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Cascade synthesis of benzofuran derivatives via laccase oxidation–Michael addition

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Abstract—The cascade synthesis of benzofuran derivatives was conducted from the reaction of catechols and 1,3-dicarbonyl compounds via oxidation–Michael addition in the presence of laccase and $Sc(OTf)_3$/SDS. This reaction was carried out under air at room temperature in aqueous medium, and provided benzofuran products in moderate to good yields. In addition, this reaction system showed recyclability.
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1. Introduction

In recent years, enzymes have been used in the development of organic synthesis reactions due to their synthetic, economical, and especially, environmental advantages.[1] Laccase (benzenediol:oxygen oxidoreductase, EC 1.10.3.2), a multi-copper-containing oxidoreductase enzyme, is one of the enzymes that is being studied as a biocatalyst in organic synthesis due to its ability to catalyze the oxidation of various substrates, specifically, phenols, *o*- and *p*-diphenols, and lignin derivatives. This oxidation is accompanied by the reduction of dioxygen to water.[2] Moreover, the stability of laccases in solution and their mild reaction condition for phenol moieties provide promising synthetic opportunities. Indeed, a number of laccase-catalyzed reactions have been reported.[3,4] Recently, laccase was examined in the field of enzyme-initiated domino reaction chemistry. For example, utilizing their well known propensity to oxidize phenolics, Lalk et al. reported a laccase-catalyzed nuclear animation tandem reaction,[3a] and recently, we reported the cascade synthesis of naphthoquinone derivatives via Diels–Alder reaction catalyzed by laccase.[4] These studies have demonstrated the synthetic research capabilities of this oxidative enzyme.

Herein, to the best of our knowledge, we present the first laccase-catalyzed carbon–carbon bond formation via oxidation–Michael addition for the cascade synthesis of benzofuran derivatives. Benzofurans have attracted much attention due to their broad spectrum of pharmacological activities, such as anticancer, antimicrobial, antioxidant, and anti-HIV-1 activities.[5] Therefore, the syntheses of benzofuran derivatives have been extensively investigated.[6] Most of these synthetic methods involve the formation of an annellated furan ring by the intramolecular cyclization of benzene derivatives. These procedures involve either multi-steps, rigorous reaction conditions, or expensive reagents. Recently, Nematollahi et al.[7] and Bu et al.[8] reported the one-pot synthesis of polyhydroxylated benzofurans via the oxidation of catechols by an electrochemical method or sodium iodate, respectively, in the presence of 1,3-dicarbonyl compounds. Nevertheless, using biocatalysis in the preparation of polyhydroxylated benzofurans has never been reported. This study reports the first study at accomplishing this synthesis via a biocatalyst.

In this procedure, *o*-quinones, generated in situ from the oxidation of catechols by laccase, underwent the Michael addition reaction with 1,3-dicarbonyl compounds, and then, underwent intramolecular cyclization to benzofuran derivatives. In addition, this study investigated the reaction system in the presence of either Lewis acid or Lewis base to improve reaction condition, and documented the recyclability of the catalytic system.

2. Results and discussion

In a preliminary study, the reaction of 3-methylcatechol (**1a**) and acetylacetone (**2a**) in the presence of laccase was investigated. The reaction was carried out under air at room temperature (23 °C) in the aqueous buffer solution for 4 h. This reaction system was chosen to be a model reaction for this study because the product, 3-acetyl-5,6-dihydroxy-2,7-dimethylbenzofuran (**3a**), gradually precipitated during the reaction and was easy to recover by filtration after the reaction.

Keywords: Laccase; Oxidation–Michael reaction; Benzofurans; Quinone; Green chemistry; Cascade reaction.
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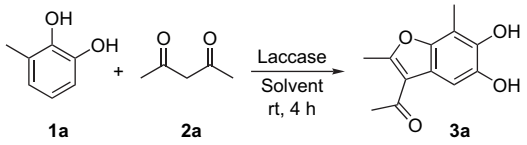
The effect of pH on this reaction system was initially studied. As summarized in Table 1, the optimal yields of **3a** were achieved when the reaction was conducted at pH 7.0. At pH 4.5, no product formed because this low pH was not basic enough to deprotonate alpha-proton from acetylacetone to facilitate the Michael addition reaction with the in situ-generated *o*-quinone. At a higher pH value of 8.0, only a small yield of **3a** was obtained due to laccase activity which was dramatically decreased at this pH.[9] Therefore, only a small amount of starting catechol was oxidized and reacted subsequently with acetylacetone. Moreover, the ratio of **1a** and **2a** also affected the yield of **3a**. The result shows that the yield of **3a** increased when using **1a** and **2a** in 1:2 ratio (entry 2).

