Electrochemically-Mediated Oxidation of Sensitive Propargylic Benzylic Alcohols

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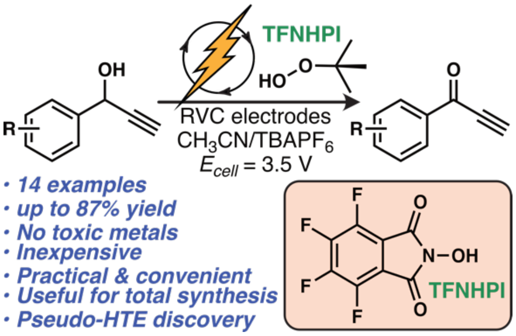
Supporting Information Placeholder



ABSTRACT: The electrochemical oxidation of sensitive propargylic benzylic alcohols having varying substituents is reported. We describe the preparation and characterization of *N*-hydroxytetrafluorophthalimide (TFNHPI) and pseudo high throughput development of a green electrochemical oxidation protocol for sensitive propargylic benzylic alcohols that employs TFNHPI as a stable electrochemical mediator. The electrochemical oxidation of propargylic benzylic alcohols was leveraged to develop short synthetic pathways to prepare gram quantities of resveratrol natural products such as the pauciflorols.

The oxidation of alcohols to the corresponding carbonyl compound is ostensibly a simple $2e^-/2H^+$ process. Conventional oxidation methods typically employ high valent metals or other electron-deficient species as electron sinks, and mechanistically these reactions all consist of an elimination type mechanism in which a proton is removed and two electrons are transferred to a stoichiometric electrophile.[1] Advances in traditional oxidation chemistry have driven the field of organic synthesis to the great modern success it is today, allowing the oxidation of many alcohols to the corresponding aldehyde, ketone, and carboxylic acid equivalents under a variety of reaction conditions.

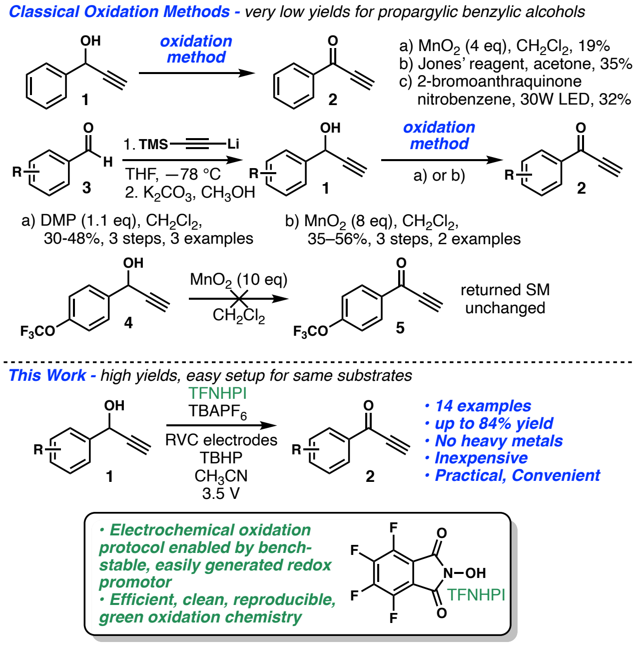
Highly genotoxic and carcinogenic hexavalent chromium-based (*i.e.,* Cr(VI)) oxidants such as Jones' reagent,[2] or gentler anhydrous homologs such as the Collins reagent[3] have been routinely employed for oxidative operations for decades. Additionally, a variety of electron-deficient species employing metals, metalloids, and non-metals have offered myriad alternative approaches and a library of highly selective reagents and reactions that can be tailored to specific applications.[1]

Despite this body of work, many thermal oxidations of organic compounds remain a challenge. Several recent synthetic efforts make this challenge plain, with propargylic benzylic alcohol substrates undergoing oxidation via typical thermal protocols (Jones' reagent,[2,4] manganese(IV) oxide,[5] Dess–Martin periodinane,[6] or photochemical processes[7] with low efficiency (Scheme 1). More electron-deficient substrates such as **4** are particularly intransigent. Illustrative of this point, we treated alcohol **4** with several equivalents of MnO_2 in CH_2Cl_2 at reflux, which only returned the starting material unchanged.

