Green Chemistry

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Cite this: DOI: 10.1039/c0xx00000x

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COMMUNICATION

A mild and highly efficient laccase-mediator system for aerobic oxidation of alcohols

Chenjie Zhu,[a,b] Zhi Zhang,[a,b] Weiwei Ding,[a,b] Jingjing Xie,[a,b] Yong Chen,[a,b] Jinglan Wu,[a,b] Xiaochun Chen,[a,b] and Hanjie Ying*[a,b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

With the aid of the highly active nitroxyl radical AZADO (2-azaadamantane *N*-oxyl), a simple method for the aerobic catalytic oxidation of alcohols is presented. The oxidations could typically proceed under practical ambient conditions (room temperature, air atmosphere, no moisture effect, and metal-free, etc.) with a broad generality of the alcohol substrates, and especially for the oxidation of complex and highly functionalized alcohols. An ionic mechanism is proposed for the present system.

The selective oxidation of alcohols to the corresponding carbonyl compounds is a fundamental transformation both in laboratory synthesis and industrial production.[1] Numerous oxidizing reagents in stoichiometric amounts have been traditionally employed to accomplish this transformation with considerable drawbacks such as the use of expensive reagents, volatile organic solvents, and discharge of environmentally pernicious wastes. Recent growing environmental concerns have spurred research activities directed toward the development of greener oxidation methods in which the use of molecular oxygen as the terminal oxidant has been drawn considerable attention.[2]

On the other hand, enzyme-catalyzed transformations have emerged as an elegant synthetic methodology that allows the development of eco-friendly processes within the basic principles of green chemistry.[3] The development of enzyme-catalyzed oxidations are highly attractive because of their great potential to remove pollutants and catalyse a great variety of redox processes with no hazardous side effects.[4] Furthermore, most enzymatic oxidations usually use aerial oxygen as terminal oxidant, and can be performed under very mild reaction conditions. In this context, laccase (benzenediol:oxygen oxidoreductase, EC 1.10.3.2), a blue multi-copper oxidase, has drawn considerable attention in white biotechnology. As a result of their nontoxic nature, high stability, and lack of substrate inhibition, laccases are nowadays ideal candidates in the fields of waste detoxification, textile dye transformation, biosensors, food industry, and pulp bleaching.[5] The demand for green chemical processes has also inspired interest in the application of this enzyme to address modern synthetic organic chemistry challenges. Due to their broad substrate scope, laccases find increasing significance in a variety of organic synthetic methodologies and the manufacture of synthetic building blocks for fine chemistry.[6]

Despite the synthetic importance of laccases, their broader application has been restricted due to the low redox potential (typically about 0.5-0.8 mV vs. the normal hydrogen electrode).[6a] For the reactions where the substrate to be oxidized has a redox potential higher than laccase, or the substrate is too large to penetrate into the enzyme active site, the presence of a low-molecular weight chemical mediator is required to facilitate oxidative reactions.[7] A mediator acts as a sort of 'electron shuttle', once it is oxidised by laccase, it diffuses away from the enzymatic pocket and in turn oxidises any substrate that, due to its size, could not directly enter the enzymatic pocket.[8] The structures and abbreviated names of representative artificial laccase mediators are given in Fig. 1. By using these so-called 'chemical mediators', the redox potential of laccases can be extended which allow the oxidation of a wide range of

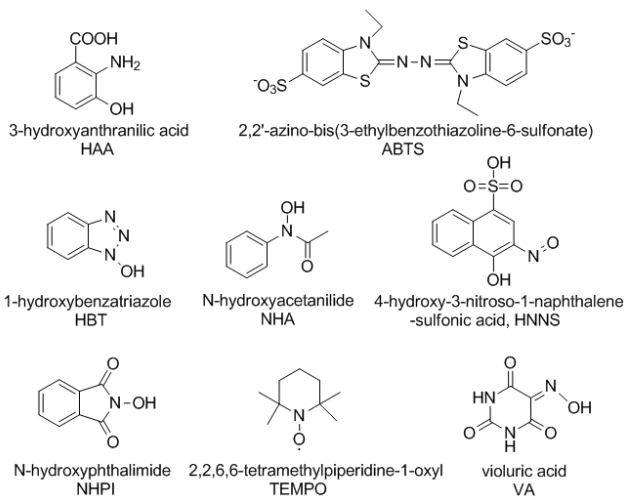


Fig. 1 Structures of representative artificial laccase mediators.

