Efficient Aerobic Oxidation of Organic Molecules by Multistep Electron Transfer

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Dedicated to Prof. Barry M. Trost on the occasion of his 80th birthday
This Minireview presents recent important homogenous aerobic oxidative reactions which are assisted by electron transfer mediators (ETMs). Compared with direct oxidation by molecular oxygen \((O_2)\), the use of a coupled catalyst system with ETMs leads to a lower overall energy barrier via stepwise electron transfer. This cooperative catalytic process significantly facilitates the transport of electrons from the reduced form of the substrate-selective redox catalyst (SSRC\(^{red}\)) to \(O_2\), thereby increasing the efficiency of the aerobic oxidation. In this Minireview, we have summarized the advances accomplished in recent years in transition-metal-catalyzed as well as metal-free aerobic oxidations of organic molecules in the presence of ETMs. In addition, the recent progress of photochemical and electrochemical oxidative functionalization using ETMs and \(O_2\) as the terminal oxidant is also highlighted. Furthermore, the mechanisms of these transformations are showcased.

1. Introduction

The development of economic and environmentally benign synthetic methods has recently become an important but challenging goal in organic chemistry.\(^{[1]}\) Oxidation reactions are involved in a broad range of chemical transformations that allow the facile preparation of various useful commodity chemicals and building blocks.\(^{[2]}\) However, in most cases stoichiometric oxidants such as iodosylbenzene, hypochlorite, persulfate, and metal salts (\(Cu^{II}\), \(Ag^+\), \(Cr^{VI}\), \(Mn^{II}\)) are used, which leads to low atom economy, and considerable amounts of undesired waste. Among various oxidants, molecular oxygen \((O_2)\) and hydrogen peroxide \((H_2O_2)\) are environmentally friendly and highly atom-efficient oxidants that generate no toxic byproducts.\(^{[3]}\) Compared to \(H_2O_2\), \(O_2\) is much less expensive since air can often be used, but it has the disadvantage that rigorous precautions are required for large-scale applications, especially for high pressure reactions.

Over the past decades, homogenous catalytic aerobic oxidations have provided the basis for the streamlined conversion of various feedstocks into valuable products in industry.\(^{[4]}\) However, the direct reoxidation of the reduced form of the substrate-selective redox catalyst (SSRC\(^{red}\)) by \(O_2\) is always challenging due to the often high energy barrier of this reaction step, as well as its low efficiency and selectivity (Scheme 1a).\(^{[5]}\) This “oxidation problem” can be explained by the slow electron transfer between SSRC\(^{red}\) and \(O_2\), compared to the fast deactivation of the catalyst.

One elegant strategy is to mimic biological oxidation systems and insert electron transfer mediators (ETMs) between the substrate-selective redox catalyst and \(O_2\) (Scheme 1b).\(^{[6]}\) It is widely recognized that nature’s elegant way of overcoming the “oxidation problem” is through the orchestration of a variety of enzymes and coenzymes that act as catalysts and ETMs, which lower the overall barrier for electron transfer from SSRC\(^{red}\) to \(O_2\).\(^{[7]}\) These ETMs are a part of what is called the electron transport chain (ETC), where \(O_2\) is typically used as the terminal oxidant. This chain bypasses the high kinetic barrier associated with the direct oxidation of SSRC\(^{red}\) by \(O_2\) and leads to a lower overall energy barrier via stepwise electron transfer.

One of the first examples of the use of an ETM in an aerobic oxidation was the Wacker process. Cupric chloride was used as an ETM to facilitate electron transfer between \(Pd^2+\) and \(O_2\).\(^{[8]}\) A nature-inspired aerobic oxidative reaction using two ETMs was reported by the Bäckvall group in the late 1980s.\(^{[9]}\) Later on, several groups explored this concept by developing mild and efficient coupled catalyst systems with ETMs in various oxidative functionalizations.\(^{[10]}\) In general, a good candidate ETM in a redox reaction should have the appropriate redox potential, lead to a low energy barrier in the electron transfer, be stable enough under the reaction conditions, and be compatible with the redox processes involved. In 2008, we summarized catalytic oxidations with \(O_2\) and \(H_2O_2\) as terminal oxidants in multistep electron

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\[ \text{Scheme 1. Aerobic oxidation of organic molecules with electron transfer mediators.} \]
transfer processes, and a related review was also published by Chang in 2004. After the publication of these reviews, considerable advances have been made in this field. Herein we provide an overview of the recent advances in aerobic oxidations assisted by ETMs. In this Minireview, we have selected recent representative examples of aerobic oxidation of organic molecules with redox catalysts, which are divided into three sections (Scheme 2): 1) transition-metal-catalyzed aerobic oxidations, using metal catalysts based on palladium, ruthenium, and iron; 2) organocatalyzed aerobic oxidations, using organocatalysts such as guanidine, NHC, DDQ, and nitroxyl; and 3) recent progress in photo- and electrocatalyzed oxidative functionalizations. It should be noted that there are also systems where the catalyst is oxidized directly by O₂. However, this strategy always requires higher reaction temperature, ancillary ligands, or external additives to facilitate the direct oxidation. Coupled catalytic systems with ETMs constitute an important complement to homogenous oxidation chemistry, which has greatly expanded the use of O₂ as a green oxidant. We hope this Minireview will be of value to chemists involved in oxidation reactions in both academic and industrial research and that it will stimulate further development in green and sustainable chemistry.

