

# A Safe and Efficient Flow Oxidation of Aldehydes with O<sub>2</sub>

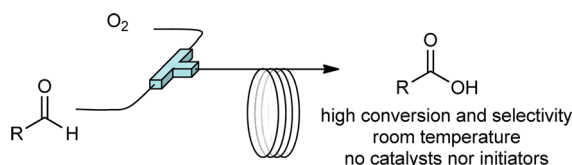
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## ABSTRACT



A safe, straightforward, and atom economic approach for the oxidation of aliphatic aldehydes to the corresponding carboxylic acids within a continuous flow reactor is reported. Typically, the reaction is performed at room temperature using 5 bar of oxygen in PFA tubing and does require neither additional catalysts nor radical initiators except for those already contained in the starting materials. In some cases, a catalytic amount of a Mn(II) catalyst is added. Such a flow process may prove to be a valuable alternative to traditionally catalyzed aerobic processes.

The metal catalyzed oxidation of aldehydes to the corresponding carboxylic acids using environmentally friendly oxidants has gained popularity in recent decades. This oxidation has been a long-standing interest in synthetic organic chemistry, since aldehydes are obtained by the straightforward transition-metal-catalyzed carbonylation of alkenes known as the oxo synthesis.<sup>1</sup> Thus, a wide range of oxidants, catalysts, and conditions have been studied for such an oxidation but generated undesirable waste products.<sup>2</sup>

The growing awareness of the environment has created a demand for efficient oxidation processes with environmentally

friendly oxidants under mild conditions. Highly efficient, selective, and metal-free oxidation of aldehydes have been reported with hydrogen peroxide<sup>3</sup> and oxone.<sup>4</sup> However, pure dioxygen or dioxygen from air are the ultimate “green” oxidants, and several procedures have been reported for the aerobic oxidation of aliphatic aldehydes to the corresponding carboxylic acids.<sup>5,6</sup>

The aerobic oxidation of aldehydes takes place in three stages (Scheme 1): (i) a free radical chain reaction (autoxidation) of aldehyde **1** to form the corresponding peracid **2**; (ii) a nucleophilic addition of the peracid to a remaining aldehyde to produce a tetrahedral adduct **3** similar to the Criegee intermediate observed in the Baeyer–Villiger reaction; and (iii) rearrangement of the tetrahedral adduct by migration of the hydrogen

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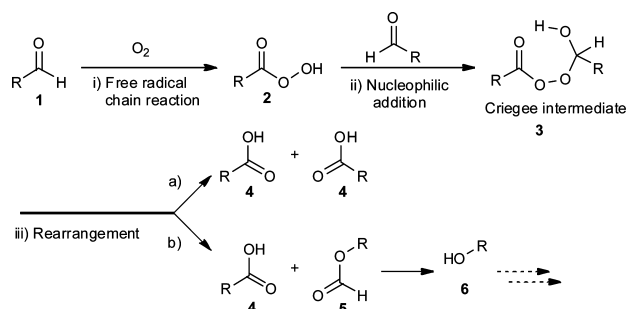
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(path a) or alkyl (aryl) group from the aldehyde (path b) leading to 2 mol of acid **4** (path a) or 1 mol of acid **4** and 1 mol of formate **5** (path b). Generally, path a dominates and the carboxylic acid is the main product. The ratio of hydride to alkyl (aryl) migration was found to depend critically on the structure of aldehydes, temperature, and solvent among others.<sup>7</sup> Furthermore, from Scheme 1, one can see that molecular oxygen is obviously an ideal oxidant for such a transformation since both oxygen atoms in O<sub>2</sub> are utilized for oxidation (100% atom efficiency).<sup>8</sup>

### Scheme 1. Stepwise Aerobic Oxidation of Aldehydes



In many of the processes used commercially or described in the literature for the liquid phase aldehyde oxidation, the reaction rate is limited by oxygen transfer.<sup>5</sup> Oxygen is typically introduced into the liquid through air bubbles. Since oxidation reactions occur in the liquid phase, either in the bulk liquid phase or in the film which surrounds air bubbles, adequate mass transfer of oxygen is critical because the oxygen solubility in common solvents is low.<sup>9</sup> The driving force for oxygen mass transfer could be significantly improved by replacing air with oxygen. However, in a conventional stirred reactor and a bubble column reactor, the oxygen partial pressure of the exiting waste air stream must be maintained below a practical safety limit of 5% in order to prevent formation of flammable gas mixtures in the reactor head space.<sup>10</sup>

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(8) An excess of O<sub>2</sub> was used in the publication in order to minimize the variation of the superficial velocity owing to the bubble shrinking. A complete conversion of O<sub>2</sub> has already been observed in microreactors in our laboratory; see: Leclerc, A.; Alame, M.; Schweich, D.; Pouteau, P.; Delattre, C.; de Bellefon, C. *Lab Chip* **2008**, *8*, 814–817. The reaction can also be performed using pressurized air. Nevertheless P(O<sub>2</sub>) decreases during the course of the reaction which has a strong effect on the rate.

