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Review

Application of Laccase Catalysis in Bond Formation and Breakage: A Review

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Abstract: Laccase belongs to the superfamily of multicopper oxidases and has been widely investigated in recent decades. Due to its mild and efficient oxidation of substrates, laccase has been successfully applied in organic catalytic synthesis, the degradation of harmful substances, and other green catalytic fields. Nevertheless, there are few reports on the green catalysis with laccase. This review focuses on reporting and collating some of the latest interesting laccase-catalyzed bond formation and breakage research. This is discussed with a focus on the effects of the medium system on the laccase-catalyzed reaction, as well as the formation and the breakage of C–N, C–C, and C–O bonds catalyzed by laccase. It provides abundant references and novel insights for furthering the industrial applications of laccase.

Keywords: laccase; laccase–mediator system; green catalysis; bond formation; bond breakage

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1. Introduction

Laccase (EC 1.10.3.2) is a copper-containing polyphenol oxidase that belongs to the blue copper oxidase (MCO) family [1,2]. It was first discovered in the Japanese lacquer tree *Rhus Vernicifera* [3,4]. Subsequently, laccases were found in different plant species [5], microbes [6,7], and animals [8]. There have been more investigations on microbial laccases than on animal and plant laccases, for which there have been relatively few. Microbial laccases are divided into fungal laccases and bacterial laccases. Bacterial laccase mainly plays a role in melanin production, spore wall defense, morphological change, and copper ion detoxification [9,10]. Fungal laccase is mainly related to pigment generation, plant disease, and lignin degradation [11,12]. Plant laccase is closely related to lignin biosynthesis [13]. At the same time, the primary function of animal laccase protein is to control the ossification of the epidermis [14].

Laccase is a glycoprotein with a molecular mass ranging from 50 to 140 kDa. Their amino acid sequence can span from 220 to 800 amino acids and may contain three cupredoxin-like domains. These domains bind copper centers involved in intermolecular electron transfer reactions and constitute the catalytic core of laccases (Figure 1) [15]. The active copper center of laccase generally contains four copper ions: a type I copper ion (T1-Cu), a type II copper ion (T2-Cu), and two type III copper ions (T3-Cu). T1-Cu is a mononuclear center that can gain electrons from the substrate and then transfer them to the trinuclear cluster (TNC), and the oxidation of the substrate occurs there. T2-Cu is a single-electron acceptor, whereas T3-Cu forms coupled ion pairs and is a double-electron acceptor. T2-Cu and T3-Cu together form a trinuclear cluster (TNC). Oxygen accepts four electrons and four protons to form water, which joins the bulk solvent [16,17]. Laccases can perform the single-electron

oxidation of the substrate without using hydrogen peroxide while reducing molecular oxygen to water; therefore, they have a surprisingly broad substrate spectrum and can oxidize simple diphenols, polyphenols, diamines, and aromatic amines. The optimum temperature and pH of laccases depend on the enzyme source and substrate properties; those ranges are, respectively, from 20 °C to 75 °C and 3 to 8 (Table 1).

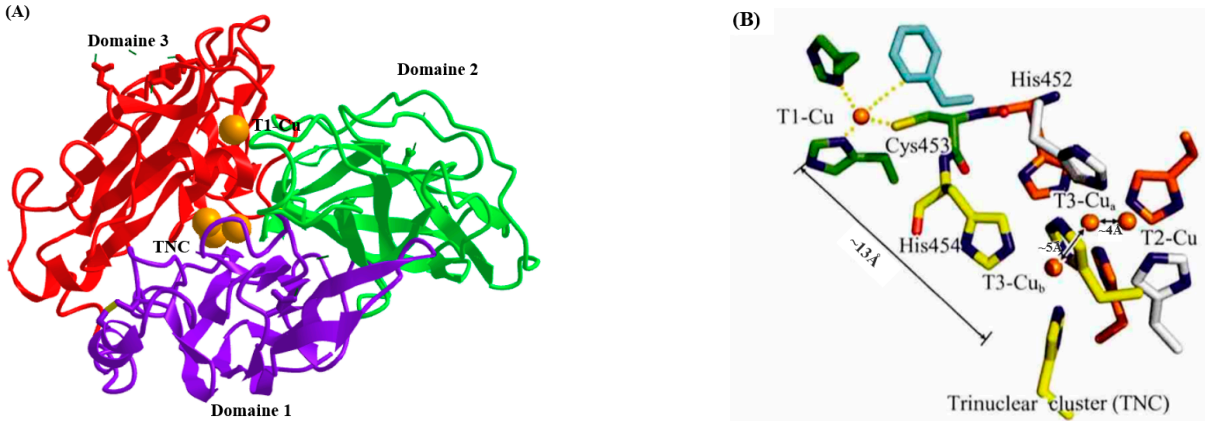


Figure 1. Crystal structure of the laccase (LccI) (PDB code: 1GYC) in *Trametes versicolor.* (**A**) The overall structure of LccI; (**B**) structure of the schematic representation of the four copper sites in LccI.

Table 1. Enzymatic properties of laccase from different sources.

Source	Molecular Mass	Optimal pH	Optimal Temperature (°C)	Ref.
Fungal	46–80 kD	2.2–6	30–55	[18–21]
Bacteria	43–114 kD	4.0–8.0	40–75	[22–26]
Plant	59.2–140 kD	6.7	20	[27–29]
Animal	73–110 kD	6.5–8.0	-	[30–32]

As an oxidase, the ability of laccase to oxidize the substrate is directly related to its redox potential (E0) [33,34]. E0 is an important characteristic of the catalytic oxidation capacity of laccase, which is the energy required for laccase to capture an electron from a reducing substrate. The E0 is critical to the reactivity of laccase and the overall reaction characteristics. Laccase can directly oxidize substrates with low E0, whereas some mediators are needed to assist laccase in oxidizing substrates with high E0. Adding a mediator not only effectively improves the reaction efficiency of laccase but also expands the scope of the substrate. For instance, with the mediator's help, laccase can oxidize nonphenolic structures with high E0 and is used in pulp bleaching [35]. Recently, laccase and the laccase–mediator system (LMS) have received extensive attention in green catalysis, such as synthesizing complex organic compounds, the selective modification of natural products, and the degradation of harmful substances [36–39]. For example, the C–N bond breakage of amines catalyzed by laccase is essential for synthesizing amino acids and nucleosides [40,41]. Existing research indicates that using *Pleurotus ostreatus* laccase and its natural mediator (syringaldehyde) to catalyze C–C bond breakage results in the removal of up to 100% and 85% of BPA at concentrations of 0.44 and 0.88 mmol/L in wastewater within 1 h [42].

