Scalable and sustainable electrochemical allylic C–H oxidation

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New methods and strategies for the direct functionalization of C–H bonds are beginning to reshape the field of retrosynthetic analysis, affecting the synthesis of natural products, medicines and materials¹. The oxidation of allylic systems has played a prominent role in this context as possibly the most widely applied C–H functionalization, owing to the utility of enones and allylic alcohols as versatile intermediates, and their prevalence in natural and unnatural materials². Allylic oxidations have featured in hundreds of syntheses, including some natural product syntheses regarded as “classics”³⁴. Despite many attempts to improve the efficiency and practicality of this transformation, the majority of conditions still use highly toxic reagents (based around toxic elements such as chromium or selenium) or expensive catalysts (such as palladium or rhodium)². These requirements are problematic in industrial settings; currently, no scalable and sustainable solution to allylic oxidation exists. This oxidation strategy is therefore rarely used for large-scale synthetic applications, limiting the adoption of this retrosynthetic strategy by industrial scientists. Here we describe an electrochemical C–H oxidation strategy that exhibits broad substrate scope, operational simplicity and high chemoselectivity. It uses inexpensive and readily available materials, and represents a scalable allylic C–H oxidation (demonstrated on 100 grams), enabling the adoption of this C–H oxidation strategy in large-scale industrial settings without substantial environmental impact.

Electrochemical oxidation presents an attractive alternative to traditional chemical reagents for large-scale applications, in a large part owing to the generation of less toxic waste than that produced by current chemical processes⁴. In addition, electrochemical conditions are compatible with a wide range of functional groups⁶–¹⁰, tend to have higher overall energy efficiency as compared to thermal processes and, owing to their limited use, offer new intellectual property space for additional chemical reagents for large-scale applications, in a large part owing to the generation of less toxic waste than that produced by current chemical processes⁴. In addition, electrochemical conditions are compatible with a wide range of functional groups⁶–¹⁰, tend to have higher overall energy efficiency as compared to thermal processes and, owing to their limited use, offer new intellectual property space for small-molecule synthesis⁴. The first electrochemical allylic oxidation was reported in 1968¹¹–¹² (Fig. 1c). Direct oxidation of α-pinene (1) led to the fragmentation of the cyclobutane ring with incorporation of methanol or acetic acid (depending on the solvent) to give products 2 in 22%–24% yield. A major advance in this field came in 1985, when the indirect oxidation of 1 using N-hydroxyphthalimide (NHPI) as an electrochemical mediator was reported¹³–¹⁵ (Fig. 1c). Unfortunately, verbenone (3) was isolated in only 13%–23% yield. Although these reactions are not useful in a preparative sense, they were a proof of concept that served as a foundation for our work.

In our own laboratory, systematic and extensive experimentation led to the identification of three modifications of the original precedent¹³–¹⁵, which transformed this process into a synthetically useful electrochemical allylic C–H oxidation (Fig. 2). As described below, these modifications include the addition of a simple co-oxidant, the identification of a new electrochemical mediator, and the design of a reliable and inexpensive set-up.

From the outset of this work, we avoided the use of expensive electrodes such as precious metals (for example, platinum or gold), focusing our efforts exclusively on carbon. Initial optimization was undertaken using graphite rods, but despite clean conversion of starting material to desired product, mass recovery was typically low. We considered that this might have partially been due to absorption of the substrate onto the graphite. Switching to reticulated vitreous carbon (100 pores per inch, acquired from K. R. Reynolds Co. for about US$3 per electrode) electrodes proved to be far more productive.

In our laboratory, the original conditions¹³ applied to valencene (4) led to only 6% isolated yield of nootkatone (5), the principal fragrance component of grapefruit aroma (Fig. 2). Our hypothesis was that air was the oxygen-atom source in this transformation, which was qualitatively confirmed by bubbling O₂ gas in the reaction, resulting in an improved isolated yield of 18%. However, NHPI/O₂ systems¹⁶–¹⁸ have been explicitly avoided by the pharmaceutical industry, along with other oxygen-mediated reactions, owing to the challenges relating to flammability, and other issues arising from reliably and safety in performing oxygen-mediated reactions on a large scale¹⁹,²⁰ as such, applications of aerobic oxidations in the pharmaceutical and fine-chemical industries remain sparse²¹–²³. Thus, a number of co-oxidants were evaluated, using NHPI as a mediator, and tert-butyl hydroperoxide (tBuOOH) led to substantial increases in reaction conversion and reproducibility, delivering 5 in 51% yield. Using tBuOOH without the NHPI mediator led to only 18% isolated yield under otherwise identical conditions.

