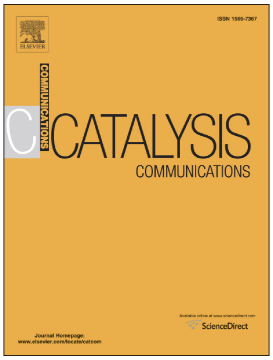

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Laccase-TEMPO as an efficient catalyst system for metal- and halogen-free aerobic oxidation of thioethers to sulfoxides in aqueous media at ambient conditions

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ABSTRACT

We present for the first time an eco-friendly procedure for the aerobic oxidation of thioethers to sulfoxides using laccase-TEMPO catalyst system. This catalyst system allows for simpler (easy work-up) and greener methodologies (room temperature, phosphate buffer) while keeping high reaction yields and selectivity. This work is superior to others due to free from any transition metal and halide co-catalysts.

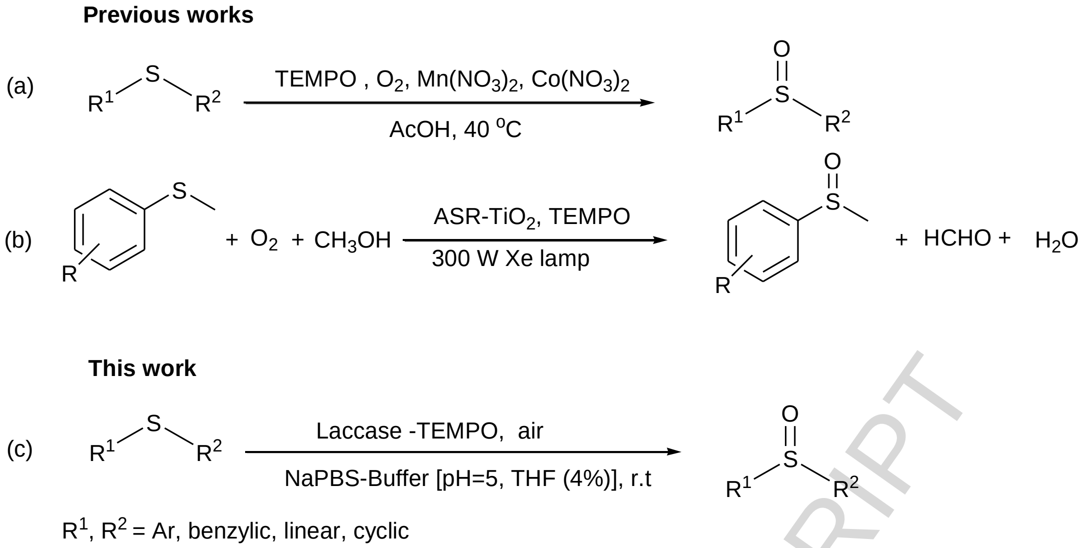
Keywords**:** laccase-mediator, aerobic oxidation, thioethers, sulfoxides

1. Introduction

Green chemistry is a philosophy of chemical research that encourages the design of green processes employing safe catalysts, minimizing the generation of hazardous substances, replacing toxic solvents with H_2O, and using O_2 or air as environmentally benign oxidant [1]. Green catalysis is one of the most important subchapters of green chemistry. In this context, the employing of enzymes as safe and biodegradable catalysts offer many benefits since biocatalytic reactions can be performed under mild conditions [2]. Laccases, multi-copper-containing oxidoreductase enzymes [3], are highly attractive biocatalysts in modern organic synthesis, they catalyze the oxidation of various compounds such as benzenediols, aminophenols, polyphenols, polyamines, and lignin-related molecules using oxygen as an electron acceptor and producing water as by-product [4-7]. The most efficient strategy to extend the range of laccase substrates is the simultaneous use of the enzyme and redox mediators [8-11].

The selective oxidation of thioethers into the corresponding sulfoxides is one of the most important reactions in organic synthesis since sulfoxides are useful intermediates for the construction of important organic compounds. Also many biologically important molecules have a sulfoxide functional group [12-13]. For these reasons, a large number of catalysts (homogeneous and heterogeneous catalysts) and stoichiometric amounts of oxidants have been reported for the synthesis of chiral and achiral sulfoxides [14-19]. Disadvantages of these methods include poor atom efficiency, utilization of environmentally unfavorable reagents, solvents, and catalysts, and the formation of large amounts of toxic waste.

