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Continuous flow photooxidation of alkyl benzenes using fine bubbles for mass transfer enhancement

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ABSTRACT

Selective photooxidation of alkyl benzenes was studied in a custom-built continuous flow photochemical reactor equipped with fine bubble generator and a low power UV light source. Fine bubbles of air were used as an oxidizing agent along with water-soluble sodium anthraquinone sulfonate as catalyst. The fine bubble containing slug-flow system using air was 1.4 times more efficient at lower feed-flow rate of 2 mL/min and 1.8 times more efficient at higher feed-flow rate of 5 mL/min. Ethylbenzene was selectively oxidized in continuous flow to acetophenone at room-temperature, with 90% ethylbenzene conversion and 92% selectivity to acetophenone, with a short residence time of 5 min. The enhanced gas/liquid mass transfer afforded by the fine bubble generator significantly increased reactor productivity, giving rise to high conversion and yield. Due to enhanced mass transfer and greater efficiency, compressed air can be used as oxidant instead of pure O_2, thus alleviating potential safety concerns and making the process safer and more amenable for scale up.

Introduction

Recently photooxidations have gained significant momentum within the pharmaceutical and fine chemical industries. Photooxidations offer several advantages such as the use of clean oxidants, like air/O_2, mild reaction conditions, waste minimization, lower cost, and increased energy efficiency. However, widespread implementation of photooxidations on a large industrial scale is still limited to low-volume, high value chemicals. [1] This underutilization is due to the numerous hurdles associated with the safe implementation, poor gas/liquid mass transfer and limitations of light penetration in batch reactors. Hence, the development of continuous flow photochemical reactors with enhanced gas/liquid mass transfer and improved light penetration is urgently required to achieve safe and scalable photooxidation processes.

A primary limitation of batch photochemical processes related to the Beer–Lambert law, which states that light transmittance decreases exponentially with the distance from the light source. [2] For a standard batch reactor, light intensity decreases considerably from the reactor walls to the middle of the reaction mixture, resulting in slow reactions and non-homogeneous irradiation of the reaction mixture. In order to alleviate this limitation, photochemical reactions can be performed in continuous flow mode in microchannels (i.e. reaction channels with an ID $\leq$ 1 mm). The lower light penetration depth allows for a higher photon flux, meaning that energy transfer is more efficient and therefore reaction times are shorter. Controlling reaction time also has the benefit of higher selectivities as over-irradiation can be mitigated meaning minimal side-products formation.

Another benefit of using microchannel reactors is that they enable and promote a segmented flow pattern, referred to often as Taylor flow. Taylor flow is characterized by an enhanced mixing within the reactor and greater interfacial mass transfer between the gas and liquid phases. [3] This enhanced mass transfer is due to vortices being created in both the liquid and gas segments. [4–5] Recently fine bubbles (FBs) of gas have been investigated for use in Taylor flow type systems. FBs have diameters $\leq$ 100 µm and therefore result in greater gas dissolution and gas-liquid surface area leading to potentially greater conversions than conventional systems. [6–9] As part of this work, the impact of using a FBG-OS type 1 unit from Process Maximize Technologies (PMT) fine bubble generator has been investigated highlighting the

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difference between the use of standard gas bubbles and ultrafine bubbles for photooxidation reactions. The mechanism of fine bubble generation combines pressurised dissolution of the gas and subsequent depressurisation creating a shear force. Work carried out by Mase *et al.* [6] utilizing this model of fine bubble generator showed that it was capable of producing nanosized bubbles with 140 nm diameters and was capable of the production of 6.4×10^7 particles/mL in a single pass for application in a hydrogenation reaction. This is advantageous as the reaction is not solely dependent on the gas/liquid interface obtained during normal Taylor flow operation.