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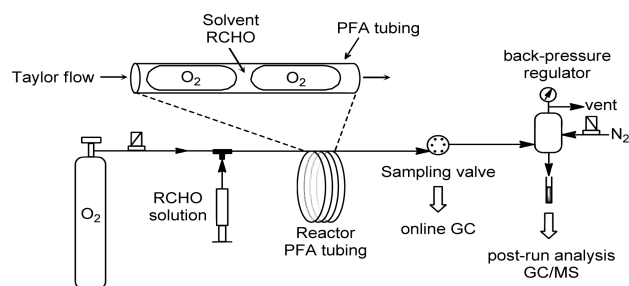
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Recently, flow chemistry has opened new, exciting opportunities in fundamental studies of chemical reactions.<sup>11</sup> In particular, flow chemistry demonstrated safety advantages in conducting highly reactive chemical processes<sup>12</sup> and, among them, oxidation processes.<sup>13</sup>

In the case of aldehyde oxidation, the flammability hazard associated with the oxygen and the organic vapor mixture could be mitigated by the reduction of the explosion region.<sup>14</sup> Furthermore, continuous flow gas–liquid processes offer advantages of large and well-defined interfacial areas, fast mixing, and reduced mass-transfer limitations.<sup>15</sup> Among the different flow modes, Taylor flow is a special case of slug flow where the liquid slugs are separated by elongated bubbles. Taylor flow has been shown to increase heat and mass transfer compared to single phase laminar flow because of the recirculation within the liquid slugs.<sup>15</sup> Thus, we investigated the possibility of utilizing Taylor flow for the oxidation of aliphatic aldehydes using pure oxygen. In designing our continuous flow reactor (Figure 1), we sought to make it as simple as possible using cheap, disposable PFA tubing (internal diameter of 1 mm) that allows simple visual monitoring (see the Supporting Information).



**Figure 1.** Experimental setup for the aldehyde oxidation under Taylor flow conditions with online GC analysis, back pressure controller, and sampling system.

Initial tests were carried out on **1a**, an industrially important aldehyde produced worldwide on a large scale (Table 1, entry 1).<sup>16</sup> Preliminary experiments were started

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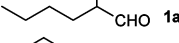
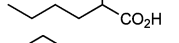
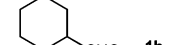
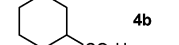
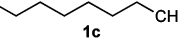
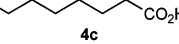


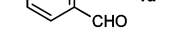
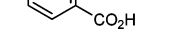
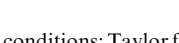
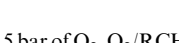
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(17) Solvent effects have been studied (see ref 5c), and heptane was found to be a rather good compromise between O<sub>2</sub> solubility, viscosity, and vapor pressure.

**Table 1.** Continuous Flow Aerobic Oxidation of Aldehydes at Room Temperature<sup>a</sup>

| entry | substrate   | product   | residence time (min) | conversion (%) <sup>b</sup> | selectivity (%) <sup>b</sup> | yield (%)       |
|-------|---|---|----------------------|-----------------------------|------------------------------|-----------------|
| 1     |   |   | 1.8                  | 52                          | 75                           |                 |
| 2     |   |   | 1.8                  | < 2 <sup>e</sup>            |                              |                 |
| 3     |  |  | 17.4                 | 100                         | 75                           | 61 <sup>d</sup> |
| 4     |  |  | 17.4                 | 90                          | > 95                         | 85 <sup>e</sup> |
| 5     |  |  | 16.3                 | 51                          | > 95                         |                 |
| 6     |  |  | 17.4                 | 100 <sup>f</sup>            | > 98                         | 91 <sup>e</sup> |
| 7     |  |  | 15.2                 | 5                           | > 95                         |                 |
| 8     |  |  | 17.4                 | 95 <sup>f</sup>             | > 98                         | 90 <sup>g</sup> |