Electrochemical organic transformations are increasingly attractive means that can be leveraged to prepare small molecules and fine chemicals. With proper reaction design, electrosynthetic methods can be inherently efficient, and replace exogenous oxidants or reductants with heterogenous electrodes that directly deliver the oxidizing (or reducing) equivalents needed to promote chemical transformations.[8-17] In the last decade, electrochemical methods have gained increased attention in synthesis owing to the growing array of transformations that such protocols can promote. Moreover, electrochemistry can also offer synthetic solutions for which there are no practical thermal reaction equivalents[16a,18-20] and the development and adoption of more sustainable and environmentally friendly methods are critical to the evolution of modern synthetic organic chemistry.[21]

Certain organic molecules can be employed as electrochemical mediators[22] that facilitate oxidative chemistry by undergoing single electron oxidations at conveniently applied potentials. Upon oxidation, such mediators are converted to a radical, cation, or other electron-deficient intermediate that can in turn induce an oxidative process on substrates of interest. Organic molecules, such as TEMPO[23] that serve various roles in thermal radical chemistries have inspired the development of such electrochemical mediators and have been described in the context of electrochemical oxidative chemistry since the early 1980s.[24]

Scheme 1. Oxidation Methods for Propargylic Benzylic Alcohols.

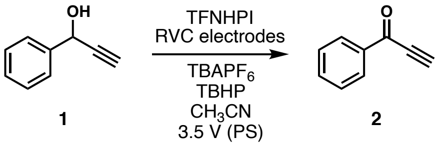


N-Hydroxyphthalimides (NHPIs) have been employed as particularly powerful electrochemical mediators in the oxidation of isolongifolene, cedrene, dehydroepianrosterone, and other terpenoid and steroidal natural products.[25] In recent work showcasing the regioselectivity that electrochemically mediated oxidations can offer, Baran and coworkers, demonstrated that the more electron-deficient *N*-hydroxytetrachlorophthalimide (TCNHPI) served to mediate the electrochemical oxidation of various allylic substrates, culminating in the oxidations of nootkatone (from valencene) and cyperone.[25] Key to this success was the generation of a considerably more reactive electron-deficient tetrachlorophthalimido *N*-oxyl radical, facilitating the oxidation of valencene to nootkatone in 77% yield (vs 56% yield employing the unhalogenated NHPI). Studies on the influence of halogen substitution on the NHPI-mediated oxidation chemistry of hydrocarbons revealed a delicate balance between the NO–H bond strength and the stability of the putative *N*-oxyl radical intermediates.[26] The reader is directed to an extensive study of NHPI electrochemical mediators that was recently reported and which elegantly describes the reaction conditions that facilitate maximum synthetic utility.[27]

Despite the community's emphasis on NHPI type mediators for oxidative electrochemistry, *N*-Hydroxytetrafluorophthalimide (TFNHPI) has been comparatively ignored within this arena. This omission was surprising to us, as TFNHPI might be expected to facilitate more challenging oxidations owing to the four electron-withdrawing fluorines on the thalimide backbone. One reason for this omission may be early reports that characterized TFNHPI as thermally unstable. [28] In contrast to those earlier studies, however, we now report TFNHPI to be an indefinitely bench stable, easily handled crystalline solid amenable to characterization by single crystal X-ray diffraction (see Supporting Information (SI)). We also show that TFNHPI can serve as a more effective electrochemical mediator than NHPI or TCNHPI in certain applications. In particular, we demonstrate the utility of TFNHPI in electrochemically mediating the highly challenging oxidation of sensitive propargylic benzylic alcohols, which typically only undergo thermal oxidation reactions in poor yields accompanied by decomposition or other undesired side reactions.[29-31]

TFNHPI was first described by Coe and coworkers in 1967 during studies of the reactivity of phthalic acid derivatives.[28] Electrochemical studies employing this material have been very limited,[32] however, previous work has suggested that oxidation of TFNHPI generates an *N*-oxyl radical stable enough to facilitate C–H oxidation chemistry.[33] Building on this precedent, we report here that TFNHPI can serve as an efficient and robust electrochemical mediator to solve the problem of oxidation of sensitive propargylic benzylic alcohols (**1**) to cleanly generate the corresponding ketones (**2**) in excellent yield, greatly outperforming thermal oxidation reactions.

