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Note

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Synthesis of *N*-Vinyl Nitrones via 1,4-Conjugate Elimination

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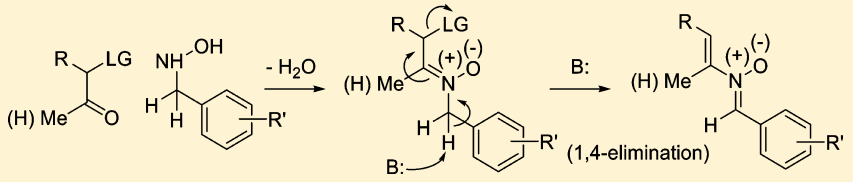
Supporting Information

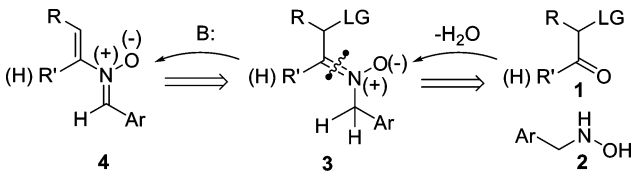


ABSTRACT: A number of structurally and electronically diverse *N*-vinyl nitrones have been synthesized by a two-step method. The sequence consists of condensation of an α-chloroaldehyde or an α-phenoxy- or α-acetoxy ketone with a substituted benzyl hydroxylamine to provide the corresponding nitrone. Treatment of these species with a base induces a 1,4-elimination to provide the desired *N*-vinyl nitrone in good to excellent yields.

Nitrones are a versatile and useful class of compounds capable of undergoing a variety of reactions.[1] The synthesis of nitrones is most commonly accomplished by the condensation of a hydroxylamine with a carbonyl derivative[2] or by the oxidation of a hydroxylamine,[3] secondary amine,[4] or imine.[5] We recently had a need to prepare *N*-vinyl nitrones; however, the common one-step syntheses described in the literature are not viable for our desired targets.[6] In 2006, Denmark and co-workers reported the first general synthesis of these species via a multistep process. Their strategy consists of masking the vinyl portion of the molecule as a selenide during the synthesis of the nitrone after which the vinyl functionality is revealed by oxidation to the selenoxide and elimination.[7] More recently, Anderson described a route wherein fluorenone oxime is subjected to Cu-catalyzed cross coupling with a boronic acid to provide the corresponding *N*-vinyl nitrone.[8] While both of these methods provide the desired compound, they suffer from some drawbacks. The Denmark route begins with a nitroalkene that is subjected to a 4-step sequence providing the desired product in 22−59% overall yield. While a landmark advance in the synthesis of this class of substrates, this method requires the use of a toxic heavy metal (Hg) and malodorous PhSe-derived reagents. Furthermore, the installation of the alkene via selenoxide elimination can lack regio- and stereocontrol. While the Anderson route is short and efficient, only a single oxime, fluorenone oxime, is utilized, suggesting a limited substrate scope.[8b]

In order to explore the reactivity of this interesting class of compounds,[9] we required a short synthesis that would allow for electronic and structural diversity. We reasoned that a nitrone bearing a leaving group at the α-carbon and an acidic proton capable of undergoing 1,4-elimination, such as nitrone **3**, could be subjected to a base to provide the desired *N*-vinyl nitrone (**4**, Scheme 1).[10] Nitrone **3** could be prepared, in turn, by the condensation of a hydroxyl amine such as **2** and the corresponding carbonyl (**1**). The successful implementation of this approach is described herein.

Scheme 1. Retrosynthesis of *N*-Vinyl Nitrones



We first studied the use of α-chloropropionaldehyde as a model substrate in order to explore the viability of this process and prepared the corresponding α-chloro nitrone[11] by condensation with (commercially available) benzyl hydroxylamine. We then subjected this material to a variety of basic elimination conditions (Table 1). We found that triethylamine was not effective and provided no reaction (Table 1, entry 1), whereas the slightly stronger amine base, DBU (2 equiv), provided the product in good yield but required several days for the reaction to proceed to full conversion (Table 1, entry 2). The stronger base, *t*-BuOK, provided the product in good yield at 23 °C (75%; Table 1, entry 3) and excellent yields at −78 °C (91%; Table 1, entry 4) in THF. The yield was comparable, though slightly diminished in Et_2O at −78 °C (85%; Table 1, entry 5), and the stronger metal amide base, KHMDS, provided useful yields at −78 °C (71%; Table 1, entry 6); however, this and other strong metal amide bases (LDA, LiHMDS, and KHMDS) provided complex mixtures at 23 °C (Table 1, entries 7−9). As such, we deemed the conditions described in entry 4 to be optimal for the elimination reaction.

