



Published in final edited form as:

Nature. 2016 May 5; 533(7601): 77–81. doi:10.1038/nature17431.

Scalable and Sustainable Electrochemical Allylic C–H Oxidation

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Abstract

New methods and strategies for the direct functionalization of C–H bonds are beginning to reshape the fabric of retrosynthetic analysis, impacting the synthesis of natural products, medicines, and even materials¹. The oxidation of allylic systems has played a prominent role in this context as possibly the most widely applied C–H functionalization due to the utility of enones and allylic alcohols as versatile intermediates, along with their prevalence in natural and unnatural materials². Allylic oxidations have been featured in hundreds of syntheses, including some natural product syntheses regarded as “classics”³. Despite many attempts to improve the efficiency and practicality of this powerful transformation, the vast majority of conditions still employ highly toxic reagents (based around toxic elements such as chromium, selenium, etc.) or expensive catalysts (palladium, rhodium, etc.)². These requirements are highly problematic in industrial settings; currently, no scalable and sustainable solution to allylic oxidation exists. As such, this oxidation strategy is rarely embraced for large-scale synthetic applications, limiting the adoption of this important retrosynthetic strategy by industrial scientists. In this manuscript, we describe an electrochemical solution to this problem that exhibits broad substrate scope, operational simplicity, and high chemoselectivity. This method employs inexpensive and readily available materials, representing the first example of a scalable allylic C–H oxidation (demonstrated on 100 grams), finally opening the door for the adoption of this C–H oxidation strategy in large-scale industrial settings without significant environmental impact.

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Author Contributions E.J.H., B.R.R., and P.S.B. conceived this work; E.J.H., B.R.R., K.C., M.D.E., and P.S.B. designed experiments; E.J.H. and B.R.R. conducted experiments and analyzed data; Y.C. and J.T. performed large-scale experiments; E.J.H., B.R.R., K.C., M.D.E., and P.S.B. wrote the manuscript.

Author Information Metrical parameters for the structure of **24** are available free of charge from the Cambridge Crystallographic Data Center under reference number CCDC-1058554. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper.

Supplementary Information is available in the online version of the paper.

Electrochemical oxidation presents an attractive alternative to traditional chemical reagents for large-scale applications, in large part due to the generation of less toxic waste than that produced by current chemical processes^{4,5}. 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, due to their limited use, offer new intellectual property space for small-molecule synthesis⁴. The first electrochemical allylic oxidation was reported by Shono and coworkers in 1968^{11,12} (**Figure 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 Masui and coworkers reported the indirect oxidation of **1** using *N*-hydroxyphthalimide (NHPI) as an electrochemical mediator¹³⁻¹⁵ (**Figure 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 Masui precedent which transformed this process into a synthetically useful electrochemical allylic C–H oxidation (**Figure 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 setup.

From the outset of this work, we avoided the use of expensive electrodes such as precious metals (*e.g.* Pt or Au), 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 may in part be due to absorption of the substrate onto the graphite. Switching to reticulated vitreous carbon (RVC, 100 ppi available from K.R. Reynolds Co. for *ca.* \$3/electrode) electrodes proved to be far more productive.

In our hands, the original Masui conditions¹⁴ applied to valencene (**4**) led to only 6% isolated yield of nootkatone (**5**), the principal fragrance component of grapefruit aroma (**Figure 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, due to the obvious challenges with flammability and other issues arising from reliability and safety in performing oxygen-mediated reactions on large scale^{19,20}; as such, applications of aerobic oxidations in the pharmaceutical and fine chemical industries remain sparse²¹⁻²³. Indeed, within Bristol-Myers Squibb such processes are explicitly avoided. Thus, a number of co-oxidants were evaluated, using NHPI as a mediator, and *tert*-butyl hydroperoxide (*t*BuOOH) led to substantial increases in reaction conversion and reproducibility, delivering **5** in 51% yield. Using *t*BuOOH 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. A variety of organic and inorganic bases were evaluated, 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 due 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 catalyst²⁴. Thus, tetrachloro-*N*-hydroxyphthalimide (Cl₄NHPI) was chosen due to its ease of preparation from tetrachlorophthalic anhydride, an industrial non-toxic flame retardant (*ca.* \$30/kg from VWR). 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 vs. Ag/AgCl in the presence of excess pyridine, whereas Cl₄NHPI shows a redox couple at 0.87 V vs. Ag/AgCl under identical conditions. This slightly increased oxidation potential is consistent with the generation of a higher-energy and more reactive phthalimido-*N*-oxyl radical, and to our delight, the use of Cl₄NHPI 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% Cl₄NHPI, pyridine (2.0 equiv), ^tBuOOH (1.5 equiv), and LiClO₄ as the supporting electrolyte (0.1 M) in acetone (6 mL/mmol substrate) under constant current conditions in an undivided cell. Notably, no precautions to exclude oxygen or water were undertaken, technical-grade solvents and reagents were employed, and a simple setup of two reticulated vitreous carbon (RVC) electrodes separated by a glass slide was used (see Supporting Information for a photographic guide of the experimental setup).