The use of molecular oxygen is very appealing as it is widely accessible, environmentally benign, and efficient in terms of atom economy. However, its use in conjunction with flammable organics raises significant safety concerns, especially for large scale applications. Such safety concerns can be alleviated with microchannel technology. Due to the relatively small dimensions of the channels, there is a low local oxygen and flammable solvent concentration. The continuous nature of the operation and the efficient thermal transfer of the microchannels also minimizes the occurrence of local hot spots and therefore a potential source of ignition. [10]

Of particular interest is the direct oxyfunctionalisation of alkyl benzenes for the production of phenyl ketones. The main routes for phenyl ketones production include Friedel-Crafts acylation, employing acyl halides or acetic anhydride along with copious amounts of aluminium trichloride [11–13] and selective oxidation of alkyl benzenes to corresponding phenyl ketones using stoichiometric oxidants based on reagents such as permanganate, chromic acid, potassium dichromate, or nitric acid. [14–16] The need for stoichiometric quantities of reagents and large amount of waste generated makes the traditional routes undesirable for scale up. For development of an environmentally benign and green process, direct photooxidation of alkyl benzenes to corresponding phenyl ketones using molecular oxygen or air is an attractive alternative as it requires mild process conditions and catalytic amounts of photocatalyst.

Recently, the photocatalytic C—H oxygenation of alkyl benzenes with oxygen has been developed using the relatively inexpensive and widely available Sodium anthraquinone-2-sulfonate (SAS). Work by W. Zhang *et al.* [17–18] and Y. Peng *et al.* [19] successfully investigated the low concentration photooxidation of various non-activated alkanes and alcohols to the respective aldehyde or ketone by employing light at >400 nm under batch conditions over a 24 h to 48 h period. SAS, upon photo-excitation acts as a hydrogen-atom acceptor, and abstracts a proton from the benzylic position, generating SAS-H radical and a benzylic radical. The SAS-H• subsequently reacts with oxygen, regenerating the catalyst along with the production of hydrogen peroxide. The benzylic radical reacts with oxygen to form a mixture of alcohol and ketone, alcohol can further react to form ketone thus resulting in high selectivity to ketone (Fig. 1). [20–21] As seen from the schematic representation of reaction mechanism, the presence of oxygen is necessary to drive the reaction forward, and hence the enhanced mass transfer and increased availability of oxygen using ultrafine bubbles benefits the reaction significantly. The use of SAS as catalyst is also advantageous due to high selectivity to ketone, as the reaction does not proceed to over oxidation of ketone to carboxylic acid. [21] Fig. 2

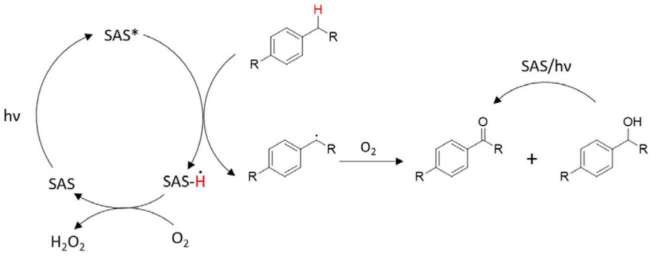

Fig. 1. Proposed reaction mechanism of SAS oxidation of the benzylic position.

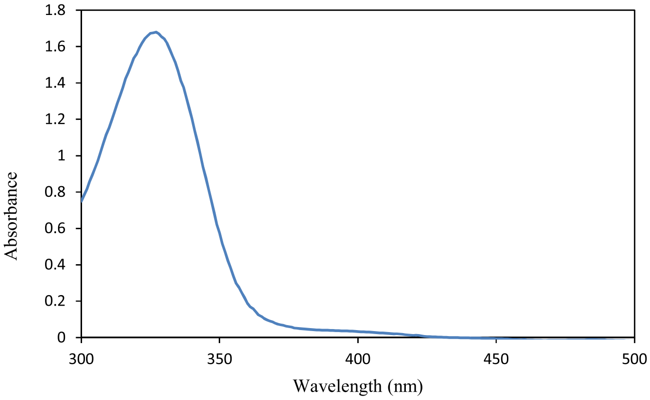

Fig. 2. UV/Vis spectra for SAS in 75 vol% acetonitrile/water (300–500 nm).

