxidation to benzoic acid (Table 4).

It should be noted, that at 120 °C both ethylbenzene and phenylethanol were fully oxidized to acetophenone. Removing the solvent from the collected reaction mixture and extraction with sat. $NaHCO_3/Et_2O$ provided the crude acetophenone contaminated with 2-bromoacetophenone. To eliminate the bromoacetophenone, the collected reaction mixture was concentrated in vacuum and the crude product was redissolved in ethanol to reduce bromoacetophenone to acetophenone with metallic zinc at room temperature.[22] The mixture was then filtered to afford acetophenone in 66% product yield after evaporation of the solvent and extraction with sat. $NaHCO_3/Et_2O$ (96% purity according H NMR with internal standard).

Replacing the 50 m PFA coil by a 120 m stainless steel coil allowed longer residence times and higher reaction temperatures. At a reaction temperature of 90 °C residence times of ~30 min were required for conversions of ethylbenzene >95%. At a temperature of 150 °C and a residence time of ~16 min, ethylbenzene was basically fully oxidized to benzoic acid (**BA**). The pure benzoic acid was isolated by evaporation of the solvent, extraction with $NaHCO_3/Et_2O$, and precipitation from the aqueous phase with conc. HCl in 71% product yield (Table 5).

CONCLUSION

In conclusion, the cobalt bromide catalyzed benzylic oxidation of ethylbenzene with either aqueous hydrogen peroxide or air in acetic acid was studied. Oxidations with hydrogen peroxide started with a rapid initial C−H oxidation of ethylbenzene to form a mixture of ethylbenzene hydroperoxide, acetophenone, 1-phenylethanol, and 1-phenylethyl acetate. Ethylbenzene hydroperoxide further decomposes to generate either phenylethanol or acetophenone, and phenylethanol is oxidized to acetophenone or acetylated to 1-phenylethyl acetate. The oxidation, however, became inhibited during the course of reaction so that a complete conversion of ethylbenzene and reaction intermediates to acetophenone could not be attained. In contrast, no deactivation of the reaction system was observed for ethylbenzene oxidations with atmospheric oxygen. The reaction gave phenylethanol as an intermediate product while ethylbenzene hydroperoxide could not be detected. Oxidation of both ethylbenzene to phenylethanol and phenylethanol to acetophenone is an order of magnitude faster than the subsequent oxidation of acetophenone to benzoic acid. Thus, after 150 min at 80 °C, a selectivity of ~74% of acetophenone could be obtained at a conversion of ~96% of ethylbenzene. The reaction time of the process reported herein is significantly shorter compared to published examples for the aerobic oxidation of ethylbenzene (reaction times are often in the range of 15 to 50 h).[5] It should be emphasized that, when the reaction rate increases (e.g., at high temperature) or the mass transfer rate decreases (e.g., upon scale-up), the mass-transfer rate may become smaller than the reaction rate and the process becomes controlled by diffusion. A continuous flow process generally offers superior mass transfer characteristics and prevents oxygen depletion during the initial period of fast oxidation. Translating the reaction conditions to a continuous flow protocol allowed increasing the reaction temperature to 110 to 120 °C, thereby decreasing the reaction time to only 6 to 7 min, without compromising the selectivity of the reaction. Essentially pure acetophenone was isolated in 66% product yield without the need for chromatography. Increasing the reaction time to 16 min at a reaction temperature of 150 °C gave benzoic acid as the final product in 71% yield.

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. GC-MS spectra were recorded using a Thermo Focus GC coupled with a Thermo DSQ II (EI, 70 eV). A HP5-MS column (30 m × 0.250 mm × 0.25 μm) was used with helium as carrier gas (1 mL min^{-1} constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. Analytical HPLC analysis (Shimadzu LC20) was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water−acetonitrile 90: 10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Products were characterized by ^1H NMR and mass spectrometry and identified by comparison of the spectra with those reported in the literature. HPLC-response factors were determined by using authentic standards (see Supporting Information for details). ***Caution!*** *Reactions/reagents described herein have the potential to release large amounts of energy in an uncontrolled way.*

These oxidations should not be undertaken without stringent hazard assessment and proper safety precautions put in place.

