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COMMUNICATION

Laccase-based oxidative catalytic systems for the aerobic aromatization of tetrahydroquinazolines and related *N*-heterocyclic compounds under mild conditions

Shaghayegh Saadati[a] Nadya Ghorashi,[b] Amin Rostami,*[b] and Farzad Kobarfard [a]

Abstract: In this work, for the first time, laccase (metalloenzyme)/3,5-di-tert-butylcatechol (DTBC) as a new class of bioinspired quinone-based cooperative catalytic oxidation system and laccase/2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) catalyst system were used for the aerobic oxidative synthesis of 2-substituted quinazolines through cascade reaction of structurally divers aldehydes with 2-aminobenzylamine. The products were obtained in good to high yields in phosphate buffer (0.1 M, 12.5 mL, pH=4.5) and acetonitrile (4 vol%) mixture as solvent at 45 ºC. Other *N*-heterocycles are also successfully oxidized to their aromatic counterparts.

Introduction

Nitrogen-containing heterocycles have been extensively studied as the core structural skeletons in a variety of drugs. Of these heterocycles, quinazolines have been particularly studied for their biological activity and have been reported to display hypotensive, [1] anti-cancer, [2] anti-inflammatory, [3] anticonvulsant, [4] kinase inhibitory [5] and antidiabetic properties. [6] Also quinazolin has been stupendously utilized as a drug-like template in medicinal chemistry. Prazosin and lapatinib have been used as α-adrenergic blockers for the treatment of high blood pressure, anxiety and panic disorder [7] and as tyrosine kinase inhibitor for the treatment of breast cancer and solid tumor, respectively (Fig. 1). [8]

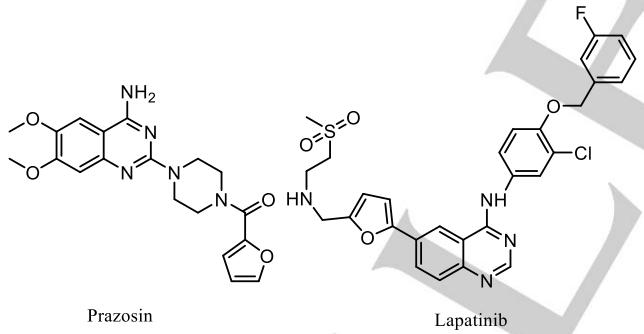

Figure 1. Drugs containing quinazoline moieties

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One strategy for the synthesis of these valuable compounds is through the oxidative cyclization of 2-aminobenzylamines with aldehydes mediated by stoichiometric amounts of strong oxidant such as DDQ, [9] MnO_2, [10] NaClO[11] and etc.[12] However, these reagents are often toxic and show poor atomic efficiency. Thus, the development of more efficient and environmentally benign reactions is necessary to realize sustainable and green methods for quinazolines synthesis.

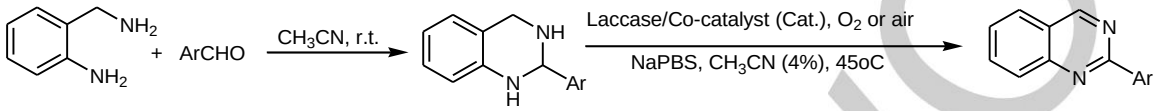
Molecular oxygen or air as the cheapest and greenest oxidizing agent represents an ideal alternative to traditionally used oxidants. Thus, oxidation of organic compounds using molecular oxygen in the presence of transition-metal catalysts or organocatalysts have been developed. [13] Only a few examples of aerobic oxidative cyclization of 2-aminobenzylamines with aldehydes to synthesize 2-aryl quinazolines have been developed. Typical examples include i) the use of Cu/*N*-ligand/TEMPO catalytic system,[14] ii) the assembly of rhodium nanoparticles (RhNPs) on carbon nanotubes (CNTs) along with redox-active quinone-type co-catalyst,[15] iii) 1,10-phenanthroline-5,6-dione associated to different metals (Zn, Fe, or Ru),[16] vi) Pt/Ir nanoclusters in combination with catechol co-catalysts.[17] Although these catalyst systems could efficiently perform oxidation reactions, these methods still require high reaction temperatures which are not suitable for thermally unstable substrates[14] and transition metals catalysts which may possibly leave toxic traces of heavy metals in the products. It is vital to eliminate the metallic catalyst (especially in pharmaceutical industry) because metal contamination is highly regulated. Therefore, the development of green and non-metallic catalysts for the aerobic oxidative synthesis of these important compounds is still desirable and is in demand. [18] A potential approach to overcome this problem is to change the transition metals catalysts to safe catalysts such as biocatalysts for the aerobic oxidation.

