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Aerobic Oxidative Coupling of Resveratrol and its Analogues by Visible Light Using Mesoporous Graphitic Carbon Nitride (mpg-C_3N_4) as a Bioinspired Catalyst

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Abstract: The first aerobic oxidative coupling of resveratrol and its analogues by mesoporous graphitic carbon nitride as a bioinspired catalyst with visible light has been developed. With this method, δ-viniferin and its analogues were synthesized in moderate to high yield. The metal-free conditions, visible-light irradiation, and the ideal oxidant, molecular oxygen, make this coupling reaction environmental friendly and practical.

Resveratrol and its analogues, a class of vital compounds in drug development, have received increasing attention in recent years, including studies into their diverse bioactivities, development of novel potent analogues for pharmaceutical purposes,[1] and exploration of their potential applications as building blocks for the construction of more complicated oligomers by means of bioinspired synthesis.[2–4]

Among its oligomers, δ-viniferin, a dimeric resveratrol with a dihydrobenzofuran skeleton, exhibited excellent bioactivities,[3c,e,5f] such as inhibition of COX-I (cyclooxygenase-I) and COX-II (cyclooxygenase-II), and modest cytotoxicity against CEM (human lymphoblastoid cells) proliferation. δ-Viniferin was initially isolated from grapevines as a phytoalexin in 1977.[5a] The first biomimetic synthesis of δ-viniferin was achieved at the same year by oxidative dimerization of resveratrol with horseradish peroxidase/H_2O_2.[3a] Although this stilbenoid dimer widely existed in a variety of species, such as, gnetum hainanense,[5b] rheum maximuwicizii,[5c] and stressed grapevine cultures,[5d–5 g] its low abundance impeded the studies of their biological properties.

To achieve biomimetic synthesis of δ-viniferin and its analogues, both chemically and enzymatically catalytic methods have been employed. The traditional chemical methods generally need use of stoichiometric metallic oxidants[2] (silver salt, manganese salts, copper salt, ferric salt, thallium salt, cerous salt, and their metallic oxides), and the enzymatic methods usually employ different oxidative enzymes,[3] for example, peroxidase/H_2O_2 and laccases botrytis cinerea, under strictly controlled conditions. Despite the great achievements in the synthesis of δ-viniferin and its analogues, the chemoselectivity of the reactions in vitro were often poor due to the complex coupling pathways of different radicals generated from the oxidation of resveratrol or its analogues (Scheme 1). In this sense, the development of a facile protocol for highly selective preparation of δ-viniferin and its analogues is still strongly demanded.

Molecular oxygen is not only a cheap, environmentally benign and most readily available oxidant in vitro, but also a major source of reactive oxygen species (ROS) in vivo.[6] It is believed that molecular oxygen and ROS are responsible for the biosynthesis of δ-viniferin by a metabolic sequence induced in response to biotic or abiotic stress factors. Unfortunately, due to the relatively unreactive properties of molecular oxygen in the triplet ground state, there is no report on the production of δ-viniferin by aerobic oxidative coupling of resveratrol at room temperature in vitro as far as we know. Recently, polymeric graphitic carbon nitride materials have attracted considerable attention because of their potential applications in sustainable chemistry as metal-free heterogeneous catalysts. g-C_3N_4 (graphitic carbon nitride), with a semiconductor band gap of 2.7 eV (conduction band (CB) at −1.3 V (pH 7) versus the normal hydrogen electrode (NHE) (E°)), in principle, can reduce O_2 to $O_2^{-\bullet}$ ($E^\circ(O_2/O_2^{-\bullet}) = -0.16$ V vs. NHE) under visible-light illumination, then trigger the aerobic oxidative reaction.[7] In the present work, we report a visible-light photocatalytic protocol for the facile preparation of δ-viniferin and its analogues by using mesoporous graphitic carbon nitride (mpg-C_3N_4) and molecular oxygen at room temperature. Herein, mpg-C_3N_4 was selected as the photocatalyst in view of its large surface area, N-containing surface and framework, high stabili-

