Selective C(sp3)−H aerobic oxidation enabled by decatungstate photocatalysis in flow

Citation for published version (APA):

Document license:
CC BY-NC

DOI:
10.1002/anie.201800818

Document status and date:
Published: 03/04/2018

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Selective C(sp^3)–H Aerobic Oxidation Enabled by Decatungstate Photocatalysis in Flow

Gabriele Laudadio, Sebastian Govaerts, Ying Wang, Davide Ravelli, Hannes F. Koolman, Maurizio Fagnoni, Stevan W. Djuric, and Timothy Noël*

Abstract: A mild and selective C(sp^3)–H aerobic oxidation enabled by decatungstate photocatalysis has been developed. The reaction can be significantly improved in a microflow reactor enabling the safe use of oxygen and enhanced irradiation of the reaction mixture. Our method allows for the oxidation of both activated and unactivated C–H bonds (30 examples). The ability to selectively oxidize natural scaffolds, such as (−)-ambroxide, pregnenolone acetate, (+)-sclareolide, and artemisinin, exemplifies the utility of this new method.

A n essential part of modern synthetic chemistry is the development of catalytic methods for C–H bond functionalization only at specific sites within a molecule. In recent years, the field has witnessed great progress with regard to metal-catalyzed distal carbon–carbon bond-forming reactions.[1] Typically, directing groups are used to navigate the metal to the appropriate position to facilitate C–H bond cleavage.[2]

In contrast, analogous C–H oxidation processes appear to be far more complicated and are only available to a limited extent, making it a challenging field in which further improvements are highly desired.[3]Promising results have been obtained using catalytic systems based on iron,[4] palladium,[5] cobalt,[6] manganese,[7] or iridium (Scheme 1a).[8]

Also, biocatalytic approaches have been reported that enable C–H oxidation processes with high substrate specificity and chemoselectivity.[9] Unfortunately, most—if not all—of these strategies suffer from scope limitations, the use of high loadings of expensive and complex catalysts, and the need for tailored strong oxidants, for example, methyl(trifluoromethyl)dioxirane (TFDO).[10] Furthermore, in order to enhance the selectivity of these procedures, directing groups are generally needed to steer the metal to the desired locus of action.

Another approach to enable C–H bond oxidation is through hydrogen-atom transfer (HAT), which can be promoted either thermally,[11] photochemically,[12] or electrochemically (Scheme 1b).[13] Following this strategy, hydrogen atoms can be abstracted to produce highly reactive radical species, which are subsequently trapped in a wide variety of synthetically useful transformations. This synthetic pathway can be considered appealing, since the transformation is promoted by the use of photons or electrons as traceless reagents, thus simplifying the catalytic systems involved and reducing the environmental impact of the transformation itself.[12,13]

Among the different reported photocatalysts, decatungstate (DT) has proved to be a versatile and inexpensive HAT catalyst which can readily perform hydrogen abstraction on C(sp^3)–H fragments upon activation by irradiation with near-ultraviolet light.[14] This strategy allowed for the construction of numerous C–C,[15] C–Si,[16] C–N,[17] and C–F[18] bonds. Intrigued by these seminal reports, we wondered if DT...
catalysis could be used to effect selective C(sp\(^3\))–H aerobic oxidation. Even though the DT-catalyzed direct oxidation of aliphatic compounds has been explored in the past from a theoretical point of view,[14, 20, 21] no synthetically useful methodology was developed so far. We recognized that oxygen as a green oxidant would be needed to highlight the sustainable nature of our methodology. However, direct use of the simple, green, and effective oxidant molecular oxygen is discouraged because of its associated safety hazards and limited solubility in organic solvents, which often leads to mass-transfer limitations. In the past few years, continuous-flow microreactor technology has been hailed as an enabling technology to overcome such limitations, as well as providing means to scale operationally complex transformations, for example, multiphase reactions,[22] hazardous processes,[23] and photochemical transformations,[24] among others.[25] As described below, we present a simple, selective, and synthetically useful decatungstate-photocatalytic aerobic oxidation of C(sp\(^3\))–H bonds using continuous-flow technology to overcome mass- and photon-transfer limitations and safety hazards (Scheme 1c).