After this preliminary study, the next phase was to improve the yield of the product by enhancing the Michael addition step. Traditionally, Michael reactions are catalyzed by strong bases, such as alkali metal, alkoxides, or hydroxides.[10] However, these strongly basic conditions can lead to a number of side reactions and subsequent reactions, and especially for this reaction system, the in situ-generated *o*-quinones are easily decomposed in the presence of hydroxides.[11] Recently, Xia et al. reported the use of a Lewis base to catalyze the Michael addition of azide ion to cyclic enones in water.[12] Herein, adding Lewis base to the catalyzed Michael addition step was investigated. Table 2 reveals that the best yield of **3a** was obtained when using pyridine as the Lewis base in phosphate buffer pH 7.0, and the ratio of **1a**:**2a**:pyridine was 1:2:1. While the use of stronger Lewis bases such as 4-dimethylaminopyridine (DMAP) and 1,4-diazabicyclo[2.2.2]octane (DABCO) provided only a low yield of the product. Although the use of pyridine gave the best result for this reaction system, the yield of the product (54%, entry 3) was still much lower than the yield of the product (64%, Table 1, entry 2) accomplished without pyridine. According to these results, adding basic reagents into this reaction did not enhance the reaction efficiency, especially, when a strong base was used.

In order to circumvent the alkaline conditions mentioned above, we decided to investigate the reaction in the presence of a Lewis acid as an alternative method. Lewis acid-catalyzed Michael reactions have been developed, allowing the reaction to be carried out under milder conditions with high efficiency.[13] Our studies focus on the use of water as the reaction medium to avoid the use of organic solvents which have become an environmental concern. Studies by Kobayashi et al. have showed that the rare earth metal triflates ($Sc(OTf)_3$, $Yb(OTf)_3$, etc.) can be used as Lewis acid catalyst in water-containing solvents.[14] Therefore, we examined a variety of Lewis acids including the water-compatible Lewis acid, $Sc(OTf)_3$, and $Yb(OTf)_3$, for the synthesis of **3a**, and also examined the recyclability of the optimal Lewis acid for this reaction as described later in this paper. The reaction was carried out under the optimal condition in the preliminary study (Table 1, entry 2) but Lewis acids were varied. The results of this Lewis acid study is summarized in Table 3. The results show that the water-stable Lewis acid, $Sc(OTf)_3$ and $Yb(OTf)_3$ can enhance the Michael addition step for this reaction system and provided a very good yield of **3a**. $Sc(OTf)_3$ showed better result than $Yb(OTf)_3$. However, we have to use 0.2 equiv of $Sc(OTf)_3$ to obtain the highest yield of **3a** (74%, entry 2) because using only 0.1 equiv of $Sc(OTf)_3$ did not have any effect on the reaction yield (63%, entry 1) when compared to the reaction without $Sc(OTf)_3$ (64%, Table 1, entry 2).

As we conducted the reaction in aqueous medium, the main drawback was the low solubility of organic substances. To overcome this problem, a small amount of surfactant, sodium dodecyl sulfate (SDS, 20 mol %) was used to improve

Table 1. The effect of pH on the reaction of 3-methylcatechol (**1a**) and acetylacetone (**2a**)

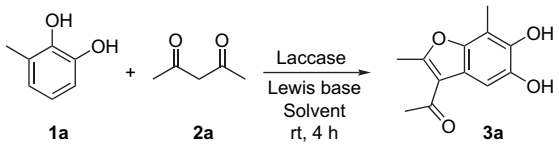


1a **2a** **3a**

Entry	Solvent	**1a**:**2a** (equiv)	Yield[a] of **3a** (%)
1	0.1 M Phosphate buffer pH 7.0	1:1	46
2	0.1 M Phosphate buffer pH 7.0	1:2	64
3	0.1 M Acetate buffer pH 4.5	1:2	0
4	0.1 M Phosphate buffer pH 8.0	1:2	6

[a] Isolated yield.

Table 2. The effect of Lewis bases on the reaction of 3-methylcatechol (**1a**) and acetylacetone (**2a**)

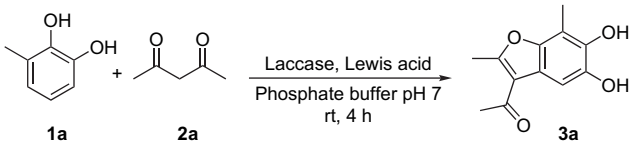


1a **2a** **3a**

Entry	Lewis bases	Solvent	**1a**:**2a**:Lewis base (equiv)	Yield[a] of **3a** (%)
1	Pyridine	Water	1:2:0.5	33
2	Pyridine	0.1 M Phosphate buffer pH 7.0	1:2:0.5	40
3	Pyridine	0.1 M Phosphate buffer pH 7.0	1:2:1	54
4	DMAP	0.1 M Phosphate buffer pH 7.0	1:2:1	9
5	DABCO	0.1 M Phosphate buffer pH 7.0	1:2:1	13

[a] Isolated yield.

