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Graphical Abstract

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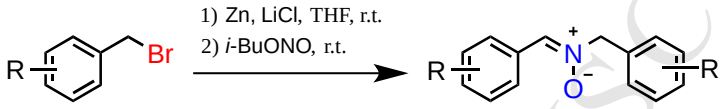
Kei Yanai and Hideo Togo
Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522 Japan



40~47% yields

R = H. Me. OMe. Bu^{t}. Bu^{n}.

Pergamon

TETRAHEDRON

Novel Preparation of *N*-Arylmethyl-*N*-arylmethyleneamine *N*-Oxides from Benzylic Bromide with Zinc and Isobutyl Nitrite

Kei Yanai and Hideo Togo*

Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522 Japan

Abstract— Treatment of benzylic bromides with Zn and LiCl, followed by the reaction with *i*-butyl nitrite gave *N*-arylmethyl-*N*-arylmethyleneamine *N*-oxides in moderate yields. The present reaction is a novel and simple method for the preparation of nitrones from benzylic bromides, although the yields are moderate.

* Corresponding author. Tel.:81-43-290-2792; fax:81-43-290-2792; e-mail: togo@faculty.chiba-u.jp.

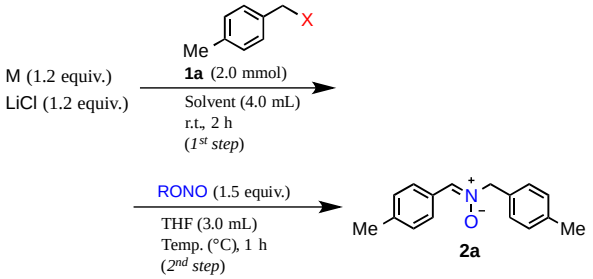
1. Introduction

Nitrones are important and useful precursors for construction of five-membered nitrogen-containing heterocycles, especially, isoxazolidines and isoxazolines with alkenes and alkynes, respectively, via 1,3-dipolar cycloadditon.[1a,1b] Moreover, nitrones possessing antimicrobial activity[1c] are known, and ribonucleoside analogues bearing isoxazolidines instead of ribose at anomeric position have moderate HIV activity.[1d] Recent reports for the construction of nitrogen-containing heterocycles with nitrones are as follows:[2] the preparation of *N*-hydroxypyrrolidines by the reaction with α,β-unsaturated aldehydes;[2a] the preparation of 3-oxazolines by the reaction with aldehydes;[2b] the preparation of isoxazolidines by the reaction with α,β-unsaturated nitro compounds;[2c] the preparation of isoxazolidine carboxylates by the reaction with ethyl pyrrolylacrylates;[2d] the preparation of isoxazolines by the reaction with ethyl propiolates,[2e] the preparation of bridged bicyclic tetrahydrobenz[b]azepin-4-ones by the reaction with allenes,[2f] and the preparation of chromenoisoxazolines by the reaction with olefinic group via intramolecular cycloaddition.[2g] Therefore, in addition to the classical methods for the preparation of nitrones,[3] such as the reaction of aldehydes with *N*-alkyl hydroxylamines,[1c,3a] the oxidation of secondary amines with *m*CPBA,[3b] the oxidation of secondary amines with H_2O_2 in the presence of titanium silicate,[3c] and the electrochemical oxidation of *N*,*N*-dialkylhydroxylamines,[3d] efficient synthetic studies of nitrones are still in progress. Recent synthetic studies of nitrones are as follows:[4] the oxidation of *N*,*N*-dibenzylamine with 5-ethyl-3-methyllumiflavin, molecular oxygen, and hydrazine in 2,2,2-trifluoroethanol,[4a] the oxidation of dibenzylic amines with phosphotungstic acid ($H_3PW_{12}O_{40}$) and aq. 2.5% H_2O_2,[4b] the oxidation of secondary amines with Oxone® in the presence of Na_2EDTA and $NaHCO_3$ in THF-CH_3CN,[4c] the oxidation of imines with urea•hydrogen peroxide in the presence of CH_3ReO_3 (MTO) in methanol,[4d] the condensation/oxidation of aromatic aldehydes and primary amines with urea•hydrogen peroxide in the presence of MTO in methanol,[4e] the oxidation of *N*,*N*-dialkylhydroxylamines with *o*-iodoxybenzoic acid (IBX) in dichloromethane,[4f] the reaction of 1-phenyl-5-(alkanesulfonyl)tetrazoles, *tert*-butyl nitrite, and Cs_2CO_3 in THF,[4g] the reaction of nitrosobenzene and aromatic aldehydes in the presence of L-proline in methanol,[4h] the coupling reaction of *N*-nosylhydrazones and nitrosoarenes with NaH in dichloromethane,[4i] the reductive coupling reaction of nitroarenes and aromatic aldehydes in the presence of carbon-decorated platinum nanoparticles under H_2 atmosphere in ethanol,[4j] and the electrochemical reaction of aldehydes and nitroarenes with BDD electrode in ethanol-water.[4k]
As our synthetic studies of nitrogen-containing heterocycles, such as isoxazoles, pyrazoles, oxazoles, tetrazoles, *etc*,[5] first we tried to prepare oximes by the reaction of benzylic zinc bromides with *i*-butyl nitrite, to use further 1,3-dipolar cycloaddition of the nitrile *N*-oxides formed from oxidation of the oximes, with alkynes. However, nitrones were obtained by the reaction of benzylic zinc bromides with *i*-butyl nitrite. Here, we would like to report a simple preparation of nitrones, such as *N*-arylmethyl-*N*-arylmethyleneamine *N*-oxides, by the reaction of benzylic bromides with zinc and *i*-butyl nitrite.