The key focus of the work presented herein is the demonstration of the methodology of continuous flow photooxidation for production of phenyl ketones by direct C—H oxidation of alkyl benzenes as model compounds utilizing SAS catalyst. The incorporation of an UFB generator within the continuous flow set-up enhanced the gas liquid mass transfer.

Results and discussion

Batch experiments

To establish process parameters and generate the benchmark conversions and product selectivity, initial experiments were performed in a batch photooxidation reactor. The initial batch experiments were performed using a process modified from literature. [19] All reactions were carried out at ambient temperature; the substrate loading was fixed at 10 g/L and catalyst loading of 20 mol%. The solvent composition consisted of 25% V/V acetonitrile/deionized (DI) water but was modified to 75% V/V acetonitrile/DI water as it was noted that ethylbenzene was poorly soluble at lower acetonitrile ratios resulting in a biphasic system which would potentially add additional complexity for transition to continuous flow in terms of efficient mass transfer. Oxygen solubility should also be much greater in higher acetonitrile mixture. [20–22] The application of a UV light source rather than blue LEDs was also investigated following determination of λ_{max} from UV/Vis absorbance spectra.

As shown in Table 1, entry 3 and 4, using low power UV light bulb (15 W), almost complete ethylbenzene conversion with 45 and 96% selectivity to acetophenone was achieved, which was higher as compared to the reactions using blue LEDs as the light source. The results are complimentary to the UV/Visible absorbance shown in Fig. 1, SAS absorbs much more strongly in the UV region than the blue light region (400 to 450 nm). It was also noted that by using higher acetonitrile concentration, higher yield of acetophenone was obtained, which may be attributed to increased solubility of O_2 in liquid phase (Table 2). All further studies were performed using UV light source and higher acetonitrile concentration for the development of the continuous flow process for selective photooxidation of ethylbenzene.

Flow reactions

A custom flow photochemical reactor was constructed from a 20 m long PTFE tube with a 1 mm I.D., giving a volume of

Table 1
Selective oxidation of ethylbenzene to acetophenone using batch photochemical reactor.

Entry	Solvent composition	Light Source	Reaction time	Conversion	Selectivity
1	25 vol% MeCN/water 20 mol% Catalyst	Blue LEDS	15 h	34%	Ketone- 84% Alcohol- 16%
2	75 vol% MeCN/water 20 mol% Catalyst	Blue LEDS	15 h	43%	Ketone- 65% Alcohol- 35%
3	25 vol% MeCN/water 20 mol% Catalyst	15 W UV Bulb	15 h	99%	Ketone- 46% Alcohol- 53% Other Imps- 2%
4	75 vol% MeCN/water 20 mol% Catalyst	15 W UV Bulb	15 h	100%	Ketone- 96% Alcohol- 1% Other Imps- 3%

Table 2
Solubility of Oxygen in water and acetonitrile [22–24]

Solvent	Temperature (°C)	Solubility O_2 (pure) (mmol L^{-1})	Solubility O_2 Air (mmol L^{-1})
Acetonitrile	24	9.1	9.1
Water	25	1.27	0.27

15.7 mL. This was wrapped around a bespoke 3D printed scaffold constructed from Polylactic acid (PLA). The reactor was illuminated by placing the UV light source in the centre of the scaffold. A peristaltic pump supplied the liquid feed to the reactor coil and compressed gas was supplied with either a mass flow controller (MFC) in the case of compressed air and oxygen or ultra-fine bubble (UFB) generator. Both inlet lines had non-return valves fitted to prevent back flow. The feeds were mixed in a PEEK Tee-piece with a 1 mm thru-hole yielding the desired Taylor flow pattern. The outlet of the reactor was fitted with a back pressure regulator (BPR). The general set-up is shown in Fig. 3

Initial reactor performance in continuous flow was assessed by performing model flow reactions using various residence times, by changing the total feed flow rates, while keeping the liquid and air flow rates equivalent. As shown in Fig. 4, at longer residence times with slower feed flow rates almost complete conversion of ethylbenzene was achieved. For instance, at a residence time of 6.3 min, over 95% ethylbenzene conversion with 80% selectivity to acetophenone was achieved, using the parameters extended from the batch experiments i.e., 20 mol% catalyst and a 1 g/L substrate loading in 75% V/V acetonitrile/DI water as solvent medium and compressed air as the source of O_2 was supplied at 5 bar.

