Selective oxidation of alkenes to carbonyls under mild conditions†

Jun Xu, Yilan Zhang, Xiaoguang Yue, Jie Huo, Daokai Xiong and Pengfei Zhang

Herein, a practical and sustainable method for the synthesis of aldehydes, ketones, and carboxylic acids from an inexpensive olefinic feedstock is described. This transformation features very sustainable and mild conditions and utilizes commercially available and inexpensive tetrahydrofuran as the additive, molecular oxygen as the sole oxidant and water as the solvent. A wide range of substituted alkenes were found to be compatible, providing the corresponding carbonyl compounds in moderate-to-good yields. The control experiments demonstrated that a radical mechanism is responsible for the oxidation reaction.

Introduction

Carbonyl compounds, such as aldehydes, ketones, and carboxylic acids, are important intermediates owing to their ubiquitous presence and versatile applications in fragrances, food additives, pharmaceuticals, agrochemical chemicals, and other chemical industries. As a consequence, the development of synthetic methodologies for the construction of these compounds has received considerable attention. The oxidative cleavage of alkenes is one of the most attractive methods as alkenes are commercially available and inexpensive building blocks in organic synthesis. Although conventional methods including the ozonolysis reaction3 and the Lemieux–Johnson oxidation reaction4 have been employed for the oxidative cleavage of alkenes, the related safety concerns and use of toxic and expensive reagents limit their applications. To overcome these problems, a number of protocols that employ transition-metals5 or stoichiometric strong oxidants6 have been demonstrated (Scheme 1a). Despite their useful applications, the requirement of expensive and toxic reagents prevents these methods from achieving the necessary green synthesis requirements and atom economy in organic synthesis.

Compared to harmful oxidants, abundant molecular oxygen (O₂) is considered to be a clean and cheap oxidant for the oxidative cleavage of alkenes to carbonyl compounds owing to its inexpensive and environmentally friendly properties. For example, in 2015, Xiao and coworkers reported an iron-catalyzed oxidative cleavage of alkenes to aldehydes and ketones with O₂.7 Later, Wang’s group demonstrated a disulfide-catalyzed, visible-light-induced strategy for the synthesis of aldehydes and ketones from alkenes.7 In 2020, Das et al. disclosed a polymeric carbon nitrides-photocatalyzed selective cleavage of C=C bonds in aryl olefins under an O₂ atmosphere.7 Despite the substantial advances made in the oxidation reaction, the requirements of transition-metal catalysts, extra additives, toxic organic solvents, a high reaction temperature, and high-pressure oxygen mean that these oxygenation transformations fail to meet the demands of ‘Principle 1, Waste Prevention’ in the Principles of Green Chemistry. In this regard, it is desirable to develop the oxidative cleavage of alkenes for the synthesis of carbonyl compounds under greener and milder conditions.

Scheme 1 An overview of methods for the synthesis of carbonyls through the oxidation of alkenes.
On the other hand, owing to the characteristics of being environmentally benign, non-flammable, non-toxic and abundantly available, the use of water as a solvent for organic reactions has attracted extensive attention. Meanwhile, the recently reported photo-induced oxidation reactions offer enormous opportunities for the sustainable synthesis of various organic molecules because they feature a green source of energy. During the preparation of our manuscript, Fu’s group reported the first catalyst-free alkene photooxidation system for the oxidative cleavage of (Z)-trialyl-substituted alkenes containing a pyridyl motif and using air as the sole oxidant. Mechanistic investigations found that the singlet oxygen generated in situ played an important role in the oxidative reaction. Our research interests are mainly focused on developing a green catalytic system for use in organic synthesis. Herein, we demonstrated a photo-induced and tetrahydrofuran (THF)-based radical strategy for the oxidative cleavage of alkenes using O2 as the sole oxidant and water as the solvent (Scheme 1b). The aqueous phase transformation proceeded under very mild conditions, providing practical and sustainable access to carbonyl compounds, such as aldehydes, ketones, and carboxylic acids in moderate-to-good yields.

Results and discussion

The reaction conditions for the oxidation of alkenes were first investigated by evaluating the light source, additive, reaction time, additive dose and reaction atmosphere (see Table 1 and Tables S1–S4, ESI†). When the oxidation reaction was carried out under an O2 atmosphere employing substrate 1a as a starting material in the presence of 50 mol% of THF and 3.0 mL of water and under irradiation from a 400–405 nm LED for 18 h, an 82% yield of aldehyde 3 and a 9% yield of carboxylic acid 52 were isolated (Table 1, entry 1). The effect of the light source on the transformation was then studied. A 52% yield of aldehyde 3 was obtained when the reaction was performed under irradiation from a 410–415 nm LED (Table 1, entry 2). It should be noted that a 25% yield of aldehyde 3 and a 65% yield of carboxylic acid 52 were generated by conducting the oxidation reaction under the irradiation of a 360–365 nm LED (Table 1, entry 3). It was obvious that the reaction was more favorable for the generation of the carboxylic acid under the irradiation using a shorter wavelength light, probably because a shorter wavelength of light is beneficial for the autoxidation of ether to generate peroxide, which plays a key role in the formation of carboxylic acid. To our delight, when the reaction was extended to 36 h, the corresponding carboxylic acid 52 was obtained in an 85% yield (Table 1, entry 4). It was found that the oxygenation efficiency and selectivity were decreased by replacing THF with 1,2-diethoxyethane (DEE) or 1,2-dimethoxyethane (DME) (Table 1, entries 5 and 6). Further experiments varying the reaction time, and additive dose did not improve the yield (Table 1, entries 7–10). The efficiency of the oxidation reactions was dramatically reduced under an air atmosphere. Furthermore, there was no product generated when the reaction was carried out under an N2 atmosphere. These results suggest that O2 may play an important role in the oxidation reaction (Table 1, entries 11 and 12).