2. Results and Discussion

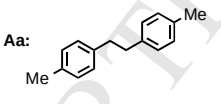
First, *p*-methylbenzylbromide **1a** (2.0 mmol) in THF (2.0 mL) was added to a pre-dried mixture of Zn powder (1.2 equiv.) and LiCl (1.2 equiv.) in THF (2.0 mL). The mixture was stirred at room temperature for 2 h to form *p*-methylbenzyl zinc bromide (1st step), and this was then treated with *i*-butyl nitrite (1.5 equiv.) at room temperature for 1 h (2nd step) to form *N*-(4-methylphenyl)methyl-*N*-(4-methylphenyl)methylene *N*-oxide **2a** in 36% yield, together with 1,2-bis(*p*-methylphenyl)ethane **Aa** and **1a** in 15% and 9% yields, respectively, as shown in Table 1 (entry 1). When Mg turnings instead of Zn powder were used under the same procedure and conditions, coupling product **Aa** was obtained as the sole product (entry 2). On the other hand, when Fe powder, In powder, and Sm powder instead of Zn powder were used under the same procedure and conditions, *p*-methylbenzylbromide **1a** was recovered (entries 3~5). Thus, Zn powder is effective for the preparation of nitrone **1a**. Then, the optimum conditions for the formation of nitrone **1a** were studied. Drying treatment of a mixture of Zn and LiCl at 50 °C for 1 h under reduced pressure, and then treatment with *p*-methylbenzylbromide **1a** in THF, followed by the reaction with *i*-butyl nitrite under the same procedure and conditions gave nitrone **2a** in 47% (entry 6). When the solvent was changed to 1,4-dioxane and diethyl ether instead of THF, nitrone **2a** was not obtained at all in 1,4-dioxane, but was obtained in 37% yield together with coupling product **Aa** in 25% yield in diethyl ether (entries 7, 8). Thus, THF was the best solvent. In the absence of LiCl under the same procedure and conditions, the yield of nitrone **2a** was decreased to 30% (entry 9). When the amounts of Zn (1.5 equiv.) and LiCl (1.5 equiv.) were increased under the same procedure and conditions, the yield of nitrone **2a** was decreased (entry 10). When the temperature of the 2nd reaction step was changed from room temperature to 0 °C, 10 °C, and 40 °C under the same procedure and conditions as those in entry 6, the yields of nitrone **2a** were decreased, respectively (entries 12-14). Changing *i*-butyl nitrite to *i*-amyl nitrite and *t*-butyl nitrite under the same procedure and conditions reduced the yield of nitrone **2a** again (entries 6, 15, 16). Finally, treatment of *p*-methylbenzyl chloride and *p*-methylbenzyl iodide instead of *p*-methylbenzyl bromide **1a** under the same procedure and conditions gave nitrone **2a** in 0% and 19% yields, respectively (entries 17, 18). This is due to the fact that *p*-methylbenzyl chloride is inert to Zn powder, and *p*-methylbenzyl iodide is unstable and decomposes slowly. Thus, the reaction using the conditions of entry 6 is the best to form nitrone **2a** in moderate yield. As a gram-scale experiment, treatment of *p*-methylbenzyl bromide **1a** (10 mmol) under the same procedure and conditions as those in entry 6 gave nitrone **2a** in 44% yield, as shown in Scheme 1.

Table 1. Optimum Reaction Conditions



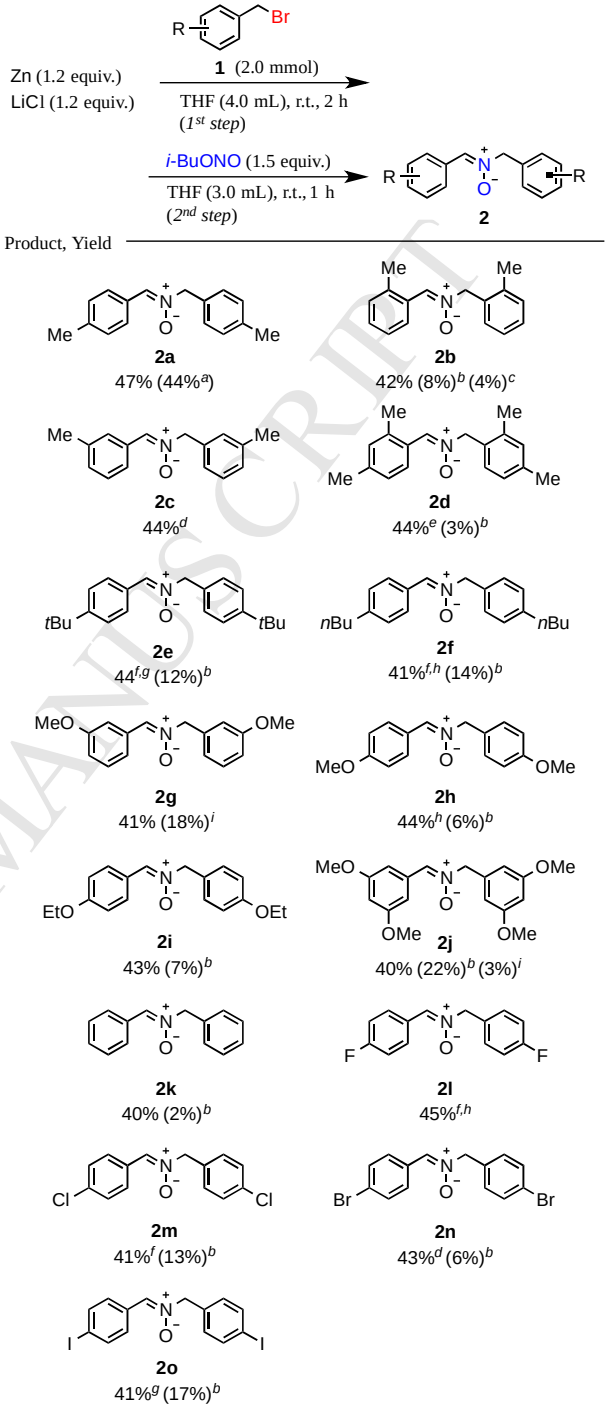
Entry	M	X	Solvent	R	Temp. (℃)	Yield (%)
1[a]	Zn	Br	THF	*i*-Bu	r.t.	36 (15)[b] (9)[c]
2[a]	Mg	Br	THF	*i*-Bu	r.t.	0 (83)[b]
3[a]	Fe	Br	THF	*i*-Bu	r.t.	0 (100)[c]
4[a]	In	Br	THF	*i*-Bu	r.t.	0 (100)[c]
5[a]	Sm	Br	THF	*i*-Bu	r.t.	0 (100)[c]
6	**Zn**	Br	**THF**	*i*-Bu	r.t.	**47**
7	Zn	Br	dioxane	*i*-Bu	r.t.	0
8	Zn	Br	Et_2O	*i*-Bu	r.t.	37 (25)[b]
9[d]	Zn	Br	THF	*i*-Bu	r.t.	30
10[e]	Zn	Br	THF	*i*-Bu	r.t.	28
11[f]	Zn	Br	THF	*i*-Bu	r.t.	11
12	Zn	Br	THF	*i*-Bu	0	34
13	Zn	Br	THF	*i*-Bu	10	44 (26)[c]
14	Zn	Br	THF	*i*-Bu	40	14 (4)[b] (5)[c]
15	Zn	Br	THF	*i*-Amyl	r.t.	19 (28)[b]
16	Zn	Br	THF	*t*-Bu	r.t.	27
17	Zn	Cl	THF	*i*-Bu	r.t.	0
18	Zn	I	THF	*i*-Bu	r.t.	19 (28)[b]