Laccases (*p*-benzenediol: oxygen oxidoreductase; [E.C. 1.10.3.2)] are extracellular enzymes that contain four copper centres per protein molecule and catalyze the oxidation of electron rich aromatic substrates, usually phenols or aromatic amines. The unique properties of laccases such as mild reaction conditions and substrate selectivity make them attractive for use in chemical synthesis.[19] Its good thermal stability coupled with its lack of substrate inhibition and high rates of oxidation (10-100 fold higher than those of lignin peroxidase or manganese peroxidase) make laccase an ideal candidate for the development of enzymatic oxidation processes.[20] In view of the low redox potential, native laccases can oxidize only electron rich aromatic substrates,[21] with the concomitant reduction of O_2. However, the oxidation of non-phenolic substrates can also take place on mediation by appropriate substances. [22] In fact, the oxidized mediator can rely on an oxidation mechanism that is not available to the enzyme. A conceivable role of the mediator could be that of a sort of -electron shuttle- between the enzyme and the substrate. [23] Therefore, the range of laccase substrates can be extended by the simultaneous use of the enzyme and redox mediators. Artificial mediators commonly used in laccase

catalysis studies include HBT (1-hydroxybenzotriazole), HPI (*N*-hydroxyacetanilide), TEMPO (2,2,6,6-tetra-methyl-piperidin-1-yloxy) and ABTS(2,20-azino-bis(3-ethylbenzthiazoline-6-sulfonate). [24]

Results and Discussion

To the best of our knowledge, there has been no report on the use of laccase/catechol as a cooperative catalytic oxidation system in the toxic transition-metal-free and halogen free aerobic oxidation of organic compounds. Herein, we present for the first time the simple and efficient methods for the synthesis of 2-substituted quinazolins from aminobenzylamine and aldehydes *via* aerobic oxidative cyclization in the presence of laccase-catechol or laccase-TEMPO as catalytic oxidation system, using O_2 or air as oxidant and a phosphate buffer solution as solvent at 45 °C (Scheme 1).



Scheme 1. Aerobic oxidative synthesis of 2-arylquinazoline catalyzed by laccase/ co-catalyst system

In order to optimize the reaction conditions initially, the dehydrogenation of 2-phenyl tetrahydroquinazoline was conducted in the presence of laccase (200 U) and O_2 as oxidant in MeCN/NaPBS (sodium phosphate buffer solution) mixture (1:25) as solvent at 45°C. Under these conditions, low yield of 2-phenyl quinazoline was obtained (Table 1, entry 1). When 20 mol% of pyrocatechol was added as a mediator, the yield increased to 50% (Table 1, entry 2). By changing mediator to 4-tert-butylcatechol the yield slightly improved (Table 1, entry 3), using a bulkier catechol, 3,5-di-tert-butylcatechol (DTBC) in this reaction resulted in a drastic enhancement in the yield of the desired product (Table1, entry 4). Employing hydroquinone afforded 2-phenyl quinazoline in only 30% yield (Table 1, entry 5).