Table 3. The effect of Lewis acids on the reaction of 3-methylcatechol (**1a**) and acetylacetone (**2a**)



1a **2a** **3a**

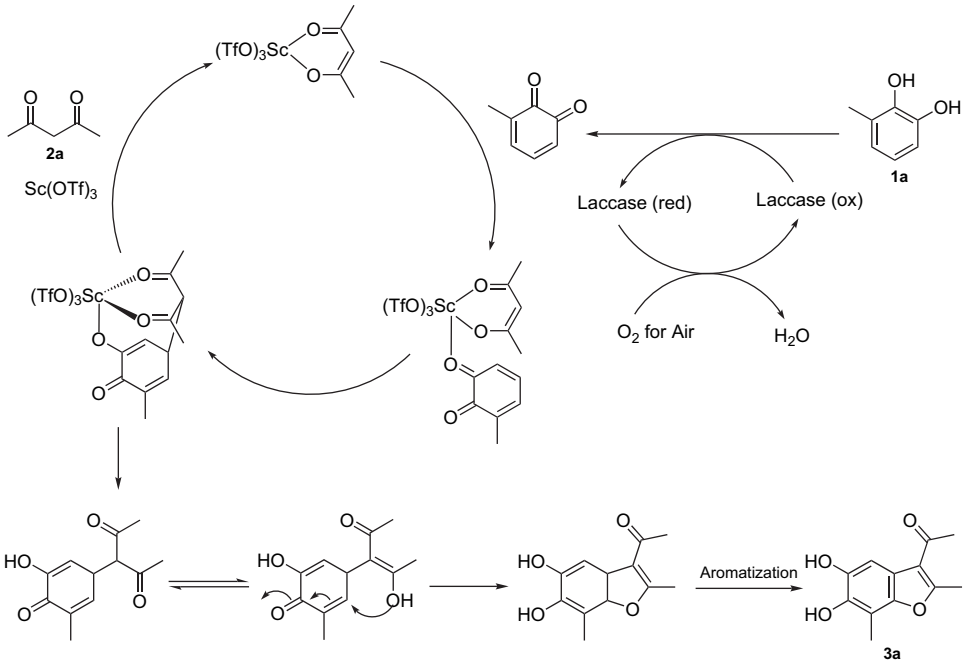
Entry	Lewis acid	**1a**:**2a**:Lewis acid (equiv)	Yield[a] of **3a** (%)
1	$Sc(OTf)_3$	1:2:0.1	63
2	$Sc(OTf)_3$	1:2:0.2	74
3	$Sc(OTf)_3$/SDS	1:2:0.2	76
4	$Yb(OTf)_3$	1:2:0.2	72
5	$InCl_3 \cdot 4H_2O$	1:2:0.2	71
6	$CuCl_2$	1:2:0.2	49

[a] Isolated yield.

the solubility, and the result shows a small increase of product yield from 74% to 76% (Table 3, entry 3). This result agrees with Kobayashi's work on the study of surfactant-aided Lewis acid catalysis in aqueous aldol reaction.[15]

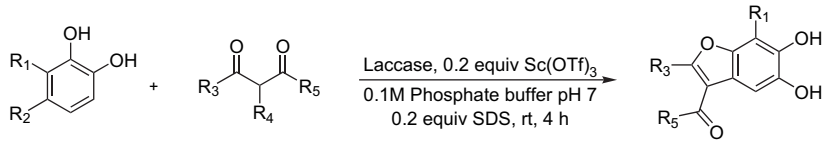
After successfully conducting the optimization experiments described above, we chose to conduct further synthesis of benzofuran derivatives by introducing 1 mmol of substituted catechols and 2 mmol of 1,3-dicarbonyl compounds in 0.1 M phosphate buffer (pH 7.0), in the presence of laccase, 20 mol % of $Sc(OTf)_3$, and 20 mol % of SDS under air at room temperature. The proposed reaction pathway of this catalytic system is illustrated in Scheme 1, and the result of the reaction of various catechols and 1,3-dicarbonyl compounds are summarized in Table 4.