There is substantial interest towards the use of molecular oxygen or air as the highly atom-economical, environmentally benign, and abundant oxidant in the oxidation of thioethers to the sulfoxides in the presence of catalysts [20-22]. Although these methods have been developed considerably, these procedures suffer from some problems such as the preparation of complex catalysts, removal or recovery of the expensive catalyst, and the use of toxic organic solvents. In addition, they may possibly leave toxic traces of heavy metals in the products. Therefore, the development of green and non-metallic catalysts such as organic oxidizing agents [23-24] for the aerobic oxidation of sulfides is still desirable and is in demand. Of particular interest in this area is the application of the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in combination with various types of non-metallic, stoichiometric co-oxidants such as *m*-chloroperbenzoic acid, sodium hypochlorite or sodium periodate as an alternative to metal-based oxidants [26-27]. Accordingly, the use of TEMPO-based catalyst systems in combination with transition metals as co-catalysts has been well documented for the oxidation of thioethers to sulfoxides using molecular oxygen as terminal oxidant. Typical examples include i) the use of Mn^{II}-Co^{II} dual metal catalysts and TEMPO as a co-catalyst under relative harsh conditions [28] (Scheme 1, eqn (a)) ii) the use of TEMPO as the redox mediator under visible-light-induced photoredox catalysis of dye-sensitized TiO_2 (Scheme 1, eqn (b)) [29]. Although these TEMPO-based catalyst presented an interesting breakthrough in the field of aerobic oxidation of thioethers, these methods still require transition metals as co-catalysts. It is vital to eliminate the catalyst (especially in pharmaceutical industry) because metal contamination is highly regulated. A potential approach to overcome this problem is to change the transition metal catalysts to safe catalysts such as biocatalysts for the aerobic oxidation of thioethers.



Scheme 1. Approaches to aerobic oxidation of thioethers

2. Experimental

The activity assays of commercial laccase from *T. versicolor*: The activity of laccase was determined spectrophotometrically with 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS, $\varepsilon = 36\,000\ M^{-1}.cm^{-1}$) as substrate (5 mM, 100 µL) in acetate buffer (100 mM, pH=5.0). The absorbance change was observed at 420 nm for 5 min at room temperature [30]. One unit of activity is defined as the amount of enzyme required to oxidize 1 µmol of ABTS per minute. The activity of laccase enzyme batch applied in this investigation was evaluated at 0.87 U/mg.

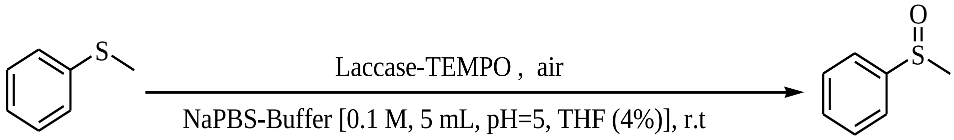
General Procedure for the aerobic oxidation of thioethers to sulfoxides catalyzed by laccase-TEMPO system

Thioether (1 mmol) and TEMPO (62.5 mg, 0.4 mmol) were added to a solution of laccase (17.4 mg, 20 U) in phosphate buffer (0.1 M, 5 mL, pH=5) and THF (4 vol%). The reaction mixture was stirred under air at room temperature for an appropriate time (see table 2). The progress was monitored by TLC (*n*-hexane/EtOAC, 4:1). After the completion of the reaction, the product was extracted with EtOAc (3 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and purification by column chromatography (*n*-hexane/EtOAc) gave the desired sulfoxide. All products were known and were identified by comparison their spectra and physical data with literature values (see supplementary material)

