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Organic Transformations using Electro-Generated Polyoxometalate Redox Mediators

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Abstract: The use of electrochemistry in organic synthesis (sometimes termed electro-organic synthesis, or just “electrosynthesis”) is a field that is attracting ever-increasing attention on account of its ability to deliver reaction outcomes that cannot be achieved in any other way and on account of its potential to replace toxic and/or sacrificial reagents with cleanly-generated electricity. In the simplest incarnation of electro-organic synthesis, an organic substrate undergoes direct electron transfer with the electrode in a type of heterogeneous catalysis process. However, such direct electrochemical processes may suffer from slow kinetics, poor product selectivities and/or lack of control over the extent of electron transfer to the substrate, all of which can lead to sub-optimal reaction outcomes. A distinct, but extremely important, sub-section of electro-organic synthesis (so-called “indirect electrolysis”) circumvents these limitations through the use of soluble redox mediator molecules, which act as electron shuttles between the heterogeneous electrode and the organic substrate in bulk solution. The advantages of indirect electrolysis for a number of organic transformations is now becoming increasingly clear, typically using either very simple metal salts or small organic molecules as the mediators. However, one particular class

of mediators, the polyoxometalates (well-defined, soluble metal oxide clusters), offers an especially wide diversity of structures and properties that could revolutionise indirect electrolysis for electro-organic synthesis. In this review, we provide a collation of reports that describe use of electro-generated polyoxometalate redox mediators for organic transformations, with a particular focus on the most recent and most exciting results.

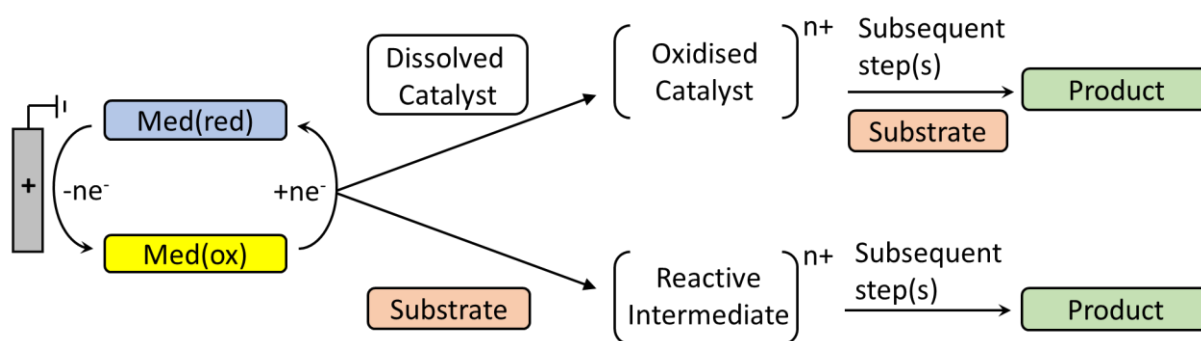
Keywords: electrosynthesis; redox mediator; indirect electrolysis; electrocatalysis; polyoxometalate; electro-organic synthesis

1. Introduction

Electrochemical organic synthesis is a mature field that can trace its origins back to the work of Michael Faraday.¹ It is currently undergoing something of a renaissance on account of its potential as a sustainable alternative to traditional routes for organic synthesis.²⁻⁶ In particular, the ability to drive organic transformations using electricity holds considerable promise for the replacement of dangerous and/or toxic reagents by electric current, reduced use of sacrificial reagents and lower overall energy consumption.^{7,8} All these features are attractive from an environmental point of view, and yet organic electrosynthesis remains rather an under-utilised approach to organic chemistry.⁹ This is at least partly due to the fact that direct electrochemical oxidation or reduction of substrates at the electrode surface can lead to sub-optimal selectivities, specificities and yields.

It is within this context that the sub-field of *indirect electrolysis* continues to attract increasing attention. In an indirect electrochemical process, a carefully selected redox mediator is used as an electron carrier between the electrode and species dissolved in solution. This redox mediator may merely shuttle electrons between the electrode and a catalyst dissolved in solution, or alternatively the mediator itself may react directly with the

substrate (in which case, the mediator can also be considered as a soluble electrocatalyst). In both cases, the key point is that it is the redox mediator molecule that undergoes electron transfer at the electrode surface, rather than the substrate itself engaging in electron transfer directly with the electrode. Scheme 1 provides some examples of the mode of action of redox mediators in organic oxidation reactions. Hence, the mediator in the reduced form is oxidised at the electrode surface, before diffusing into bulk solution where it reacts either with a dissolved catalyst (top pathway), or directly with an organic substrate (bottom pathway). The mediator (now reduced again) cycles back to the electrode to be re-oxidised, whilst the oxidised catalyst or substrate undergo any number of subsequent chemical reactions in solution. In this way, and assuming that the mediator is stable to multiple such redox cycles, a small amount of mediator can be employed to transform a much larger amount of substrate. The mediator can either be used “in-cell” (where the mediator and the organic substrate are both present in the electrochemical cell, as in the examples in Scheme 1), or “ex-cell”, whereby the mediator is oxidised or reduced into its active form in an electrochemical cell on its own, and is then subsequently introduced to the substrate in a separate, purely chemical reaction vessel.¹⁰



Scheme 1: A general and simplified illustration of the possible modes of operation of a redox mediator in an indirect “in-cell” electrochemical process, using the example of an organo-oxidation reaction.

Depending on the desired reaction outcome, indirect electrolysis can hold a number of advantages for organic synthesis.¹¹ Firstly, the heterogeneous step (electron transfer from the electrode to species in solution) occurs only between the electrode and the (ideally) robust and recyclable redox mediator, and this heterogeneous step is decoupled from the subsequent solution-phase chemistry. The substrate therefore no longer reacts directly at the electrode, preventing uncontrolled oxidation or reduction of the organic substrate that might lead to polymerisation or degradation. The heterogeneous step can then be optimised for a particular electrode-mediator pairing, whilst the subsequent reactions in the cascade (*e.g.* between the oxidised mediator and the substrate) all occur in solution under more classical (chemical) control. These solution-phase processes can themselves be optimised, possibly even in the absence of any electrode processes. This allows greater scope for otherwise incompatible conditions to be employed. Secondly, the redox mediator will have defined redox levels and a defined level of oxidation/reduction at any given cell potential, which means that its subsequent reaction with the organic substrate will be more controlled, both in the number and reducing power of the electrons added to (or removed from) the substrate. This adds the prospect of selectivity to what might otherwise be a rather unselective direct reaction at the electrode surface. Well-chosen mediators might also exhibit lower barriers to electron transfer with the electrode than the substrates themselves do (improving reaction kinetics) and/or they may allow the use of bias potentials that are lower than that required for the direct electrochemical conversion and hence permit milder reaction conditions to be employed.¹²

In a well-found mediator system, only the mediator will undergo oxidation or reduction at the electrode surface and none of the substrates, intermediates or products will interfere with the regeneration of the mediator. The mediator should also be stable to multiple redox cycles, reactive in its active form towards the desired substrate and long-lived enough in its active form to travel from the electrode surface to bulk solution to react with the substrate.