With a suitable co-oxidant selected, attention turned to the optimization of base, solvent and electrolyte. We evaluated a variety of organic and inorganic bases, with pyridine proving to be ideal. The use of acetone as solvent led to a slightly increased yield (56% 5 isolated) and was chosen as a general solvent for this reaction owing to its ability to solubilize a wide range of organic substrates. Acetonitrile, dichloromethane, pyridine or mixtures of these four solvents could also be used. The electrolyte LiBF₄ could be used in place of LiClO₄ with little decrease in yield, but tetraalkylammonium salts were not competent electrolytes.

Although most of the other mediators studied were inferior to the original NHPI, we reasoned that the addition of electron-withdrawing groups to the phthalamide scaffold would improve the reactivity of the catalyst¹⁴. Thus, tetrachloro-N-hydroxyphthalimide (Cl₄NHPI) was chosen, owing to its ease of preparation from tetrachlorophthalic anhydride, an industrial non-toxic flame retardant (which is easily obtained for about US$30 per kilogram from suppliers of chemicals for laboratories). The expectation of increased reactivity was supported by cyclic voltammetry data. In the case of NHPI, a reversible redox couple is observed at 0.78 V versus Ag/AgCl in the presence of excess pyridine, whereas Cl₄NHPI shows a redox couple at 0.87 V versus Ag/AgCl under identical conditions. This slightly increased oxidation potential is consistent with the generation of a higher-energy and more-reactive

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phthalimido-N-oxyl radical, and the use of Cl3NHPI as a mediator led to a cleaner reaction profile and an isolated yield of 77%.

The final optimized conditions for oxidation of 4 to 5 is as follows: 20 mol% Cl3NHPI, pyridine (2.0 equiv.), BuOOH (1.5 equiv.), and LiClO4 as the supporting electrolyte (0.1 M) in acetone (6 ml per mmol of substrate) under constant-current conditions in an undivided cell. No precautions to exclude oxygen or water were undertaken, and technical-grade solvents and reagents and a simple set-up of two reticulated vitrous carbon electrodes separated by a glass slide were used (see Supplementary Information for a photographic guide of the experimental set-up).

Our initial explorations into the tolerance focused on several cycloalkene-derived substrates relevant to drug discovery (Fig. 3); tert-butyl cyclohexenone 6 could be prepared as a single regioisomer in 52% yield, whereas phenyl cyclohexenone 7 was prepared in 55% yield. Cyclopentenone 8 could be prepared from trimethylsilyl (TMS)-protected cyclopentenol in 52% yield. Unprotected tertiary alcohols 9–12 could be prepared from the corresponding aryl-substituted cyclohexenols in reasonable yields. The Lewis-basic pyridine-containing enone 12 was prepared in 60% yield. No alcohol elimination and aromatization was observed, and no allylic transposition occurred; this complimentary reactivity to most chromium-based oxidants and the use of unprotected alcohols is particularly notable. Furthermore, the unsubstituted cyclohexenone products 13 and 14 were prepared in 56% and 51% yield, respectively, comparing favourably to previously reported (see Supplementary Information) Cr3+-mediated oxidation for the synthesis of 13. Substitution at the alpha position of the enone was tolerated as well, with 15 being isolated in 58% yield. In addition to the cyclic substrates described above, several acrylic alkenes of various chain lengths were successfully oxidized under the reaction conditions. Enones 16 and 17 were prepared in 46% and 51% yields, respectively. Propargylic alcohol 18 was formed in 52% yield from its corresponding alkyne.

Owing to their prevalence in the drug discovery, flavour and fragrance industries, our subsequent efforts focused on a variety of representative terpene classes. The oxidation products of monoterpenes are among the most widely used and correspondingly valuable substances not only as fragrances and flavours, but also as building blocks in synthesis. As such, we evaluated the efficiency with which the electrochemical allylic oxidation could be applied to these substances. Verbenone (3), previously prepared in 13%–23% yield14, was prepared in 67% yield. Both isomers of the food additive theaspirane could be oxidized to the natural products cis- and trans-theaspirone 19 and 20 in 63% and 49% yield, respectively. Carvone-derived enone 21 was prepared in 47% yield, whereas carvone (22) was prepared in 42% yield. Myrtenol acetate and nopol acetate were converted to the corresponding oxo-myrtenol and oxo-nopol compounds 23 and 24 in 64% and 43% yield, respectively. Furthermore, aza-nopol analogues 25 and 26 were prepared in 42% and 53% yield, respectively, further highlighting the tolerance for nitrogen-containing functionalities under these reaction conditions. In all cases, isolated yields are comparable to those in the literature using other methods, and low product yields were obtained when using previously reported NHPI/O2 conditions after prolonged heating15–17. To put these results in context, an extensive comparative survey of literature conditions and yields is included in Supplementary Information.