Our initial explorations into the tolerance focused on several cycloalkene-derived substrates of interest to Bristol-Myers Squibb process chemistry as part of ongoing drug discovery efforts (**Figure 3**). Thus, *tert*-butyl cyclohexenone **6** could be prepared as a single regioisomer in 52% yield, while phenyl cyclohexenone **7** was prepared in 55% yield. Pleasingly, cyclopentenone **8** could be prepared from TMS-protected cyclopentenol in 52% yield. Unprotected tertiary alcohols **9–12** could be prepared from the corresponding aryl-substituted cyclohexenols in reasonable yields. Most notably, 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, comparing favorably to our previously reported Cr^V-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 acyclic alkenes of various chain lengths were successfully oxidized under the reaction conditions. Enones **16** and **17** were prepared in 46% and 51% yields, respectively. Interestingly, propargylic alcohol **18** was formed in 52% yield from its corresponding alkyne.

Due to their prevalence in the drug discovery, flavor, and fragrance industries, subsequent efforts focused on a variety of representative terpene classes. The oxidation products of monoterpenes are amongst the most widely used and correspondingly valuable substances not only as fragrances and flavors, 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**), prepared in 13–23% yield in Masui's original report, 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% yields. Carvone-derived enone **21** was prepared in 47% yield, while 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. Furthermore, aza-nopol analogues **25** and **26** were prepared in 42% and 53% yield, further highlighting the tolerance for nitrogen-containing functionalities under these reaction conditions. Notably, in all cases, isolated yields are comparable to those in the literature using other methods, and low product yields were obtained in all cases in our hands under Ishii's NHPI/O₂ conditions after prolonged heating^{16–18}. To put these results in context, an extensive comparative survey of literature conditions and yields is included in the Supporting Information.

Sesquiterpenoid and diterpenoid natural products, many of which are components of essential oils, have provided inspiration for countless novel strategies and methods in synthesis primarily due to their complex and dense structures as well as their promising biological activities²⁵. Allylic oxidation of valencene gave nootkatone (**5**) in 77% yield (*vide supra*). Sclareolide-derived terpene **27** was synthesized in 75% yield using the electrochemical method. Eudesmane natural products carissone (**28**, as its TMS ether) and cyperone (**29**) were prepared in 54% and 51% yields, respectively. The related aubergenone skeleton was successfully oxidized to give enone **30** in 67% yield. Isolongifolenone (**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% yields, 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. Interestingly, while the starting material contained the ^{7,8} bond, isomerization to the ^{8,9} olefin occurred, and no ^{7,8}-enone was observed. This anomalous result may be due to hydrogen-atom abstraction at the C-9 position followed by trapping of the allylic radical at the C-7 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 importance²⁶. Electrochemical oxidation of acetate-protected dehydroepiandrosterone (DHEA) gave enone product **36** in 81% yield. Notably, unprotected DHEA could also be oxidized to give enone **37** in 72% yield. Diosgenin acetate underwent smooth oxidation to give **38** in 74% yield. Encouraged by the tolerance for free alcohols and sensitive acetals, glycosylated derivatives of DHEA were evaluated. The tetrabenzoyl protected glycoside **39** was prepared in 60% yield, and, remarkably, the unprotected glycoside **40** could be prepared in 38% yield, demonstrating chemoselectivity that would be

out of reach using classical oxidants such as chromium. Free hydroxyl-containing methyl oleanolate derivative **41** was prepared in 43% isolated yield, while oxidation of the ketone-containing substrate gave the desired enone **42** in 46%. Methyl glycyrrhetinate (**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 favorably to literature precedent using traditional reagent-based oxidants. In some cases, such as the known conversion of **4** to **5** using 15 equivalents of $\text{CrO}_3 \cdot \text{pyridine}$ 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/isolation.