Likewise, if the environmental benefits of electrosynthesis are to be fully realised, processes that work well in aqueous solution need to be developed (where water's low toxicity and high abundance make it an ideal solvent medium and proton source).^{13,14}

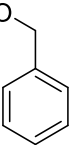
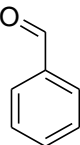
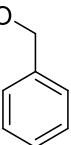
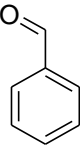


Polyoxometalates are a class of molecular metal oxides that consist of three or more transition metal oxyanions (typically from groups 5 and 6 of the periodic table) in their highest oxidation states linked by shared oxygen atoms.¹⁵ A large number of such clusters display high water solubility and the ability to reversibly receive and donate multiple electrons and protons, normally through outer-sphere mechanisms.^{16,17} Such features render polyoxometalates of particular interest as inorganic molecular redox mediators for organic transformations,¹⁸ where the addition/removal of multiple electrons and protons to/from a substrate is often required. Polyoxometalates may also act to prevent electrode fouling by organic species (during the electro-oxidation of phenols, for example).¹⁹ However, compared to their use in purely chemical electron transfer and catalysis processes,²⁰⁻²² the use of polyoxometalates as electrocatalysts and redox mediators in organic synthesis remains a rather niche area.

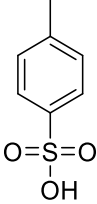
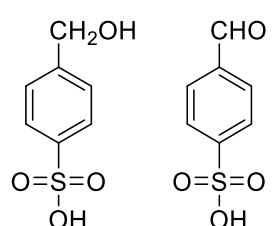
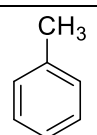
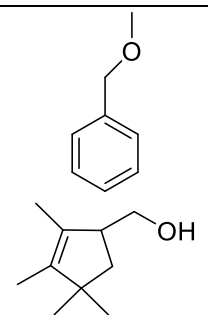
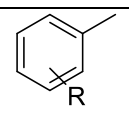
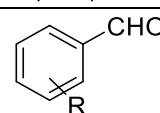
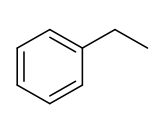
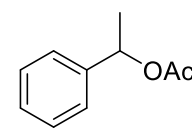
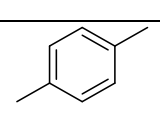
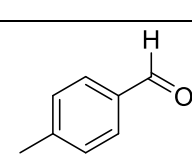

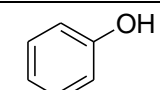
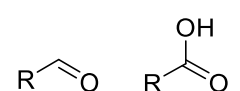
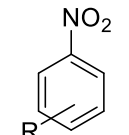
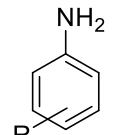
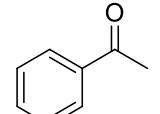
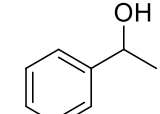
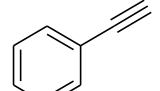
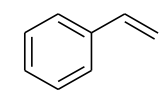
Indirect electrochemical processes for organic synthesis were first reviewed by Steckhan in the 1980s,²³ and Francke and Little produced a seminal survey of the field in 2014.¹¹ More recently, Stahl and co-workers have reviewed the use of certain specific mediators in indirect electrolysis.²⁴ However, the main focus of most of these reviews has been on the use of organic species such as quinone and *N*-oxyl mediators; there has been no comprehensive review of the use of polyoxometalate redox mediators in electro-organic synthesis for at least twenty years.²⁵ This could well be to the detriment of those seeking to employ indirect electrolysis for the development of sustainable and environmentally-friendly processes. In this review, we seek to address this gap by providing a coherent and readily-accessible collation of examples of the use of polyoxometalate redox mediators for electro-organic

synthesis. In doing so, we shall restrict ourselves to the discussion of systems for the controlled interconversion of organic substrates for chemical synthesis, excluding indirect electrochemical approaches to sensing^{26,27} and processes concerning purely inorganic species such as the oxidation and reduction of nitrite, oxygen reduction or water splitting (a field which has been reviewed recently).²⁸

We shall start with a brief overview of the classical work in this field, before then exploring more recent developments in the use of polyoxometalate redox mediators for electro-organic synthesis in more depth, dividing these more recent studies into examples of oxidation of organic substrates and (much less common) examples of reduction of organic substrates. The key results from the works that are reviewed herein are summarised in Table 1.

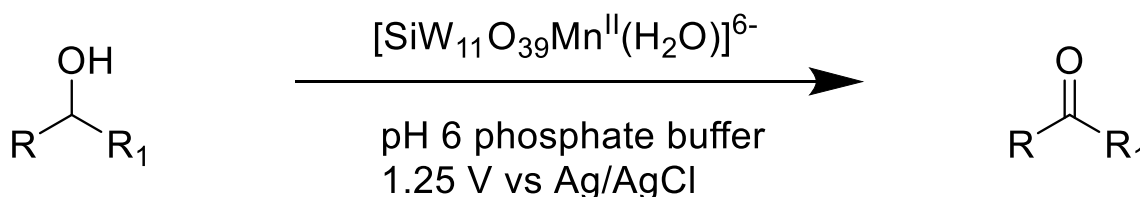
Table 1: A summary of the organic transformations mediated by electro-generated polyoxometalate redox mediators discussed in this review.

Substrate(s)	Main Product(s)	Mediator(s)	N° of electrons transferred to/from mediator	Relevant mediator redox potential	Reference
		α - [PW ₁₁ O ₃₉ Cr ^{III} (H ₂ O)] ⁴⁻ α_2 - [P ₂ W ₁₇ O ₆₁ Cr ^{III} (H ₂ O)] ⁷⁻	2	1.25-1.60 V vs Ag/AgCl	29
		α - [PW ₁₁ O ₃₉ Ru ^{III} (H ₂ O)] ⁴⁻	3	1.3 V vs SSCE	30
		K ₆ [SiW ₁₁ O ₃₉ Mn ^{II} (H ₂ O)]	2	1.25 V vs Ag/AgCl	31

		$[H_3PMo_{12}O_{40}]$	2	0.7 V vs Ag/AgCl	32
		$(NH_4)_3H_4[P(Mo_2O_7)_6]$	Not reported	30 V cell potential	37
		$H_5PV_2Mo_{10}O_{40}$	2	1.3 V vs NHE	38
		$[Co^{IV}W_{12}O_{40}]^{4-}$	1	1.8 V vs Ag/AgNO ₃	40
		$[Co^{IV}W_{12}O_{40}]^{4-}$	1	1.8 V vs Ag/AgNO ₃	40
		$[Co^{IV}W_{12}O_{40}]^{4-}$	1	1.8 V vs Ag/AgNO ₃	40
$R-CH_2OH$ R = H or CH ₃		$[\{Ru_4O_4(OH)_2(H_2O)_4\}(\gamma-SiW_{10}O_{36})_2]^{10-}$	Up to 4	Varies from 0.66 – 0.93 V vs Fc/Fc ⁺	44
Light hydrocarbons, e.g. ethane, propane, ethene	Corresponding acids and aldehydes	$\{Fe^{II}_{10}Fe^{III}_{20}W^{VI}_{72}\}$	10	1.8 V cell potential	47
		$[H_4SiW_{12}O_{40}]$	2	-0.56 V vs Ag/AgCl	50
		$[H_4SiW_{12}O_{40}]$	2	8.3 V cell potential	53
		$[H_4SiW_{12}O_{40}]$	2	8.3 V cell potential	53

