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Article

Facile Approach to Diverse Diarylmethane Scaffolds via DBU-Catalyzed 1,6-Addition Reaction: Discovery of an Antibacterial Agent

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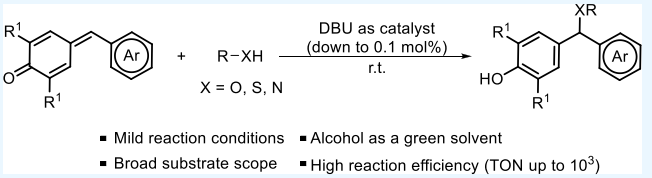
ABSTRACT: Herein, a DBU-catalyzed 1,6-Michael addition of para-quinone methides (p-QMs) under mild reaction conditions with high efficiency (turnover number up to 10^3) and good to excellent yields is reported. The transformation proceeds smoothly with a range of nucleophiles, providing diverse diarylmethane scaffolds with good efficiency. Mechanistic studies revealed that DBU is an excellent proton acceptor and donor and that DBU can promote the addition of methanol to *p*-QMs. A preliminary investigation was also conducted of the antibacterial properties of the products.



INTRODUCTION

Substituted diarylmethane derivatives are interesting structural motifs and widely exist in natural products, pharmaceuticals, and functional materials. Among these derivatives, compounds based on the diaryl ether derivatives have attracted increasing attention due to their significant pharmacological properties.[1−3] For example, bepotastine besilate and carbinoxamine are useful H_1-antihistamines,[1] and DAMNI derivatives[3] are found to potently inhibit HIV-1 reverse transcriptase (Scheme 1a).

Para-quinone methides (*p*-QMs), which exist in a variety of natural products such as fungal metabolites, terpenes, and plant pigments,[4] renowned for their distinctive fusion of carbonyl and olefinic functionalities, have served as valuable building blocks in the synthesis of diarylmethane derivatives.[5] Among the classical synthetic routes, 1,6-Michael addition stands out as one of the most efficient and atom-economical methods for constructing structurally intricate diaryl ether derivatives, possessing a significant practical value, all starting from basic materials (Scheme 1b). The Mei group reported the utilization of Lewis acid $[UO_2(NO_3)_2{\cdot}6H_2O]$ as a metal-based catalyst for activating vinylogous Michael acceptors (*p*-QMs) to synthesize substituted diaryl ether derivatives.[6] Following a similar strategy, Lu and co-workers reported the activation of *p*-QMs by Lewis acid $[(C_4H_{12}N_2)_2[BiCl_6]Cl{\cdot}H_2O]$ to form diaryl ether derivatives.[7] The Waghmode group reported the activation of *p*-QMs by excess Brönsted strong acid (trifluoroacetic acid) to form diaryl methanol derivatives with diol.[8] Despite the elegant achievements mentioned above in Micheal additions of *p*-QMs, these methods present several disadvantages, such as the need for problematic acetonitrile as solvent[9] and low turnover number (TON) and turnover frequency (TOF). There is still room for innovation and development in terms of novel, practical, and efficient chemistry.

One of the most important future goals of organic reactions will be the development of a simple, green, and efficient catalytic reaction, which has a high TON. This will not only improve the economy of the catalytic process but also limit the problems of product contamination. Inspired by the above impressive advancements and our group's research on green chemistry,[10] herein, we demonstrate the first example of the DBU-catalyzed 1,6-Michael addition of *p*-QMs with kinds of nucleophiles under mild reaction conditions with high efficiency (TON up to 10^3) and good to excellent yields (Scheme 1c).

RESULTS AND DISCUSSION

To achieve this strategy, the model reaction using 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**1a**) and CH_3OH (**2a**) at room temperature under air conditions was tested, as shown in Table 1. The effects of different bases on the product yields were investigated. Initially, NEt_3 (1 equiv) was selected as an additive, and the desired product **3a** was obtained in an 83% yield (Table 1, entry 1). To improve the yield of **3a**, other alkaloids, such as NMM, DABCO, and DBU, were examined. Encouragingly, an excellent yield was attained when 1.0 equiv of DBU was added (99%, Table 1, entry 4). Other bases, such as ^{t}BuOK, CH_3ONa, NaOH, K_2CO_3, and NaOAc (Table 1, entries 5−9), were also tested. However, no better yield of **3a** was observed compared with that of DBU. Pleasingly,

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Scheme 1. Molecules of Interest and Current Technologies

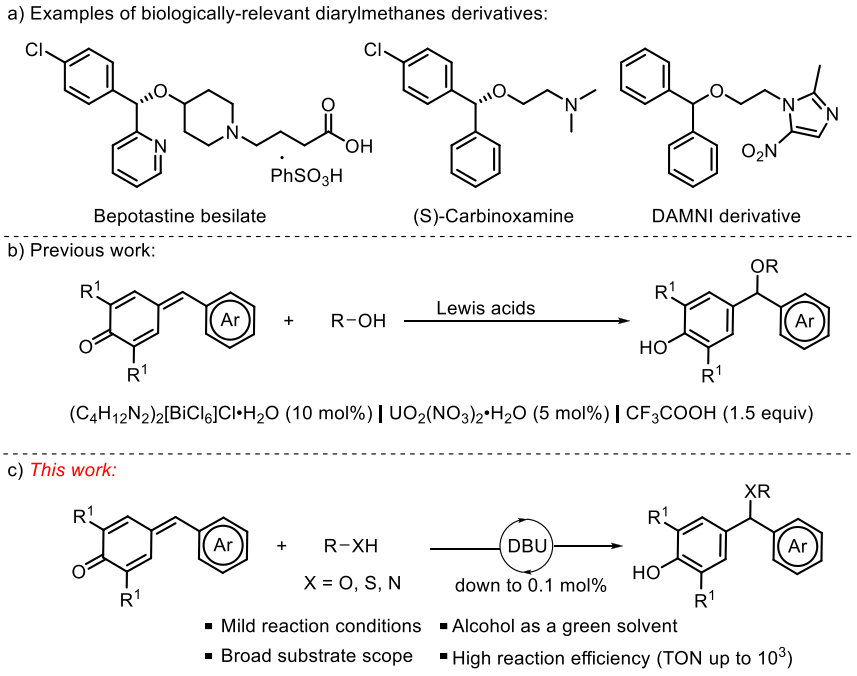
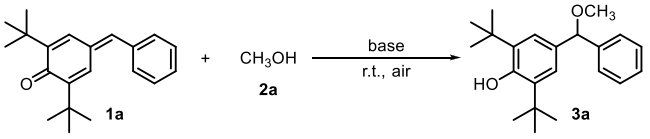