Sesquiterpenoid and diterpenoid natural products, many of which are components of essential oils, have provided inspiration for many strategies and methods in synthesis, primarily owing to their complex and dense structures and their promising biological activities15. Allylic oxidation of valencene gave nootkatone (5) in 77% yield (see above). Scareolide-derived terpene 27 was synthesized in 75% yield using the electrochemical method. Eudesmane natural products carisone (28), as its TMS ether) and cyperone (29) were prepared in 54% and 51% yields, respectively. The related aubergerone skeleton was successfully oxidized to give enone 30 in 67% yield. Isolongifolone (31) was prepared from the feedstock chemical isolongifolene in 91% yield. Natural products in the guaiane family were oxidized to afford the natural products pancherione acetate (32) and rotundone (33) in 41% and 44% yield, respectively, and the complex [3.2.1]-bicyclic system in cedrene was oxidized to give cedren-10-one (34) in 53% yield. Under electrochemical conditions, abietic acid derivative 35 could be prepared in 66% isolated yield along with 12% recovered starting material. Although...
Figure 3 | Scope of the electrochemical allylic oxidation. Yields refer to isolated yields of products after chromatography on SiO₂. Standard conditions: terpenoid substrate (0.5 mmol), Cl₄NHPI (0.1 mmol), pyridine (1.0 mmol), tBuOOH (0.75 mmol), LiClO₄ (0.3 mmol), acetone (3 ml). †MeCN (3 ml) replaced acetone as solvent. ‡Terpenoid substrate (0.25 mmol), Cl₄NHPI (0.1 mmol), pyridine (1.0 mmol), LiClO₄ (0.3 mmol), CH₂Cl₂ (1.5 ml) and acetone (1.5 ml) were used. §See Supplementary Information for references. s.m., starting material.
the starting material contained the $\Delta^{7,8}$ bond, isomerization to the $\Delta^{6,9}$ olefin occurred, and no $\Delta^{7,8}$-eneone was observed. This anomalous result may be due to hydrogen-atom abstraction at the C9 position followed by trapping of the allylic radical at the C7 position.

The oxidation of steroid and triterpene substrates has been shown to improve properties such as solubility and pharmacokinetics, and the development of tools to modify their ‘oxidation barcodes’ are of immediate importance\textsuperscript{20}. Electrochemical oxidation of acetate-protected dehydroepiandrosterone (DHEA) gave enone product \textit{36} in 81\% yield. Unprotected DHEA could also be oxidized to give enone \textit{37} in 72\% yield. Diosgenin acetate underwent smooth oxidation to give \textit{38} in 74\% yield. Encouraged by the tolerance for free alcohols and sensitive acetals, glycosylated derivatives of DHEA were evaluated. The tetra benzoyl protected glycoside \textit{39} was prepared in 60\% yield and the unprotected glycoside \textit{40} could be prepared in 38\% yield, demonstrating chemoselectivity that would not be possible using classical oxidants such as chromium. Free-hydroxyl-containing methyl oleate derivative \textit{41} was prepared in 43\% isolated yield, whereas oxidation of the ketone-containing substrate gave the desired enone \textit{42} in 46\% yield. Methyl glycyrrheta tine (\textit{43}), an important starting material for a variety of oxidized, medicinally relevant triterpenes, was also prepared in 41\% yield.

In nearly all substrates evaluated, isolated yields compare favourably to literature precedent using traditional reagent-based oxidants. In some cases, such as the known conversion of \textit{4} to \textit{5} using 15 equivalents of CrO$_3$-pyridine in 80\% yield, not only is the isolated yield comparable, but our conditions obviate the need for the excessive use of toxic reagents and minimize the use of solvent and aqueous media for extraction and isolation.

We demonstrate the feasibility of adopting this technology in a process setting, using the described conditions. These reactions were conducted using inexpensive graphite plate electrodes in a beaker opened to air (Fig. 4a, inset photograph), and LiBF$_4$ was used as the supporting electrolyte. Using this set-up, \textit{22} was prepared on a 27-g scale (198 mmol) from limonene in 44\% yield, and \textit{3} was prepared in 55\% yield on a 27-g scale. Further scale-up to 100 g (734 mmol) gave 46\% yield of \textit{3}. Carrying out the identical transformation with traditional chromium reagents (for example, toxic chromium hexacarbonyl) would require at least 81 g of chromium reagent followed by extensive efforts to remove chromium-based contaminants. Sterol \textit{37} and its acetate \textit{36} were produced in 48\% yield (100 g, 347 mmol) and 62\% yield (100 g, 303 mmol), respectively. Highlights of this successful external field test include operational simplicity, safe procedure, simple workup and ease of product isolation.