[a] A mixture of Zn and LiCl was heated with a heat gun for 5 min under reduced presure, instead of vacuum pumping for 1 h at 50 °C. [b] Yield of coupling product **Aa.** [c] Yield of starting material **1a**. [d] LiCl was not used. [e] Zn (1.5 equiv.) and LiCl (1.5 equiv.) were used. [f] 1st step reaction was conducted at 40 °C.

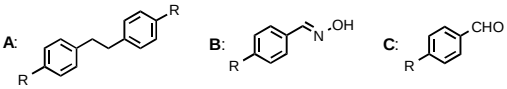


Based on those results, benzylic bromides (2.0 mmol), such as *o*-methylbenzyl bromide **1b**, *m*-methylbenzyl bromide **1c**, 2,4-dimethylbenzyl bromide **1d**, *p*-*t*-butylbenzyl bromide **1e,** *p*-*n*-butylbenzyl bromide **1f**, *m*-methoxybenzyl bromide **1g**, *p*-methoxybenzyl bromide **1h**, *p*-ethoxybenzylbromide **1i**, 3,5-dimethoxybenzyl bromide **1j**, and benzyl bromide **1k**, were treated with a mixture of pre-dried Zn powder and LiCl in THF at room temperature for 2 h, and then the mixtures were reacted with *i*-butyl nitrite (1.5 equiv.) for 1 h at room temperature to give nitrones **2b**~**2k** in moderate yields, as shown in Scheme 1. The treatment of *p*-fluorobenzyl bromide **1l**, *p*-chlorobenzyl bromide **1m**, *p*-bromobenzyl bromide **1n**, and *p*-iodobenzyl bromide **1o**, all of which have halogen groups as the electron-withdrawing group, under the same procedure and conditions also gave the corresponding nitrones **2l**~**2o** in moderate yields, respectively. However, the same treatment of *p*-(ethoxycarbonyl)benzyl bromide, *p*-nitrobenzyl bromide, and *p*-(trifluoromethyl)benzyl bromide, all of which have strong electron-withdrawing

Scheme 1. Generality of Benzyl Bromides **1** for Nitrones **2**



[a] Substrate (10.0 mmol) was used. [b] Yield of coupling product **A**. [c] Yield of oxime **B**. [d] 1st step reaction was carried out for 2.5 h. [e] 1st step reaction was carried out for 1.5 h. [f] 1st step reaction was carried out for 3 h. [g] *i*-BuONO (1.8 equiv.) was used. [h] 2nd step reaction was carried out at 10 °C. [i] Yield of aldehyde **C**.

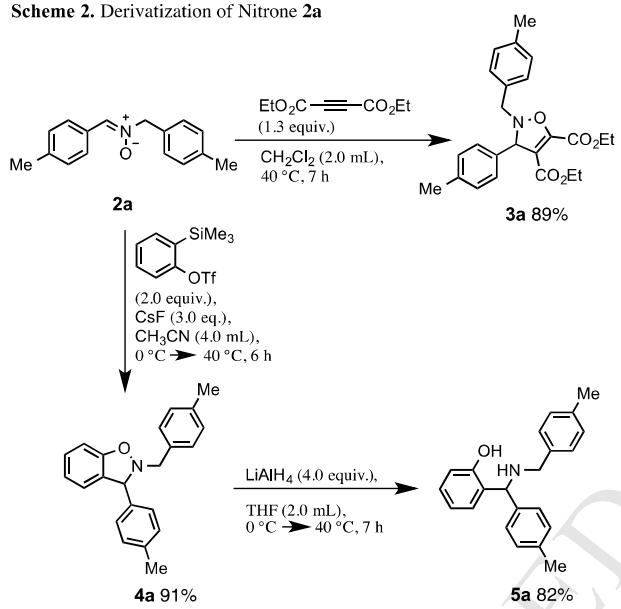


groups, under the same procedure and conditions did not generate the corresponding nitrones at all; instead, the corresponding coupling products **A** were obtained mainly (47~57% yields). In addition, the same treatment of 3-phenylpropyl bromide, which is not a benzylic bromide,

did not give the corresponding nitrones at all, and instead, the starting bromide was recovered (100% yield).

