Quinone Catalysis

International Edition: DOI: 10.1002/anie.201505017
German Edition: DOI: 10.1002/ange.201505017

Quinone-Catalyzed Selective Oxidation of Organic Molecules

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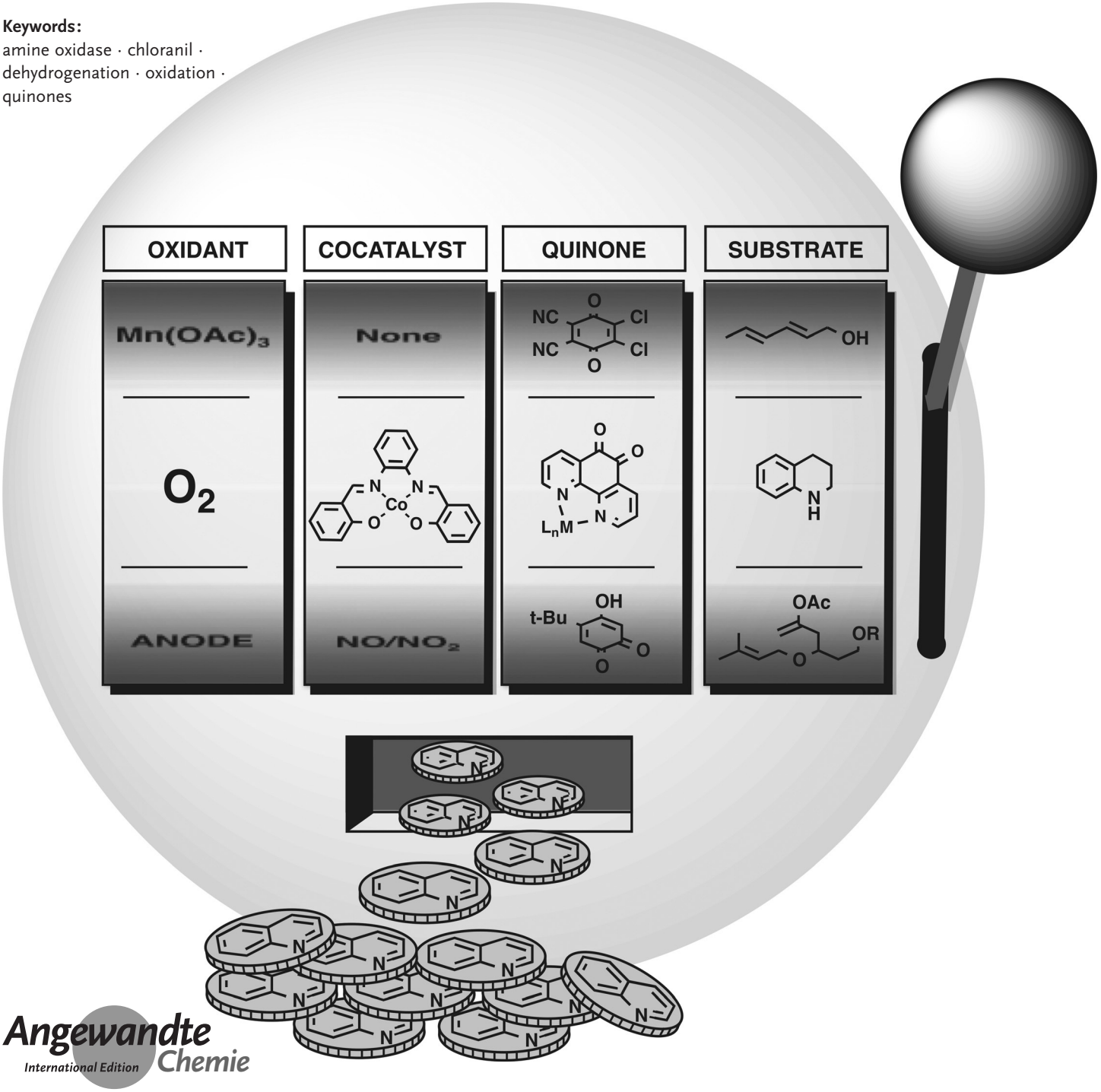
Keywords:
amine oxidase · chloranil · dehydrogenation · oxidation · quinones



Quinones are common stoichiometric reagents in organic chemistry. Para-quinones with high reduction potentials, such as DDQ and chloranil, are widely used and typically promote hydride abstraction. In recent years, many catalytic applications of these methods have been achieved by using transition metals, electrochemistry, or O_2 to regenerate the oxidized quinone in situ. Complementary studies have led to the development of a different class of quinones that resemble the ortho-quinone cofactors in copper amine oxidases and mediate the efficient and selective aerobic and/or electrochemical dehydrogenation of amines. The latter reactions typically proceed by electrophilic transamination and/or addition-elimination reaction mechanisms, rather than hydride abstraction pathways. The collective observations show that the quinone structure has a significant influence on the reaction mechanism and has important implications for the development of new quinone reagents and quinone-catalyzed transformations.

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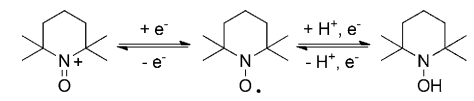
1. Introduction

The selective oxidation of organic compounds is a prominent challenge in the chemical industry. Considerable effort has focused on the development of transition-metal reagents and catalysts to accomplish such reactions, but redox-active organic molecules also serve as robust and efficient (co-) catalysts for oxidative transformations. Nitroxyl radicals are one of the most broadly used classes of organic oxidation catalysts. For example, 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) [Eq. (1)] and its derivatives promote a range of oxidative transformations, perhaps most prominently, alcohol oxidation reactions.[1] Additionally, phthalimide *N*-oxyl (PINO)—generated in situ from *N*-hydroxyphthalimide (NHPI)—is widely employed in aerobic autoxidation reactions [Eq. (2)].[2] Both reagents are amenable to industrial-scale oxidation processes.[3] The use of organic (co)catalysts provides access to reaction mechanisms that are often distinct from those mediated by transition-mediated catalysts, thereby leading to complementary reactivity, selectivity, and reaction conditions. Selective oxidation reactions promoted by organic catalysts and co-catalysts represent promising targets for future development.

Quinones are important redox-active organic molecules that have applications in diverse redox processes, including in the manufacture of industrial chemicals, in oxidation reactions for organic synthesis, and as electron carriers, antioxidants, and cofactors in biological processes.[4] Similar to nitroxyl radicals, quinones feature three readily accessible oxidation states, namely, fully oxidized quinone, one-electron-reduced semiquinone, and two-electron-reduced hydroquinone [Eq. (3)], and they are capable of mediating both closed- and open-shell redox processes. Relative to nitroxyl radicals, however, quinones are more commonly used as stoichiometric reagents, with less-extensive use as catalysts for the oxidation of organic molecules.



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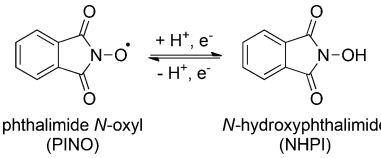

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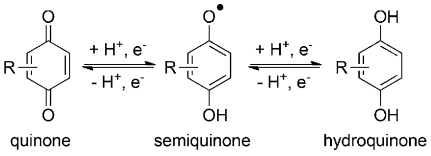

(3)

Redox cycling between oxidized and reduced quinone species forms the basis of the anthraquinone-mediated industrial synthesis of hydrogen peroxide.[5] Hydrogen peroxide is produced in near quantitative yields by the stoichiometric autoxidation of 2-alkyl-9,10-anthrahydroquinone (Scheme 1, autoxidation step). The resulting oxidized anthraquinone coproduct is subsequently reduced in a separate step by catalytic hydrogenation (Scheme 1, hydrogenation step). This sequence enables the net conversion of molecular oxygen and hydrogen into hydrogen peroxide (Scheme 1, net reaction). Over 95% of the world supply of hydrogen peroxide is made using this quinone-mediated process.

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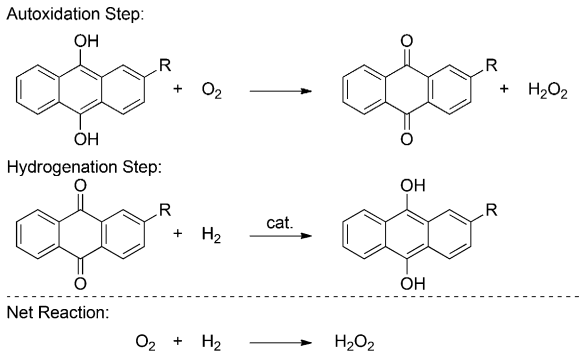
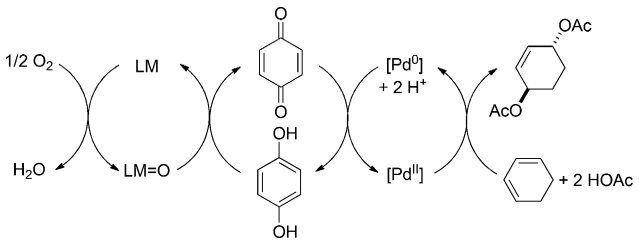


Scheme 1. The anthraquinone oxidation (AO) process for the industrial synthesis of H_2O_2 consists of the sequential autoxidation and hydrogenation of a quinone mediator.

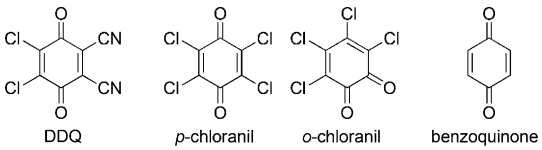


Scheme 2. Use of quinones as redox shuttles in organic synthesis, represented here by the Pd-catalyzed aerobic diacetoxylation of cyclohexadiene with Pd, quinone, and metal macrocycle (LM) coupled catalytic cycles.[6]

Although the incompatibility of the oxidation and reduction steps requires sequential operation of the two stoichiometric half reactions in this case, the use of a quinone mediator common to both half reactions suggests a broader potential for engaging quinones as catalysts in redox processes.

Nature provides a framework for the use of catalytic quinones as redox shuttles in oxidative transformations: plastoquinone and ubiquinone act as electron carriers in the photosynthetic and mitochondrial electron transport chains (ETCs), respectively. In the mitochondrial ETC, a series of cofactors shuttle electrons from a sacrificial reductant (nicotinamide adenine dinucleotide, NADH) to molecular oxygen. The reduction of molecular oxygen to water ultimately provides the thermodynamic driving force for the synthesis of ATP by oxidative phosphorylation. Conceptually related synthetic "electron-transfer mediators" (ETMs) often feature quinones as catalytic redox shuttles in metal-catalyzed aerobic oxidation reactions, such as the Pd-catalyzed 1,4-diacetoxylation of cyclohexadiene (Scheme 2).[6] Substrate oxidation first occurs through a transition-metal-mediated step, and a quinone (commonly, benzoquinone[7] or a related derivative[8]) acts as a redox shuttle to transfer protons and electrons from the transition-metal catalyst to a macrocyclic metal co-catalyst LM, such as [Co(salophen)] (salophen = *N*,*N*-salicylidenephenylenediamine), [Fe(pc)] (pc = phthalocyanine), or [Co(tpp)] (tpp = 5,10,15,20-tetraphenylporphyrin). Finally, the macrocyclic metal co-catalyst is reoxidized by molecular oxygen, the terminal oxidant. The series of coupled catalytic cycles are proposed to account for the efficient reactivity in these systems. In addition to serving as a redox shuttle between the Pd and macrocyclic metal co-catalysts, benzoquinone additives may also promote an oxidatively induced reductive elimination of the substrate from Pd^{II}.[9] The application of quinones as redox shuttles/ETMs is the subject of an extensive recent review by Piera and Bäckvall.[10] Although not revisited here, many of the fundamental principles associated with quinone co-catalyzed reactions of the type in Scheme 2 may be exploited in oxidation reactions involving direct oxidation of the organic molecule by a quinone catalyst.

