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ARTICLE

Metal-free synthesis of triarylated (*Z*)-nitrones *via* H_2O-mediated 1,3-dipolar transfer under aerobic conditions

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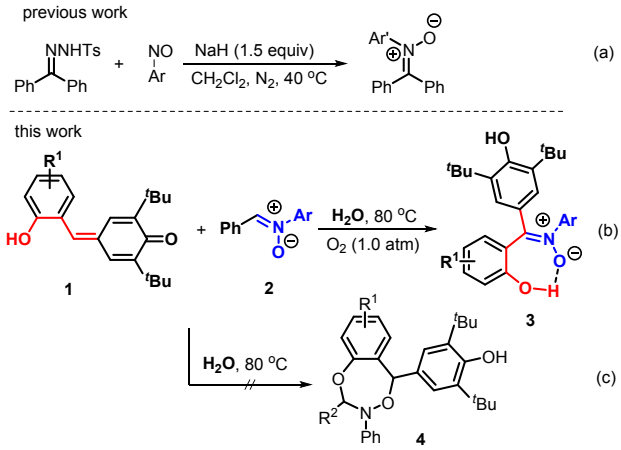
A new and environmentally benign protocol aimed at the generation of triarylated (*Z*)-nitrones in generally good yields has been developed *via* metal- and catalyst-free H_2O-mediated 1,3-dipolar transfer reaction of *para*-quinone methides (*p*-QMs) with diarylated nitrones under aerobic conditions. The purification of these products only needs to be recrystallized by the mixed solvent of small amount of petroleum ether and ethyl acetate, thereby avoiding traditional chromatography. The current new 1,3-dipolar strategy features broader substrate scope, green process and mild conditions.

Introduction

The research for an efficient and practical synthetic strategy toward valuable target molecules, with simultaneous consideration of the economic and environmental aspects, is one of the most significant goals in both academia and industry.[1] Due to organic solvents are generally thought to be the highest contributors toward environmental waste, water as a safe and eco-friendly solvent proved to be a highly attractive and sustainable choice without percolating hazardous organic solvents to the environment during the reaction process.[2] On the other hand, numerous fine chemicals and pharmaceutically active ingredients are typically allowed in low levels of the heavy metal content.[3] Consequently, metal-free organic transformations are generally believed to be an utmost prior alternative since such transformations could avoid the blend of heavy metal into these target compounds.[4] It has become clear that the development of new metal-free chemical transformations following the combination of water as an environmentally compatible solvent to facilitate the preparation of significant molecules continues to be of great interest in pharmaceutical sciences and drug discovery.[5]

Meanwhile, nitrones are a kind of competent 1,3-dipoles endowed with both nucleophilic and electrophilic sites, serving as three-atom building units for many important targets of chemical and biomedical potentials.[6] In particular, nitrones can be used as applicable 1,3-dipoles in various cycloadditions to access nitrogen-containing heterocycles.[7-9] Consequently, substantial efforts have been contributed to establish reliable methods for the preparation of nitrones, including *N*-alkylation of oximes,[10] oxidation of secondary amines,[11] hydroxylamines,[12] or imines,[13] and condensation between carbonyls with *N*-substituted hydroxylamine[14] as well as zinc-mediated reduction coupling between aldehydes and nitrobenzenes.[15] Most of these approaches lead to the formation of disubstituted nitrones while the investigation on the preparation of trisubstituted nitrones, especially triarylated analogues, were quite less.[16] Due to triarylated nitrones enable cycloadditions to easily access target cyclic structures with bis-benzylic quaternary stereocenters,[17] Wang, Hu and co-workers recently developed a metal-free coupling of *N*-nosylhydrazones with nitrosoarenes to synthesize such molecules, but this protocol demanded NaH as a base promoter and suffered from poor stereoselectivity with the use of unsymmetrical diarylated hydrazones (Scheme 1a).[18] Therefore, the development of a green and mild synthetic strategy for the stereoselective synthesis of triarylated nitrones from readily available substrates is still highly desirable.



Scheme 1. Synthesis of triarylated nitrones

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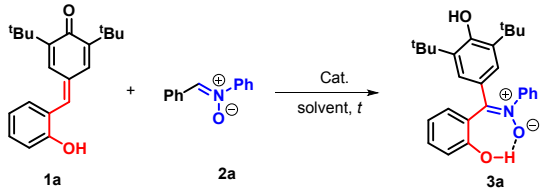
Electronic Supplementary Information (ESI) available. CCDC 1879547 (**3a**) [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Over the years, *para*-quinone methides (*p*-QMs) are a class of versatile precursors in the construction of oxygen-containing molecules.[19] Very recently, we have reported Ag/Brønsted acid co-catalyzed double cycloaddition of *p*-QMs with *β*-alkynyl ketones for synthesizing functionalized 6,6-benzannulated spiroketals.[19a] To continue our efforts in this project, we reasoned that [4 + 3] cycloaddition of *p*-QMs **1** with nitrones **2** could generate new functionalized benzo[*e*][1,4,2] dioxazepines **4** (Scheme 1c). Surprisingly, the reaction directed an unexpected pathway to form triarylated (*Z*)-nitrones **3** with high regio- and stereoselectivity *via* 1,3-dipolar transfer (Scheme 1b). Herein, we report this H_2O-promoted 1,3-dipolar transfer reaction, in which H_2O played dual roles as a reaction mediator as well as reaction media. Notably, pure triarylated (*Z*)-nitrones were readily isolated by recrystallizing the crude products with the mixed solvent of petroleum ether and ethyl acetate, thereby avoiding traditional column chromatography while significantly saving silica gels, solvents and manpower. Thus, this transformation follows the concept of group-assisted purification (GAP) chemistry.[20] To the best of our knowledge, the present 1,3-dipolar transfer protocol first represents a green and stereoselective synthesis of triarylated (*Z*)-nitrones that belong to a family of important building blocks for organic synthesis and drug design.