Once the nitrones were formed, they could be easily transformed into nitrogen-containing heterocycles. For example, treatment of nitrone **2a** with diethyl acetylenedicarboxylate (1.3 equiv.) in CH_2Cl_2 at 40 °C for 7 h gave isoxazolidine derivative **3a** in 89% yield, as shown in Scheme 2. Treatment of nitrone **2a** with *O*-(*o*-trimethylsilyl)phenyl triflate and CsF in CH_3CN at 0 °C to 40 °C for 6 h generated benzoisoxazolidine derivative **4a** in 91% yield. Reduction of benzoisoxazolidine derivative **4a** with $LiAlH_4$ at 0 °C to 40 °C for 7 h generated aminophenol **5a** in 82% yield.

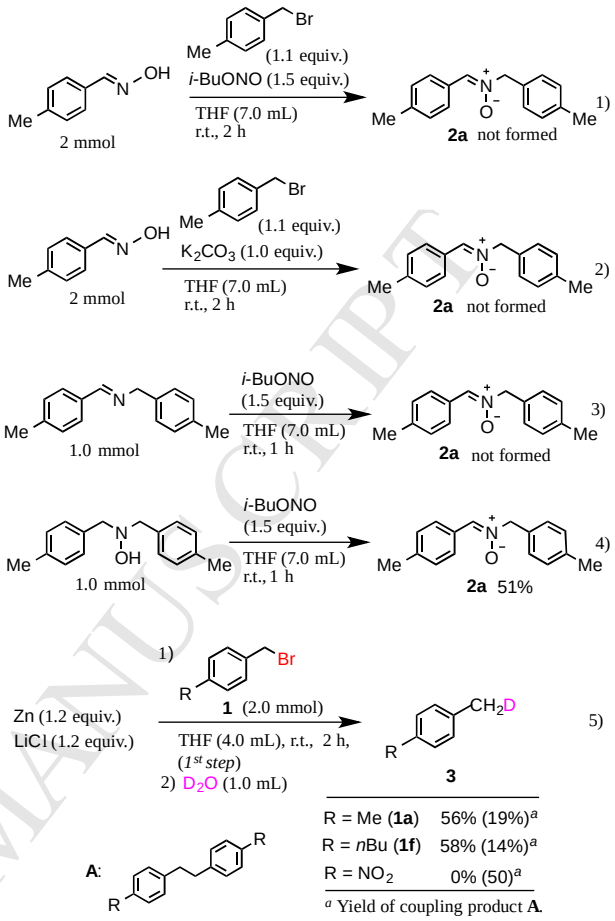
Scheme 2. Derivatization of Nitrone **2a**



As control experiments to clarify the reaction mechanism for the formation of nitrones from benzylic zinc bromides **I** with *i*-butyl nitrite, the reaction of *p*-methylbenzaldoxime with *p*-methylbenzyl bromide in the presence of *i*-butyl nitrite for 2 h at room temperature (eq. 1), the reaction of *p*-methylbenzaldoxime and *p*-methylbenzyl bromide in the presence of K_2CO_3 for 2 h at room temperature (eq. 2), and the reaction of imine prepared from the reaction of *p*-methylbenzaldehyde and *p*-methylbenzylamine, with *i*-butyl nitrite for 1 h at room temperature (eq. 3), were carried out, as shown in Scheme 3. However, nitrone **2a** was not formed at all. Thus, oxime and imine are not the intermediates in the present reaction. On the other hand, when TEMPO (1.2 equiv.) was added to the mixture before the 2nd reaction step, nitrone **2a** was not obtained at all. In addition, treatment of *N*,*N*-bis(*p*-methylbenzyl) -hydroxylamine with *i*-butyl nitrite (1.5 equiv.) at room temperature for 1 h gave nitrone **2a** in 51% yield (eq. 4).

On the other hand, To see the formation of benzylic zinc bromides, benzylic bromides **1** (2.0 mmol), such as *p*-methylbenzyl bromide **1a** and *p*-*n*-butylbenzyl bromide **1f**, were treated with a mixture of pre-dried Zn powder and

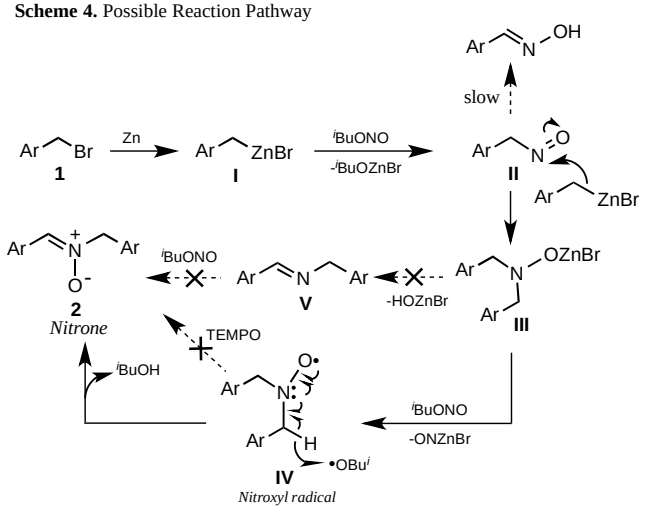
Scheme 3. Control Experiments



LiCl in THF at room temperature for 2 h, and then the mixtures were quenched with D_2O to form *p*-methyltoluene-d_1 and *p*-butyltoluene-d_1 in 56% and 58% yields, together with coupling products, 1,2-bis(*p*-methylphenyl)ethane **Aa** in 19% yield and 1,2-bis(*p*-butylphenyl)ethane **Af** in 14% yield, respectively, as shown in eq. 5). Thus, the coupling products are formed before the reaction with *i*-butyl nitrite. On the other hand, the same treatment of *p*-nitrobenzyl bromide did not give *p*-nitrotoluene-d_1 at all, and instead, 1,2-bis(*p*-nitrophenyl)ethane was obtained in 50% yield. This would be the reason why the nitrones were not obtained from benzylic bromides bearing strong electron-withdrawing groups, such as nitro and ester groups.