Table 1. Optimization of reaction conditions for aerobic dehydrogenation of 2-phenyl tetrahydroquinazoline[a]

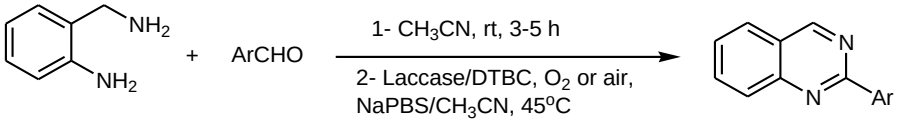
Entry	Co-catalyst	Temp °C)	Laccase (U)	GC Yield (%)
1	-	45	200	20
2	Pyrocatechol	45	200	50
3	4-*tert*-butylcatechol	45	200	70
4	**DTBC**	**45**	**200**	**100** [b]
5	Hydroquinone	45	200	30
6	DTBC	45	100	70
7	DTBC	60	200	30
8	DTBC	r.t	200	50
9	DTBC	45	200	70[c]
10	**DTBC**	**45**	**200**	**90** [b], [d]
11	3,5-di-tert-butyl-*o*-benzoquinone	45		80[e]

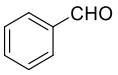
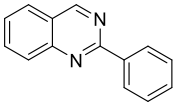
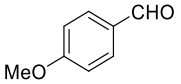
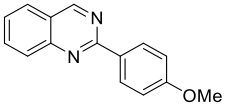
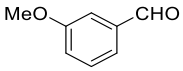
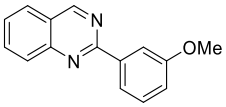
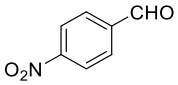
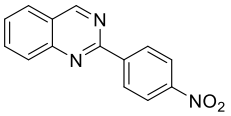
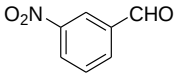
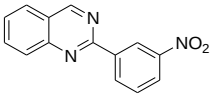
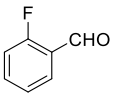
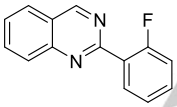
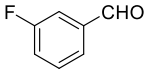
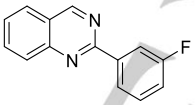
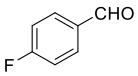
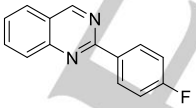
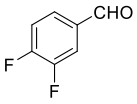
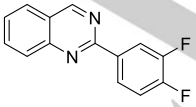
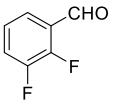
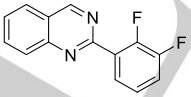
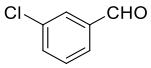
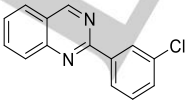
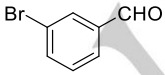
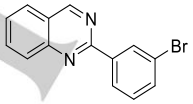
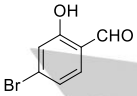
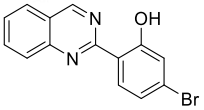
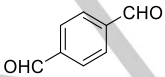
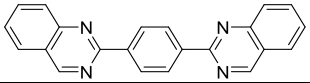
[a]Reaction conditions unless stated otherwise:yl tetrhydroquinazoline (1 mmol), Laccase (200 U), mediator (20 mol%), O_2 (balloon), phosphate buffer (0.1 M, pH 4.5, 12.5 mL)/ CH_3CN (4 %, 0.5 mL), and 24 h. [b]The bolds represent the effective reaction conditions. [c]15 mol% of DTBC was used. [d]The reaction was performed under air conditions. [e] 1 mmol of 3,5-di-tert-butyl-*o*- benzoquinone was used.