Results and discussion

Our initial trial began with the reaction of *p*-QM **1a** and nitrone **2a** in the presence of $Sc(OTf)_3$ (10 mol %) as a Lewis acid in toluene at 80 °C, the desired product **3a** was generated in 28% yield (Table 1, entry 1). With this preliminary result in hand, further optimization of the reaction conditions including solvents, catalysts and reaction temperatures was subsequently implemented. A variety of reaction media, such as 1,2-dichloroethane (DCE), acetonitrile (CH_3CN), EtOH, tetrahydrofuran (THF), 1,4-dioxane, and H_2O, was then screened for this 1,3-dipolar transfer cascade by employing $Sc(OTf)_3$ as the catalyst. The use of DCE led to a slightly lower yield of product **3a** as compared with toluene (entry 1 vs entry 2). Exchanging other four organic solvents including CH_3CN, EtOH, THF, and 1,4-dioxane for DCE all completely suppressed the generation of **3a** (entries 3-6). To our delight, the yield of **3a** was increased to 67% when H_2O was selected as the reaction solvent (entry 7). Subsequently, the phase transfer catalysts (PTCs) such as tetrabutylammonium bromide (TBAB) and tetrabutylammonium iodide (TBAI) were employed to further improve the yield of **3a** due to the relatively low solubility of nitrone in water. Unfortunately, both PTCs were not beneficial for this transformation and resulted in a remarkably reduced yield of **3a** (entries 8-9). The following screening of several other common Lewis acids, including $Cu(OTf)_2$, $FeCl_3{\cdot}6H_2O$, $Ni(ClO_4)_2{\cdot}6H_2O$, $Co(ClO_4)_2{\cdot}6H_2O$, and $Co(NO_3)_2{\cdot}6H_2O$. (entry 10-14) indicated that all of these Lewis acids could promote the conversion into product **3a**, in which $Cu(OTf)_2$ and $Co(ClO_4)_2{\cdot}6H_2O$ showed good catalytic performance in the conversion of **1a** into **3a**, which is similar to $Sc(OTf)_3$ (entries 10 and 14 vs entry 7). Surprisingly, without any Lewis acid, the current transformation could also give a 70% yield of product **3a** (entry 15). Next, our endeavors aimed at improving the formation of **3a** were paid by adjusting other reaction parameters. The reaction efficiency was found to have an important temperature dependence. A relatively lower conversion was obtained when the reaction temperature was changed to either 70 or 90 °C (entries 16-17). In addition, an attempt to conduct the transformation under oxygen conditions proved to display a positive impact on the reaction yield as the product **3a** was provided in a higher yield of 74% (entry 18). In contract, the reaction under Ar conditions seriously inhibited the generation of **3a** (entry 19). These results suggest that oxygen plays a key role in the success of this transformation, which may act as an oxidant. Without H_2O, the reaction only gave a trace amount of product **3a**, indicating that H_2O could facilitate the transformation (entry 20).

Table 1. Optimization of the reaction conditions[a]



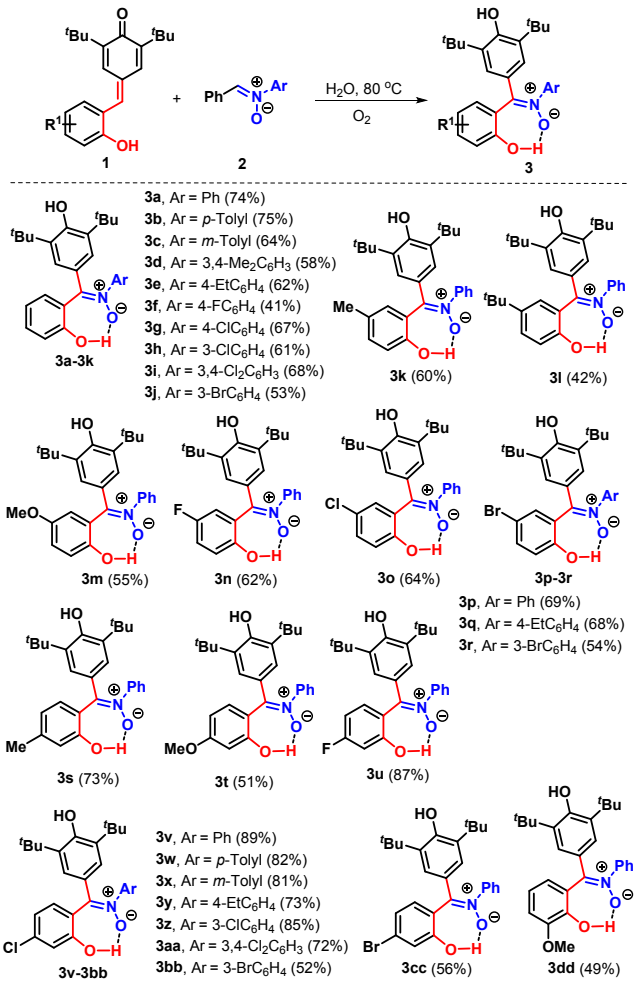
1a 2a 3a

Entry	Cat. (10 mol %)	Solvent	*t* (°C)	Yield (%)[b]
1	$Sc(OTf)_3$	toluene	80	28
2	$Sc(OTf)_3$	DCE	80	26
3	$Sc(OTf)_3$	MeCN	80	trace
4	$Sc(OTf)_3$	EtOH	80	trace
5	$Sc(OTf)_3$	THF	80	N.R.[c]
6	$Sc(OTf)_3$	1,4-dioxane	80	N.R.
7	$Sc(OTf)_3$	H_2O	80	67
8[d]	$Sc(OTf)_3$	H_2O	80	46
9[e]	$Sc(OTf)_3$	H_2O	80	38
10	$Cu(OTf)_2$	H_2O	80	68
11	$FeCl_3{\cdot}6H_2O$	H_2O	80	56
12	$Ni(ClO_4)_2{\cdot}6H_2O$	H_2O	80	52
13	$Co(ClO_4)_2{\cdot}6H_2O$	H_2O	80	70
14	$Co(NO_3)_2{\cdot}6H_2O$	H_2O	80	60
15	-	H_2O	80	70
16	-	H_2O	90	58
17	-	H_2O	70	54
18[f]	-	H_2O	80	74
19[g]	-	H_2O	80	<10
20	-	-	80	trace

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), catalyst (10 mol %), solvent (2.0 mL), under air condition. [b]Isolated yield of product **3a** based on **1a**. [c]No Reaction (N.R.). [d]Use of TBAB (10 mol %). [e]Use of TBAI (10 mol %). [f]Under O_2 conditions. [g]Under Ar conditions.