2. Early Work in Polyoxometalate-mediated Electrosynthesis

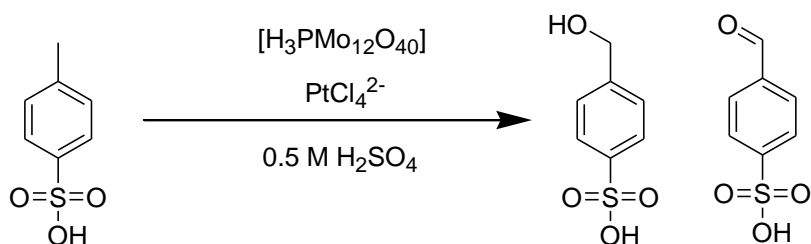
A number of polyoxometalates were examined in the 1990s as electrocatalysts for the oxidation of alcohols to their corresponding ketones and carboxylic acids. Rong and Anson oxidised the chromium-containing polyoxometalates α -[PW₁₁O₃₉Cr^{III}(H₂O)]⁴⁻ and α -[P₂W₁₇O₆₁Cr^{III}(H₂O)]⁷⁻ electrochemically to the analogous Cr^V=O complexes and used these species as ex-cell mediators to effect the oxidation of ethyl and benzyl alcohols,²⁹ whilst Bart and Anson reported similar activity for the ruthenium-containing polyoxometalate α -[PW₁₁O₃₉Ru^{III}(H₂O)]⁴⁻ after its electrochemical production from α -[PW₁₁O₃₉Ru^{III}(H₂O)]⁵⁻.³⁰ In all these cases, however, the reaction rates of the polyoxometalates with the substrates were concluded to be too slow to warrant further investigation of these species as organo-oxidation catalysts. Meanwhile, Sadakane and Steckhan employed α -[SiW₁₁O₃₉Mn^{II}(H₂O)]⁶⁻ as a redox mediator for the indirect electrochemical oxidation of a number of alcohols as shown in Scheme 2,³¹ although the rate constants for the reactions between this polyoxometalate and the alcohol substrates are on the same order as those reported by Anson and co-workers for their {PW₁₁O₃₉}-based polyoxometalates, which might also suggest that α -[SiW₁₁O₃₉Mn^{II}(H₂O)]⁶⁻ oxidises alcohols too slowly to be an attractive electrocatalyst.



Scheme 2: Indirect electrochemical reduction of alcohols using K₆[SiW₁₁O₃₉Mn^{II}(H₂O)] as the redox mediator as reported by Sadakane and Steckhan.³¹

At around the same time, Freund *et al.* investigated a system for the electrocatalytic hydroxylation of *p*-toluenesulfonic acid (*p*-HO₃SC₆H₄CH₃) to the alcohol *p*-

(hydroxymethyl)benzenesulfonic acid (p -HO₃SC₆H₄CH₂OH) and aldehyde p -formylbenzenesulfonic acid (p -HO₃SC₆H₄CHO) using PtCl₄²⁻ as a C-H activation catalyst and the polyoxometalate phosphomolybdic acid ([H₃PMo₁₂O₄₀]) as the redox mediator in 0.5 M H₂SO₄ (see Scheme 3).³² No conversion was evident in the absence of the phosphomolybdic acid redox mediator, but conversions of >30% were possible using 0.2 M phosphomolybdic acid, with coulombic yields for the hydroxylated products approaching 100%. However, the product selectivity was lost after extended electrolysis times (more than six turnovers), which the authors suggested could be due to the formation of Pd(0) from PtCl₄²⁻, citing the known activity of Pd(0) for alcohol oxidation. Some oxidation of the aromatic ring was also observed, again attributed to oxidation catalysed by Pt(0).



Scheme 3: Indirect electrocatalytic hydroxylation of p -toluenesulfonic acid as reported by Freund *et al.*³²

Perhaps because of these relatively modest performances, interest in polyoxometalates as electro-generated redox mediators for organic transformations waned somewhat in the following years. This is understandable when one considers that polyoxometalates are molecules with comparatively high molecular weights, and hence performance has to significantly exceed that which might be produced using smaller (*e.g.* organic) mediators in order to justify the use of such massive species. In the last five years or so, however, interest in polyoxometalates as electro-generated mediators for organic chemistry has been revived and this field now stands poised for considerable growth thanks to the development of new concepts such as decoupled electrolysis,³³⁻³⁵ where polyoxometalates often display superior

stability and electron/proton storage capacity.³⁶ This new and exciting chapter in electro-organic synthesis with polyoxometalates will form the bulk of the remainder of this review.

3. Oxidation of Aromatic Organic Substrates with Polyoxometalate Redox Mediators

Between the mid-1990s and 2015, very little work appears to have been performed on driving organic transformations using electro-generated polyoxometalate redox mediators. One of the very few (possibly the only) example from this time was published in 2007 by Ma and co-workers. These authors employed the polyoxomolybdate $(\text{NH}_4)_3\text{H}_4[\text{P}(\text{Mo}_2\text{O}_7)_6]$ as a redox mediator for the oxidation of toluene in methanolic solution to give 1-methoxymethylbenzene as the dominant product.³⁷ Their set-up (Figure 1) consisted of a parallel plate cell with two large (25 cm^2) porous graphite electrodes held a distance of 1 cm apart, and between which a bias of 30 V was applied, delivering initial current densities on the order of 90 mA cm^{-2} . The electrolyte (which appears to have been a somewhat inhomogeneous suspension from the authors' description) consisted of 0.5 M KF in a roughly 1:1 mixture of methanol and toluene, to which was added the polyoxometalate to give a concentration of approximately 20 mM. This mixture was both cooled during electrolysis (to minimise evaporation of the methanol) and stirred in order to maintain some uniformity.

