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Lipase-Catalyzed Highly Efficient 1,6-Conjugated Addition for Synthesis of Triarylmethanes

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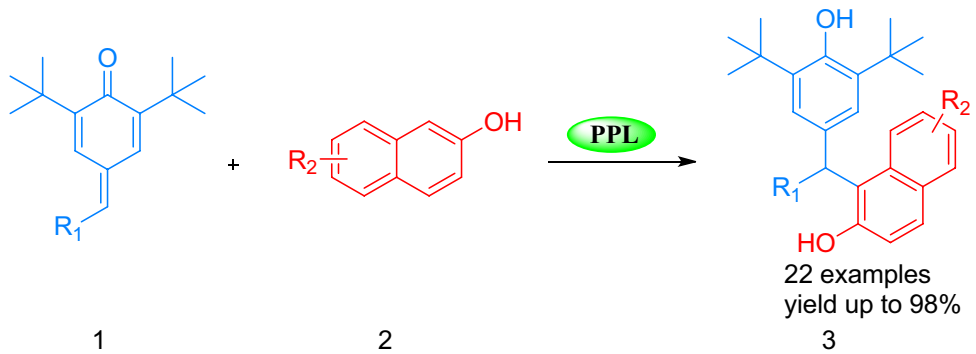
Abstract

Lipase from porcine pancreas (PPL) is first reported to catalyze direct 1,6-conjugated addition for synthesis of triarylmethanes using *p*-quinonemethides (*p*-QMs) and 2-naphthols. The catalytic activity of PPL was evaluated through investigating the solvent, the ratio of substrates, the enzyme loading and the temperature of the enzyme-catalyzed reactions. The present method proves to be environmentally friendly and efficient in terms of high yield, green catalyst and simple synthesis method.

GraphicAbstract



Keywords Lipase · Biocatalysis · 1,6-Conjugated addition · Triarylmethanes · One-pot synthesis · Ecofriendly

1 Introduction

As a kind of versatile structural skeleton, triarylmethanes plays an important role not only in the dye industry but also in the neighborhood of organic functional materials [1, 2]. In addition, triarylmethane compounds have been found to be part of some naturally occurring molecules, and such symmetrical and asymmetric compounds have been observed in drug discovery and screening with many interesting biological and medicinal properties [3, 4]. For example, 4,4′-dihydroxy-triphenylmethane (Fig. 1a) is a class of antiviral agents that show high activity against HSV-1. Bis-(4-acetoxypheny1)-2-pyridyl methane (Fig. 1b) is the main component of the bisacodyl enteric-coated tablets. The thiophene-containing triarylmethane (Fig. 1c) is an antitubercular agent having significant inhibitory activity against the proliferation of mycobacterium tuberculosis in mouse

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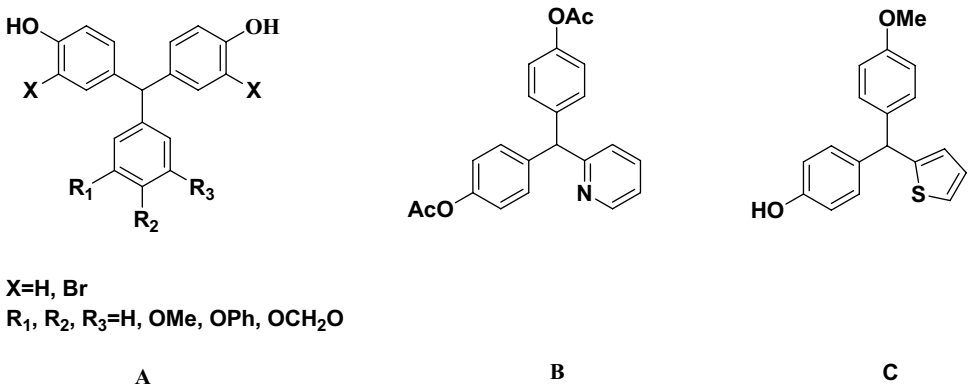


Fig. 1 Selected examples of triarylmethanes embodied with biological and pharmacological activity

and human macrophages [5–8]. Therefore, it is becoming more and more important to seek an effective synthetic route for triarylmethane and its derivatives. The most common method for the synthesis of triarylmethanes includes the Lewis acid or Brønsted acid catalyzed Friedel–Crafts type reaction of diarylmethanol or its derivatives with arenes or heteroarenes [9–12]. Lewis acid-surfactant combined catalyst developed by Kobayashi has gained much attention in catalysis during the past decades because of its dual behavior. Common Brønsted acids like $MeSO_3H$, CF_3SO_3H were also found effective for the transformation. Although the above synthetic strategy can exhibit a wide range of substrates and excellent functional group tolerance, the atomic economy is poor and harsh reaction conditions are required. Therefore, it is meaningful and necessary to develop a mild and atomic economic method for the synthesis of triarylmethane compounds.