2. Metal-Catalyzed Aerobic Oxidation with ETMs

2.1. Palladium-Catalyzed Oxidations (SSRC = Pd)

Palladium-catalyzed aerobic oxidations have emerged as powerful and valuable tools in modern organic synthesis. Despite significant advances in this field, a severe problem often encountered is the fast aggregation of palladium black from participating palladium species (Pd-H or Pd°) which slows down and finally stops the homogenous reaction (Scheme 3). Extensive endeavors to solve this problem have focused on the use of air-stable ligands such as sulfoxides, amines, pyridines, and carbenes, to prevent Pd° precipitation during the catalytic cycle. Stahl and co-workers published a review on the use of various ligands that improve catalyst efficiency and stability in aerobic oxidations with increased selectivity. On the other hand, coupled catalytic systems with an ETM can facilitate the relay of electrons between the Pd catalyst and O₂. These coupled catalytic systems have been demonstrated to be highly efficient in Wacker oxidations, allylic oxidations, C-H activations, and carbocyclizations.
The Pd-catalyzed Wacker–Tsuji reaction is one of the most famous homogenous reactions which provides reliable access to carbonyl compounds (aldehydes or ketones) under mild reaction conditions.[15] This reaction refers generally to the transformation of a terminal or 1,2-disubstituted olefin to an aldehyde or ketone, respectively, through the action of Pd²⁺, water, and a co-oxidant. Conversion of ethylene to acetaldehyde by stoichiometric PdCl₂ was discovered over a century ago,[16] however, it was not until sixty years later that a catalytic method was developed. In the 1950s, researchers at Wacker Chemie reported that a transformation took place in an aqueous, acidic solution of catalytic PdCl₂ and a stoichiometric amount of CuCl₂ through which oxygen was bubbled.[17] Later on, in the 1960s Farbwerke Hoechst developed a one-stage process using oxygen as the terminal oxidizing agent (Scheme 4).[18] This process quickly attracted great interest around the world since acetaldehyde is an important intermediate in industrial chemistry, with over two million tons being produced annually today.

To encourage sufficient mixing of the organic reactants with the aqueous phase, a co-solvent is generally employed along with water. When dimethylformamide (DMF) is used as a co-solvent with CuCl₂ as the ETM under atmospheric pressure of oxygen, the reaction is called the “Tsuji–Wacker oxidation”.[19] This version allows a range of olefins, which are not soluble in water, to be used. The mechanism of the Wacker oxidation has been studied for over 60 years with one of the earliest studies being reported by Smidt et al.[15c,20] The generally accepted mechanism is the one in which an alkene coordinates to Pd²⁺ with subsequent nucleophilic attack by water and β-hydride elimination to afford the carbonyl product. Conventionally, CuCl₂ and O₂ are used as the oxidants to regenerate Pd²⁺ from the Pd⁰ formed.

Despite the success of the Wacker reaction, the presence of chloride ions has a negative effect on the reaction efficiency and causes selectivity problems through the formation of chlorinated side products. To solve these problems associated with the use of chloride, Bäckvall reported a chloride-free Wacker oxidation by using Pd(OAc)₂ together with hydroquinone (HQ) and a metal macrocycle, such as a cobalt Schiff base complex (Co(salophen)) and iron phthalocyanine (FePc) as ETMs (Scheme 5).[21] This triple catalytic system has led to a faster and more efficient reaction, giving high yields under mild conditions with 5 mol% Pd catalyst as shown in Scheme 6a. This catalytic procedure is approximately 16 times faster than the corresponding chloride-based Wacker-type oxidation.[22]

However, Bäckvall’s reaction was limited to the oxidation of terminal olefins. This is because internal olefins show relatively low reactivity and selectivity. Kaneda and coworkers developed a copper-free Wacker oxidation of internal olefins.[23] This protocol requires the use of relative high oxygen pressures (3–9 atm) in an autoclave. In 2013, Grubbs developed a general and practical Pd-catalyzed oxidation to access ketones from a wide variety of internal olefins (Scheme 6b).[24] The use of HBF₄ as an acid additive in the DMA/MeCN/H₂O solvent mixture resulted in high conversion of internal olefin 5 to the corresponding ketone 6. It is likely that a dicaticonic complex is generated in situ in the presence of HBF₄ through protonation of the acetate ligands. This process showed wide functional-group tolerance for the preparation of ketones with a triple catalytic system using O₂ as the terminal oxidant.

![Scheme 4.](image1)

**Scheme 4.** a) Overview of the history of Wacker oxidation; b) General mechanism of the Wacker oxidation of ethylene to acetaldehyde.

![Scheme 5.](image2)

**Scheme 5.** Chloride-free Pd-catalyzed Wacker-type oxidations.

![Scheme 6.](image3)

**Scheme 6.** Representative Wacker-type reactions and the key intermediates for regioselectivity.
Another key issue in the Wacker oxidation is the regioselectivity of the product. The majority of terminal alkenes produce predominately methyl ketones, which is in accordance with Markovnikov's rule. Feringa reported that anti-Markovnikov selectivity could be achieved through the Pd-catalyzed oxidation of ester- or amide-protected allylic substrates using BQ as an oxidant. The regioselectivity can be explained by the weak coordinating influence of the Lewis basic oxygen or nitrogen functional groups. In 2013, Grubbs developed a nitrite-modified Wacker-type catalyst system for the conversion of simple aliphatic alkenes to aldehydes (Scheme 6c). The addition of a nitrite source, such as AgNO₃, led to good anti-Markovnikov selectivity and synthetically useful yields. It is proposed that the catalyst facilitates in situ formation of an NO₂ radical from the nitrite salt, followed by a radical-type addition of the NO₂ radical to the olefin at the terminal position. This determines the ultimate origin of anti-Markovnikov selectivity.

Palladium-catalyzed allylic C-H activation represents a powerful synthetic strategy in organic chemistry. In 1990, the Bäckvall group reported a coupled quinone/metal macrocycle system for the aerobic allylic acetoxylation of olefins. This reaction is efficient and gives the allylic acetate in good yield through the oxidation of cyclohexene under atmospheric O₂. However, only acetic acid was applied as the coupling partner in this reaction. In 2010, Stambuli showed that the sulfide ligand L₁ can improve the allylic acetoxylation of terminal olefins when O₂ is used in combination with 5 mol% Cu(OAc)₂ (Scheme 7a). Also, in this reaction only acetic acid was applied as the coupling partner. A method compatible with diverse carboxylic acids was developed by the Stahl group (Scheme 7b). The use of 4,5-diazafluoren-9-one (DAF, L₂) as a ligand, in combination with a quinone/FePc co-catalyst system leads to efficient oxidation of Pd by O₂ which then promotes acyloxylation of the allylic C-H bond. A more sterically hindered 2,6-dimethylbenzoquinone (Me₂BQ) was found to improve the product yield. The quinone is not only a co-catalyst for transporting electrons between the Pd catalyst and the metal macrocycle, but can also act as a ligand, which coordinates to the Pd species during the catalysis. In addition to C-O couplings, Pd-catalyzed allylic C-H amination was reported by the White group in 2016 (Scheme 7c). The use of redox-active co-catalysts, Co(salophen), and HQ as ETMs significantly improved the reaction efficiency under ambient oxygen pressure.