In order to explore the scope of this process, we synthesized a number of aldehyde-derived α-chloro nitrones[12] and subjected them to the optimized 1,4-elimination conditions (Table 2). In all cases, the reaction was highly stereoselective and provided the *E*-alkene as the only isomer detected by ^{1}H

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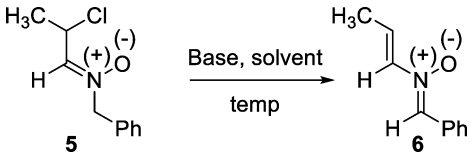
Table 1. Optimization of Elimination Conditions



entry	base[a]	solvent	temp	time	yield[b]
1	TEA	THF	23 °C	24 h	0%
2	DBU[c]	THF	23 °C	72 h	90%
3	*t*-BuOK	THF	23 °C	5 min	75%
4	***t*-BuOK**	**THF**	**-78 °C**	**5 min**	**91%**
5	*t*-BuOK	Et_2O	−78 °C	5 min	85%
6	KHMDS	THF	−78 °C	5 min	71%
7	LDA	THF	23 °C	5 min	0%[d]
8	LiHMDS	THF	23 °C	5 min	0%[d]
9	KHMDS	THF	23 °C	5 min	0%[d]

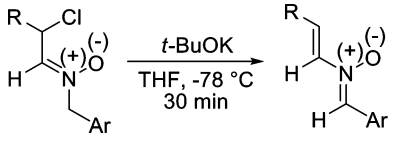
[a]1.1 equiv of base was used unless otherwise noted. [b]Isolated yield after flash chromatography. [c]2.0 equiv base was used. [d]A complex mixture was observed from which no product was isolated.

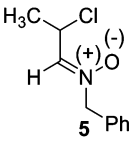
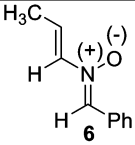
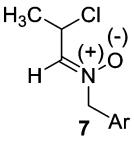
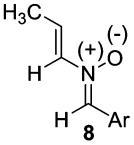
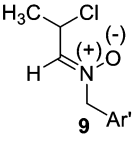
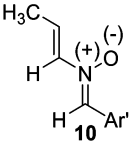
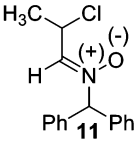
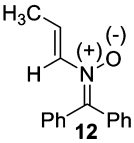
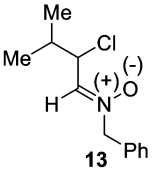
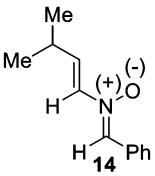
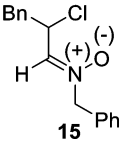
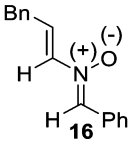
NMR. In addition, the products survive aqueous work up and purification by flash chromatography. Electron-withdrawing groups on the arene facilitated the reaction (*p*-nitrophenyl, Table 2, entry 2), while the electron-donating *p*-methoxyphenyl group provided the product in a slightly diminished yield (72%, Table 2, entry 3). This data suggests that an acidic proton at the benzyl position facilitates the reaction. These conditions are tolerant of steric hindrance at either end of the molecule (Table 2, entries 4 and 5) and of a phenyl group at the β-carbon of the nitrone allowing for the synthesis of β-benzyl *N*-vinyl nitrones without isomerization of the arene into conjugation with the phenyl group (Table 2, entry 6).

We next turned our attention to the synthesis of *N*-vinyl nitrones derived from ketones. The condensation of hydroxylamines with ketones is known to be more challenging than with aldehydes.[13] Our attempts to apply the conditions that were successful with α-chloro aldehydes to α-chloro ketone **17a** provided no conversion (Scheme 2). Under more forcing conditions (THF or protic solvents with protic or Lewis acids), we were able to observe conversion to the desired α-chloro nitrone product but were unable to isolate pure material due to the inherent instability of this product. We, therefore, studied the use of less reactive leaving groups in anticipation of preparing a more stable nitrone product and were able to prepare methoxy-, phenoxy-, and acetoxy-substituted nitrones (**17b−d**) in high yields by condensation of the corresponding ketone with benzyl hydroxylamine using modified Barton conditions (*N*-benzyl hydroxylamine·HCl, $NaHCO_3$, EtOH; **18b**, 88%; **18c**, 91%; **18d**, 83%; Scheme 2).[14,15] The nitrones were produced as *E*/*Z* mixtures though this has no effect on the efficacy of the overall sequence as both isomers are competent substrates for subsequent transformations (*vide infra*).

A variety of conditions were then explored to induce 1,4-elimination of these substrates (Table 3). The optimal conditions that were effective with the aldehyde-derived substrates were applied to compound **18b**, but only partial decomposition was observed, and no product was isolated (Table 3, entry 1). We also studied milder conditions consisting of catalytic MeONa (10%) in MeOD; however, no conversion to the desired product was observed, and after 3 h essentially complete deuterium exchange of the protons at the Me group α to the nitrone was observed by ^{1}H NMR (Table 3, entry 2).

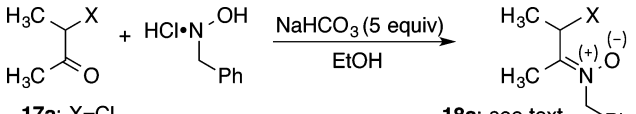
Table 2. Scope of *t*-BuOK Induced 1,4-Elimination of HCl from α-Chloro Nitrones



entry	Cl-nitrone	*N*-vinyl nitrone	yield[a]
1			91%
2[b]			94%
3[c]			72%
4			86%
5			86%
6			69%

[a]Isolated yield after flash chromatography. [b]Ar = *p*-NO_2Ph. [c]Ar′ = *p*-MeOPh.

Scheme 2. Synthesis of α-Substituted Nitrones[a]



17a; X=Cl
17b; X=OMe
17c; X=OPh
17d; X=OAc

18a; see text
18b; 88%
18c; 91%
18d; 83%

[a]For the synthesis of analogues of **17c−d**, see Supporting Information.