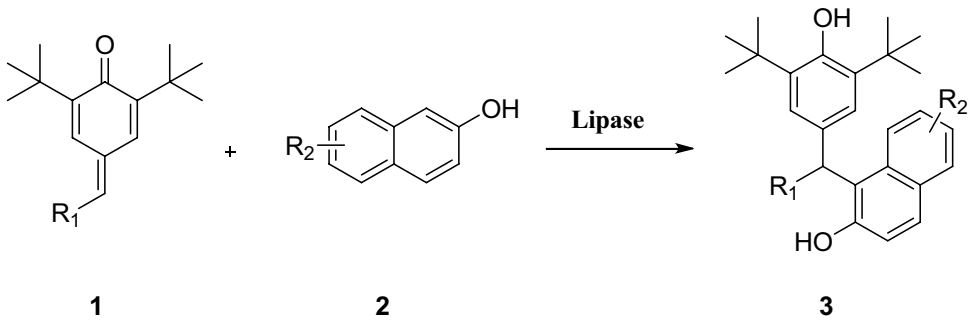
In recent years, lipases have received extensive attention as biocatalysts due to their attractive properties, such as exhibited stability in organic solvents, no cofactors required, broad substrate tolerance, commercial availability and high chemo-, regio- and stereo-selectivity [13, 14]. Lipase (EC 3.1.1.3) is a class of enzymes ubiquitous in all organisms and plays an important role in the food, beverage, biodiesel production and biopolymer industries [15, 16]. Recently, enzymes with promiscuous catalytic activity have been identified, and several new examples of catalytic promiscuity of hydrolases have been reported for their ability to catalyze carbon–carbon or carbon-heteroatom bond formations, such as aldol reaction, Michael addition, Mannich reaction, Henry reaction, Knoevenagel reaction, Hantzsch reaction and Biginelli reaction [17–26]. In our previous work, we have reported a variety of enzymatic promiscuous reactions [27–34], such as in 2008, we first reported that lipase from porcine pancreas have a promiscuous ability to catalyze asymmetric aldol reactions between acetones and aldehydes in the presence of water. To clarify the enzymatic process, we performed some experiments to tentatively hypothesize the mechanism of the new biocatalytic promiscuity. Since this novel catalytic promiscuity is enantioselective and can especially tolerate a wide range of substrates, it not only could extend the enzymatic reaction specificity, but also might be practically utilized in organic synthesis. In 2009, we described the first MML-catalyzed direct, three-component Mannich reaction with ketone, aldehyde and amine (under aqueous conditions) to form β-amino-ketone compounds. Interestingly, these promiscuous reactions can be greatly promoted by water and generally require aromatic aldehydes. A series of substrates have been explored, resulting in moderate to good yields.

Continuing our interests in lipase-catalyzed organic synthesis, we herein used lipase from porcine pancreas as a biocatalyst to catalyze the 1,6-conjugated addition reaction of a substrate to *p*-quinonemethides and 2-naphthol under mild reaction conditions to synthesize triarylmethanes. After several optimizations of the reaction conditions, the yield of the template reaction reached 95% and had good substrate tolerance (Scheme 1).

2 Experimental

PPL (lipase from porcine pancreas, 6.8 U/mg), BPL (Lipase from Bovine pancreas, 15–35 u/g), MJL (Amano Lipase M from *Mucor javanicus*, 10,000 U/mg), PFL(Amano Lipase AK from *Pseudomonas fluorescens*, ≥ 600 U/g), α-BSA(α-Amylase from *Bacillus subtilis*, 50 U/mg), AOA (α-Amylase from *Aspergillus oryzae*, 28.7 U/mg), CAL-B (Lipase from *Candida antarctia* B, 2 U/mg) were purchased from Sigma-Aldrich. BSA (Bovine serum albumin), Trypsin from Bovine pancreas, 2500 U/mg were purchased from Aladdin. Unless otherwise mentioned, all reagents were obtained from commercial suppliers and used without further purification. ^{1}H NMR, ^{13}C NMR spectra were measured on Bruker AM400 NMR spectrometer (400 MHz or 100 MHz, respectively) with $CDCl_3$ as solvent and recorded in ppm relative to tetramethylsilane (TMS). Thin layer chromatography (TLC) experiments were performed on glass-backed silica plates

Scheme 1 Lipase-catalyzed highly efficient 1,6-conjugated addition



1 **2** **3**

and visualized with UV-detection. HPLC was performed on an Agilent instrument (LC 1200 UV/Vis Detector) by using a chiral column (4.6 mm, 250 mm). HRMS were performed on Bruker Daltonics BIO TOF mass spectrometer. Column chromatography was carried on silica gel (200–300 mesh) using ethyl acetate-petroleum ether as mobile phase.