In order to demonstrate the feasibility of adopting this technology in a process setting, the described conditions were applied to substrates of relevance to Asymchem Laboratories. These reactions were conducted using inexpensive graphite plate electrodes in a beaker open to air (**Figure 4A**, inset photograph), and LiBF_4 was used as the supporting electrolyte. Using this modest setup, **22** was prepared on 27-gram scale (198 mmol) from limonene in 44% yield, and **3** was prepared in 55% yield on 27-gram scale. Further scale-up to 100 grams (734 mmol) gave 46% yield of **3**. Notably, carrying out the identical transformation with traditional chromium reagents (*e.g.* toxic chromium hexacarbonyl) would require at least 81 grams of chromium reagent followed by extensive efforts to remove Cr-based contaminants. Sterol **37** and its acetate **36** were produced in 48% yield (100 g, 347 mmol) and 62% yield (100g, 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 (PGS) for the electrochemical preparation of **36** to two known literature methods^{20,27} (**Figure 4B**). The PGS is a method often utilized by industrial companies, such as Bristol-Myers Squibb, to evaluate the potential environmental impact of chemical manufacturing processes. The scoring parameters are closely aligned with the 12 principles of green chemistry²⁸, amongst which limiting waste generation and maximizing process efficiency are two main metrics of environmentally friendly processes. A greener reaction exhibits a *higher* PGS. Oxidation reactions, especially aliphatic C-H oxidations, are generally associated with lower than average PGS due to typically low process yields and the common use of toxic metal mediators in stoichiometric quantities. Unsurprisingly, the CrO_3 -mediated oxidation of deoxy-**36** scored lowest in terms of PGS (32.1%). The RuCl_3 -catalyzed oxidation had an improved, albeit still modest, PGS of 37.1%. We were pleased to find that the electrochemical allylic oxidation showed a dramatically improved PGS of 55.8% (an improvement of >50%). This difference is significant 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 55–70%, while the PGS of the widely employed Pd-catalyzed cross-coupling of aryl halides with boronic acids falls between 45–60%. As a further testament to its robustness, the electrochemical oxidation was carried out using a 6-volt lantern battery^{29,30} (**Figure 4C**),

with valencene being converted to nootkatone 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, while 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, though with prolonged reaction times these products are converted to the desired enones. Yields for some substrate classes were modest (*e.g.* **32** and **33**), in part due to incomplete conversion, substrate decomposition, or adsorption to the electrode surface. In nearly all cases, however, 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-catalyzed oxidations^{16–18} (**Figure 5**). Thus, deprotonation of Cl₄NHPI by pyridine, followed by anodic oxidation, leads to the *tetra*-chlorophthalimido *N*-oxyl radical species. Olefinic substrate **44** would then undergo hydrogen atom abstraction, regenerating Cl₄NHPI as well as the relatively stable allylic radical species **45**. Reaction with electrochemically-generated ^tBuOO• would then give allylic peroxide **46**, which, upon elimination of ^tBuOH, affords enone **47** (see Supporting Information for more details).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by an NSF predoctoral fellowship (B.R.R.), National Institute of General Medical Sciences Grant GM-097444, Asymchem, and Bristol-Myers Squibb. We thank Dr. D.-H. Huang and Dr. L. Pasternack for assistance with NMR spectroscopy; Dr. A. L. Rheingold, Dr. C. E. Moore, and Dr. M. A. Galella for x-ray crystallographic analysis; and Dr. D. G. Blackmond, Dr. O. Luca, Dr. T. Paschkewitz, Dr. Y. Ishihara and Dr. T. Razler for helpful discussions.