Surprisingly, prolonged exposure to these conditions for 1 week provided no evidence of deuterium incorporation elsewhere in the molecule as judged by ^{1}H NMR. The use of the metal amide bases KHMDS and LiHMDS produced a complex mixture from which no desired product could be isolated (Table 3, entries 3 and 4, respectively). Turning to the more labile phenoxy and acetoxy leaving groups, we found that the

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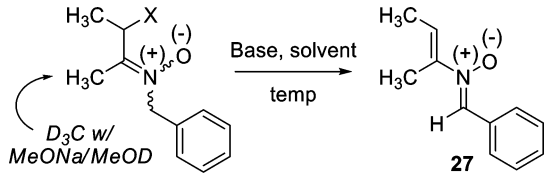
Table 3. Optimization of Elimination Conditions



entry	X	base	solvent	temp	yield[a]
1	OMe(18b)	*t*-BuOK	THF	−78 °C/*RT*	0%[b]
2	OMe(18b)	MeONa	MeOD	RT	0%[c]
3	OMe(18b)	KHMDS	THF	−78 °C	0%[d]
4	OMe(18b)	LiHMDS	THF	−78 °C	0%[d]
5	**OPh(18c)**	***t*-BuOK**	**THF**	**−78 °C**	**85%**
6	**OPh(18c)**	**KHMDS**	**THF**	**−78 °C**	**89%**
7	OPh(18c)	LiHMDS	THF	−78 °C	65%
8	OPh(18c)	KOH	EtOH	0 °C/*RT*	0%[e]
9	OPh(18c)	DBU	THF	0 °C/*RT*	0%[e]
10	OPh(18c)	NaH	THF	0 °C/*RT*	0%[e]
11	**OAc(18d)**	***t*-BuOK**	**THF**	**−78 °C**	**79%**

[a]Isolated yield after flash chromatography. [b]No product was isolated; partial decomposition was observed. [c]Deuterium incorporation was cleanly observed exclusively at the methyl group α- to the nitrone. [d]A complex mixture was observed from which no product was isolated. [e]No reaction was observed.

use of *t*-BuOK or KHMDS were both effective at −78 °C in THF and provided the product in high yields (85% and 89% yields, respectively; Table 3, entries 5, 6, and 11).

The scope of this process is shown in Table 4. As in the case of the aldehyde-derived substrates, the reaction is stereoselective and provides the *E*-isomers of the *N*-vinyl nitrones to the limit of detection by ^{1}H NMR. While the phenoxy-derived substrates are suitable in most cases, *p*-nitro benzyl nitrone **22** and *p*-methoxy benzyl nitrone **23** required the combination of the acetoxy leaving group and *t*-BuOK base. The reaction is tolerant of alkyl or aryl substitutents in the β-position (Table 4, entries 1−4) and works well with the cyclic ketone-derived nitrone **27** (Table 4, entry 5). Finally, substrates that bear both alkoxy and phenoxy substitution at the α-carbon of the nitrone preferentially eliminate the phenoxy group, thereby providing access to β-alkoxy *N*-vinyl nitrones (Table 4, entry 6).

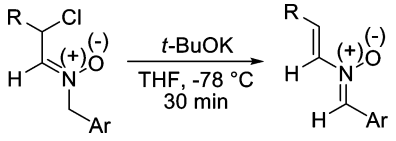
In conclusion, we have developed a direct two-step synthesis of *N*-vinyl nitrones possessing different substitution patterns. This route provides rapid access to a previously difficult to synthesize class of compounds.

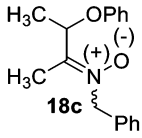
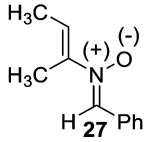
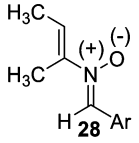
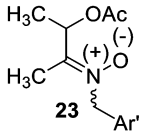
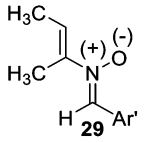
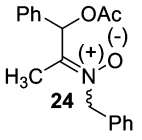
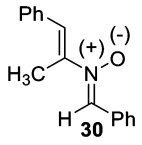
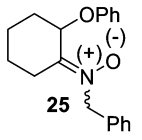
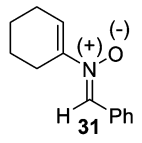
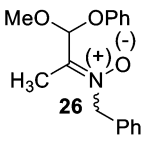
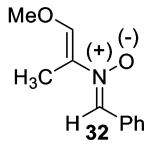
EXPERIMENTAL SECTION

General Considerations. All reactions were performed in oven-dried or flame-dried glassware under a dry nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 under nitrogen prior to use. THF and Et_2O were distilled from Na benzophenone ketyl under nitrogen prior to use. The chloroaldehydes,[16] α-aryloxy ketones,[17] and α-acyl ketones[18] were prepared by known methods. All other chemicals were used as received from the supplier. Flash chromatography was performed using 60 Å silica gel (37−75 μm). ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz in $CDCl_3$ using residual $CHCl_3$ (7.24 ppm) as the internal reference. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using residual $CHCl_3$ (77.26 ppm) as the internal reference. Infrared (IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization (ESI-TOF).