2.1 General Procedure for the Preparation of *p*-Quinonemethides

2, 6-Di-*tert*-butylphenol (0.2 mmol) and the corresponding aromatic aldehyde (25 mmol) were added to toluene (100 mL), and then the mixture was heated to reflux. Piperidine (50 mmol, 4.94 mL) was added drop wise over 1 h then the reaction mixture was refluxed for 6–15 h. After this step, drop temperature, and when it was just below the boiling point of the reaction mixture, acetic anhydride (50 mmol, 2.55 g) was added and stirring was continued for 15 min. The reaction was detected by TLC (observed under a UV lamp), and after the reaction was completed, the reaction mixture was cooled to room temperature, and the organic phase was removed under reduced pressure. The crude product was purified by silica gel rapid column chromatography and recrystallized with n-hexane to obtain the desired product.

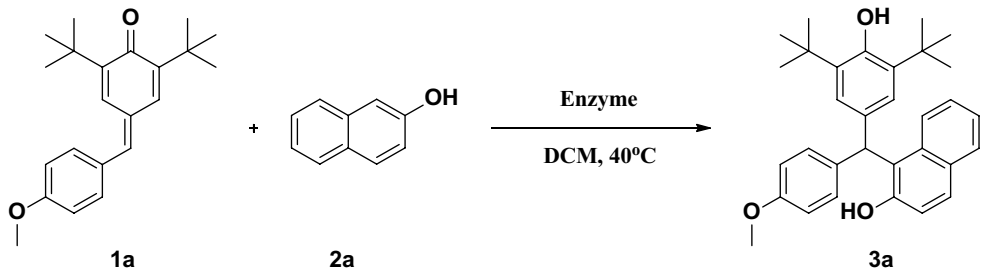
2.2 General Procedure for the Preparation of Triarylmethanes(3a-v)

Add *p*-methyl compound (0.2 mmol), 2-naphthol (0.4 mmol), 60 mg PPL, 1 mL of dichloromethane to a 10 mL Erlenmeyer flask and shaken at 40 °C, 200 rpm. The TLC traces the detection reaction (observed under ultraviolet light), and after the reaction is completed, the enzyme is removed by filtration and the solvent in the reaction is removed by a rotary evaporator. Finally, the target product was obtained by column chromatography (silica gel: 200–300 mesh, mobile phase: petroleum ether/ethyl acetate = 40:1–20:1).

3 Results and Discussion

Initially, we chose the reaction of the substrate methylene benzoquinone (**1a**) and 2-naphthol (**2a**) in dichloromethane as a model reaction. In order to select a suitable biocatalyst to catalyze the synthesis of triarylmethane compounds, the catalytic effects of different commercial enzymes on the model reaction were first investigated. The results are shown in Table 1. The catalytic activities of lipases from different sources are quite different, compared with the poorer activity of lipase from Bovine pancreati(BPL), and the difference in source and the difference between the sources of lipase from *Mucor jaranicus* and lipase from *Candida antarctia* B (MJL and CAL-B) showed moderate activity, and lipase from porcine pancreas (PPL) showed significant catalytic ability, yielding the highest yield of 95% (entries 2–4, 6, Table 1). Trypsin from Bovine pancreas also exhibited poor catalytic activity (entry 5, Table 1). The catalytic activity of different amylase sources is similar to that of lipase. α-Amylase from *Aspergillus oryzao* (AOA) has lower activity in this template reaction, while α-amylase from *Bacillus subtilis* exhibits high catalytic activity (entries 8, 9, Table 1). Under the same experimental conditions, pepsin and α-chymotrypsin were used as catalysts to obtain a moderately low yield (entries 10–11, Table 1). In addition, almost no target product was produced under the conditions of no catalyst (entry 1, Table 1). When the PPL is deactivated at 120 °C, no product could be obtained.(entry 12, Table 1).The similar result has been found when PPL was pretreated with urea as a denaturing agent (entry 14, Table 1). The results show that the denatured PPL loses its natural activity as well as its catalytic ability of non-natural reactions. In order to determine the effect of urea on the model reaction, only urea was used to catalyze the model reaction, and no catalysis activity was observed (entry 13, Table 1). Heavy metal ions can also be used to deactivate enzymes because they can react with some structural groups (such as sulfhydryl groups) and cause irreversible damage, or they can interact with some amino acid residues, causing changes in tertiary structure. Therefore, Cu^{2+} was used for pretreatment of PPL. Metal ion pretreated PPL lost the ability to catalyze model reactions