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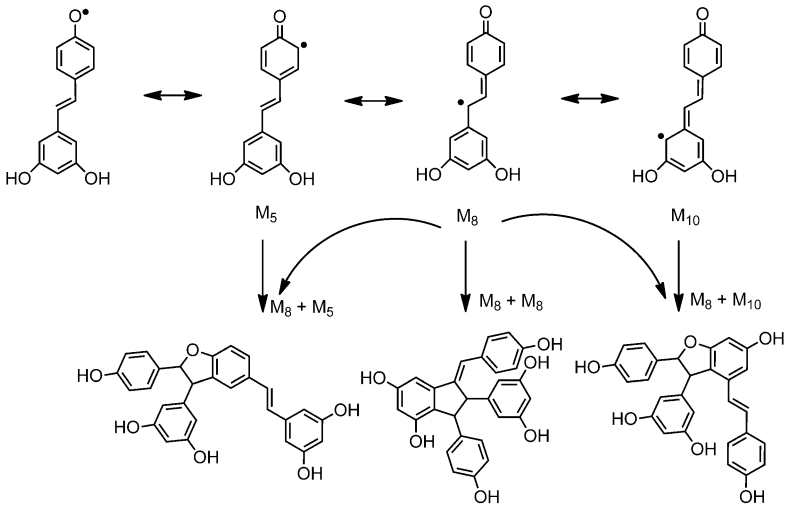


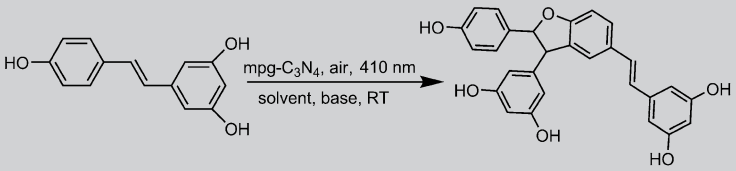
Scheme 1. Proposed biosynthetic pathways of resveratrol dimers.

ty, and unique properties of a semiconductor (redox potential).[8] With this method, 4-hydroxy-*trans*-stilbenes including resveratrol were smoothly transformed to δ-viniferin and its analogues in moderate to high yields.

Initial success was obtained upon subjecting *trans*-resveratrol to irradiation by a purple LED (3 W, 410 nm) with mpg-C_3N_4 (5% w/w) as the photocatalyst in acetonitrile bubbled with air, and the δ-viniferin was generated in 34% yield (19% conversion) after 24 hous irradiation (Table 1, entry 1). Because the reactivity of resveratrol could be influenced by environmental pH in a great manner (see Figure S2 in the Supporting Information),[9] a series of bases were selected to improve the efficiency of the oxidative coupling. Although K_2CO_3, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and 1,4-diazabicyclo [2.2.2] octane (DABCO) failed to produce δ-viniferin (entries 2–5), addition of pyridine, 2,6-lutidine, or 2,4,6-collidine significantly improved both the yield and conversion (entries 6–8). The best result was obtained when the reaction was performed with 2,6-lutidine (86% yield, 79% conversion). The attempts to further increase the yield by prolonging irradiation time (entry 7, footnote [d]) and increasing the amount of the photocatalyst mpg-C_3N_4 (entry 7, footnote [c]) were unsuccessful. Subsequently, a rapid solvent screening was performed (entries 9–13), and the results revealed the superiority of acetonitrile as the reaction medium. To further optimize the conditions, pure oxygen instead of air was bubbled into the solution, but the yield of δ-viniferin decreased slightly (entry 14). Other oxidants including H_2O_2, *t*BuOOH (TBHP), and CCl_3Br were also less efficient (entries 15–17). Control experiments showed that the presence of photocatalyst, oxidant, and light source is necessary for the desired reaction to proceed (entries 18–20).