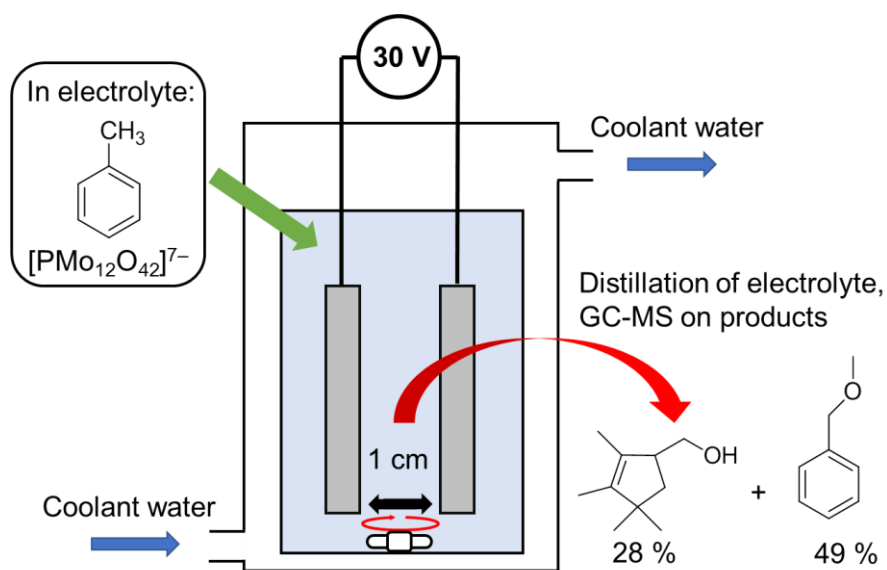
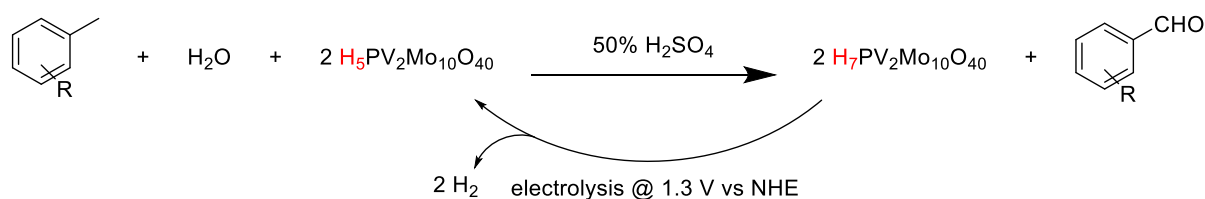


Figure 1: The oxidation of toluene in methanolic solution mediated by $(\text{NH}_4)_3\text{H}_4[\text{P}(\text{Mo}_2\text{O}_7)_6]$ as described by Ma and co-workers.³⁷

After electrolysis, the electrolyte mixture was distilled and the volatiles analysed by gas chromatography-mass spectrometry (GC-MS). This allowed the main products of the reaction to be determined as 1-methoxymethylbenzene (49% by mass) and 2,3,4,4-(tetramethylcyclopent-2-ienyl)methanol (28% by mass), with the remainder of the products unidentified. A possible mechanism for the generation of these products was proposed, whereby a toluene radical cation is formed upon oxidation by the polyoxometalate, with this radical then combining with O_2 in solution to give benzaldehyde, which then in turn reacts with methoxy species generated at the cathode to give 1-methoxymethylbenzene. However, very little evidence was presented to support this putative mechanism.

In 2015, Neumann and co-workers reported an electrochemical cycle for the oxidation of methylarenes to their benzaldehyde derivatives using the phosphovanadomolybdate $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ as both an ex-cell and in-cell mediator for oxygen transfer catalysis.³⁸ Sustainable and low-waste routes from methylarenes to benzaldehydes are highly desirable, as most conventional methods for the synthesis of benzaldehydes do so with low atom economy, accompanied by the formation of significant amounts of waste and frequently employing toxic reagents. To address this issue, the authors selected $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ for study on account of its known activity as a chemical oxygenation catalyst of organic substrates in the presence of O_2 .³⁹ Their approach is summarised in Scheme 4, whereby the polyoxometalate was reacted with the relevant benzaldehyde using 50% aqueous H_2SO_4 as the solvent. For a wide range of substrates, the corresponding aldehydes could be formed

with high conversion and excellent selectivity after a few hours, with almost no evidence of over-oxidation to the carboxylic acids.



Scheme 4: The oxidation of methylarenes to their aldehyde derivatives mediated by H₅PV₂Mo₁₀O₄₀ as described by Neumann and co-workers.³⁸

After oxidation of the organic substrate, the polyoxometalate mediator exists as the two-electron reduced form, H₇PV₂Mo₁₀O₄₀. Although spontaneous re-oxidation of the polyoxometalate by O₂ to re-generate H₅PV₂Mo₁₀O₄₀ is thermodynamically feasible, this reaction was found to be very slow in the highly acidic solvent environment required to allow the oxygen transfer reaction to proceed. The authors therefore chose to re-generate the active form of the redox mediator by electrolysis in a two compartment cell, re-oxidising green H₇PV₂Mo₁₀O₄₀ to orange H₅PV₂Mo₁₀O₄₀ at a Pt anode with concomitant production of H₂ at a Pt cathode. In this way, the polyoxometalate could be recycled and re-used in oxygen transfer catalysis. Five such cycles were demonstrated for a number of substrates, with substrate conversions and product selectivities found to be within $\pm 3\%$ for each cycle, demonstrating that H₅PV₂Mo₁₀O₄₀ functions very well as an ex-cell mediator for benzaldehyde oxidation under these conditions.

The authors then demonstrated that H₅PV₂Mo₁₀O₄₀ can also work as an in-cell redox mediator for this conversion in catalytic quantities. Hence a solution of toluene (2 M) and H₅PV₂Mo₁₀O₄₀ (50 mM) in 50% H₂SO₄ was subjected to a cell potential of 1.5 V between two Pt electrodes in a single chamber cell at 70 °C, delivering nearly 30 turnovers of the mediator for a 65% yield of benzaldehyde over 10 hours.

A mechanism for the activation of the methylarenes was proposed on the basis of experimental findings and Density Functional Theory (DFT) calculations (see Figure 2). Together, these data suggested that the highly acidic solvent protonates the polyoxometalate, producing $[\text{H}_6\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^+$, where both vanadium centres are in the +5 oxidation state. $[\text{H}_6\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^+$ then oxidises the methylarene to give $[\text{H}_6\text{PV}_2\text{Mo}_{10}\text{O}_{40}]$ (where one vanadium has been reduced to V^{4+}) and the radical cation of the methylarene. A further protonation of the polyoxometalate (this time with the proton coming from the methylarene radical cation) generates a neutral methylarene radical species and $[\text{H}_7\text{PV}_2\text{Mo}_{10}\text{O}_{40}]^+$. These two intermediates were calculated to be the highest in energy in the overall process, making the formation of this neutral radical the rate determining step. Moreover, the radical nature of this process was supported by the observation of a large kinetic isotope effect (4.95) for this step. The next step in the proposed mechanism is oxygen transfer from solvent water to the neutral radical to generate benzyl alcohol. Traces of benzyl alcohol were indeed detected in the early stages of the reaction by GC-MS, lending credence to this proposed pathway. The benzyl alcohol is then readily oxidised to benzaldehyde.