Table 1 The catalytic activities of different enzymes for 1,6-addition reaction



Entry	Catalysts	Yield[a] (%)
1	No enzyme	2
2	Lipase from Porcine pancreas (PPL)	95
3	Lipase from *Bovine pancreatic* (BPL)	29
4	Lipase from *Mucor jaranicus* (MJL)	50
5	Trypsin from Bovine pancreas	11
6	Lipase from *Candida antarctia* B (CAL-B)	64
7	Amano lipase from *Pseudomonas fluorescens*	75
8	α-Amylase from *Aspergillus oryzao* (AOA)	21
9	α-Amylase from *Bacillus subtilis*	71
10	Pepsin	45
11	α-Chymotrypsin	30
12	Denatured PPL	0[d]
13	Urea (200 mg)	0
14	PPL (pretreated with urea)	1[b]
15	$CuSO_4$ (39.9 mg)	0
16	PPL (pretreated with 250 mM Cu^{2+})	0[c]

Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), enzyme (30 mg), DCM (1000 μL) were added to10 mL Erlenmeyer flask, and shaken at 200 rpm at 40 °C for 48 h

[a]All yields were determined by HPLC

[b]PPL (30 mg) in urea solution (6.7 M) [urea (400 mg) in deionized water (1 mL)] was stirred at 25 °C for 24 h, and then water was removed by lyophilization before use

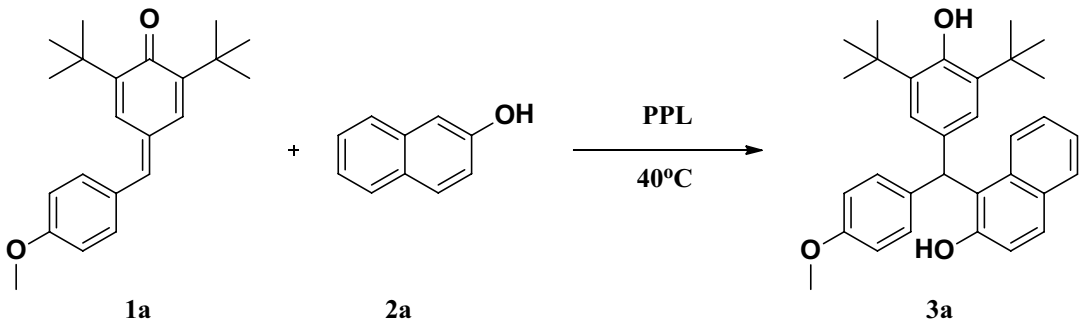
[c]PPL (30 mg) in Cu^{2+} solution (250 mM) [CuSO4 (39.9 mg) in deionized water (1 mL)] was stirred at 25 °C for 24 h, and then water was removed by lyophilization before use

[d]PPL (30 mg) at 120 °C for 48 h

with yields of only 0% (entry 16, Table 1). Metal ion treatment also results in a severe decrease in the natural activity of PPL. The blank reaction using only Cu^{2+} as a catalyst failed to give the product (entry 15, Table 1). The above control experiments show that the PPL catalyzes the model reaction, and its specific three-dimensional structure is crucial for the catalytic activity. Thus, we finally chose PPL as the best biocatalyst to catalyze this 1,6-addition reaction.

Since the reaction medium can directly or indirectly affect the enzyme activity, the choice of the solvent for the enzymatic reaction is also one of the key factors for the reaction to be effective. We selected a series of solvents with different polarities to examine their effect on the template reaction. The results are shown in Table 2. The extent to which different types of solvents affect the reaction varies widely. When acetonitrile, tetrahydrofuran, dimethyl sulfoxide, N, N-dimethylformamide, water, 1, 4-dioxane, ethanol and ethyl acetate were used as the reaction solvent, almost no target product was formed (Table 2, entries 1–8). The yields obtained with n-hexane, isopropyl ether and dichloroethane as solvents were all lower (Table 2, entries 9, 10, 13). Comparing the three similar chlorinated hydrocarbon solvents of dichloroethane, chloroform and dichloromethane, it can be found that the yields of the target products obtained by the three are significantly different, and the highest yield of 95% can be obtained in dichloromethane. When dichloroethane was used as a solvent, only a yield of 19% was obtained. This may be