To verify the improved environmental footprint of the electrochemical allylic oxidation, we compared the Process Greenness Scores (PGSs) for the electrochemical preparation of \textit{36} to two known literature methods\textsuperscript{20,27} (Fig. 4b). The PGS is a method often used by industrial companies to evaluate the potential environmental impact of chemical manufacturing processes. The scoring parameters are closely aligned with the 12 principles of green chemistry\textsuperscript{28}, among which limiting waste generation and maximizing process efficiency are two main metrics of environmentally friendly processes. A greener reaction has a higher PGS. Oxidation reactions, especially aliphatic C–H oxidations, are generally associated with lower-than-average PGSs due to typically low process yields and the common use of toxic metal mediators in stoichiometric quantities. Unsurprisingly, the CrO$_3$-mediated oxidation of \textit{36} scored lowest in terms of PGS (32.1\%). The RuCl$_3$-catalysed oxidation had an improved, albeit still modest, PGS of 37.1\%. We were pleased to find that the electrochemical allylic oxidation showed a markedly improved PGS of 55.8\% (an improvement of >50\%). This difference is substantial and shows the step-change in applicability of this new technology. For comparison, the PGS for a typical amide bond formation (EDC, HOBT) ranges from 55\% to 70\%, whereas the PGS of the widely used palladium-catalysed cross-coupling of aryl halides with boronic acids falls between 45\% and 60\%. As a further testament to its robustness, the electrochemical oxidation was carried out using a 6-V lantern battery\textsuperscript{29}\textsuperscript{30}, using valencene being converted to noo ketone in 37\% yield with 15\% recovered starting material.

Although this reaction is useful for the oxidation of numerous natural and unnatural carbon skeletons, it is not without its limitations. For example, although cyclic substrates are all reactive, not all acyclic alkenes give very high conversion to enone products, nor do electron-deficient alkenes. In some cases, allylic alcohol products were isolated alongside enone products, although with prolonged reaction times these products are converted to the desired enones. Yields for some substrate classes were modest (for example, \textit{32} and \textit{33}), in part owing to incomplete conversion, substrate decomposition, or adsorption to the electrode surface. However, in nearly all cases isolated yields are comparable to alternative procedures present in the literature.

Mechanistic aspects of the initiation step of this new transformation may have parallels to other NHPI-catalysed oxidations\textsuperscript{16–18} (Fig. 5). Thus, deprotonation of Cl$_4$NHPI by pyridine, followed by anodic toxicity associated with chromium and ruthenium use and disposal are not included in the PGS. c. Use of 6-V lantern battery as a readily available power source for allylic oxidation. r.s.m., recovered starting material.
oxidation, leads to the tetra-chlorophthalimido N-oxyl radical species. Olefinic substrate 44 would then undergo hydrogen atom abstraction, regenerating Cl₄NHPI and the relatively stable allylic radical species 45. Reaction with electrochemically generated ‘BuOO’ would then give allylic peroxide 46, which, upon elimination of ‘BuOH, affords enone 47 (see Supplementary Information for more details).