An example of aerobic C(sp³)-H activation was reported by the Sanford group in 2012, which focused on the use of NaN₃ or NaNO₂ as an ETM in a Pd-catalyzed aerobic oxidation of unactivated C(sp³)-H bonds using oxime ethers or quinoline derivatives as effective directing groups (Scheme 8). This process proceeds through the decomposition of nitrate to NO, which is the active ETM. The presence of NO was confirmed through the addition of butylated hydroxytoluene (BHT) to the reaction, which is known to form 2,6-di-tert-buty1-4-methyl-4-nitrosocyclohexa-2,5-dien-1-one (TBMND) on exposure to NO.

The oxidative functionalization of simple aromatic C–H bonds was originally reported by Fujiwara and Moritani. Much progress has been achieved in this field following this pioneering work, which is now recognized as a powerful method for the construction of valuable building blocks. The Stahl group described the use of nitrite and nitrate sources (fuming HNO₃) as NO₂-based redox mediators in the acetoxylation of benzene (Scheme 9a). These reaction conditions avoid the formation of biphenyl as a side product, and strongly favor formation of phenyl acetate over nitrobenzene (selectivity PhOAc:PhNO₂ up to 40:1). Under the optimized reaction conditions, with 0.1 mol% Pd(OAc)₂, 136 turnovers of the Pd catalyst are achieved with only 1 atm of O₂ pressure. The Bäckvall group reported an efficient Pd-catalyzed aerobic oxidative dehydrogenative coupling between arene and nonbiased olefin (Scheme 9b). This reaction took place in the presence of catalytic amounts of BQ and FePc as the ETMs under ambient oxygen pressure.
In 2017, Jiang and Li described a Pd-catalyzed cascade oxidative arylation/olefination for the synthesis of dihydrobenzofurans 17 (Scheme 10). Similar to Wacker-type oxidations, the use of a catalytic amount of Cu(OAc)$_2$ as the ETM allows efficient reoxidation of the Pd catalyst under aerobic conditions. In this reaction, the addition of BQ increased the yield from 76% to 85%. This result can be explained by the fact that BQ stabilizes the Pd$^{0}$ species through the in situ generation of Pd$^{0}$-BQ complexes, and no palladium black was observed. The mechanism of the reaction involves electrophilic metalation of substrate 16 by PdX$_2$ (X = OTFA or OAc) to give aryl-Pd species Int-1. Then, intramolecular insertion of the olefin forms the alkyl-Pd intermediate Int-2, which is followed by insertion of activated olefin to give Int-3. A β-hydride elimination affords the corresponding product 17 and the active Pd$^{II}$ species is regenerated through oxidation of Pd$^{0}$ by CuX$_2$/O$_2$.

Pd-catalyzed oxidative carbocyclizations have become powerful methods for the construction of carbocyclic and heterocyclic compounds. The Bäckvall group reported an aerobic catalyst system for the oxidative carbocyclization of allenyne 18 to five-membered carbocycle 19 (Scheme 11). Initially, the coordination of the allene and the assisting olefin to Pd$^{II}$ in Int-7 promotes the formation of vinylpalladium Int-8. Then, the vinylpalladium intermediate Int-9 would be generated from Int-8 via ligand exchange (from Int-7). The reaction of Pd$^{II}$ with allene 18 bearing the assisting olefin produces vinylpalladium Int-8 via allenic C–H bond cleavage, which is promoted by the coordination of the allene and the assisting olefin to Pd$^{II}$ in Int-7. Then, the vinylpalladium intermediate Int-9 would be generated from Int-8 via ligand exchange (from Int-6) and the Pd$^{0}$ species.

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proximal olefin to remote olefin). Next, Int-9 would undergo a remote olefin insertion to give cyclic intermediate Int-10. Subsequent transmetalation of Int-10 with B$_2$pin$_2$ or arylboronic acid, followed by reductive elimination would give the target cyclohexene derivatives 21 or 22. The biomimetic approach using catalytic amounts of Co(salophen) and BQ as the ETMs led to aerobic borylative and arylative carbocyclizations in good yields.

In addition to the previous catalyst system with the quinone and metal macrocycle as separate ETMs, a homogeneous hybrid catalyst was developed by Bäckvall, in which the metal macrocycle and quinone are merged into one molecule (Scheme 13a).[42,43] In 1993, Bäckvall developed an efficient hybrid catalyst (Co(TQP), Co-1), involving a cobalt-porphyrin with pendant hydroquinone groups in one molecule for aerobic Pd-catalyzed 1,4-diacetoxylation of 1,3-cyclohexadiene, but the stereoselectivity of the reaction was moderate and the catalyst was difficult to synthesize. In 2008, the same group designed an improved hybrid Schiff base–hydroquinone as a redox relay catalyst for aerobic oxidations.[44] In this type of hybrid catalyst, cobalt Schiff base complexes were chosen as the oxygen-activating center because of their demonstrated efficiency in coupled aerobic oxidation, and their simple and modular synthesis. For example, the hybrid cobalt catalyst Co-2 Co(salmdpt)-HQ (salmdptH$_2$ = bis-[3(salicylideneimino)propyl]methylamine), and Co-3 Co(salophen)-HQ were used as efficient ETMs in the Pd-catalyzed aerobic oxidative carbocyclizations of enallene 23 and 24 (Scheme 13b).[45] The authors mentioned that the slower reaction of 24 to 25 with Co-3 is most likely due to the fact that Co-3 is quite insoluble in ethanol.