Furthermore, laccase-catalyzed C–N, C–C, and C–O bond formation can be widely employed in the green synthesis of some functional polymers, environmental remediation, and other areas. In contrast, there are few reviews on laccase catalysis at present. This review starts with the application of the laccase–mediator system; it also focuses on the analysis of the laccase-catalyzed formation of small-molecule compounds through C–N, C–O, and C–C bonds to obtain functional phenol polymers and important chemical pharmaceutical skeletons, as well as the laccase-catalyzed breakage of the C–N, C–O, and C–C bonds of

macromolecular refractory organic compounds to form organic molecules organics. Furthermore, this review summarizes and forecasts the prospects of the laccase-catalyzed formation and breakage of C–N, C–O, and C–C bonds, aiming to provide rich reference value and novel ideas for expanding and developing the multifunctional applications of laccase in the field of biotechnology.

2. The Effect of the Mediator System on Laccase Catalysis

Currently, some problems still need to be solved urgently to directly apply laccase to industrial production. For instance: (1) Numerous substrates cannot directly bind to laccase specifically. (2) With laccase, it is difficult to oxidize nonphenolic compounds with high E0 (E0 > 1.3 V) due to its low E0 (E0 < 0.8 V). Thus, the development of laccase in industries such as lignin degradation and bio-bleaching is limited [43,44]. In order to reduce the oxidation potential of substrates and improve the oxidation efficiency, some mediators can be used as an intermediate substrate for laccase to form new intermediate states to transport electrons [41,45]. These mediators are compounds with low molecular mass and low E0, such as 2,2′-Azino-bis-(3-ethylbenzothiazoline-sulphonate) (ABTS) and 2,2,6,6-Tetramethyl-1-piperidinylox (TEMPO), which can easily gain and lose electrons. They can form highly active and stable intermediates under the action of laccase and act on the substrate to is oxidized. In the LMS, laccase first oxidizes the mediator into a free radical. The oxidized mediator rapidly applies to compounds above the E0 of laccase and to those polymers that cannot directly access the laccase active center [46–48] (Figure 2).

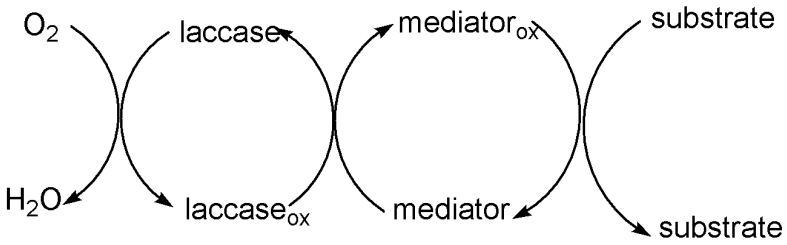


Figure 2. Oxidation of substrates by LMS.

Laccase mediators are usually divided into artificial and natural mediators (Figure 3) [49]. Due to their high efficiency and inexpensive availability, artificial mediators are widely used in lignin degradation, polycyclic aromatic hydrocarbon (PAH) oxidation, and dye decolorization. Common artificial mediators include ABTS, TEMPO, and 1-hydroxybenzotriazole (HBT) (Figure 3B) [50–52]. Three mechanisms have been proposed for the function of mediators in the LMS: (1) hydrogen atom transfer (HAT), (2) electron transfer (ET), and (3) the ionic mechanism (IM). ABTS was the first mediator found to promote the laccase-catalyzed oxidation of nonphenolic lignin. The action mechanism of ABTS belongs to the electron transfer mechanism (ET), which undergoes two stages (Figure 4): forming an ABTS+· cationic radical and slowly oxidizing to ABTS2+. ABTS2+ with higher reduction potential (but not ABTS+·) performs a more critical function in the laccase–ABTS system, which mediates the oxidation of nonphenolic lignin substrates [53–55]. The HAT mechanism, which is generally the oxidation mechanism mediated by the N-OH type mediator, uses a form of nitryl (>N-O·) to perform oxidation, such as the HBT system. Meanwhile, the purpose of the ion mechanism (IM) is mainly to form an ammonium oxide ion (>N=O·) through the nitryl group (>N-O·) to carry out the oxidation, such as the TEMPO system [39,56].

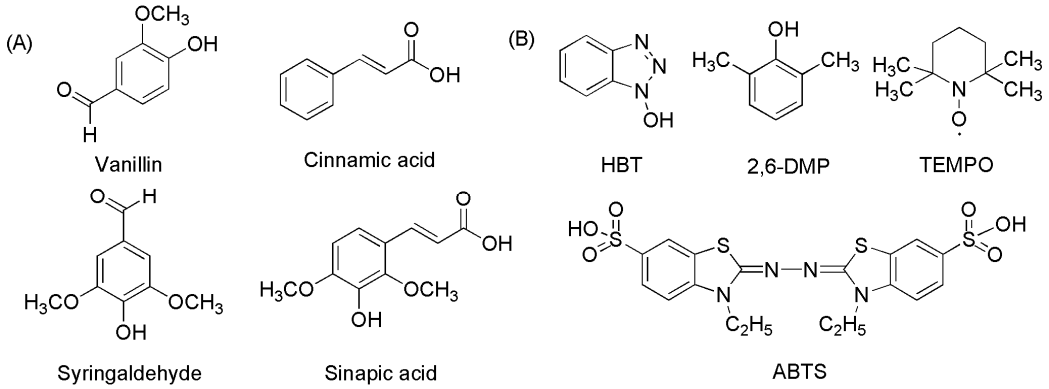


Figure 3. The chemical structures of several artificial and natural redox mediators in laccase-catalyzed oxidation reaction systems. (**A**) natural redox mediators; (**B**) artificial redox mediators.

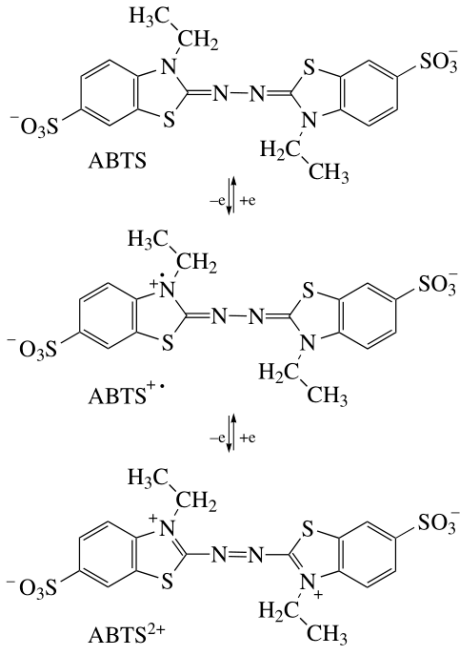


Figure 4. Oxidation of ABTS by Laccase.