After the optimal reaction conditions were established, a series of resveratrol analogues were subjected to this reaction system and the results of the aerobic oxidative coupling are shown in Table 2. We were pleased to observe that pterostilbene (4-hydroxy-3′,5′-dimethoxy-*trans*-stilbene (**2a**)), a natural methoxylated analogue of resveratrol, which showed the antihyperglycemic activity,[1b] antioxidant activity,[1e] and moderate inhibitory activity of COX-I, COX-II,[1d] smoothly produced the dehydrodimers with the δ-viniferin skeleton in 85% yield and 100% conversion. In addition, an acetylated analogue of resveratrol (4-hydroxy-3′,5′-diacetyl-*trans*-stilbene (**3a**)), which exhibited cancer cell-growth inhibition activity,[1g] was also tolerated in this oxidative cou-

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Base	Oxidant	Conv. [%]	Yield [%][b]
1	CH_3CN	–	air	19	34
2	CH_3CN	K_2CO_3	air	0	0
3	CH_3CN	DBU	air	0	0
4	CH_3CN	DBN	air	0	0
5	CH_3CN	DABCO	air	0	0
6	CH_3CN	pyridine	air	32	81
7	CH_3CN	2,6-lutidine	air	79	86[c]/80[d]/86
8	CH_3CN	2,4,6-collidine	air	72	78
9	MeOH	2,6-lutidine	air	38	60
10	toluene	2,6-lutidine	air	19	55
11	TFT[e]	2,6-lutidine	air	34	74
12	THF	2,6-lutidine	air	23	61
13	acetone	2,6-lutidine	air	37	45
14	CH_3CN	2,6-lutidine	O_2[f]	78	76
15	CH_3CN	2,6-lutidine	H_2O_2[g]	37	62
16	CH_3CN	2,6-lutidine	TBHP[e,g]	64	64
17	CH_3CN	2,6-lutidine	CCl_3Br[g]	55	51
18[h]	CH_3CN	2,6-lutidine	air	0	0
19[i]	CH_3CN	2,6-lutidine	–	0	0
20[j]	CH_3CN	2,6-lutidine	air	0	0

[a] Reaction conditions: *trans*-resveratrol (**1a**) (20 mg), mpg-C_3N_4 (4 mg, 5% w/w), bases (5 equiv), solvents (5 mL), the bubbling rate of air is one bubble per second, purple LEDs (3 W, 410 nm), RT, 24 h. [b] Isolated yield after purification by chromatography on polyamide. [c] mpg-C_3N_4 (8 mg) was used, reaction time: 24 h. [d] Reaction time: 48 h. [e] TFT = trifluorotoluene, TBHP = *tetr*-butyl hydroperoxide (5-6 M in decane), [f] The bubbling rate of the oxygen is one bubble per second. [g] Oxidants (5 equiv), the reaction was carried out under argon. [h] No photocatalyst. [i] The reaction was carried out under argon without oxidants. [j] The reaction was carried out in the dark.

pling reaction, affording the desired product **3b** in 51% yield and 100% conversion. Then the 4-hydroxy-*trans*-stilbenes with electron-neutral (**4a**) and -donating groups (**9a**, **10a**) were applied to the reaction system giving the desired products with typical dihydrofuran structure in good yields. To our delight, the 4-hydroxy-*trans*-stilbenes bearing electron-withdrawing groups, such as fluorine (**5a**), chlorine (**6a**), bromine (**7a**), and trifluoromethyl (**8a**), could be effectively converted into the corresponding dihydrobenzofuran-based stilbene dimers in similar yields except for fluorine-substituted substrate (**5a**, 40% yield, 100% conversion). The oxidation potentials of these substrates measured by cyclic voltammetry under our mimetic reaction conditions (pH 7.55) were similar, which was in accordance with the experimental fact that the effects of functional groups were negligible (see Figure S4 in the Supporting Information). Moreover, incorporation of one or two methoxyl substituents at different positions on the B ring of the substrates (**10a**–**13a**) revealed that steric modification of the substrate can be accomplished, and the reaction gave the corresponding products in 73–83% yields. Besides the 4-hydroxy-*trans*-stilbenes, we also employed 3,4-dihydroxy-*trans*-stilbenes (**14a**, **15a**), which showed excellent radical-scavenging activities.[1 h] However, benzodioxane-based stilbenes dimers (**14b**, **15b**) instead of dihydrobenzofurans were formed dominantly.

