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RESEARCH ARTICLE

Iron Catalyzed Dehydrogenation of Alcohols Using Benzoquinones as Electrochemically Regenerable Mediators

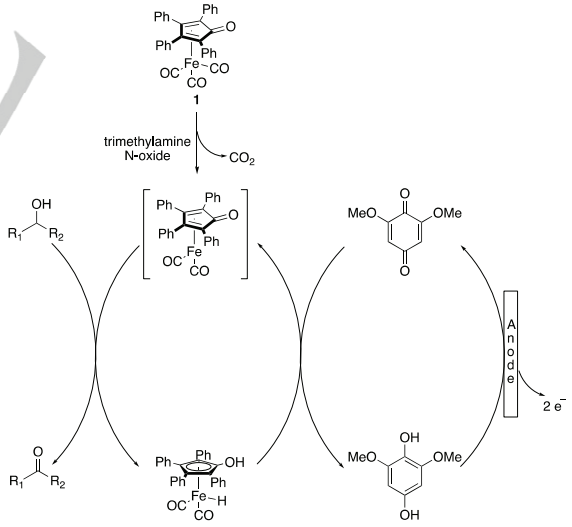
Mikhaila D. Ritz,[a] William D. Jones*[a]

The efficient and atom economical iron catalyzed dehydrogenation of alcohols using benzoquinones as electrochemically regenerable mediators has been developed. Herein an iron cyclopentadienone complex was electrochemically studied and tested for its effectiveness within this system. This methodology was then extended to various secondary and primary alcohols affording moderate to good yields of product.

Introduction

The oxidation of alcohols to ketones and aldehydes is a fundamental organic reaction which provides a wide variety of important synthetic and industrial building blocks.[1] While many organic reactions and reagents have been developed to perform this transformation, these methods often require stoichiometric amounts of reagents, are prone to over-oxidations, and/or produce large amounts of chemical waste.[2] An alternative oxidative strategy uses transition metal-catalyzed dehydrogenation, a thermodynamically uphill process that is driven forward by the release of hydrogen gas or its trapping with acceptors.[3] However, these hydrogen-acceptors diminish the overall catalytic efficiency, as they are needed in stoichiometric amounts. An attractive solution to circumvent this drawback is the implementation of hydrogen acceptors that can be catalytically regenerated under the reaction conditions.

In particular, the use of benzoquinones to act as mediators has been explored in a variety of different systems. One of the first examples was shown by Bäckvall et al. where they developed a palladium catalyzed system for the oxidation of 1,3-dienes that could selectively give cis or trans products depending on reaction conditions. The benzoquinone in this case was utilized both as an oxidant, that was electrochemically regenerated at the anode, and as a ligand for the palladium catalyst to aid in selectivity.[4] Furthermore in 1990, Bäckvall et al. took the previous palladium catalyzed oxidation of 1,3-diene systems and developed new, mild, triple catalyst conditions, using $Pd(OAc)_2$, hydrooquinone, and a transition-metal macrocycle. Three different types of oxidations were successfully developed utilizing these new conditions: 1,4 oxidation of conjugated dienes, oxidation of terminal olefins to methyl ketones, and allylic oxidation. In all cases, the Pd interacted with the substrate and was re-oxidized from Pd(0) back to the active Pd(II) by the benzoquinone. The hydroquinone that forms was then oxidized by the macrocycle, which in turn was oxidized by molecular oxygen, completing the catalytic cycle.[5] Additionally, Jutand et al. have shown that $Pd(OAc)_2$, in the presence of catalytic amounts of benzoquinone, can be re-oxidized to its active form to perform Heck-type coupling, electro-oxidative homocoupling of arylboronates or arylboronic acids, and oxidation of alcohols.[6-8] The hydroquinone formed in-situ was electrochemically oxidized back to the benzoquinone. Taking a similar approach to his triple catalyst Pd system, Bäckvall demonstrated the oxidation of a variety of alcohols using $RuCl(OAc)(PPh_3)_3$ and Shvo's catalyst, a ruthenium cyclopentadienone complex, that once reduced could be regenerated in the presence of benzoquinones. Rather than employing electrochemical methods to reform the benzoquinones, a cobalt salen complex was used and was then re-oxidized using O_2.[9,10] Wanting to move away from using oxygen as a terminal oxidant, Tehrani et al. showed that combining Shvo's catalyst with electrochemical methods to regenerate the benzoquinones could readily dehydrogenate an array of alcohols and showed chemoselectivity for secondary alcohols in the presence of diols.[11] While these examples provide excellent precedent for the use of benzoquinones as regenerable mediators, they all employ precious metals.