<sup>a</sup> Reaction conditions: Taylor flow, rt, 5 bar of O<sub>2</sub>, O<sub>2</sub>/RCHO molar ratio of 2.5, 1000 μm of PFA tubing. <sup>b</sup> One-line GC and GC-MS analysis. <sup>c</sup> In the presence of 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), see text. <sup>d</sup> Isolated yield after purification on IXRs (see the Supporting Information). <sup>e</sup> Isolated yield after removal of the solvent under vacuum. Purity higher than 98% by GC/MS and NMR. <sup>f</sup> 100 ppm of Mn(II) 2-ethylhexanoate was added in the aldehyde solution. <sup>g</sup> Isolated yield after removal of the solvent under vacuum and washing the crystal with heptane.

with a PFA tubing of 0.5 m, an oxygen pressure of 5 bar,<sup>8</sup> and 0.8 M aldehyde in heptane.<sup>17</sup> Liquid and gas flows were adjusted to produce a constant Taylor flow (see movie in the Supporting Information), and an excess of oxygen compared to the aldehyde was used (O<sub>2</sub>/RCHO molar ratio of 2.5).<sup>8</sup> At room temperature (25 °C ± 3 °C) and without using metal catalysts or radical initiators, conversions up to 50% were obtained for **1a** in heptane with a residence time of 1.8 min (Table 1, entry 1).

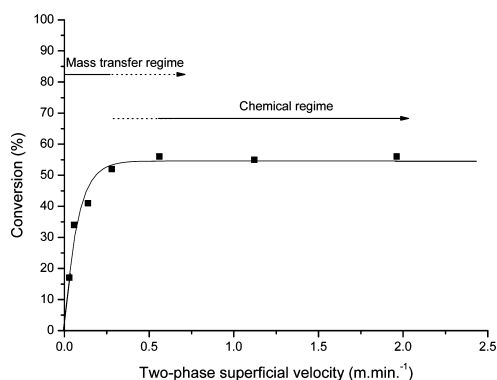
Since oxygen has a paramagnetic ground state (i.e., triplet O<sub>2</sub>), autoxidation relies on the occurrence of other open-shell species, e.g. radicals derived from catalysts or substrates. However, in our conditions, oxidation was performed in the absence of added metals salts that could promote the initiation step. Furthermore, organic solutions are in contact only with glass and PFA and photoactivation can be neglected under our conditions. Thus, extensive control experiments were undertaken, using different suppliers, tubes, and syringes, but the conversion and selectivity were the same within experimental errors.

GC and NMR analysis of the crude material reveals byproducts (i.e., **5a**, **6a**, and 3-heptanone) compatible with a Criegee intermediate (Scheme 1). In order to ascertain the formation of free radical intermediates during the uncatalyzed aldehyde oxidation in the continuous flow reactor, we use EPR spectroscopy and spin trap methodology.<sup>18</sup> Reaction of **1a** with oxygen in the presence of 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) (Table 1, entry 2) suppressed oxidation but gave rise to a persistent free radical with a sufficiently long lifetime which was identified by EPR as an acyl adduct by comparison with the literature data (see the Supporting Information).<sup>18</sup> As the

observation of such acyl adducts is consistent with the free radical autoxidation ((step i), Scheme 1), it can be expected that the autoxidation process was initiated by a trace amount of overoxidized aldehyde present at the ppm level in the starting materials.<sup>19</sup>

Gas liquid transfer efficiency was then evaluated by following the oxidation of **1a** by oxygen with increasing two-phase superficial velocity (Figure 2) while maintaining the residence time constant (1.8 min). This can be obtained by varying the tube length (from 0.05 to 3.5 m) and gas and liquid flow (see the Supporting Information).

As reported in Figure 2, the conversion was shown to increase with the increase of the two-phase superficial velocity to reach an optimum up to 55% for a two-phase superficial velocity above 0.5 m·min<sup>-1</sup>.



**Figure 2.** Conversion of **1a** as the function of the two-phase superficial velocity. Reaction conditions: Taylor flow, residence time 1.8 min, rt, 0.8 M of **1a** in heptane, 5 bar of O<sub>2</sub>, O<sub>2</sub>/RCHO molar ratio of 2.5, 1000 μm PFA tubing; see the Supporting Information for further details.

This result can be explained by an enhancement of the mass transfer due to the increase of the recirculation velocity within the liquid slug.<sup>15</sup>

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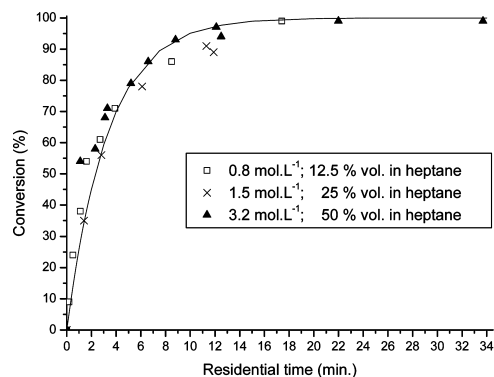
(19) Analysis of the starting materials follows the specification of the suppliers. Others impurities are below the limit of detection. Further investigations are in due course. No radicals could be detected by EPR before reaction.