3. Results and discussions

In continuation of our research interest in the development of green and sustainable methods [31-33], herein, we present for the first time a simple and efficient method for the aerobic oxidation of a wide range of thioethers to the corresponding sulfoxides in the presence of laccase-TEMPO catalyst system in an aqueous media at ambient temperature (Scheme 1, eqn (c)). We started with the oxidation of the methyl phenyl thioether as a model reaction under air in phosphate buffer (Table 1). No product formation was observed when methyl phenyl thioether was reacted with 20 U of laccase under specified conditions (Table 1, entry 1). This result confirms that the laccase-catalyzed oxidation of the model compound require a mediator. It is also notable that methyl phenyl sulfoxide was obtained in low yield in the presence of the bare TEMPO (Table 1, entry 2). Therefore, in order to improve the yields of the laccase-catalyzed oxidation, the reaction requires the cooperation between laccase and TEMPO. Gentili and Co-worker tested laccase-TEMPO (10U/6 mM) catalyst system on oxidation of methyl phenyl thioether (20 mM) at room temperature for 24h. Under these conditions, the reaction failed.This study was performed to mechanistic survey of the oxidation of alcohols and etherswith Laccaseas catalyst and TEMPO as mediator [34]. The result indicated that the used amounts of the Laccase and specially TEMPO are important. The effect of different amounts of TEMPO and laccase was investigated on yield and time (Table 1, entries 3-6). The effect of air auto-oxidation was also studied for 48 h. This conditions did not result in the desired product, leaving methyl phenyl sulfide intact (Table 1, entry 7). In term of the amount of laccase and TEMPO, better results were obtained when the laccase-catalyzed oxidation of the methyl phenyl thioether was done with 20 U of laccase and 0.4 mmol of TEMPO in phosphate buffer (0.1 M, 5 mL, pH=5) and THF (4 vol %).

Table 1. Optimization of the laccase-TEMPO-catalyzed oxidation of methyl phenyl thioether (1 mmol)[a]



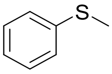
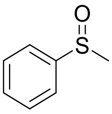
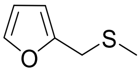
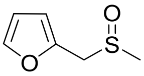
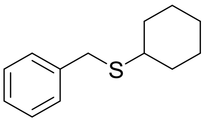
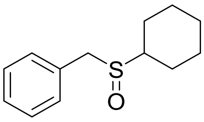
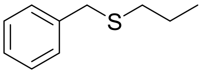
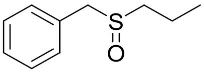
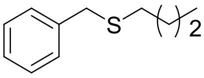
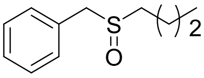
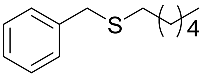
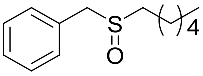
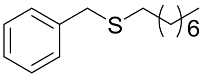
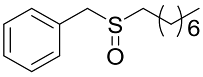
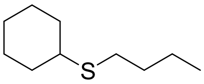
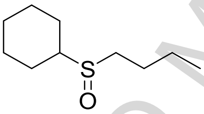
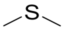
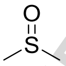
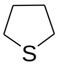
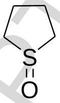
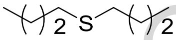
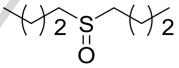
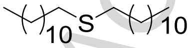
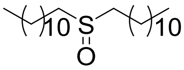
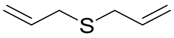
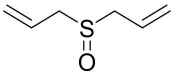
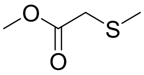
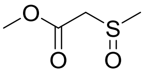
Entry	Laccase (U)	TEMPO (mmol)	Time (h)	GC Yield (%)
1	20	0	24	0
2	0	0.4	48	50
3	20	0.4	48	100
4	20	0.3	48	60
5	20	0.5	24	100
6	40	0.3	48	60
7	0	0	48	0

[a] All reactions were done under aerial O_2 in phosphate buffer (0.1 M, 5 mL, pH=5) and THF (4 vol%).

Under the optimized conditions (Table 1, entry 3), the oxidation of a series of structurally diverse thioethers was examined (Table 2). The summarized results in Table 2 depict that a variety of thioethers including aryl alkyl (Table 2, entry 1), benzyl alkyl (Table 2, entries 2-7) and dialkyl (Table 2, entries 8-12) thioethers were successfully used to synthesize the corresponding sulfoxides. We were pleased to find that, the sulfur group was oxidized chemoselectively in the presence of C=C as an oxidation-prone functional group (Table 2, entry 13) and ester group in the substrate remain intact under reaction conditions (Table 2, entry 14). Noteworthy to mention is that because of the mild conditions of the method, sulfoxides were obtained in high yields and any over-oxidation to sulfones during the course of the reaction was not observed.