Scheme 1. Proposed electrochemical mechanism

An interesting alternative to this is the use of the iron analog of Shvo's catalyst. These cyclopentadienone iron tricarbonyl complexes constitute a large class of hydrogen transfer catalysts and were first synthesized in the 1950's by Reppe and Vetter;[12,13] however, it was not until 2010 that the first report of alcohol oxidation using this type of catalyst was published.[14,15] More recently, Funk et al. synthesized several (3,4-diphenyl-1,2-

[a] *M. D. Ritz, Prof. W. D. Jones*
Department of Chemistry, University of Rochester
Rochester, NY 14627 (USA)
E-mail: jones@chem.rochester.edu
http://www.sas.rochester.edu/chm/people/faculty/jones-william/index.php

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diaryl/alkyl-cyclopentadienone)iron tricarbonyl complexes and compared their reactivity for transfer dehydrogenation of alcohols with previously established iron tricarbonyl catalysts.[16] Furthermore, initial studies have shown that the cyclopentadienone iron complexes undergo an analogous mechanism to Shvo's catalyst suggesting that benzoquinones could be implemented similarly with **1** as catalysts as shown in Scheme 1.[17] Additionally, Bäckvall has shown evidence of this by demonstrating the dehydrogenation of alcohols using an iron cyclopentadienone catalyst in the presence of catalytic amounts of benzoquinone. These benzoquinones were re-oxidized by a cobalt salen type complex and the salen was regenerated using air.[18] Currently, despite these new breakthroughs, there is no literature discussing the combination of the iron tricarbonyl cyclopentadienone complexes in the presence of benzoquinones that can be regenerated electrochemically.

Results and Discussion

Herein we report the first example of iron catalyzed dehydrogenation an of alcohol using a benzoquinone as an electrochemically regenerable mediator. Our initial analysis began by investigating reaction conditions using benzoquinones as stoichiometric oxidants in the presence of 1-(4-methylphenyl)ethanol, **1**, as the catalyst, and trimethylamine N-oxide dihydrate (TMANO) to activate the iron complex. It was found that under these conditions, 2,6-dimethoxybenzoquinone (DMBQ) worked the best out of the 4 benzoquinones examined (see SI for others), giving 64% of the desired ketone in 24 hours. Moving forward, several solvents were tested to examine their effect on this transformation, considering that the solvent must be able to dissolve electrolyte. It was seen that dichloroethane (DCE) was able to catalyze the reaction best, yielding 85% of the ketone in 24 hours (DCE is an electrochemically compatible solvent). Further reaction optimization of both catalyst loading and concentration found that 15 mol% of **1**, 20 mol% of TMANO in 4 mL of DCE at 100 °C in the presence of stoichiometric amounts of DMBQ gave 96% of product **3e** in 2 hours (see SI for further optimization details).

With preliminary conditions in hand, we turned to cyclic voltammetry studies to gain a better understanding of the catalyst and the reaction conditions necessary for an electrochemical system. In a solution of DCE with 0.1M NBu_4PF_6 as the supporting electrolyte, the iron complex was probed using a glassy carbon working electrode. The red curve (a) in Figure 1 shows the electrochemical trace of just the catalyst between potentials -0.2V to +1.6V; no apparent redox activity is seen. Upon scanning to more reducing potentials, new redox events can be seen and are attributed to the ligand, similar to what was detected with Shvo's catalyst.[11] However, with the addition of TMANO, 1-(4-methylphenyl)ethanol, and DMBQ at 80 °C, a large oxidation peak appears at +1.1V (Figure 1, blue curve (b)). When compared to the oxidation peak potential of the 2,6-dimethoxyhydroquinone in DCE (Figure 1, grey curve (c)), it is seen that the two oxidation potentials are the same suggesting that under the reaction conditions the hydroquinone is formed and subsequently oxidized back to the benzoquinone. This supports that this process is indeed mediated by the electrochemical regeneration of the benzoquinone.