General Procedure for the Synthesis of α-Chloro Nitrones. Freshly distilled α-chloro aldehyde (1 equiv) was dissolved in a 1:1 mixture of CH_2Cl_2/Et_2O (0.1 M), and sodium sulfate (5 equiv) was

Table 4. Scope of 1,4-Elimination of HOPh/HOAc from α-Phenoxy/α-Acetoxy Nitrones



entry	nitrone	*N*-vinyl nitrone	yield[a]
1			89%
2[b]			77%
3[c]			71%
4			81%
5			74%
6			60%

[a]Isolated yield after flash chromatography. [b]Ar = *p*-NO_2Ph. [c]Ar′ = *p*-MeOPh.

added. The suspension was placed in an ice bath at 0 °C and allowed to stir for 15 min. Solid benzylhydroxylamine (1 equiv) was added in one portion, and the reaction was purged with N_2, sealed with a yellow cap, and allowed to stir at 4 °C for 16 h. The suspension was then filtered through a pad of Celite and the filter cake rinsed with additional CH_2Cl_2 and concentrated at reduced pressure in a room temperature water bath. The crude α-chloro nitrones were purified by flash chromatography (silica gel, MeOH/$CHCl_3$).

*(Z)-N-(2-Chloropropylidene)-1-phenylmethanamine Oxide (**5**).* White solid (1.5 g, 96%). R_f = 0.38 (97:3 $CHCl_3$/MeOH); mp = 91−92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (broad s, 5H), 6.76 (d, *J* = 7.4, 1H), 5.20 (apparent p, *J* = 6.9, 1H), 4.88 (s, 2H), 1.60 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 132.3, 129.6, 129.5, 129.3, 69.9, 49.0, 22.2. IR (thin film): 3402, 3143, 3093, 3068, 3036, 3010, 2890, 2972, 2930, 2883, 2866, 1577, 1457, 1426, 1213, 1204, 930, 706 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{24}Cl_2N_2O_2Na$ [2 M + Na]$^+$, 417.1108; found, 417.1071.

*(Z)-N-(2-Chloropropylidene)-1-(4-nitrophenyl)methanamine Oxide (**7**).* Yellow solid (0.135 g, 95%). R_f = 0.52 (97:3 $CHCl_3$/MeOH); mp = 97−99 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (broad d, *J* = 8.7 Hz, 2H), 7.58 (broad d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.18 (apparent p, *J* = 7.2 Hz, 1H), 4.98 (s, 2H), 1.64 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 139.3, 130.0, 124.3, 100.2, 68.8, 48.7, 22.2. IR (thin film): 3110, 3081, 2987,

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2934, 2865, 1602, 1581, 1521, 1349, 1211, 914, 717 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{12}ClN_2O_3$ $[M + H]^+$, 243.0531; found, 243.0533.

*(Z)-N-(2-Chloropropylidene)-1-(4-methoxyphenyl)methanamine Oxide (**9**).* Off-white solid (0.613 g, 90%). R_f = 0.39 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (broad d, J = 8.8 Hz, 2H), 6.90 (broad d, J = 8.8 Hz, 2H), 6.69 (d, J = 7.4 Hz, 1H), 5.19 (apparent p, J = 7.0 Hz, 1H), 4.80 (s, 2H), 3.80 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 137.9, 131.3, 124.2, 114.7, 69.3, 55.6, 49.0, 22.2. IR (thin film): 3393, 3073, 3036, 2997, 2960, 2935, 2911, 1613, 1587, 1515, 1442, 1456, 1424, 1033, 913 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{29}Cl_2N_2O_4$ $[2 M + H]^+$, 455.1500; found, 455.1515.

*(Z)-N-(2-Chloropropylidene)-1,1-diphenylmethanamine Oxide (**11**).* White solid (0.250 g, 91%). R_f = 0.57 (2:1 hexanes/EtOAc); mp = 109−111 °C (decomp); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.24 (m, 10H), 6.85 (d, J = 7.4, 1H), 6.19 (s, 1H), 5.29 (apparent p, J = 6.9, 1H), 1.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 136.52, 136.49, 129.13, 129.08, 129.05, 129.0, 128.9, 128.8, 82.7, 49.2, 22.3. IR (thin film): 3067, 3033, 2992, 1561, 1496, 1457, 1449, 1278, 1128, 744, 717, 623 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{32}Cl_2N_2O_2Na$ $[2 M + Na]^+$, 569.1733; found, 569.1728.

*(Z)-N-(2-Chloro-3-methylbutylidene)-1-phenylmethanamine Oxide (**13**).* White solid (0.829 g, 93%). R_f = 0.25 (2:1 hexanes/EtOAc); mp = 68−69 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (broad s, 5H), 6.77 (d, J = 7.9, 1H), 5.04 (dd, J = 7.9, 5.8 Hz, 1H), 4.90 (s, 2H), 2.12 (pd, J = 6.7, 5.8 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 132.5, 129.46, 129.45, 129.3, 70.1, 59.7, 33.2, 19.4, 18.7. IR (thin film): 3422, 3068, 3032, 2981, 2960, 2869, 1578, 1588, 1120, 723, 697, 678 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{32}Cl_2N_2O_2Na$ $[2 M + Na]^+$, 473.1739; found, 473.1741.