[a] *College of Biotechnology and Pharmaceutical Engineering, Nanjing University of Technology, Xin mofan Road 5, Nanjing 210009, China. E-mail: yinghanjie@njut.edu.cn, zhucj@njut.edu.cn Fax: 86 25 58139389; Tel: 86 25 86990001*
[b] *National Engineering Technique Research Center for Biotechnology, Nanjing, China*

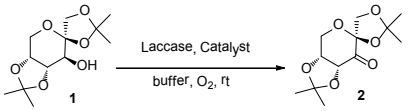
† Electronic Supplementary Information (ESI) available: General experimental procedures and compound characterization data including ^{1}H and ^{13}C NMR. See DOI: 10.1039/b000000x/

non-phenolic substrates, such as sugars,[9] ethers,[10] alkenes,[11] amides,[12] aromatic methyl groups,[13] polycyclic aromatic hydrocarbons,[14] lipids,[15] and alcohols.[16] Despite all the associated advantages of using these mediators, there still have several drawbacks from a practical point of view. These are, i) low catalytic efficiency, excess amounts of mediator (typically 30 mol% on substrate) are needed, some even need more than 1 equiv; ii) in some cases, laccase is inactivated by the mediator radicals, or the latter can be transformed into inactive compounds with no more mediating capability (e.g. generation of benzotriazol from HBT by losing the hydroxyl group); iii) some of mediators can generate toxic derivatives; iv) long reaction time are usually required. In view of the aforementioned drawbacks of existing routes and the desire for aerobic oxidation of multifunctionalized complex molecules, the development of new and highly efficient laccase-mediator system is particularly attractive.

In continuation of our efforts to exploration of green approaches for synthetic chemistry,[17] we report herein a new and highly efficient laccase-mediator system for the oxidation of alcohols using O_2 as a green and economic oxidant under mild reaction conditions.

Initial experiments was carried out using 1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose **1** as a model substrate, the corresponding product ketone **2** (1,2:4,5-di-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexadiulo-2,6-pyranose, Shi's catalyst) is a useful reagent, which often used as a precursor for transition metal free catalytic asymmetric olefin epoxidation.[18] Catalytic oxidation of **1** has proved particularly difficult, numerous methods such as TPAP-O_2 system,[19] NHPI-O_2 system,[20] Pd(bathophenanthroline)-$(AcO)_2$-O_2 system,[21] which were successfully applied to oxidation of alcohols, failed to convert **1** to **2** due to the steric reason. In the laccase catalysed aerobic oxidation of alcohols, TEMPO and its derivatives proved to be the most effective.[22] However, using TEMPO as the catalyst, the yield of **2** was less than 10% (Table 1, entry 1). The low catalytic efficience of TEMPO as well as recent significant advances in designing the structure of nitroxyl radicals[23] prompted us to reconsider the TEMPO catalyst and provided an opportunity of using a more reactive mediator for laccase. We were very pleased to find that in the case of using AZADO (2-azaadamantane *N*-oxyl) as a catalyst, desired product was obtained in 63% yield (Table 1, entry 2). In the control experiments, there were no products formation in the absence of laccase, AZADO, or using heat-killed laccase (see Table S1 in the Supporting Information). With the aim of finding an appropriate mediator for laccase, we evaluated the catalytic performance of other nitroxyl radicals (Table 1, entries 3-5). Among them, Nor-AZADO (9-azanoradamantane *N*-oxyl) shows comparable catalytic activity to AZADO, serve as another good catalyst to enhance the reaction remarkably. However, the catalytic activity of ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl) and ABOO (8-azabicyclo[3.2.1]octane *N*-oxyl) is much lower than AZADO, probably due to the stability of the corresponding cations.[23b, 24] Encouraged by these results and in order to search for the optimum reaction conditions, we screened a variety of parameters of this reaction, such as different source of laccase, the type and pH of buffer and a broad range of co-solvent (for more details see Table S2 in the Supporting Information).