Once confirmed that this system could perform electrochemically, further optimization was done using catalytic amounts of DMBQ under controlled potential experimental

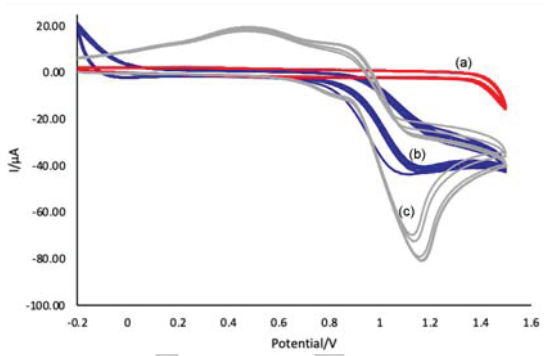
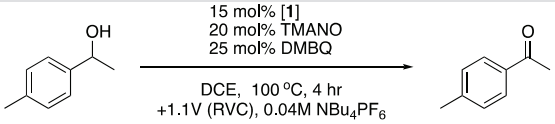


Figure 1. Cyclic Voltammetry of [**1**] and Reaction Conditions. (a) Red curve: [**1**] in 0.1M NBu_4PF_6 of 5.0 mL DCE with a scan rate of 100 mVs^{-1}, (b) Blue curve: [**1**], TMANO, DMBQ, 1-(4-methylphenyl)ethanol, 0.1M NBu_4PF_6 in 5.0 mL of DCE at 80 °C, with a scan rate of 100 mV s^{-1}, (c) Gray curve: 2,6-methoxyhydroquinone in 0.1M NBu_4BF_4 of 5.0 mL of DCE with a scan rate of 100 mV s^{-1}.

conditions (Table 1). Using a three-neck round bottom flask equipped with a condenser and reticulated vitreous carbon (RVC) as the working electrode, potential reaction conditions were probed. It was seen that 1-(4-methylphenyl)ethanol (**2e**), in the presence of 15 mol% of [**1**], 20 mol% of TMANO, 25 mol% of DMBQ, at 1.1V at 100 °C for 4 hours formed a 76% yield of the desired ketone. Upon lowering either the temperature, catalyst loading, or amount of DMBQ, the yield of **3e** decreased (Table 1, entries 2, 5, 6). Furthermore, when increasing the reaction time from 4 hours to 6 hours a decrease in yield from 76% to 63% was seen, which is attributed to the electrochemical back reaction as this system was in an undivided cell. Further control reactions were run, demonstrating that without any current, one turnover was seen with the initially activated iron complex [**1**] and then the remaining product formation was from stoichiometric oxidation with the DMBQ (Table 1, entry 7). In the absence of catalyst or DMBQ, hardly any product formation was seen (Table 1, entry 8).

Table 1. Reaction Optimization for Controlled Potential Experiments



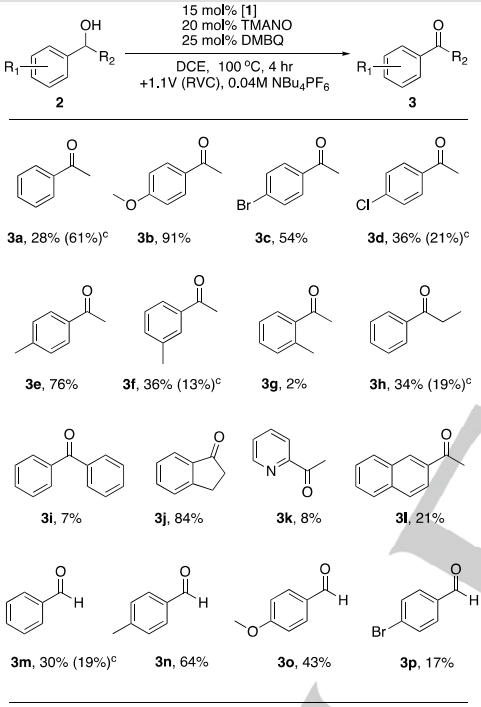
2e **3e**

Entry[a]	Change in conditions	Yield[b]
1	None	76%
2	80 °C	66%
3	6 hr	63%
4	2 hr	65%
5	10 mol% [**1**]	47%
6	20 mol% DMBQ	42%
7	No current	34%
8	No [**1**]/ DMBQ	6%
9	Anisole solvent	30%