The present Review highlights recent progress in the development of quinone-catalyzed oxidations of organic substrates, specifically, reactions involving the direct reaction of the organic substrate with the quinone catalyst.[11] The quinone catalysts may be divided into two general families: 1) quinones with a high reduction potential, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and chloranil; and 2) *o*-quinone catalysts reminiscent of the *o*-quinone cofactors found in copper amine oxidases (CAOs) and related enzymes.



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DDQ is the most widely used quinone with a high reduction potential, and it commonly mediates hydride transfer reactions. DDQ has found broad utility as a stoichiometric oxidant in the functionalization of activated C–H bonds and the dehydrogenation of saturated C–C, C–O, and C–N bonds, including in several process-scale pharmaceutical syntheses.[12,13] The cost and toxicity of DDQ underlies recent efforts to develop methods that employ catalytic quantities of DDQ in combination with alternative stoichiometric oxidants. These efforts are the focus of Section 2 of this Review. This section begins with an overview of the types of transformation and reaction mechanisms promoted by quinones with high reduction potentials, such as DDQ and chloranil. This context provides a foundation for the consideration of methods that have been developed by using these quinones as catalysts. Reactions promoted by catalytic DDQ closely parallel those accessible with stoichiometric DDQ, although applications that benefit from or are only effective with catalytic DDQ have also been identified.

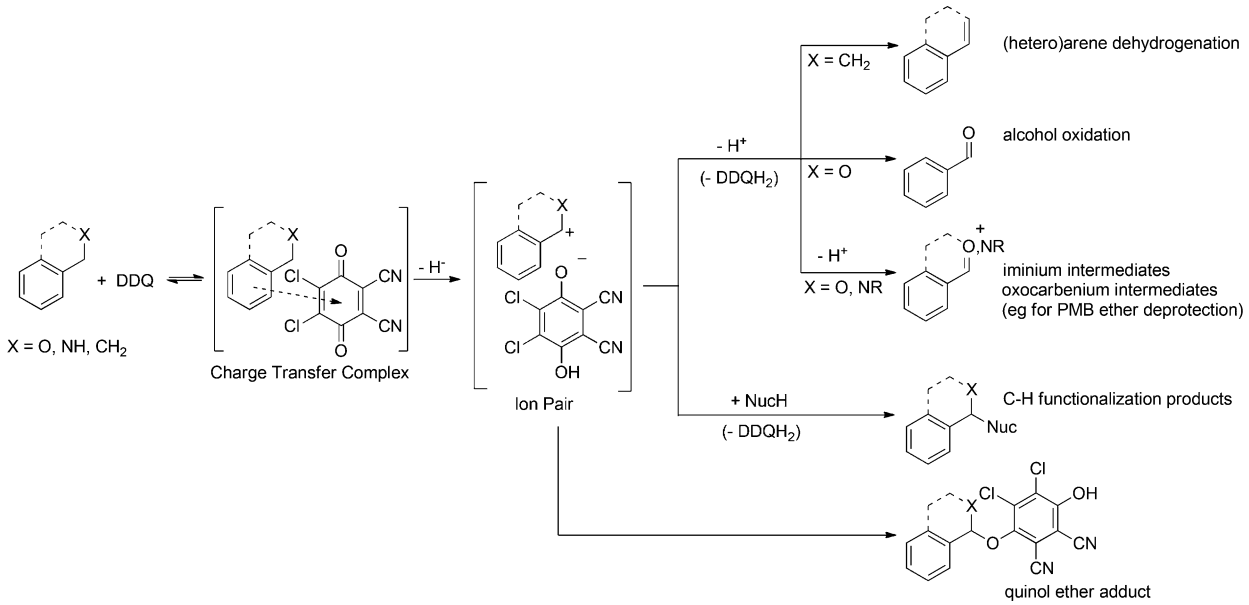
A second family of quinone catalysts resembles the *o*-quinone cofactors found in enzymatic oxidases and dehydrogenases. These bio-inspired quinones typically have lower reduction potentials than DDQ or chloranil, and they react through different mechanisms. Consequently, different substrate scopes and reactivity patterns are observed relative to quinones with high reduction potentials. Section 3 begins with an overview of copper amine oxidases and related naturally occurring quinoenzymes, highlighting the oxidation mechanisms employed by these enzymes. This context provides the basis for consideration of synthetic *o*-quinone catalysts and their applications to the aerobic and electrochemical dehydrogenation of saturated C–N bonds in amines, including nitrogen heterocycles.

2. DDQ-Catalyzed Oxidations of Organic Substrates

2.1. Mechanistic Insights from Stoichiometric DDQ-Mediated Transformations

Quinones with a high reduction potential, notably DDQ and chloranil, are important stoichiometric reagents for the oxidation of organic compounds.[4,14] The synthetic applications of DDQ fit into several categories, many of which feature quinone-mediated hydride abstraction from a substrate. This mechanism is thought to proceed through the formation of a quinone–substrate charge-transfer complex (Scheme 3).[15,16] Oxidation of the substrate subsequently occurs by hydride transfer from the substrate to the quinone, thereby forming an ion-pair product.[17] The specific mechanism of hydride abstraction by DDQ and/or chloranil has been the subject of some controversy. Depending on the substrate, net hydride abstraction may be initiated by single-electron transfer[18] or hydrogen atom transfer;[19] however, polar reaction mechanisms involving direct hydride transfer[20,21] are typically favored.[22]

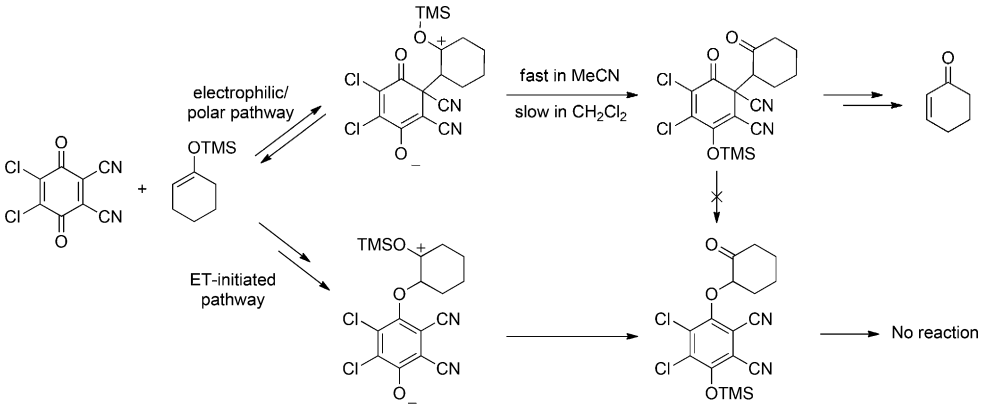
The substrate-cation/$DDQH^-$ ion pair formed upon hydride transfer can then undergo a range of subsequent chemical steps (Scheme 3). Deprotonation of the substrate by $DDQH^-$ can afford the corresponding dehydrogenated product,[23,24] as featured in the formation of (hetero)aromatic compounds from unsaturated precursors,[25] aldehydes and ketones from activated alcohols,[26] and oxocarbenium and iminium species from ethers and amines, respectively.[27,28] Alternatively, a carbocationic intermediate can undergo intramolecular rearrangement (for example, a Wagner–Meerwein rearrangement[29]) or be subject to intra- or intermolecular addition reactions that lead to oxidative C–H functionalization products.[30] Collapse of the ion pair may also occur, thereby leading to (typically undesired) quinol ether prod-



Scheme 3. Hydride transfer initiated reaction pathways that account for the majority of known DDQ-mediated oxidation/dehydrogenation reactions. Nuc = nucleophile.

ucts.[31,32] These types of reactions initiated by hydride abstraction account for the majority of DDQ-mediated transformations in the literature.

A second mechanistic pathway has been proposed for the DDQ-mediated dehydrogenation of ketones and silyl enol ethers to α,β-unsaturated ketones.[33,34] In this case, an "electrophilic" reaction pathway is proposed, rather than a hydride abstraction pathway.[35] Guo and Mayr have provided evidence for competing electrophilic and electron-transfer (ET) pathways in the reaction of DDQ with silyl enol ethers and silyl ketene acetals.[36] In the stoichiometric reaction of DDQ with 1-trimethylsilyloxycyclohexene, two adducts are observed: a C–C-linked adduct resulting from reversible conjugate addition of the silyl enol ether to the quinone, and a C–O-linked quinol ether resulting from irreversible single-electron transfer and radical coupling (Scheme 4). The ratio of C–C and C–O product formation is a consequence of the reaction conditions (solvent, temperature, concentration) as well as the identity of the quinone and reactant.[37] Productive reaction of the C–C adducts



Scheme 4. An electrophilic/polar pathway proposed for the DDQ-mediated dehydrogenation of ketones and silyl enol ethers, together with an unproductive, competing electron-transfer (ET) pathway leading to a C–O coupled adduct. Scheme adapted from Ref. [36].

obtained from polar addition of the nucleophile to the quinone is typically achieved at elevated temperatures and results in the formation of dehydrogenation products. The C–O-linked quinol ether products, in this case initiated by ET pathways, are not competent intermediates en route to substrate dehydrogenation.

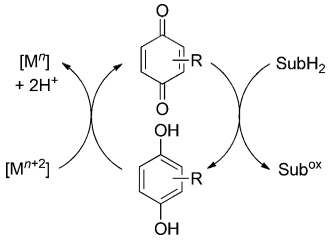
The mechanistic studies summarized here have several important implications for understanding the reactivity of quinones with a high reduction potential and for subsequent development of catalytic reactions: 1) Although DDQ is a strong thermodynamic oxidant, a reaction mechanism involving direct hydride abstraction limits dehydrogenation reactions to substrates containing quite activated C–H bonds (e.g. benzylic, allylic). 2) Electrophilic reaction mechanisms involving DDQ may lead to different reaction products relative to oxidation reactions initiated by electron or hydride transfer. Studies by Mayr and co-workers highlight the potential generality of the electrophilic pathway and the involvement of covalent substrate/quinone intermediates in dehydrogenation reactions mediated by a range of different quinones.[37] This mechanistic pathway provides kinetic access to reactions that may not be possible by hydride abstraction pathways.