Table 1 Optimiaztion studies for the aerobic oxidation of **1**[a]



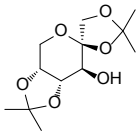
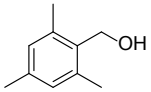
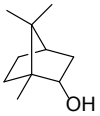
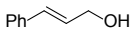
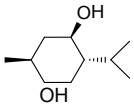
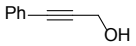
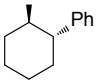
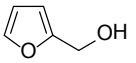
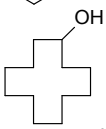
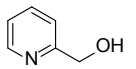
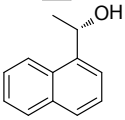
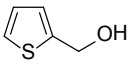
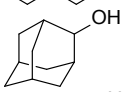
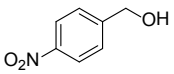
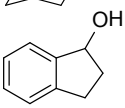
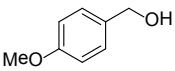
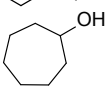
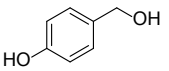
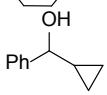
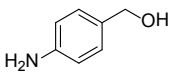
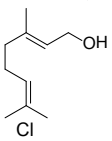
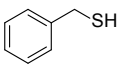
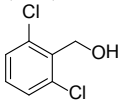
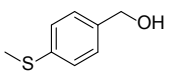
Entry	Catalyst	Equiv	Additive	Yield(%)[b]
1	TEMPO	0.2	--	7
2	AZADO	0.2	--	63
3	Nor-AZADO	0.2	--	60
4	ABNO	0.2	--	46
5	ABOO	0.2	--	29
6[c]	AZADO	0.2	CTAB	66
7[d]	AZADO	0.2	SDS	52
8[e]	AZADO	0.2	Tween-20	67
9[f]	AZADO	0.2	Rhamnolipid R_1	55
10[g]	AZADO	0.2	$PhCF_3$	87(85)
11	AZADO	0.1	$PhCF_3$	85
12	AZADO	0.05	$PhCF_3$	80
13[h]	AZADO	0.05	$PhCF_3$	82

[a] Reactions were performed by using **1** (1 mmol), laccase (40U), nitroxyl radical in acetate buffer (pH 4.5) under O_2 atmosphere at room temperature for 12h unless otherwise noted. [b] Yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] CTAB (cetrimonium bromide, 0.2 equiv) was used. [d] SDS (sodium dodecylsulfate, 0.2 equiv) was used. [e] Tween-20 (sorbitan monooleate ethoxylate, 0.1 g) was used. [f] Rhamnolipid R_1 (3-(3-[(6-deoxy-alpha-L-mannopyranosyl) oxy] decanoyl oxy) decanoic acid, 0.1 g) was used. [g] $PhCF_3$ (1 mL) was used as co-solvent; Isolated yield is shown in parenthese. [h] This reaction was run using air as oxidant for 24h.