To demonstrate the greenness, Sheldon´s E-value (kg waste per kg product) was calculated for the oxidation of the methyl phenyl thioether, the amount of 2.27 kg kg^{-1} was obtained. This value compares well with the E-factors of other synthetic methods for the synthesis of methyl phenyl sulfoxide (Table 3) [14-16]. The TON and TOF values of the procces confirm the catalytic efficiency of the method (Table 2). The calculation of the amounts of E-factors, TONs and TOFs have been provided in the supplementary material.

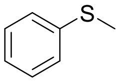
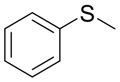
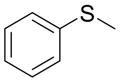
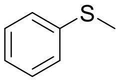
Table 2. The selective aerobic oxidation of thioethers to sulfoxides by using Laccase-TEMPO catalyst system in PBS (0.1 M, 5 mL, pH=5) and 4 vol % THF at room temperature[a]

Entry	Thioether	Sulfoxide[b]	Time (h)	Isolated yield (%)	TON[TOF (h^{-1})][b]
1			48	96	5352 (111)
2			27	90	5017(186)
3			27	94	5240(194)
4			24	90	5017(209)
5			25	92	5129(205)
6			20	93	5185(259)
7			27	95	5296(196)
8			18	90	5017(279)
9			10	82	4571(457)
10			10	90	5017(502)
11			12	87	4850(404)
12			15	93	5185(346)
13			48	87	4850(101)
14			18	84	4683(260)

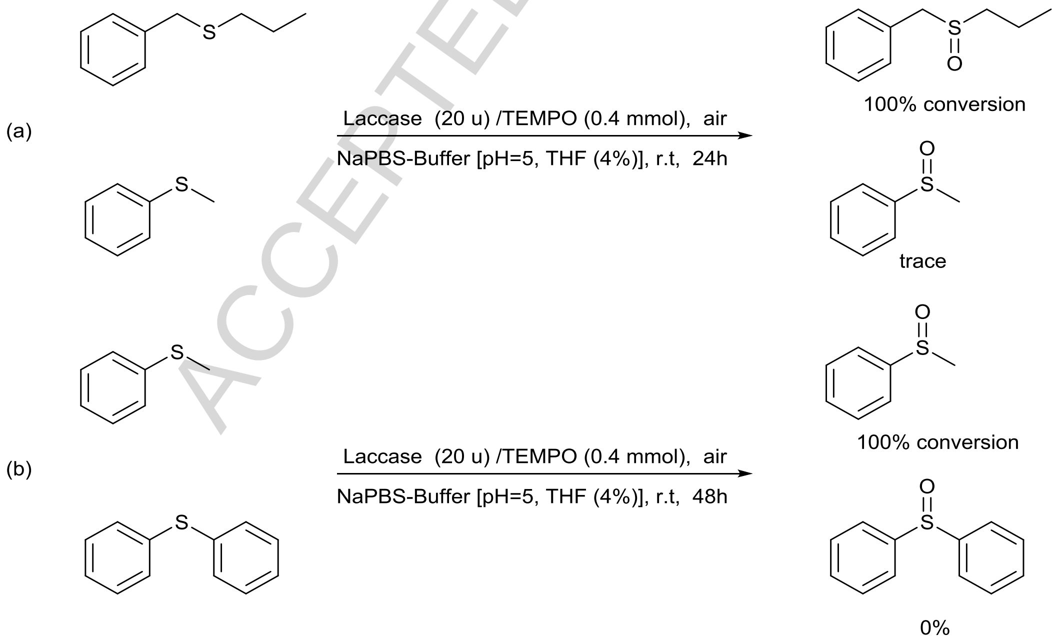
[a] Reaction conditions: sulfide (1 mmol), laccase (20 U), TEMPO (0.4 mmol), phosphate buffer (0.1 M, 5 mL, pH=5) and THF (4 vol %), r.t.