It was observed that the main by-product was 1-phenylethanol, which implies that oxygen availability was not sufficient to achieve complete conversion to the desired ketone. As such, the use of pure O_2 instead of compressed air was investigated for the photooxidation of ethylbenzene. The gas flow rate of O_2 was kept consistent (for direct comparison with use of compressed air) at 2.5 mL/min and the liquid flow rate was varied systematically. All other conditions were kept the same as per previous experiments. As shown in Fig. 5, upon decreasing the liquid feed flow rate to 0.5 mL/min, 98%

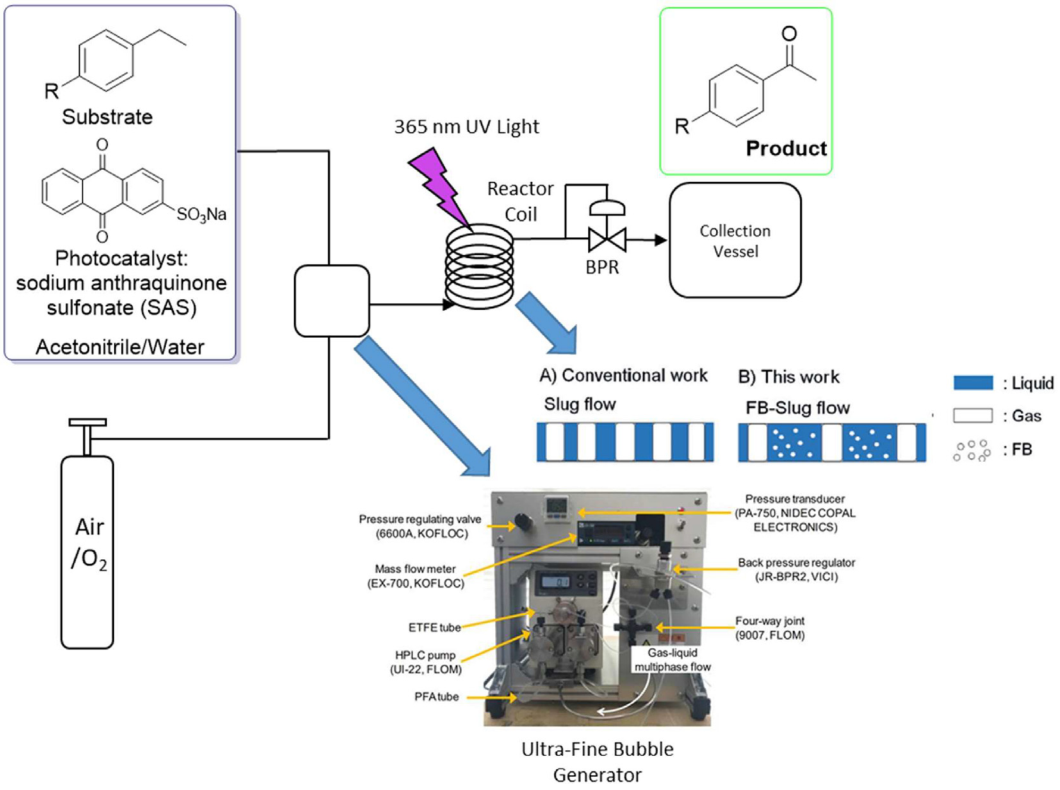

Fig. 3. Schematic representation of custom-built photochemical reactor.