Artificial mediators have potential applications in the areas of lignin degradation and polycyclic aromatic hydrocarbon (PAH) oxidation for dye decolorization, but some disadvantages limit their use. For instance: (1) poor stability, (2) potential toxicity [57], and (3) difficulty in regeneration when the molar ratio of mediators to substrates is as high as 40:1 [53,58]. Compared to artificial mediators, natural mediators have more economic value because they are readily obtained, environmentally friendly, and reproducible (Figure 3A) [35,53]. Some fungal metabolites and lignin derivatives could be used as natural mediators of laccase, including but not limited to vanillin, acetyl vanillin, acetosyringone, syringaldehyde, 2,4,6-trimethyl phenol, and *p*-coumaric acid [59]. Taking the laccase *p*-coumaric acid system as an example, it can remove 95% anthracene (80% with HBT) and benzoin anthracene within 24 h [57].

Besides indirectly assisting laccase-catalyzing substrates, mediators show synergism with each other, and the degradation efficiency increases with the increase in mediator concentration [60]. For example, the complex mediator system composed of laccase, ABTS, and HBT can oxidize phenanthrene with only one intermediary phase with a degradation rate that can be increased by 30–40% compared with a single-mediator system (such as the ABTS system or HBT system) [61]. Therefore, with intensive research on and development of the LMS, the biocatalytic substrates of laccase can be further expanded.

3. Laccase-Catalyzed C–N, C–C, and C–O Bond Breakage

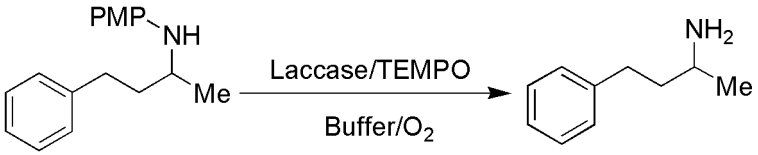
Laccase-catalyzed C–N, C–C, and C–O bond breakage has been used in preparing multifunctional polymer materials, the purification of water pollution, organic synthesis, and other fields. It is similar to the catabolic process in vivo, in which laccase mediates the oxidative degradation of large organic compounds to form small molecules [62–65]. The laccase-TEMPO system can catalyze C–N bond breakage to deprotect and provide amino donors for organic synthesis. In this chapter, the breakage of the C–N, C–C, and C–O bonds will be introduced from three perspectives.

3.1. C–N Bond Breakage

Due to the abundance of amines in organic molecules, the employment of amino-protecting groups is commonplace in many synthetic schemes, such as carbamates, amides, and sulfonamides [66]. The chemical method is generally used to remove the amino-protecting groups and has the disadvantages of high price, harsh reaction conditions, and severe pollution [66–69]. The N-para-methoxyphenyl (N-PMP) and N-benzyl group could be removed in an aqueous solution with the oxidative fracture of the C–N bond catalysis by laccase [41].

3.1.1. N-PMP Removal

The para-methoxyphenyl (PMP) group is being increasingly used as a nitrogen-protecting group for amines [70]. In most cases, ceric ammonium nitrate (CAN) has been used for deprotection, which is expensive and highly toxic. It requires increasingly cost-effective, environmentally friendly, and scalable deprotection procedures to make these processes commercially viable. Recently, a novel enzymatic method for the oxidative deprotection of p-methoxyphenyl (PMP)-protected amines has been reported [71]. Using laccase AB (laccase from *Agaricus bisporus*) under mildly acidic conditions results in the highest efficiency (with the highest yield reaching 89%) when the cosolvent is DMSO and pH = 3 is used. Further screening of the substrate showed that laccase had activity on substrates 1–7 (Scheme 1, Table 2). Due to the reaction conditions being green and mild with a high catalytic efficiency, laccase has excellent potential as a conventional PMP removal biocatalyst in organic synthesis.



Scheme 1. N-PMP removal reaction by Laccase.

Table 2. Substrates catalyzed by Laccase for N-PMP removal.

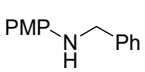
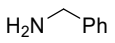
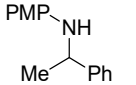
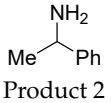
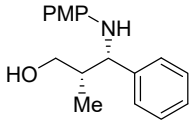
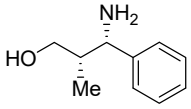
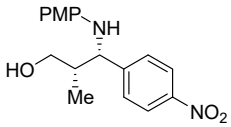
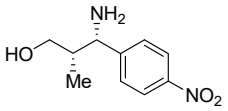
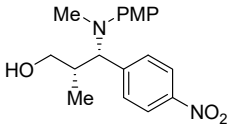
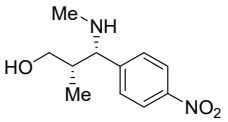
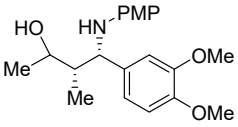
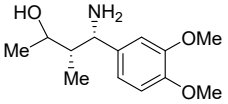
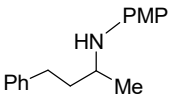
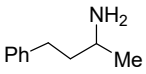
Entry	PMP Amine	Laccase	Product and Yield
1 2	 Substrate 1	T AB	 Product 1 0% 0%
3 4	 Substrate 2	T AB	 Product 2 31% 56%

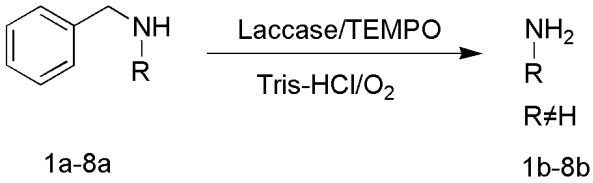
Table 2. *Cont.*

Entry	PMP Amine	Laccase	Product and Yield
5 6	 Substrate 3	T AB	 Product 3 67% 71%
7 8	 Substrate 4	T AB	 Product 4 64% 74%
9 10	 Substrate 5	T AB	 Product 5 89% 52%
11 12	 Substrate 6	T AB	 Product 6 34% 41%
13 14	 Substrate 7	T AB	 Product 7 30% 47%

AB: laccase from *Agaricus bisporus*, T: laccase from *Trametes versicolor*.