Table 1. Optimization of electrochemical oxidation conditions.[a]



Entry	Mediator (mol%)	Peroxide (equiv)	Time (h)	Yield %
1	20	10	5	77%
2	10	10	5	75%
3	5	10	5	71%
4	2.5	10	3	84%
5	0	10	3	39%
6	2.5	7.5	3	44%
7	2.5	2.5	3	24%
8	2.5	1.25	3	16%
9	2.5	0	27	NR
10[b]	2.5	10	5	45%[c]
11[d]	2.5	10	5	60%[c]

[a]General reaction conditions: 1.0 mmol alcohol, 0.1 M $TBAPF_6$, 10.0 equiv. 5.5 M *t*-BuOOH in decane, RVC electrodes. [b]TCNHPI mediator. [c]Product obtained as an inseparable mixture with multiple unidentified contaminants. [d]NHPI mediator.

We prepared TFNHPI in five-gram (17 mmol) lots in 75% overall yield from commercial materials via a modified procedure based on the work of Coe (see Supporting Information for details). Cyclic voltammograms recorded for TFNHPI (1 mM) in CH_3CN containing pyridine (2 mM) and 0.1 M tetra-*n*-butylammonium hexafluorophosphate ($TBAPF_6$) as supporting electrolyte revealed that this compound undergoes an oxidation event at $E \sim 895$ mV (vs. Ag/AgCl – note that all potentials herein are reported relative to this reference electrode), which is more oxidizing than previously reported potentials of NHPI (793 mV vs. Ag/AgCl) and TCNHPI (870 mV vs. Ag/AgCl) (Figure S2).[5] The above pseudo-reversible couples were not observed when pyridine was excluded from the electrolyte solution (Figure S3), and instead the voltammetry resulted in large oxidation waves at potentials more positive that 2.0 V. Under these conditions, the potentials at which oxidative current is observed vary for NHPI, TCNHPI, and TFNHPI, indicating that the identity of the phthalimide relates to the oxidation waves that are observed. The oxidative wave observed in the presence of TFNHPI is found at $E \sim 2.4$ V. Unlike the CVs shown in Figure S2, we note that the shape and magnitude of the CV waves observed in the absence of pyridine (Figure S3) are far more complex than would be expected for a simple reversible oxidation event.

Although prior CV analyses of NHPI derivatives conducted in MeCN solutions in the absence of base have shown quasi-reversible waves at much less positive potentials,[16d,t] we note that these studies employed electrolyte solutions containing inorganic salts (*i.e.*, $NaClO_4$, KPF_6, etc.) rather than the $TBAPF_6$ based electrolytes we have used in this work. Since TBA^+ cannot bind to phthalimides and adjust their pK_a in the same manner as alkali metal ions, it is perhaps not surprising that we observe a significant difference in the CVs recorded for NHPI, TCNHPI, and TFNHPI in the presence/absence of pyridine.