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1. Gutekunst, W. R. & Baran, P. S. C–H functionalization logic in total synthesis. Chem. Soc. Rev. 40, 1976–1991 (2011).
2. Weidmann, V. & Maison, W. Allylic oxidations of olefins to enones. Synthesis 45, 2201–2221 (2013).
3. Nakamura, A. & Nakada, M. Allylic oxidations in natural product synthesis. Synthesis 45, 1421–1451 (2013).
4. Sequeira, C. A. C. & Santos, D. M. F. Electrochemical routes for industrial synthesis. J. Braz. Chem. Soc. 20, 387–406 (2009).
5. Regen, P. in Electrochemistry (ed. Steckhan, E.) 1–95 (Springer, 1988).
6. Moeller, K. D. Synthetic applications of anodic electrochemistry. Tetrahedron 56, 9527–9554 (2000).
7. Sperry, J. B. & Wright, D. L. The application of cathodic reductions and anodic oxidations in the synthesis of complex molecules. Chem. Soc. Rev. 35, 605–621 (2006).
8. Yoshiba, J.-I., Kataoka, K. Horajada, R. & Nagaki, A. Modern strategies in electroorganic synthesis. Chem. Rev. 108, 2265–2299 (2008).
9. Franke, R. & Little, R. D. Redox catalysis in organic electrochemistry: basic principles and recent developments. Chem. Soc. Rev. 43, 2492–2521 (2014).
10. Gütz, C., Bänziger, M., Bucher, C., Galvão, T. R. & Waldvogel, S. R. Development and scale-up of the electrochemical dehalogenation for the synthesis of a key intermediate for NS5A inhibitors. Org. Process Res. Dev. 19, 1428–1433 (2015).
11. Shono, T. & Kosaka, T. Organic synthesis by electrolysis III anodic allylic substitution. Tetrahedr. Lett. 9, 6207–6208 (1968).
12. Shono, T. & Ikeda, A. Electroorganic chemistry X anodic allylic substitution. J. Am. Chem. Soc. 94, 7892–7898 (1972).
13. Masui, M., Hara, S., Ueshima, T., Kawaguchi, T. & Ozaki, S. Anodic oxidation of compounds having benzyl or allylic carbon and α-carbon to hetero atom using N-hydroxyphthalimide as a mediator. Chem. Pharm. Bull. 31, 4209–4211 (1983).
14. Masui, M., Hosomi, K., Tsuchida, K. & Ozaki, S. Electrochemical oxidations of olefins using N-hydroxyphthalimide as a mediator. Chem. Pharm. Bull. 33, 4798–4802 (1985).
15. Ueda, C., Noyama, M., Ohmor, H. & Masui, M. Reactivity of phthalimido-N-oxyl: a kinetic study. Chem. Pharm. Bull. 35, 1372–1377 (1987).
16. Anest, C., Förbringer, J., Förbringer, C. & Pliwtertner, K. Process for the catalytic oxidation of isoprenoids having allylic groups. US patent 5,030,739 (1991).
17. Ishii, Y. et al. A novel catalysis of N-hydroxyphthalimide in the oxidation of organic substrates by molecular oxygen. J. Org. Chem. 60, 3934–3935 (1995).
18. Recupero, F. & Punta, C. Free radical functionalization of organic compounds catalyzed by N-hydroxyphthalimide. Chem. Rev. 107, 3800–3842 (2007).
19. Miller, R. A., Li, W. & Humphrey, G. R. A ruthenium catalyzed oxidation of steroidal alkenes to enones. Tetrahedr. Lett. 37, 3429–3432 (1996).
20. Harre, M. et al. Some reaction safety aspects of ruthenium-catalyzed allylic oxidations of 3-S-steroids in the pilot plant. Org. Process Res. Dev. 2, 100–104 (1998).
21. Campbell, A. N. & Stahl, S. S. Overcoming the ‘oxidant problem’: strategies to use O₂ as the oxidant in organometallic C–H oxidation reactions catalyzed by Pd (and Cu). Acc. Chem. Res. 45, 851–863 (2012).
22. Osterberg, P. M. et al. Experimental limiting oxygen concentrations for nine organic solvents at temperatures and pressures relevant to aerobic oxidations in the pharmaceutical industry. Org. Process Res. Dev. 19, 1537–1543 (2015).
23. Mudryk, B., Zheng, B., Chen, K. & Eastgate, M. D. Development of a robust process for the preparation of high-quality diclopropamylphosphate hydrochloride. Org. Process Res. Dev. 18, 520–527 (2014).
24. Cai, Y., Koshino, N., Saha, B. & Esperson, J. H. Kinetics of self-decomposition and hydrogen atom transfer reactions of substitute phthalimide N-oxyl radicals in acetic acid. J. Org. Chem. 70, 238–243 (2005).
25. Modzelewskas, A., Sur, S., Kumar, S. K. & Khan, S. R. Sesquiterpenes: natural products that decrease cancer growth. Curr. Med. Chem. Anticancer Agents 5, 477–499 (2005).
26. Michaudel, O. et al. Improving physical properties via C-H oxidation: chemical and enzymatic approaches. Angew. Chem. Int. Ed. 53, 12091–12096 (2014).
27. Marwa, P. & Lardy, H. A. Process for effecting allylic oxidation using dicarboxylic acid imides and chromium reagents. US patent 6,384,251 (2002).
28. Anantas, P. T. & Warner, J. C. Green Chemistry: Theory and Practice (Oxford Univ. Press, 1998).
29. Frey, D. A., Wu, N. & Moeller, K. D. Anodic electrochemistry and the use of a 6-volt lantern battery: a simple method for attempting electrochemically based synthetic transformations. Tetrahedr. Lett. 37, 8317–8320 (1996).
30. Frankowski, K. J., Liu, R., Milligan, G. L., Moeller, K. D. & Aubé, J. Practical electrochemical anodic oxidation of polycyclic lactams for late stage functionalization. Angew. Chem. Int. Ed. 54, 10555–10558 (2015).

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