2.2. DDQ- and Chloranil-Catalyzed Reactions

Despite the versatility of DDQ as a stoichiometric reagent, there are numerous limitations to the use of DDQ on a large scale. Issues include its relatively high toxicity ($LD_{50} = 82\ mg\,kg^{-1}$ rat) and high cost (> $500/mol), environmental hazards associated with water-mediated liberation of HCN, and challenges in removing $DDQH_2$ from the reaction products. DDQ exhibits unique reactivity relative to chloranil and other quinones, however, and the use of alternative, more-benign reagents is not always possible. Therefore, despite its limitations, DDQ continues to be an important reagent for the process-scale synthesis of pharmaceutical intermediates and drug candidates.[12,13,35] A widely cited example is the process-scale synthesis of Finasteride by Merck.[35] In this case, it was possible to lower the process costs by isolating the hydroquinone ($DDQH_2$) from the aqueous waste stream (96% recovery) and treating it with HNO_3/AcOH in a subsequent step to regenerate DDQ (75% yield).[35,38]

2.3. Transition-Metal Salts as Stoichiometric Terminal Oxidants

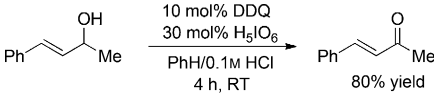
The considerations noted above have provided the motivation to develop methods capable of using catalytic amounts of DDQ or choranil in quinone-mediated reactions. Catalytic quantities of DDQ may be used by employing an alternative stoichiometric reagent such as $FeCl_3$, $Mn(OAc)_3$, PbO_2, or MnO_2 as the terminal oxidant (Scheme 5). Although these reactions are catalytic in DDQ, catalyst loadings remain rather high (10–



Scheme 5. A generic representation of quinone-catalyzed substrate oxidation with a stoichiometric transition metal as the terminal oxidant. $SubH_2$ = substrate, Sub^{ox} = oxidized substrate.

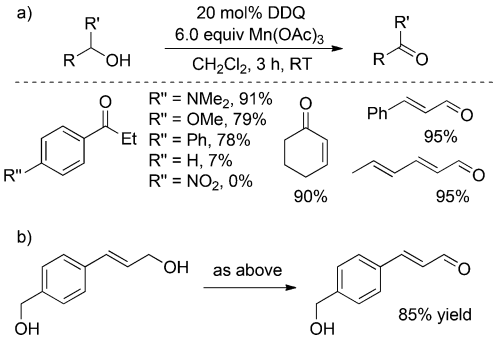
20 mol%), and a large excess of the terminal oxidant is typically employed.

Cacchi et al. reported the first DDQ-catalyzed transformation in 1978, and showed that the oxidation of allylic alcohols to α,β-unsaturated ketones could be accomplished using 10 mol% DDQ in the presence of 30 mol% periodic acid under slightly acidic,[39] biphasic conditions at room temperature (Scheme 6).[40]



Scheme 6. Catalytic oxidation of activated alcohols by using catalytic DDQ with periodic acid under biphasic conditions.[40]

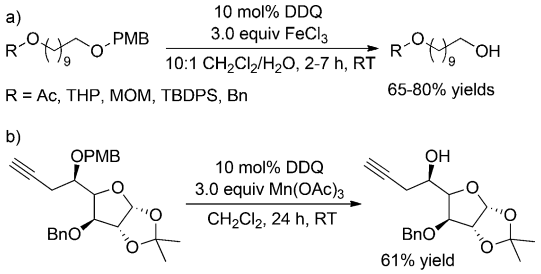
Helquist and co-workers subsequently demonstrated similar reactivity with $Mn(OAc)_3$ as the stoichiometric oxidant. By using 20 mol% DDQ and 6.0 equiv $Mn(OAc)_3$, allylic alcohols and electron-rich benzylic alcohols are oxidized to the corresponding aldehydes and ketones under mild conditions (Scheme 7a).[41] Good chemoselectivity for allylic alcohols over benzylic alcohols was observed (Scheme 7b).



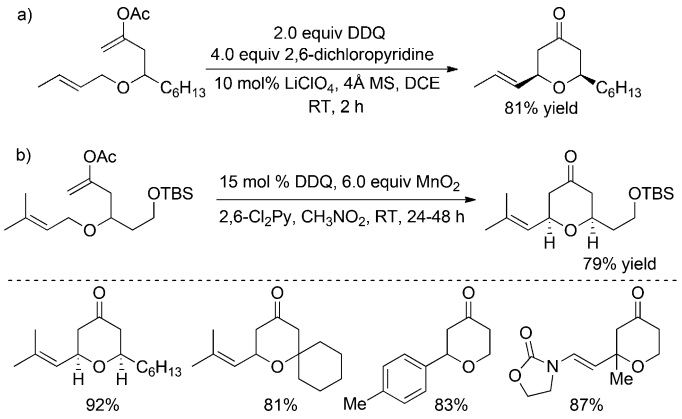
Scheme 7. a) Oxidation of activated alcohols by using a catalytic amount of DDQ with $Mn(OAc)_3$ as the terminal oxidant. b) Selective oxidation of allylic alcohols over benzylic alcohols.[41]

Chandrasekhar et al. reported the cleavage of PMB (4-methoxybenzyl) and DMB (3,4-dimethoxybenzyl) ethers using 10 mol% DDQ in combination with 3.0 equiv $FeCl_3$ under biphasic conditions (Scheme 8a).[42] Although substrate scope is limited, these catalytic conditions allow for the same selective removal of PMB ether protecting groups as with a stoichiometric application of DDQ. To avoid incompatibility with acid-sensitive substrates, Sharma et al. reported neutral conditions for cleavage of PMB ethers by using 10 mol% DDQ and 3.0 equiv $Mn(OAc)_3$ in CH_2Cl_2 at room temperature (Scheme 8b).[43]

Floreancig and co-workers have reported several innovative examples of DDQ-mediated oxidative C–C bond-forming reactions, including intramolecular dehydrogenative cou-



Scheme 8. Catalytic cleavage of PMB ethers by using DDQ in combination with a) 3.0 equiv $FeCl_3$ or b) 3.0 equiv $Mn(OAc)_3$ as the (super)-stoichiometric terminal oxidant.[42] Bn = benzyl, MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, THP = tetrahydropyran.



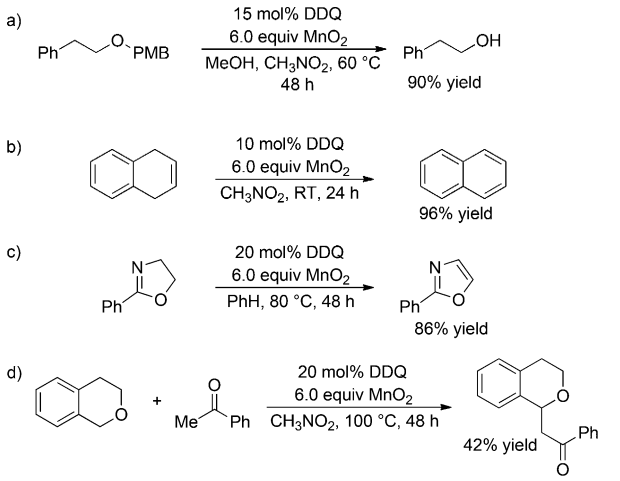
Scheme 9. a) Stoichiometric DDQ-mediated oxidative intramolecular synthesis of tetrahydropyranone derivatives[28k] and b) subsequently developed catalytic conditions for similar transformations.[44] 2,6-Cl_2Py = 2,6-dichloropyridine, DCE = 1,2-dichloroethane, TBS = *tert*-butyldimethylsilyl.

pling of allylic ethers to form tetrahydropyranone (Scheme 9a).[28g–o] In connection with this work, Liu and Floreancig developed conditions for carrying out some of these reactions catalytically (15–20 mol% DDQ) with either excess PbO_2 or MnO_2 (Scheme 9b).[44]

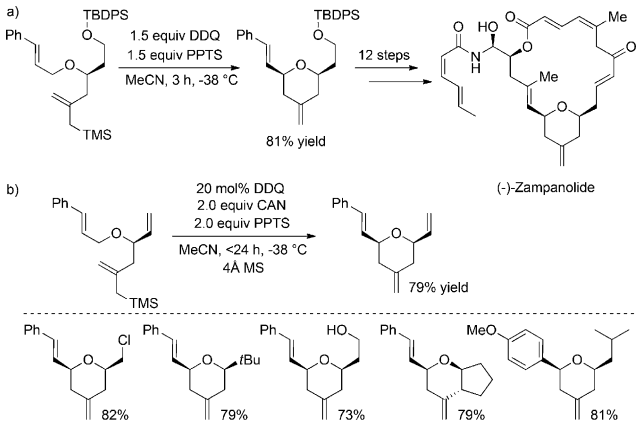
The versatility of these catalytic conditions was demonstrated in a series of other applications, including cleavage of PMB ethers (Scheme 10a), arene and heteroarene dehydrogenation reactions (Scheme 10b,c, respectively), and a cross-dehydrogenative coupling reaction of isochroman with acetophenone (Scheme 10d), originally developed as a stoichiometric DDQ-mediated reaction by Zhang and Li.[28c]

Ghosh and Cheng disclosed a similar DDQ-catalyzed synthesis of tetrahydropyran derivatives based on a stoichiometric DDQ-mediated transformation developed in their studies towards (−)-Zampanolide (Scheme 11a).[45] A variety of substituted tetrahydropyran derivatives were obtained using 20 mol% DDQ, 2.0 equiv pyridinium *p*-toluenesulfonate (PPTS), 2.0 equiv ceric ammonium nitrate (CAN), and 4 Å MS in MeCN at −38 °C (Scheme 11b).[46]

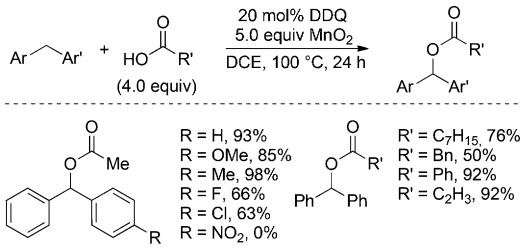
A DDQ-catalyzed method for the oxidative C–O coupling of diarylmethane C–H bonds with carboxylic acids was reported by Lei and co-workers. Good yields of cross-coupled products could be obtained by using 20 mol% DDQ and



Scheme 10. Examples of DDQ-catalyzed transformations with MnO_2 as the terminal oxidant: a) PMB cleavage, b) arene and c) heteroarene dehydrogenation reactions, as well as d) a cross-dehydrogenative coupling reaction of isochroman with acetophenone, based on reaction conditions developed for the synthesis of tetrahydropyranones.[44]



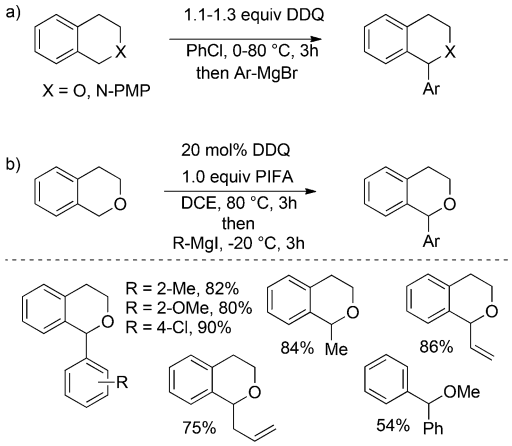
Scheme 11. a) Stoichiometric DDQ-mediated oxidative cyclization reaction towards the synthesis of Zampanolide[45] and b) subsequently developed DDQ-catalyzed conditions with 2.0 equiv CAN as the terminal oxidant.[46]



Scheme 12. DDQ-catalyzed oxidative C–O coupling of diarylmethane C–H bonds with MnO_2 as the terminal oxidant.[47]

5.0 equiv MnO_2 in 1,2-dichloroethane at 100 °C (Scheme 12).[47]