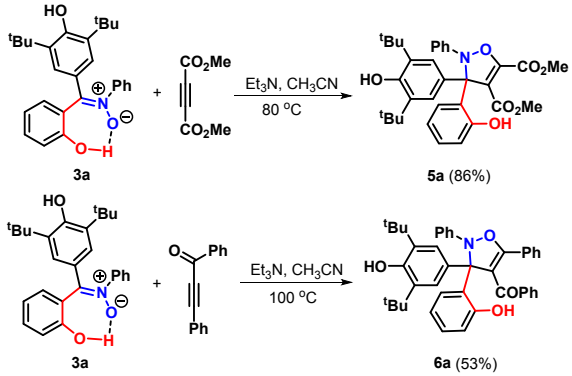
With the optimized conditions established, we set out to explore the generality of this 1,3-dipole transfer reaction by examining a variety of *p*-QM and nitrone components. As shown in Scheme 2, *p*-QM **1a** was first selected to evaluate the influence of substituents in the aromatic ring directly bound to the *N*-atom of nitrones. As anticipated, all these transformations completely oriented the stereoselectivity to

the generation of the expected triarylated (*Z*)-nitrones **3b**-**3j** in 41%-75% yields. Both electron-donating (methyl **2b**-**2d** and ethyl **2e**) and electron-withdrawing (fluoro **2f**, chloro **2g-2i** and bromo **2j**) groups located at different positions of the phenyl ring could tolerate this reaction system well. Functional groups at *para*-position relative to the *N*-atom seemed to improve the efficiency of the reaction, as the corresponding products **3b** and **3g** could be produced in slightly higher yields than those at the *meta*-position (**3b** vs **3c** and **3g** vs **3h**). Next, *p*-QMs **1** bearing methyl, *t*-butyl, methoxy, fluoro, chloro and bromo groups at different positions in the phenol ring could participate successfully in this metal-free H_2O-mediated 1,3-dipolar transfer reaction, enabling the direct assembly of the sole stereoisomeric triarylated (*Z*)-nitrones **3k–3dd** in 42%–89% yields. Among them, *p*-QM with chloride group residing in the 4-position of phenol ring was found to show the high reactivity when reacting with nitrone **2a**, furnishing the corresponding product **3v** in 89% yield. However, the presence of *tert*-butyl group at 5-postion seems reluctant to undergo the reaction process as the rather lower conversion into **3l** was observed (42% yield). Notably, the sterically more demanding C6 methoxy group would be accommodated in this transformation, furnishing triarylated (*Z*)-nitrone **3dd** in 42% yield.

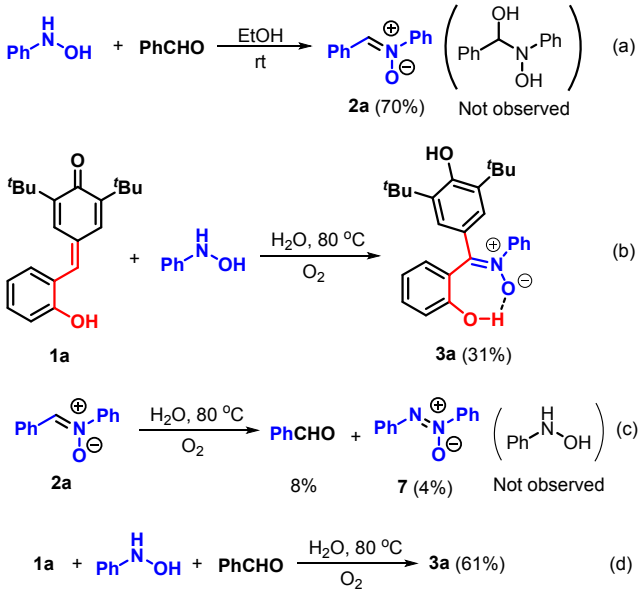


Scheme 2. Substrate scope for forming triarylated (*Z*)-nitrones

To demonstrate the synthetic potential of this method, several transformations were carried out. As shown in Scheme 3, Et_3N-promoted [3 + 2] cycloaddition of nitrone **3a** with dimethyl acetylenedicarboxylate proceeded successfully to access dimethyl 2,3-dihydroisoxazole-4,5-dicarboxylate **5a** with bis-benzylic quaternary stereocenters in 86% yield. Then, the treatment of nitrone **3a** with diphenylpropynone provided multi-substituted 2,3-dihydroisoxazole **6a** in 53% yield. These transformations provide facile strategies for the construction of dihydroisoxazole skeleton with one tetrasubstituted carbon stereocenter. The structures of products **3**, **5a** and **6a** have been characterized by their NMR and HRMS analysis. Furthermore, in the case of **3a**, its structure was based on X-ray diffraction analysis (Figure 1, see the Supporting Information).



Scheme 3. Transformations of product **3a**



Scheme 4. Control experiments

To gain a mechanistic insight into the generation of products **3**, several control experiments were conducted. Due to α-amino alcohol **A** may behave as an intermediate for the formation of products **3**, we attempted to prepare this compound by treatment of *N*-phenylhydroxylamine with benzaldehyde in EtOH at room temperature. Unfortunately, the reaction only provided nitrone **2a** in 70% yield[21] without observation of α-amino alcohol **A** (Scheme 4a). The reason for this may be that

the α-amino alcohol is very unstable, which easily undergoes dehydration to give nitrones. Subsequently, *N*-phenylhydroxylamine was subjected to the reaction of *p*-QM **1a** in 2:1 mole ratio under the standard conditions and the desired product **3a** was provided in 31% yield, indicating *N*-phenylhydroxylamine may also be a reaction intermediate (Scheme 4b). Next, in absence of *p*-QM **1a**, the reaction of nitrone **2a** was carried out under the standard conditions. The reaction almost did not work and only 8% yield of benzaldehyde and 4% yield of diazene 1-oxide **7** was obtained without observation of *N*-phenylhydroxylamine (Scheme 4c), showing that *N*-phenylhydroxylamine is not an intermediate in the reaction process. Interestingly, when 2.0 equivalents of benzaldehyde were added into the reaction system of *p*-QM **1a** and *N*-phenylhydroxylamine, the yield of product **3a** was remarkably increased to 61% yield (Scheme 4d). These results support α-amino alcohol **A** is a reaction intermediate in the current transformation.