Table 1. Optimization of the Reaction Conditions[a]



entry	base (equiv)	time	yield (%)[b]
1	NEt_3 (1.0)	72 h	83
2	NMM (1.0)	72 h	N.R.
3	DABCO (1.0)	72 h	60
4	DBU (1.0)	5 min	99
5	^{t}BuOK (1.0)	1 h	80
6	CH_3ONa (1.0)	1 h	84
7	NaOH (1.0)	1 h	90
8	K_2CO_3 (1.0)	1 h	81
9	NaOAc (1.0)	75 h	42
10	DBU (0.5)	10 min	99
11	DBU (10%)	10 min	99
12	DBU (5%)	10 min	99
13	DBU (1%)	1 h	99
14	DBU (0.1%)	48 h	99
15	NaOH (5%)	48 h	61

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (5.0 mL), base, r.t., in air. [b]Yield of the isolated product, N.R. = no reaction.

even with 1 mol % DBU as catalyst, a quantitative yield of **3a** was still achieved under otherwise identical reaction conditions (Table 1, entry 13). Further decreasing the DBU loading to 0.1 mol % gave a 99% yield (Table 1, entry 14). Nevertheless, the reaction time requires 48 h. Reduction of the NaOH loading to 5 mol % gave only a 61% yield of **3a** (Table 1, entry 15).

With the optimized reaction conditions in hand and with a focus on reaction efficiency, the developed protocol was extended to various p-QMs, each possessing different electronic and steric properties, utilizing 1 mol % DBU as the catalyst. It was found that p-QMs containing electron-donating groups, such as Me, Et, ^{i}Pr, and OMe, at the para or ortho positions of the phenyl group afforded the corresponding products in moderate to good yields (Schemes 2 and 3a–f). P-QMs containing halogen groups, such as Cl and Br, at the ortho, meta, or para positions of the aromatic rings could also give satisfactory yields (Schemes 2 and 3g–i). We were delighted to note that *p*-QMs with naphthyl and thienyl were also suitable and provided the corresponding products in excellent yields (Schemes 2 and 3j,k). For further investigation, a series of nucleophiles were evaluated. The substrates, such as ethanol, isopropyl alcohol, thiophenol, and aniline, were successfully employed in the reaction with *p*-QM **1a** for the synthesis of corresponding products in moderate to good yields (Schemes 2 and 3l–o). In addition, d_3-methanol as a nucleophile provided the desired product $\boldsymbol{d_3}$**-3a** in a 90% yield.

Inspired by these results, we embarked on investigating the addition of diverse α-amino acid esters to the reaction with *p*-QM. Recently, Panda and co-workers developed a proficient strategy for the one-pot synthesis of diverse diaryl methyl amino acid esters by K_2CO_3-promotion.[11] However, the need for large amounts of K_2CO_3 (6 equiv) and a toxic solvent ($CHCl_3$) has hindered its further application. Remarkably, our DBU-catalyzed system allows for a smooth reaction of *p*-QM with α-amino acid esters using DBU as a catalyst and EtOH as a green solvent at room temperature. As depicted in Scheme 3, α-amino acid esters containing alkyl groups, such as glycine, valine, isoleucine, and leucine derivatives, proved to be highly suitable and yielded the desired products with commendable conversion efficiencies (**5a–5d**). Subsequently, amino acid esters featuring phenyl and indolyl groups were tested to demonstrate the widespread applicability of this reaction.

The scalability of this transformation to the gram-scale level has been validated through the utilization of model substrates, as showcased in Scheme 4a. In an open-air beaker, **3a** was produced by recrystallization, yielding 95% (1.55 g) using 0.1 mol % DBU as a catalyst. This result demonstrates the practical potential of this procedure in the preparation of useful molecules, paving the way for further insightful studies. To

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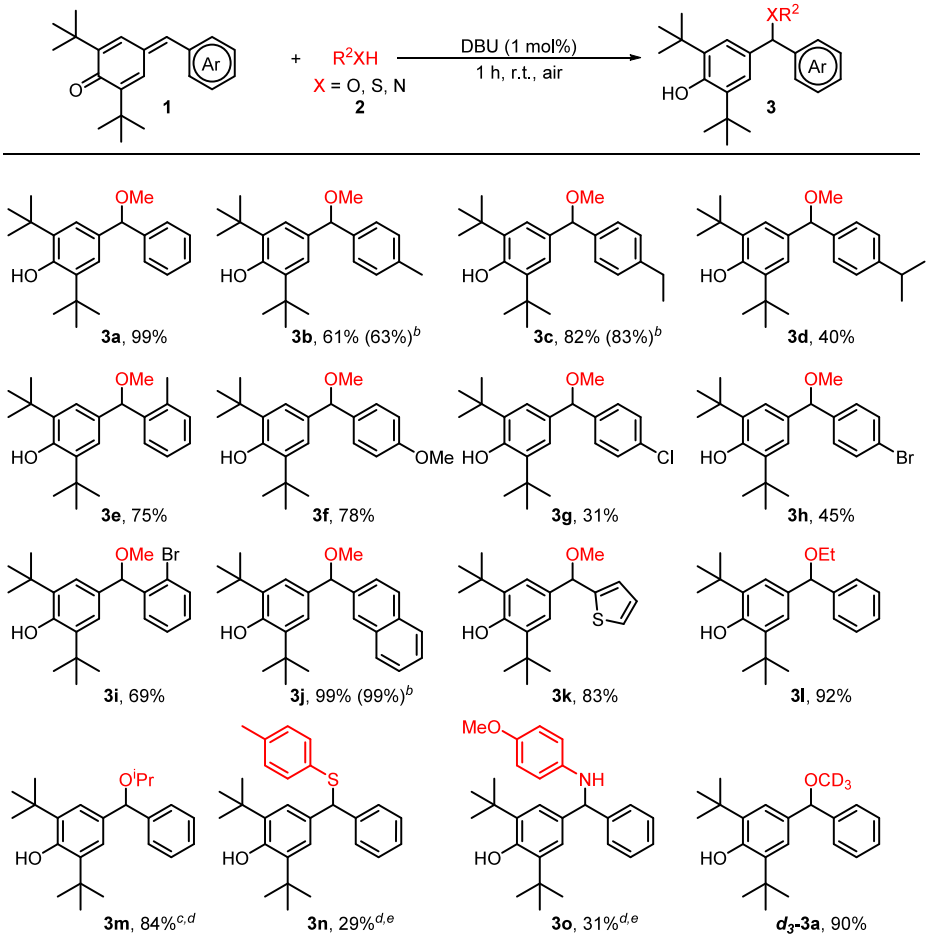
Scheme 2. Scope of the Diarylmethane[a]



[a]Reaction conditions: **1** (0.50 mmol), **2** (5.0 mL), DBU (1 mol %), r.t., 1 h, in air. Yield of the isolated product. [b]DBU (1 mol %), 48 h. [c]70 °C. [d]DBU (5 mol %). [e]**2** (1.2 equiv) in iPrOH (5.0 mL).

illustrate the synthetic applications of the product, further transformations of **3a** demonstrated its potential to serve as a versatile building block (Scheme 4b). The methoxy group of **3a** was smoothly converted to $-N_3$, allyl, and alkynyl groups, catalyzed by $FeCl_3$.