*(Z)-N-(2-Chloro-3-phenylpropylidene)-1-phenylmethanamine Oxide (**15**).* White solid (0.273 g, 89%). R_f = 0.62 (1:1 hexanes/EtOAc); mp = 97−99 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 3H), 7.29−7.22 (m, 5H), 7.16−7.10 (m, 2H), 6.73 (d, J = 7.4 Hz, 1H), 5.34 (apparent q, J = 7.0 Hz, 1H), 4.85 (A of AB, J = 14.0 Hz, 1H), 4.84 (B of AB, J = 14.0 Hz, 1H), 3.19 (A of ABX, J = 14.1, 7.0 Hz, 1H), 3.16 (B of ABX, J = 14.1, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 136.0, 132.2, 129.59, 129.51, 129.4, 129.3, 128.7, 127.4, 70.0, 53.5, 41.4. IR (thin film): 3071, 3026, 2937, 1575, 1496, 1455, 1418, 1354, 1285, 1233, 1194, 1142, 1108, 1078, 1017, 943, 914, 830, 760, 708, 696 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{17}ClNO$ $[M + H]^+$, 274.0994; found, 274.0998.

General Procedure for the Synthesis of Aldehyde Derived *N*-Vinyl Nitrones by 1,4-Conjugate Elimination of α-Chloro Nitrones. The α-chloro nitrone was taken up in THF (0.15 M), cooled to −78 °C (dry ice/acetone), and allowed to stir for 15 min at which point a *t*-BuOK solution (1 M in THF; 1.1 equiv) was added via syringe. The reaction was allowed to stir at −78 °C until the disappearance of starting material was observed by TLC. The cold solution was then poured directly into a separatory funnel containing pH 7 buffer solution (monobasic potassium phosphate/sodium hydroxide buffer), and the reaction flask was rinsed with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with brine, and the brine was back-extracted with EtOAc. The combined organic layers were dried over magnesium sulfate and concentrated at reduced pressure in a room temperature water bath. The crude *N*-vinyl nitrones were purified by flash chromatography (silica gel, hexanes/EtOAc).

*(1E,NZ)-N-Benzylideneprop-1-en-1-amine Oxide (**6**).* White solid (0.148 g, 91%). R_f = 0.35 (2:1 hexanes/EtOAc); mp = 109−111 °C (decomp); ^1H NMR (300 MHz, $CDCl_3$) δ 8.52−7.95 (m, 2H), 7.40−7.32 (m, 3H), 7.30 (s, 1H), 6.92−6.65 (m, 2H), 1.79 (d, J = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.0, 130.8, 130.5, 129.4, 128.6, 124.7, 14.2. IR (thin film): 3108, 3070, 1593, 1151, 1347, 1312, 1167, 939, 921, 866 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{23}N_2O_2$ $[2 M + H]^+$, 323.1755; found, 323.1765.

*(1E,NZ)-N-(4-Nitrobenzylidene)prop-1-en-1-amine Oxide (**8**).* Yellow solid (0.080 g, 94%). R_f = 0.35 (2:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (broad A of AB, J = 9.1 Hz, 2H), 8.26 (broad B of AB, J = 9.1 Hz, 2H), 7.45 (s, 1H), 7.12−6.67 (m, 2H), 1.91 (d, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 137.2, 136.3, 132.7, 129.7, 127.3, 124.1, 14.5. IR (thin film): 3108, 3070, 2973, 2360, 1593, 1151, 1347, 1312, 1167, 939, 921, 866 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{20}N_4O_6Na$ $[2 M + Na]^+$, 435.1276; found, 435.1284.

*(1E,NZ)-N-(4-Methoxybenzylidene)prop-1-en-1-amine Oxide (**10**).* White solid (0.232 g, 72%). R_f = 0.41 (1:1 hexanes/EtOAc); mp = 103−106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (broad d, J = 9.1 Hz, 2H), 7.25 (s, 1H), 6.94 (broad d, J = 9.1 Hz, 2H), 6.88−6.64 (m, 2H), 3.84 (s, 3H), 1.86 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 137.0, 134.8, 131.7, 123.9, 123.7, 114.3, 55.6, 14.4. IR (thin film): 3397, 3064, 3002, 2967, 2936, 2917, 2839, 1601, 1553, 1506, 1255, 1159, 1155, 1028, 932, 922, 847 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{26}N_2O_4Na$ $[2 M + Na]^+$, 405.1785; found, 405.1792.

*(E)-N-(Diphenylmethylene)prop-1-en-1-amine Oxide (**12**).* White solid (0.096 g, 86%). R_f = 0.39 (1:1 hexanes/EtOAc); mp = 86−87 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02−7.85 (m, 2H), 7.57−7.38 (m, 3H), 7.35−7.25 (m, 5H), 6.90 (dq, J = 12.8, 7.2 Hz, 1H), 6.71 (qd, J = 12.8, 1.6 Hz, 1H), 1.73 (dd, J = 7.2, 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 135.2, 134.9, 134.4, 131.0, 130.9, 130.1, 129.8, 129.1, 128.0, 126.0, 14.9. IR (thin film): 3443, 3091, 3056, 2966, 2939, 2914, 2875, 2851, 2360, 2342, 1492, 1444, 1437, 1349, 1263, 1234, 954, 936 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{30}N_2O_2Na$ $[2 M + Na]^+$, 497.2200; found, 497.2211.

*(1E,NZ)-N-Benzylidene-3-methylbut-1-en-1-amine Oxide (**14**).* White solid (0.072 g, 86%). R_f = 0.52 (2:1 hexanes/EtOAc); mp = 79−80 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34−8.24 (m, 2H), 7.46−7.38 (m, 3H), 7.36 (s, 1H), 6.84 (A of ABX, J = 13.0, 6.9 Hz, 1H), 6.72 (B of ABX, J = 13.0, 0.9 Hz, 1H), 2.53 (apparent od, J = 6.9, 0.9 Hz, 1H), 1.10 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 135.5, 134.6, 131.0, 130.7, 129.5, 128.8, 28.6, 22.3. IR (thin film): 3426, 3056, 2961, 2928, 2869, 1574, 1550, 1456, 1165, 1139, 946, 755 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{30}N_2O_2Na$ $[2 M + Na]^+$, 401.2200; found, 401.2210.