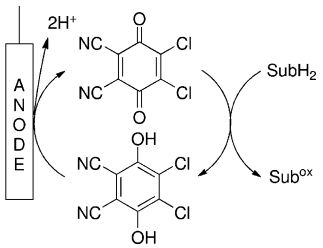
Muramatsu and Nakano reported a DDQ-catalyzed cross-dehydrogenative coupling reaction, again based on an earlier transformation that used stoichiometric DDQ (Scheme 13 a).[48] New C–C bonds are formed by the oxidation of isochroman or tetrahydroisoquinoline substrates followed by addition of aryl Grignard reagents. A catalytic amount of DDQ (20 mol %) was employed with 1.0 equiv of [bis(trifluoroacetoxy)iodo]benzene (PIFA) as the stoichiometric oxidant (Scheme 13 b).[49]



Scheme 13. Cross-dehydrogenative coupling of activated C–H bonds with aryl Grignard reagents by using a) stoichiometric DDQ[48] or b) catalytic DDQ with PIFA as a stoichiometric oxidant.[49]

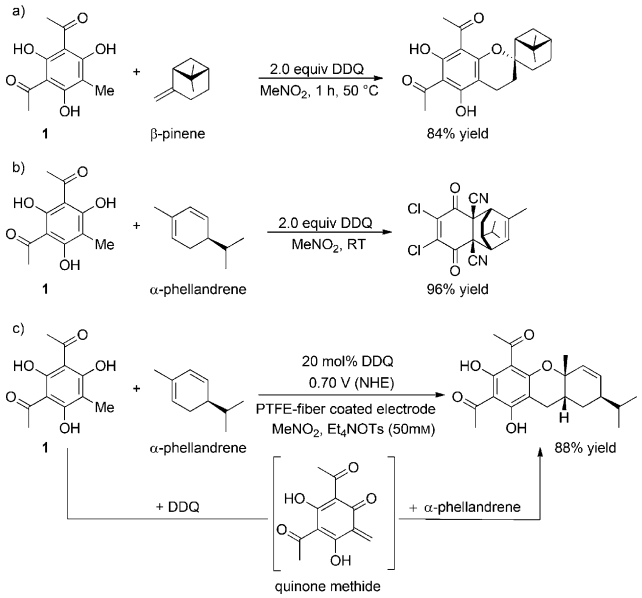
2.4. Electrochemical Regeneration of DDQ

Electrolysis has been used as a method for the regeneration of DDQ after a reaction,[50] and in situ electrochemical oxidation of $DDQH_2$ provided a means to achieve catalytic applications of DDQ (Scheme 14). Although redox mediators have been widely studied for the electrochemical oxidation of organic substrates,[51] applications in which DDQ has been used as the electrochemical mediator are still rare.



Scheme 14. Generic representation of the electrochemical quinone-catalyzed oxidation of organic substrates.

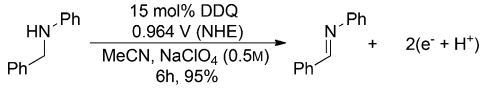
In the course of synthetic studies on the euglobal family of natural products, Chiba et al. found that a stoichiometric amount of DDQ (2.0 equiv) could promote a Diels–Alder reaction between grandinol (and related model compounds, such as **1**) and pinene derivatives (Scheme 15 a).[52] Under these conditions, however, one of the desired reaction partners, α-phellandrene, undergoes an undesired Diels–Alder reaction with DDQ in near-quantitative yield, and no desired product is formed (Scheme 15 b). The researchers



Scheme 15. A stoichiometric DDQ-promoted Diels–Alder reaction of **1** leads to the desired product with a) β-pinene, but not with b) α-phellandrene as the reaction partner.[52] c) The reaction with α-phellandrene is successful under electrochemical conditions when catalytic DDQ is employed.[53] Et_4NOTs = tetraethylammonium *p*-toluenesulfonate, NHE = normal hydrogen electrode.

subsequently developed an electrocatalytic method, involving the DDQ-catalyzed oxidation of **1** to an intermediate quinone methide species at a working electrode coated with polytetrafluoroethylene (PTFE) fiber at 0.70 V (NHE) in Et_4NOTs (50 mM in $MeNO_2$). The steady-state concentration of DDQ is kept low under these conditions, and the desired Diels–Alder reaction of the quinone methide intermediate with α-phellandrene or α- or β-pinene generates the desired euglobal analogue in excellent yield (Scheme 15c).[53] Six euglobal natural products were prepared by using this electrochemical approach. This work elegantly shows how catalytic conditions may be used to overcome synthetic limitations that may be encountered when using a reactive stoichiometric reagent (DDQ).

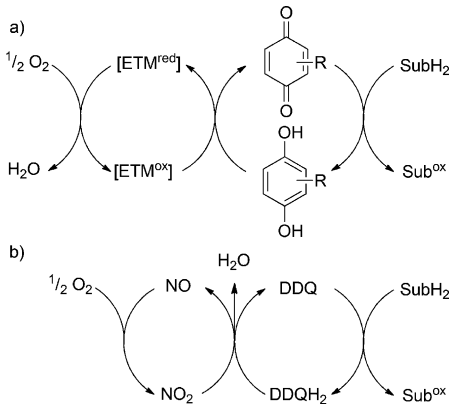
Crabtree and co-workers have reported conditions for the electrochemical regeneration of DDQ during their research on "virtual hydrogen storage". By using 15 mol% DDQ in MeCN (0.5 M $NaClO_4$) at room temperature, *N*-phenylbenzylidene could be obtained from *N*-phenylbenzylamine in 95% yield (Scheme 16) after a controlled potential electrolysis at 0.964 V (NHE) for 6 h.[16] Independently, Utley and Rosenberg employed DDQ as an electrocatalyst for the benzylic oxidation of electron-rich 2-alkylnaphthalenes to the corresponding benzylic ethers and ketones.[32f,54]



Scheme 16. Electrochemical DDQ-catalyzed dehydrogenation of C–N bonds by controlled-potential electrolysis at 0.964 V.[16]

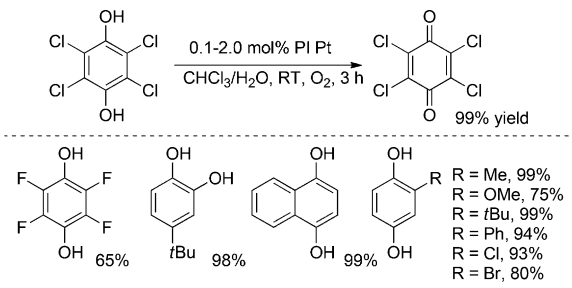
2.5. Aerobic Regeneration of DDQ/Quinones

Molecular oxygen is an ideal terminal oxidant, and quinone-mediated oxidations of organic molecules are well-suited for "oxidase"-type aerobic oxidation reactions (see Scheme 2).[55] In contrast to the facile autoxidation of quinones with a low reduction potential (see Scheme 1), direct aerobic oxidation of hydroquinones derived from high-potential quinones is typically not feasible.[56] Nevertheless, several strategies have been identified to mediate the aerobic oxidation of hydroquinone species by using a heterogeneous co-catalyst or a soluble co-catalytic electron-transfer mediator (ETM, Scheme 17a), such as a polyoxometalate or "NO_x" source, the latter of which contributes to a NO/NO_2 redox cycle (Scheme 17b).



Scheme 17. A generic representation of aerobic quinone-catalyzed substrate oxidation with a) an ETM or b) an NO/NO_2 redox couple to facilitate hydroquinone reoxidation.

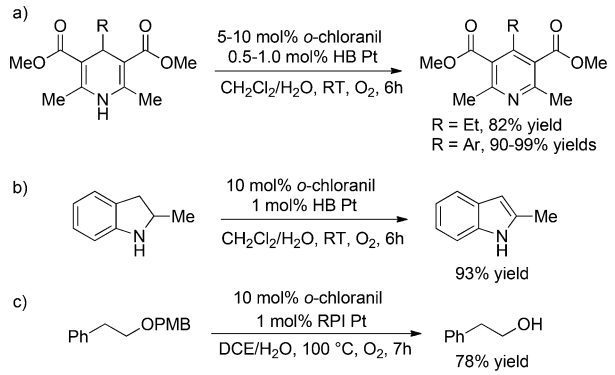
The aerobic oxidation of hydroquinones to quinones, either uncatalyzed (autoxidation)[5] or using catalysts such as metal macrocycles[57] and various catecholase mimics,[58] has been studied previously, but examples of such studies with quinones having a high reduction potential, such as DDQ or chloranil, are rare. Miyamura, Kobayashi et al. reported the aerobic oxidation of a wide variety of hydroquinone derivatives with heterogeneous, polymer-incarcerated Au[59] (PI Au) and Pt[60] (PI Pt) nanoclusters. The reaction conditions are mild, and involve low catalyst loadings at room temperature in $CHCl_3/H_2O$ under 0.1 MPa O_2 (Scheme 18). Of



Scheme 18. Aerobic oxidation of tetrachlorohydroquinone and other hydroquinone derivatives to the corresponding quinones by using polymer-incarcerated Pt (PI Pt) nanoclusters.[60]

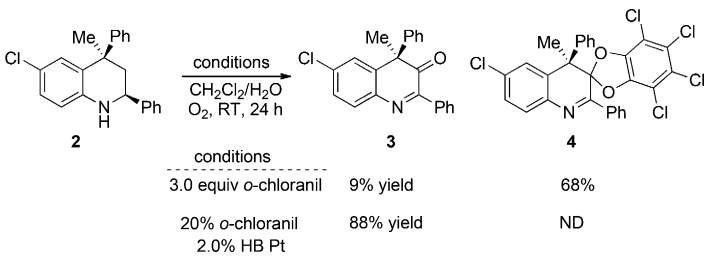
particular note is the oxidation of tetrachlorohydroquinone to *p*-choranil in 99% yield at room temperature within 3 h by using 1 mol% PIPt catalyst.

A subsequent study demonstrated that a catalyst system composed of catalytic *o*-chloranil and a co-catalytic hybrid organic/inorganic platinum nanocluster catalyst (HBPt) can be employed in the oxidation of organic substrates by using molecular oxygen as the terminal oxidant.[61] Efficient oxidation of Hantzsch-type dihydropyridines to substituted pyridines was accomplished using 5–10 mol% *o*-chloranil in combination with 0.5–1.0 mol% HBPt in CH_2Cl_2/H_2O solvent at room temperature under 0.1 MPa O_2 (Scheme 19a).