We made some control experiments to shed light on the catalyst activation step of DBU. The intermolecular competitive reaction was carried out with CH_3OH and CD_3OD as the substrates to determine the kinetic isotopic effect (KIE), yielding a value of K_H/K_D = 0.84, as shown in Scheme 5a. This result suggests that C−H cleavage of CH_3OH is unlikely to be a part of the rate-determining step. Chemical shift of methanol in DBU as an additive has changed obviously via ^1H NMR spectra, compared with the methanol alone in $CDCl_3$, which reveals the interaction between DBU and the protons on methanol (Scheme 5b).

The DBU's mode of action was investigated by means of DFT studies at the (SMD)B3LYP-D3(BJ)/6-311+G(d,p)//B3LYP-D3(BJ)/6-31G(d) level of theory (Figure 1). The calculation results indicated that DBU is an excellent proton acceptor and donor and that DBU can promote the addition of methanol to intermediate **II** via the transition state **TS1** with an energy barrier of only 10.5 kcal/mol.

Based on the experimental results above and literature reports, the possible mechanistic pathway of the 1,6-Michael addition reaction of *p*-QMs and alcohol catalyzed by DBU is illustrated in Scheme 6. Initially, DBU abstracts a proton from methanol to form intermediate **A**, the ketone oxygen of *p*-QM **1a** coordinates with the proton of intermediate **A**, and this interaction leads to molecular polarization, followed by aromatization, yielding intermediate **C** with a more electropositive feature. Finally, intermediate **C** underwent an intermolecular nucleophilic addition reaction with methanol, promoted by DBU, to give desired product **3a**. The regenerated intermediate **A** can then initiate the next catalytic cycle.

With diarylmethanes in hand, we conducted a preliminary investigation of their antibacterial properties against *Streptococcus mutans* and *Staphylococcus aureus*, where minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) were determined by the broth microdilution method. Fortunately, as depicted in Figure 2, product **5a** exhibited antibacterial activity (*S. mutans*: MIC = 16 μg/mL, MBC = 32 μg/mL; *S. aureus*: MIC = 16 μg/mL; MBC = 32 μg/mL).

CONCLUSIONS

In conclusion, the DBU-catalyzed 1,6-Michael addition of *p*-QMs under mild reaction conditions with high efficiency (TON up to 10^3) and good to excellent yields is reported. The transformation proceeds smoothly with kinds of nucleophiles,

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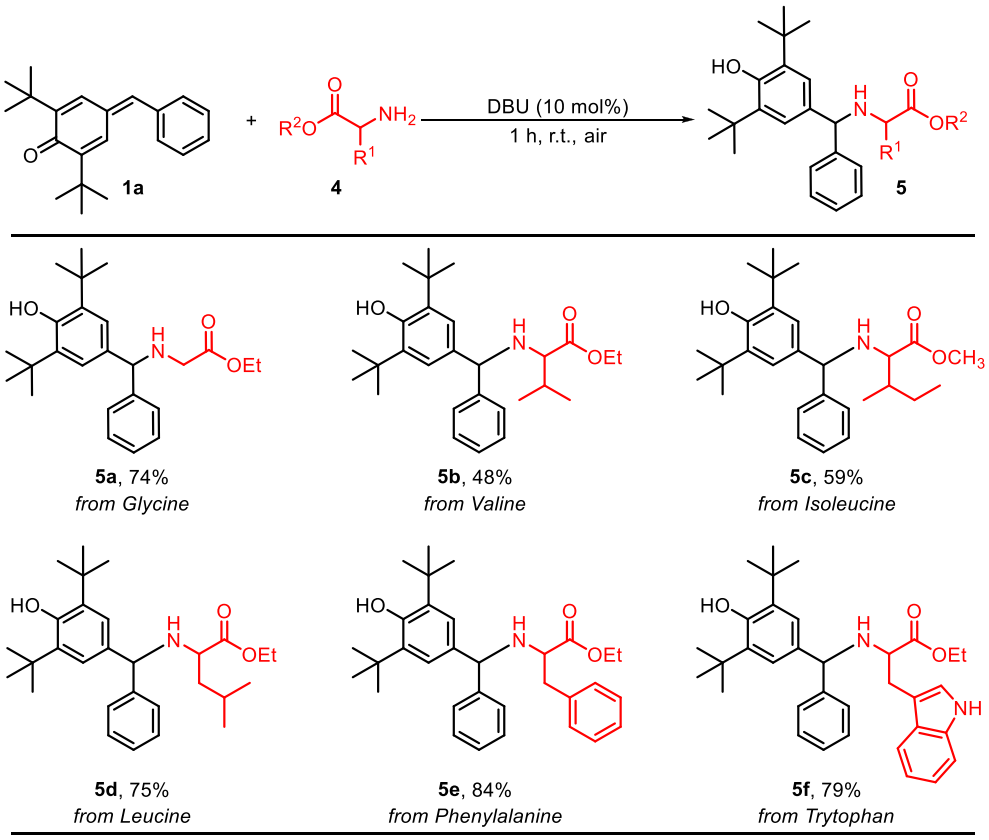
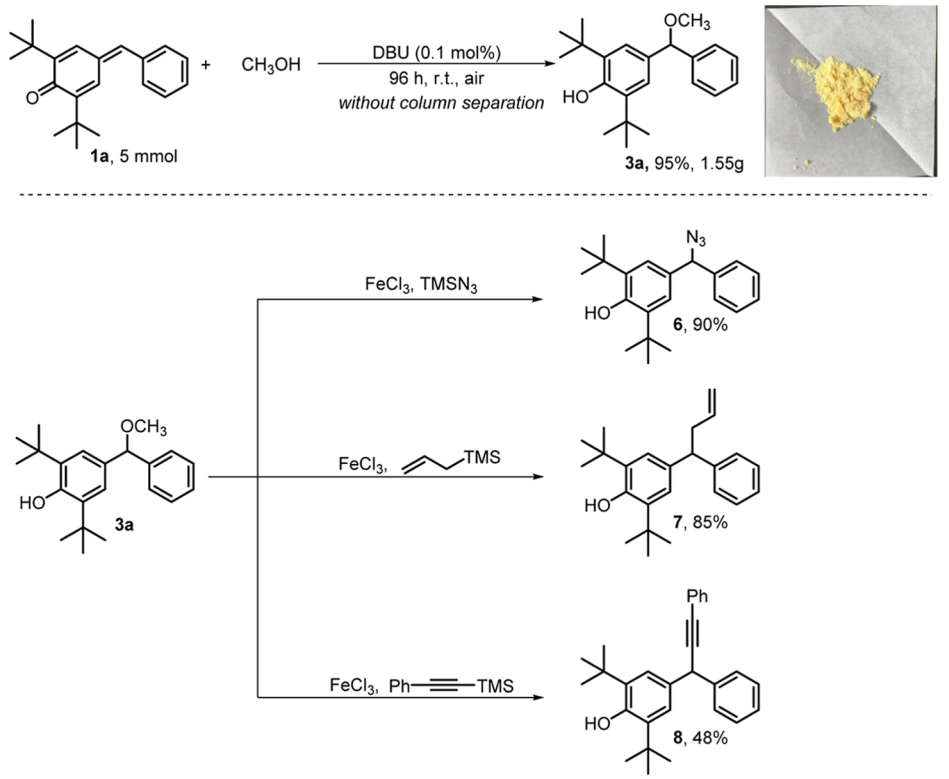
Scheme 3. Scope of the Amino Acid Esters[a]