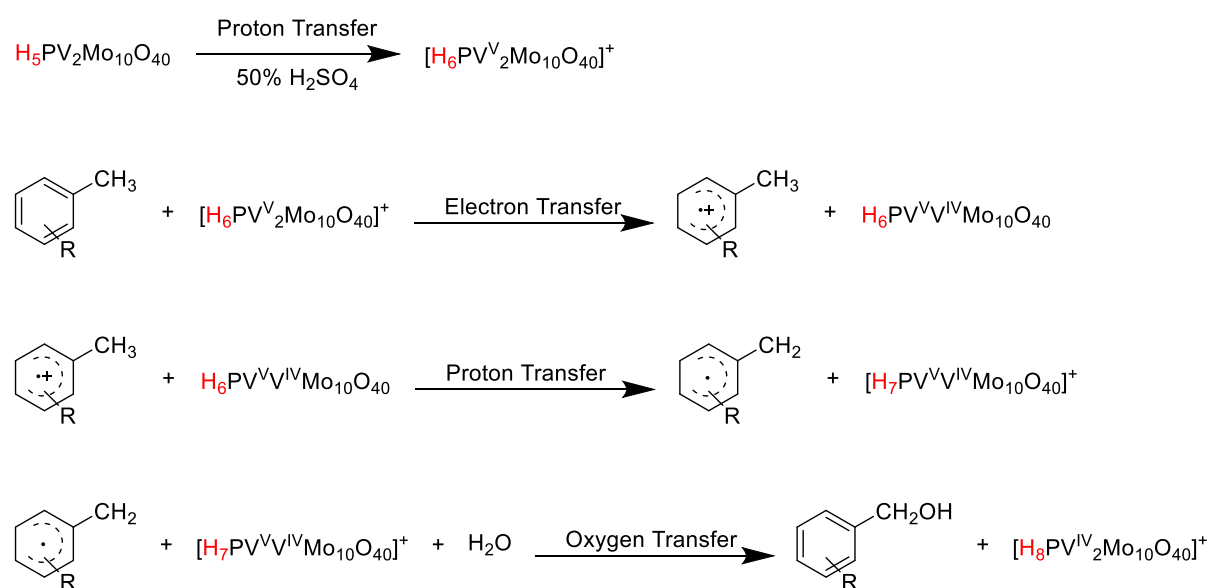
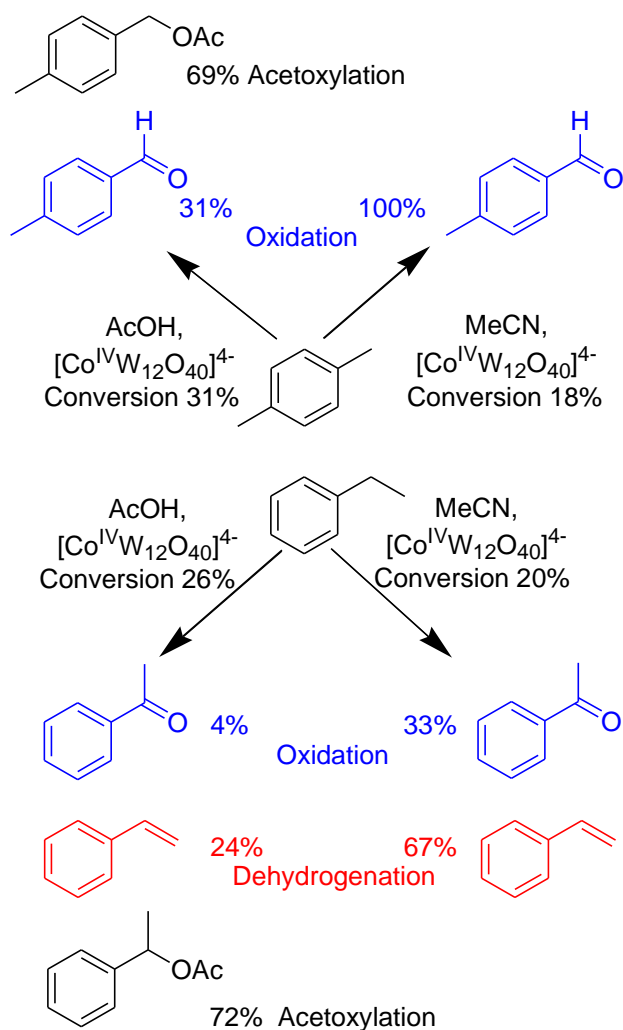


Figure 2: The proposed mechanistic steps for the oxidation of methylarenes to their aldehyde derivatives using the polyoxometalate $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ as a catalyst.

Overall, this approach has the potential to oxidise methylarenes to their aldehyde derivatives with 100% atom economy, in aqueous solvent and with product yields that are typically greater than 95%, and thus has considerable promise for the development of more sustainable routes for this broad class of chemical transformations.

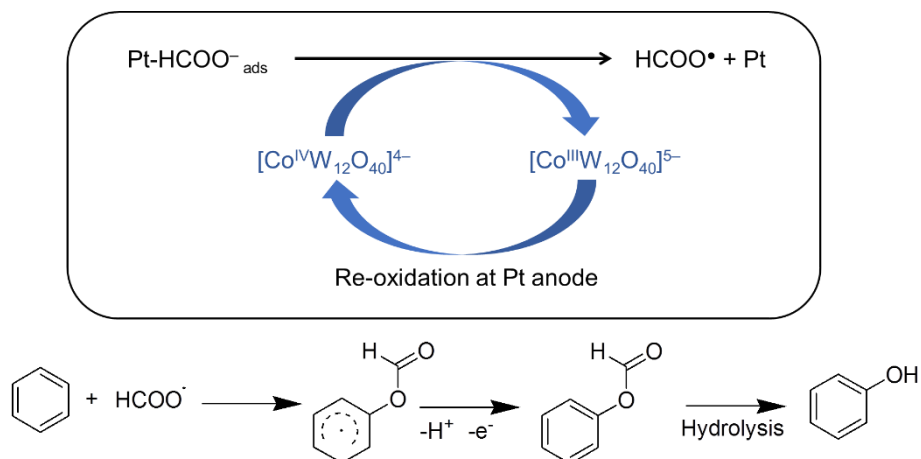
The Neumann group have also investigated the electrochemical dehydrogenation, oxidation, acetoxylation and hydroxylation of arenes using polyoxometalate redox mediators.⁴⁰ In this case, the authors electrochemically oxidised the cobalt-centred polyoxotungstate $[\text{Co}^{\text{III}}\text{W}_{12}\text{O}_{40}]^{5-}$ (originally reported by Ebersson^{41,42}) to give the powerful oxidising agent $[\text{Co}^{\text{IV}}\text{W}_{12}\text{O}_{40}]^{4-}$. This oxidised species proved to show activity for electrochemical dehydrogenation, oxidation and acetoxylation reactions on arene substrates in acetic acid and acetonitrile solvent systems as summarised in Scheme 5.



Scheme 5: Electrochemical dehydrogenations, oxidations and acetoxylation of arenes mediated by $[\text{Co}^{\text{IV}}\text{W}_{12}\text{O}_{40}]^{4-}$ as described by Khenkin *et al.*⁴⁰ Electrochemical conditions were 1.8 V vs. Ag/AgNO₃.

O₂ was determined to be the source of the oxygen in the ketone and aldehyde products on the basis of ¹⁸O₂ labelling studies, and a mechanism involving the formation of a radical cation and subsequent proton and electron transfers was proposed on the basis of the observation of a kinetic isotope effect. Benzene itself, however, was found not to react under these conditions, which the authors ascribed to the difficulty in forming the required phenyl radical cation.