The effect of laccase concentration on the reaction rate was next investigated. When the amount of laccase was reduced to 100 U, the GC yield dropped to 70% (Table 1, entry 6). The optimal enzyme concentration was found to be 200 U (Table 1, entry 4), and therefore it was selected as a standard concentration in all further reactions. The effect of temperature on the reaction yield was also checked in both high and low temperatures. When the reaction temperature was increased up to 60 °C, the yield dropped due to enzyme deactivation[25] (Table 1, entry 7). At room temperature, the desired product was obtained in low yield (Table 1, entry 8). When the amount of DTBC was reduced to 15 mol%, the GC yield dropped to 70 % (Table 1, entry 9). Using air as an oxidant instead of molecular oxygen in the reaction, gave 90% yield of the 2-phenyl quinazoline (Table 1, entry 10). When laccase/DTBC catalyst system was replaced with stoichiometric amount 3,5-di-tert-butyl-*o*-benzoquinone, the 2-phenyl quinazoline was obtained in 80 % yield (Table 1, entry 11). Encouraged by the initial success, the generality and applicability of this method was further examined for the synthesis of 2-substituted quinazolines from the oxidative cyclization reactions of 2-aminobenzylamine and structurally diverse aldehydes. Under optimized reaction conditions (Table 1, entries 4 and 10), the expected products were obtained in moderate to high yields (Table 2). Various substituents, including both electron-donating (methyl and methoxy) and electron-withdrawing (fluoro, chloro, bromo and nitro) groups at the different positions of the benzaldehyde ring would be compatible with the present oxidative system and gave the desired products in good to high yields (Table 2, entries 2-13). Terephthaldehyde as a bifunctional aromatic aldehyde was satisfactorily subjected to oxidative cyclization as well (Table 2, entry 14).

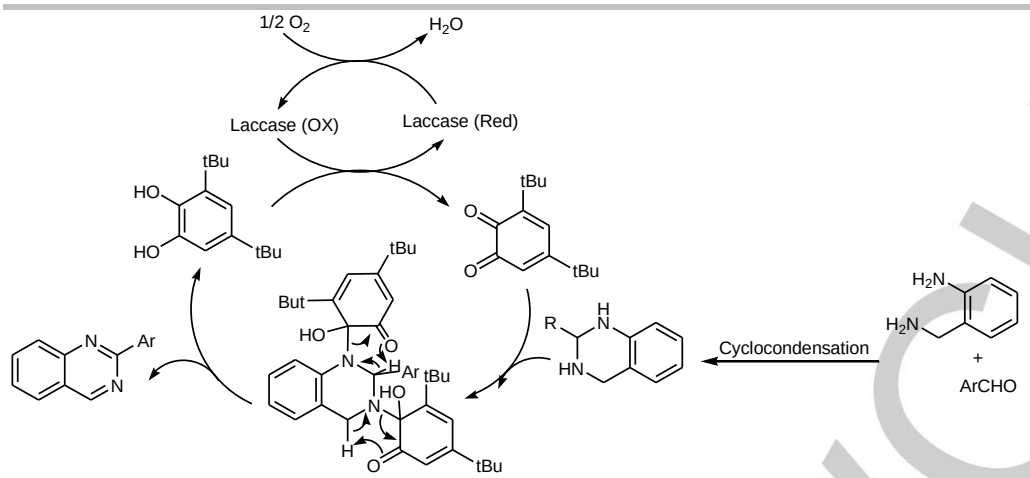
Although, the exact mechanism is not clear and should be further studied in detail, however, based on our observation during the course of the reaction (Table 1, entries 5, 11) and previously reported mechanisms about application of laccase in oxidation of catechol in tandem reactions[29] and oxidative dehydrogenation of *N*-heterocyclic rings using catechol as a co-catalyst[15-17], a plausible reaction pathway for the dehydrogenation of 2-substituted tetrahydroquinazolines in the presence of laccase/catechol catalyst system has been proposed in scheme 2. Mechanism involves oxidation of catechol to *o*-benzoquinone using laccase followed by the reduction of one molecule of oxygen to two molecules of water. Then, quinone catalyzes the aerobic dehydrogenation of secondary amines *via* an addition-elimination reaction.