It is well known that in aqueous-phase reactions, addition of surfactants can improve the reactions by solubilization or micelle formation effect. To improve the solubility of the reactant and catalyst in the buffer, we examined a variety of surfactants, including cationic, anionic, nonionic, and biological surfactants (Table 1, entries 6-9). However, all of them were unsatisfactory although CTAB and Tween-20 showed a slight improvement. Further investigation of co-solvent on this reaction showed that a strong solvent dependence effect. Earlier studies revealed that laccase are often deactivated by organic solvents.[25] A broad range of co-solvents were tested for this reaction (see Table S2 in the Supporting Information), among them, $PhCF_3$ was proved to be the most efficient co-solvent, giving the highest yield of **2** (Table 1, entry 10). Further study showed that co-solvent was not necessary for the reaction, for most reactant, the use of buffer as solvent was effective enough to complete the oxidation. With regard to the AZADO dosage, it was possible to decrease the amount of AZADO to as low as 0.05 equiv without a significant loss in catalytic efficiency (Table 1, entry 12). Notably, the reaction can also proceed smoothly even using air as oxidant, albeit a longer reaction time was required (Table 1, entry 13).

With the aim to develop and define the scope and limitation of the present method, this laccase-AZADO catalytic oxidation system was then extended for the oxidation of a wide range of alcohols, including benzylic, allylic, heterocyclic, alicyclic, and aliphatic alcohols (Method A in Table 2). Using a similar strategy, the laccase-TEMPO system was also applied for the purpose of comparison (Method B in Table 2).

Table 2 Green and selective oxidation of alcohols

Entry	Alcohols	Method[a]	Yield(%)[b]/Time	Entry	Alcohols	Method	Yield(%)/Time
1[c]		A B	85/12h 7/12h[d]	13		A B	82/24h(87/6h[g]) 45/24h
2		A B	92/12h 61/24h	14		A B	92/6h 90/12h
3[c]		A B	84/12h(80/24h[e]) 5/36h[d]	15		A B	79/6h 71/12h
4[c]		A B	90/12h 23/24h	16		A B	92/6h 85/6h
5		A B	72/12h 35/24h	17		A B	86/12h 80/12h
6		A B	92/8h 73/12h	18		A B	94/6h 87/6h
7[c]		A B	90/8h 67/12h	19[c]		A B	93/6h 90/6h
8		A B	88/8h 65/12h	20		A B	98/4h 96/4h
9		A B	76/12h 47/24h	21		A B	--[h]
10		A B	93/8h 85/12h	22		A B	--[i]
11[f]		A B	89/12h 72/12h	23		A B	--/8h[j] --/8h
12[c]		A B	78/24h 22/24h	24		A B	94/6h 88/8h

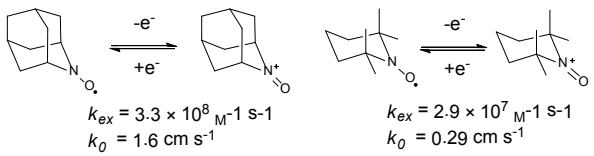
[a] Method A: laccase-AZADO system. Method B: laccase-TEMPO system. [b] Isolated yields unless otherwise noted. [c] The reaction was carried out in the presence of $PhCF_3$ as co-solvent. [d] Yield was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [e] Yield of large-scale synthesis on a 100 mmol scale. [f] Yield was determined by GC-MS. [g] 20 mol % AZADO was used. [h] Formation of black tar was observed in this reaction. [i] The reaction mixture was too complex to identify. [j] Unchanged substrate is recovered (91%).

As shown in Table 2, most alcohols underwent oxidation to afford the corresponding carbonyl products in excellent yields. The present laccase-AZADO system afforded aldehydes from primary alcohols and ketones from secondary alcohols. Excellent chemoselectivity was observed under the present system. For the oxidation of primary alcohol, no noticeable over-oxidation of aldehyde to carboxylic acid was detected. As the functional groups, several oxidation-sensitive alkenes, electron-rich aromatic, heteroaromatic rings, halogens, and alkyne groups were also tolerated during the reactions. Notably, 2,6-dichlorobenzyl alcohol and 2,4,6-trimethylbenzyl alcohol, which often resist oxidation using laccase-mediator system due to the steric hindrance effect,[16b] were also readily oxidized to the corresponding aldehydes in high yields (Table 2, entries 12 and 13). However, the oxidation of 4-hydroxybenzyl alcohol and 4-aminobenzyl alcohol were not successful, which may be due to laccase oxidizes -OH or $-NH_2$ group by inducing dimerisation and oligomerization through the intermediacy of resonance-