The Co(salophen)-HQ Co-3 was also found to be highly efficient in the Pd-catalyzed aerobic carbocyclization of the rationally designed enallene 26 (Scheme 14a).[45] The enallene 26 contains three different C–C π-bond functionalities (allene, olefin, and alkyne groups), and this combination presents a challenge concerning the control of regioselectivity in the reaction. Interestingly, cyclization takes place between the allene moiety and the distal triple bond of the enallene 26, while the olefin group remains intact. The mechanism is similar to that of the carbocyclization of enallene 20, in which a “helping olefin” triggers the C(sp$^3$)–H bond cleavage followed by a replacement of the coordinated pendant olefin by the remote unsaturated C–C ligand.

Control experiments showed that the initial step of the allenic C(sp$^3$)–H bond cleavage by Pd$^{II}$ requires the coordination of a pendant olefin bond in the substrate. The use of Co-3 resulted in a significantly higher reaction rate than that with Co(salophen) and quinone as separate ETMs. The authors proposed that the hybrid catalyst, Co-3 enhances the overall electron transfer between the Pd catalyst and O$_2$, due to intramolecular electron transfer in Co-3, thereby leading to a more efficient overall reaction under aerobic conditions. In addition, the catalyst Co-3 is also highly efficient in the oxidative carbocyclization of dienallenes 28 and bisallenes 29 to six- or seven-membered heterocycles 30 and 31 (Scheme 14b).[46]
2.2. Ruthenium- and Iron-Catalyzed Oxidations (SSRC = Ru or Fe)

Ruthenium-catalyzed oxidation reactions are a class of important transformations in organic synthesis.[47] In the past decades, mild dehydrogenations of alcohols to give aldehydes or ketones through the use of low-valent Ru complexes have been reported, which were subsequently extended to the dehydrogenation of amines to imines.[48] The Stahl group reported a Ru-based catalyst system that shows high activity for amine oxidation, including the successful aerobic dehydrogenation of diverse tetrahydroquinolines at room temperature with ambient air (Scheme 15).[49] In this work, the ruthenium complex \([\text{Ru}(\text{phd})_3]^+\) (Ru-1, phd = 1,10-phenanthroline-5,6-dione) was applied for the oxidative dehydrogenation of tetrahydroquinoline 32 to afford quinoline 33. The structure of \([\text{Ru}(\text{phd})_3](\text{ClO}_4)_2\) was characterized via X-ray crystallography. The use of a Co(salophen) as the ETM allows the reaction to proceed efficiently. In the absence of Co(salophen), the reaction is very slow. The synthetic utility of the catalytic method was demonstrated by the preparation of various medicinally relevant quinolines.

A dimeric ruthenium catalyst called Shvo catalyst Ru-2 has been known since the 1980s and has been demonstrated to be highly efficient in a large variety of hydrogenation and oxidation transformations.[50] The dissociation of Ru-2 gives two complementary active monomeric species Ru-3 and Ru-4 bearing a non-innocent active functionalized ligand (Scheme 16a). The hydroxycyclopentadienyl ligand in Ru-3 has a proton on the oxygen and the Ru center has a hydride ligand. The proton and the hydride are involved in hydrogen transfer reactions. The cyclopentadienone in Ru-4 has a proton-acceptor site at oxygen and a hydride-acceptor site at the Ru center and can catalyze oxidations. The dehydrogenation of alcohols occurs through an outer-sphere pathway in which the alcohol binds to the Ru complex through bridging hydrogens (Int-11). The alcohol complex Int-11 undergoes simultaneous hydride and proton transfer to produce Int-12, which finally releases the ketone. The Bäckvall group developed efficient Ru-catalyzed aerobic oxidations via a biomimetic catalytic system (Scheme 16b).[51] Dehydrogenation of the alcohol by Ru-4 affords the oxidized product and the ruthenium hydride Ru-3. The latter species is reoxidized by O$_2$ with the aid of an electron transfer system. The Shvo catalyst (Ru-2) showed excellent activity and a more electron-rich quinone, 2,6-dimethoxy-1,4-benzoquinone (DMBQ), and Co(salmdpt) complex Co-4 were used as the ETMs. The authors speculated that the slow step in the electron transfer chain is the reoxidation of the hydroquinone, and the more electron-rich 2,6-dimethoxy-1,4-hydroquinone is oxidized faster than the 1,4-hydroquinone by \([\text{Co(salmdpt)}]^{\text{ox}}\). The oxidation of alcohols, amines, diols, and amino alcohols could be performed with high selectivity to give the corresponding carbonyl products in generally good yields.

Given the cost-effective and sustainable nature of earth-abundant first-row transition metals, the development of less toxic, inexpensive 3d metal catalysts for aerobic oxidations has gained considerable momentum as a more environmentally friendly and economically attractive alternative.[52] Iron is the most abundant transition metal in the Earth’s crust. In addition to the economic benefit, the development of iron-catalyzed reactions also provides an opportunity to access complementary chemoselectivity and discover new reactivities.[53] Cyclopentadienone iron hydride complexes such as Fe-1 (Scheme 17a) have been known since the 1950s, long before the Shvo precatalyst. In the 1990s, Knölker and co-workers isolated the first iron hydride hydroxycyclopentadienyl complex Fe-3 from the precursor Fe-2 and confirmed its structure.
The first catalytic application of hydrogenations and transfer hydrogenations with this type of catalyst was reported by Casey and Guan in 2007. Since then, given their unique catalytic behavior, easy access from abundant iron sources, and good stability, there has been a dramatic increase in the number of catalytic applications using these catalysts. An outer-sphere mechanism of dehydrogenation analogous to that of the Shvo system was proposed for iron-catalyzed oxidations. Very recently, Bäckvall reported on an iron-catalyzed aerobic biomimetic oxidation of alcohols (Scheme 17b).