[a]Reaction conditions: **1** (0.50 mmol), **4** (1.2 equiv), DBU (10 mol %), EtOH (5.0 mL), r.t., 1 h, in air. Yield of the isolated product.

Scheme 4. Scale-Up Reaction and Synthetic Applications



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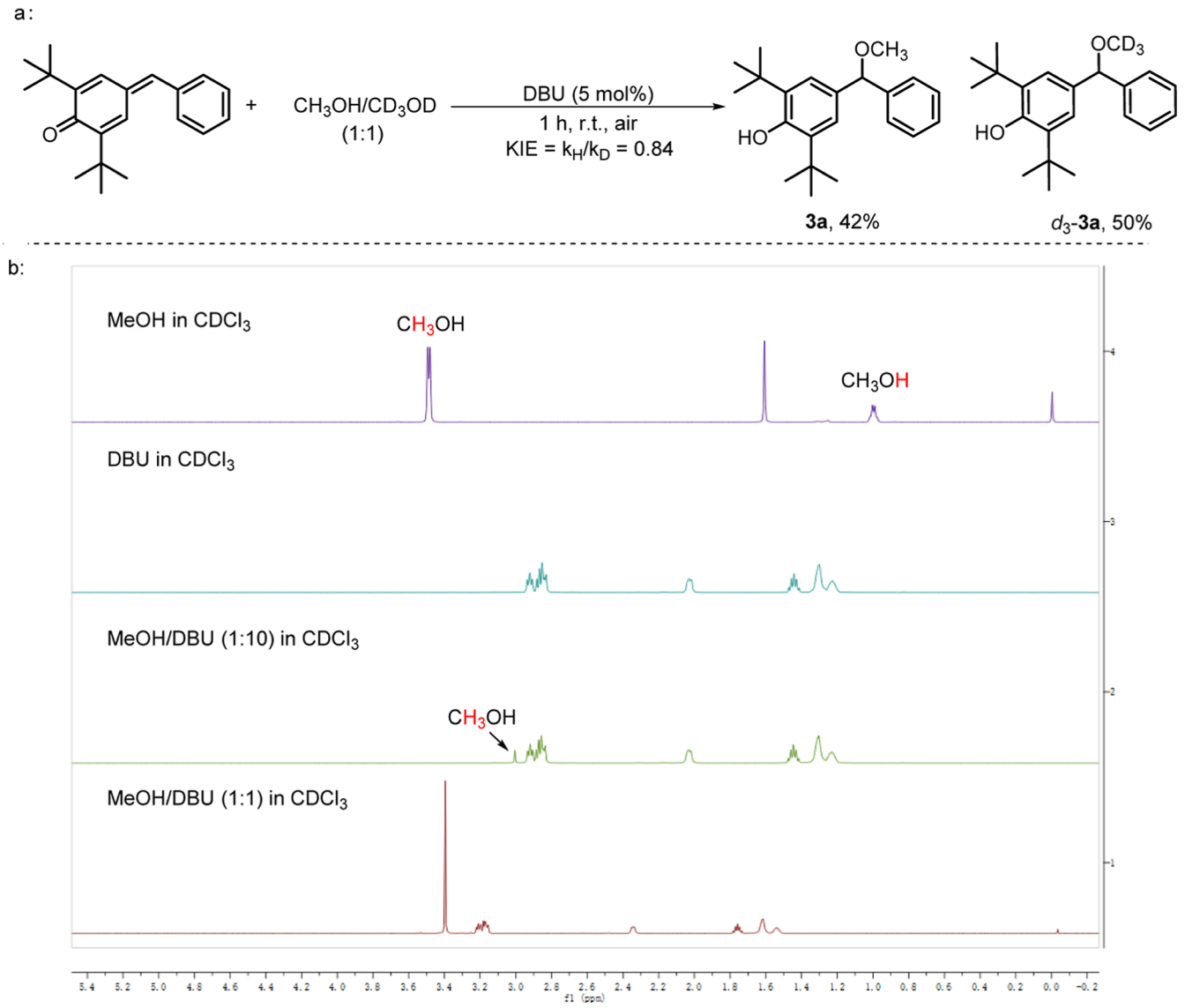
Scheme 5. Control Experiments



such as alcohol, thiophenol, aniline, and amino acid ester, providing valuable diarylmethanes with good efficiency. Detailed control experiments and mechanistic studies give strong supportive evidence of the proposed mechanism. In addition, a preliminary investigation into the antibacterial properties of the products was initiated.

EXPERIMENTAL SECTION

General Methods. Chemicals were received from commercial sources without further purification or prepared by literature methods. Melting points are uncorrected and recorded on a Digital Melting Point Apparatus WRS-1B. ^{1}H NMR and ^{13}C NMR spectra were measured on a 400 or 500 MHz Bruker spectrometer, using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, and m = multiplet. Chemical shifts are given in δ relative to TMS; coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectrometry (HRMS) was performed with a TOF MS instrument with an ESI source. Column chromatography was performed using EM silica gel 60 (300−400 mesh). Reactions were monitored by thin-layer chromatography (TLC). Visualization was achieved under a UV lamp (254 and 365 nm).