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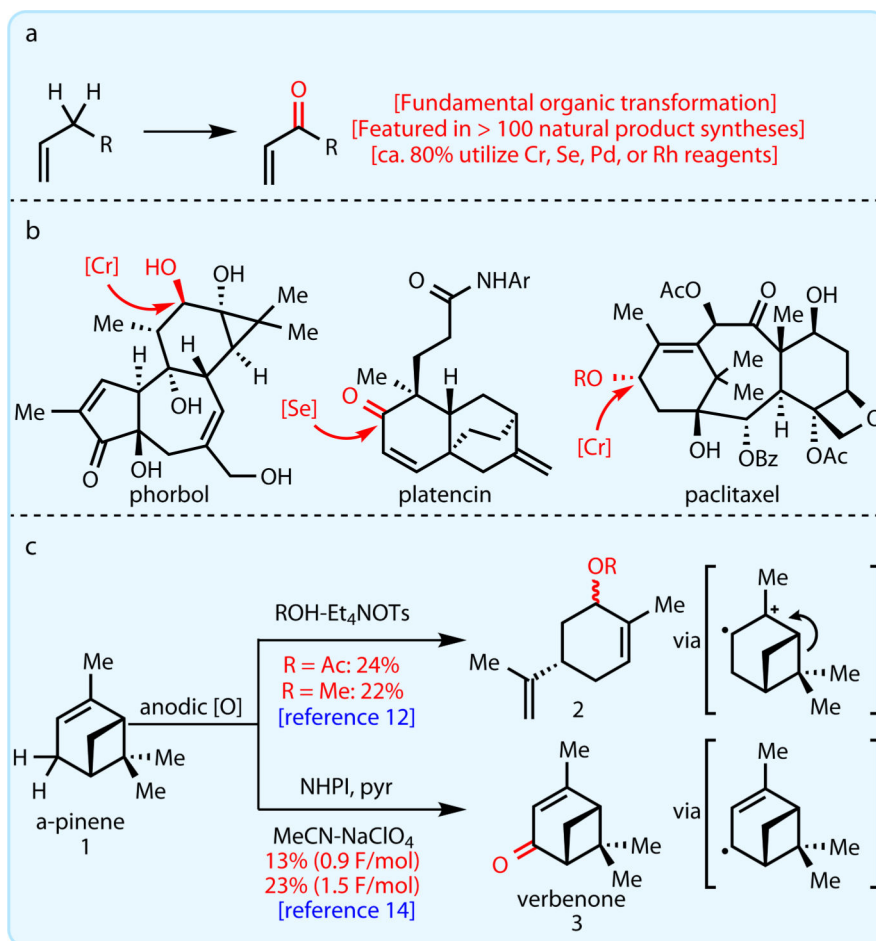


Fig. 1. Widely applied allylic oxidation

a, Sustainable allylic C–H oxidation is an unsolved problem. **b**, Case studies from classic total syntheses. **c**, Electrochemical oxidation represents a potential solution.