Scheme 19. Aerobic *o*-chloranil-catalyzed dehydrogenation of a) dihydropyridines to pyridines and b) 2-methylindoline to 2-methylindole by using a co-catalytic hybrid organic/inorganic platinum nanocluster catalyst (HB Pt), and c) PMB ether cleavage under similar conditions by employing an oxidation-resistant polymer-incarcerated Pt co-catalyst (RPI Pt).[61]

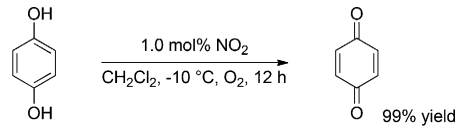
The dehydrogenation of 2-methylindoline to 2-methylindole was also accomplished with this catalyst system (Scheme 19b), and efficient cleavage of PMB ethers was demonstrated under modified reaction conditions consisting of 1 mol% of an oxidation-resistant polymer-incarcerated Pt catalyst (RPIPt) and 10 mol% *o*-chloranil in DCE/H_2O at 100°C (Scheme 19c). When stoichiometric *o*-chloranil (3.0 equiv) was used in the oxidation of tetrahydroquinoline derivative **2**, a substrate/chloranil-derived ketal adduct **4** was obtained as the major product. Under catalytic conditions, however, the desired oxygenated compound **3** was obtained in 88% yield (Scheme 20).[61]



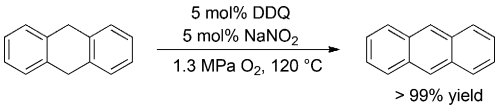
Scheme 20. Stoichiometric oxidation of tetrahydroquinoline derivative **2** with 3.0 equiv *o*-chloranil leads to substrate/chloranil ketal adduct **4**. The desired product **3** can be obtained under previously developed catalytic conditions.[61] ND = not detected.

Polyoxometalates (also called heteropoly acids) are effective co-catalysts for the aerobic regeneration of quinones with a high reduction potential. Neumann et al. reported the aerobic oxidation of allylic and benzylic alcohols by using 5 mol% *o*-chloranil with 1.5 mol% $Na_5PV_2Mo_{10}O_{40}$ at 90°C in H_2O/decalin under 0.1 MPa O_2.[62]

In 1994, Kochi and co-workers demonstrated the quantitative aerobic oxidation of hydroquinone to benzoquinone by using 1 mol% NO_2 in CH_2Cl_2 at −10°C under 0.1 MPa O_2 (Scheme 21).[63] A range of substituted quinones were generated in this manner.[64] It wasn't until 2008, however, that the NO/NO_2 redox couple was used in combination with DDQ to catalyze the aerobic oxidation of an organic molecule (see Scheme 17b). Xu and co-workers used a catalyst system consisting of 5 mol% DDQ and 5 mol% $NaNO_2$ under 1.3 MPa O_2 at 120°C to dehydrogenate dihydroanthracene to anthracene in >99% yield in 8 h (Scheme 22).[65a,b]



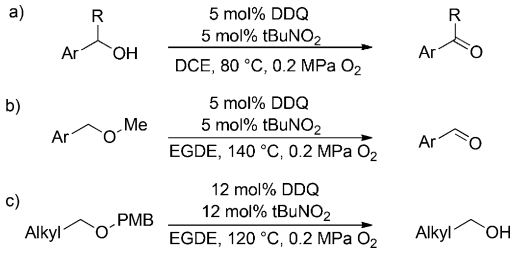
Scheme 21. NO_2-catalyzed aerobic oxidation of hydroquinones to quinones.[63]



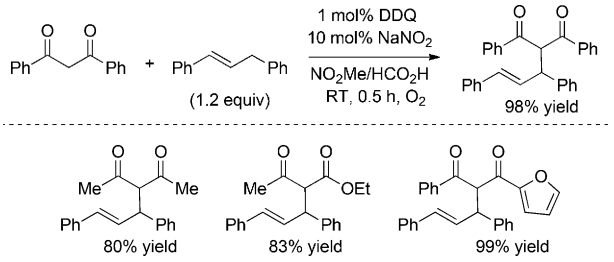
Scheme 22. DDQ-catalyzed aerobic dehydrogenation of dihydroanthracene by employing co-catalytic $NaNO_2$ at elevated temperatures and pressures.[65a,b]

The observation that an NO/NO_2 redox couple enables the aerobic DDQ-catalyzed oxidation of organic molecules is quite significant. Traditional electron-transfer mediators (ETMs), which couple the oxidation of hydroquinone to the reduction of O_2 to H_2O_2, are typically not effective with DDQ because the reduction potential of $DDQ/DDQH_2$ ($E° = 0.750$ V versus NHE) is higher than the O_2/H_2O_2 reduction potential (0.670 V versus NHE). The reduction of O_2 by NO, however, proceeds through a $4e^-$ reduction of O_2 without formation of H_2O_2, and NO_2 is a sufficiently strong oxidant to promote the oxidation of $DDQH_2$ to DDQ.[65c]

Mo, Hu, and co-workers have reported a similar catalyst system for the oxidation of activated alcohols, which used 5 mol% DDQ and 5 mol% *t*$BuNO_2$ in 1,2-dichloroethane at 80°C under 0.2 MPa O_2 pressure. Excellent yields of the corresponding aldehydes and ketones were obtained (Scheme 23a).[66] Under modified reaction conditions (ethylene glycol diethyl ether (EGDE) as solvent, 120–140°C), the authors found that methyl aryl ethers are converted into the corresponding benzylic aldehydes (Scheme 23b), and PMB ethers undergo selective cleavage (Scheme 23c).

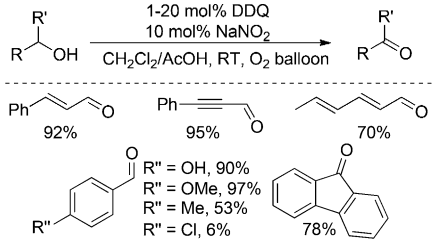


Scheme 23. DDQ-catalyzed aerobic oxidation of a) alcohols and b) ethers, and c) selective cleavage of PMB by using *tert*-butylnitrite as a co-catalyst.[66]



Scheme 25. DDQ-catalyzed aerobic C–C coupling of diarylpropenes and 1,3-dicarbonyl compounds by employing co-catalytic $NaNO_2$.[73]

Gao and co-workers reported a DDQ-catalyzed (1–20 mol%) method for the aerobic oxidation of allylic and benzylic alcohols to the corresponding aldehydes.[67] The reaction requires 10 mol% $NaNO_2$ and is carried out in a CH_2Cl_2/AcOH solvent mixture at ambient temperatures under an O_2 balloon (Scheme 24). Reactions could also be carried out in good yield under air. The DDQ-catalyzed aerobic oxidation of alcohols has been applied to lignin depolymerization using an NO_x co-catalyst system,[68,69] and other aerobic alcohol oxidation reactions have been reported in which additional co-catalysts, such as 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO)[70a] or *N*-bromosuccinimide,[70b] are used in combination with DDQ and NO_x.



Scheme 24. DDQ-catalyzed aerobic oxidation of activated alcohols to aldehydes by employing co-catalytic $NaNO_2$ under mild conditions.[67]

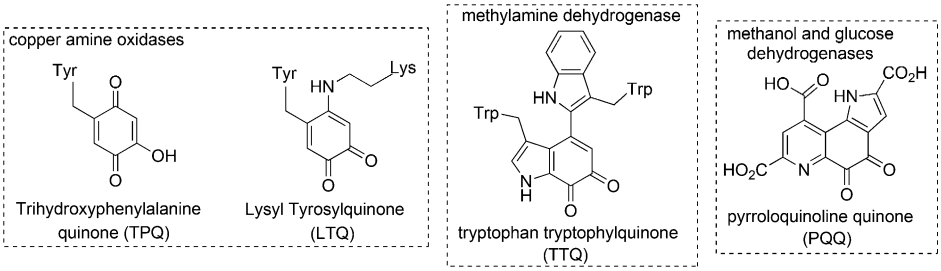
Shen et al. then reported a modified method for the aerobic DDQ-catalyzed cleavage of PMB ethers to the corresponding alcohol in excellent yield.[71] The conditions resembled those developed by Gao and co-workers for the oxidation of activated alcohols (5 mol% DDQ, 5 mol% $NaNO_2$), but the reactions were carried out at 100 °C in chlorobenzene (which represent somewhat milder conditions that those shown in Scheme 23). Moody and co-workers then reported even milder conditions for the cleavage of PMB ethers in AcOH as the solvent by employing 1.5–5 mol% DDQ and 3–10 mol% $NaNO_2$ at room temperature under 0.1 MPa O_2 (balloon).[72]

Yan and co-workers reported an aerobic DDQ-catalyzed oxidative coupling of diarylpropenes with 1,3-diketones.[73] A range of new C–C coupled products were obtained in good-to-excellent yields by using 1 mol% DDQ and 10 mol% $NaNO_2$ in $MeNO_2/HCO_2H$ at room temperature under an O_2 balloon (Scheme 25). Aerobic DDQ-catalyzed transformations have also been promoted by using azobis(isobutyronitrile) (AIBN)[74] and [Fe(pc)][75] co-catalysts.

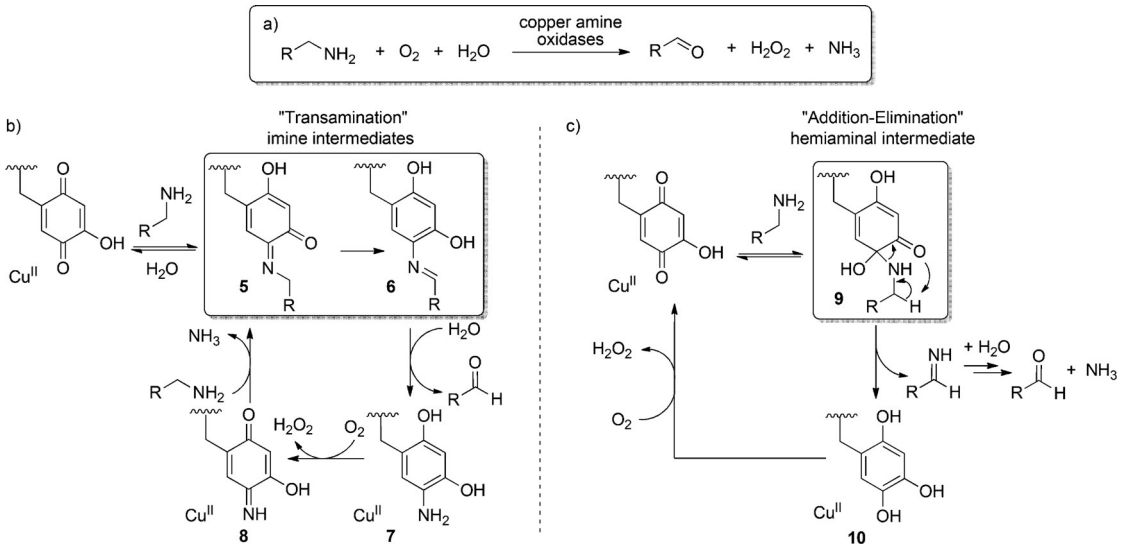
3. Bioinspired *o*-Quinone-Catalyzed Oxidation of Amines

3.1. Enzymatic Context

Quinones play an important role as cofactors in the enzymatic oxidation of organic substrates. Several families of "quinoenzymes"[76] are known, and include copper amine oxidases (containing active-site cofactors TPQ[77] and LTQ[78]), methylamine dehydrogenase (TTQ[79]), and methanol and glucose dehydrogenases (PQQ).