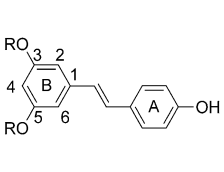
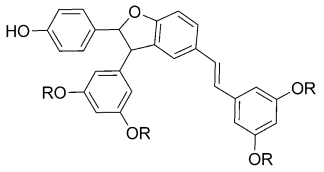
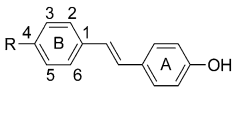
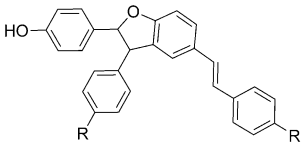
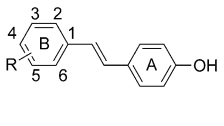
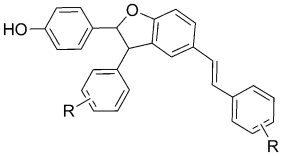
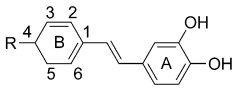
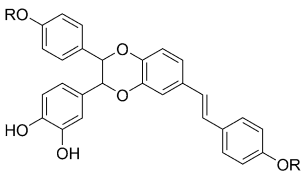
To further confirm the necessity of the 4-hydroxy group in stilbenes for the aerobic oxidative coupling, unsubstituted *trans*-stilbene (**16a**) and trimethylated resveratrol (**17a**) were applied to the photoreaction system. As shown in Scheme 2A, when the two compounds were subjected to the standard conditions for 24 hours, most of substrates were recovered and only a small amount of compounds were formed. Based on TLC and GCMS analysis, no dehydrodimers but corresponding aldehydes were detected. The formation of aldehydes could be attributed to the cleavage of [2+2] cycloaddition products generated by the reaction of stilbenes with singlet oxygen.[10] The sharp contrast between stilbenes without 4-hydroxy benzene moieties (**16a**, **17a**) and 4-hydroxy-substituted stilbenes (**1a**, **4a**) in the photoreaction indicated that a quinone methide radical should be included during the formation of the dehydrodimer.[3f]

It has been reported that the formation of a δ-viniferin skeleton could proceed by the coupling of two quinone methide radicals[2b,3d,e] or the addition of a quinone methide radical to another double bond of stilbenes.[4g] If the latter pathway is possible, a hybrid of resveratrol (**1a**) and unreactive *trans*-stilbene (**16a**) should be produced when the two compounds were mixed together under the standard conditions. However, only δ-viniferin was formed in 79% yield (based on 76% conversion of **1a**). In contrast, the reaction between resveratrol (**1a**) and five equivalents of 4-hydroxy-*trans*-stilbene (**4a**) afforded not only the dimers of self-coupling (**1b**, **4b**), but also the hybrid (**18**) (Scheme 2B). The results of these two experiments strongly indicate that the reaction was performed through a radical–radical coupling pathway.

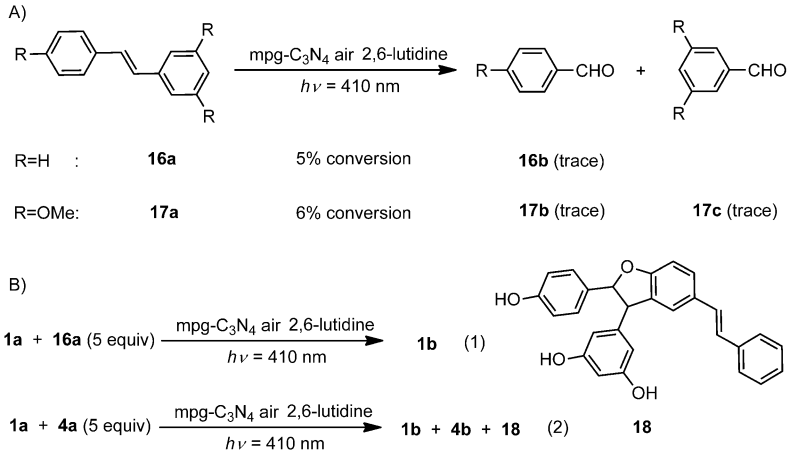
Up to now, there is the only one previous report on the photochemistry between resveratrol and molecular oxygen.[10] This involves energy transfer from a sensitizer to generate singlet oxygen that reacted with resveratrol resulting in the formation of cycloaddition products rather than dehydrodimers. The highly selective generation of δ-viniferin in the present system might be attributed to the unique properties of mpg-C_3N_4. The large surface area (ca. 200 $m^2 g^{-1}$) and the basic residue groups of mpg-C_3N_4 could absorb molecular oxygen on the surface of the catalyst efficiently, and the low potential of the CB (−1.3 V versus NHE) under irradiation provided a favorable driving force in reducing molecular oxygen to produce superoxide radical anion ($O_2^{-\bullet}$), thereby suppressing the generation of singlet oxygen.[7a] As a result, δ-viniferin was produced with high chemoselectivity.