*(1E,NZ)-N-Benzylidene-3-phenylprop-1-en-1-amine Oxide (**16**).* Clear oil (0.090 g, 69%). R_f = 0.54 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.41−8.12 (m, 2H), 7.49−7.16 (m, 9H), 7.06 (dt, J = 12.9, 7.1 Hz, 1H), 6.69 (dt, J = 12.9, 1.5 Hz, 1H), 3.56 (dd, J = 7.1, 0.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.5, 135.2, 131.2, 130.6, 129.64, 129.02, 128.94, 128.85, 128.77, 126.9, 35.2. IR (thin film): 3061, 3027, 1719, 1602, 1574, 1547, 1495, 1446, 1431, 1323, 1306, 1155, 1076, 1029, 950, 921, 752, 691 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}NO$ $[M + H]^+$, 238.1227; found, 238.1227.

General Procedure for the Synthesis of α-Aryloxy and α-Acyl Nitrones. The α-aryloxy or α-acyl ketone (1.1 equiv) and benzylhydroxylamine HCl (1 equiv) were dissolved in EtOH (0.5M). $NaHCO_3$ (5 equiv) was added in one portion, and the resulting suspension was allowed to stir at room temperature for 16 h. The suspension was filtered through a pad of Celite, the filter cake rinsed with CH_2Cl_2, and concentrated at reduced pressure in a room temperature water bath. The crude α-aryloxy or α-acyl nitrones were purified by flash chromatography (silica gel, hexanes/EtOAc). Most compounds were formed as *E*/*Z* mixtures with no attempt made at separating the mixtures as both isomers provide the same product after elimination. The α-phenoxy nitrones are bench stable with no noticeable decomposition after 1 week at room temperature. The α-acetoxy nitrones can be stored at −20 °C without noticeable decomposition but undergo slight to moderate decomposition upon storage at room temperature overnight.

*N-(3-Phenoxybutan-2-ylidene)-1-phenylmethanamine Oxide (**18c**).* Clear oil (2.99 g, 91%). R_f = 0.31 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H), 7.22−7.13 (m, 2H), 6.99−6.85 (m, 1H), 6.77 (m, 2H), 5.85 (apparent q, J = 6.5 Hz, 1H), 5.02 (broad s, 2H), 1.91 (s, 3H), 1.47 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 148.5, 133.3, 129.9, 129.1, 128.6, 128.0,

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121.4, 114.8, 69.5, 65.2, 16.4, 12.7. IR (thin film): 3405, 3063, 3032, 2981, 2933, 2869, 1599, 1587, 1496, 1455, 1373, 1342, 1294, 1162, 1086, 1028, 755, 695 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$, 270.1489; found, 270.1492.

*N-(3-Acetoxybutan-2-ylidene)-1-(4-nitrophenyl)methanamine Oxide (**22**).* Yellow oil (0.052 g, 78%). R_f = 0.67 (2% MeOH/DCM). ^1H NMR (300 MHz, $CDCl_3$) major: δ 8.21 (broad d, J = 8.9 Hz, 2H), 7.54 (broad d, J = 8.9 Hz, 2H), 6.02 (q, J = 6.7 Hz, 1H), 5.15 (A of AB, J = 14.7 Hz, 1H), 5.09 (B of AB, J = 14.7 Hz, 1H), 2.06 (s, 3H), 1.93 (s, 3H), 1.39 (d, J = 6.7 Hz, 3H). Minor: δ 8.20 (broad d, 9.0 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 5.75 (q, J = 6.7 Hz, 1H), 5.54 (A of AB, J = 14.7 Hz, 1H), 5.20 (B of AB, J = 14.7 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.23 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) mixture of major and minor compounds: δ 170.5, 170.3, 148.1, 147.6, 141.0, 140.5, 129.7, 129.1, 128.5, 124.39, 124.26, 123.8, 68.8, 67.9, 64.0, 63.8, 21.0, 20.9, 18.2, 15.1, 13.22, 13.17. IR (thin film): 3399, 3112, 3079, 2987, 2937, 2856, 1740, 1603, 1522, 1496, 1452, 1371, 1348, 1313, 1236, 1170, 1109, 1081, 1027, 647, 912, 859, 812, 771, 736, 704 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{17}N_2O_5$ $[M + H]^+$, 281.1132; found, 281.1135.

*N-(3-Acetoxybutan-2-ylidene)-1-(4-methoxyphenyl)methanamine Oxide (**23**).* Clear oil (0.881 g, 97%). R_f = 0.36 (3% MeOH/$CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) major: δ 7.29 (broad d, J = 8.9 Hz, 2H), 6.87−6.84 (m, 2H), 6.05 (q, J = 6.6 Hz, 1H), 4.95 (broad s, 1H), 3.78 (s, 3H), 2.05 (s, 3H), 1.94 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H). Minor: δ 7.35 (broad d, J = 9.0 Hz, 2H), 6.87−6.84 (m, 2H), 5.87 (q, J = 6.6 Hz, 1H), 5.43 (d, J = 14.0 Hz, 1H), 5.00 (d, J = 14 Hz, 1H), 3.77 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.13 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8 159.53, 159.45, 145.5, 144.6, 129.2, 128.9, 126.2, 125.3, 114.19, 114.13, 68.5, 67.8, 64.6, 64.3, 55.2, 25.8, 20.8, 20.7, 17.6, 14.9, 12.9, 12.7. IR (thin film): 2983, 2936, 2837, 1740, 1613, 1585, 1514, 1456, 1371, 1304, 1248, 1177, 1079, 1029, 821, 776 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{39}N_2O_8$ $[2 M + H]^+$, 531.2701; found, 531.2704.