Table 2. Substrate scope for the synthesis of 2-substituted quinazoline derivatives[a]



Entry	RCHO	Product	Time (h)	Yield (air)[b] (%)	Mp °C [Lit.]
1			24	95 (82)	97-98 [15]
2			20	96 (88)	78-80 [15]
3			20	94 (84)	91-93 [17]
4			24	55 (44)	218-119 [15]
5			24	50 (40)	194-195 [28]
6			24	60 (55)	71-73 [11]
7			22	93 (83)	89-90[26]
8			24	80 (75)	120-122 [11]
9			24	70 (60)	140-142 [27]
10			24	60 (50)	78-80
11			24	96 (87)	148-150[15]
12			24	90 (80)	153-155[15]
13			22	90 (83)	195-197
14[c]			24	95 (82)	270

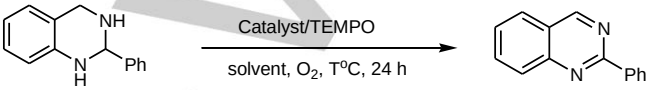
[a] General procedure: aldehyde (1 mmol), 2-aminobenzyl amine (1 mmol), Laccase (200U), DTBC (20 mol%), O_2 (balloon), NaPBS (12.5 mL), CH_3CN (0.5 mL), 45 °C. [b] solated yield under air conditions is shown in parentheses. [c] Conditions: Aldehyde (1 mmol), 2-aminobenzyl amine (2 mmol), laccase (400 U), DTBC (40 mol%), O_2 (balloon), NaPBS (25 mL), CH_3CN (1 mL), 45 °C.



Scheme 2. Plausible mechanism for the synthesis of 2-substituted quinazolines in the presence of laccase/catechol catalyst system

Laccase/TEMPO has been reported as an efficient catalyst system in the oxidation of some organic compounds.[24] These investigations prompted us to explore the prospects of this catalytic system for the synthesis of 2-substuted quinazolines from oxidative cyclization of aldehydes and 2-aminobenzylamine. Inspired by the successful result above, we first conducted dehydrogenation of 2-phenyl tetrhydroquinazoline in the presence of laccase (200 U) and TEMPO (20 mol%) under O_2 in NaPBS (pH=4.5, 0.1 M) and 4 vol% of MeCN at 45 °C. Under these conditions, the desired product was obtained in 100% GC yield (Table 3, entry 1). When the amount of laccase or TEMPO was reduced, the GC yield dropped (Table 3, entries 2 and 3). Employing MeOH/NaPBS as a solvent in the reaction gave 80% yield of the desired product (Table 3, entry 4). By decreasing the reaction temperature to 25 °C, the lower yield was observed (Table 3, entry 5). For comparison purposes, the combination of TEMPO with $NiFe_2O_4$ or $CuFe_2O_4$ magnetic nanoparticles has been also studied in MeCN at 80°C on the model reaction.
Subsequently, a series of various 2-substituted quinazoline derivatives were synthesized successfully with optimal conditions in hand (Table 3, entries 1 and 8).

Table 3. The optimization of the reaction conditions for the dehydrogenation of 2-phenyl tetrahydroquinazoline[a]



Entry	Catalyst (U or mmol)	Temp (°C)	GC Yield (%)
1[b]	**Laccase (200)**	**45**	**100**
2	Laccase (100)	45	50
3[c]	Laccase (200)	45	80
4	Laccase (200)	45	80
5	Laccase (200)	r.t	50
6	$NiFe_2O_4$ (0.4)	45	60
7	$CuFe_2O_4$ (0.4)	45	50
8[b], [d]	**Laccase (200)**	**45**	**90**

[a]Reaction conditions unless stated otherwise: 2-phenyl tetrquinazoline (1 mmol), TEMPO (20 mol%), O_2 (balloon) and solvent (13 mL). [b]The bolds represent the effective reaction conditions. [c]The reaction was performed in the presence of 15 mol % of TEMPO. [d]Under air conditions.

The result obtained from the oxidative cyclization of different aldehydes with 2-aminobenzylamine have been summarized in Table 4.