stabilized radicals (Table 2, entries 21 and 22). Oxidation of benzyl mercaptan was also not successful, no oxidation to benzaldehyde was detected, in spite of its structural analogy with benzyl alcohol (Table 2, entry 23). Free thiol group (-SH) have been shown to be potent inhibitor of laccases, presumably via co-ordination of the thiol to the copper atoms in the enzyme active site.[7c] Even so, the present laccase-AZADO system still has enough activity to oxidation of thioether-containing molecules, thioanisaldehyde was produced from the corresponding alcohol with a high yield (94%) (Table 2, entry 24), this is a very selective reaction with no sulphoxide, sulphone, or Dakin-type (phenols) by-products being produced.

To assess the feasibility of using this method on a preparative scale, the multigram-scale catalytic system was then examined for the oxidation of menthol on a 100 mmol scale. As expected, the reaction proceeded smoothly, similar to the smaller-scale case, and the desired menthone was obtained in 80% isolated yield (Table 2, entry 3).

The different catalytic activities between laccase-AZADO and laccase-TEMPO system observed in Table 2 can not be explained simply on the basis of redox potential of the nitroxyl radicals. TEMPO and AZADO produced electrochemically reversible responses with redox potentials at 294mV and 236mV versus Ag/AgCl, respectively.[23h] However, the T1 copper centre in laccase from *Trametes versicolor* has a redox potential of ca. 790mV versus NHE.[22b, 26] Consequently, laccase from *Trametes versicolor* has sufficient oxidation potential to convert TEMPO or AZADO into their corresponding oxidised state. The different catalytic reactivity between TEMPO and AZADO seems to appear another rule, that is, the lower the redox potential, the easier the oxidation into the corresponding oxoammonium species by laccase, the higher catalytic activity. To check this point, the experiments on the reaction rate were carried out using TEMPO, AZADO, 1-Me-AZADO and 1,3-dimethyl-AZADO as catalysts. As shown in Fig. 2, the catalytic activities of these nitroxyl radicals are in the order of AZADO > 1-Me-AZADO > 1,3-dimethyl-AZADO > TEMPO. However, the E^{o}' values (vs Ag/Ag^{+}) of these nitroxyl radicals are in the order of TEMPO (294 mV) > AZADO (236 mV) > 1-Me-AZADO (186 mV) > 1,3-dimethyl-AZADO (136 mV).[23a] No obvious correlation between the two orders is found. Thus, we believe that another factor that affects catalytic activity is due to the steric hindrance effect, compared to TEMPO or 1,3-dimethyl-AZADO, in which the oxygen-centered unpaired electron is sterically protected by the surrounding four or two methyl groups, the α-hydrogen of AZADO furnishes a less hindered reaction center, thereby enabling smooth contact between the active species due to the reduced steric hindrance effect, this influence is more obvious in the oxidation of sterically hindered alcohols (Table 2, entries 1-4, 12, 13).



Scheme 1 One-electron transfer redox reaction of nitroxyl radicals.