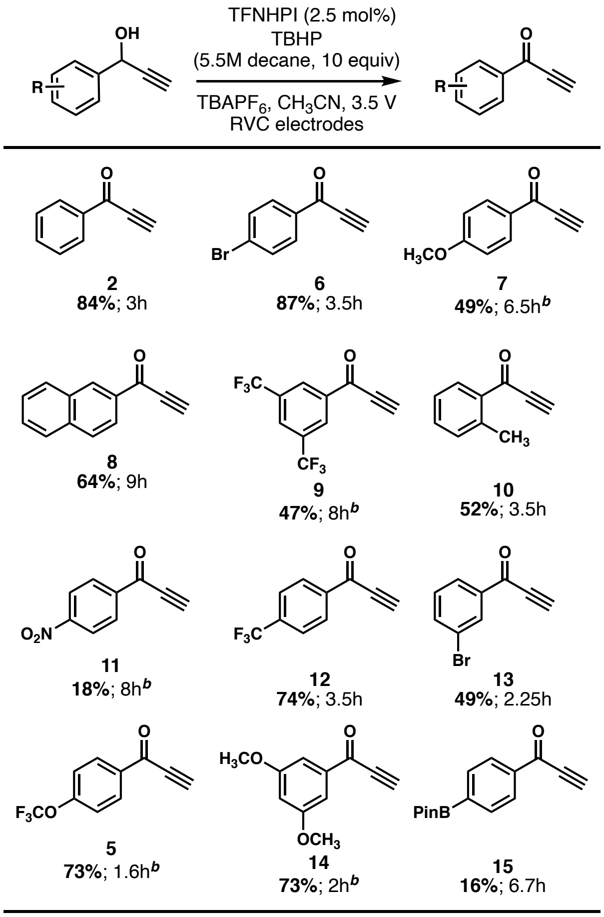
To test the ability of TFNHPI to serve as an electrochemical mediator for oxidation of propargylic benzylic alcohols, constant potential electrolysis (CPE) experiments were carried out using a conventional three electrode configuration in a single compartment electrolysis cell containing 1-phenyl-2-propyn-1-ol (**1**), 20 mol% TFNHPI, 10 equivalents 5.5 M tert-butyl hydroperoxide in decane, 10 mL acetonitrile, and 0.1 M $TBAPF_6$. Both the anode and cathode were comprised of reticulated vitreous carbon (*i.e.*, RVC = carbon foam). The working electrode (*i.e.*, the anode) was poised at $E_{app} = 2.4$ V versus Ag/AgCl and over the course of the reaction, the full cell potential (*i.e.*, the potential difference between anode and cathode) was measured to be $E_{cell} \sim 3.5$ V. Under these electrolytic conditions, oxidation of alcohol **1** to ketone **2** proceeded in over 75% yield over the course of 5 hours. We note that propargylic benzylic ketones are highly conjugated systems that are reduced at fairly negative potentials (approx. –1.7 V versus Ag/AgCl).[34] Accordingly, reduction of the ketone product back down to the starting secondary alcohol is not a concern, despite the fact that it can diffuse freely to the auxiliary electrode, since the cathode was only poised at approximately –1.0 V versus Ag/AgCl. We note that efforts to reduce the potential at the working electrode resulted in significantly longer reaction times.

By noting the full cell potential under the CPE, we were able to optimize the loading of electrochemical mediator (TFNHPI) and co-oxidant in pseudo high throughput fashion by using an array of ten inexpensive commercially available power supplies (see Figure S1 in SI). By using power supplies (as opposed to a potentiostat), we were able to drive electrolysis experiments using a more convenient two electrode configuration while maintaining the potential difference of $E_{cell} = 3.5$ V across anode and cathode. These electrolyses also employed the reticulated carbon foam anodes and cathodes and could be easily carried out open to atmosphere in disposable 15 mL falcon tubes with a simple glass microscope slide serving as a physical barrier to prevent the anode and cathode from contacting each other.

Initial electrolysis screens for the oxidation of **1** to **2** were conducted with 70% aqueous tert-butyl hydroperoxide (*t*Bu–OOH), however, 5.5 M *t*Bu–OOH in decane solution was ultimately determined to be preferable to minimize the moisture content of the reaction mixture. Optimization of the reaction began with loading of TFNHPI (Table 1) starting with 20 mol% mediator with model substrate **1** (*i.e.,* 1-phenyl-2-propyn-1-ol) and excess (10 equiv) *t*Bu–OOH, which afforded the desired propargyl phenone **2** in 77% yield after a 5h electrolysis at E_{cell} = 3.5 V.

Further reaction optimization determined that 10 equiv of 5.5 M *t*Bu–OOH resulted in the highest isolated yield of ketone **2** at 84%, as reducing the loading of peroxide resulted in decreased yields of **2** (Table 1, entries 4, 6–8). Not surprisingly, control experiment excluding the *t*Bu–OOH from the electrolysis solution resulted in no ketone product being produced over a 27-hour period with the starting alcohol recovered unchanged (Table 1, entry 9). NHPI and TCNHPI were also examined under our optimized reaction conditions, and though products were formed, we were unable to purify the ketone product when employing the more electron rich phthalimides. Under the electrolysis conditions employed in this work, the NHPI and TCNHPI mediators suffered from unproductive background decomposition reactions and fouled the RVC electrodes, rendering them inactive for further oxidative chemistry (Table 1, entries 10 and 11).