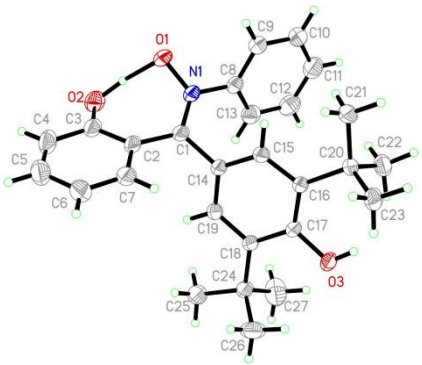
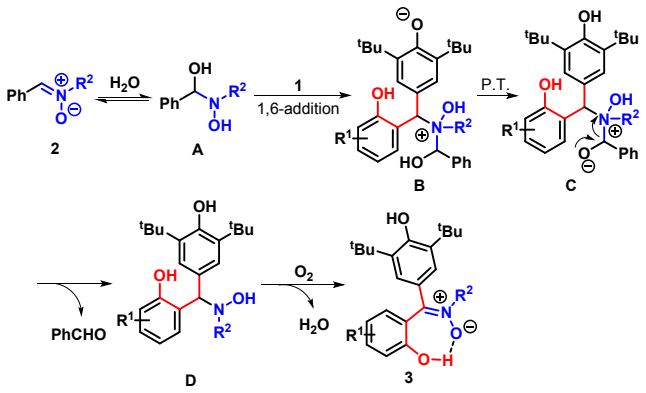


Figure 1. X-Ray structure of **3a**



Scheme 5 Proposed mechanisms for forming products **3**

On the basis of the above results, a reasonable mechanism for this reaction was proposed as shown in Scheme 5. At first, nucleophilic addition of H_2O into nitrones **2** generates unstable intermediate **A**, which is a reversible process. When electrophilic *p*-QMs **1** exist in the reaction system, a fast 1,6-addition of *N*-atom from α-amino alcohol **A** into *p*-QMs **1** occurs, providing intermediate **B**, followed by proton transfer (P.T.) and the release of benzaldehyde to give intermediate **D**. Finally, intermediate **D** is converted into products **3** through the oxidization in the presence of O_2.

Conclusions

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In summary, starting from easily available *p*-QMs and simple nitrones, we have established a metal-free H_2O-mediated 1,3-dipolar transfer strategy to effectively synthesize triarylated (*Z*)-nitrones with high stereoselectivity and generally good yields. Interestingly, water plays dual roles as a mediator as well as a green solvent, and oxygen as a green oxidant. This new reaction features environmental friendliness, being simple to perform, occurring under mild conditions and high functional tolerance. Further application of these resulting nitrones is underway in our laboratory.

Experiment

General Information

All one-pot reactions were carried out in a 10-mL reaction tube equipped with a magnetic stir bar under the O_2 conditions. All melting points are uncorrected. The NMR spectra were recorded in $CDCl_3$ (or DMSO-d_6) on a 400 MHz instrument with TMS as internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiples), coupling constant (J, Hz) and integration. HRMS analyses were carried out using a TOF-MS instrument with an ESI source.

General procedure for the synthesis of products **3**

Example for the synthesis of **3a**. Under the oxygen (1.0 atm) conditions, 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene) cyclohexa-2,5-dienone (**1a**, 0.2 mmol, 62.0 mg), (*Z*)-*N*-benzylideneaniline oxide (**2a**, 0.4 mmol, 78.8 mg) were added in a 10-mL Schlenk tube. Then, H_2O (2.0 mL) was added into this reaction system. The reaction vial was sealed and heated at 80 °C for 12 hours until TLC (petroleum ether: ethyl acetate= 5:1) revealed that conversion of the starting material **1a** was completed. The reaction mixture was extracted with EtOAc and concentrated by vacuum distillation and was purified by recrystallization with the mixed solvent petroleum ether/ethyl acetate (about 3.0 ml) to afford the pure product **3a** as pale yellow solid.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl) methylene)aniline oxide (3a)

Pale yellow solid, 62 mg, 74%; mp 221-222 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 11.13 (s, 1H), 7.53-7.49 (m, 1H), 7.34-7.29 (m, 4H), 7.28-7.27 (m, 1H), 7.19-7.17 (m, 1H), 7.05-7.03 (m, 1H), 6.90 (s, 2H), 6.87-6.83 (m, 1H), 5.46 (s, 1H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.9, 157.6, 155.3, 147.3, 135.8, 133.9, 133.8, 129.4, 128.8, 128.6, 125.6, 124.9, 122.0, 120.9, 118.9, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3481, 3415, 2955, 1601, 1507, 1437, 1235, 1114, 768. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{30}NO_3$ 416.2226; Found 416.2208.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)-4-methylaniline oxide (3b)

Pale yellow solid, 65 mg, 75%; mp 224-225°C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.52-7.48 (m, 1H), 7.20-7.17 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.05-7.03 (m, 1H), 6.89 (s, 2H), 6.86-6.82 (m, 1H), 5.46 (s, 1H), 2.32 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.8, 157.4, 155.2, 144.9, 138.8, 135.8, 133.9, 133.7, 129.4, 129.2, 125.8, 124.7, 122.0, 120.9, 118.8, 34.2, 30.0, 21.0. IR (KBr, *ν*, cm^{-1}) 3550, 3421, 2953, 1599, 1510, 1437, 1234, 1119, 768. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{28}H_{32}NO_3$ 430.2382; Found 430.2368.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)-3-methylaniline oxide (3c)

Yellow solid, 55 mg, 64%; mp 178-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.53-7.48 (m, 1H), 7.19-7.12 (m, 3H), 7.09-7.05 (m 3H), 6.90 (s, 2H), 6.87-6.83 (m, 1H), 5.47 (s, 1H), 2.25 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.8, 157.5, 155.2, 147.2, 138.9, 135.8, 133.9, 133.7, 129.2, 128.6, 125.8, 125.6, 121.9, 121.9, 120.9, 118.8, 34.2, 30.0, 21.0. IR (KBr, *ν*, cm^{-1}) 3541, 3426, 2968, 1598, 1508, 1438, 1238, 1120, 795. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{28}H_{32}NO_3$ 430.2382; Found 430.2385.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)-3,4-dimethylaniline oxide (3d)