Copper amine oxidases (CAOs) convert primary amines into aldehydes using molecular oxygen (Scheme 26a).[80] The copper present in the active site of these enzymes reacts with oxygen and mediates post-translational modification of an active-site tyrosine residue to generate the *o*-quinone cofactor (i.e. TPQ or LTQ).[81] Oxidation of the amine substrate is mediated by the quinone without direct involvement of the Cu center. Two mechanisms were initially proposed for oxidation of the substrate by the quinone cofactor: a "transamination" mechanism and an "addition-elimination" mechanism (Scheme 26b,c). In the transamination mechanism, oxidation of the substrate occurs by an initial condensation of the primary amine with the quinone cofactor to give an imine adduct, **5**.[82] Imine **5** undergoes tautomerization with net

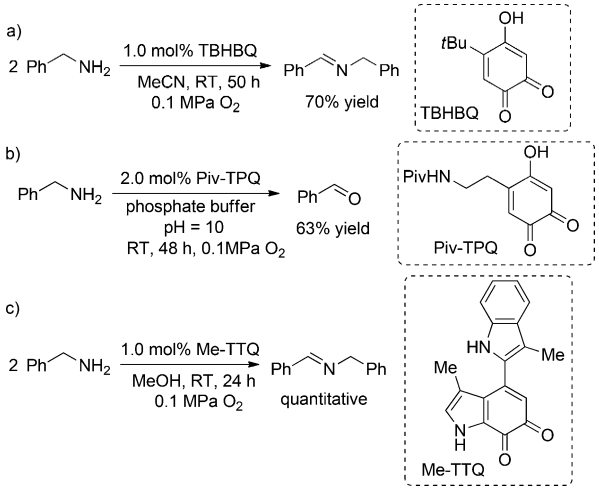


Scheme 26. Copper amine oxidases carry out a) the aerobic oxidation of primary amines in vivo. Two initially proposed substrate oxidation mechanisms: b) a transamination mechanism, and c) an addition-elimination mechanism. Adapted from Ref. [116].

prototropic rearrangement to give a second imine species, **6**. Hydrolysis of the imine group in **6** liberates the aldehyde product and affords the reduced aminohydroquinone cofactor **7**. Aerobic reoxidation of **7** to an iminoquinone species **8**, followed by transamination with another equivalent of amine, closes the catalytic cycle (Scheme 26b). In the addition-elimination mechanism, oxidation of the substrate occurs via an initially formed hemiaminal adduct **9**, which directly liberates an aldimine product through a pericyclic mechanism, together with formation of the reduced hydroquinone cofactor **10** (Scheme 26c).

Extensive mechanistic studies demonstrated that oxidation of amines by these enzymes proceeds through a transamination mechanism. In connection with mechanistic studies of CAO and methylamine dehydrogenase quinoenzymes, the research groups of Klinman,[83] Sayre,[84] Itoh,[85] and others developed biomimetic model quinones that promote the selective aerobic oxidation of primary amines to imines and aldehydes in the absence of the enzymes (Scheme 27). Similar to the native enzymes, oxidation of the substrate by these model quinones was proposed to proceed through a transamination mechanism.

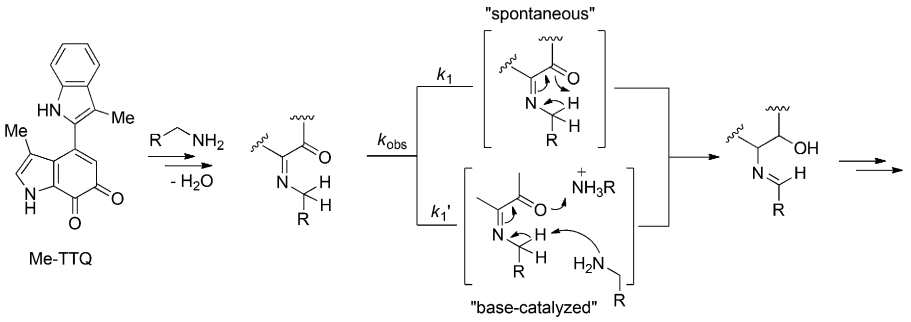
Itoh et al. further examined the mechanistic features of the C–H bond-cleaving step in the tryptophan tryptophylquinone (TTQ) model quinone Me-TTQ.[85a] Kinetic studies, including observation of large kinetic isotope effects (KIEs; 7.8–9.2), provided evidence for two competing C–H bond-cleavage processes: a slow "spontaneous" intramolecular prototropic rearrangement, k_1; and a faster bimolecular "base-catalyzed" rearrangement step, k_1' (Scheme 28). These findings suggest a possible distinction between these biomimetic *o*-quinone catalysts with comparatively low reduction potentials and the quinones with a high reduction potential, such as DDQ: the former induce a deprotonation-type C–H bond cleavage, while the latter promote C–H bond cleavage by hydride transfer.



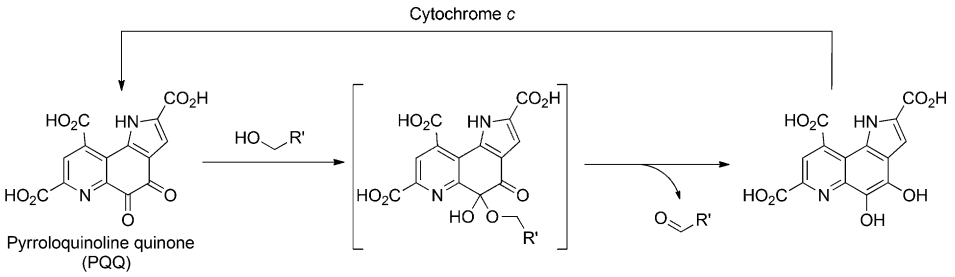
Scheme 27. Aerobic oxidation of primary amines catalyzed by model quinone cofactors a) TBHBQ,[83] b) Piv-TPQ,[84] and c) Me-TTQ.[85] Piv = pivaloyl.

Another quinone cofactor, pyrroloquinoline quinone (PQQ) is found in bacterial methane and glucose dehydrogenases. Biochemical studies of the PQQ cofactor established a complementary mechanism for substrate oxidation.[86] In this case, an "addition-elimination" mechanism is supported, whereby oxidation of the substrate (typically an alcohol, such as methanol) occurs via a hemiacetal intermediate (Scheme 29).[87]

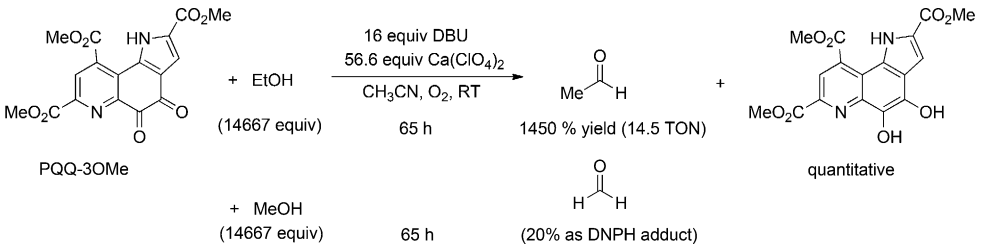
In model studies, Itoh, Fukuzumi et al. showed that the oxidation of low-molecular-weight alcohols such as ethanol and methanol are oxidized to the corresponding aldehydes by using the trimethyl ester of PQQ (Scheme 30).[88,89] PQQ is not regenerated by O_2 in nature, but the synthetic model is capable of using molecular oxygen as the terminal oxidant.



Scheme 28. Mechanistic proposal for the C–H bond-breaking step in biomimetic model quinone-catalyzed aerobic oxidations of primary amines to imines, involving competing intramolecular ("spontaneous") and intermolecular ("base-catalyzed") C–H cleavage steps.[85a]



Scheme 29. Proposed mechanism of alcohol oxidation mediated by cofactor PQQ.

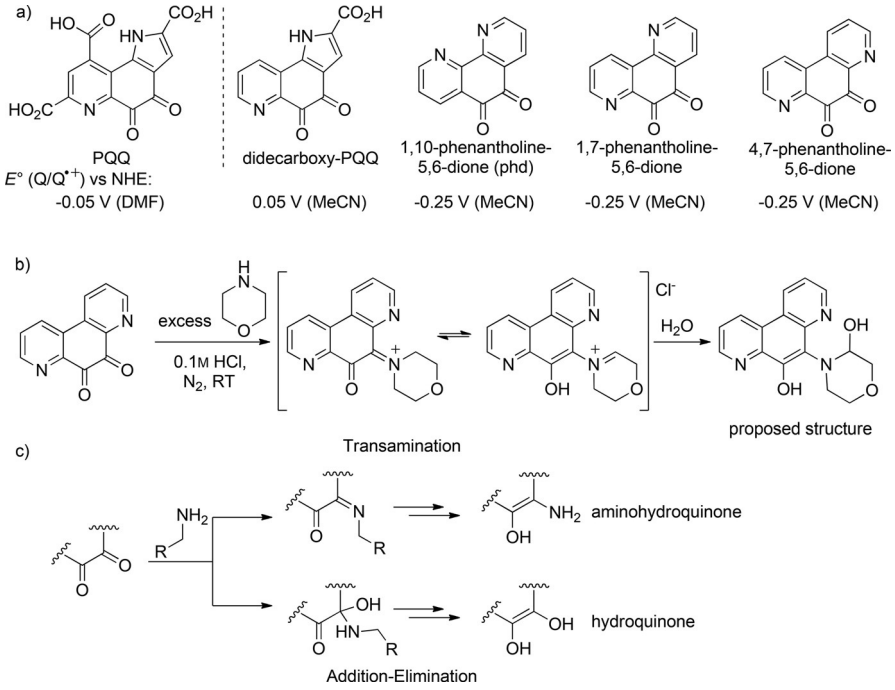


Scheme 30. Biomimetic, aerobic oxidation of methanol and ethanol catalyzed by PQQ-3OMe.[88] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DNPH = 2,4-dinitrophenylhydrazine, TON = turnover number.

The thermodynamic potential of PQQ-3OMe is low, estimated at 0.05 V (versus NHE in MeCN; cf. free PQQ −0.05 V versus NHE in DMF).[96] In contrast, DDQ has a significantly higher reduction potential (0.750 V versus NHE in MeCN).[90] Nevertheless, DDQ has not been shown to oxidize methanol, and many DDQ-mediated substrate oxidations actually take place in methanol as solvent. These observations together with the efficient dehydrogenation of methanol by PQQ clearly show that quinone reactivity is not controlled solely by its reduction potential. This conclusion has important implications for the design of new quinone catalysts for organic oxidation reactions.

Unlike other quinone cofactors, PQQ is not covalently bound to the enzyme. The glucose dehydrogenase apoenzyme can be reconstituted with simplified PQQ derivatives (related to 1,7- and 4,7-phenanthroline quinones) to give an active enzyme, although with somewhat lower activity.[91] In addition, Eckert and Bruice have carried out a series of mechanistic studies on the non-enzymatic oxidation of alcohols and amines using PQQ and simplified PQQ analogues such as didecarboxy-PQQ as well as 1,10-, 1,7-, and 4,7-phenanthroline-derived quinones (Scheme 31 a).[92,93] In a series of mechanistic studies, Eckert and Bruice showed that the stoichiometric reduction of phenanthroline-derived *o*-quinones by primary amines (cyclohexylamine and glycine) results in the formation of aminohydroquinone products, consistent with a transamination mechanism.[93] The secondary amine morpholine reacts more slowly and forms a substrate–quinone adduct as the predominant product (Scheme 31 b), also consistent with a transamination-type mechanism. Oxidation of the tertiary amine *N*,*N*-dimethylbenzylamine is also significantly slower than the oxidation of primary amines, and leads to the formation of hydroquinone as well as benzaldehyde and formaldehyde products. The stoichiometric oxidation of *p*-methylbenzyl alcohol was also tested with these phenanthroline-derived quinones. No reaction was observed after 7 days at 60 °C with 1,10- and 1,7-phenanthrolinedione, and only 6 % yield was observed using 4,7-phenanthrolinedione. In contrast, 90 % yield was obtained when DDQ was employed as the oxidant under otherwise identical conditions. Across each of these substrate classes, it was found that quinones containing a nitrogen atom adjacent to the quinone carbonyl groups (e.g. 1,7- and 4,7-phenanthrolinedione) mediate substrate oxidation more rapidly that 1,10-phenanthrolinedione, despite nearly identical electrochemical potentials.