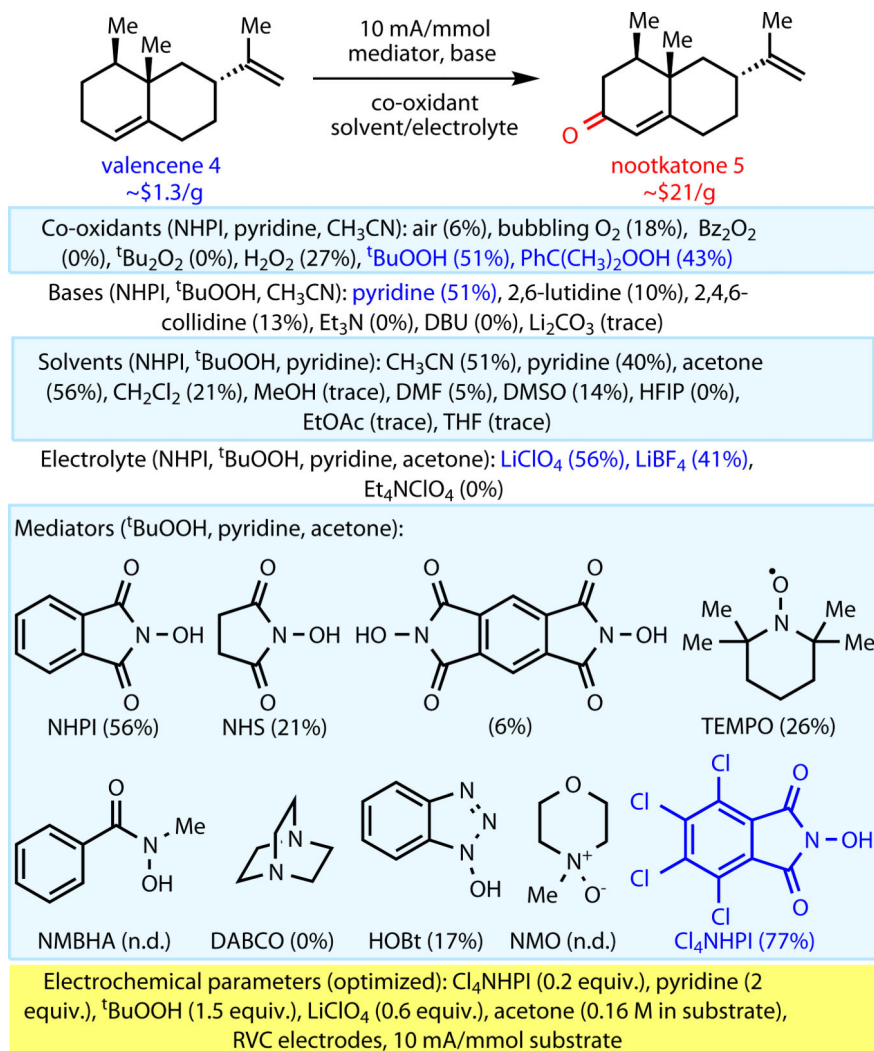


Fig. 2.
 Optimization of a new sustainable allylic C–H oxidation.