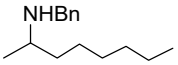
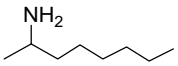
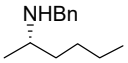
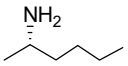
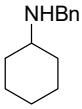
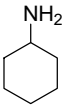
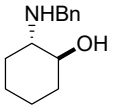
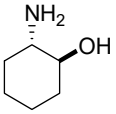
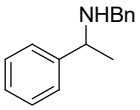
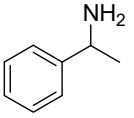
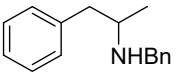
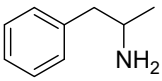
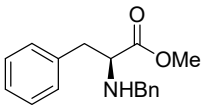
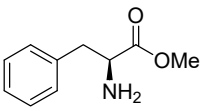
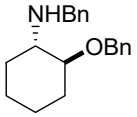
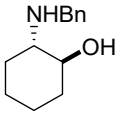
3.1.2. N-Benzyl Removal

N-Benzyl groups are typically cleaved using reductive methods, often employing palladium-catalyzed hydrogenolysis [72], which is accompanied by high cost, poor reaction conditions, and severe pollution. Reports have indicated that laccase from *Trametes versicolor* and TEMPO catalyzes the debenzylation of n-benzyl-1-phenylethylamine to α-phenylethylamine at 30 °C, pH 5, and O_2 (Scheme 2, Table 3) [40]. This methodology could be successfully applied over different aliphatic, cyclic, and aromatic amines affording deprotected derivatives of 1a–7a smoothly and immaculately, with no undesired by-products or oxidative transformations (Conversion > 97%). In contrast to the high cost, poor reaction conditions, and severe pollution of palladium-catalyzed hydrogenolysis, laccase-catalyzed N-benzyl removal is accompanied by mild reaction conditions, pollution-free, and easy extraction of the final derivatives.



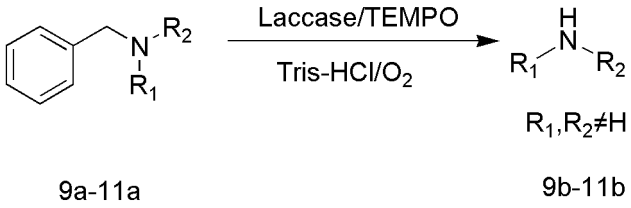
Scheme 2. Debenzylation of N-protected secondary amine by laccase/TEMPO system.

Table 3. Laccase-catalyzed secondary amine benzyl removal of substrate.

Entry	Amine	Product and Yield
1	 1a	 1b 7%
2	 2a	 2b 97%
3	 3a	 3b 99%
4	 4a	 4b 99%
5	 5a	 5b 97%
6	 6a	 6b 99%
7	 7a	 7b 99%
8	 8a	 8b <1%

Although this reaction occurred efficiently for N-benzylated secondary amines (Scheme 2, Table 3), it did not modify O-benzylated alcohols or N-protected tertiary amines (Scheme 3,

Table 4). It is speculated that laccase has a particular selectivity for N-benzyl, which effectively removes N-benzyl from the secondary amine and has no activity for O-benzylated amine. Compared to the secondary amine, the steric hindrance of the tertiary amine of the N-benzyl group is more significant, which results in the low efficiency in the benzyl removal of tertiary amines by laccase. In addition, the laccases that catalyze secondary N-benzyl removal are the fungal laccases with the highest E0. Tertiary amines and o-benzylated amines with higher dissociation energies are not catalyzed because the E0 of laccases is insufficient. Modifying laccase to magnify the binding pocket of laccase and increase the E0 of laccase is necessary to catalyze N-benzylated tertiary amines and O-benzylated alcohols with laccase [73–75].



Scheme 3. Debenzylation of N-protected tertiary amine by laccase/TEMPO system.

Table 4. Laccase-catalyzed tertiary amine benzyl removal of substrate.

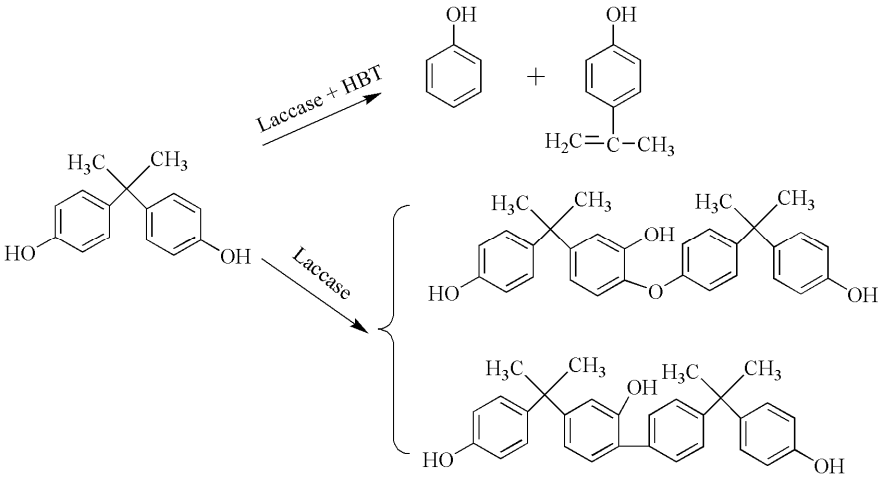
Entry	Amine	Product and Yield
1	9a	9b 4%
2	10a	10b <1%
3	11a	11b <1%

3.2. C–C Bond Breakage

As an important organic chemical raw material, bisphenol A (BPA) is extensively involved in manufacturing polycarbonate and epoxy resin plastics [76,77]. It causes imbalances and disturbances in the endocrine system of organisms and even induces a risk of cancer when it accumulates in wild organisms and humans [78]. BPA can be effectively removed from wastewater using adsorption, Fenton oxidation, electrochemistry, photodegradation, and biofilm filtration [79–81]. However, these conventional methods struggle to eliminate trace BPA and easily cause secondary damage to the ecological environment. The degradation rates of BPA can be up to 100% catalyzed by laccase-hydroxy benzotriazole (HBT) within 4 h, which can cause the effective removal of BPA from industrial wastewater [82].

The intermediate products of BPA catalyzed by laccase include macromolecular polymerization and small-molecule oxidative decomposition, which are mainly affected by the

source of laccase and the type of media [37,83]. Laccase can catalyze BPA to form phenoxy radical intermediates and covalently couple outside the enzymatic reaction site to form BPA oligomers and polymers [84,85]. Although in the LMS, the mediator as an electron shuttle prompts laccase to catalyze the cleavage of the C–C bond of oxidized BPA, forming a variety of small-molecule oxidative decomposition products [42,86,87] (Scheme 4). Furthermore, the LMS can also catalyze the breakage of C–C bonds of estrogen, antibiotics, polycyclic aromatic hydrocarbons, and so on to effectively degrade organic pollutants [88]. For instance, the LMS with HBT can effectively degrade polyethylene and nylon-66 by catalyzing the breakage of C–C bonds. In previous experiments, after 3 days of treatment with the LMS, the weight average molecular mass (Mw) of polyethylene decreased from 242,000 to 28,300, and that of nylon-66 from 79,300 to 14,700. LMS also decreased the polydispersity (weight average molecular mass/number average molecular mass, Mw/Mn) of polyethylene and nylon-66. Furthermore, these reductions in elongation, tensile strength, and molecular mass were accompanied with the morphological disintegration of the polyethylene and nylon-66 membranes [89–91].