As a model system, we selected cyclohexane as a substrate containing unactivated C(sp\(^3\))–H bonds and used tetrabutylammonium decatungstate (TBADT) as the HAT photocatalyst and oxygen as the oxidant (Table 1). Initial reaction optimization was carried out in a cylindrical batch reactor, which allows maximization of the gas–liquid interfacial area and irradiation surface in batch.[26] The reaction mixture was subjected to irradiation generated by a solar simulator. A mixture of cyclohexanone and cyclohexanol was obtained in 37% overall yield when the reaction was carried out in acetonitrile (Table 1, entry 1). Other solvent systems proved less effective, partially because of the limited solubility of TBADT (Table 1, entry 2; see Table S4 in the Supporting Information). By adding an acid to the reaction mixture, the reaction rate could be significantly enhanced, and the selectivity towards cyclohexanone was increased (Table 1, entries 3–5).[26] A survey of different acids (see Tables S2 and S3) revealed that hydrochloric acid was optimal for the desired transformation. In contrast, the addition of a base completely inhibited the oxidation process, most likely owing to the instability of the decatungstate ion under basic conditions.[26] The use of 2 mol% of TBADT appeared to be optimal in terms of catalyst loading (Table 1, entries 4, 6, and 7). No reaction occurred in the absence of TBADT (Table 1, entry 8), thus confirming the photocatalytic nature of our transformation. Finally, increasing the reaction time from 4 to 6 h improved the reaction conversion (Table 1, entry 9).

Despite the promising results obtained in batch, full conversion could not be reached. We surmised that the hampered diffusion of oxygen into the liquid reaction mixture and the limited light penetration were causing the lower efficiency of the batch reactor.[27] Furthermore, the scaling photochemical reaction conditions is known to be very challenging in batch. Hence, we constructed a continuous-flow photomicroreactor consisting of a 750 μm inner-diameter PFA capillary and LED irradiation.[28] The liquid reagents were infused using a syringe pump and merged with an oxygen stream delivered by a mass flow controller (MFC). This setup resulted in the formation of a segmented flow regime, in which ideal mixing occurs through Taylor recirculation patterns (see Table 2).[29] The choice of the appropriate light source is crucial (Table 2, entries 1–3), as optimal results were obtained with 365 nm LEDs, which matched the absorption characteristics of TBADT. Interestingly, higher

### Table 1: Reaction optimization of the C(sp\(^3\))–H oxidation enabled by decatungstate photocatalysis in batch.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>TBADT (mol%)</th>
<th>Solvent</th>
<th>Yield [%][b]</th>
<th>2a</th>
<th>2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>CH(_3)CN</td>
<td>23</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>acetone/(\text{H}_2\text{O}) (4:1)</td>
<td>13</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>CH(_3)CN/(\text{c-HCl}) (1:1)</td>
<td>42</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>CH(_3)CN/(\text{c-HCl}) (2.5:1)</td>
<td>53</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>CH(_3)CN/(\text{H}_2\text{SO}_4) (2.5:1)</td>
<td>42</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>CH(_3)CN/(\text{c-HCl}) (2.5:1)</td>
<td>36</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>CH(_3)CN/(\text{c-HCl}) (2.5:1)</td>
<td>47</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>CH(_3)CN/(\text{c-HCl}) (2.5:1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9(\text{a})</td>
<td>2</td>
<td>CH(_3)CN/(\text{c-HCl}) (2.5:1)</td>
<td>61</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1.0 mmol of cyclohexane, 7 mL of solvent, 4 h. [b] The yield was determined by GC–MS with hexafluorobenzene as an internal standard. [c] Reaction time: 6 h.

### Table 2: Reaction optimization of the C(sp\(^3\))–H oxidation enabled by decatungstate photocatalysis in flow.

<table>
<thead>
<tr>
<th>Entry(\text{a})</th>
<th>(t) [min]</th>
<th>(V) [mL]</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>5</td>
<td>81</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1.0 mmol of cyclohexane, 7 mL of solvent, 4 h. [b] The yield was determined by GC–MS with hexafluorobenzene as an internal standard. [c] Reaction time: 6 h. [d] 365 nm LEDs were used as the light source. [e] A back-pressure regulator (5.2 bar) was used. [f] The reaction was carried out with 5 mol% of TBADT.
oxygen pressures did not lead to an increase in performance, thus suggesting an optimal oxygen concentration in the liquid phase at atmospheric pressure (Table 2, entry 4; see also Table S8). Longer residence times up to 45 min resulted in excellent yields (Table 2, entries 5 and 6). A further improvement was observed when the catalyst loading was increased to 5 mol%, with the formation of the target product in 90% combined yield (Table 2, entry 7).