Table 2 The effect of solvents on the 1,6-addition reaction



Entry	Solvents	Log P	Yield[a] (%)
1	H_2O	–	Trace
2	Ethanol	−0.24	3
3	CH_3CN	−0.33	Trace
4	DMF	−1	Trace
5	1,4-Doxane	−1.1	Trace
6	DMSO	−1.3	2
7	THF	0.49	1
8	Ethyl acetate	0.68	Trace
9	Dichloroethane	1.3	19
10	Isopropyl ether	1.9	19
11	Chloroform	2	54
12	Dichloromethane	3.4	95
13	n-Hexane	3.5	16

Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), PPL (30 mg), Solvents (1000 μL) were added to a 10 mL Erlenmeyer flask, and shaken at 200 rpm at 40 °C for 48 h

[a]All yields were determined by HPLC

due to the fact that the polarity of methylene chloride is relatively larger than that of the former two, and the solvating ability is stronger than the former two, it is precisely the suitable polarity that makes the conformation of the enzyme satisfied with the catalytic reaction, which means that it can interact better with PPL to increase the reactivity of the enzyme to the template. Therefore, we used dichloromethane as the optimal reaction solvent for the 1,6-addition reaction.

Next, we further explored the effect of the molar ratio between *p*-quinonemethides and 2-naphthol on the reaction. The results are shown in Fig. 2. It can be observed that the relative excess of the *p*-quinonemethide (**1a**) and the relative excess of 2-naphthol (**2a**) have a noticeable effect on the effect of the reaction. The yield obtained by the relative excess of **1a** is significantly higher than the relative excess of **2a**. When **2a** is excessive, the yield decreases directly (relative to 1:1). When the molar ratio between the *p*-quinonemethide and 2-naphthol is 2:1, the highest yield of 93% can be obtained, as the ratio increases further, the yield begins

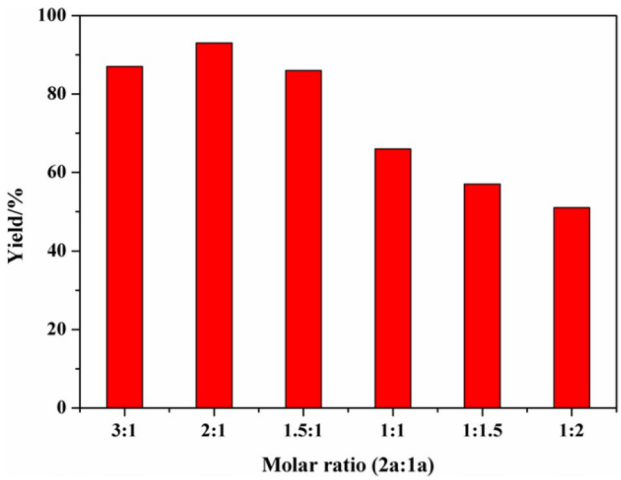


Fig. 2 The effect of molar ratio on the 1,6-addition reaction[a]. [a]Reaction conditions: In this figure, 1 is equiv 0.1 mmol, such as 3:1=2a (0.3 mmol):1a (0.1 mmol); 1:2=2a (0.1 mmol):1a (0.2 mmol). PPL (30 mg), DCM (1000 μL) were added to a 10 mL Erlenmeyer flask, and shaken at 200 rpm at 40 °C for 48 h. [b]All yields were determined by HPLC

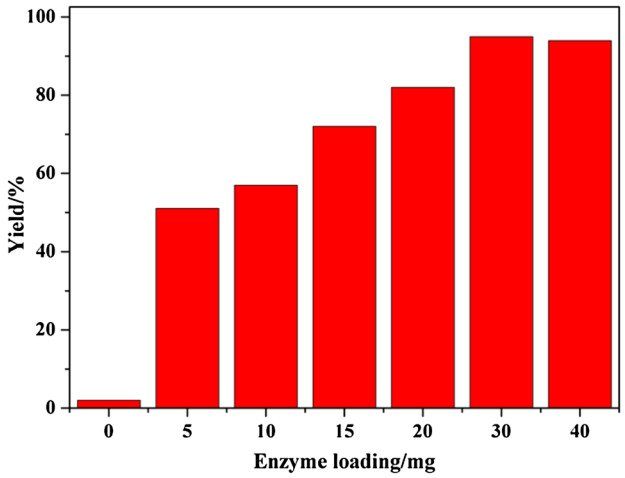


Fig. 3 The effect of enzyme loading on the 1,6-addition reaction. [a]Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), PPL (0–40 mg), DCM (1000 μL) were added to 10 mL Erlenmeyer flask, and shaken at 200 rpm at 40 °C for 48 h. [b]All yields were determined by HPLC