With the optimal reaction conditions in hand, we next explored the substrate scope of alkenes for the oxidation reactions. As shown in Table 2, a wide range of aldehydes were obtained in moderate-to-good yields when substituted styrenes (R = aryl and R’ = H) were employed as starting materials. In general, styrenes bearing para-substituents (3–8) demonstrate a better reactivity than those that bear meta- (9–13) or ortho-substituents (14–17) probably owing to the reduced steric hindrance. Alkenes with a fused ring can also be converted into the aldehyde (18) with a 65% yield. It should be noted that heterocyclic alkenes such as 2-vinylpyridine were tolerated, giving the corresponding product (19) in a 52% yield. Subsequently, the substrate scope of the alkenes (R = aryl and R’ = alkyl or aryl) for the synthesis of ketones was studied. The α-methyl styrenes, which bear both electron-donating and electron-withdrawing substituent groups at the ortho-, meta-, or para-positions, can be transformed into the corresponding ketones (20–31) in moderate-to-good yields. Some α-substituted styrenes were also tested under standard conditions, affording the target products (32–35) in acceptable yields. The α-substituted alkenes that contain heterocycles, such as furyl, pyridyl and thieryl, provided the corresponding products (36–39) in lower yields, probably because of the inherent electron deficiency of the substrates or the side reactions. In addition, the reactivity of the terminal alkenes bearing two aryl groups was also evaluated, and a variety of diarylethenes with different functional groups could be oxidized to the corresponding ketones (40–51) in good yields.

Next, the substrate scope for the synthesis of carboxylic acids was investigated. As demonstrated in Table 3, various aromatic carboxylic acids could be obtained by treating the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from given conditions</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td>410–415 nm LED was used</td>
<td>92%</td>
</tr>
<tr>
<td>3</td>
<td>360–365 nm was used</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>360–365 nm was used (36 h)</td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td>THF was replaced with DEE</td>
<td>32%</td>
</tr>
<tr>
<td>6</td>
<td>THF was replaced with DME</td>
<td>32%</td>
</tr>
<tr>
<td>7</td>
<td>0.3 equivalents of THF were used</td>
<td>32%</td>
</tr>
<tr>
<td>8</td>
<td>1.0 equivalents of THF were used</td>
<td>32%</td>
</tr>
<tr>
<td>9</td>
<td>Reaction was performed for 12 h</td>
<td>32%</td>
</tr>
<tr>
<td>10</td>
<td>Reaction was performed for 36 h</td>
<td>32%</td>
</tr>
<tr>
<td>11</td>
<td>Reaction was performed under air</td>
<td>32%</td>
</tr>
<tr>
<td>12</td>
<td>Reaction was performed under N2</td>
<td>32%</td>
</tr>
</tbody>
</table>

Reaction conditions: 1a (0.5 mmol), tetrahydrofuran (50 mol%), H2O (3.0 mL), 400–405 nm LED, rt, O2 (balloon), 18 h. Isolated yields.
corresponding alkenes with THF and O$_2$ under the irradiation of a 360–365 nm LED. It should be noted that the alkenes with halogen groups, which could be further functionalized, were very compatible under the standard conditions, yielding the carboxylic acids (55–62) in moderate-to-good yields.

Furthermore, the 2-vinylpyridine could also be converted into 2-picolinic acid (64) with a relatively lower yield.

To expand the substrate scope, some specific alkenes were tested under the standard conditions (Scheme S1, ESI†). It was found that a 36% yield of benzaldehyde (4) could be obtained by using dienes (1da) as a starting material. Unfortunately, the rest of the alkenes, including enol-ether (1db), aliphatic olefin (1dc) and enone (1dd), were not compatible.

To demonstrate the practicality and efficiency of the oxidation reaction, large-scale synthesis experiments were studied. As demonstrated in Scheme 2a, scaled-up model reactions were carried out to give the corresponding aldehyde 3, ketone 40 and carboxylic acid product 52 in 71%, 74% and 76% yields, respectively. In addition, biologically active compounds such as fenofibrate and ibuprofen derivatives were efficiently synthesized (Scheme 2b). Furthermore, the obtained carbonyl compounds could be further transformed into many useful organic compounds (67–70) in excellent yields by treating them with different reaction conditions (Scheme 3). These results clearly verify that our method has a good application value in the area of organic synthesis.