General Procedure for the Synthesis of 3a−3l. To a solution of *p*-QMs (**1**, 0.5 mmol) with DBU (1 mol %) and R^2OH (**2**, 5.0 mL) were added to a Schlenk reaction tube. After being stirred gently at room temperature for 1 h, the reaction mixture evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate to afford the desired product **3a−3l**.

Procedure for the Synthesis of 3m−3o. To a solution of *p*-QMs (**1**, 0.5 mmol) with DBU (10 mol %), R^2XH (**2**, 1.2 equiv) and ^{i}PrOH (5.0 mL) were added to a Schlenk reaction tube. After being stirred for 1 h (**3m** at 70 °C; **3n−3o** at room temperature), the reaction mixture was washed with saturated $NaHCO_3$ (2 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate to afford the desired products **3m−3o**.

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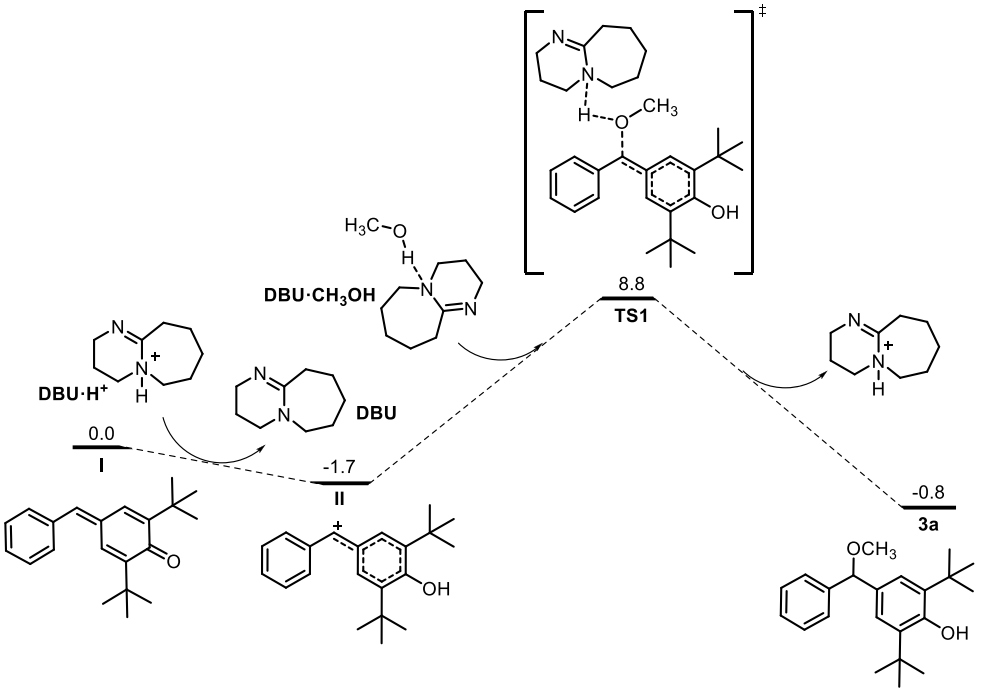
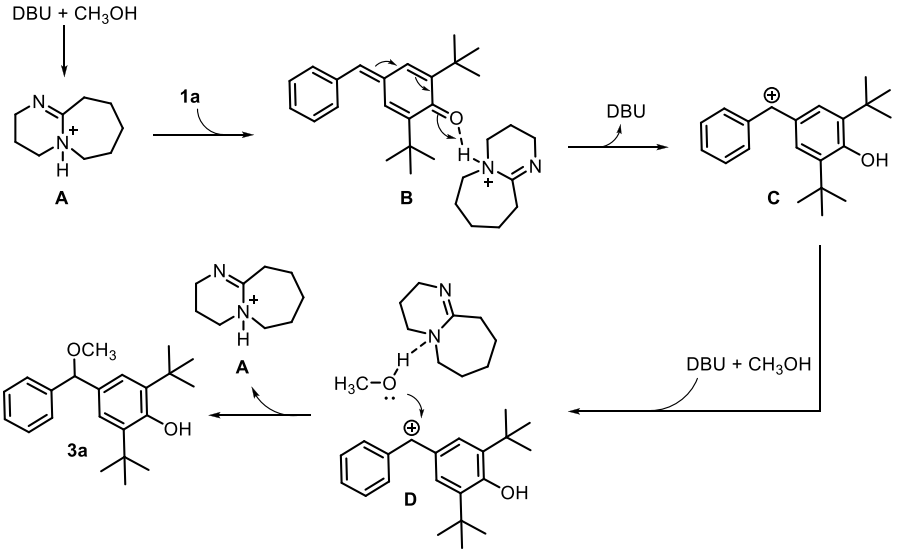


Figure 1. DFT calculation.

Scheme 6. Proposed Mechanism



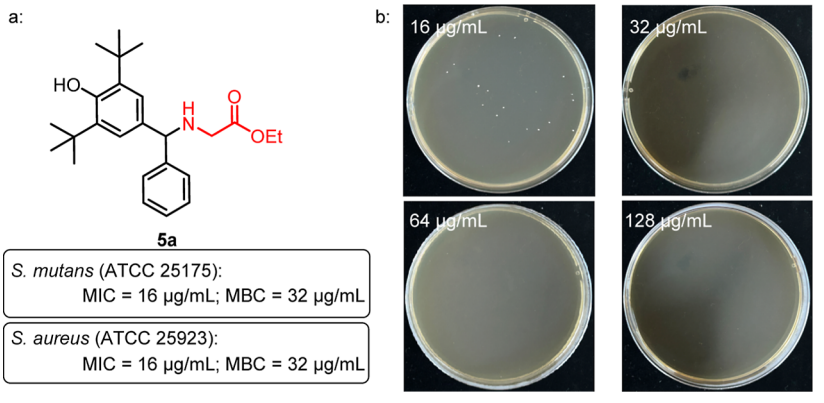


Figure 2. (a) MIC and MBC values of **5a** against *S. mutans* and *S. aureus*. (b) MBC testing graphs of **5a** against *S. mutans* after 48 h.