Scheme 2. Electrochemical Oxidation of Sensitive Alcohols.[a]

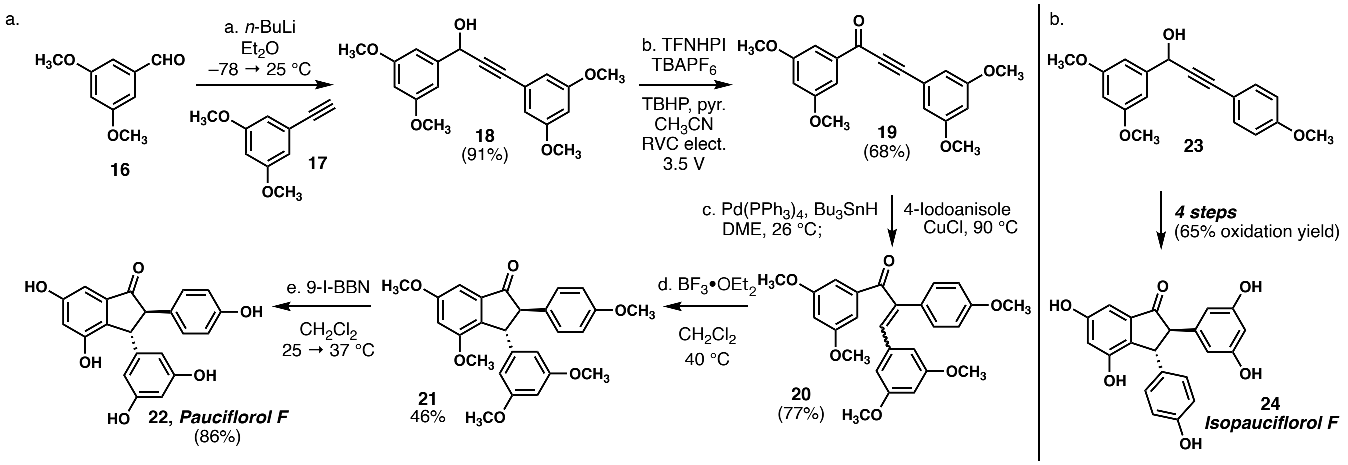


[a] 1.0 mmol alcohol, isolated yield. [b] Divided cell.

Reduction to 2.5 mol% TFNHPI with 10 equiv of peroxide co-oxidant afforded clean conversion of starting alcohol **1** to propargyl phenone **2** in just three hours (40% shorter reaction time) with a boost to 84% isolated yield (Table 1, entry 4). Oxidation of **1** to **2** was also observed upon dropping the loading of TFNHPI to 1.0 mol%, albeit with slightly lower yields (~70%) for the same 3 hour electrolysis. Accordingly, TFNHPI loadings of 1 mol% can be used to facilitate the process highlighted in Scheme 2 provided one can tolerate slightly longer reaction times. Importantly, control experiments excluding any mediator from the electrolysis cell reduced conversion of alcohol **1** to ketone **2** significantly (39% isolated yield over the course of a 3h electrolysis, Table 1, entry 5). The electrochemical homolysis of the O–H bond of *t*Bu–OOH[35] presumably facilitates a small amount of background oxidation of **1** to **2** in the absence of TFNHPI.

Having optimized the electrolysis conditions, we turned our attention to assessing substrate scope for the electrochemical oxidation reaction. The electrochemical oxidation of propargylic benzylic alcohols tolerates a variety of electron-rich and electron-poor substrates, however substrates sensitive to unproductive electrochemical reduction require the use of a divided cell (Scheme 2) to circumvent unwanted side reactions at the cathode. For example, substrates containing aromatic ethers and nitro groups are successfully oxidized to the corresponding ketones (**7**, **11**, **5**, and **14**) in a divided cell that prevents substrate migration to the cathodic side of the electrolysis cell. In general, we find that implementation of the electrochemical method described above provides a means to generate a variety of propargyl phenyl ketones in 16–87% yield, *including those that we could not oxidize at all under thermal conditions* (e.g. **5**, *vide supra*). *Moreover, the electrochemical oxidations can be routinely conducted on multi-gram scale in inexpensive, readily available glassware or in disposable falcon tubes while open to ambient air and moisture*. No exotic preparations or precautions need be taken, and reactions could be conveniently monitored by conventional thin-layer chromatography.