ethylbenzene conversion with close to 100% acetophenone selectivity was achieved using air flow rate at 2.5 mL/min. While varying liquid feed flow rates, high conversion and selectivity was observed at low feed flow rates using both air or oxygen but improved selectivity to acetophenone was observed at low conversions using O_2 instead of air. Literature reports that difference between employing compressed air vs oxygen is negligible if the gas to liquid ratio is sufficiently high as demonstrated. [25]

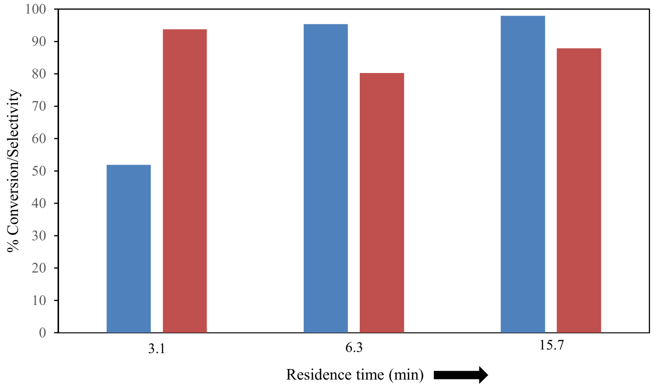

Fig. 4. Effect of increasing residence time (min) on continuous flow photooxidation of ethylbenzene. 🟦-%conversion of ethylbenzene; 🟥-%selectivity to acetophenone; Reaction conditions: Liquid and gas flow rates were kept equivalent.

In continuous flow processes involving gas/liquid phases, excellent mixing and enhanced mass transfer are essential attributes of the process, in particular for scale up. To achieve enhanced gas/liquid mass transfer, the use of UFB generator was investigated. A series of continuous flow experiments were carried out to compare the performance of compressed air, pure oxygen and ultra-fine bubbles of air. An FBG-OS type 1 unit from Process Maximize Technologies (PMT) was used to generate the UFBs, gas flow rate was kept at 50 % of the liquid flow rate, and all other parameters were kept constant. The use of compressed air and pure oxygen without UFB at 2 mL/min liquid feed flow rate, showed similar conversion and marginal improvement in selectivity to acetophenone with O_2, while at higher liquid feed flow rate 5 mL/min without UFB, higher conversion and yield was observed with O_2 in comparison to air (Fig. 6). A significant improvement both in conversion and acetophenone selectivity was observed while using the UFB. Using UFB of compressed air, 90% ethylbenzene conversion with 92% selectivity to acetophenone was achieved at 2 mL/min liquid feed

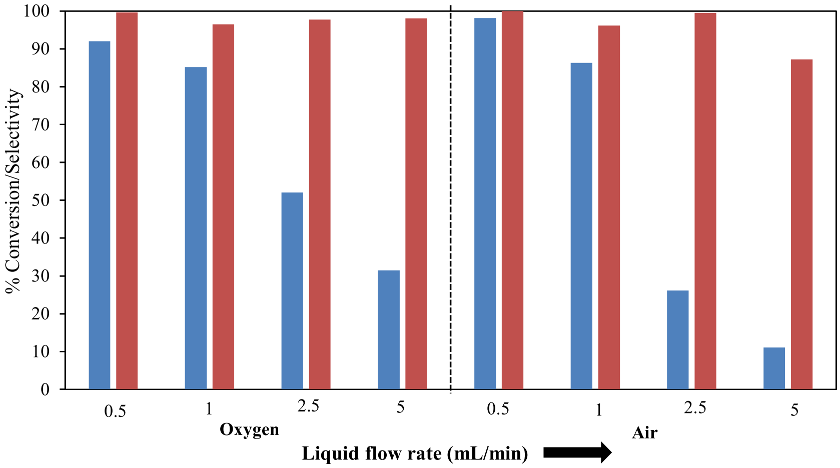

Fig. 5. Effect of the use of pure O_2 or compressed air for the photooxidation of ethylbenzene for various liquid flow rates. 🟦-%conversion of ethylbenzene; 🟥-%selectivity to acetophenone; The gas flow rate was fixed at 2.5 mL/min. Liquid flow rate was varied between 0.5 and 5 mL/min.