Scheme 4. Free radical coupling and oxidative decomposition of BPA catalyzed by fungal laccase.

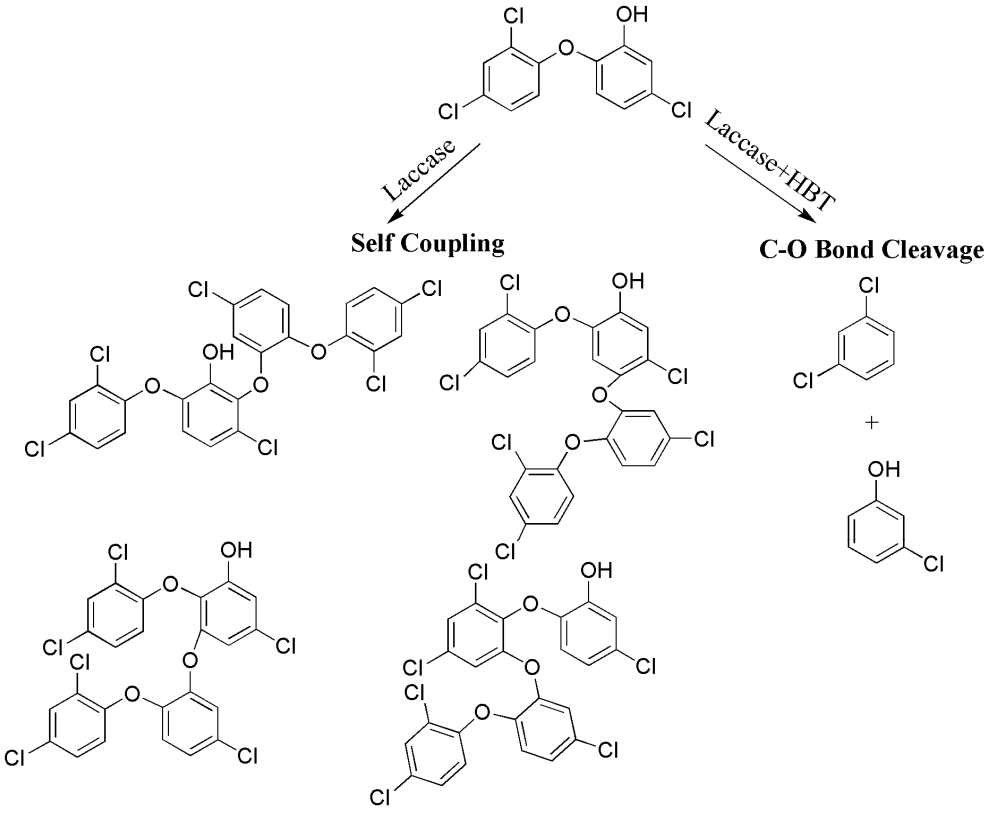
Although laccase is effective in wastewater treatment, it is challenging to separate, purify, and recover free laccase due to its high price, which limits its practical application in wastewater treatment [92,93]. The recovery and reuse of laccase benefits from immobilized enzyme technology, which can significantly improve laccase's stability and catalytic efficiency [94–96]. In one study, amino-functionalized magnetic nanoparticles were attached to laccase nanoflowers, and it was found that the degradation rate of BPA was up to 100% within 5 min, with a prolonged storage period and excellent recycling performance [97]. Therefore, this technology is expected to improve the removal efficiency of bisphenol A by laccase and guarantee the mass implementation of this enzyme in sewage treatment [98].

3.3. C–O Bond Breakage

Triclosan has been widely used in detergents, skin creams, and other dairy products as a broad-spectrum antibacterial agent. However, when the concentration of triclosan in water is higher than a specific range, it will lead to the death of fish and other organisms [99]. Triclosan can be effectively removed from wastewater using photochemical degradation and oxidation. Nevertheless, secondary damage to the ecological environment is caused by these conventional methods. Reports have shown that laccase can effectively remove and convert triclosan in water by catalyzing its C–O bond break to produce small-molecule chemicals. In these reports, the removal efficiency of triclosan catalyzed by the laccase–HBT system was about 80% (the HBT concentration was 1.0 mmol/L) [100,101].

In the laccase catalytic system, the triclosan removal efficiency can be improved by adding HBT. Without HBT, the primary mechanism of laccase-catalyzed oxidation of

triclosan is the formation of oligomers, such as a dimer, trimer, and tetramer, through a free-radical-mediated coupling reaction. In the laccase–HBT system, triclosan conversion primarily involves generating 2,4-dichlorophenol and 3-chlorophenol through ether bond cleavage [102,103] (Scheme 5).



Scheme 5. Proposed triclosan transformation pathways in the absence and presence of HBT by laccase-mediated reaction systems.

The mechanism of laccase-catalyzed C–N, C–C, and C–O bond breakage is similar to that of anabolic metabolism in vivo. First, the mediators are oxidized into an ionic type with high redox potential and oxygen is reduced to water by laccase in the presence of the mediators [104]. Then, the ionic mediators attack the substrate's C–N, C–C, and C–O bonds, generating an unstable oxidation intermediate containing double bonds. Finally, the oxidation state intermediates are oxidized to the product in the presence of H^+, reducing oxygen to water (Figure 5). The laccase-catalyzed breakage of C–N, C–C, and C–O bonds can be used in preparing multifunctional polymeric materials, water pollution purification, and organic synthesis. Among these, laccase-catalyzed C–N bond breakage can be applied to remove the amino-protecting group in chemical synthesis. This type of bond breakage as well as that of C–O can be harnessed in sewage treatment, environmental remediation, and other fields [105,106]. In conclusion, the laccase-catalyzed breakage of C–N, C–C, and C–O bonds has essential applications in preparing multifunctional polymeric materials, water pollution purification, and organic synthesis [102].