The phenanthroline-derived quinones studied share a number of physical and chemical similarities with PQQ, including similar electrochemical potentials (cf. Scheme 31 a), facile formation of covalent adducts with water, methanol, and acetone, and ability to mediate the stoichiometric oxidation of simple organic substrates.[94–96] In contrast, although secondary and tertiary amines react with phenanthroline-derived quinones, they are not substrates for the didecarboxy-PQQ model compound. Analysis of the end products of the reaction of didecarboxy-PQQ with primary



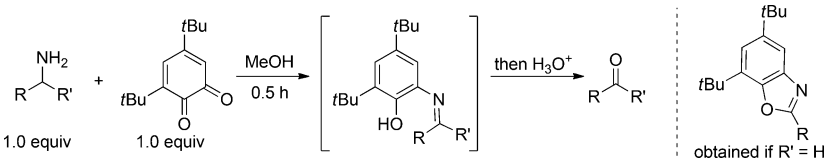
Scheme 31. a) PQQ and model compounds, didecarboxy-PQQ and phenanthroline-derived quinones. b) Adduct formation is observed in the reaction of 4,7-phenanthroline-1,10-dione with excess morpholine, thus implicating the transamination mechanism.[93] c) Different reaction mechanisms lead to different reduction products, as detected by end-product analysis.

amines reveals the formation of hydroquinone, rather than aminohydroquinone (cf. Scheme 31 c).[97] These findings are consistent with the proposal by Itoh et al. that the oxidation of primary amines by PQQ itself proceeds through an "addition-elimination"-like mechanism.[98] This proposal was supported by kinetic evidence, as well as by the observation of mixtures of aminohydroquinone (transamination product) and hydroquinone (addition-elimination product) species at the end of model reactions.[99]

3.2. *o*-Quinone-Catalyzed Dehydrogenation of C–N Bonds

The early mechanistic and model studies of enzymatic quinones discussed in Section 3.1 have provided the basis for a number of bioinspired quinone-mediated transformations in recent years. The majority of these studies have focused on *o*-quinones that resemble the enzymatic quinones and are distinct from DDQ and the other *p*-quinones with a high reduction potential described in Section 2. Perhaps not surprisingly, many applications of *o*-quinones have targeted amine dehydrogenations.[100]

Even before the quinone cofactors were identified in amine oxidase enzymes, Corey and Achiwa demonstrated that branched primary amines could be oxidized with stoichiometric 3,5-di-*tert*-butyl-*o*-quinone in MeOH to give a tautomeric imine adduct.[101] Upon hydrolysis, ketone products were obtained in excellent yields (Scheme 32).[102] Unbranched primary amines were not effective substrates, as they generated benzoxazole products instead.[103]

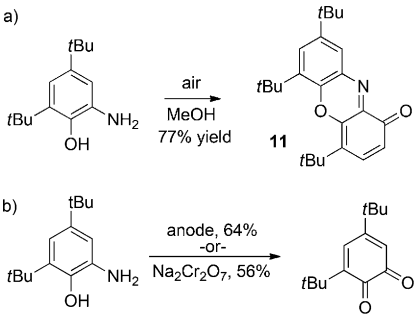


Scheme 32. Stoichiometric oxidation of branched primary amines to ketones by using 3,5-di-*tert*-butyl-*o*-quinone. Oxazole adducts are obtained when unbranched primary amines are used as substrates.[101]

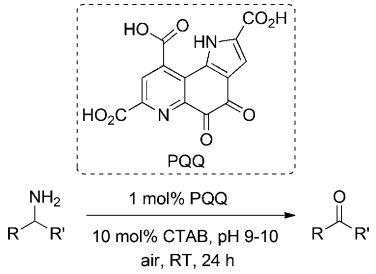
Independent attempts to regenerate 3,5-di-*tert*-butylquinone from the reduced aminophenol by O_2 led to the dimeric species **11** (Scheme 33 a), while electrochemical and chromate regeneration under acidic conditions gave the quinone in 64% and 56% yields, respectively (Scheme 33 b).[104]

The catalytic aerobic oxidation of primary amines to ketones and aldehydes was achieved by Itoh and coworkers under aqueous micellar conditions by using 1 mol% of the quinone PQQ and 10 mol% hexadecyltrimethylammonium bromide (CTAB) at pH 9–10 under ambient air at room temperature (Scheme 34).[105,106]

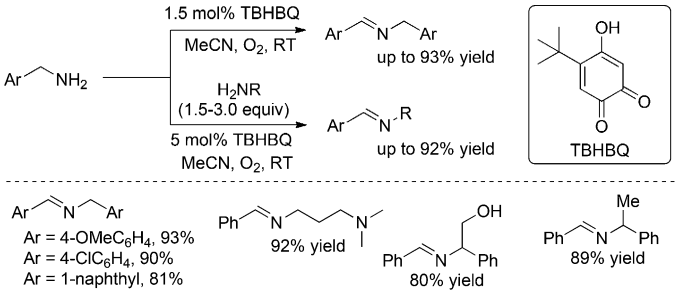
Largeron and Fleury developed *o*-quinones $Q1^{red}$ and $Q2^{red}$ as catalysts for the electrochemical oxidation of primary amines to imines.[107] Controlled-potential electrolysis of benzylic or aliphatic primary amines was accomplished by using 2 mol% of precatalyst $Q1^{red}$ or $Q2^{red}$ at 0.60 V versus the saturated calomel electrode (SCE) with a Pt anode in MeOH at room temperature



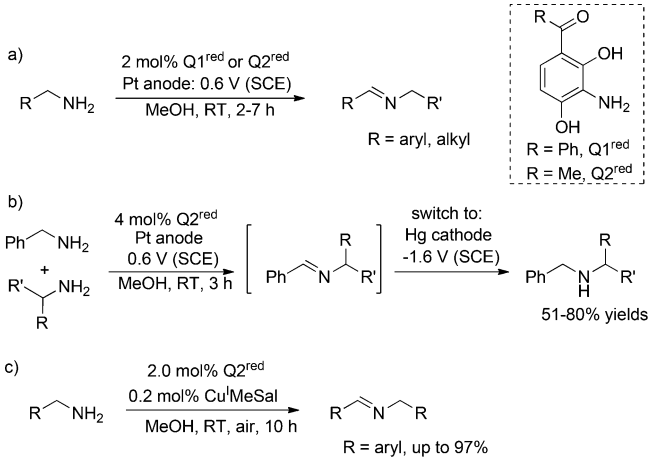
Scheme 33. a) Aerobic oxidation of aminohydroquinone results in formation of dimeric species **11**, and b) additional approaches to regenerate quinone from reduced aminohydroquinone.[104]



Scheme 34. Catalytic oxidation of primary amines to aldehydes and ketones with PQQ promoted by micellar conditions.[105]



Scheme 36. Aerobic oxidation of primary amines to imines with biomimetic *o*-quinone catalyst TBHBQ.[110]



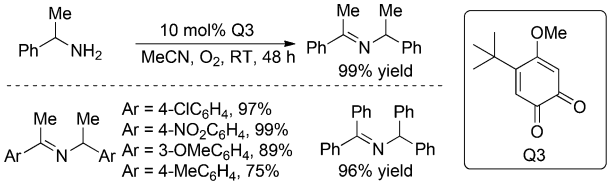
Scheme 35. a) Electrochemical oxidation of amines to imines[107] and b) secondary amines,[108] by CAO mimics $Q1^{red}$ and $Q2^{red}$. c) When Cu^{I} is added as a co-catalyst, the aerobic oxidation of primary amines is also achieved.[109]

(Scheme 35a). Good catalyst turnover numbers could be obtained, but the products had to be isolated as dinitrophenyl hydrazones. To address this limitation, Largeron et al. generated cross-coupled imine compounds by carrying out the oxidation of benzylamine in the presence of a second, less-readily oxidized, amine. After electrolysis, the Pt anode is replaced with a Hg pool cathode. Electrolysis at −1.6 V for 1 h reduces the cross-coupled imines to secondary amines, which could be isolated after workup (Scheme 35b).[108]

Largeron and Fleury later showed that the $Q2^{red}$ catalyst is effective in aerobic oxidation reactions. Primary amines undergo efficient aerobic oxidation at room temperature under ambient air in the presence of 2 mol% $Q2^{red}$ and 0.2 mol% Cu^{I}(MeSal) (MeSal = methylsalicylate) as a co-catalyst.[109] Dimeric and cross-coupled imine products were obtained in excellent yields (Scheme 35c).

Wendlandt and Stahl have demonstrated the aerobic oxidation of diverse benzylic amines to the corresponding secondary imines using TBHBQ,[110,111] a model quinone initially developed by Mure and Klinman[83] (Scheme 36). Selective cross-coupling products could be obtained by running the reaction in the presence of a second, unactivated (and nonreactive) amine. The homocoupled benzylamine-derived imine is formed at early stages of the latter reactions; however, imine exchange under the reaction conditions enables full oxidation of the benzylamine and selective formation of the cross-coupled product.

Unbranched amines are readily oxidized by $Q1^{red}$, $Q2^{red}$, and TBHBQ, but these catalysts react poorly with α-branched substrates. Luo and co-workers recently reported that branched benzylic primary amines are readily dehydrogenated to imines by 4-methoxy-5-*tert*-butyl-*o*-quinone (Q3).[112] Excellent yields of dimeric imine products were obtained using 10 mol% Q3 at room temperature under an O_2 atmosphere (Scheme 37).

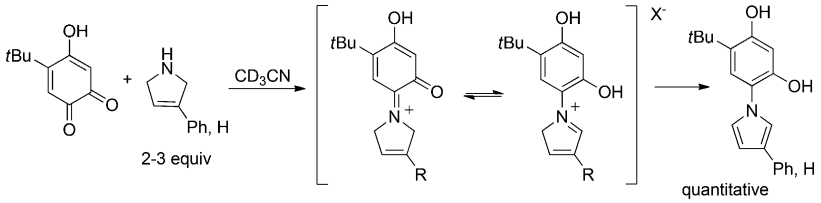


Scheme 37. Aerobic oxidation of α-branched primary amines to imines by using the biomimetic *o*-quinone catalyst Q3.[112]

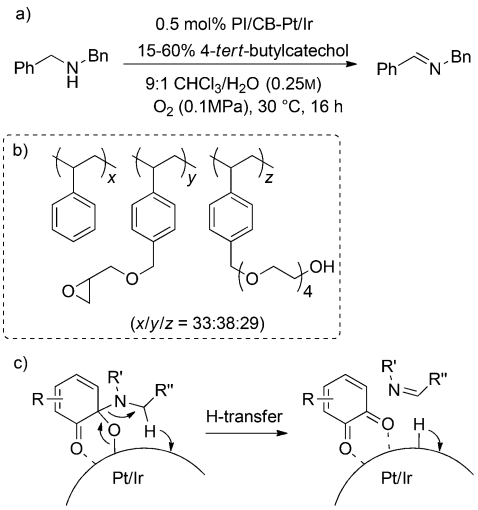
$Q1^{red}$, $Q2^{red}$, and TBHBQ are also not effective for the dehydrogenation of secondary and tertiary amines, nor are primary alcohols oxidized under the reaction conditions. These limitations are beneficial for chemoselective oxidation reactions, but they also limit the scope. The exquisite selectivity for primary amines can be rationalized by the transamination mechanism, in which oxidation of the substrate involves formation of an imine adduct. Secondary amines have been shown to be mechanism-based inhibitors of quinones such as TBHBQ.[113] In these cases, the iminium adducts are precursors to the irreversible modification of the catalyst (Scheme 38).