Based on those results, a possible reaction pathway is shown in Scheme 4. Benzylic zinc bromide **I** reacts with *i*-butyl nitrite to form nitroso compound **II**. Before its tautomerization into oxime, nitroso compound **II** reacts with benzylic zinc bromide **I** to form zinc salt of *N*,*N*-bis(arylmethyl)hydroxylamine **III**. Single-electron oxidation of **III** by *i*-butyl nitrite occurs to form nitroxyl radical **IV**, together with the generation of *i*-BuO• and ONZnBr. *i*-BuO• abstracts a β-hydrogen atom of nitroxyl radical **IV** to form nitrone **2**.

Scheme 4. Possible Reaction Pathway



3. Conclusion

The reaction of benzylic bromides with Zn powder and LiCl, followed by the reaction with *i*-butyl nitrite provided the corresponding nitrones in moderate yields. Although the yields of the nitrones are moderate and the substrates are limited, the present reaction is a novel method for the preparation of *N*-arylmethyl-*N*-arylmethyleneamine *N*-oxides. We believe the present method would be useful for the preparation of simple *N*-arylmethyl-*N*-arylmethyleneamine *N*-oxides from benzylic bromides with Zn powder and *i*-butyl nitrite.

4. Experimental Section

4.1. General: ^{1}H NMR spectra were measured on 400 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; sext = sextet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on 100 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). Characteristic peaks in the infrared (IR) spectra were recorded in wave number, cm^{-1}. High-resolution mass spectra (HRMS) were recorded by Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Melting points were uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F254). The products were purified by column chromatography on neutral silica gel 60N (63-200 mesh).

4.2 Typical Procedure for Preparation of Nitrones 2: A mixture of Zinc powder (157.0 mg, 2.4 mmol) and LiCl (101.8 mg, 2.4 mmol) in a 30 mL two-necked round-bottom flask was dried for 1 h at 50 °C. THF (2.0 mL) was added to the flask, and then, a solution of *p*-methylbenzyl bromide **1a** (370.1 mg, 2.0 mmol) in THF (2.0 mL) was added dropwise to the flask at room temperature and the mixture was stirred for 2 h at room temperature under argon atmosphere. Then, the resulting mixture was added to a solution of *i*-butyl nitrite (350.0 μL, 3.0 mmol) of THF (3.0 mL) in a 50 mL two-necked round-bottom flask, and the obtained mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was quenched by the addition of saturated aqueous NH_4Cl (10.0 mL). The mixture was extracted with $CHCl_3$ (3 × 20.0 mL). The combined organic layer was dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt, 1:1) to afford *N*-(4-methylphenyl)methyl-*N*-(4-methylphenyl)methyleneamine *N*-oxide **2a** (112.1 mg, 47%).

4.2.1 *N*-(4-Methylphenyl)methyl-*N*-(4-methylphenyl) -methyleneamine *N*-Oxide 2a: Yield: 112.1 mg (47%); white solid; mp: 110-111 °C. IR (neat): ν = 2912, 1587, 1417, 1311 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.37 (s, 3H), 2.37 (s, 3H), 5.00 (s, 2H), 7.20 (d, 2H, *J* = 7.9 Hz), 7.22 (d, 2H, *J* = 5.4 Hz), 7.31 (s, 1H), 7.36 (d, 2H, *J* = 8.1 Hz), 8.10 (d, 2H, *J* = 8.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.6, 70.7, 127.7, 128.6, 129.1, 129.3, 129.6, 130.2, 134.0, 138.8, 140.8 ppm. HRMS (ESI) Calcd for $C_{16}H_{18}ON$ $[M+H]^+$ = 240.1383, Found = 240.1388

4.2.2 *N*-(2-Methylphenyl)methyl-*N*-(2-methylphenyl) -methyleneamine *N*-Oxide 2b: Yield: 100.1 mg (42%); white solid; mp: 78-80 °C. IR (neat): ν = 3064, 1561, 1341, 1213cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 2.43 (s, 3H), 5.14 (s, 2H), 7.14 (t, 1H, *J* = 4.5 Hz), 7.27-7.35 (m, 5H), 7.39 (d, 1H, *J* = 7.0 Hz), 9.14 (dd, 1H (*J* = 9.4, 1.4 Hz) ppm. ^{13}C NMR (100 MHz,$CDCl_3$): δ = 18.9, 19.3, 69.0, 126.0, 126.4, 127.5, 128.4, 129.1, 129.9, 129.9, 130.3, 130.6, 130.7, 131.1, 136.1 137.4 ppm. HRMS (ESI) Calcd for $C_{16}H_{18}ON$ $[M+H]^+$ = 240.1383, Found = 240.1384.

4.2.3 *N*-(3-Methylphenyl)methyl-*N*-(3-methylphenyl) -methyleneamine *N*-Oxide 2c: Yield: 104.2 mg (44%); colorless liquid; IR (neat): ν = 2921, 1584, 1457, 1294 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.38 (s, 3H), 5.01 (s, 2H), 7.20 (d, 1H, *J* = 7.6 Hz), 7.22 (d, 1H, *J* = 8.5 Hz), 7.27-7.31 (m, 4H), 7.36 (s, 1H), 7.92 (d, 1H, *J* = 7.6 Hz), 8.15 (s, 1H) ppm. ^{13}C NMR (100 MHz,$CDCl_3$): δ = 21.3, 21.4, 71.2, 126.0, 126.3, 128.3, 128.8, 129.0, 129.7, 129.9, 130.3, 121.3, 133.1, 134.4, 138.1, 138.7 ppm. HRMS (ESI) Calcd for $C_{16}H_{18}ON$ $[M+H]^+$ = 240.1383, Found = 240.1384.