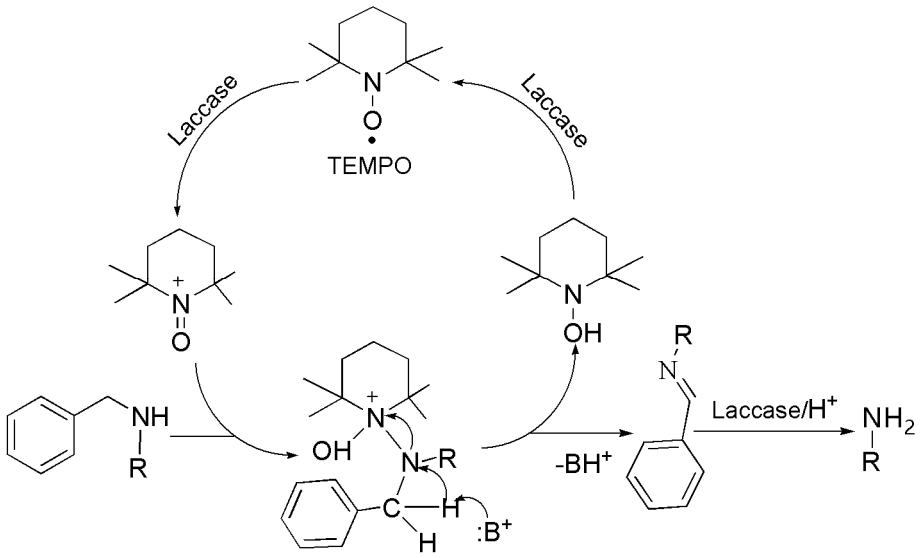


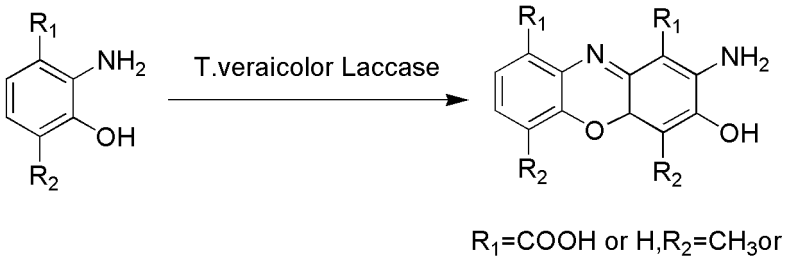
Figure 5. Possible mechanism of C–N bond breakage catalyzed by laccase.

4. Laccase-Catalyzed C–N, C–C, C–O Bond Formation

The formation of C–C, C–N, and C–O bonds catalyzed by laccase has crucial application potential for preparing multifunctional polymer materials and the organic synthesis of amino acid derivatives [107]. It is similar to the anabolic process in vivo, which catalyzes the homologous/heterologous oxidative coupling of low-molecular-weight organic compounds from polymeric products [108]. For example, laccase from *Trametes versicolor* can catalyze the C–C homologous coupling of free radicals to prepare biaryl compounds, with the highest yield of the product being 85% [109]. In this chapter, the formation of the C–N, C–C, and C–O bonds will be introduced from three perspectives.

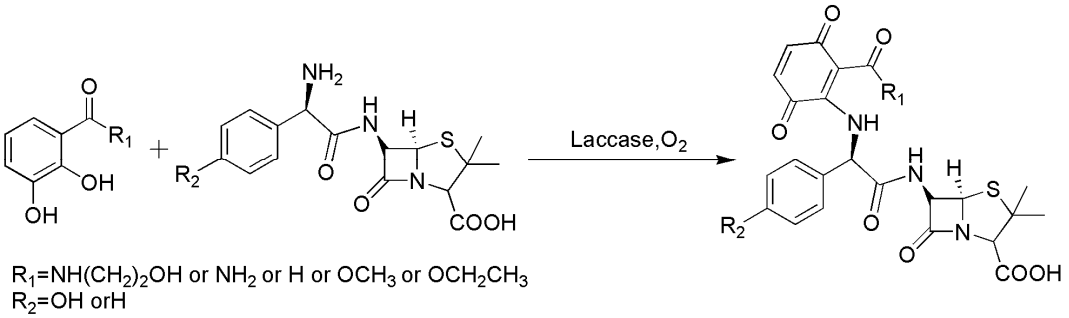
4.1. C–N Bond Formation

A single low-molecular-weight organic compound can be catalyzed by laccase to form multiple homologous isomers through a mild, green, and efficient process that can be widely used in the green synthesis of some essential antibacterial drugs [110]. It has been reported that 2-amino-4,6-dimethyl-3-oxo-phenoxazine-1,9-dicarboxylic acid (actinocin) was prepared with the oxidative coupling of 4-methyl-3-hydroxy-2-aminobenzoic acid catalyzed by laccase (from *Trametes versicolor*) with a yield of 53% (Scheme 6). Actinocin is a kind of actinomycin which can effectively block the transcription of cancer cell DNA, so it has a good anticancer ability [111]. Moreover, 2-amino-3H-phenoxazine-3-ketone has been synthesized by using laccase catalysis under similar conditions [112].

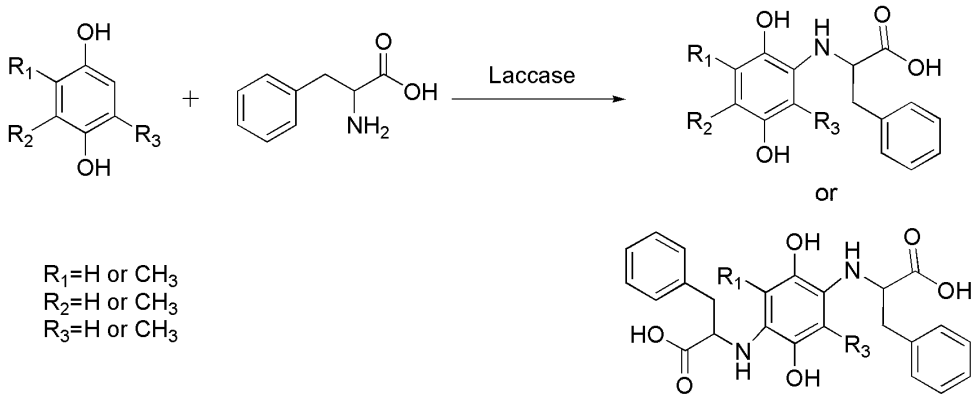


Scheme 6. Preparation of actinocin by laccase catalyzed by 4-methyl-3-hydroxy-2-aminobenzoic acid.