Yellow solid, 52 mg, 58%; mp 178-179°C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.52-7.48 (m, 1H), 7.19-7.17 (m, 1H), 7.07-7.05 (m, 2H), 7.00-6.97 (m, 2H), 6.89 (s, 2H), 6.86-6.82 (m, 1H), 5.45 (s, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.8, 157.4, 155.2, 145.0, 137.4, 137.1, 135.7, 133.8, 133.6, 129.6, 129.2, 126.0, 125.9, 122.1, 121.9, 120.9, 118.8, 34.2, 30.0, 19.5, 19.4. IR (KBr, *ν*, cm^{-1}) 3554, 3450, 2959, 1574, 1512, 1437, 1234, 1108, 827. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{29}H_{34}NO_3$ 444.2539; Found 444.2567.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl) methylene)-4-ethylaniline oxide (3e)

Yellow solid, 55 mg, 62%; mp 237-238 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.52-7.48 (m, 1H), 7.24-7.20 (m, 2H), 7.18-7.16 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.05-7.03 (m, 1H), 6.89 (s, 2H), 6.86-6.82 (m, 1H), 5.45 (s, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.25 (s, 18H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.8, 157.3, 155.2, 145.2, 145.1, 135.7, 133.9, 133.6, 129.4, 128.1, 125.7, 124.8, 122.1, 120.9, 118.8, 34.2, 30.0, 28.5, 15.7. IR (KBr, *ν*, cm^{-1}) 3481, 3409, 2962, 1576, 1507, 1437, 1230, 1112, 736. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{29}H_{34}NO_3$ 444.2539; Found 444.2544.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl) methylene)-4-fluoroaniline oxide (3f)

Yellow solid, 36 mg, 41%; mp 257-258 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.54-7.50 (m, 1H), 7.34-7.31 (m, 2H), 7.20-7.17 (m, 1H), 7.04-6.96 (m, 3H), 6.89 (s, 2H), 6.88-6.84 (m, 1H), 5.51 (s, 1H), 1.27 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 162.0($^1J_{CF}$ = 230.4 Hz), 160.6, 157.9, 155.4, 144.9, 143.5, 138.6, 136.0, 134.9, 133.9($^4J_{CF}$ = 6.0 Hz), 131.2, 129.3, 126.9($^3J_{CF}$ = 8.7 Hz), 125.5, 121.8, 121.0, 119.0, 115.6($^2J_{CF}$ = 23 Hz), 107.2, 34.3, 30.0. IR (KBr, *ν*, cm^{-1}) 3545, 3420, 2963, 1558, 1507, 1436, 1234, 1114, 773. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}FNO_3$ 434.2131; Found 434.2147.

(Z)-4-chloro-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)aniline oxide (3g)

Yellow solid, 60 mg, 67%; mp 246-247 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.54-7.50 (m, 1H), 7.26 (s, 4H), 7.19-7.17 (m, 1H), 7.05-7.02 (m, 1H), 6.89-6.84 (m, 3H), 5.53 (s, 1H), 1.27 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.9, 158.0, 155.6, 145.8, 136.1, 134.4, 134.0, 133.9, 129.4, 128.8, 126.3, 125.4, 121.7, 121.0, 119.0, 34.3, 30.0. IR (KBr, *ν*, cm^{-1}) IR (KBr, *ν*, cm^{-1}) 3551, 3425, 2965, 1600, 1507, 1437, 1234, 1118, 771. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{39}ClNO_3$ 450.1836; Found 450.1840.

(Z)-3-chloro-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)aniline oxide (3h)

Yellow solid, 55 mg, 61%; mp 183-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.55-7.51 (m, 1H), 7.33-7.29 (m, 1H), 7.26-7.16 (m, 4H), 7.07-7.05 (m, 1H), 6.90 (s, 2H), 6.89-6.85 (m, 1H), 5.53 (s, 1H), 1.28 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.9, 158.3, 155.6, 148.1, 136.2, 134.4, 134.1, 134.0, 129.8, 129.3, 128.7, 125.6, 125.3, 123.1, 121.6, 121.0, 119.0, 34.3, 30.0. IR (KBr, *ν*, cm^{-1}) 3566, 3419, 2958, 1558, 1509, 1439, 1236, 1112, 683. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}ClNO_3$ 450.1836; Found 450.1850.

(Z)-3,4-dichloro-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)aniline oxide (3i)

Yellow solid, 66 mg, 68%; mp 205-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 10.89 (s, 1H), 7.56-7.52 (m, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.20-7.14 (m, 2H), 7.07-7.05 (m, 1H), 6.90-6.85 (m, 3H), 5.56 (s, 1H), 1.29 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.0, 158.6, 155.9, 146.2, 136.4, 134.3, 134.0, 132.8, 132.7, 130.2, 129.2, 127.3, 125.2, 124.2, 121.4, 121.1, 119.2, 34.3, 30.0. IR (KBr, *ν*, cm^{-1}) 3567, 3418, 2970, 1599, 1506, 1438, 1233, 1120, 772. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{28}Cl_2NO_3$ 484.1446; Found 484.1430.

(Z)-3-bromo-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl)methylene)aniline oxide (3j)

Yellow solid, 52 mg, 53%; mp 184-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 10.99 (s, 1H), 7.55-7.51 (m, 1H), 7.43-7.38 (m, 2H), 7.31-7.29 (m, 1H), 7.17 (t, *J* = 8.0 Hz, 2H), 7.07-7.05 (m, 1H), 6.90 (s, 2H), 6.89-6.85 (m, 1H), 5.52 (s, 1H), 1.28 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.9, 158.3, 155.6, 148.1, 136.2, 134.1, 134.0, 131.6, 130.0, 129.2, 128.5, 125.3, 123.6, 121.9, 121.5, 121.0, 119.1, 34.3, 30.0. IR (KBr, *ν*, cm^{-1}) 3566,3418, 2946, 1559, 1507, 1472, 1236, 1115, 770. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}BrNO_3$ 494.1331; Found 494.1321.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxy-5-methylphenyl)methylene)aniline oxide (3k)

Yellow solid, 52 mg, 60%; mp 206-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.33-7.29 (m, 4H), 7.28-7.26 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.89 (s, 2H), 6.79 (d, *J* = 2.0 Hz, 1H), 5.47 (s, 1H), 2.21 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 158.7, 157.5, 155.2, 147.4, 135.7, 134.9, 133.3, 129.5, 128.8, 128.5, 127.9, 125.6, 125.0, 121.6, 120.6, 34.2, 30.0, 20.4. IR (KBr, *ν*, cm^{-1}) 3481, 3420, 2961, 1497, 1456, 1231, 1097, 766. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{28}H_{32}NO_3$ 430.2382; Found 430.2371.