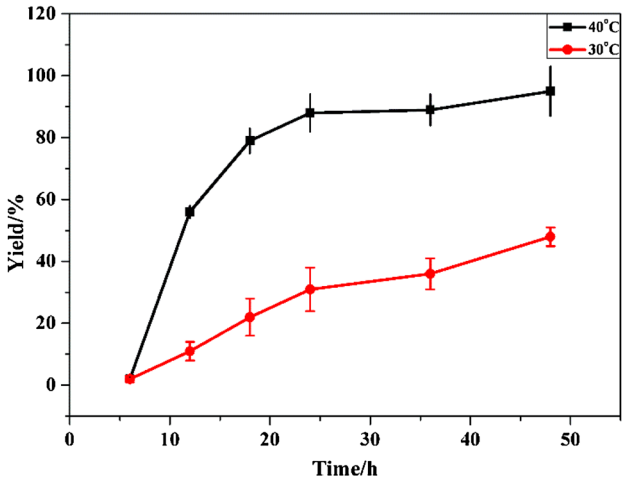


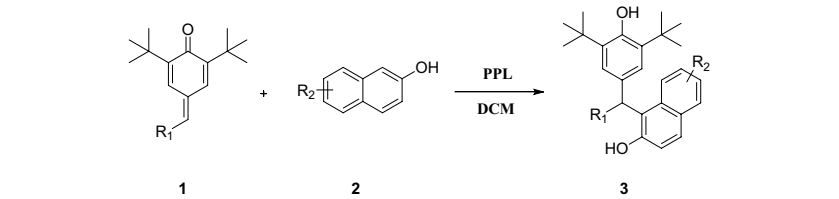
Fig. 4 The effect of temperature on the 1,6-addition reaction. [a]Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), PPL (30 mg), DCM (1000 μL) were added to a 10 mL Erlenmeyer flask, and shaken at 200 rpm at 40 °C or 30 °C for 6–48 h. [b]All yields were determined by HPLC

to decrease, so we used **2a**:**1a** = 2:1 as the best molar ratio for subsequent studies.

Subsequently, we studied the effects of the amount of enzyme, reaction temperature and time on the reaction, and the results are shown in Figs. 3 and 4, respectively. It can be observed from Fig. 3 that when the amount of the enzyme is increased from 0 mg to 30 mg, the yield of the target product is increased from 2 to 91%. However, as the amount of enzyme loading is further increased, the yield remains substantially unchanged. Based on the amount of 30 mg of enzyme loading, the reaction yield as a function of time at 30 °C and 40 °C was investigated. In order to increase the authenticity of the experiment, we performed three parallel reactions at the same time. The standard deviation was taken as the error bar and the average of the three time points as the final yield value. It can be seen from Fig. 4 that the yield of the target product obtained at 40 °C as the reaction temperature at the same reaction time is generally higher than that obtained at 30 °C. In the initial period of time, the reaction yields not only at 40 °C increased with the gradual increase of the reaction time, but also at 30 °C. Under the condition of 40 °C as the reaction temperature, the yield of the target product was 95% when the reaction time reached 48 h, and then reached a plateau.

Based on the optimal reaction conditions for the above the template, a series of studies including a variety of 2-naphthols and *p*-quinones on the conversion of the reaction has been executed to investigate the scope of substrates. The results are shown in Table 3. It can be seen from the table that the electronic effect on the aryl substituent on the methylene benzoquinone has a great influence on the reaction. Although most of the *p*-methylene benzoquinone compounds derived from electron-deficient or electron-rich aromatic aldehydes can be smoothly converted into the corresponding triarylmethane products, the yields obtained are greatly different. It can be observed from the table that compounds composed of *p*-quinonederivatives containing electron-rich like **3(a, d, g–l)** can be obtained a good yield of 69–95%. However, *p*-quinoneswith electron-deficient like **3p** yields only a 14% yield. In general, this enzymatic method is more suitable for the reaction of a *p*-quinonemethides substrate derived from an electron-rich aromatic aldehyde. However, compound **3f**, which has a methyl in the ortho position of the aryl group, is a special case, and the yield obtained is only 19%, and the methoxy group is also in the ortho position of the aryl group. A yield of 80% can be obtained for the methylene benzoquinone substrate **3i**. The reason for this disparity may be that, besides the difference in the electron donating ability of the two groups, it is also possible that the hydroxyl group on the naphthol interacts with the methoxy group in the ortho position of the aryl group in the **1i** substrate. This facilitates the attack of carbon atoms on the substrate 2-naphthol. The substrate **1f** plays a leading role due to steric hindrance, which makes the reaction more inclined to the attack direction of the hydroxyl group on the substrate 2-naphthol, and other by-products are formed, resulting in a decrease in the yield of the target product. The steric hindrance effect is prominent in such reactions. For example, the yield obtained by participating in the reaction of *p*-quinonemethide **1 m** with a relatively large naphthyl group as a substrate is low, and the aryl group is investigated. When the benzene ring of **1a** was altered to naphthalene ring, the yield plunged from 69 to 22%. Also, no product could be obtained when the benzene ring was altered to anthracene