4.2.4 *N*-(2,4-Dimethylphenyl)methyl-*N*-(2,4-dimethylphenyl) -methyleneamine *N*-Oxide 2d: Yield: 119.0 mg (44%); white solid; mp: 72-74 °C. IR (neat): ν = 2920, 1578, 1469, 1246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.31 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 5.07 (s, 2H), 6.97-7.08 (m, 4H), 7.25 (d, 1H, *J* = 5.4 Hz), 7.29 (s, 1H), 9.06 (d, 1H, *J* = 8.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 19.4, 21.1, 21.4, 68.8, 126.0, 126.8, 127.2, 127.8, 128.2, 130.7, 130.7, 130.9, 131.6, 136.2, 137.5, 139.1, 140.3 ppm. HRMS (ESI) Calcd for $C_{18}H_{22}ON$ $[M+H]^+$ =268.1696, Found = 268.1696

4.2.5 *N*-(4-*t*-Butylphenyl)methyl-*N*-(4-*t*-butylphenyl)methylene -amine *N*-Oxide 2e: Yield: 142.1 mg (44%); white solid; mp: 89-91 °C. IR (neat): ν =2961, 1580, 1454, 1201 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 1.32 (s, 9H), 5.02 (s, 2H), 7.38-7.43 (m, 7H), 8.15 (d, 2H, *J* = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 31.1, 31.2, 34.6, 35.0, 70.7, 125.3, 125.9, 127.8,

128.5, 128.9, 130.4, 134.0, 151.9, 153.9 ppm. HRMS (ESI) Calcd for $C_{22}H_{30}ON$ $[M+H]^+$ = 324.2322, Found = 324.2323.

4.2.6 *N*-(4-*n*-Butylphenyl)methyl-*N*-(4-*n*-butylphenyl) -methyleneamine *N*-Oxide 2f: Yield: 131.2 mg (41%); white solid; mp: 62-63 °C. IR (neat): ν = 2955, 1577, 1455, 1312 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 4.5 Hz), 0.93 (t, 3H, *J* = 4.5 Hz) 1.31-1.38 (m, 4H), 1.55-1.63 (m, 4H), 2.62 (t, 2H, *J* = 7.7 Hz), 2.62 (t, 2H, *J* = 7.7 Hz), 5.01 (s, 2H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.22 (d, 2H, *J* = 8.2 Hz), 7.32 (s, 1H), 7.38 (d, 2H, *J* = 7.9 Hz), 8.12 (d, 2H, *J* = 8.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.2, 22.3, 33.2, 33.4, 35.3, 35.7, 70.7, 127.0, 127.9, 128.4, 128.6, 128.9, 129.2, 130.4, 134.2, 143.8, 145.8 ppm. HRMS (ESI) Calcd for $C_{22}H_{30}ON$ $[M+H]^+$ = 324.2322, Found = 324.2317.

4.2.7 *N*-(3-Methoxyphenyl)methyl-*N*-(3-methoxyphenyl) -methyleneamine *N*-Oxide 2g: Yield:111.8 mg (41%); colorless liquid; IR (neat): ν = 2939, 1584, 1318, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.826 (s, 3H), 3.834 (s, 3H), 5.03 (s, 2H), 6.92-6,99 (m, 2H), 7.02 (s, 1H), 7.06 (d, 1H, *J* = 7.5 Hz), 7.30 (t, 1H, *J* = 7.9 Hz), 7.33 (t, 1H, *J* = 7.9 Hz), 7.39 (s, 1H), 7.46 (d, 1H, *J* = 7.70 Hz), 8.21 (s,1H) ppm. ^{13}C NMR (100 MHz,$CDCl_3$): δ = 55.3(2C), 71.3, 112.2, 114.5, 114.8, 117.5, 121.5, 121.7, 129.2, 130.0, 131.6, 134.4, 134.5, 159.4, 159.9 ppm. HRMS (ESI) Calcd for $C_{16}H_{18}O_3N$ $[M+H]^+$ = 272.1281, Found = 272.1278.

4.2.8 *N*-(4-Methoxyphenyl)methyl-*N*-(4-methoxyphenyl) -methyleneamine *N*-Oxide 2h[4d]: Yield: 119.2 mg (44%); white solid; mp: 111-112 °C. IR (neat): ν = 2913, 1587, 1457, 1311 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (d, 3H), 3.84 (s, 3H), 4.96 (s, 2H), 6.92 (d, 2H, *J* = 9.0 Hz), 6.94 (d, 2H, *J* = 6.9 Hz), 7.40 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, *J* = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3(2C), 70.1, 113.7, 114.3, 123.4, 125.3, 130.5, 130.9, 133.4, 160.0, 161.0 ppm. HRMS (ESI) Calcd for $C_{16}H_{18}O_3N$ $[M+H]^+$ = 272.1281, Found = 272.1279.

4.2.9 *N*-(4-Ethoxyphenyl)methyl-*N*-(4-ethoxyphenyl) -methyleneamine *N*-Oxide 2i: Yield: 129.4 mg (43%); white solid; mp: 115-117 °C. IR (neat): ν = 3002, 1603, 1396, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, 3H, *J* = 7.0 Hz), 1.42 (t, 3H, *J* = 7.0 Hz), 4.02-4.09 (m, 4H), 5.00 (s, 2H), 6.89 (d, 2H, *J* = 10.8 Hz), 6.92 (d, 2H, *J* = 10.6 Hz), 7.23 (s, 1H), 7.38 (d, 2H, *J* = 8.5 Hz), 8.18 (d, 2H, *J* = 9.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 14.8, 63.5(2C), 70.1, 114.2, 114.8, 123.3, 125.2, 130.6, 130.9, 133.5, 159.4, 160.4 ppm. HRMS (ESI) Calcd for $C_{18}H_{22}O_3N$ $[M+H]^+$ = 300.1594, Found = 300.1593.