Table 4. Laccase /TEMPO -catalyzed aerobic oxidation of 2-substituted tetrahydroquinazolines [a]

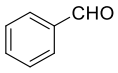
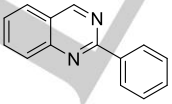
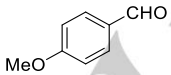
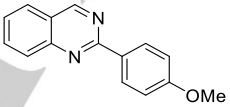
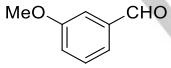
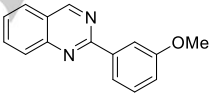
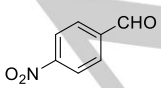
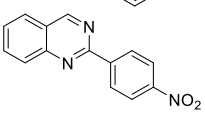
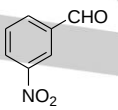
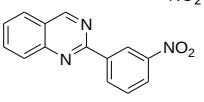
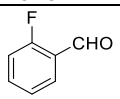
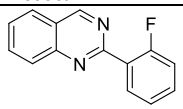
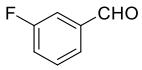
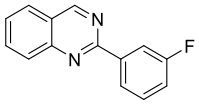
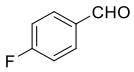
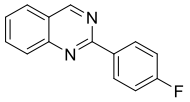
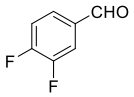
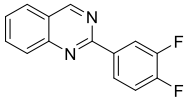
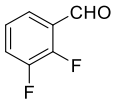
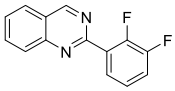
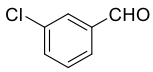
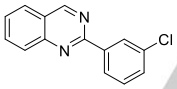
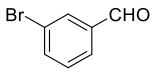
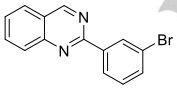
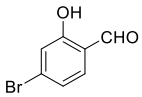
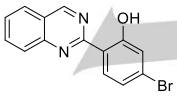
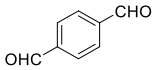
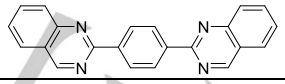
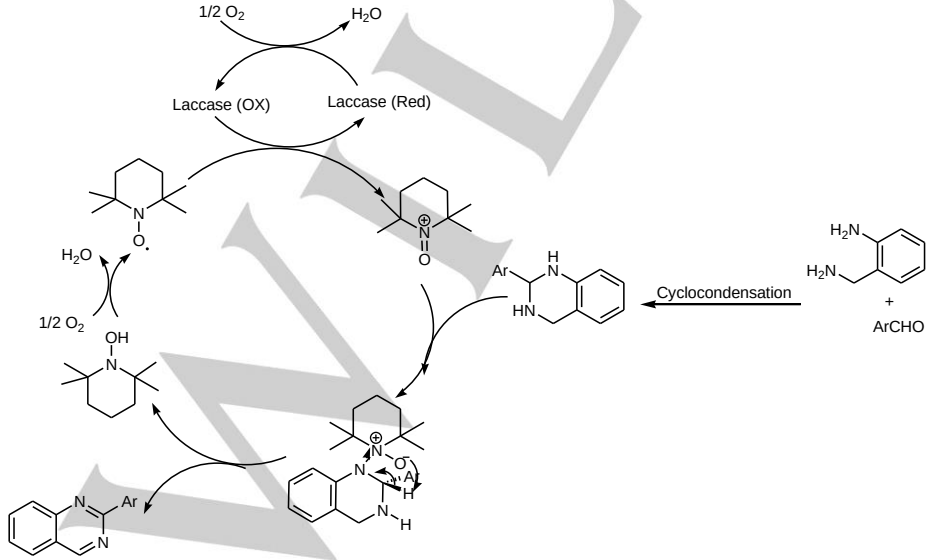
Entry	RCHO	Product	Time (h)	Yield (air)[b] (%)
1			24	95 (82)
2			20	93 (80)
3			22	96 (85)
4			24	40 (35)
5			24	40 (35)

Table 4. (Continued)

Entry	RCHO	Product	Time (h)	Yield (air)[b] (%)
6			26	70 (60)
7			24	80 (73)
8			24	85 (78)
9			24	75 (62)
10			24	72 (60)
11			22	94 (83)
12			24	90 (80)
13			23	90 (80)
14[c]			24	90 (83)

[a] General procedure: aldehyde (1 mmol), 2-aminobenzyl amine (1 mmol), Laccase (200U), TEMPO (20 mol %), O_2 (balloon), NaPBS (12.5 mL), CH_3CN (0.5 mL), 45 °C. [b] Isolated yield under air conditions is shown in parentheses. [c]Conditions: Aldehyde (1 mmol), 2-aminobenzyl amine (2 mmol), Laccase (400 U), TEMPO (40 mol%), O_2 (balloon), NaPBS (25 mL), MeCN (0.5 mL), 45 °C.