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Procedure for the Synthesis of 5. To a solution of *p*-QMs (**1a**, 0.5 mmol) with DBU (10 mol %), **4** (1.2 equiv) and EtOH (5.0 mL) were added to a Schlenk reaction tube. After being stirred gently at room temperature for 1 h, the reaction mixture evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate to afford the desired product **5**.

Procedure for the Synthesis of 6. **3a** (0.5 mmol), $TMSN_3$ (0.75 mmol, 1.5 equiv), and $FeCl_3$ (0.05 mmol, 10 mol %) were added successively under ambient temperature to CH_2Cl_2 (5 mL) in air. After stirring at room temperature for the appropriate time (monitored by TLC), the reaction was quenched by the addition of H_2O (3 mL), and then the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether or petroleum ether/ethyl acetate) to afford product **6**.

Procedure for the Synthesis of 7. **3a** (0.5 mmol), allyltrimethylsilane (0.75 mmol, 1.5 equiv), and $FeCl_3$ (0.05 mmol, 10 mol %) were added successively under ambient temperature to CH_2Cl_2 (5 mL) in air. After stirring at room temperature for the appropriate time (monitored by TLC), the reaction was quenched by the addition of H_2O (3 mL), and then the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether or petroleum ether/ethyl acetate) to afford product **7**.

Procedure for the Synthesis of 8. **3a** (0.5 mmol), trimethyl(phenylethynyl)silane (0.75 mmol, 1.5 equiv), and $FeCl_3$ (0.05 mmol, 10 mol %) were added successively under ambient temperature to CH_2Cl_2 (5 mL) in air. After stirring at room temperature for the appropriate time (monitored by TLC), the reaction was quenched by the addition of H_2O (3 mL), and then the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether or petroleum ether/ethyl acetate) to afford product **8**.

Large-Scale Reaction of 1a. To a solution of *p*-QMs (**1a**, 5 mmol) with DBU (0.1 mol %), and CH_3OH (50 mL) were added to a Schlenk reaction tube. After being stirred gently at room temperature for 96 h, the reaction mixture evaporated under a vacuum. The residue was purified by recrystallization with petroleum ether/ethyl acetate to afford the desired product **3a** (1.55 g, 95%).

*2,6-Di-tert-butyl-4-(methoxy(phenyl)methyl)phenol (**3a**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3a**. Yellow solid (106.9 mg, 99%), mp 72−79 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.30 (m, 4H), 7.25−7.20 (m, 1H), 7.11 (s, 2H), 5.16 (s, 1H), 5.12 (s, 1H), 3.36 (s, 3H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.1, 142.3, 135.6, 132.5, 128.3, 127.2, 126.8, 123.8, 86.0, 57.0, 34.3, 30.2.

*2,6-Di-tert-butyl-4-(methoxy(p-tolyl)methyl)phenol (**3b**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3b**. Yellow oil (62.2 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.6 Hz, 2H), 7.11 (s, 2H), 5.13 (s, 1H), 5.11 (s, 1H), 3.35 (s, 3H), 2.32 (s, 3H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.1, 139.4, 136.7, 135.6, 132.7, 129.0, 126.8, 123.7, 85.9, 57.0, 34.3, 30.3, 21.1.

*2,6-Di-tert-butyl-4-((4-ethylphenyl)(methoxy)methyl)-phenol (**3c**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3c**. Yellow oil (87.1 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 7.12 (s, 2H), 5.13 (s, 1H), 5.11 (s, 1H), 3.35 (s, 3H), 2.62 (q, J = 7.6 Hz, 2H), 1.40 (s, 18H), 1.21 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.1, 143.1, 139.6, 135.6, 132.7, 127.8, 126.8, 123.7, 86.0, 57.0, 34.3, 30.3, 28.5, 15.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{34}O_2$, 355.2632; found, 355.2635.

*2,6-Di-tert-butyl-4-((4-isopropylphenyl)(methoxy)methyl)-phenol (**3d**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3d**. Yellow oil (44.2 mg, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.12 (s, 2H), 5.13 (s, 1H), 5.11 (s, 1H), 3.36 (s, 3H), 2.93−2.83 (m, 1H), 1.40 (s, 18H), 1.23 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.1, 147.8, 139.8, 135.6, 132.7, 126.8, 126.3, 123.7, 86.0, 57.0, 34.3, 33.8, 30.3, 24.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{36}O_2$, 369.2789; found, 369.2792.

*2,6-Di-tert-butyl-4-(methoxy(o-tolyl)methyl)phenol (**3e**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3e**. Yellow solid (76.8 mg, 75%), mp 93−101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46−7.44 (d, J = 7.6 Hz, 1H), 7.24−7.30 (t, J = 7.2 Hz, 1H), 7.17−7.11 (m, 2H), 7.09 (s, 2H), 5.33 (s, 1H), 5.12 (s, 1H), 3.36 (s, 3H), 2.28 (s, 3H) 1.39 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.1, 140.0, 135.7, 135.5, 131.3, 130.4, 127.0, 126.2, 125.9, 124.3, 82.9, 57.1, 34.3, 30.2, 19.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{32}O_2$, 341.2476; found, 341.2472.

*2,6-Di-tert-butyl-4-(methoxy(4-methoxyphenyl)methyl)-phenol (**3f**).*[12] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3f**. Yellow solid (83.3 mg, 78%), mp 93−98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28−7.26 (m, 2H), 7.10 (s, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.12 (s, 2H), 3.79 (s, 3H), 3.34 (s, 3H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.8, 153.0, 135.6, 134.6, 132.7, 128.2, 123.7, 113.7, 85.6, 56.9, 55.2, 34.3, 30.3.

*2,6-Di-tert-butyl-4-((4-chlorophenyl)(methoxy)methyl)-phenol (**3g**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3g**. Yellow solid (33.6 mg, 31%), mp 87−93 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (s, 4H), 7.07 (s, 2H), 5.15 (s, 1H), 5.13 (s, 1H), 3.35 (s, 3H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.3, 141.0, 135.8, 132.8, 132.0, 128.4, 128.2, 123.7, 85.3, 57.0, 34.3, 30.2.

*4-((4-Bromophenyl)(methoxy)methyl)-2,6-di-tert-butyl-phenol (**3h**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3h**. Yellow solid (54.6 mg, 45%), mp 93−101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.30 (m, 4H), 7.25−7.22 (m, 1H), 7.11 (s, 2H), 5.16 (s, 1H), 5.12 (s, 1H), 3.36 (s, 3H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.3, 141.6, 135.8, 131.9, 131.4, 128.5, 123.7, 121.0, 85.3, 57.0, 34.3, 30.2.