Scheme 3. An Electrochemically-Enabled Synthesis of the Pauciflorols.[a]



[a] Conditions: (a) *n*-BuLi, **15**, Et_2O, −78 °C, then **14**, −78 → 25 °C, 91%. (b) 20 mol% TFNHPI, 0.1M $TBAPF_6$, 10.0 equiv. 5.5M *t*-BuOOH in decane, pyridine, CH_3CN, RVC electrodes, 3.5V, 23 °C, 68%. (c) 3 mol% $Pd(PPh_3)_4$, 1.05 equiv *n*-Bu_3SnH, DME, 26 °C, then 1.1 equiv 4-iodoanisole, 0.83 equiv CuCl, 90 °C, 77%. (d) BF_3•OEt_2, CH_2Cl_2, 40 °C, 46%. (e) 9-I-BBN, CH_2Cl_2, 25 → 37 °C, 86%.

The electro-oxidation protocol detailed can be used to achieve the expedient synthesis of several classes of phenolic natural products such as the pauciflorols, the ampelopsins, the caraphenols, the parthenocissins, and the quadrangularins.[36] To this end, we completed the five-step syntheses of pauciflorol F[37] and isopauciflorol F enabled by the oxidation of alcohols **18** and **23** as shown in Scheme 3. We prepared alcohols **18** and **23** in 91% and 83% yield, respectively, by the addition of lithium acetylide to methoxybenzaldehydes in cold ethyl ether. Alcohol **18** was electrochemically oxidized to the ynone **19** in 68% yield on multi-gram scale in a divided electrolysis cell.[38] We note that while base was not required for conversion of any of the simple substrates shown in Scheme 2, the addition of exogenous pyridine did facilitate oxidation of **18**, which is the most electron rich substrate assessed in this study. Ynone **19** was converted to the α,β-unsaturated ketone **20** by a reductive Stille-type coupling with an aryl halide under the action of low-valent palladium and tri-*n*-butyltin hydride in 77% yield.[39] Subsequent Nazarov[40] cyclization of enone **20** results in the *trans*-disubstituted ketone **21** in 46% yield. Global deprotection results in pauciflorol F (**22**) in five steps and 23% overall yield from commercial starting materials. A similar sequence transforms alcohol **23** into isopauciflorol F (**24**) (see Scheme 3), including the electrochemical oxidation of **23** in 65% yield. Thus, by utilizing the oxidation protocol we have developed, a single researcher can generate gram quantities of pauciflorol F (**22**) and isopauciflorol F (**24**) in a single week,[41] providing significantly larger amounts of these materials for biological exploration than previous efforts. While we were disappointed to find that pauciflorol F (**22**) and isopauciflorol F (**24**) exhibited no significant activity in the NCI60 panel (despite prior reports of promising anti-cancer potential), further studies exploring biological activity of the pauciflorols is ongoing.

In summary, the TFNHPI mediator allows for an array of new electrochemical transformations that have been otherwise difficult or impossible to realize using conventional thermal chemistries. This electrochemical platform is being used as a springboard in our laboratories for new opportunities in complex molecule synthesis and is the subject of additional electroanalytical interrogation as well. Some of transformations being pursued include allylic oxidations/peroxidations, direct oxygenations of fully saturated sp^3–carbon centers, transient generation of unstable dienes in Diels–Alder chemistry, and various nitrogen-based chemistries which are all being studied for their applications in total syntheses of terpenoid and alkaloid natural products. These methods, along with the accompanying total syntheses, will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, photographs of experimental apparatus, characterization data for all compounds, cyclic voltammograms, X-ray crystallographic data, and hypothetical mechansism for the electrochemical oxidation method. The Supporting Information is available free of charge on the ACS Publications website.

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41. We expect to complete an array of similar natural products for future biological investigations based on this platform.