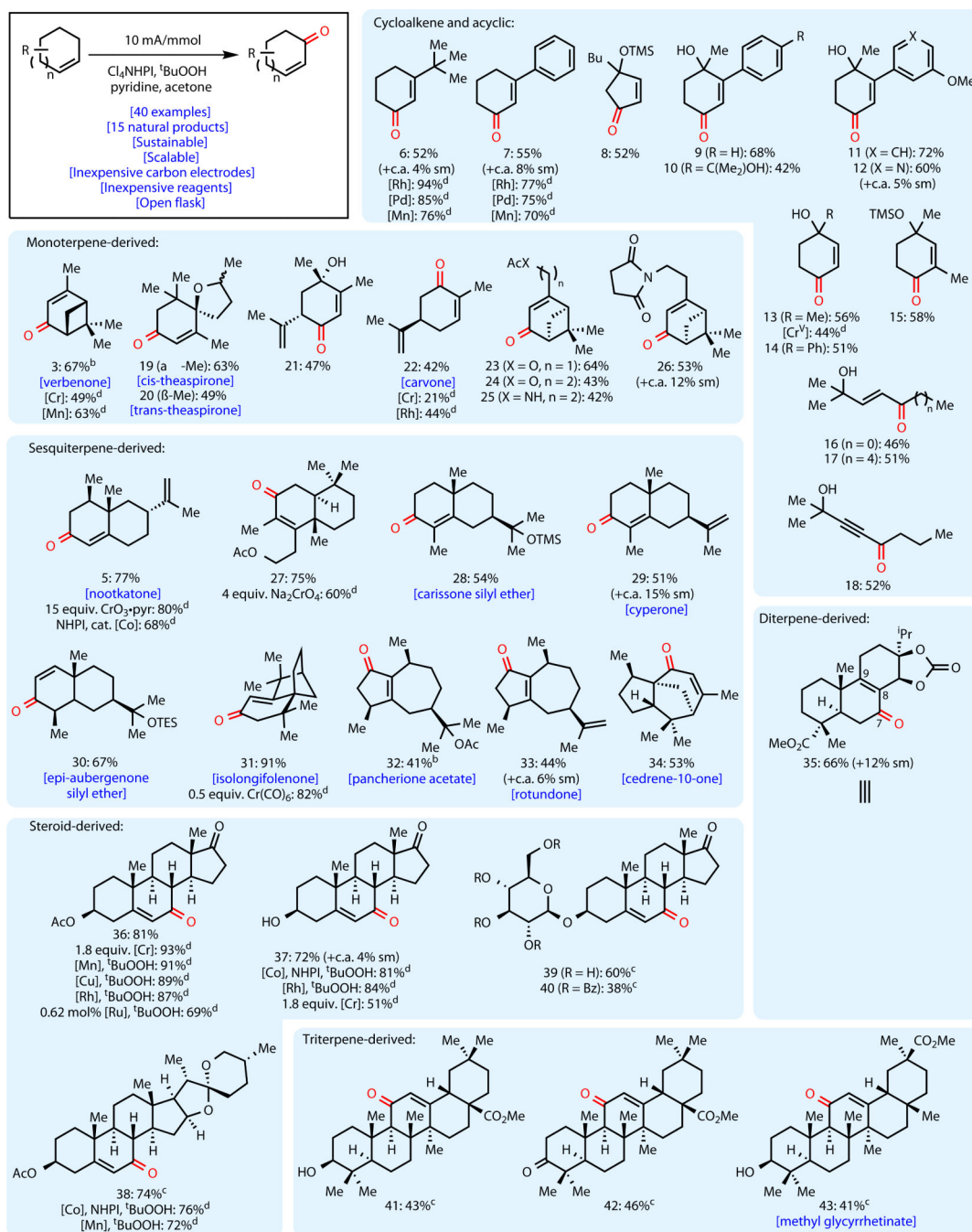


Fig. 3. Scope of the electrochemical allylic oxidation

Yields refer to isolated yields of products after chromatography on SiO₂. ^aStandard conditions: terpenoid substrate (0.5 mmol), Cl₄NHPI (0.1 mmol), pyridine (1.0 mmol), ^tBuOOH (0.75 mmol), LiClO₄ (0.3 mmol), and acetone (3 mL). ^bMeCN (3 mL) replaced acetone as solvent. ^cterpenoid 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. ^dSee Supporting Information for references.

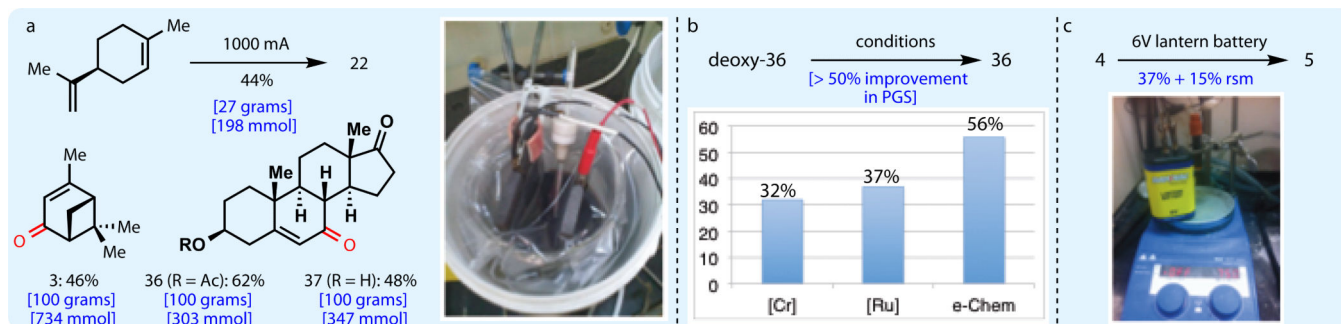


Fig. 4. Practicality of electrochemical method

a. 100-gram scale electrochemical allylic oxidation. **b.** Calculated Process Greenness Score (PGS) for CrO_3 -mediated, RuCl_3 -catalyzed, and electrochemical oxidation of deoxy-**36** to **36** shows improvement from 32.1% to 55.8%. Cost and toxicity associated with chromium and ruthenium use and disposal are not included in PGS. **c.** Use of 6-volt lantern battery as readily-available power source for allylic oxidation.

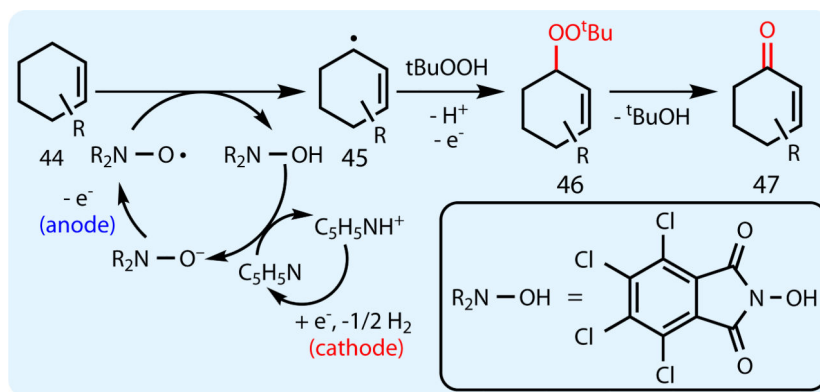


Fig. 5.
Proposed mechanism for electrochemical allylic oxidation.