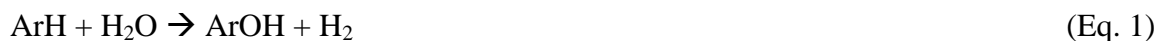
The situation changed quite considerably when the electrolyte was altered to lithium formate in formic acid. Under these conditions, benzene was oxidised to phenol according to the mechanism given in Scheme 6.



Scheme 6: Electrochemical hydroxylation of arenes according to Khenkin *et al.*⁴⁰

The first step in this mechanism (shown in the box in Scheme 6) occurs at the (Pt) anode, whereby $[\text{Co}^{\text{III}}\text{W}_{12}\text{O}_{40}]^{5-}$ is electrochemically oxidised to $[\text{Co}^{\text{IV}}\text{W}_{12}\text{O}_{40}]^{4-}$. Meanwhile, formate adsorbed on the anode is also oxidised at the same time to give the formyloxyl radical, HCOO^\bullet . Through various control reactions, the authors established that it is the formation of HCOO^\bullet that is catalysed by $[\text{Co}^{\text{IV}}\text{W}_{12}\text{O}_{40}]^{4-}$. These formyloxyl radicals then react with benzene to produce a cyclohexadienyl formate radical intermediate, which subsequently forms the benzyl formate. In order for this to be a feasible pathway, the formyloxyl radicals must be sufficiently long lived, and in this regard it is interesting to note that HCOO^\bullet is known to be more stable than the corresponding acetyloxyl radical,⁴³ perhaps suggesting a reason as to why the formate/formic acid electrolyte facilitates benzene oxidation whereas an acetic acid electrolyte under otherwise similar conditions does not. The radical nature of the process to generate benzyl formate was confirmed by radical trap experiments and the observation of a kinetic isotope effect for benzene oxidation. Aryl formates are sensitive to hydrolysis, allowing phenol to be obtained from the benzyl formate

rapidly by mild acid catalysis. This step also leads to the generation of formic acid, effectively making formic acid a catalyst in this process. The overall process can then be considered as (Equation 1):

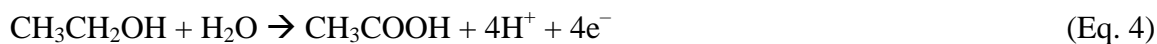


which the authors showed could proceed with Faradaic yields of up to 75% (with decomposition of formic acid to CO_2 and H_2 being the main side reaction). Meanwhile, selectivity was observed for the formation of the mono-oxidised arene products, with yields of up to 35%, suggesting that further optimisation of the reaction conditions could prove fruitful for more sustainable access to these key chemical feedstocks.

4. Oxidation of Non-Aromatic Organic Substrates with Polyoxometalate Redox Mediators

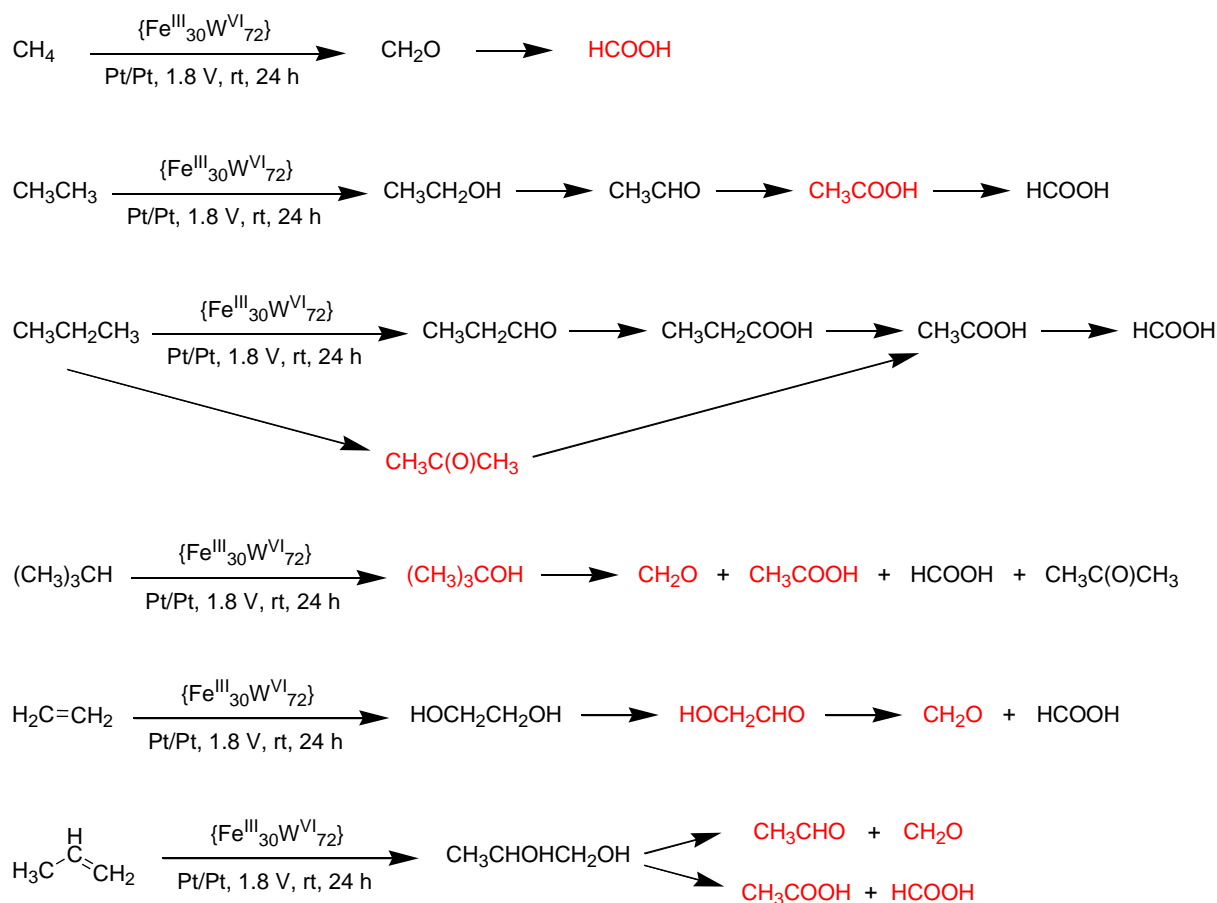
In terms of non-aromatic substrates, Bond, Zhang and co-workers reported a study on the electrocatalytic oxidation of light alcohols by $[\{\text{Ru}_4\text{O}_4(\text{OH})_2(\text{H}_2\text{O})_4\}(\gamma\text{-SiW}_{10}\text{O}_{36})_2]^{10-}$ at carbon cloth electrodes.⁴⁴ Over a wide pH range, whether in solution or confined to the electrode, the polyoxometalate was found to be an effective electrocatalyst for the oxidation of methanol and ethanol, producing dimethoxymethane and methyl formate as the ultimate products of methanol oxidation and 1-diethoxyethane and ethyl acetate as the ultimate products of ethanol oxidation. The formation of these species was proposed to occur by the initial production of the acid and aldehyde products of oxidation (formaldehyde and formic acid for methanol, and acetaldehyde and acetic acid for ethanol) followed by the condensation of these species with remaining excess alcohol to give the products observed. These processes (taking the example of ethanol oxidation) are shown in Equations 2-5:





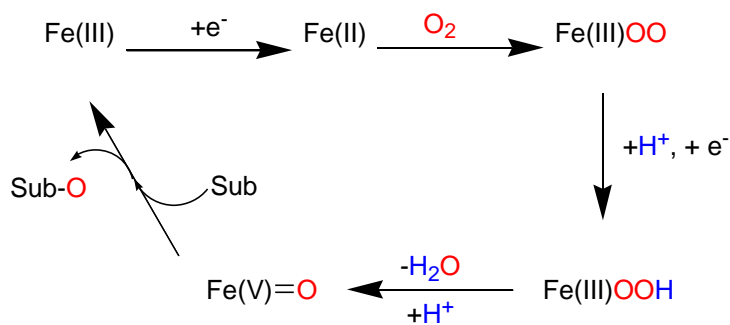
Such mechanisms would suggest that the electrocatalytic oxidation of the alcohols occurs by two- and four-electron oxidation processes to give the aldehydes and acids respectively. Further oxidation of the substrates (*e.g.* to CO_2) was not observed, and indeed control reactions whereby $[\{\text{Ru}_4\text{O}_4(\text{OH})_2(\text{H}_2\text{O})_4\}(\gamma\text{-SiW}_{10}\text{O}_{36})_2]^{10-}$ was employed for the attempted oxidation of formate showed that the polyoxometalate does not oxidise formate under the conditions used in the study. The combined Faradaic yields of the aforementioned electrochemical oxidation products was always >94% for both methanol and ethanol. In terms of both electrochemical activity and stability, $[\{\text{Ru}_4\text{O}_4(\text{OH})_2(\text{H}_2\text{O})_4\}(\gamma\text{-SiW}_{10}\text{O}_{36})_2]^{10-}$ was found to display metrics for alcohol oxidation that compared very favourably to some of the better-performing molecular catalysts for alcohol oxidation then known.^{45,46}

Polyoxometalate redox mediators have also been employed for the selective electrochemical oxidation of light (non-aromatic) hydrocarbons using O_2 as the oxygen source.⁴⁷ To this end, Bugnola *et al.* showed that the porous, spherical iron–tungsten polyoxometalate capsule, $\{\text{Fe}^{\text{III}}_{30}\text{W}^{\text{VI}}_{72}\}$, originally reported by Müller and co-workers,⁴⁸ can be electrochemically reduced by 10 electrons per capsule, yielding the species $\{\text{Fe}^{\text{II}}_{10}\text{Fe}^{\text{III}}_{20}\text{W}^{\text{VI}}_{72}\}$. Armed with this information, the authors used $\{\text{Fe}^{\text{III}}_{30}\text{W}^{\text{VI}}_{72}\}$ as an in-cell redox mediator in aqueous solution (without additional supporting electrolyte) under mixed air/hydrocarbon atmospheres at Pt working/counter electrodes and a cell potential 1.8 V. Under these conditions, various aliphatic hydrocarbons such as ethane, propane and 2-methylpropane can be oxidised with modest Faradaic efficiency (*ca.* 20-35%, with the main competing reaction being reduction of the oxidised polyoxometalate to give water) and turnover frequencies on the order of 300-400 min^{-1} as shown in Scheme 7.



Scheme 7: Oxidation of light hydrocarbons using $\{\text{Fe}^{\text{III}}_{30}\text{W}^{\text{VI}}_{72}\}$ as a redox mediator as reported by Bugnola *et al.*⁴⁷ The main reaction products are shown in red, and “rt” = room temperature.

It was noted that in the absence of polyoxometalate, or in the presence of the analogous vanadium-containing polyoxometalate ($\{\text{V}_{30}\text{W}_{72}\}$), no product formation was observed. This implies that iron is essential for catalytic activity. On account of the considerable distance between the Fe centres in the crystal structure (on the order of 6 Å), the authors then suggested that the active species were likely to contain only one Fe. Radical trapping experiments using 5,5-dimethyl-1-pyrroline *N*-oxide then suggested that Fe^{III} superoxide species are formed by the reaction of the Fe^{II} centres with O_2 (from the introduced air) at an early stage in the reaction. On this basis, a mechanism of action for the polyoxometalate electrocatalyst was proposed as shown in Scheme 8.



Scheme 8: Proposed mechanism of electrocatalytic oxygen transfer to organic substrates using the polyoxometalate $\{\text{Fe}^{\text{III}}_{30}\text{W}^{\text{VI}}_{72}\}$, showing the suggested pathway for oxygen incorporation into the organic substrates (“Sub”).

Very recently, some of the same authors have expanded on this preliminary report and have shown that benzene and various other more elaborate hydrocarbons can be activated by this mediator.⁴⁹ Of particular note in this regard, cyclopentanone could be converted into cyclopent-2-en-1-one in yields exceeding 98%. For most substrates, however, yields of specific products remained <50%. The mechanism of action of the reduced polyoxometalate was also probed in this study by a number of techniques. Whilst spectral identification of the key intermediates remains elusive, labelling studies using $^{18}\text{O}_2$ showed that ^{18}O is incorporated into the oxidised products, whilst various kinetic isotope effects were observed, supporting the mechanism postulated in Scheme 8. The ability to activate light hydrocarbons in this way could be of considerable industrial benefit, although further study of this system is required in order to determine the precise mode of action and hence improve product yields and selectivities.

5. Reduction of Organic Substrates using Polyoxometalate Redox Mediators

In contrast to reports on the use of electro-generated polyoxometalate redox mediators for the oxidation of organic substrates, the controlled reduction of organic substrates using

polyoxometalate redox mediators has been much less-well explored. In 2018, Cronin and co-workers demonstrated an approach for the electrochemical reduction of nitroarenes to their corresponding aniline derivatives using the polyoxometalate silicotungstic acid $[H_4SiW_{12}O_{40}]$ as an ex-cell redox mediator.⁵⁰ The polyoxometalate was first reduced by two electrons at a carbon felt cathode in a two-compartment electrochemical cell (where the anode reaction was the oxygen evolution reaction), to yield an aqueous solution of the active form of the mediator, $[H_6SiW_{12}O_{40}]$.^{51,52} To this mediator solution were then added aliquots of the various nitroarenes shown in Figure 3, allowing direct reduction of these substrates to their corresponding aniline derivatives in generally excellent yields. In the case of 4-aminobenzoic, the authors attributed the relatively low isolated yield of this product (45%) to its high water solubility, which may have prevented its full recovery from the aqueous phase during work-up, and similar arguments were used to explain the modest yield of 4-ansidine (65% yield) in the event that the methyl group on this molecule was cleaved. The redox mediator could be recycled using a simple separation process and then re-used without any appreciable drop in performance. In contrast to conventional routes for nitroarene reduction, this indirect electrolysis approach did not require the use of any sacrificial reducing agents, co-catalysts or the handling of hydrogen gas. Another point worth mentioning with regard to this report is the excellent reaction yields that could be obtained even for organic substrates with very low solubility in water (*e.g.* 4-nitroanisole and 4-nitrobenzoic acid). The ability to obtain good conversions from reactions where the substrates are not fully dissolved will be crucial in permitting wider use of aqueous solvent systems (and by extension, most polyoxometalates) in indirect electrochemical methods, and thus helping to facilitate the development of more sustainable chemical processes.