2.3. Metal-Free SSRC with Metal-Containing ETMs

In addition to transition-metal-catalyzed aerobic oxidations, organic molecules can also act as substrate-selective redox catalysts for aerobic oxidations. The Himmel group reported a redox-active guanidine, 1,2,4,5-tetrakis-(tetramethylyguanidino)benzene Cat-1, that can act as a catalyst in the green aerobic oxidation of organic molecules (Scheme 18). Cat-1 is a rather strong electron donor ($E_{1/2} = -0.7$ V vs. Fe$^{3+/2+}$) for the redox pair Cat-1$^{2+}$/Cat-1. Reduction of the oxidized form, Cat-1$^{2+}$, by proton-coupled electron transfer is favored by the strong Bronsted basicity of guanidines and the restoration of the aromatic system. This property enables efficient dehydrogenative oxidation of 3,5-di-tert-butylcatechol 34 to ortho-benzoquinone 35, 2,4-di-tert-butylphenol 36 to biphenol 37, and benzoin 38 to benzil 39 in excellent yields. In the other half-reaction, reoxidation of the guanidine to the oxidized state is achieved with O$_2$ in the presence of a copper catalyst.

The N-heterocyclic carbene (NHC)-catalyzed aerobic oxidative esterification of aldehydes with alcohols is a green and sustainable process for the synthesis of versatile esters. Sundén and co-workers described a strategy for oxidative NHC-catalyzed esterifications of $\alpha$, $\beta$-unsaturated aldehydes 40 in the presence of FePc and 2,6-di-tert-butylphenol (2,6-DTBP) as ETMs (Scheme 19). In this reaction, the key steps are the oxidation of homoenoate intermediate Int-14 by quinone (from 2,6-DTBP) to the acyl azolium Int-15, which reacts with the alcohol to give the unsaturated ester 41.
and regenerating NHC Int-13. The reaction has a broad substrate scope and the products were isolated in good to excellent yields. The use of air as the terminal oxidant offers an environmentally friendly and inexpensive way to scale up this important oxidation reaction via NHC chemistry.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a powerful oxidant, which has been applied in many oxidative reactions. Catalytic oxidation systems with DDQ as the catalyst and O₂ as the terminal oxidant have seen much development in recent years. Hu and Shen reported the use of DDQ as substrate-selective redox catalyst for the aerobic oxidative deprotection of PMB (p-methoxybenzyl) ether, alcohol oxidation, and aromatization of indoline in high conversions and excellent selectivity (Scheme 20). In this reaction, FePc was employed as the ETM, and O₂ was used as the environmentally benign terminal oxidant. For the purpose of reusing the FePc employed as ETM, it was supported in multiwalled carbon nanotubes (MWCNTs), which provided good reactivity and recyclability in the aerobic deprotection of PMB ethers.

Nitroxyl catalysts, such as TEMPO (2,2,6,6-tetramethylpiperidine N-oxyl) and ABNO (9-azabicyclo[3.3.1]nonane N-oxyl), have been identified as highly effective catalyst systems for aerobic oxidation (Scheme 21). Various oxidation products can be obtained with the metal/nitroxyl catalyst system under aerobic conditions. For example, Ma and co-workers reported an Fe(NO₃)₃·9H₂O/TEMPO catalyst system for the selective and mild aerobic oxidation of a wide range of alcohols to carboxylic acids. The simplified catalytic mechanism with the Cu/TEMPO system is depicted in Scheme 21. Initially, aerobic oxidation of Cu(I) and TEMPOH affords the Cu(II)-OH species Int-17 and TEMPO. The oxidation of the alcohol proceeds through the formation of the Cu(II)-alkoxide species Int-18, which is then followed by hydrogen atom transfer to TEMPO with formation of the aldehyde and TEMPOH. The Cu/TEMPO catalyst system was extensively studied and applied in the aerobic oxidation of alcohols and amines. An elegant review on this topic was published by Stahl and co-workers in 2014.

N-hydroxyphthalimide (NHPI) is also widely used as a substrate-selective redox catalyst (SSRC) in selective oxidation reactions. Several 3d transition metals, such as V⁴⁺, Fe³⁺, Co²⁺, and Cu²⁺ have been utilized as ETM catalysts together with NHPI as SSRC for the oxygenation of C(sp³)-H bonds (Scheme 22a). The reaction initially converts NHPI to the phthalimide N-oxyl radical (PINO) in the presence of the 3d metal catalyst and O₂. PINO then mediates the selective H abstraction from the benzylic C-H bond in 42 to generate an organic radical Int-19 that can react with O₂. Then H-atom transfer generates peroxide intermediate Int-21 and finally produces the oxygenated products 43, such as ketones or aldehydes and water. Several reviews were published recently on this topic, where the scope and mechanism of these reactions are discussed. Stahl demonstrated an aerobic oxidation of heteroarenes 44 to their corresponding heteroarylketones 45 using NHPI and Co-
The heterocycles play an important role in this type of oxidation since an enamine or a similar tautomer can often form which is more amenable to oxidation at the benzylic position. In 2018, Van Humbeck reported an interesting related dual-catalysis approach in which Fe(BF$_4$)$_2$·6H$_2$O, aborate ligand, and an N$_2$-substituted analogue of NHPI were used in tandem for the aerobic oxidation of substrates bearing an azaheterocycle (46 and 47) (Scheme 22c). The iron complex is introduced to selectively oxidize a benzylic position adjacent to an azaheterocycle because it can act as a Lewis acid, which coordinates to the nitrogen and weakens the C–H bond at the benzylic position, making the hydrogen abstraction and subsequent oxidation easier.