In principle, quinone-catalyzed dehydrogenation of secondary and tertiary amines would be possible if the reaction proceeded by an addition-elimination, rather than a transamination, mechanism (cf. Scheme 26). Thus, a shift between these two mechanistic pathways has important implications for the reaction scope.

Kobayashi and co-workers reported a method for the aerobic dehydrogenation of amines with 0.5 mol% of a block copolymer-incarcerated Pt/Ir alloy catalyst in combination with 15–60 mol% catechol as a co-catalyst (Sche-



Scheme 38. Irreversible pyrrolation of TBHBQ catalyst by a transamination-type mechanism is observed when 3-pyrroline substrates are used.[113]

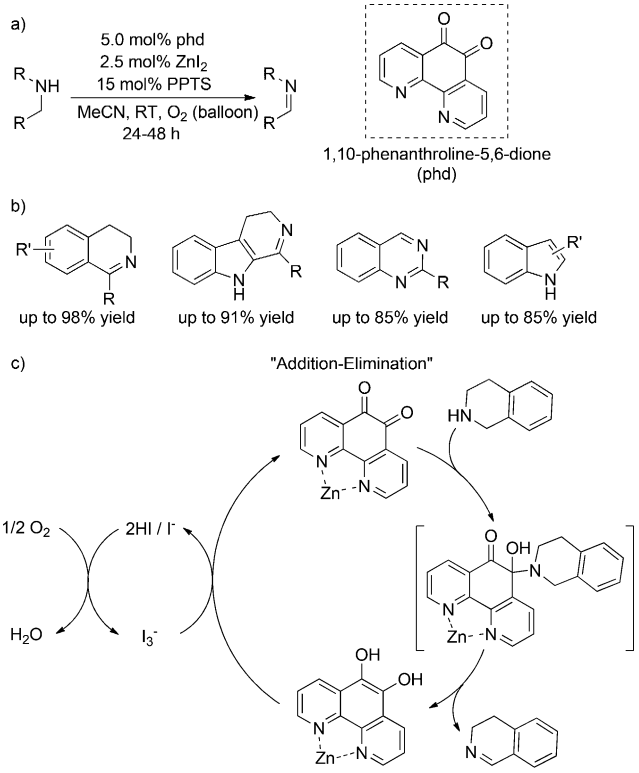


Scheme 39. a) Dehydrogenation of C–N bonds using a Pt/Ir alloy incarcerated block copolymer catalyst, b) used in combination with co-catalytic catechol additives. c) A mechanism is proposed wherein substrate oxidation by Pt involved quinone–substrate hemiaminal intermediates.[114]

me 39a,b).[114] Cleavage of the C–H bond of the amine was proposed to be mediated by the Pt/Ir nanocluster, but *o*-quinone was proposed to play a crucial role in activating the substrate. A hemiaminal intermediate, reminiscent of the addition-elimination mechanism, was proposed (Scheme 39c). Similar reactivity was reported recently by Doris and co-workers, who showed that Rh nanoparticles supported on carbon nanotubes (Rh-CNTs) are efficient co-catalysts with 4-*tert*-butyl-*o*-quinone for the aerobic dehydrogenation of N-heterocycles.[115]

The first definitive evidence for an addition-elimination pathway was reported by Wendlandt and Stahl, who used the PQQ model 1,10-phenanthroline-5,6-dione (phd). This catalyst was shown to mediate the aerobic dehydrogenation of secondary amines and a diverse range of N-heterocycles in the presence of co-catalytic quantities of ZnI_2 and pyridinium *p*-toluenesulfonic acid (PPTS; Scheme 40). The hemiaminal intermediate shown in Scheme 40c was observed and characterized by NMR spectroscopy.[116]

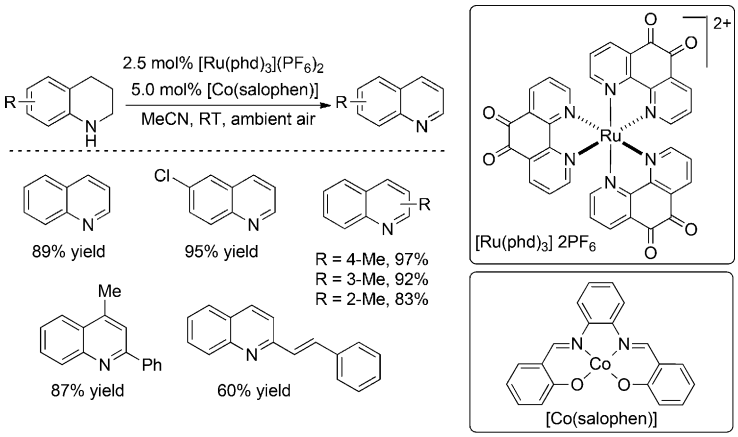
ZnI_2 plays two roles in this catalytic reaction. The coordination of phenanthroline nitrogen atoms to Zn^{2+} activates the quinone and enhances the rate of substrate oxidation. In addition, the iodide counterions serve as redox-active co-catalysts to promote aerobic turnover of the quinone catalyst (Scheme 40c). The origin of the shift in mechanism from transamination to addition-elimination is not fully understood, but this mechanism provides the basis for the significantly improved substrate scope, specifically allowing the dehydrogenation of a broad range of secondary amine based heterocycles.



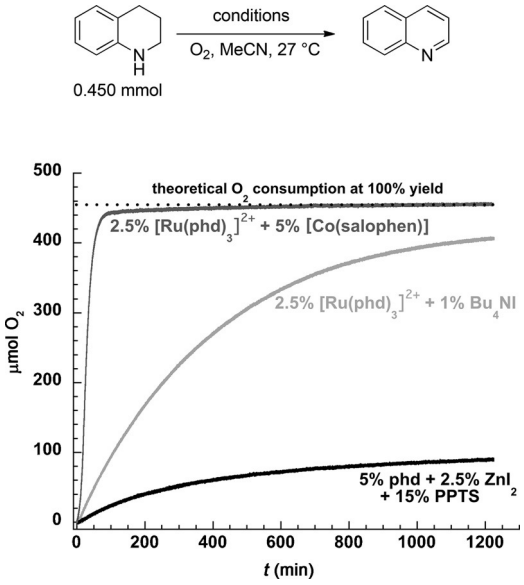
Scheme 40. a) Conditions for the aerobic phd-catalyzed oxidation of a variety of secondary amines (b). c) An "addition-elimination" mechanism is proposed with a hemiaminal intermediate.[116]

Wendlandt and Stahl used the modularity of the catalyst system to develop improved phd-based catalysts. For example, dehydrogenation of 1,2,3,4-tetrahydroquinolines to quinolines was not effective with the phd/ZnI_2 catalyst, but a broad range of quinoline products were obtained by using a $[Ru(phd)_3](PF_6)_2$ catalyst in combination with [Co(salophen)] as a co-catalyst (Scheme 41).[117] Changing the co-catalyst from I^-/I_3^- to [Co(salophen)] results in a marked improvement in the reaction rate (Scheme 42), and allowed the reaction to be carried out using ambient air rather than pure O_2. [Co(salophen)] has been widely used as a co-catalyst in aerobic redox chains, such as Pd-catalyzed oxidation reactions that use benzoquinone as a co-catalyst.[6–9]

PQQ and related phenanthroline-derived quinones, including phd and metal-phd complexes have seen extensive application in the aerobic and electrochemical oxidation of NADH to NAD^+[118,119] for synthetic enzymatic transformations,[120] as well as in applications as biosensors.[121,122]



Scheme 41. Dehydrogenation of tetrahydroquinolines to quinolines under ambient conditions with a co-catalyst system consisting of $[Ru(phd)_3](PF_6)_2$ and [Co(salophen)].



Scheme 42. Influence of different Lewis acid promoters and co-catalysts on the quinone-catalyzed aerobic dehydrogenation of tetrahydroquinoline to quinoline by phd and phd-coordinated Ru complexes. Adapted from Ref. [117].

4. Summary and Outlook

This Review has focused on two rather distinct classes of quinones and their use as catalysts for the selective oxidation of organic molecules. Quinones with a high reduction potential, such as DDQ and chloranil, often operate through hydride abstraction mechanisms and, therefore, typically react with electron-rich substrates capable of stabilizing carbocationic intermediates. Examples of single-electron transfer and addition-elimination reactions have also been implicated with these quinones. DDQ and related quinones with a high reduction potential are usually used as stoichiometric reagents, but significant progress has been made in the development of catalytic methods in which the quinone is used in combination with a more-desirable terminal oxidant. Methods compatible with O_2 as the stoichiometric oxidant have been developed, and the collective findings have important implications for the large-scale implementation of DDQ-based oxidation reactions.

The second class of quinones consists of *o*-quinone catalysts inspired by cofactors in enzymes that mediate amine dehydrogenations. This family of quinones has been shown to be compatible with electrochemical and aerobic catalytic turnover. Mechanistic studies show that these quinones engage in electrophilic reaction pathways such as transamination and addition-elimination mechanisms, which are quite different from the pathway commonly featured with DDQ and the quinones with high reduction potentials. Although the applications emphasize amine oxidation reactions, the synthetic scope has been expanded well beyond that known for the enzymes. The differences, which include the dehydrogenation of diverse heterocyclic secondary amines, arise primarily from the development of catalysts that operate through an addition-elimination, rather than the enzymatic transamination mechanism.

The bioinspired *o*-quinones have significantly lower reduction potentials than DDQ or chloranil, but their unique mechanisms introduce kinetically accessible pathways not readily available to the more-oxidizing *p*-quinones (see Scheme 29). These observations hint towards a broader, but still largely unexplored, opportunity to achieve catalyst control within quinone-mediated transformations. The differences in reactivity between DDQ and chloranil are typically rationalized on the basis of their differential reduction potentials, but many of the findings discussed herein and elaborated elsewhere in the literature[37,85a] suggest that reactivities observed across diverse quinone structure types do not exhibit simple linear free-energy correlations. Instead, reactivity is closely linked to the reaction pathways accessible to the different quinone structures. The ability to exploit different reaction pathways will benefit from closely coupling reaction development efforts with mechanistic studies of new catalytic reactions.

Finally, the results summarized herein highlight the ability to use quinones as catalysts, rather than stoichiometric reagents. The use and/or development of new co-catalysts that enable efficient catalytic turnover with O_2 as the terminal oxidant has important implications for "green" large-scale applications of quinone-catalyzed oxidations of organic molecules.

Acknowledgements

We thank the NIH (R01-GM100143) for financial support of our work on catalytic dehydrogenation reactions.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14638–14658
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Received: June 2, 2015
Published online: November 4, 2015