To investigate the oxidation reaction mechanism, a series of control experiments were conducted (Table 4). The yield of the product was obviously decreased when 2,6-di-tertbutyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinoxylo
(TEMPO) was added, respectively. These results suggest that a radical pathway was involved. The addition of tert-butanol or benzoquinone to the reaction displayed lower yields, which indicated that the hydroxide radical and superoxide radical species could be involved in this transformation. Further addition of sodium azide to the reaction demonstrated that a singlet oxygen species may not be included. 18O-Labelling experiments were then performed to study the actual source of oxygen in the products. The successful observation of 18O-labelled aldehyde 3 and carboxylic acid 52–218O confirmed that the oxygen atoms in the products came from the O2 rather than the water (Scheme 4). The above experimental results indicate that the autoxidation of THF to form peroxide may be involved in this reaction. Then, the control experiments were carried out by using 50 mol% of tert-butyl hydroperoxide (TBHP) as an additive instead of THF (Table 5). To our surprise, a 47% yield of aldehyde 3 and a 41% yield of carboxylic acid 52 were produced. However, the reaction was completely suppressed when the reaction was performed without light, under an N2 atmosphere or with radical inhibitors. These results not only confirmed our previous assumptions, but also demonstrated that after the autoxidation of THF, light, O2 and generated radicals were still the key factors needed to complete the catalytic cycle.

Based on the results of above control experiments and previous reports, a plausible mechanism for the photo-induced selective oxidation reaction was proposed (Scheme 5). Initially, the autoxidation of THF with O2 under the irradiation of LED gives peroxide A,12b,c which is converted to alkox radical B through homolysis. Then, the alkox radical B is electrophili-
General procedure for the synthesis of the aldehydes (3–19)
To a 15 mL tube was added olefins (1) (0.5 mmol), THF (50 mol%) and H2O (3.0 mL). The above mixture was vigorously stirred under O2 (bloon) with the irradiation of light (LEDs, 400–405 nm, 10 W) for 18 h. After this, the resulting aqueous phase was extracted with ethyl acetate and the collected organic layer was washed with brine and dried using MgSO4. The solvent was removed under reduced pressure, and the crude product was further purified using silica gel column chromatography (200–300 mesh silica gel, PE/EA = 10:1) to afford the target product.

General procedure for the synthesis of the ketones (20–51)
To a 15 mL tube was added olefins (1) (0.5 mmol), THF (50 mol%) and H2O (3.0 mL). The above mixture was vigorously stirred under O2 (bloon) with the irradiation of light (LEDs, 400–405 nm, 10 W) for 18 h. After this, the resulting aqueous phase was extracted with ethyl acetate and the collected organic layer was washed with brine and dried using MgSO4. The solvent was removed under reduced pressure, and the crude product was further purified using silica gel column chromatography (200–300 mesh silica gel, PE/EA = 10:1) to afford the target product.

General procedure for the synthesis of the carboxylic acids (52–64)
To a 15 mL tube was added olefins (1) (0.5 mmol), THF (50 mol%) and H2O (3.0 mL). The above mixture was vigorously stirred under O2 (bloon) with the irradiation of light (LEDs, 360–365 nm, 10 W) for 36 h. After this, the resulting aqueous phase was extracted with ethyl acetate and the collected organic layer was washed with brine and dried using MgSO4. The solvent was removed under reduced pressure, and the crude product was further purified using silica gel column chromatography (200–300 mesh silica gel, PE/EA = 3:1) to afford the target product.

Conclusions
In summary, we have reported an efficient and sustainable aqueous reaction for the synthesis of aldehydes, ketones, and carboxylic acids through the photo-induced and THF-based oxidative cleavage of alkenes by using molecular oxygen as the sole oxidant. As displayed using the model systems described, a variety of alkenes can smoothly undergo the reaction, giving the corresponding products in moderate-to-good yields. Control experiments demonstrated that a radical pathway was responsible for the oxidation reaction.

Experimental section

General information
All reagents and deuterated solvents were commercially available and used without further purification. All products were separated using silica gel (200–300 mesh) column chromatography with petroleum ether (PE) (60–90 °C) and ethyl acetate (EA). 1H and 13C NMR spectra were recorded on a Bruker Advance 500 spectrometer at ambient temperature with CDCl3 or CD3SOCD3 as the solvent and tetramethylsilane (TMS) as the internal standard. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC (silica gel 60 F254) plates. High resolution mass spectrometry (HRMS) analysis of the compounds and positive mode electrospray ionization (ESI) were performed using an Agilent 6530 QTOF mass spectrometer. The photoreactor (PL-SX100A) and condenser (CW-5000) were purchased from Beijing Princess Technology Co., Ltd. The Schlenk tube used in the photocatalysis was purchased from Beijing Synthware Glass.

Conflicts of interest
There are no conflicts to declare.

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Notes and references