*4-((2-Bromophenyl)(methoxy)methyl)-2,6-di-tert-butyl-phenol (**3i**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 8:1, v/v) afforded **3i**. Yellow solid (83.7 mg, 69%), mp 80−85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58−7.55 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.34−7.30 (m, 1H), 7.207 (s, 2H), 7.11−7.07 (m, 1H), 5.57 (s, 1H), 5.13 (s, 1H), 3.37 (s, 3H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.2, 141.5, 135.5, 132.7, 131.0, 128.6, 128.0, 127.6,

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124.0, 123.5, 84.0, 57.1, 34.3, 30.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{29}BrO_2$, 405.1424, 407.1404; found, 405.1422, 407.1402.

*2,6-Di-tert-butyl-4-(methoxy(naphthalen-2-yl)methyl)-phenol (**3j**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3j**. Yellow oil (111.9 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84−7.79 (m, 4H), 7.50−7.42 (m, 3H), 7.18 (s, 2H), 5.32 (s, 1H), 5.13 (s, 1H), 3.40 (s, 3H), 1.39 (s, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.2, 139.8, 135.7, 133.3, 132.8, 132.4, 128.1, 128.0, 127.6, 125.9, 125.6, 125.6, 125.0, 123.9, 86.1, 57.1, 34.3, 30.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{32}O_2$, 377.2476; found, 377.2479.

*2,6-Di-tert-butyl-4-(methoxy(thiophen-2-yl)methyl)-phenol (**3k**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 8:1, v/v) afforded **3k**. Yellow solid (82.6 mg, 83%), mp 81−88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.24 (m, 1H), 7.20 (s, 2H), 6.93−6.91 (m, 1H), 6.85 (d, J = 3.6 Hz, 1H), 5.37 (s, 1H), 5.18 (s, 1H), 3.37 (s, 3H), 1.42 (s, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.5, 146.8, 135.7, 131.7, 126.3, 125.2, 125.2, 123.7, 82.0, 56.9, 34.3, 30.3.

*2,6-Di-tert-butyl-4-(ethoxy(phenyl)methyl)phenol (**3l**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **3l**. Yellow oil (94.0 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, J = 6.8 Hz, 2H), 7.33−7.31 (m, 2H), 7.12 (s, 2H), 5.28 (s, 1H), 5.11 (s, 2H), 3.51 (t, J = 6.8 Hz, 2H), 1.39 (s, 18H), 1.25 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.0, 142.8, 135.5, 132.9, 128.2, 127.1, 126.9, 123.9, 84.0, 64.5, 34.3, 30.2, 15.4.

*2,6-Di-tert-butyl-4-(isopropoxy(phenyl)methyl)phenol (**3m**).*[6] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 20:1, v/v) afforded **3m**. Brown solid (89.1 mg, 84%), 113−118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36−7.35 (d, J = 5.6 Hz, 2H), 7.33−7.30 (t, J = 6.4 Hz, 2H), 7.23−7.22 (d, J = 4.4 Hz, 1H), 7.11 (s, 2H), 5.42 (s, H), 5.11 (s, 1H), 3.107 (s, 1H), 3.69−3.61 (m, 1H), 1.39 (s, 18H), 1.24−1.20 (q, J = 5.2 Hz, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.0, 143.2, 135.5, 133.2, 128.2, 127.2, 127.0, 124.0, 80.9, 68.9, 34.3, 30.3, 22.4, 22.2.

*2,6-Di-tert-butyl-4-(phenyl(p-tolylthio)methyl)phenol (**3n**).*[13] Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 15:1, v/v) afforded **3n**. Brown oil (28.9 mg, 29%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46−7.44 (d, J = 7.6 Hz, 2H), 7.30−7.26 (m, 2H), 7.21−7.17 (m, 1H), 7.12 (s, 1H), 7.10 (s, 3H), 6.97−6.95 (d, J = 8.0 Hz, 2H), 5.37 (s, 1H), 5.10 (s, 1H), 2.25 (s, 3H), 1.37 (s, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.8, 141.7, 136.7, 135.5, 132.4, 131.9, 131.5, 129.3, 128.4, 128.3, 126.9, 125.1, 58.5, 34.4, 30.2, 21.0.

*2,6-Di-tert-butyl-4-(((4-methoxyphenyl)amino)(phenyl)-methyl)phenol (**3o**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 20:1, v/v) afforded **3o**. Brown solid (38.8 mg, 31%), 97−104 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41−7.39 (m, 2H), 7.33−7.29 (m, 2H), 7.23−7.20 (m, 1H), 7.08 (s, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 8.8 Hz, 2H), 5.32 (s, 1H), 5.13 (s, 1H), 3.70 (s, 3H), 1.38 (s, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.9, 151.9, 143.4, 142.0, 135.9, 134.3, 128.5, 127.1, 126.8, 124.5, 116.4, 114.8, 114.7, 114.5, 64.0, 55.7, 34.4, 30.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{35}NO_2$, 418.2741; found, 418.2738.

*Ethyl ((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)-methyl)glycinate (**5a**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **5a**. Yellow oil (147.1 mg, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43−7.41 (m, 2H), 7.30−7.27 (m, 2H), 7.22−7.17 (m, 3H), 5.09 (s, 1H), 4.79 (s, 1H), 4.17 (q, J = 5.6 Hz, 2H), 3.35 (dd, J_1 = 7.8 Hz, J_1 = 14 Hz, 2H), 2.1 (brs, 1H), 1.40 (s, 18H), 1.24 (t, J = 5.7 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 172.6, 152.8, 143.7, 135.7, 133.9, 128.4, 127.4, 126.9, 123.9, 66.9, 60.6, 49.1, 34.3, 30.3, 14.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{35}NO_3$, 398.2690; found, 398.2688.

*Ethyl ((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)-methyl)valinate (**5b**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **5b**. Yellow oil (105.5 mg, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−7.44 (m, 1H), 7.38−7.36 (m, 1H), 7.30−7.16 (m, 5H), 5.07−5.06 (m, 1H), 4.64−4.62 (m, 1H), 4.20 (q, J = 5.6 Hz, 2H), 2.95−2.90 (m, 1H), 2.00−1.89 (m, 2H), 1.41−1.39 (m, 18H), 1.29−1.26 (m, 3H), 0.99−0.93 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.6, 175.4, 152.8, 152.7, 145.5, 143.4, 135.6, 135.6, 135.5, 133.0, 128.4, 128.2, 127.8, 127.3, 126.9, 126.8, 124.2, 124.0, 65.9, 65.0, 64.7, 60.2, 60.2, 34.3, 34.3, 31.8, 31.8, 30.4, 30.3, 19.9, 19.6, 18.6, 18.5, 14.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{41}NO_3$, 440.3160; found, 440.3163.