A higher conversion of **1a** could be simply obtained by increasing the residential time (by increasing the length of the PFA tubing and adjusting the gas and liquid flows). Under these mild conditions (room temperature, no added catalyst), a conversion up to 95% was obtained for **1a** (Table 1, entry 3) with a residential time of 15.2 min. The selectivity toward **4a** (i.e., 75%) was comparable to literature.<sup>5–7</sup>

In order to investigate the scope and potential of this technology we have explored the aerobic oxidation of different commercially available aldehydes. As expected from literature data, the reactivity and selectivity were found to critically depend on aldehyde structure (Table 1, entries 4–8). High conversion and selectivity could be obtained with **1b** (Table 1, entry 4) whereas only a 50% conversion was observed for **1c** under the same conditions (Table 1, entry 5). For **1d**, conversions below 5% occurred under these conditions (i.e., rt, 5 bar of O<sub>2</sub>, 15 min) (Table 1, entry 7). In order to improve the oxidation of these aldehydes, Mn(II) could be used as a catalyst.<sup>5c</sup> Under those conditions, almost quantitative conversions of these aldehydes were obtained (Table 1, entries 6 and 8) which emphasizes the scope of such a continuous flow reactor for safe aerobic oxidation. These corresponding carboxylic acids **4a–d** could be isolated in high yield (see Table 1).

The conversion as the function of residence time was then studied while two-phase superficial velocities were maintained above 0.5 m·min<sup>-1</sup> (Figure 3). Compound **1a** was quantitatively converted (>98%) at room temperature without an added transition metal catalyst or radical initiators for residence times above 15 min. The selectivity for **4a** was almost constant (75%) and independent of the residence time.

Then, the influence of aldehyde concentration was studied. The concentration of **1a** was increased up to 3.2 mol·L<sup>-1</sup> (i.e., 50% vol) while holding constant the other experimental parameters (i.e., O<sub>2</sub>/RCHO molar ratio, two-phase superficial velocity; see the Supporting Information). Such a concentration limit has been chosen to limit modifications of the liquid phase properties that could impact flow characteristics (i.e., viscosity at high conversion, etc.) as well as reaction rate or oxygen solubility. As reported in Figure 3, under those conditions and for a concentration below 3.2 mol·L<sup>-1</sup>, the conversion of **1a** as the function of the residence time was independent of the aldehyde concentration which seems to indicate an order of reaction in aldehyde substrate close to 1. Thus, for a residential time above 15 min, a 50% vol of **1a** in heptane could be safely oxidized using 5 bar of oxygen to **4a**. Under those conditions (uncatalyzed, rt), the selectivity toward acid (75%) was not modified within experimental errors.



**Figure 3.** Uncatalyzed **1a** oxidation as the function of the residence time and concentration. Reaction conditions: Taylor flow, rt, 5 bar of O<sub>2</sub>, O<sub>2</sub>/RCHO molar ratio > 2.5, 1000 μm PFA tubing (see the Supporting Information for further details).

In conclusion, although aerobic oxidation of aldehyde is a well-known reaction,<sup>5–7</sup> an important advantage of this continuous flow process was proven. Indeed aliphatic aldehydes could be safely and effectively oxidized into the corresponding carboxylic acid using 5 bar of O<sub>2</sub> at room temperature using neither a transition metal catalyst nor a radical initiator. The selectivity toward carboxylic acid obtained using the continuous Taylor flow regime is comparable to that for aerobic catalyzed batch reactions.<sup>6,7</sup> The simple experimental setup in combination with the benefits given by continuous flow technology, including safety, renders the procedure synthetically very interesting. For less reactive aldehydes, 100 ppm of a Mn(II) catalyst could be implemented in the flow reactor. Further optimization of the aldehyde concentration, solvent, and catalyst is required. Also, development of scale-up strategies for industrial productions is needed.

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**Supporting Information Available.** Safety statements, materials and reagents, general procedure for catalyzed and uncatalyzed reactions, experimental conditions, copies of <sup>1</sup>H, <sup>13</sup>C NMR, and EPR spectra, online GC chromatogram, and Taylor flow movie. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.