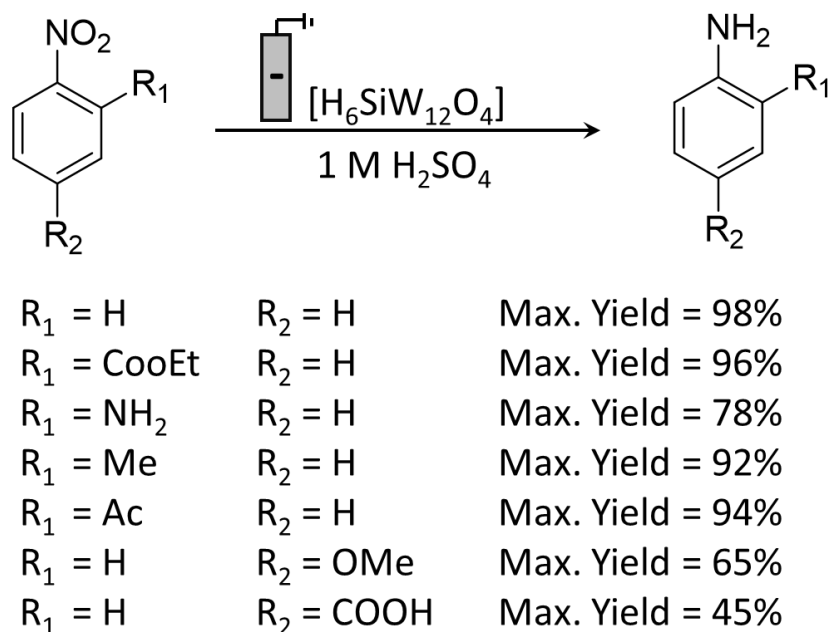
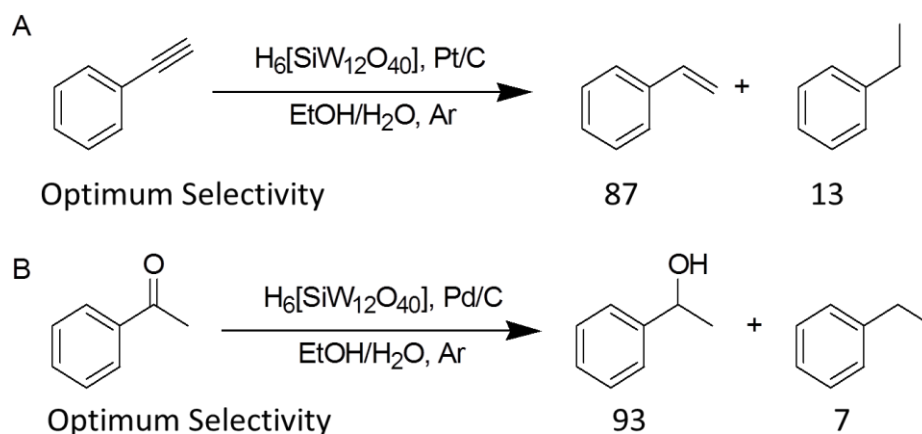


Figure 3: Graphic representation of the reduction of nitroarenes to their aniline derivatives mediated by electrochemically-generated $[\text{H}_6\text{SiW}_{12}\text{O}_{40}]$.

This same silicotungstic acid polyoxometalate has also been used as an ex-cell redox mediator in the semihydrogenation of phenylacetylene and acetophenone without the use of additional extraneous hydrogen gas as reported by Wu *et al.*⁵³ In this system, the reduced mediator ($[\text{H}_6\text{SiW}_{12}\text{O}_{40}]$) was used together with Pd/C and Pt/C co-catalysts as a hydrogen source to promote the reduction of organic substrates in a 1:1 mixture of water and ethanol (Scheme 9). Under these conditions, it seems likely from previous reports that hydrogen would be formed *in situ* from $[\text{H}_6\text{SiW}_{12}\text{O}_{40}]$ when it comes into contact with the precious metal catalysts.⁵¹ Therefore, the polyoxometalate here is acting as an electron and proton shuttle between the electrode and the heterogeneous Pt/C or Pd/C catalysts dispersed in solution, rather than as a direct catalyst for organic substrate reduction as in the case of Cronin's nitroarene reduction reactions mentioned above.



Scheme 9: Semihydrogenation of organic compounds using a silicotungstic acid redox mediator. Pathway A shows the catalytic hydrogenation of phenylacetylene on Pt/C using protons and electrons delivered by the mediator. Pathway B shows an analogous reduction of acetophenone over a Pd/C catalyst.

6. Conclusions and Outlook

In this review, we have given an overview of the use of polyoxometalate redox mediators for electro-organic synthesis, with a special emphasis on studies conducted in the last five years. Polyoxometalates are diverse in their structures and properties, and many polyoxometalates possess attributes which make them attractive as mediators in organic electrosynthesis, including (sometimes multiple) reversible redox waves, well-understood electron transfer processes, and solubility in a range of common solvent environments. Polyoxometalates' redox properties can also often be manipulated as a function of the polarity of the medium,⁵⁴ and in this regard the exploration of perfluorinated solvents and ionic liquids as media for electro-organic synthesis with polyoxometalates could act to broaden the field considerably. To date, polyoxometalate mediators have been utilised mostly in electro-oxidation processes, but recent results have also highlighted their potential as electro-generated reducing equivalents. The sheer number of possible polyoxometalates means that the results that are collated in this review represent only a tiny fraction of the possible mediator-substrate

pairings, and so there is clearly tremendous scope for further discoveries to be made in this area.

What, then, are the most pressing challenges and most promising future directions for polyoxometalate redox mediators in electro-organic synthesis? Compared to more common organic mediators, polyoxometalates suffer the drawback that they tend to be very large molecules with high molecular weights: their performance in any particular reaction therefore needs to be a significant improvement over that possible with smaller mediators in order to justify the use of polyoxometalates. It is also harder to design systems where the mediator is covalently attached to an electrode for polyoxometalates when compared to organic mediators: polyoxometalates can be functionalised with organic tethers,⁵⁵ but there are only a very few studies where such methodology has been used to covalently attach polyoxometalates to electrodes and then study the effects this has on the electrochemical properties of those polyoxometalates.^{56,57} On the other hand, polyoxometalates make ideal mediators for the concerted movement of both protons and electrons,⁵⁸ their redox processes are very well understood from a theoretical point of view,^{59,60} and the prospects for combining photoredox chemistry with indirect electrolysis with polyoxometalates look good, as many polyoxometalates display intrinsic photoredox properties.⁶¹ It seems likely, therefore, that polyoxometalates will find ever-increasing application in the electro-conversion of organic substrates in complimentary roles to those filled by smaller organic mediator molecules. We hope that this review will serve as an inspiration to electrochemists, organic chemists and inorganic chemists alike to explore polyoxometalate redox mediators in greater detail.

Acknowledgments

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