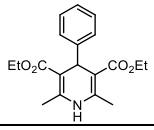
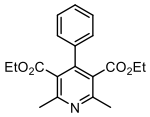
Mechanism for this reaction is proposed on the basis of previously reported mechanism for the oxidation of organic compounds catalyzed by laccase/TEMPO system.[24] As shown in scheme 3, one electron oxidation of TEMPO by the oxidized (cupric) form of the laccase followed by the reaction of oxidized mediator with the substrate. One electron oxidation of TEMPO affords the oxoammonium cation, which oxidizes the C-N bond of substrate *via* a heterolytic pathway, giving the product.



Scheme 3. Plausible mechanism for the synthesis of 2-substituted quinazolines catalyzed by Laccase/TEMPO system

Having successfully achieved the aerobic oxidative synthesis of 2-substituted quinazolines from 2-substituted tetrahydroquinazolines, we expanded Laccase/DTBC and Laccase/TEMPO catalytic systems for the synthesis of other heteroaromatics such as quinoxaline, quinoline, indole and Hantzsch-type pyridine from aerobic dehydrogenation of their partial saturated counterparts. The aerobic dehydrogenation of 1,2,3,4-tetrahydroquinoxaline using both two catalyst systems under optimized reaction conditions led to quinoxaline in high yields (Table 5, entry 1). Tetrahydroquinoline, indoline and Hantzsch-type dihydropyridine exhibited more activity as compared to the tetrahydroquinoxaline and tetrahydroquinazolines (Table 5, entries 2-4) and afforded high yields of products at room temperature. Strange, the oxidation of Hantzsch-type dihydropyridine in the presence of laccase/DTBC catalyst system afforded the desired product in only 20% yield even after prolonged reaction time and using higher temperature (Table 5, entry 4).

Table 5. Laccase /DTBC or Laccase /TEMPO -catalyzed aerobic oxidation of other classes of *N*-Heterocycles [a]

Entry	substrate	Product[b]	Temp (°C)	DTBC		TEMPO	
				Time (h)	Yield (%)	Time (h)	Yield (%)
1			45	24	95	24	93
2			25	24	90[c]	24	80[c]
3			25	24	95	24	90
4			25	24	20[d]	15	97

[a] Conditions: Substrate (1 mmol), Laccase (200U), TEMPO or DTBC (20 mol %), O_2 (balloon), NaPBS (12.5 mL), CH_3CN (0.5 mL). [b] All compounds are known and were characterized by ^1H NMR (see supporting information). [c] A trace amount of dihydroquinloline was also formed. [d] Temp: 45 °C

Conclusions

In summary, we have developed laccase/DTBC and laccase/TEMPO as efficient catalyst systems for the aerobic oxidative synthesis of 2-substitited quinazolines and other important *N*-heterocycles compounds such as quinoxaline, quinoline, indole and Hantzsch-type pyridine under mild reaction conditions. These procedures offer several novelties and advantages are as following:

1) This is the first report of laccase/DTBC for use as an efficient cooperative catalytic oxidation system for aerobic oxidation of organic compounds.
2) This is the first time that laccase/TEMPO has been used for the aerobic oxidative dehydrogenation tetrahydroquinazolines.
3) The synthesis of structurally diverse 2-substituted quinazolines using ideal oxidant with good to high yields in green solvent.
4) The present methods are superior to other currently available methods due to being free from any halide and toxic and expensive transition metals co-catalysts. Therefore thes methods can be applied in pharmaceutical and other sensitive synthetic procedures.
5) The methods conform to several of the guiding principles of green chemistry.