Hypervalent iodine reagents are a useful class of chemical oxidants which find application in diverse chemical syntheses. The current liabilities of hypervalent iodine reagents include the frequent need for stoichiometric amounts of these compounds and their wasteful synthesis using metal-based oxidants such as KMnO$_4$, NaIO$_4$, oxone, and mCPBA. Very recently, the Powers group reported an efficient formation of hypervalent iodine compounds from aryl iodides, cobalt, aldehydes, and O$_2$ (Scheme 23). In this reaction, CoCl$_2$·6H$_2$O acts as an initiator for aldehyde autoxidation. The aerobically generated peracid Int-22 (e.g. AcOOH) allows for the oxidation of the aryl iodide to the hypervalent iodine reagent Int-23 (e.g. PhI(OAc)$_2$). With this method, a family of hypervalent iodine reagents were successfully generated in situ using O$_2$ as the terminal oxidant. The hypervalent reagents were used in aerobic oxidation in a variety of reactions, such as alcohol oxidation (50 to 51), α-oxygenation of acetophenone (52 to 53), bromination of a β-keto ester (54 to 55), and intermolecular C–H amination (56 to 57).

3. Metal-Free Aerobic Oxidations with ETMs

In the aerobic oxidation of organic molecules, many of the processes rely on a metal catalyst or co-catalyst to facilitate the redox process. However, the presence of trace amounts of metals in the desired products always has several negative effects for biological and medicinal applications. In this context, aerobic oxidations using metal-free catalytic systems are of great interest in organic synthesis.

Hu and Mo reported a DDQ/TBN (TBN = tert-butyl nitrite) catalyst system for the selective oxidation of benzylic alcohol 58 to the corresponding aldehyde 59 (Scheme 24). Key to the success for this aerobic oxidation is that the NO released from TBN can act as an ETM between DDQ and molecular oxygen. The same catalyst system can also be applied in the catalytic benzylic oxidation of the lignin β-O-4 model 60 to 61 in high yields for efficient biomass conversion and oxygenation of C(sp$_3$)–H bonds. Recently, Lei and co-workers described an oxidative C(sp$_3$)–H/N–H cross coupling by introducing DDQ and TBN under aerobic conditions. This amination reaction can be applied to a wide range of alkyl (hetero)arenes and triazoles, pyrazoles and their derivatives. This reaction starts with a hydrogen atom transfer (HAT) process between DDQ and the alkyl (hetero)arene, which then generates the alkyl radical Int-25. Subsequently asingle-electron oxidation of the alkyl radical Int-25 leads to the alkyl cation Int-27, which reacts with the N-nucleophile to furnish the amination product 66. Meanwhile, DDQ$_2$ is oxidized to DDQ by NO$_2$, which is generated from TBN and O$_2$.

TEMPO is a well-known, commercially available, and stable nitroxyl radical. One-electron oxidation of TEMPO affords the oxoammonium species Int-28 which can be used
as an oxidant. For example, oxoammonium-mediated alcohol oxidation results in two-electron reduction of the oxoammonium species to afford hydroxylamine. Hu and co-workers reported a transition-metal-free aerobic oxidation of benzylic and heteroaromatic alcohols, with TEMPO as an efficient substrate-selective redox catalyst (Scheme 25). In this example, Br₂ and NaNO₂ are used as the co-catalysts to relay the electrons between TEMPOH and O₂. A wide range of primary and secondary alcohols were effectively oxidized. In addition, the use of HBr/TBN or DDQ/TBN instead of Br₂/NaNO₂ as ETMs also promotes the aerobic oxidation of alcohols to the corresponding carbonyl compounds in excellent yields.

It is worth mentioning that flavins, a family of the most versatile redox cofactors in nature, can be used as the substrate-selective redox catalyst for mild chemical oxidations. The general catalytic cycle is outlined in Scheme 26. The oxidation of the reduced flavin FIEtH Int-30 with O₂ occurs readily to give hydroperoxide FIEtOOH Int-31. Then, this intermediate oxidizes the substrate to the product, generating hydroxyl flavin FIEtOH Int-32. After elimination of the OH group to give FIEt⁺ Int-33, a reduction process occurs to regenerate FIEtH Int-30, and subsequently Int-30 can be oxidized by O₂ to Int-31.

In nature, flavins occurring in monooxygenases use O₂ as the oxidant. This process requires a cofactor that reduces the hydroxyflavin that is produced after the hydroperoxyflavin has oxidized the substrate, and in nature this cofactor is NADPH (Scheme 26). In an elegant study, Imada, Murahashi, and co-workers mimicked this process with the development of a flavin-catalyzed aerobic oxidation of sulfides and tertiary amines at ambient temperature. Hydrazine was used as a stoichiometric reductant and constitutes a mimic of the NADPH cofactor. In addition, other reductants such as metallic zinc, Hantzsch ester, and formic acid were also applied in flavin-catalyzed aerobic oxidation.

The naturally based flavin derivatives in Scheme 26 involving FIEtOOH (Int-31) have been used as SSRCs in aerobic oxidations, but not so far as ETMs. However, with a related flavin, involving the (N,N)-1,3-dimethyl isomer instead of the FIEtOOH (N,N)-3,10-dimethyl flavin, a hydrogen peroxide-based biomimetic asymmetric dihydroxylation of olefins was developed, where the flavin and N-methylmorpholine (NMM) act as ETMs with OsO₄ as the SSRC.

Carbery and co-workers demonstrated a catalytic flavin-based catalyst system in the biomimetic oxidation of benzylamines to imines (Scheme 27). The combination of an synthetic flavin with alloxan significantly facilitates biomimetic amine oxidation to imines. The mechanism of this aerobic oxidation combines several multistep electron transfer processes. Initially, the flavin catalyst Cat-2 is reduced by Me₂S to generate the neutral semiquinone Int-34. Subsequently, H-atom transfer (HAT) takes place between Int-34 and benzylamine 6 to give semiquinone Int-35 and α-amino radical Int-36. This α-amino radical Int-36 can reduce alloxan to α-hydroxyl carbon radical Int-38 forming Int-37. The coupling of Int-37 with benzylamine 6 leads to the desired product imine 68. Int-38 subsequently reacts with O₂, thus generating peroxyl radical Int-39. The peroxyl radical Int-39 oxidizes Int-35 to Int-34, to produce hydroperoxide Int-40. MeS mediates the reduction of Int-40 to alloxan and formation of stoichiometric DMSO.
4. Photo- and Electrochemically Mediated Aerobic Oxidations with ETMs

Photoredox chemistry and electrochemistry have attracted broad interest for the development of green chemical synthesis. These transformations, which employ inexpensive, ubiquitous light and electricity constitute a powerful strategy for the activation of small molecules. Photoredox catalysis offers access to the unique chemical reactivities of organic molecules in the excited state, which allows the generation of reactive intermediates with high redox potential in a transient state. Electrochemistry also offers a solution to this issue by using electric current as the traceless redox agent, and the introduction of a mediated electron transfer can occur against a potential gradient, meaning that lower potentials are needed, reducing the probability of undesired side reactions.