Table 3 Substrate scope of the 1,6-addition reaction



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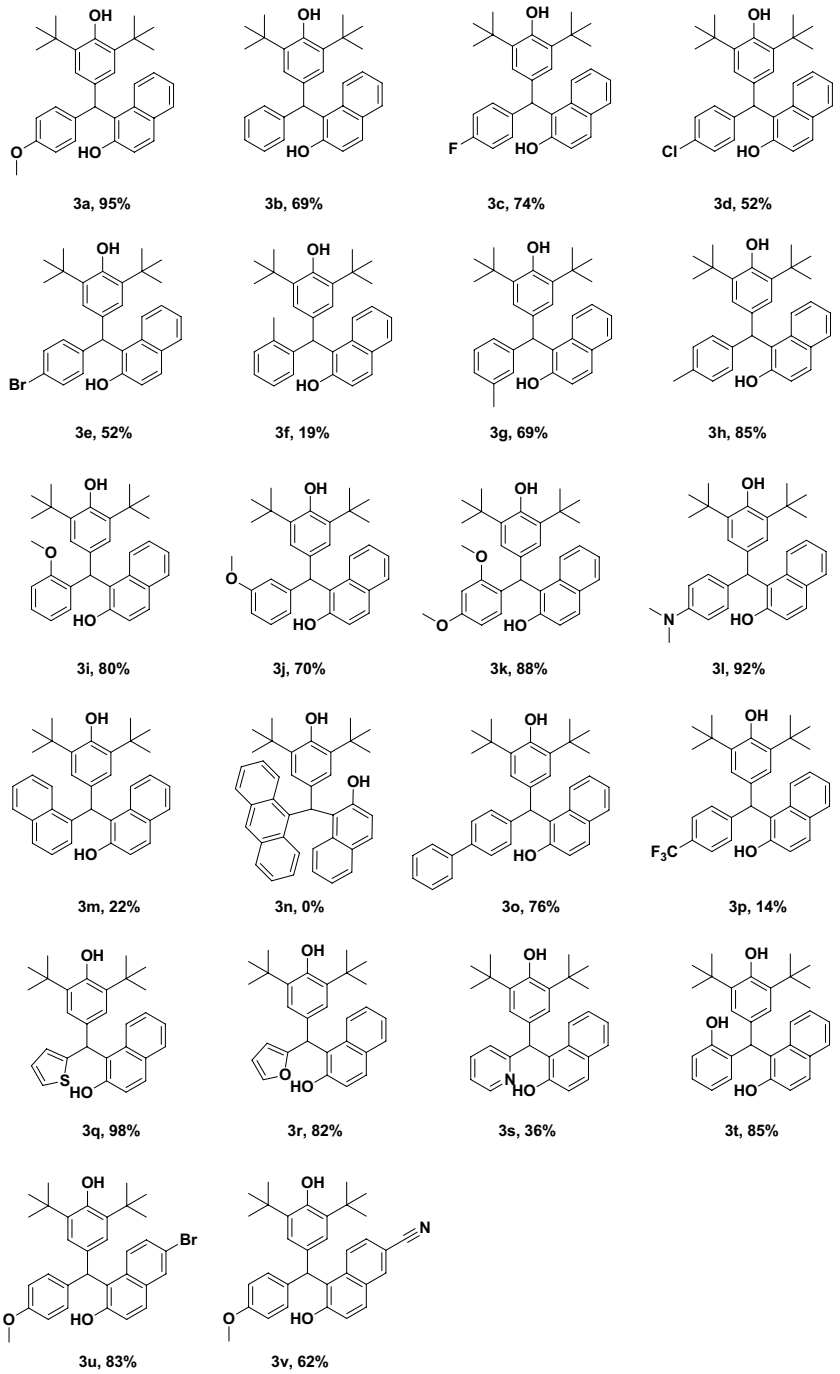