Having established optimal flow conditions, we next set out to evaluate the scope of the photocatalytic C(sp³)–H oxidation for the conversion of substrates containing activated sp³-hybridized carbon atoms into the corresponding ketones (Scheme 2). Our method enabled the selective oxidation of allylic positions in good yield (product 3, 70%), as well as benzylic positions (products 4–11). Interestingly, tolyl C–H bonds were left untouched in the presence of longer aliphatic chains (product 4), thus highlighting the mild nature of this oxidation method.[30] Tetrahydronaphthalene could be oxidized, yielding the targeted product 1-tetralone (5a) along with the oxidized product naphthoquinone (5b; 91% yield, 1:1 selectivity). A higher selectivity for 1-tetralone (5a) could be obtained in the absence of hydrochloric acid, as the rate of overoxidation is reduced. Another interesting selective oxidation was observed at benzylic positions in the presence of pyridine moieties (products 10 and 11).[15b] Such distal oxidation patterns can be explained by the electron-poor nature of pyridines.[15b] Also, α-alkoxy C–H bonds were oxidized effectively (products 12 and 13). When Boc-protected pyrrolidine was subjected to our reaction conditions, selective oxidation occurred at the α-C–H bond (Shono-type oxidation) in moderate yield (product 14, 23%). Other heterocycles were tolerated as well, such as alkyl-substituted benzofuran derivatives (product 15, 69%). The capacity of this method to selectively modify natural scaffolds was demonstrated by the selective oxidation of (−)-ambr-oxide and pregnenolone acetate in synthetically useful yields (products 16 and 17).

Having established a broadly applicable oxidation protocol for activated carbon atoms, we turned our attention to applying this method to the selective oxidation of unactivated C(sp³)–H bonds. Smaller cycloalkanes, such as cyclopentane, could be oxidized in low yields (product 18, 35%), whereas larger cycloalkanes were converted into the corresponding ketones in excellent yield (products 2a, 82% and 19, 79%).

**Scheme 2.** Scope of the C(sp³)–H oxidation enabled by decatungstate photocatalysis in flow. The oxidation site is indicated in gray and with an asterisk, unless otherwise noted. [a] The yield was determined by GC. [b] The reaction was carried out in the absence of 1 M HCl. [c] The reaction was carried out with CH₂CN/dichloromethane (2.5:1) as the solvent. [d] The reaction was carried out with a residence time of 1.5 h. Boc = tert-butoxycarbonyl.
substituted cyclohexanes, both distal positions γ and δ were successfully oxidized, with a preference for the γ position (products 20 and 21). Ester and ketone functional groups on the cyclohexane ring were well tolerated (products 22 and 23). Interestingly, the only observed oxidation product for cyclohexanone was 1,4-cyclohexanediol (22, 67%) resulting from oxidation at the δ position.[24] In the case of trans-decalin, both the 2- and the 1-position were oxidized in a 1:1:1 ratio (product 24, 49%). Distal C–H bonds were selectively oxidized when the benzylic position was either unavailable (product 25, 42%) or deactivated (product 26, 56%). Biologically active compounds, such as eucalyptol (product 27, 66%) and (1R)-(+)-camphor (product 28, 63%) were also successfully oxidized. In the case of eucalyptol, the less sterically hindered position was selectively targeted, which can probably be attributed to the large size of the tungstate cluster.[33] Another proof of this steric-hindrance-driven selectivity was observed in the oxidation of (+)-scareolide, in which the oxidation occurred preferentially at the C2 position (product 29, 44%).[34] Finally, the utility of our oxidation protocol was convincingly demonstrated by the scalable oxidation of another complex compound, artemisinin, to its natural derivative artemisitene-9 (30) in good yield (59%, 5 mmol scale).

In conclusion, a photochemical C(sp3)–H oxidation method was successfully developed. The method relies on the use of molecular oxygen as a green and sustainable oxidant and inexpensive and commercially available TBADT as the photocatalyst. In order to accelerate the reaction, an operationally simple continuous-flow setup was designed, making this transformation safe and readily scalable. The method enabled the C–H oxidation of both activated and unactivated aliphatic bonds (30 examples). These examples include natural scaffolds, such as (−)-ambroxide, pregnenolone acetate, (+)-scareolide, and artemisinin, thus exemplifying the efficacy of this method.

Acknowledgements

Financial support was provided by the Dutch Science Foundation (NWO) through a VIDI grant for T.N. (Grant No. 14150).

Conflict of interest

The authors declare no conflict of interest.

Keywords: aerobic oxidation · C(sp3)–H functionalization · decatungstate · flow chemistry · photocatalysis