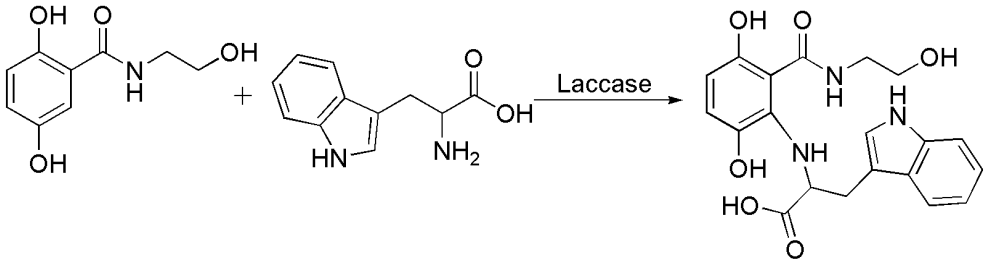
Furthermore, the amination of hydroquinone catalyzed by laccase has excellent advantages in synthesizing novel antibiotics and amino acid derivatives. For instance, eight new penicillin can be synthesized through the coupling of ampicillin or amoxicillin-2,5-dihydroxybenzoic acid derivatives catalyzed by laccase (Scheme 7) [112]. L-phenylalanine and L-tryptophan derivatives are synthesized by laccase catalysis (Schemes 8 and 9) [113–115].



Scheme 7. Laccase-catalyzed synthesis of penicillin.



Scheme 8. Synthesis of L-phenylalanine derivatives catalyzed by laccase.



Scheme 9. Synthesis of L-tryptophan derivatives catalyzed by laccase.

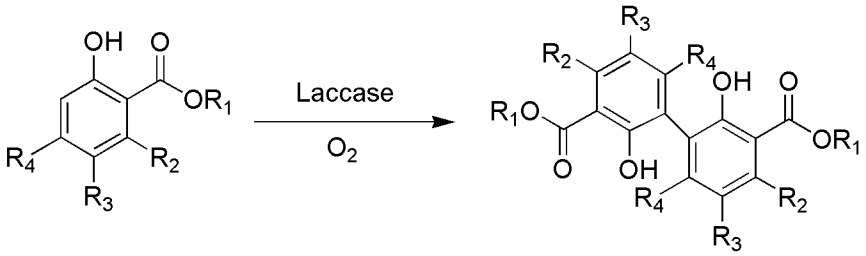
Multifunctional dimers materials are synthesized through the C–N formation of low-molecular-weight organic compounds catalyzed by laccase. The process is mild, green, and efficient and can be widely utilized in the green synthesis of some drugs and amino acids [111,114]. However, its practical applications in the synthesis of some critical antibacterial drugs and acid derivatives are limited because the efficiency of laccase-catalyzed C–N formation is low, and laccase is expensive and not easy to separate, purify, or recycle. The stability of laccase can be improved through immobilization, achieving recyclability and reducing costs, which will help promote the popularization and application of this enzyme in green synthesis [116].

4.2. C–C Bond Formation

Biaryl compounds are essential components of many natural organic compounds, and are becoming increasingly widely used in the chemical industry, medicine, food, and other fields. In recent years, biaryl compounds have generally been synthesized using reductive coupling and oxidative coupling, with the problems of low atomic utilization rates, high cost, and severe environmental pollution. Consequently, the mild catalytic synthesis of biaryl compounds is one of the most studied areas in organic chemistry [117]. In 2005, a small library of biaryl compounds was prepared using the laccase-catalyzed C–C

homologous coupling of free radicals (Table 5), with the highest yield of the product being 85% [109].

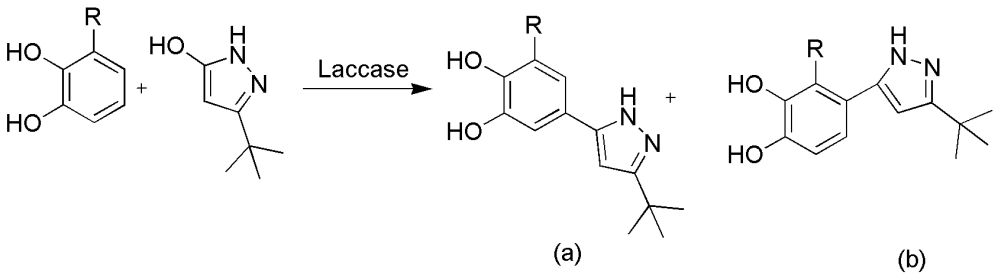
Table 5. Overview of the oxidative homocoupling of salicylic esters conducted by Ciecholewski.



R_1	R_2	R_3	R_4	Yield%	Number of Products
H	H	H	H	0	0
Me	H	H	H	0	0
Me	Me	Me	Me	84	1
Me	Me	$(CH_2)_2Cl$	Me	85	1
Me	Me	$(CH_2)_2Cl$	Me	85	5
Et	Me	$(CH_2)_2Cl$	Me	74	5
Et	Me	$(CH_2)_2Cl$	H	0	>7
Me	H	Me	H	78	3
Me	Me	H	Me	0	>7

In order to highlight the potential of laccase-mediated biaryl synthesis, Beifuss and coworkers provided an elegant approach for 3-tert-butyl-1H-pyrazole-5(4H)-one that contains biaryl compounds using the bio-oxidation of catechol, which obtained a very high biaryl compound yield of 98% when isolated (Table 6) [118].

Table 6. The 3-tert-butyl-1H-pyrazol-5(4H)-one containing biaryl compounds obtained by laccase-catalyzed oxidation of catechol.



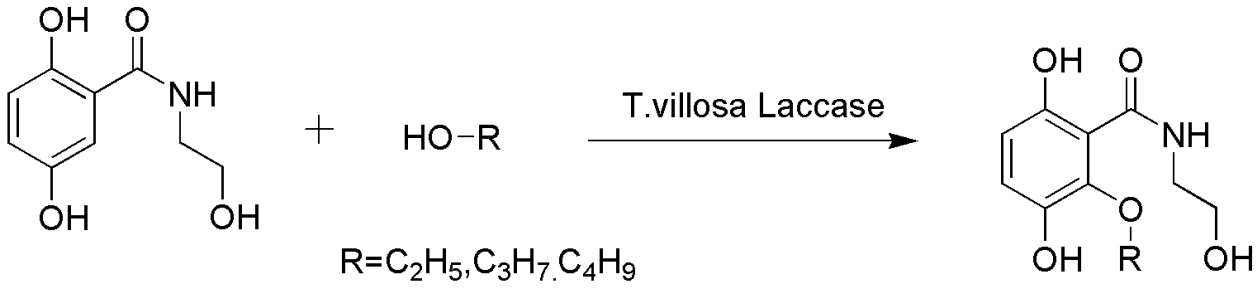
R	Regioisomer	Ratio	Yield%
H	a	-	95
Me	a,b	91:9	98
OMe	a	-	80
F	a,b	60:40	98
Br	b	-	96

Although laccase-catalyzed C–C bond formation can be used to obtain biaryl compounds mildly and efficiently, using laccases to prepare biaryl compounds is still a challenging synthetic application which appears difficult to generalize as it is entirely rationalized. As exemplified by Constantin and coworkers, laccase-mediated bio-oxidations are prone to forming unexpected and unpredicted products because subtle differences in the structure of the oxidized substrates can largely influence the outcome of a reaction [119]. The application of laccase in biaryl compound synthesis could be improved by enhancing the

substrate specificity of laccase catalysis by modifying laccase [120]. For instance, bacterial laccase with single or multiple mutations more efficiently oxidizes benzo[α]pyrene than the wild-type enzyme (the mutant exhibits about seven fold higher activity than wild-type CueO) [121].