Experimental Section

General Remarks

2,2',6,6'-tetramethyl-1-piperidinyloxy free radical (TEMPO), 2,2'-azinobis(3-ethylbenzthiazolin-6-sulfonate (ABTS), 3,5-di-tert-butylcatechol (DTBC) were obtained from Sigma-Aldrich Co. Llc. (St. Louis, America). Laccase (E.C 1.10.3.2) from *Trametes Versicolor* was also purchased from Sigma and used without further purification. Sodium phosphate buffer (0.1 M) at pH 4.5 was used for preparing solutions for the activity assay. All other chemicals were of analytical grade and used without further purification.

^1H NMR spectra were recorded on 400 or 250 MHz Bruker NMR spectrometers. MS spectra were recorded on an Agilent Technologies 7890A GC system with an Agilent 5975 inert mass selective detector or a triple-axis detector (EI). Melting points were measured on a Barnstead Electrothermal IA 9100 and are uncorrected.

Activity assays of free laccase from *T. Versicolor*

The activity of commercial enzyme laccase from *T. Versicolor* was determined *via* UV-Vis spectroscopy by monitoring the oxidation of 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS, $\varepsilon = 36000\ M^{-1}.cm^{-1}$). The reaction mixture contained 5 mM of ABTS (100 µL) in acetate buffer (100 mM, pH=5.0) and laccase enzyme. The absorbance change was observed at 420 nm for 5 min at room temperature.[30] One unit was defined as the amount of enzyme that oxidizes 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 synthesis of 2-substituted quinazolines from aldehydes and 2-aminobenzylamine

A solution of 2-aminobenzylamine (1 mmol) and aldehyde (1 mmol) in CH_3CN (5 mL) was stirred at room temperature for 3-5 h. After complete conversion of 2-aminobenzylamine to 2-substituted tetrahydroquinazoline (TLC), the solvent was concentrated to ca. 0.5 mL. Then, phosphate buffer (0.1 M, 12.5 mL, pH=4.5), DTBC or

TEMPO (20 mol%) and Laccase (174 mg, 200U) were added and the mixture was stirred at under O_2 (balloon) or air at 45 °C for the time specified in Tables 2 and 4. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (75:25) as a mobile phase. All products were characterized by ^{1}H NMR, MS (see supporting information) and melting point (Table 2).

General procedure for the synthesis *N*-heterocyclic aromatic compounds (quinoxaline, quinoline, indole and Hantzsch pyridine)

To a solution of 1mmol *N*-heterocyclic aromatic compounds in CH_3CN (0.5 mL), was added a solution of phosphate buffer (0.1 M, 12.5 mL, pH=4.5) including laccase (174 mg, 200U) and DTBC or TEMPO (20 mol%). The mixture was stirred at under O_2 (balloon) or air at 45 °C or room temperature for the time specified in Table 5. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude products were purified by silica gel column chromatography using hexane/ethyl acetate (75:25).

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Keywords: laccase; cooperative catalytic oxidation system; aerobic oxidative dehydrogenation; 2-substituted quinazolines; Nitrogen heterocycles

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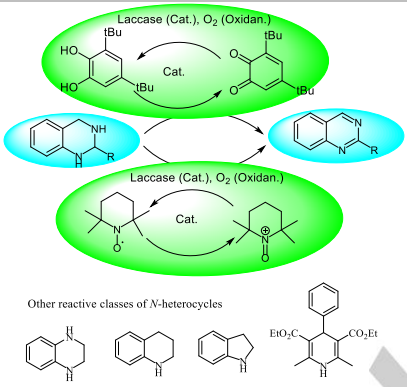
Aerobic oxidative synthesis of quinazolines and other *N*-heterocyclic aromatic compounds has been accomplished using O_2/laccase/catechol (or TEMPO) as bioinspired catalytic oxidation system.



Cooperative catalyst system*

Shaghayegh Saadati, Nadya Ghorashi, Amin Rostami and Farzad Kobarfard**

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Laccase-based oxidative catalytic systems for the aerobic aromatization of tetrahydroquinazolines and related *N*-heterocyclic compounds under mild conditions