In this section, we discuss recent examples in photo- and electrochemically mediated aerobic oxidation reactions (Scheme 28).

Phenol is an important precursor for many chemicals and industrial products. One-step oxygenation of benzene to phenol is one of the dream chemical reactions. The Fukuzumi group reported the direct oxygenation of benzene (69) to phenol (70) under visible-light irradiation of DDQ under aerobic conditions (Scheme 29a). This catalyst was also applied in the aerobic amination of aromatics and heteroaromatics by Lei and Koenig (Scheme 29b). This photooxygenation reaction is initiated by photoinduced electron transfer from benzene (69) to the triplet excited state of DDQ to give a benzene radical cation (Int-42) and a DDQ radical anion (Int-43), the protonation of which gives (Int-45). The benzene radical cation (Int-42) could react with nucleophiles such as water or amines to yield (Int-44), which subsequently reacts with the (Int-44) to form phenol or an aniline derivative, and DDHQ. TBN was used as an ETM to convert DDHQ to DDQ under aerobic conditions. The same catalyst system was also applied for the oxygenation of C(sp^3)@H bonds in diarylmethane 72 to the corresponding ketones 73 (Scheme 29c).

The Nicewicz group reported an efficient photoredox-based catalyst system consisting of the photocatalyst Mes-Acr^+BF_4^- (Mes, mesityl; Acr, acridinium) and TEMPO for site-selective amination of a variety of simple and complex aromatics (Scheme 30). The authors proposed that an arene cation radical (Int-46) is generated upon photoinduced electron transfer from the arene to an excited-state photoredox catalyst (Mes-Acr^*). This arene cation radical (Int-46) could react with imidazole, followed by deprotonation to provide the radical intermediate (Int-47). The subsequent H-atom transfer with TEMPO would deliver the desired aminated arene 75. In this catalytic cycle, O_2 can oxidize acridine radical Mes-Acr^•, regenerating acridinium Mes-Acr^+ and superoxide O_2•^-.
donates TEMPOH via a hydrogen atom transfer process, ultimately forming H₂O₂ and regenerating TEMPO.

Samec and Wang developed an interesting photoinduced dearomatization of nonphenolic biaryl compounds to generate spirolactones (Scheme 31).[95] The dearomatization can be performed via aerobic photocatalysis using Mes-Acr⁺BF₄⁻ as the photocatalyst and TEMPO as the ETM. This reaction is induced by electrophilic attack of the carboxyl radical Int-48 generated from single-electron transfer with the excited photocatalyst Mes-Acr⁺* and substrate 76. Carboxyl radical Int-48 then induces dearomatization by intramolecular cyclization to form a spirodiene radical Int-49, which is then captured by O₂ to form Int-50 in aerobic systems, after which H-atom transfer generates peroxide intermediate Int-51 and finally spirodienone 77 is produced through the release of water. This method represents a novel route to synthesize spirolactones from the biaryl motif.

Jiang and co-workers demonstrated a benzylic oxygenation using a novel photocatalyst, a dicyanopyrazine (DPZ) derivative in combination with catalytic amounts of N-hydroxysuccinimide (NHS) (Scheme 32).[96] In the presence of light, the photocatalyst DPZ is activated to an excited state DPZ*, which can oxidize NHS in a single-electron-transfer process. The succinimide-N-oxyl (SNO) radical then abstracts the H atom at the benzylic C–H position of the substrate 78 or 79 to generate a benzylic radical that reacts with O₂, finally delivering the ketone 80 or 81.

Flavins have been extensively studied as organic photoredox catalysts for oxidative organic transformations.[97] For example, riboflavin tetraacetate (RFT) is a readily available compound with an oxidation potential of +1.67 V (vs. SCE) upon irradiation (λmax = 440 nm). This characteristic allows RFT and its derivatives to function as photocatalysts in aerobic oxidations and the mechanism is depicted in Scheme 33a. Upon irradiation, electron transfer followed by proton transfer between excited RFT* and urea results in thyl radical Int-52 and semiquinone form (RFT⁻H). The thyl radical Int-52 abstracts the α-hydrogen atom from the alcohol to produce α-hydroxyl carbon radical Int-53, which can further react with (RFT⁻H) by hydrogen-atom transfer to afford the desired product ketone. Finally, the reduced species (RFT⁻H)₂ is oxidized by O₂ to regenerate the RFT catalyst and H₂O₂. Based on the interaction of RFT and urea, Koenig designed an efficient bifunctional catalyst consisting of a flavin backbone and a thiourea group (Scheme 33b).[98] This catalyst is able to catalyze the aerobic oxidation of 4-methoxybenzyl alcohol (82) to the corresponding aldehyde 83 in low catalyst loading (TON = 580).