[a] Reactions were run in an undivided cell on a 0.5 mmol scale in 10 mL of DCE and 0.04 M of NBu_4PF_6 at +1.1V with an RVC working electrode, Pt wire auxiliary electrode, and an Ag wire reference electrode, for the specified amount of time. [b] Yields were determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Moving forward with these optimized electrochemical conditions, a variety of secondary alcohols were tested for reactivity (Table 2). 1-Phenylethanols with electron donating substituents were well tolerated by this system including the *para*-methyl and *para*-methoxy substrates (**3e** and **3b**). While more challenging, electron withdrawing substituted 1-phenylethanols such as the *para*-bromo (**3c**) and *para*-chloro (**3d**) were able to undergo dehydrogenation in this system. Fused bicyclic naphthyl (**3l**) and nitrogen-containing pyridyl (**3k**) substrates are oxidized in low yields. The *meta*- and *para*-pyridyl substrates were tested in addition to the *ortho*-substituted pyridyl substrate (**3k**) shown in Table 2; however, these both did not undergo oxidation. Surprisingly, the unsubstituted 1-phenylethanol was among the least reactive, although a higher concentration of alcohol more than doubled the yield.

Table 2. Substrate Scope of Alcohols Screened[a,b]



[a] Reactions were run in an undivided cell on a 0.5 mmol scale in 10 mL of DCE and 0.04M of NBu_4PF_6 at +1.1V with an RVC working electrode, Pt auxiliary electrode, and an Ag wire reference electrode. [b] Yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. (c) 1.0 mmol alcohol.

Wanting to probe the amount of steric hindrance this system could tolerate, several bulkier 1-phenylethanols were tested. As shown previously, the *p*-methyl-1-phenylethanol worked well; however, when the methyl substituent is in the *ortho*-position very little reactivity is seen (**3g**). Furthermore, when moving from 1-phenylethanol (**3a**) to the slightly bulkier 1-phenyl-1-propanol (**3h**), similar reactivity is seen. However, increasing the steric hindrance further with a phenyl group, as shown with substrate **3i**, heavily stunts reactivity. Additionally, this system can be extended to primary alcohols. For primary alcohols, electron donating groups enhance reactivity (**3n** and **3o**) while electron withdrawing groups show decreased yields (**3p**). In contrast, for secondary alcohols, both electron donating and electron withdrawing groups favor oxidation with the former having a larger effect over the unsubstituted 1-phenylethanol. Oxidations of several alcohols were examined at higher concentration (0.1 M vs. 0.05 M) to see if a more rapid reaction could be effected prior to catalyst deactivation. While this initially was promising for the unsubstituted 1-phenylethanol, showing an increase in yield from 28% to 61%, the remaining four substrates tested at higher concentration gave lower yields with all other factors remaining the same (Table 2, yields (c)).

Conclusions

In summary, we have electrochemically examined complex **1** and showed its effectiveness in catalyzing the dehydrogenation of alcohols while utilizing benzoquinones as regenerable mediators. This methodology was extended to both primary and secondary alcohols, showing moderate to good yields for a variety of different substrates. Notably, this system is the first example utilizing complex **1** to catalyze the dehydrogenation of alcohols in the presence of electrochemically regenerable benzoquinones.