(Z)-N-((5-(tert-butyl)-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3l)

Yellow solid, 40 mg, 42%; mp 200-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 10.98 (s, 1H), 7.56-7.53 (m, 1H), 7.37-7.34 (m, 2H), 7.33-

7.29 (m, 3H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.89 (s, 2H), 5.48 (s, 1H), 1.24 (s, 18H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 158.7, 157.8, 155.3, 147.5, 141.2, 135.6, 131.2, 130.6, 129.8, 128.8, 128.6, 125.5, 125.0, 121.2, 120.2, 34.2, 34.0, 31.3, 30.0. IR (KBr, *v*, cm^{-1}) 3631, 3415, 2953, 1486, 1437, 1238, 1155, 765. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{31}H_{38}NO_3$ 472.2852; Found 472.2866.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxy-5-methoxyphenyl)methylene)aniline oxide (3m)

Yellow solid, 49 mg, 55%; mp 150-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 11.42 (s, 1H), 7.34-7.29 (m, 4H), 7.28-7.26 (m, 2H), 7.07-7.05 (m, 1H), 6.88 (s, 2H), 6.77 (t, *J* = 8.0 Hz, 1H), 6.62-6.59 (m, 1H), 5.45 (s, 1H), 3.99 (s, 3H), 1.24 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 157.9, 155.2, 151.5, 151.0, 147.2, 135.7, 129.4, 128.8, 128.6, 125.6, 125.3, 125.0, 122.1, 118.3, 114.1, 56.2, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3482, 3420, 2957, 2507, 2456, 1249, 1112, 767. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{28}H_{32}NO_4$ 446.2331; Found 466.2307.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(5-fluoro-2-hydroxyphenyl)methylene)aniline oxide (3n)

Yellow solid, 54 mg, 62%; mp 197-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.32-7.29 (m, 5H), 7.27-7.22 (m, 1H), 7.15-7.12 (m, 1H), 6.89 (s, 2H), 6.75-6.72 (m, 1H), 5.50 (s, 1H), 1.26 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 156.9, 156.3($^4J_{CF}$ = 2.6 Hz), 155.5, 155.3($^1J_{CF}$ = 235.2 Hz), 147.2, 136.1, 129.2, 128.8, 125.0, 124.8, 122.4($^3J_{CF}$ = 7.8Hz), 122.1, 122.0, 121.3, 121.1, 118.2($^2J_{CF}$ = 24.3 Hz), 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3481, 2414, 2958, 1507, 1465, 1239, 1190, 765. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}FNO_3$ 434.2131; Found 434.2135.

(Z)-N-((5-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3o)

Yellow solid, 58 mg, 64%; mp 240-241 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.47-7.44 (m, 1H), 7.31 (d, *J* = 6.8 Hz, 6H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 6.88 (s, 2H), 5.52 (s, 1H), 1.26 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 159.5, 156.5, 155.6, 147.2, 136.1, 133.6, 132.5, 129.4, 128.8, 124.9, 124.8, 123.6, 123.2, 122.5, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3481, 3416, 2964, 1559, 1456, 1222, 1095, 767. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}ClNO_3$ 450.1836; Found 450.1830..

(Z)-N-((5-bromo-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3p)

Yellow solid, 68 mg, 69%; mp 241-242 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.60-7.57 (m, 1H), 7.31 (d, *J* = 6.8 Hz, 6H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 5.52 (s, 1H), 1.26 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.1, 156.4, 155.7, 147.2, 136.4, 136.1, 135.6, 129.5, 128.9, 124.8, 123.8, 122.9, 110.6, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3482, 3417, 2954, 1558, 1473, 1222, 1095, 767. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}BrNO_3$ 494.1331; Found 494.1312.

(Z)-N-((5-bromo-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)-4-ethylaniline oxide (3q)

Yellow solid, 71 mg, 68%; mp 193-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.58-7.56 (m, 1H), 7.22-7.19 (m, 2H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.87 (s, 2H), 5.52 (s, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.26 (s, 18H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.1, 156.1, 155.6, 145.6, 144.9, 136.2, 135.9, 135.6, 129.5, 128.2, 124.9, 124.7, 124.0, 122.9, 110.5, 34.3, 30.0, 28.6, 15.7. IR (KBr, *v*, cm^{-1}) 3560, 3421, 2957, 1581, 1469, 1439, 1226, 1137, 789. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{29}H_{33}BrNO_3$ 522.1644; Found 522.1640.

(Z)-3-bromo-N-((5-bromo-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3r)

Yellow solid, 62 mg, 54%; mp 157-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 10.94 (s, 1H), 7.61-7.58 (m, 1H), 7.43-7.40 (m, 2H), 7.28-7.26 (m, 1H), 7.20-7.16 (m, 2H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 5.58 (s, 1H), 1.29 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.1, 157.1, 156.0, 148.0, 136.7, 136.4, 135.5, 131.9, 130.1, 129.3, 128.3, 124.5, 123.5, 123.4, 123.0, 122.0, 110.8, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3562, 2423, 2958, 1581, 1465, 1438, 1227, 1136, 788. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{28}Br_2NO_3$ 572.0436; Found 572.0442.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxy-4-methylphenyl)methylene)aniline oxide (3s)

Yellow solid, 63 mg, 73%; mp 264-265 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.31-7.29 (m, 1H), 7.29-7.23 (m, 4H), 6.99 (s, 1H), 6.91 (d, *J* = 6.4 Hz, 3H), 6.67-6.65 (m, 1H), 5.46 (s, 1H), 2.40 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 160.9, 157.7, 155.2, 147.3, 145.0, 135.8, 133.7, 129.4, 128.7, 128.7, 128.5, 125.7, 125.0, 121.1, 120.3, 119.1, 34.2, 30.0, 21.6. IR (KBr, *v*, cm^{-1}) 3483, 3419, 2954, 1558, 1438, 1223, 1097, 768. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{28}H_{32}NO_3$ 430.2382; Found 430.2358.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxy-4-methoxyphenyl)methylene)aniline oxide (3t)