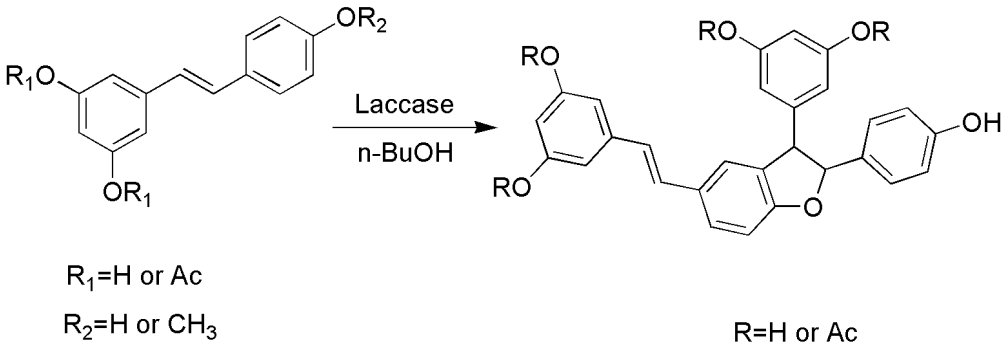
4.3. C–O Bond Formation

Moreover, laccase-catalyzed coupling reactions can add hydroxyl groups from water or fatty alcohol nucleophiles to p-dihydroxy aromatic substrates to form new C–O binding products [109]. Due to their mild conditions (air, room temperature, atmospheric pressure, and lack of toxic substances), these laccase-catalyzed reactions provide a cost-effective, environmentally friendly method for the simple and rapid cross-coupling of hydroxylated substances to the C–O binding of alcohols (Scheme 10) [122,123].

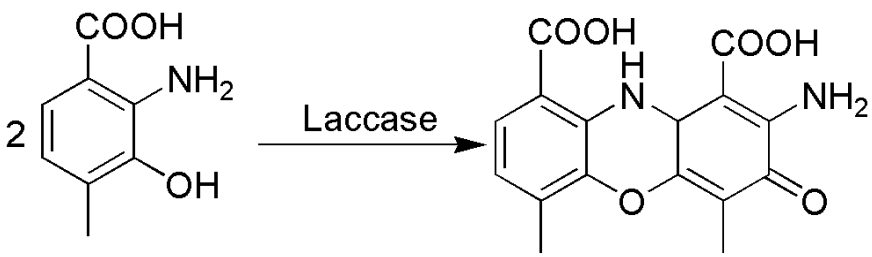


Scheme 10. Carbon–oxygen bond formation by fungal laccases: cross-coupling of 2, 5-dihydroxy-N-(2-hydroxyethyl)-benzamide with the solvents water, methanol, and other alcohols.

Moreover, laccase from different sources has been used for the selective oxidation of diphenyl phytotoxin trans-resveratrol (3,5,4-trihydroxystilbene) [108,124]: specifically, the laccases from *Myceliophthora Thermophila* and *Chrysophyceae* catalyze the production of homologous dimers from trans-resveratrol (3,5,4-trihydroxystilbene) (Scheme 11) [125] and homodimers that synthesize trans-resveratrol for the removal of ROS, respectively. In addition, the formation of actinomycin and hexazinone can be involved in antimicrobials, which are synthesized by laccase-catalyzed aminophenol C–C and C–O bond formation (Scheme 12) [111].



Scheme 11. Laccase catalyzes trans-resveratrol to form homologous dimers.



Scheme 12. Laccase-catalyzed synthesis of actinocin via oxidative homocoupling.

The laccase-catalyzed mechanism of forming C–N, C–C, and C–O bonds is similar to anabolism in vivo. First, unstable phenoxy active radical intermediates are formed by the loss of electrons from the hydroxyl phenol functional group and aromatic ring structure while reducing oxygen to water. Subsequently, oligomers are spontaneously formed by free radical intermediates; then, polymer self- or cross-polymerization products are formed with long-term repeated coupling. Laccase-catalyzed C–N, C–C, and C–O bond formation in single low-molecular-weight organic compounds can be used to obtain various functional polymer materials, for example, some critical antibacterial drugs and amino acid derivatives. In summary, the laccase-catalyzed formation of C–N, C–C, and C–O bonds has crucial application potential in preparing multifunctional polymer materials and in the organic synthesis of amino acid derivatives [67,114].

5. Conclusions and Perspectives

With the development of molecular biology and bioengineering, more laccase protein structures and mechanisms of action have been clarified. The laccase-catalyzed formation and breakage of C–C, C–N, and C–O bonds have also been increasingly involved in multifunctional polymer materials, water pollution purification, and organic synthesis. Moreover, promising theoretical breakthroughs in formation and breakage these bonds in organic compounds have been made since the development of the LMS. For example, the conversion rate for LMS-catalyzed secondary amine C–N breakage can reach up to 99%. Thus, as a green catalyst, laccase has great potential in industrial applications.

Although laccase has been widely used, the further promotion and application of this enzyme are limited by the problems of its primary source being direct extraction, its high price, and its poor stability. Therefore, research on laccase can be strengthened in the following aspects: (1) improving the efficiency of autonomous expression and reducing costs, (2) immobilizing laccase to improve stability and realize recovery, and (3) modifying the selectivity to improve the oxidation activity and increase pocket size. These studies will create a solid foundation for the further application of laccase.

Author Contributions: H.L.: conceptualization, writing—original draft, writing—review and editing. Z.Y.: conceptualization, writing—original draft, writing—review and editing. Q.W.: validation, formal analysis. Y.L.: validation, formal analysis. L.J.: validation, formal analysis. M.X.: writing—review and editing, supervision. C.X.: writing—review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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