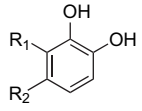
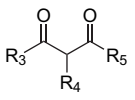
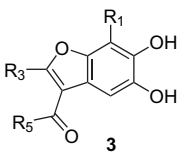
The data in Table 4 show that the reaction depends on the reactivity of the in situ-generated *o*-quinones. The very



Scheme 1. Proposed mechanism of laccase/$Sc(OTf)_3$ catalytic system for the synthesis of 3-acetyl-5,6-dihydroxy-2,7-dimethylbenzofuran (**3a**).

Table 4. The reaction of catechols and 1,3-dicarbonyl compounds



Entry	Catechol	1,3-Dicarbonyl compound	Product (% yield)[a]
	 **1**	 **2**	 **3**
1	**1a**: R_1=Me, R_2=H	**2a**: R_3=R_5=Me, R_4=H	**3a** (76)
2	**1a**	**2b**: R_3=R_5=Me, R_4=Cl	**3a** (79)[b]
3	**1a**	**2c**: R_3=Me, R_4=Cl, R_5=OEt	**3b** (48)[b]
4	**1b**: R_1=R_2=H	**2a**	**3c** (68)
5	**1b**	**2b**	**3c** (66)[b]
6	**1b**	**2c**	**3d** (46)[b]
7	**1c**: R_1=OMe, R_2=H	**2a**	No product formed
8	**1d**: R_1=F, R_2=H	**2a**	No product formed
9	**1e**: R_1=H, R_2=Cl	**2a**	**3a** (9)
10	**1f**: R_1=H, R_2=COOH	**2a**	**3a** (11)

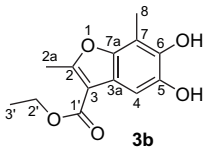
[a] Isolated yield.
[b] Reaction time is 1 h.

reactive quinones, such as 3-methoxy-1,2-benzoquinone and 3-fluoro-1,2-benzoquinone, which have rich electron donating group (OMe) and a strong electron withdrawing group (F), respectively, did not provide any desired products (entries 7 and 8). This reactivity pattern may be caused by side reactions of these highly reactive quinones. In contrast, the reaction of catechols, such as 3-methylcatechol and catechol with laccase generated moderately reactive quinones that gave excellent yields of the corresponding benzofuran products as shown in entries 1–6. Moreover, the reactivity of 1,3-dicarbonyl compounds also has an effect on the reaction. When we used 1,3-dicarbonyl compounds that had an electron withdrawing group (Cl) at alpha-position, the reaction time was only 1 h. The shorter reaction time caused by the increase of alpha-proton acidity of these 1,3-dicarbonyl compounds make them easier to deprotonate and ready to react with in situ-generated *o*-quinone in the reaction. Besides 3-substituted catechols, 4-substituted catechols, such as 4-chlorocatechol and 3,4-dihydroxy benzoic acid, can also be used for the synthesis of polyhydroxylated benzofurans (entries 9 and 10). However, the yield of the product is low.

In addition, we observed that the reactions summarized in Table 4 gave only one isomer from other potential products that could form. This could be explained by the existence of a substituent at the C-3 position of catechols that probably causes the Michael acceptors, in situ-generated *o*-quinones, to be attacked by 1,3-dicarbonyl compounds only at less hindered C-5 position to yield the observed product (see Scheme 1). Most of the products from this study are known compounds. Only product **3b** is unknown. Therefore, the structure of **3b** was confirmed by the ^{1}H NMR, ^{13}C NMR and HMBC correlations as shown in Table 5.

Next, we examined the recyclability of the two-component catalytic system, laccase/Sc(OTf)$_3$, for the synthesis of benzofuran **3a** by the reaction of **1a** and **2a** in 0.10 M phosphate buffer pH 7.0 and 20 mol % SDS. Due to the product **3a** precipitated during the reaction, we can directly reuse this catalytic system after product filtration. The results shown in Table 6 demonstrate that this catalytic system was readily recyclable for three runs, with approximately a 10% drop of the product yield/reaction.