Yellow solid, 46 mg, 51%; mp 254-255 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 12.11 (s, 1H), 7.31-7.29 (m, 1H), 7.28-7.24 (m, 4H), 6.92 (d, *J* = 9.6 Hz, 3H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.45-6.42 (m, 1H), 5.45 (s, 1H), 3.88 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 165.0, 163.7, 157.8, 155.3, 147.2, 135.8, 135.2, 129.5, 128.7, 128.3, 125.6, 125.1, 114.6, 108.0, 103.5, 100.0, 55.5, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3545, 3422, 2958, 1616, 1517, 1436, 1231, 1119, 768. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{28}H_{32}NO_4$ 446.2331; Found 446.2326.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-fluoro-2-hydroxyphenyl)methylene)aniline oxide (3u)

Pale yellow solid, 76 mg, 87%; mp 237-238°C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.30 (m, 4H), 7.28-7.26 (m, 1H), 7.03 (m, 1H), 6.89 (s, 2H), 6.86 (m, 1H), 6.59 (m, 1H), 5.50 (s, 1H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 167.0 ($^1J_{CF}$ = 252.1 Hz), 163.4, 163.3, 157.4, 155.5, 147.0, 136.0, 135.7, 135.6, 129.4, 128.7 ($^3J_{CF}$ = 12.0 Hz), 125.3, 124.9, 118.5 ($^4J_{CF}$ = 2.4 Hz), 107.4, 107.2 ($^2J_{CF}$ = 19.0 Hz) 107.0, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3539, 3425, 2961, 1584, 1514, 1420, 1235, 1118, 768. HRMS (ESI) m/z: [M-H]$^-$ Calcd for $C_{27}H_{29}FNO_3$ 434.2131; Found 434.2132.

(Z)-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3v)

Yellow solid, 80 mg, 89%; mp 260-261 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 11.58 (s, 1H), 7.31-7.29 (m, 4H), 7.29-7.26 (m, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 6.84-6.82 (m, 1H), 5.51 (s, 1H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.7, 157.2, 155.5, 147.1, 139.9, 136.0, 134.7, 129.3, 128.8, 128.8, 125.1, 124.9, 121.0, 120.6, 119.4, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3546, 3415,

2960, 1559, 1507, 1436, 1224, 1119, 768. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{27}H_{29}ClNO_3$ 450.1836; Found 450.1847.

(Z)-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)-4-methylaniline oxide (3w)

Yellow solid, 76 mg, 82%; mp 248-249°C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.19-7.16 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.87 (s, 2H), 6.83-6.81 (m, 1H), 5.49 (s, 1H), 2.32 (s, 3H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.7, 156.9, 155.4, 144.7, 139.7, 139.0, 136.0, 134.7, 129.3, 129.2, 125.3, 124.7, 121.0, 120.7, 119.3, 34.2, 30.0, 21.0. IR (KBr, *v*, cm^{-1}) 3558, 3477, 2856, 1572, 1511, 1384, 1221, 1106, 912. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{28}H_{31}ClNO_3$ 464.1992; Found 464.2001.

(Z)-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)-3-methylaniline oxide (3x)

Yellow solid, 75 mg, 81%; mp 191-192°C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.19 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.11-7.05 (m, 3H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 6.84-6.81 (m, 1H), 5.50 (s, 1H), 2.25 (s, 3H), 1.26 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 157.1, 155.5, 146.9, 139.8, 138.9, 136.0, 134.7, 129.4, 129.2, 128.6, 125.5, 125.3, 121.9, 121.0, 120.6, 119.4, 34.2, 30.0, 21.0. IR (KBr, *v*, cm^{-1}) 3550, 3426, 2958, 1587, 1508, 1439, 1224, 1121, 793. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{28}H_{31}ClNO_3$ 464.1992; Found 464.1996.

(Z)-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)-4-ethylaniline oxide (3y)

Yellow solid, 70 mg, 73%; mp 241-242°C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.21-7.18 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 6.84-6.81 (m, 1H), 5.49 (s, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.25 (s, 18H), 1.19 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.7, 156.9, 155.5, 145.5, 144.8, 139.7, 135.9, 134.7, 129.4, 128.2, 125.2, 124.7, 121.0, 120.7, 119.3, 34.2, 30.0, 28.5, 15.7. IR (KBr, *v*, cm^{-1}) 3554, 3427, 2960, 1568, 1508, 1424, 1224, 1115, 847. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{29}H_{33}ClNO_3$ 478.2149; Found 478.2150.

(Z)-3-chloro-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3z)

Yellow solid, 82 mg, 85%; mp 183-184°C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.28-7.22 (m, 3H), 7.21-7.20 (m, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 2H), 6.85-6.83 (m, 1H), 5.57 (s, 1H), 1.28 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.8, 157.8, 155.9, 147.8, 140.3, 136.4, 134.8, 134.5, 129.8, 129.2, 128.9, 125.5, 124.8, 123.1, 121.1, 120.2, 119.6, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3555, 3451, 2959, 1584, 1508, 1437, 1224, 1120, 789. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{27}H_{28}Cl_2NO_3$ 484.1446; Found 484.1470.

(Z)-3,4-dichloro-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3aa)

Yellow solid, 75 mg, 72%; mp 205-206°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.17 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 2H), 6.86-6.84 (m, 1H), 5.60 (s, 1H), 1.29 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.8, 158.1, 156.1, 145.9, 140.5, 136.6, 134.7, 133.0, 132.8, 130.3, 129.2, 127.2, 124.7, 124.1, 121.2, 120.1, 119.7, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3553, 3428, 2953, 1560, 1501, 1438, 1222, 1120, 885. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{27}H_{27}Cl_3NO_3$ 518.1057; Found 518.1050.

(Z)-3-bromo-N-((4-chloro-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3bb)

Yellow solid, 55 mg, 52%; mp 173-174°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.27-7.26 (m, 1H), 7.20-7.15 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 2H), 6.86-6.83 (m, 1H), 5.57 (s, 1H), 1.28 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.8, 157.9, 155.9, 147.9, 140.3, 136.4, 134.7, 131.7, 130.1, 129.2, 128.4, 124.8, 123.5, 121.9, 121.1, 120.2, 119.6, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3529, 3412, 2955, 1584, 1508, 1437, 1224, 1111, 726. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{27}H_{28}BrClNO_3$ 528.0941; Found 528.0930.