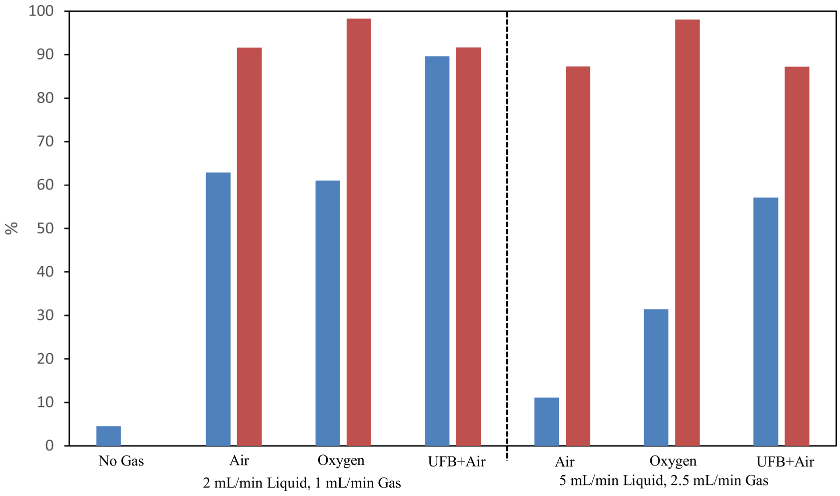

Fig. 6. Comparison of continuous flow photooxidation of ethylbenzene using no air, air, oxygen, and UFB generator with air at varying gas and liquid feed flow rates. 🟦-% conversion of ethylbenzene; 🟥-%selectivity to acetophenone.

flow rate. This is a very promising result as it represents a ~30% increase in reactor throughput as well as being inherently safer than utilizing pure oxygen as the microbubbles consist of compressed air.

Substrate scope

To extend the scope and demonstrate the robustness of the methodology, selective oxidation of several other model substrates, namely 4-ethylanisole 1-bromo-4-ethylbenzene and pentylbenzene, were also investigated using the experimental conditions investigating further the effect of utilization of UFB. As shown in Fig. 7, 96% 4-ethylanisole conversion was achieved with 98.5% selectivity to 4-methoxyacetophenone with the uplift in conversion and selectivity attributed to the electron donating nature of the methoxy group. On the contrary, photooxidation of 1-bromo-4-ethylbenzene (Fig. 8) with the electron withdrawing nature of the functionalization resulted in only moderate conversion and selectivity to 4-bromoacetophenone compared to unsubstituted ethylbenzene substrate. Importantly though there was still a marked improvement in conversion and selectivity to corresponding ketone upon the use of UFB. The results obtained for pentylbenzene (Fig. 9) also showed significant increase in pentylbenzene conversion and selectivity to corresponding ketone. There was also a noticeable improvement in the selectivity to valerophenone, with the major by-products being fenipentol (the alcohol functionality) at 15% and benzaldehyde 14%. Thus, the implementation of the ultra-fine bubble generator yielded superior yields of corresponding ketones for all substrates investigated. Further work is on-going to assess and optimize a broader range of substrates utilizing this method.

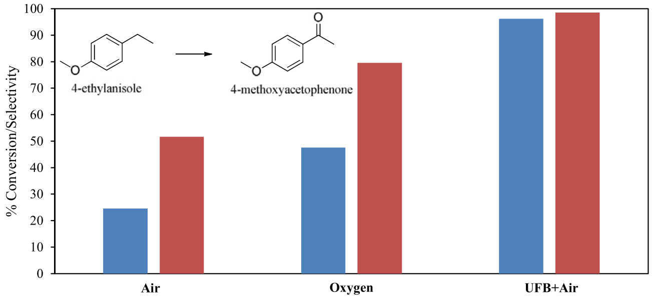

Fig. 7. Comparison of continuous flow photooxidation of ethylanisole using air, oxygen, and UFB generator with air. 🟦-% conversion of 4-ethylanisole; 🟥-% selectivity to 4-methoxyacetophenone. *Reaction conditions: Liquid feed flow rate 2 mL/*min, *gas flow rate 1 mL/*min, *solvent 75 vol% acetonitrile/water, catalyst 20 mol% SAS, low power UV lamp (15 W), room temperature.*