Experimental Section

General Information

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were acquired on 400 MHz Bruker NMR instruments. ^{1}H NMR chemical shifts are reported in ppm and are referenced to the residual solvent peak for CD_2Cl_2 δ = 5.32 ppm or $CDCl_3$ δ = 7.26 ppm. Coupling constants (*J*) are reported in Hertz. All electrochemical experiments were run using a BASi Epsilon potentiostat connected to a Lenovo laptop equipped with Epsilon software. For cyclic voltammetry experiments, the working electrode was 3 mm glassy carbon electrode (BASi), auxiliary electrode was a platinum wire, and the reference electrode was a silver wire further referenced with ferrocene. For electrolysis experiments, an 80 ppi (pores per inch) reticulated vitreous carbon (RVC) working electrode (Duocel), a 1 cm x 1 cm platinum square auxiliary electrode, and a silver wire reference electrode were used. Dichloroethane (DCE) was dried over 4Å mol sieves and underwent 4-5 freeze-pump-thaw cycles before use. Elemental analyses were obtained from the CENTC Elemental Analysis Facility at the University of Rochester. Microanalysis samples were weighed with a PerkinElmer Model AD6000 Autobalance and their compositions were determined with a PerkinElmer 2400 Series II Analyzer. TMANO is an abbreviation for trimethylamine N-oxide dihydrate and DMBQ stands for 2,6-dimethoxy-1,4-benzoquinone.

General Procedure for Cyclic Voltammetry Experiments

All electrochemical experiments were run using a BASi Epsilon potentiostat connected to a Lenovo laptop equipped with Epsilon software. The cyclic voltammetry measurements were run in a 3-electrode cell using a 3 mm diameter glassy carbon working electrode, a platinum wire auxiliary electrode, and a silver wire electrode further referenced with ferrocene. The working electrode was polished using a slurry of 0.05μm alumina powder and deionized water on a velvet alumina polishing pad (BASi). It was then rinsed and sonicated for 1 minute in deionized water, then rinsed further with acetone and dried before use. All solutions of NBu_4PF_6/DCE were freshly made and purged with argon gas for five minutes to remove oxygen before each experiment. Experiments at 80 °C were done using a heating block for the cell to sit in.

General Procedure for Electrolysis Experiments

In a dried, 3-neck, 25 mL round bottom flask equipped with a stir bar was added trimethylamine N-oxide dihydrate (11.2 mg, 0.1 mmol, 0.2 equiv), **1** (39.2 mg, 0.075 mmol, 0.15 equiv), DMBQ (21 mg, 0.125 mmol, 0.25 equiv), NBu_4PF_6 (0.154 g, 0.4 mmol, 0.8 equiv), and the appropriate alcohol (0.5 mmol, 1.0 equiv). Using a needle to puncture the septum, an 80 ppi (pores per inch) reticulated vitreous carbon working electrode and a silver wire reference electrode were introduced. A 1 cm x 1 cm platinum square auxiliary electrode was introduced through a second septum, making sure the electrodes outside and inside the cell were not touching. A condenser was attached to the middle neck of the round bottom flask and a steady stream of nitrogen gas flushed out the reaction set-up for 5-10 min. Using a syringe, 10 mL of dry/degassed DCE was added. Once the electrodes were connected to the potentiostat, the system was then allowed to stir (700 rpm) at 100 °C in an oil bath for the appropriate amount of time. This was done at a set potential of +1.1V under a slow stream of nitrogen gas. After the specified time had elapsed, the system was removed from the oil bath and cooled to room temperature before transferring the reaction solution to a scintillation vial. The solution was then rotary evaporated to remove the DCE. The residue was redissolved in a minimal amount of dichloromethane and filtered through a 5 ¾" glass pipette filled halfway with silica to remove any remaining iron complex. The filtrate was rotary evaporated, dissolved in either CD_2Cl_2 or $CDCl_3$, and added to an NMR tube along with 10 mg of 1,3,5-trimethoxybenzene as an internal standard. A ^1H NMR spectrum was recorded to quantify the product yield.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: dehydrogenation, alcohols, electrochemistry, iron, quinones

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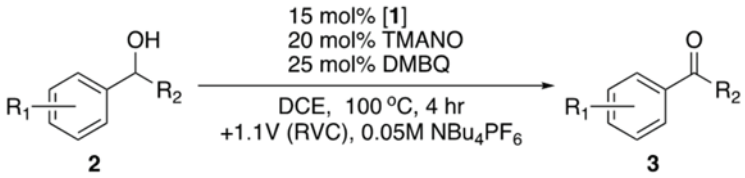

Cyclopentadienoneirontricarbonyl complex **1**, activated by trimethylamine *N*-oxide, electrocatalyzes the dehydrogenation of benzyl alcohols using a benzoquinone as a regenerable hydrogen-accepting mediators. This methodology was extended to both primary and secondary alcohols, showing moderate to good yields for a variety of different substrates.