(Z)-N-((4-bromo-2-hydroxyphenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methylene)aniline oxide (3cc)

Yellow solid, 55 mg, 56%; mp 258-259 °C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 11.56 (s, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.30 (d, *J* = 6.8 Hz, 5H), 6.99-6.96 (m, 1H), 6.89 (d, *J* = 10.8 Hz, 3H), 5.50 (s, 1H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 161.6, 157.3, 155.5, 147.1, 136.0, 134.7, 129.3, 128.8, 128.8, 128.4, 125.1, 124.9, 124.1, 122.2, 121.0, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3547, 3421, 2959, 1585, 1558, 1436, 1224, 1121,768. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{27}H_{29}BrNO_3$ 494.1331; Found 494.1333.

(Z)-N-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxy-3-methoxyphenyl)methylene)aniline oxide (3dd)

Yellow solid, 44 mg, 49%; mp 152-153 °C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.33-7.29 (m, 4H), 7.28-7.26 (m, 2H), 7.07-7.05 (m, 1H), 6.88 (s, 2H), 6.78 (t, *J* = 8.0 Hz, 1H), 6.62-6.60 (m, 1H), 5.45 (s, 1H), 3.99 (s, 3H), 1.24 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 157.9, 155.2, 151.5, 151.0, 147.2, 135.7, 129.4, 128.8, 128.6, 125.6, 125.3, 125.0, 122.1, 118.3, 114.1, 56.2, 34.2, 30.0. IR (KBr, *v*, cm^{-1}) 3468, 3412, 2957, 1507, 1436, 1249, 1112, 688. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{28}H_{32}NO_4$ 446.2331; Found 446.2326.

General procedure for the synthesis of product 5a

(*Z*)-*N*-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl) methylene)aniline oxide (**3a**, 0.1 mmol, 41.7 mg), dimethyl but-2-ynedioate (0.15 mmol, 21.3 mg), Et_3N (0.1 mmol, 10.1 mg) were added in a 10-mL reaction vial. Then, CH_3CN (3.0 mL) was added into this reaction system. The reaction vial was sealed and heated at 80 °C for 12 h until TLC (petroleum ether: ethyl acetate= 5:1) revealed that conversion of the starting material **3a** was completed. Then the reaction mixture was extracted concentrated by vacuum distillation and was purified by flash column chromatography (silica gel, mixtures of petroleum ether / acetic ester, 15:1, v/v) to afford the pure products **5a** (48 mg, 86%) as orange solid.

Dimethyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(2-hydroxyphenyl) -2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate (5a)

Orange solid, 48 mg, 86%; mp 142-143 °C; ^1H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.37-7.35 (m, 1H), 7.27-7.18 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 3H), 6.97-6.93 (m, 1H), 6.86-6.83 (m, 1H), 4.99 (s, 1H), 4.90 (s, 1H), 3.91 (s, 3H), 3.31 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 169.8, 164.9, 153.1, 149.8, 147.8, 136.4, 131.5, 129.0, 127.2, 122.0, 122.0, 121.2, 119.7, 119.1, 117.4, 116.5, 95.9, 54.0, 51.5, 34.5, 30.2. IR (KBr, *v*, cm^{-1}) 3614, 3428, 2958,

1754, 1684, 1593, 1435, 1361, 1257, 760. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{33}H_{36}NO_7$ 558.2492; Found 558.2497.

General procedure for the synthesis of product **6a** (*Z*)-*N*-((3,5-di-tert-butyl-4-hydroxyphenyl)(2-hydroxyphenyl) methylene)aniline oxide (**3a**, 0.1 mmol, 41.7 mg), 1,3-diphenylprop-2-yn-1-one (0.15 mmol, 30.9 mg), Et_3N (0.1 mmol, 10.1 mg) were added in a 25-mL reaction vial, Then, CH_3CN (3.0 mL) was added into this reaction system. The reaction vial was sealed and heated at 100 °C for 12 h until TLC (petroleum ether: ethyl acetate= 5:1) revealed that conversion of the starting material **3a** was completed. Then the reaction mixture was extracted concentrated by vacuum distillation and was purified by flash column chromatography (silica gel, mixtures of petroleum ether / acetic ester, 15:1, v/v) to afford the pure products **6a** (33 mg, 53%) as yellow solid.

(3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(2-hydroxyphenyl)-2,5-diphenyl-2,3-dihydroisoxazol-4-yl)(phenyl)-methanone (6a)

Yellow solid, 33 mg, 53%; mp 167-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 8.17 (d, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.61-7.58 (m, 1H), 7.45-7.35 (m, 5H), 7.27-7.18 (m, 4H), 7.18-7.04 (m, 5H), 6.88 (s, 2H), 6.30 (s, 1H), 5.11 (s, 1H), 1.29 (s, 18H).^{13}C NMR (100 MHz, $CDCl_3$; *δ*, ppm) 188.5, 163.7, 157.7, 151.9, 148.2, 145.3, 140.7, 136.6, 133.4, 132.1, 131.0, 130.3, 129.7, 129.4, 129.0, 128.7, 128.5, 127.9, 127.8, 127.1, 125.6, 124.9, 124.4, 122.2, 104.2, 34.3, 30.0. IR (KBr, *v*, cm^{-1}) 3612, 3420, 2972, 1733, 1525, 1481, 1427, 1214, 701. HRMS (ESI) m/z: $[M-H]^-$ Calcd for $C_{42}H_{40}NO_4$ 622.2957; Found 622.2958.

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Metal-free synthesis of triarylated (Z)-nitrones *via* H_2O-mediated 1,3-dipolar transfer under aerobic conditions

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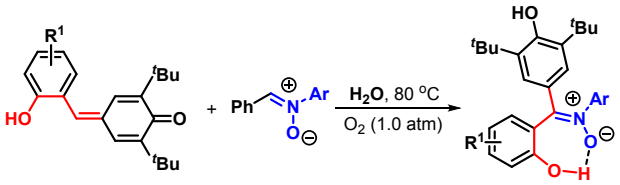

A new and environmentally benign protocol aimed at the generation of triarylated (*Z*)-nitrones in generally good yield has been developed *via* metal- and catalyst-free H_2O-mediated 1,3-dipolar transfer reaction of *para*-quinone methides (*p*-QMs) with diarylated nitrones under the aerobic conditions.