*Methyl 2-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)-methyl)amino)-3-methylpen-tanoate (**5c**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 5:1, v/v) afforded **5c**. Yellow oil (129.7 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44−7.43 (m, 1H), 7.37−7.36 (m, 1H), 7.30−7,15 (m, 5H), 5.07−5.06 (m, 1H), 4.62−4.61 (m, 1H), 3.70 (s, 3H), 3.04−2.99 (m, 1H), 2.03 (brs, 1H), 1.67−1.61 (m, 2H), 1.40−1.39 (m, 18H), 0.91−0.83 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.6, 175.4, 152.8, 152.7, 145.5, 143.4, 135.6, 135.6, 135.4, 133.0, 128.4, 128.2, 127.8, 127.3, 126.9, 126.8, 124.2, 124.0, 65.9, 65.0, 64.7, 60.2, 60.2, 34.3, 34.3, 31.8, 31.8, 30.4, 30.3, 19.9, 19.6, 18.6, 18.5, 14.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{41}NO_3$, 440.3160; found, 440.3162.

*Ethyl ((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)-methyl)leucinate (**5d**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **5d**. Yellow oil (170.1 mg, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−7.43 (m, 1H), 7.39−7.37 (m, 1H), 7.31−7.25 (m, 2H), 7.21−7.14 (m, 3H), 5.07−5.06 (m, 1H), 4.69−4.67 (m, 1H), 4.19−4.16 (m, 2H), 3.16−3.13 (m, 1H), 1.97−1.80 (m, 2H), 1.49−1.43 (m, 1H), 1.40−1.39 (m, 18H), 1.30−1.25 (m, 3H), 0.91−0.89 (m, 3H), 0.81−0.78 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.4, 176.3, 152.8, 152.7, 145.3, 143.3, 135.6, 135.6, 135.2, 133.0, 128.3, 128.2, 127.7, 127.2, 126.9, 126.8, 124.2, 124.0, 65.8, 65.7, 60.3, 60.3, 57.9, 57.5, 43.3, 34.3, 30.3, 30.2, 24.8, 24.7, 23.2, 23.1, 22.1, 22.1, 14.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{43}NO_3$, 454.3316; found, 454.3313.

*Ethyl ((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)-methyl)phenylalaninate (**5e**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **5e**. Yellow oil (204.8 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.09 (m, 12H), 5.06−5.05 (m, 1H), 4.71−4.70 (m, 1H), 4.12−4.07 (m, 2H), 3.46−3.37 (m, 1H), 2.95−2.87 (m, 2H), 2.06 (brs, 1H), 1.39−1.36 (m, 18H), 1.17−1.16 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 174.8, 172.8, 152.7, 152.7, 144.8, 143.3, 137.8, 137.7, 135.6, 135.6, 135.2, 133.0, 129.6, 129.3, 128.3, 128.2, 128.2, 128.0, 127.4, 127.3, 126.8, 126.7, 126.4, 126.4, 124.0, 123.8, 65.6, 65.5, 60.4, 60.4, 40.2, 40.2, 34.3, 34.2, 30.3, 30.2, 14.2, 14.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{41}NO_3$, 488.3160; found, 488.3157.

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*Ethyl ((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)-methyl)tryptophanate (**5f**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **5f**. Yellow oil (208.0 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04−8.02 (m, 1H), 7.55−7.50 (m, 1H), 7.37−7.35 (m, 1H), 7.30−7.29 (m, 1H), 7.25−7.09 (m, 6H), 7.05−7.02 (m, 1H), 6.89−6.87 (m, 1H), 5.04 (s, 1H), 4.75−4.73 (m, 1H), 4.11−4.00 (m, 2H), 3.58−3.51 (m, 1H), 3.15−3.13 (m, 2H), 2.07 (brs, 1H), 1.36−1.34 (m, 18H), 1.12−1.07 (m, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 175.5, 175.3, 152.9, 145.1, 143.7, 136.3, 136.2, 135.8, 135.8, 135.2, 133.3, 128.5, 128.4, 127.8, 127.5, 127.0, 126.9, 124.1, 124.0, 122.9, 122.9, 122.0, 121.9, 119.4, 119.3, 119.1, 118.9, 111.6, 111.5, 111.2, 111.1, 65.9, 65.9, 60.5, 60.1, 59.9, 34.4, 34.5, 30.4, 30.4, 29.8, 29.7, 14.3, 14.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{34}H_{42}N_2O_3$, 526.3195; found, 526.3192.

*4-(Azido(phenyl)methyl)-2,6-di-tert-butylphenol (**6**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **6**. Yellow oil (151.9 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.31 (m, 5H), 7.09 (s, 2H), 5.24 (s, 1H), 5.06 (s, 1H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.7, 136.7, 136.5, 129.0, 128.0, 127.7, 126.5, 124.5, 120.3, 42.5, 34.4, 30.1. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{27}N_3O$, 338.2227; found, 338.2231.

*2,6-Di-tert-butyl-4-(1-phenylbut-3-en-1-yl)phenol (**7**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 10:1, v/v) afforded **7**. Yellow oil (143.0 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.4−7.26 (m, 4H), 7.23−7.19 (m, 1H), 7.09 (brs, 2H), 5.82−5.72 (m, 1H), 5.10−5.06 (m, 2H), 5.49 (d, J = 10.2 Hz, 1H), 3.97 (t, J = 7.9 Hz, 1H), 2.84 (dd display t, J = 7.6 Hz, 1H), 1.46 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.0, 145.1, 137.4, 135.6, 135.1, 128.3, 128.0, 125.9, 124.3, 115.9, 51.3, 40.7, 34.4, 30.4. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{32}O$, 337.2526; found, 337.2528.

*2,6-Di-tert-butyl-4-(1,3-diphenylprop-2-yn-1-yl)phenol (**8**).* Purification by flash column chromatography on silica gel (eluent: PE/EtOAc = 8:1, v/v) afforded **8**. Yellow oil (95.2 mg, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54−7.50 (m, 4H), 7.37−7.27 (m, 8H), 5.20 (s, 1H), 5.18 (s, 1H), 1.49 (s, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.7, 142.4, 135.9, 132.2, 131.6, 128.5, 128.2, 127.9, 127.8, 126.7, 124.5, 123.8, 91.2, 84.4, 43.7, 34.4, 30.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{32}O$, 397.2526; found, 397.2525.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c09847.

Experimental procedures, full characterization, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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