4.2.10 *N*-(3,5-Dimethoxyphenyl)methyl-*N*-(3,5-dimethoxy -phenyl)methyleneamine *N*-Oxide 2j: Yield: 134.0 mg (40%); white solid; mp: 111-112 °C. IR (neat): ν = 2939, 1589, 1346, 1291 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 6H), 3.81 (s, 6H), 5.00 (s, 2H), 6.48 (t, 1H, *J* = 2.3 Hz), 6.55 (t, 1H, *J* = 2.3 Hz), 6.61 (d, 2H, *J* = 2.3 Hz), 7.34 (s, 1H), 7.45 (d, 2H, *J* = 2.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 55.5, 71.5, 100.8, 103.8, 106.2, 107.2, 131.9, 134.6, 135.0, 160.5, 161.1 ppm. HRMS (ESI) Calcd for $C_{18}H_{22}O_5N$ $[M+H]^+$ = 332.1492, Found = 332.1488.

4.2.11 *N*-Benzyl-*N*-phenylmethyleneamine *N*-Oxide 2k[4d,6]: Yield: 84.5 mg (40%); white solid; mp: 80-82 °C (mp: 82-83 °C)[6]. IR (neat): ν = 2998, 1581, 1458, 1211 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.07 (s, 2H), 7.40-7.45 (m, 7H), 7.49 (dd, 2H, J_1 = 7.6 Hz, J_2 = 2.0 Hz), 8.21 (dd, 2H, J_1 = 5.7 Hz, J_2 = 2.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =71.2, 128.4, 128.6, 129.0, 129.2, 130.3, 130.4, 133.2, 134.3 (2C) ppm. HRMS (ESI) Calcd for $C_{14}H_{14}ON$ $[M+H]^+$ = 212.1070, Found = 212.1072.

4.2.12 *N*-(4-Fluorophenyl)methyl-*N*-(4-fluorophenyl) -methyleneamine *N*-Oxide 2l: Yield: 110.5 mg (45%); white solid; mp: 88-89 °C. IR (neat): ν = 2974, 1597, 1436, 1230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.02 (s, 2H), 7.06-7.14 (m, 4H), 7.39 (s, 1H), 7.48 (dd, 2H, J_1 = 8.8 Hz, J_2 = 5.4 Hz), 8.26 (dd, 2H, J_1 = 8.8 Hz, J_2 = 5.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.2, 115.5 ($J_{C\text{-}F}$ = 21.6 Hz), 115.8, 116.1, 128.7 ($J_{C\text{-}F}$ = 224.6 Hz), 130.8, 130.9, 131.2 ($J_{C\text{-}F}$ = 8.5 Hz), 133.0 (2C) ppm. HRMS (ESI) Calcd for $C_{14}H_{12}ONF_2$ $[M+H]^+$ = 248.0881, Found = 248.0884.

4.2.13 *N*-(4-Chlorophenyl)methyl-*N*-(4-chlorophenyl) -methyleneamine *N*-Oxide 2m: Yield: 115.4 mg (41%); white solid; mp: 124-125 °C. IR (neat): ν = 2963, 1585, 1410, 1307 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =5.02 (s, 2H), 7.37-7.44 (m, 7H), 8.17 (d, 2H, *J* = 8.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.3, 128.6, 128.7, 129.1, 129.7, 130.5 131.4, 133.2, 135.1, 136.0 ppm HRMS (ESI) Calcd for $C_{14}H_{12}ONCl_2$ $[M+H]^+$= 280.0290, Found = 280.0294.

4.2.14 *N*-(4-Bromophenyl)methyl-*N*-(4-bromophenyl) -methyleneamine *N*-Oxide 2n: Yield: 160.0 mg (43%); white solid; mp: 159-161 °C. IR (neat): ν =2930, 1579, 1395, 1227 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.00 (s, 2H), 7.36 (d, 2H, *J* = 8.6 Hz), 7.38 (s, 1H), 7.53 (d, 2H, *J* = 6.1 Hz), 7.55 (d, 2H, *J* = 6.1 Hz,), 8.09 (d, 2H, *J* = 8.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.5, 123.4, 128.5, 129.0, 129.9, 130.9, 131.6, 131.7, 131.9, 132.2 ppm. HRMS (ESI) Calcd for $C_{14}H_{12}ON^{79}Br_2$ $[M+H]^+$ = 367.9280, Found = 367.9285, Calcd for $C_{14}H_{12}ON^{79}Br^{81}Br$ $[M+H]^+$ = 369.9260, Found = 369.9263. Calcd for $C_{14}H_{12}ON^{81}Br_2$ $[M+H]^+$ = 371.9239, Found = 371.9244.

4.2.15 *N*-(4-Iodophenyl)methyl-*N*-(4-iodophenyl)methylene -amine *N*-Oxide 2o: Yield: 188.3 mg (41%); white solid; mp: 191-193 °C. IR (neat): ν = 2920, 1575, 1391, 1229 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 4.97 (s, 2H), 7.22 (d, 2H, *J* = 8.4 Hz), 7.36 (s, 1H), 7.74 (d, 2H, *J* = 3.6 Hz), 7.76 (d, 2H, *J* = 3.4 Hz), 7.94 (d, 2H, *J* = 8.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.8, 95.2, 96.7, 129.5, 129.8, 131.0, 132.5, 133.4, 137.7, 138.1 ppm. HRMS (ESI) Calcd for $C_{14}H_{12}ONI_2$ $[M+H]^+$ = 463.9001, Found = 463.9003.