[b] Turnover number = number of moles of product per mol of catalyst precursor; TOF = TON per hour (values in brackets)

Table 3. Comparison of E-factor of Laccase-TEMPO catalyst system with some of the reported catalysts for the oxidation of the methyl phenyl thioether

Entry	Substrate	Catalyst	Oxidant	Yield (%)	E-factor (kg.kg^{-1})	Ref.
1		Merrifield resin supported peroxomolybdenum (VI)	H_2O_2	98	6.06	[14]
2		Ionic liquid compounds based on Kepleratepolyoxometalates	H_2O_2	99	22.12	[15]
3		Fe_3O_4/salen of Cu(II)	H_2O_2	83	82.89	[16]
4		Laccase-TEMPO	aerobic oxidation	96	2.27	This work

As shown in Table 2, in the case of methyl phenyl thioethers longer reaction time was required. Therefore, we used this procedure for the selective aerobic oxidation of benzyl propyl thioether (as model for benzyl alkyl thioethers) in the presence of methyl phenyl thioether (as model for phenyl alkyl thioether). The result shows that the method has excellent selectivity and benzyl propyl thioether was completely converted to the corresponding sulfoxide, while trace conversion for methyl phenyl thioether was detected (Scheme 2a). Similarly, the excellent selectivity was observed for the oxidation of methyl phenyl thioether in the presence of diphenyl thioether (Scheme 2b).



Scheme 2. Selective reactions of different binary mixtures

Although, it is well-known that TEMPO-oxoammonium ion is generated from the reaction of Laccase and TEMPO in the presence of O_2 or air and it is actual oxidant in the reaction [35], however, at this time the exact mechanism of this reaction is not clear and the actual role of TEMPO-oxoammonium in the oxidation of sulfide to sulfoxide should be further studied in detail.

4. Conclusion

In conclusion, a simple, practical, highly efficient and sustainable protocol for the aerobic oxidation of thioethers using laccase-TEMPO catalyst system under toxic transition-metal free reaction conditions has been developed. We report the first example of biocatalytic aerobic oxidation of thioethers that can replace traditional oxidation processes. The merits of the current catalytic system include: (a) the use of laccase as green biocatalyst in due to its ecological advantages (b) the use of air as greenest, most abundant and inexpensive oxidant and producing water as an only by- (c) mild reaction conditions including atmospheric pressure, room temperature, phosphate buffer as the green solvent (d) efficient for the selective oxidation of various thioethers in high yields (e) other functional groups are tolerable and compatible with the present oxidative system. This method is easier and more eco-friendly and practical than the available protocols for the synthesis of sulfoxide and can be applied in pharmaceutical and other sensitive synthetic procedures.

Acknowledgments

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Appendix A. Supplementary data

Supplementary dat to this article can be found online at......

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Graphical Abstract

Laccase-TEMPO as an efficient catalyst system for metal- and halogen-free aerobic oxidation of thioethers to sulfoxides in aqueous media at ambient conditions

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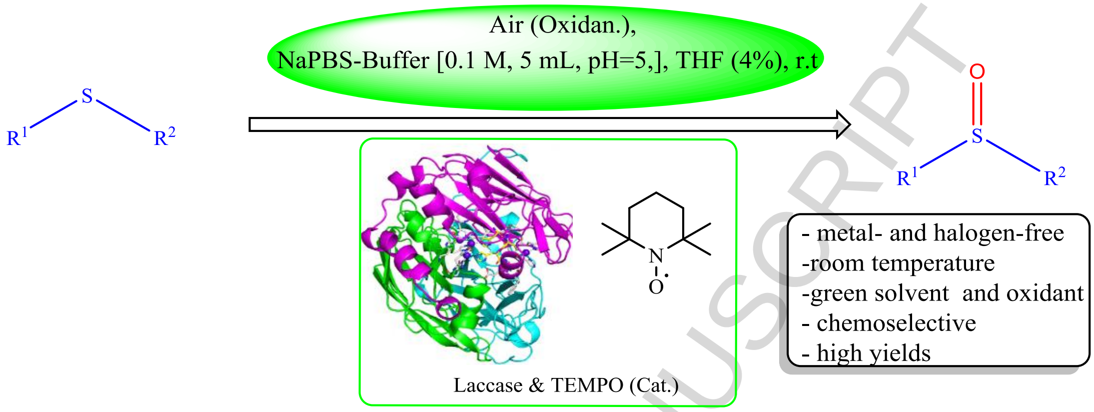

Highlights

1. The first example of a Laccase-TEMPOcatalyzed aerobic oxidation of sulfides was reported.
2. The use of air as eco-friendly, most abundant and inexpensive oxidant.
3. The reactions are occur in phosphate buffer as the green solvent at room temperature.
4. This system allows for greener methodology while keeping high reaction yields and selectivity.
5. Free from metal and halide make this method more eco-friendlythan the available protocols