3a, 95% 3b, 69% 3c, 74% 3d, 52%

3e, 52% 3f, 19% 3g, 69% 3h, 85%

3i, 80% 3j, 70% 3k, 88% 3l, 92%

3m, 22% 3n, 0% 3o, 76% 3p, 14%

3q, 98% 3r, 82% 3s, 36% 3t, 85%

3u, 83% 3v, 62%

Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), PPL (60 mg), DCM (1000 uL) were added to a 10 mL Erlenmeyer flask, and shaken at 200 rpm at 40 °C for 48 h

[b]Column chromatography to obtain isolated yield

ring. Moreover, the larger side groups of **1a** also reduced the yield. The reaction of the *p*-quinonemethide substrates **3c**, **3d** and **3e** containing a halogen group was found to give a moderate yield. In addition, *p*-quinonemethides prepared from 2-thenaldehyde, 2-furaldehyde and 2-pyridinecarboxaldehyde is also used as a substrate to participate in the reaction, and triarylmethane **3q**, **3r** and **3 s** containing heteroaryl groups can be obtained, respectively. It can be observed that the yield obtained is sequentially decreased, which may be attributed to the sequential decrease in electron density on thiophene, furan and pyridine. To further explore the range of substrates, we simply selected two substituted 2-naphthols and **1a** for the 1,6-conjugated addition reactions. It can be seen from the table that the method is also effective for the two 2-naphthol derivatives as substrates, and a moderate to good yield can be obtained. The relatively electron-deficient 2-naphthol derivative **2v** gave a lower yield of the corresponding product than the other 2-naphthol derivative **2u**.

Based on the results of the reaction and similar transformations reported in the literature, we have reasonably speculated about the possible mechanism of action of this reaction, as shown in Fig. 5. First, *p*-quinonemethide **1a** enters the binding pocket of the enzyme, was stabilized by three hydrogen bonds. A proton is then transferred from 2-naphthol **2a** to imidazolylofHis, 2-naphthalene oxide anion immediately attacks the *p*-quinonemethide to produce intermediate **I**, and a transition state is formed. Subsequently the intermediate **I** undergoes aromatization to form intermediate **II**, the latter followed by accepting protons on the imidazole of His ultimately leads to the formation of the product **3a**.

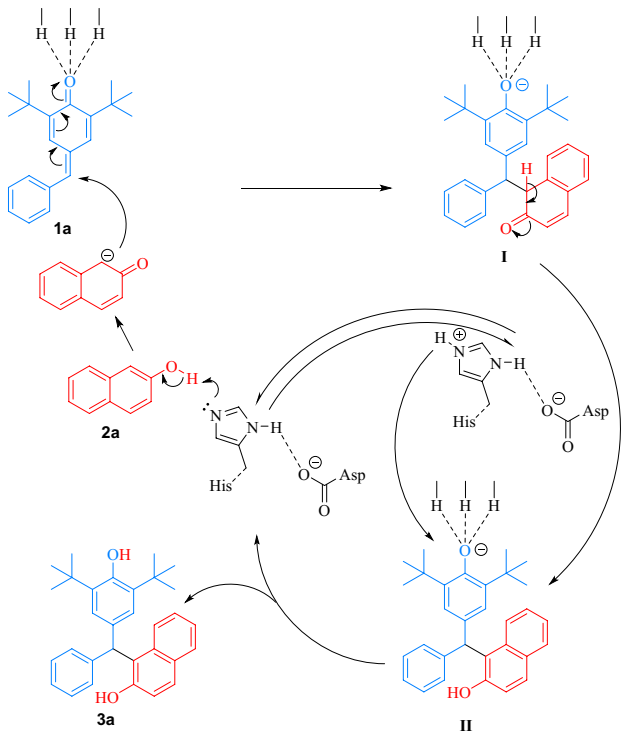

Fig. 5 Proposed reaction mechanism of the lipase-catalyzed 1,6-conjugated addition reaction

4 Conclusions

In the present work, the PPL-catalyzed synthesis of triarylmethanes by 1,6-conjugated addition reaction between a *p*-quinonemethide compounds and 2-naphthols is reported for the first time. The optimal reaction conditions were obtained by investigating factors such as enzyme source, reaction solvent, molar ratio, enzyme amount and temperature, and reaction time. A series of substrates were extended based on the final reaction conditions, and although the yield of the individual target compounds was low, the overall performance was moderate to good, and the highest yield was 98%. The method for synthesizing triarylmethane compounds is atomic economical and the reaction conditions are mild, which expands the application of lipase in organic synthesis.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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