To verify the generation of the $O_2^{-\bullet}$ in the initial step of the reaction, potassium superoxide was used as another source of

Table 2. The scope of aerobic oxidative coupling of resveratrol and its analogues.[a]

Entry	Substrate	Product	Conv. [%]	Yield [%]
				
1	**1a** R = H	**1b**	79	86
2	**2a** R = Me	**2b**	100	85
3	**3a** R = Ac	**3b**	100	51
				
4	**4a** R = H	**4b**	100	71
5	**5a** R = F	**5b**	100	40
6	**6a** R = Cl	**6b**	100	77
7	**7a** R = Br	**7b**	100	71
8	**8a** R = CF_3	**8b**	100	70
9	**9a** R = OH	**9b**	90	88
10	**10a** R = OMe	**10b**	100	77
				
11	**11a** R = 3-OMe	**11b**	100	78
12	**12a** R = 2-OMe	**12b**	100	73
13	**13a** R = 3,4-OMe	**13b**	100	84
				
14	**14a** R = OH	**14b**	86	81
15	**15a** R = OMe	**15b**	90	85

[a] Reaction conditions: substrates (20 mg), mpg-C_3N_4 (4 mg, 5% w/w), 2,6-lutidine (5 equiv), CH_3CN (5 mL), the bubbling rate of air is one bubble per second, purple LEDs (3 W, 410 nm), RT, 24 h. [b] Isolated yield after purification by chromatography on polyamide or silica gel.



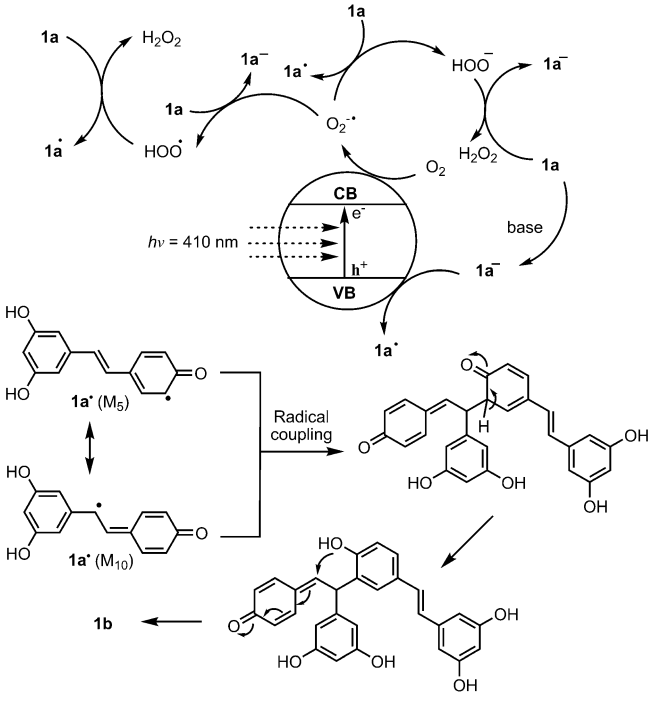
Scheme 2. A) The reaction of resveratrol analogues without 4-hydroxyl substituents under standard conditions; B) The hybrid reaction of stilbenes.

superoxide anion instead of the photocatalytic aerobic conditions and resveratrol **1 a** was transformed to δ-viniferin in 44% yield with 65% conversion.[11] Moreover, addition of 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), a superoxide anion and phenoxy radical quencher, to the photocatalytic aerobic oxidative coupling system entirely suppressed the reaction, no δ-viniferin was detected by TLC analysis even after 24 hours of irradiation.[12] The results indicated that the $O_2^{-\bullet}$ generated by the electron-transfer pathway between mpg-C_3N_4 and molecular oxygen was the vital ROS in the initial step of the radical coupling pathway.