Table 5. ^{1}H and ^{13}C assignments and HMBC correlations for compound **3b**[a]

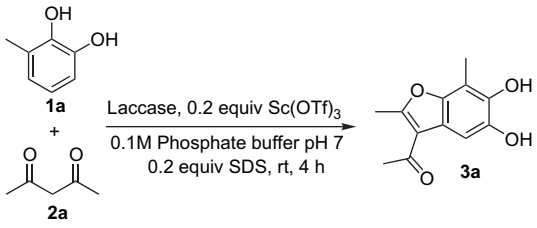


3b

Carbon	^{13}C (δ)	^{1}H (δ)	^{1}H–^{13}C correlations
2a	14.2	2.66, s, 3H	C2, C3
4	102.8	7.13, s, 1H	C3, C5, C6, C7a
8	8.9	2.25, s, 3H	C6, C7, C7a
2′	59.8	4.29, q, 2H (7)	C1′, C3′
3′	14.2	1.35, t, 3H (7)	C2′
OH (5)		9.31, s, 1H	C4, C5
OH (6)		8.42, s, 1H	C6, C7

[a] Measured in DMSO-d_6 at 125 MHz (^{13}C) or 500 MHz (^{1}H, *J* (Hz) values in parentheses). Chemical shifts are expressed in δ (ppm).

Table 6. Recycling of the catalytic system for the synthesis of 3-acetyl-5,6-dihydroxy-3,7-dimethylbenzofuran (**3a**)



Run	Yield[a] of **3a** (%)
1	76
2	62
3	51

[a] Isolated yield.

3. Conclusions

In conclusion, this study provides an efficient green chemistry synthesis of benzofuran derivatives from the reaction of catechols and β-dicarbonyl compounds using a catalytic system of laccase and Sc(OTf)$_3$ in surfactant aqueous medium. This reaction is regioselective providing only one isomer product and the first example of a two-component catalytic system employing laccase and a lanthanide Lewis acid catalyst. The yield of the products from reaction depended on both the reactivity of catechols and β-dicarbonyl compounds. For this reaction system, catechols with moderate reactivity yield benzofuran products in excellent yield. In addition, the newly developed catalytic system could also be recycled and reused for two additional runs, with only a minor drop in product yields.

4. Experimental

4.1. General

All chemicals were obtained from Aldrich and used as received without further purification. Laccase (EC 1.10.3.2) from *Trametes Villosa* was donated by Novo Nordisk Biochem, North Carolina. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. For HMBC correlations, the experiment was carried out on a Bruker-DRX 500 spectrometer. Column chromatography was performed on Combiflash Companion instrument (Teledyne Isco Company) using RediSep normal-phase flash columns. TLC was performed on aluminum sheets precoated with silica gel 60 F254 (EMD Chemicals). Mass spectra were carried out in The Georgia Institute of Technology Bioanalytical Mass Spectrometry Facility.

4.2. Enzyme assay

Laccase activity was determined by oxidation of 2,2′-azinobis-(3-ethylbenzyl thiozoline-6-sulfonate) (ABTS).[16] The assay mixture contained 25 μM ABTS, 0.10 M sodium acetate (pH 5.0), and a suitable amount of enzyme. The oxidation of ABTS was followed by an absorbance increase at 420 nm (ε_{420}=3.6×10^{4} M^{-1} cm^{-1}). Enzyme activity was

expressed in units (U=micromoles of ABTS oxidized per minute).

4.3. General procedure for benzofuran derivatives

In a 250-mL round-bottom flask, 30 mL of 0.10 M phosphate buffer pH 7.0 and catechol (1 mmol) were mixed together. Next, 100 U of laccase was added to the reaction mixture and then, 1,3-dicarbonyl compound (2 mmol), $Sc(OTf)_3$ (0.2 mmol, 0.0984 g), and SDS (0.2 mmol, 0.0576 g) were added. The reaction was then stirred under air at room temperature for 1–4 h. After the reaction was finished, the reaction mixture was then filtered and washed with water to collect the precipitated product. If the product did not precipitate, the reaction mixture was extracted by EtOAc. The organic phase was combined, dried over $MgSO_4$, and evaporated. The resulting crude products were purified by silica column chromatography, using ethyl acetate and petroleum ether as the eluent to obtain the benzofuran product. Products were characterized by ^{1}H NMR, ^{13}C NMR, and MS. Products **3a**, **3c**, and **3d** are known compounds and their ^{1}H and ^{13}C NMR data are consistent with those in the literature.

4.3.1. Ethyl-5,6-dihydroxy-2,7-dimethyl-3-benzofuran carboxylate (3b). Mp: 183–185 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.4 (t, J=7 Hz, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.3 (q, J=7 Hz, 2H, CH_2), 7.1 (s, 1H, Ar–H), 8.4 (s, 1H, OH), 9.3 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 8.9, 14.2, 14.2, 59.8, 102.8, 107.2, 108.3, 115.9, 141.9, 143.0, 146.7, 161.0, 163.9; MS (EI) m/z 250 (M^+, 98%), 221 (100), 176 (11), 93 (4), 43 (7); HRMS (EI) 250.08453 ($C_{13}H_{14}O_5$ requires 250.08412).

Acknowledgements

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