4.3. Preparation of Diethyl 2-(*p*-Methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylate 3a: To a *N*-(4-methylphenyl)methyl-*N*-(4-methylphenyl)methylene -amine *N*-oxide **2a** (239.3 mg, 1.0 mmol) in a 50 mL two-necked round-bottom flask was added a solution of diethyl acetylenedicarboxylate (230.4 mg, 1.3 mmol) in dichloromethane (2.0 mL) under argon atmosphere. The mixture was stirred for 7 h at 40 ℃. The resulting mixture was quenched by the addition of H_2O (10.0 mL). The mixture was extracted with $CHCl_3$ (3 × 20.0 mL). The combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt, 5:1) to afford diethyl

2-(*p*-methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylate **3a** (364.9 mg, 89%).

4.3.1 Diethyl 2-(*p*-Methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylate 3a : 364.9 mg (89%); yellow oil; IR (neat): ν = 2982, 1709, 1700, 1301, 1188, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, 3H, *J* = 7.2 Hz), 1.36 (t, 3H, *J* = 7.2 Hz), 2.31 (s, 3H), 2.34 (s, 3H) 4.04-4.13 (m, 3H), 4.34-4.39 (m, 3H), 5.17 (s, 1H), 7.09-7.24 (m, 6H) 7.25 (d, 2H, *J* = 9.9 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9(2C), 21.1(2C), 60.6, 62.7, 63.1, 72.3, 109.0, 127.2, 129.1, 129.4, 131.8(2C), 136.7, 137.6, 137.7, 152.0, 159.3, 162.3 ppm. HRMS (ESI) Calcd for $C_{24}H_{28}O_5N$ $[M+H]^+$ = 410.1962, Found = 410.1963

4.4 Preparation of 2-(*p*-Methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydrobenzoisoxazole 4a: To a mixture of *N*-(4-methylphenyl)methyl-*N*-(4-methylphenyl)methyleneamine *N*-oxide **2a** (239.3 mg, 1.0 mmol) and CsF (460.3 mg, 3.0 mmol) in a 50 mL two-necked round-bottom flask was added a solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (510.65 μL, 2.0 mmol) in acetonitrile (4.0 mL) at 0 ℃ under argon atmosphere. The mixture was stirred for 6 h at 40 °C. The resulting mixture was quenched with H_2O (10.0 mL). The mixture was extracted with $CHCl_3$ (3 × 20.0 mL), and the combined organic layer was dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt, 9:1) to afford 2-(*p*-methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydrobenzoisoxazole **4a** (288.6 mg, 91%).

4.4.1 2-(*p*-Methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydrobenzoisoxazole 4a: Yield: 288.6 mg (91%); colorless oil; IR (neat): ν = 2921, 1474, 1458, 1245, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 2.34 (s, 3H), 4.11 (d, 1H, *J* = 13.4 Hz), 4.31 (d, 1H, *J* = 13.4 Hz), 5.30 (s, 1H), 6.84 (d, 1H, *J* = 7.9 Hz), 6.89 (t, 1H, *J* = 7.5 Hz), 6.99 (d, 1H, *J* = 7.5 Hz), 7.11-7.21 (m, 7H), 7.29 (d, 2H, *J* = 7.9 Hz) ppm.. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 21.1, 21.2, 62.2, 72.2, 108.1, 121.3, 124.1, 127.7, 128.8, 129.0, 129.1, 129.2, 129.3, 133.3, 137.2, 137.4, 137.6, 156.1 ppm. HRMS (ESI) Calcd for $C_{22}H_{22}ON$ $[M+H]^+$ = 316.1682, Found = 316.1687.

4.5 Preparation of *o*-{[(*p*-methylbenzyl)amino](*p*-methylphenyl)methyl}phenol 5a: To a solution of 2-(*p*-methylbenzyl)-3-(*p*-methylphenyl)-2,3-dihydrobenzoisoxazole **4a** (315.4 mg, 1.0 mmol) of THF (2.0 mL) in a 50 mL two-necked round-bottom flask was added $LiAlH_4$ (159.8 mg, 4.0 mmol) at 0 ℃ under argon atmosphere. The mixture was stirred for 7 h at 40 °C. The resulting mixture was quenched with ice water (10 mL) and then saturated aqueous NH_4Cl (10.0 mL). The mixture was extracted with $CHCl_3$ (3 × 20.0 mL), and the combined organic layer was dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt, 9:1) to afford *o*-{[(*p*-methylbenzyl)amino](*p*-methylphenyl)methyl}phenol **5a** (261.3 mg, 82%).

4.5.1 *o*-{[(*p*-methylbenzyl)amino](*p*-methylphenyl)methyl}-phenol 5a: Yield: 261.3 mg (82%); colorless oil; IR (neat): ν = 3301, 3267, 2921, 1471, 1254, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 2.35 (s, 3H), 3.73 (d, 1H, *J* = 12.9 Hz), 3.87 (d, 1H, *J* = 12.5 Hz), 4.93 (s, 1H), 6.74 (t, 1H, *J* = 7.5 Hz), 6.85 (d, 1H, *J* = 6.6 Hz) , 6.89 (d, 1H, *J* = 7.9 Hz), 7.11-7.22 (m, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.1, 51.5, 66.3, 117.0, 119.1, 124.6, 127.3, 128.4, 128.7, 129.1, 129.3, 129.5, 135.0, 137.2, 137.5, 138.6, 157.7 ppm. HRMS (ESI) Calcd for $C_{22}H_{24}ON$ $[M+H]^+$ = 318.1852, Found = 318.1848.

Supporting Information. Copies of the ^1H NMR and ^{13}C NMR spectra of all nitrones **2a**~**2o**, their derivatives **3a**, **4a**, and **5a**.

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