*N-(1-Acetoxy-1-phenylpropan-2-ylidene)-1-phenylmethanamine Oxide (**24**).* Clear oil (0.112 g, 60%). R_f = 0.37 (2% MeOH/DCM). ^1H NMR (300 MHz, $CDCl_3$) 5:1 Mixture of E/Z isomers: major, δ 7.52−7.45 (m, 2H), 7.39−7.20 (m, 8H), 7.18 (s, 1H), 5.05 (A of AB, J = 14.0 Hz, 1H), 5.03 (B of AB, J = 14.0 Hz, 1H), 2.13 (s, 3H), 2.03 (s, 3H). The resonances for the minor ones that could be distinguished include 6.92 (broad s, 1H), 6.88−6.81 (m, 2H), 5.66 (d, J = 14.3 Hz, 1H), 5.19 (d, J = 14.3 Hz, 1H), 2.14 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.1, 169.6, 144.3, 136.1, 135.6, 134.4, 133.3, 129.19, 129.08, 128.94, 128.87, 128.76, 128.71, 128.69, 128.66, 128.59, 128.40, 128.27, 127.56, 126.70, 125.81, 72.29, 72.22, 65.8, 65.3, 21.08, 20.95, 14.7, 13.8. IR (thin film): 3063, 3032, 2933, 1745, 1603, 1583, 1496, 1454, 1432, 1372, 1233, 1164, 1082, 1028, 1002, 978, 916, 844, 808, 754, 736, 700 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{20}NO_3$ $[M + H]^+$, 298.1438; found, 298.1441.

*N-(2-Phenoxycyclohexylidene)-1-phenylmethanamine Oxide (**25**).* Clear oil (0.105 g, 93%). R_f = 0.28 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.18 (m, 7H), 7.05 (m, 2H), 6.91 (m, 1H), 5.92 (broad s, 1H), 5.06 (A of AB, J = 14.1 Hz, 1H), 5.04 (B of AB, J = 14.1 Hz, 1H), 2.61−1.53 (m, 7H), 1.31−1.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.9, 133.8, 129.9, 129.1, 128.6, 128.0, 121.3, 115.2, 68.1, 65.1, 32.1, 27.7, 27.5, 19.8. IR (thin film): 3386, 3061, 2940, 2863, 1726, 1596, 1495, 1455, 1360, 1294, 1231, 1152, 1126, 1072, 1028, 1000, 978, 755, 729, 696 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{38}H_{42}N_2O_4Na$ $[2 M + Na]^+$, 613.3037; found, 613.3039.

*N-(1-Methoxy-1-phenoxypropan-2-ylidene)-1-phenylmethanamine Oxide (**26**).* Clear oil (0.330 g, 65%). R_f = 0.44 (2% MeOH/$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 3:1 mixture of E/Z isomers. Major: δ 7.45−7.30 (m, 5H), 7.30−7.14 (m, 2H), 7.10−6.89 (m, 3H), 6.48 (s, 1H), 5.04 (s, 2H), 3.52 (s, 3H), 2.07 (s, 3H). Signals for the minor diastereomer that are discernible (others are buried in the aromatic region): 6.85−6.77 (m, 2H), 5.83 (s, 1H), 5.18 (s, 2H), 3.39 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); mixture of major and minor isomers, δ 156.4, 155.9, 144.4, 143.4, 133.5, 132.9, 129.95, 129.90, 129.12, 129.06, 128.71, 128.69, 128.31, 128.16, 123.51, 122.4, 117.6, 116.6, 99.2, 97.3, 65.5, 65.1, 56.9, 54.6, 14.1, 13.1. IR (thin film): 3063, 3033, 3006, 2960, 2936, 2835, 1590, 1492, 1456, 1382, 1355, 1292, 1244, 1197, 1161, 1115, 1078, 1065, 1028, 1003, 969, 849, 756, 996 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}NO_3$ $[M + H]^+$, 286.1438; found, 286.1437.

General Procedure for the Synthesis of Ketone Derived *N*-Vinyl Nitrones by 1,4-Conjugate Elimination of α-Aryloxy or α-Acyl Nitrones. The α-aryloxy or α-acyl nitrone (1 equiv) was dissolved in THF (0.15 M), cooled to −78 °C (dry ice/acetone), and allowed to stir for 15 min. KHMDS (1 M THF; 1.1 equiv) or *t*-BuOK solution (1 M in THF; 1.1 equiv) was added via syringe and the reaction allowed to stir until the starting material was no longer visible by TLC. The cold solution was then poured into a separatory funnel containing pH 7 buffer solution (monobasic potassium phosphate/sodium hydroxide buffer) and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with brine, and the brine was back-extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated at reduced pressure in a room temperature water bath. The crude *N*-vinyl nitrones were purified by flash chromatography (silica gel, hexanes/EtOAc).