The formation of H₂O₂ as a by-product is a major drawback of the RFT-catalyzed photocycle because H₂O₂ can degrade RFT under irradiation which leads to the corresponding ketones being produced in poor yields. Wolf reported that the addition of an iron complex can significantly improve the yield under aerobic conditions because the iron complex can catalyze H₂O₂ disproportionation (Scheme 33c). The combination of the RFT and the biomimetic non-heme iron complex Fe(TPA)(MeCN)₃(ClO₄)₂ Cat-5 (TPA = tris(2-pyridylmethyl)amine), gave the best yield of 85 from 84 under visible-light irradiation and aerobic conditions.[99]

Many catalytic aerobic reactions operate with two half-reactions: 1) oxidation of an organic molecule, and 2) reduc-
tion of O\textsubscript{2} to water. Efficient reduction of O\textsubscript{2} to water is a central challenge in many aerobic oxidation reactions as well as in energy conversions.\textsuperscript{[100]} The electrochemical oxygen reduction reaction (ORR) can be achieved by using electron-transfer mediators to promote efficiency and selectivity. Recently, the Stahl group demonstrated that by combining nitroxyls (such as TEMPO) with NO\textsubscript{x}, it is possible to achieve efficient electrocatalytic O\textsubscript{2} reduction at high potentials (Scheme 34).\textsuperscript{[101]} In the coupled redox reactions, the nitrogen oxide catalyst drives aerobic oxidation of an itroxyl mediator to an oxoammonium species, which is then reduced back to the nitroxyl at the cathode. The same group also explored a molecular cobalt complex, Co(salophen), and HQ as ETMs for the electrochemical reduction of O\textsubscript{2} to water.\textsuperscript{[102]} They showed that redox cooperativity between Co(salophen) and HQ enables O\textsubscript{2} reduction at higher potentials and with faster rates than those observed with either individual catalyst partner. These coupled catalyst systems with ETMs demonstrate a unique strategy to achieve improved performance in electrochemical ORR.

It is widely recognized that simple aliphatic C–H bonds are more difficult to oxidize and selectivity is more difficult to achieve compared with activated C(sp\textsuperscript{3})–H bonds (benzylic or allylic).\textsuperscript{[103]} Recently, the Baran group reported an efficient aerobic electrochemical oxidation of unactivated C–H bonds (in 86 and 87) to the corresponding ketones or alcohols (88 and 89) (Scheme 35a).\textsuperscript{[104]} Inspired by their previous work on the anodic allylic C–H oxidation,\textsuperscript{[105]} in this reaction, the use of one equivalent of quinuclidine as an electrochemical mediator allows efficient electrooxidation of C–H bonds. Mechanistically, the electrochemical C–H oxidation involves a quinuclidine radical cation Int-54 generated through anodic oxidation. This high-energy species can homolytically cleave an unactivated C–H bond. Then a reaction between the carbon-centered radical and O\textsubscript{2} affords the oxidation product. This method has the potential to facilitate the synthesis of complex molecules in good yields with high selectivity. Jensen presented a continuous electrolysis system engineered for
NHPI-mediated electrochemical aerobic oxidation of benzyl-
ic C–H bonds (Scheme 35b). Here, NHPI and pyridine
were used as efficient mediators for electron transfer. The
deprotonation of NHPI by pyridine, followed by anodic
electron transfer, leads to a PINO radical. The PINO radical
subsequently mediates abstraction of a benzyl hydrogen
atom in 90 to generate a benzyl radical. This radical can be
trapped by O₂ to form a peroxy radical, which then yields the
carbonyl products 91. The corresponding cathode reaction is
the reduction of pyridinium cation to evolve H₂ and
regenerate pyridine. The use of an electrochemical flow
system for aerobic oxidation enables a process for further scaling-up and opens up potential for an industrial process.

5. Conclusion and Outlook

Aerobic oxidation reactions are of fundamental impor-
tance in chemical science and are widely applied in synthetic
organic chemistry. In this Minireview, recent progress made in
aerobic oxidations using electron transfer mediators has been
summarized and discussed. The coupled catalytic system
significantly facilitates the transport of electrons from the
reduced substrate-selective catalyst to O₂, thereby increasing the
efficiency of aerobic oxidation. This strategy has proven to
be powerful and valuable in the assembly of carbon–carbon
and carbon–heteroatom bonds, which provides useful applica-
tions in homogenous catalysis and organic synthesis.

Despite the advances reported in recent years, we feel that
many exciting opportunities and challenges still lie ahead in
the field of aerobic oxidative transformations:

1) The design of novel and efficient ETMs is highly
important and desirable for aerobic oxidations. For
example, the use of chiral ETMs for stereoselective
synthesis can be explored and that deserves more atten-
tion. Additionally, new concepts like solid-supported
mediators can be developed in order to improve the
efficiency of aerobic processes and simplify product
isolation. Computational methods can also be routinely
used to assist in tailoring the properties of redox catalysts
to meet specific purposes.

2) The use of first-row transition metals as substrate-selective
redox catalysts (SSRCs) is one of the key developments in aerobic oxidations, due to the abundance, low price, and
low toxicity of these metals.

3) The recent progress in photo- and electrochemical reac-
tions in aerobic oxidations will attract broad interest for
the development of green chemical synthesis. These transformations, which use inexpensive, ubiquitous visible
light and electric current constitute a powerful strategy for
the activation of small molecules.

Clearly, the field of mediated electron transfer in aerobic
oxidation constitutes a fertile arena in which to conduct
research. We have no doubt that many important and exciting
developments will be forthcoming in the future.

As mentioned in the introduction, large-scale industrial
applications with molecular oxygen at high pressure require
rigorous precautions. The advantage of many of the biomim-
etic aerobic oxidations described in this Minireview is that
they can often be run under mild conditions at ambient
pressure. Furthermore, dilute concentrations of O₂ as in air or
<5% O₂ in N₂ can also be used in many cases. Under the
latter conditions the safety problems are dramatically
reduced.

6. Addendum

After the submission of the present article, two papers
related to its content on aerobic oxidation have been
published by Stahl and co-workers. The first paper
describes the Pd-catalyzed aerobic homocoupling of thio-
phenes using phenanthroline dione and a Cu(OAc)₂ as
electron transfer mediators (ETMs). In the second article
involving Pd-catalyzed aerobic C–H arylation it was found
that tailored quinones such as 2,5-di-tert-butyl-p-benzoqui-
none led to high turnovers (> 1900) on Pd.

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Conflict of interest

The authors declare no conflict of interest.

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