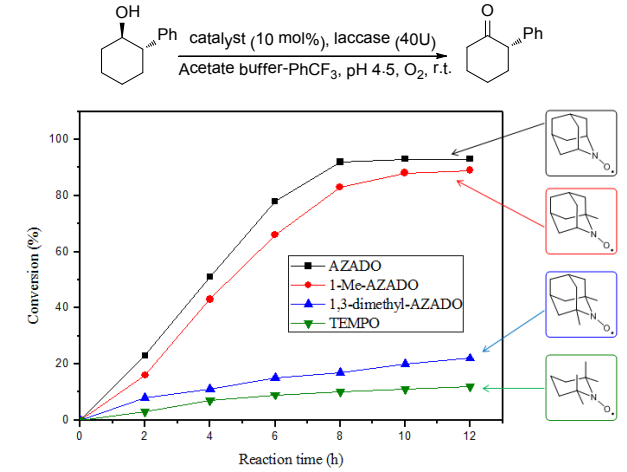
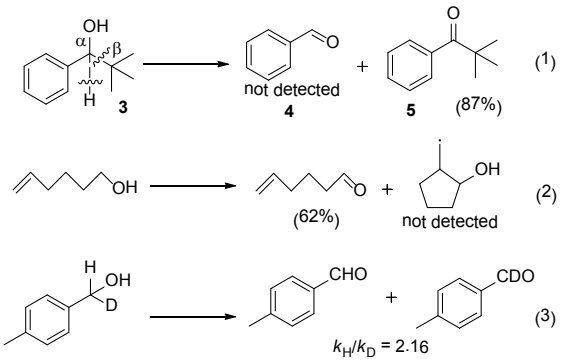


Fig. 2 Comparison of the catalytic activity of AZADO, 1-Me-AZADO, 1,3-dimethyl-AZADO, and TEMPO.

In contrast to the redox potential, the energy level, or the chemical structures of the mediator, little attention has been paid to the kinetic features of the redox mediator during oxidative regeneration or electron self-exchange reaction among mediator molecules. These differences between AZADO and TEMPO may be the other important factors that affect the catalytic activity. Recently, the electrochemical and spectroscopic properties of these nitroxyl radicals were measured by Nishide group.[27] According to their report, the electron self-exchange reaction rate constant (k_{ex}) of AZADO is about 3.3×10^{8} $_{M}^{-1}$ s^{-1}, which is 10 times higher than that of TEMPO (2.9×10^{7} $_{M}^{-1}$ s^{-1}) (Scheme 1). In addition, the heterogeneous electron-transfer rate constant (k_0) of AZADO and TEMPO is 1.6 and 0.29 cm s^{-1}, which is an important parameter indicating how fast the regeneration reaction of the mediator cation. The significantly faster regeneration and self-exchange reaction rate of AZADO are expected to responsible for its excellent catalytic activity through smooth contact and easier oxidized by laccase.

The mechanistic details of laccase-mediator catalyzed aerobic oxidation system are still unclear.[28] However, they are generally believed to involve one electron oxidation of the mediator by the oxidized form of laccase (cupric of T1 site in laccase), followed by the reaction of oxidized mediator with the substrate, either via radical hydrogen-atom transfer route (HAT) which suggested for laccase-HBT, laccase-NHPI, and laccase-VA system, or via electron transfer route (ET) which suggested for laccase-ABTS system, or via ionic oxidation route which suggested for laccase-TEMPO system. To shed light on the reaction pathway of the present laccase-AZADO system, we conducted the following experiments (Scheme 2). We first treated 2, 2-dimethyl-1-phenyl-1-propanol **3** with the present laccase-AZADO system. Under ET route, oxidation of **3** will produce benzaldehyde **4** and *tert*-butyl radical by C_{α}-C_{β} bond cleavage. Conversely, under HAT route, **3** undergo cleavage of the C_{α}-H benzylic bond, and produces ketone **5**. This clear-cut behaviour makes **3** as a useful model substrate, enabling it to assess the oxidation mechanism from product analysis.[28b,e, 29] Result shown that the ketone **5** was the only product produced from the laccase-AZADO system, thereby suggesting the reaction pathway does not involve the ET route.