*(2E,NZ)-N-Benzylidenebut-2-en-2-amine Oxide (**27**).* Prepared from α-phenoxy nitrone **18c** with KHMDS. White solid (0.208 g, 89%). R_f = 0.33 (1:1 hexane/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.38−8.18 (m, 2H), 7.59 (s, 1H), 7.47−7.34 (m, 3H), 6.11 (qq, J = 7.1, 1.2 Hz, 1H), 2.13 (apparent p, J = 1.1 Hz, 3H), 1.76 (dq, J = 7.1, 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 133.5, 131.0, 130.8, 129.2, 128.7, 120.1, 13.6, 13.1. IR (thin film): 3172, 3056, 3025, 2979, 2924, 2859, 1686, 1575, 1551, 1486, 1446, 1407, 1376, 1322, 1302, 1188, 1125, 1072, 1029, 972, 948, 932, 755, 692 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{26}N_2O_2Na$ $[2 M + Na]^+$, 373.1887; found, 373.1896.

*(2E,NZ)-N-(4-Nitrobenzylidene)but-2-en-2-amine Oxide (**28**).* Prepared from α-acetoxy nitrone **22** with *t*-BuOK. Yellow solid (0.030 g, 77%). R_f = 0.32 (1:1 hexanes/EtOAc); mp = 99−102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (broad d, J = 9.0 Hz, 2H), 8.22 (broad d, J = 9.0 Hz, 2H), 7.73 (s, 1H), 6.18 (qq, J = 7.1, 1.2 Hz, 1H), 2.13 (apparent p, J = 1.1 Hz, 3H), 1.78 (dq, J = 7.1, 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 145.8, 136.6, 131.2, 129.4, 124.0, 121.4, 13.6, 13.1. IR (thin film): 3107, 1742, 1668, 1538, 1505, 1441, 1415, 1382, 1332, 1164, 1131, 1109, 1099, 1005, 952, 883, 866, 856, 807, 748, 692 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{13}N_2O_3$ $[M + H]^+$, 221.0921; found, 221.0927.

*(2E,NZ)-N-(4-Methoxybenzylidene)but-2-en-2-amine Oxide (**29**).* Prepared from α-acetoxy nitrone **23** with *t*-BuOK. White solid (0.203 g, 71%). R_f = 0.33 (2% MeOH/DCM); ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (broad d, J = 9.0, Hz, 2H), 7.52 (s, 1H), 6.93 (broad d, J = 9.0 Hz, 2H), 6.11 (qq, J = 7.1, 1.1 Hz, 1H), 3.84 (s, 3H), 2.12 (apparent p, J = 1.1 Hz, 3H), 1.76 (dq, J = 7.1, 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 145.0, 132.9, 131.1, 123.9, 119.5, 113.9, 55.4, 13.4, 12.9. IR (thin film): 3173, 2933, 2838, 1602, 1575, 1507, 1458, 1442, 1419, 1401, 1322, 1305, 1255, 1170, 1113, 1072, 1029, 949, 842 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{31}N_2O_4$ $[2 M + H]^+$, 411.2279; found, 411.2291.

*(1E,NZ)-N-Benzylidene-1-phenylprop-1-en-2-amine Oxide (**30**).* Prepared from the α-acetoxy nitrone **24** with *t*-BuOK. (0.022 g, 74%). The data are consistent with the published values.[7]

*(Z)-N-Benzylidenecyclohex-1-enamine Oxide (**31**).* Prepared from the α-phenoxy nitrone **25** with KHMDS. Clear oil (0.055 g, 81%). R_f = 0.62 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.35−8.19 (m, 2H), 7.58 (s, 1H), 7.48−7.34 (m, 3H), 6.45 (tt, J = 4.1, 1.5 Hz, 1H), 2.54 (dddq, J = 6.4, 5.2, 2.6, 1.2 Hz, 2H), 2.23 (m, 2H), 1.84−1.74 (m, 2H), 1.68−1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 132.8, 131.0, 130.8, 129.4, 128.8, 122.8, 25.5, 24.5, 22.6, 21.7. IR (thin film): 3417, 3052, 2936, 2860, 1550, 1445, 1408, 1170, 1147, 1079, 1056, 1035, 927, 884, 804, 754, 691 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{16}NO$ $[M + H]^+$, 202.1232; found, 202.1239.

*(1E,NZ)-N-Benzylidene-1-methoxyprop-1-en-2-amine Oxide (**32**).* Prepared from α-phenoxy nitrone **26** with KHMDS. Clear oil (0.097 g, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.32−8.25 (m, 2H), 7.44

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(broad s, 1H), 7.43−7.35 (m, 4H), 3.79 (s, 3H), 2.12 (d, J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 131.8, 131.2, 130.6, 129.4, 128.7, 127.3, 61.3, 11.5. IR (thin film): 3065, 2960, 2930, 2854, 1670, 1594, 1558, 1491, 1474, 1446, 1403, 1376, 1320, 1259, 1242, 1191, 1144, 1089, 1028, 971, 887, 847, 803, 754, 691 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{14}NO_2$ $[M + H]^+$, 192.1019; found, 192.10260.

■ ASSOCIATED CONTENT

Supporting Information

Scope of the α-phenoxyketone and α-acetoxyketone hydroxylamine condensation, and ^{1}H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01138.

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Notes

The authors declare no competing financial interest.

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