General Experimental Procedure for Batch Oxidations with H_2O_2 (Figures 1 and 2, Table 1). Into a 5 mL Pyrex screw cap reaction vial equipped with a magnetic stir bar were placed 375 μL of AcOH, 125 μL of 35% aqueous H_2O_2, 5.5 mg of anhydrous $CoBr_2$ (5 mol %), and 0.5 mmol of ethylbenzene. The vial was sealed with a PTFE seal and a screw cap and stirred in a SiC heating block preheated on a hot plate to 80 °C (see Supporting Information, Figure S1).

General Experimental Procedure for Continuous Flow Oxidations with H_2O_2 (Table 2). The reaction feed consisted of 20 mmol of ethylbenzene, 218.7 mg of anhydrous $CoBr_2$ (5 mol %), and 2.8 mL of aqueous 50% H_2O_2 (2.5 equiv) in 15 mL of AcOH. The feed was pumped by two HPLC pumps through a 6.4 m stainless steel tube reactor heated to 130 °C (1.0 mm i.d., 5 mL reactor volume). The processed reaction mixture was cooled in a plate heat exchanger and left the flow system through a 500 psi back pressure regulator (see Supporting Information, Figure S4)

General Experimental Procedure for Aerobic Oxidations under Batch Conditions (Figure 3, Table 3). Into a 5 mL Pyrex screw cap reaction vial equipped with a magnetic stir bar were placed 375 μL of AcOH, 2.7 mg of anhydrous $CoBr_2$ (2.5 mol %), 2.2 mg of $Mn(OAc)_2$ (2.5 mol %), and 0.5 mmol of ethylbenzene. The open vial was stirred in a SiC heating block preheated on a hot plate to 80 °C (see Supporting Information, Figure S1).

General Experimental Procedure for Continuous Flow Aerobic Oxidations to Acetophenone (Tables 4 and 5). Feed A consisted of 5 mmol of ethylbenzene, 27.3 mg of anhydrous $CoBr_2$ (2.5 mol %), 21.6 mg of $Mn(OAc)_2$ dissolved in 5 mL of AcOH. Feed B was synthetic air from a gas cylinder (purity 5.0). Feed A and the gaseous stream were mixed together in a T-shaped mixing device, and the resulting biphasic reaction stream was passed through a 50 m PFA (0.8 mm i.d.) or 120 m stainless steel (0.8 mm i.d.) reactor heated in a GC-oven (Figure 4). The product stream left the system through a heat exchanger and a back pressure regulator adjusted to ∼12 bar.

Acetophenone. Conditions: 120 °C, 6 min residence time. The reaction mixture was collected at the outlet of the flow system, and the mixture was concentrated under reduced pressure. The crude mixture was redissolved in 15 mL of EtOH. One mmol Zn granules were added, and the mixture was stirred for 30 min at room temperature. The mixture was filtered and the solvent removed under reduced pressure. Extraction with sat. $NaHCO_3/Et_2O$ gave 66% of acteophenone as yellowish oil in 96% purity (^{1}H NMR with internal standard). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00−7.89 (m, 2H), 7.59−7.50 (m, 1H), 7.48−7.40 (m, 2H), 2.59 (s, 3H).

Benzoic Acid. Conditions: 150 °C, 16 min residence time. The reaction mixture was collected at the outlet of the flow system, and the solvent was removed under reduced pressure. The crude mixture was extracted with sat. $NaHCO_3/Et_2O$. The aqueous phase was acidified with conc. HCl to ∼pH 1, the precipitate collected by filtration and washed thoroughly with cold 1 N HCl to give 71% of benzoic acid as white crystals. ^{1}H NMR (300 MHz, DMSO) δ = 12.97 (s, 1H), 8.01−7.91 (m, 2H), 7.66−7.58 (m, 1H), 7.52−7.47 (m, 2H).

ASSOCIATED CONTENT

Supporting Information

Supplementary Tables S1−S4 and Figures S1−S7. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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