We have shown in Table 1 that the base 2,6-lutidine is crucial for the high efficiency of the oxidative dimerization. The pH value of the acetonitrile solution containing resveratrol (1.75×10^{-2} mol L^{-1}) is about 7.10, whereas the value approximately increased to 7.58 when 2,6-lutidine (8.75×10^{-2} mol L^{-1}) was introduced to the reaction system. Meanwhile, in the buffered aqueous solution, the voltammograms showed the first oxidation peak of resveratrol was shifted to more negative potentials with increasing pH values (see Figure S2 in the Supporting Information). Because the first oxidation peak is due to the oxidation of the phenol moiety,[13] the decrease of the oxidation potential indicated the generation of the corresponding phenolate anion, a much stronger electron donor. Therefore, it is believed that the acceleration of the reaction by 2,6-lutidine should be attributed to the increased phenolate anion generated by the ionization of resveratrol and its analogues.

On the basis of the above results, the photocatalytic aerobic oxidative coupling reaction can be rationalized by the following mechanism (Scheme 3). When mpg-C_3N_4 was irradiated with visible light, excitation of electrons from the valence band into the conduction band generates electron and hole pairs. Subsequently, electron transfer from the conduction band of mpg-C_3N_4 to molecular oxygen produced a superoxide radical anion ($O_2^{-\bullet}$), which can further react with resveratrol by hydrogen abstraction following proton transfer or proton transfer following hydrogen abstraction to afford **1 a**$^{\bullet}$ radical and **1 a**$^{-}$ anion along with the formation of H_2O_2. On the other hand, the holes generated in the valence band of mpg-C_3N_4 are injected by electrons available from **1 a**$^{-}$, a phenolate anion generated by the reaction of **1 a** with $O_2^{-\bullet}$ radical anion or the ionization of resveratrol in the presence of 2,6-lutidine, thus leading to the formation of phenoxy radical **1 a**$^{\bullet}$. In turn, the delocalization of radical **1 a**$^{\bullet}$ could afford a quinone methide radical (M_5) or a benzyl radical (M_{10}). The coupling of one radical M_5 and another radical M_{10}, followed by tautomeric rearrangement and intramolecular nucleophilic attack to the methylene of the intermediate semiquinone, gave δ-viniferin as shown in Scheme 3.

In summary, we have developed a facile and efficient photochemical approach for specifically generating ROS ($O_2^{-\bullet}$) to achieve the oxidative coupling of resveratrol and its analogues in vitro by mpg-C_3N_4, a metal-free heterogeneous catalyst. The photoreaction of resveratrol and molecular oxygen catalyzed by mpg-C_3N_4 provided an ideal model to mimic biotransformation of resveratrol to δ-viniferin. With this method, 4-hydroxy-*trans*-stilbenes, including resveratrol, were smoothly transformed to δ-viniferin and its analogues in moderate to high yields. Because the successful applications of mpg-C_3N_4 in the photoreaction are still rare,[7,8] the work described here is also



Scheme 3. Proposed mechanism.

expected to be valuable for the design of elegant phototransformations by oxidation using molecular oxygen as the oxidant and mpg-C_3N_4 as the photocatalyst.

Experimental Section

General procedure for photocatalytic oxidative coupling of resveratrol and its analogues

Substrates **1**–**15 a**, 5% w/w mpg-C_3N_4, CH_3CN (5 mL), and base (5 equiv) were added to a 10 mL reaction tube equipped with a magnetic stir bar. The solution was bubbled into air in the rate of one bubble per second. After this, the solution was stirred at a distance of ~2 cm from a 3 W 410 nm purple LEDs at room temperature for 24 h. Upon the completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography.

Acknowledgements

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Keywords: mpg-C_3N_4 · oxidative coupling · oxygen · photochemistry · resveratrol

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