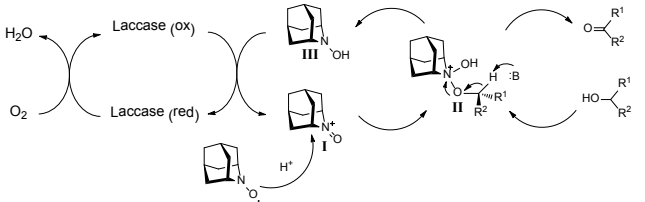


Scheme 2 Oxidation with laccase-AZADO system.

Further experiment was using 5-hexen-1-ol as a probe substrate, oxidation of 5-hexen-1-ol with laccase-AZADO system produced only 5-hexen-1-al. In case of HAT route, removal of α-H to the hydroxy group is known to afford cyclopentyl alcohol through intramolecular radical rearrangement.[29a, 30] The absence of rearrangement product confirms that the present laccase-AZADO system also does not follow the HAT route.

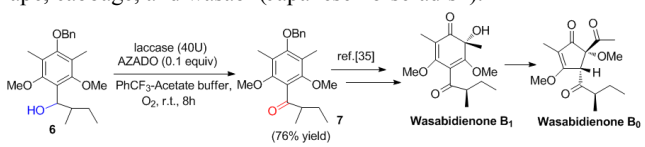
We determined the intramolecular kinetic isotope effect in the oxidation of a suitably synthesized α-monodeutero-*p*-methylbenzyl alcohol[31] using Sheldon's method.[32] The kinetic isotope effect (k_H/k_D value) for the laccase-AZADO catalysed aerobic oxidation of this alcohol at room temperature was determined to be 2.16 by ^{1}H NMR. This value is much lower than those obtained for laccase-NHA system (6.2), laccase-HBT system (6.4), and laccase-VA system (6.4),[7a] which are expected for HAT route. However, this value is in the range found for the stoichiometric oxidation of benzyl alcohols by the oxoammonium ions (1.7-3.1)[33] and compares exceptionally well with the isotope effect observed with laccase-TEMPO system (2.32).[22b] As a further proof, the AZADO oxoammonium chloride AZADO$^+$Cl$^-$ was synthesized ex-situ[23k] and used as a stoichiometric oxidant to oxidise α-monodeutero-*p*-methylbenzyl alcohol. The KIE value for AZADO$^+$Cl$^-$ oxidation of this alcohol was determined to be 2.11, which is much close to that obtained from laccase-AZADO system (2.16). The similar kinetic isotope effects strongly suggests that oxoammonium cation AZADO$^+$ was generated during the reaction, the oxoammonium ion oxidizes alcohol via a ionic route which is similar to the proposed mechanism for laccase-TEMPO system.[28]

On the basis of all of the aforementioned results, an ionic oxidation mechanism is suggested for the present laccase-AZADO system (Scheme 3). In this route, one electron oxidation of AZADO affords the oxoammonium cation (**I**), a nucleophilic attack of the lone-pair of alcohol onto the oxoammonium cation takes place to form an adduct (**II**), deprotonation of the adduct either via intramolecularly (from N-O$^-$) or via intermolecularly (from the base in the buffer, i.e. B),[34] gives the carbonyl product and the hydroxylamine (**III**). Laccase oxidises the hydroxylamine to regenerate AZADO, and further oxidation leads to the oxoammonium cation. Beyond that, the oxoammonium cation (**I**) also can be restored through acid-induced disproportionation of AZADO.[23f] The laccase is finally re-oxidised by oxygen, thereby completing this green catalytic cycle.