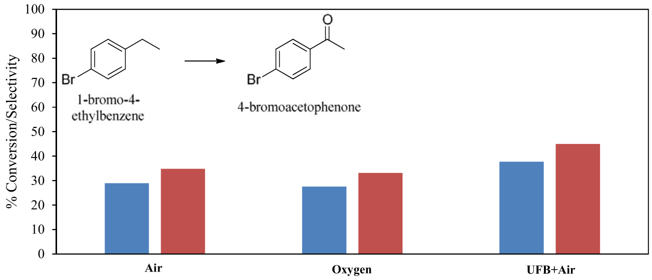

Fig. 8. Comparison of continuous flow photooxidation of 1-bromo-4-ethylbenzene using air, oxygen, and UFB generator with air. 🟦-%conversion of 1-bromo-4-ethylbenzene; 🟥-%selectivity to 4-bromoacetophenone. *Reaction conditions: Liquid feed flow rate 2 mL/*min, *gas flow rate 1 mL/*min, *solvent 75 vol% acetonitrile/water, catalyst 20 mol% SAS, low power UV lamp (15 W), room temperature.*

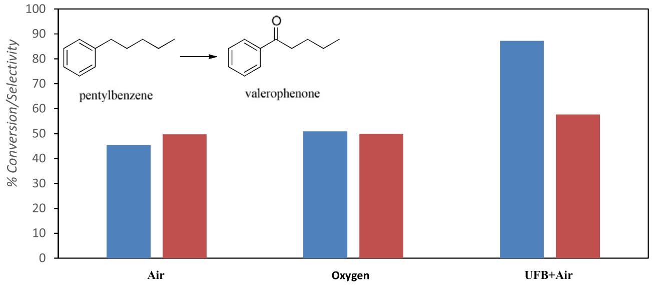

Fig. 9. Comparison of continuous flow photooxidation of pentylbenzene using air, oxygen, and UFB generator with air. 🟦-% conversion of pentylbenzene; 🟥-% selectivity to valerophenone. *Reaction conditions: Liquid feed flow rate 2 mL/*min, *gas flow rate 1 mL/*min, *solvent 75 vol% acetonitrile/water, catalyst 20 mol% SAS, low power UV lamp (15 W), room temperature.*

Conclusions

In summary, a novel methodology for continuous flow photooxidation of alkyl benzenes to corresponding phenyl ketones is demonstrated with high yields, under ambient temperature and high feed flow rates, using a custom-built photochemical reactor. Translating the batch process conditions to continuous flow platform equipped with UFB, allowed to achieve near complete ethylbenzene conversion with 92% selectivity to acetophenone at room temperature. By using ultra-fine bubble generation, it was possible to enhance the gas/liquid mass transfer and achieve significant improvements in the conversion and overall yield of corresponding phenyl ketones at relatively short residence times. The continuous flow photooxidation of ethylbenzene equipped with the UFB, was found to be 1.4 times more efficient at lower feed-flow rate of 2 mL/min and 1.8 times more efficient at higher feed-flow rate of 5 mL/min. The scope of this methodology was further extended to other substrates including the selective oxidation of 4-ethylanisole, 1-bromo-4-ethylbenzene and pentylbenzene to corresponding ketones. The use of UFB generator not only significantly improves the through-put over standard segmented flow, but also has an inherent safety advantage as it negates the need for the use of pure oxygen. Herein, a robust and scalable continuous flow platform for photooxidations under ambient temperature has been developed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153613.

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