Scheme 3 Suggested mechanism for laccase-AZADO catalyzed aerobic oxidation

One of the applications of the present green laccase-AZADO system is to synthesize 1-(4-(benzyloxy)-2,6-dimethoxy-3,5-dimethylphenyl)-2-methylbutan-1-one (**7**). Oxidation of 1-(4-(benzyloxy)-2,6-dimethoxy-3,5-dimethylphenyl)-2-methylbutan-1-ol (**6**) has proved difficult due to the steric hindrance effect. Quideau group reported the successful oxidation of **6** to **7** using stabilized IBX (3 equiv) in THF-DMSO solution.[35] However, this method involves use of expensive and excess amounts of oxidant. In the case of using laccase-AZADO system, desired product **7** was obtained in 76% yield (Scheme 4). **7** is precursor to synthesize natural products wasabidienone B_1 and wasbidienone B_0. These fungal polyketides were isolated in 1980s by Soga and co-workers from a potato culture of *Phoma wasabiae* Yokogi, a fungus responsible for the blackleg disease causing widespread destruction among cruciferous crops such as rape, cabbage, and wasabi (Japanese horseradish).[36]



Scheme 4 Synthesis of wasabidienone B_1 and wasbidienone B_0

In conclusion, a new and highly efficient mediator of laccase has been comparatively evaluated, with the aid of the highly active nitroxyl radical AZADO, a simple green method for the aerobic catalytic oxidation of alcohols is presented. The advantages of this catalytic oxidation system are summarized as follows: 1) Avoids the use of transition metal catalyst; 2) Highly atom economy and environmental consciousness, the only by-product is H_2O; 3) Mild reaction conditions (room temperature, air atmosphere, and no moisture effect). Moreover, the present non-transition metal catalytic system also provides an easy scale-up and separation protocol.

Experimental

Laccase from *Trametes versicolor*, *Rhus vernicifera*, and *Agaricus bisporus* were purchased from Sigma-Aldrich as light brown lyophilized powder and used without modification. Nor-AZADO, ABNO and ABOO were synthesized according to reported procedures.[23b,c] Other reagents were ACS reagent grade and used without further purification. NMR spectra were recorded on a Bruker Ascend 400 MHz NMR spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Chemical shifts are reported in parts per million (ppm). ^{1}H and ^{13}C chemical shifts are referenced relative to the tetramethylsilane. GC-MS were recorded on a Thermo Trace DSQ GC-MS spectrometer using a TRB-5MS (30 m×0.25 mm×0.25 mm) column. ESI-MS were recorded on a Thermal Finnigan TSQ Quantum ultra AM spectrometer using a TRB-5MS (30 m×0.25 mm×0.25 mm)

column. Melting points were determined in an open capillary tube with a Mel-temp II melting point apparatus. Infrared spectra were recorded as a KBr pellet on a Perkin-Elmer 1600 series FT-IR spectrophotometer.

General experimental procedure for green oxidation of alcohols using laccase-AZADO system (Table 2): To a stirred solution of alcohol (1 mmol), AZADO (0.1 mmol) in acetate buffer (0.2 M, pH 4.5, 5mL), laccase from *Trametes versicolor* (4 mg, 10U/mg) was then added. In case of some solid water insoluble substrates, $PhCF_3$ (1 mL) was added. The solution was stirred at room temperature under oxygen atmosphere (balloon) for several hours while checking the reaction progress by using gas or thin-layer chromatography. After completion, the mixture was extracted with diethyl ether (3×5 mL). The organic phase was concentrated under vacuum and the crude product was purified by column chromatography (hexane:EtOAc = 10:1) to provide the analytically pure product, which was characterized by ^{1}H NMR, ^{13}C NMR and GC-MS. The supporting information provides details of these measurements.

Acknowledgements

The work was supported by the National Science Fund for Distinguished Youth Scholars (Grant No.: 21025625); Program for Changjiang Scholars and Innovative Research Team in University (Grant No.: IRT1066); National High-Tech Research and Development Plan of China (863 Program, 2012AA021201); The Major Research plan of the National Natural Science Foundation of China (Grant No. 21390204).

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Textual abstract for the table of content:

A mild and efficient system for enzyme laccase-catalyzed aerobic oxidation of alcohols has been developed with the aid of the highly active nitroxyl radical AZADO.

Graphical abstract for the table of content: