Dienamine-catalyzed nitrone formation via redox reaction

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Contents

General Information.

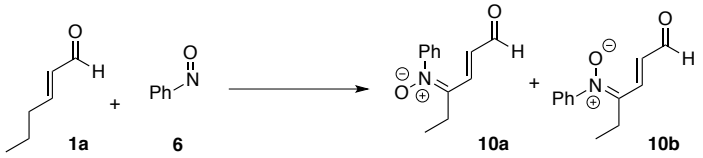
NMR data were acquired on Bruker 400 MHz and 500 MHz NMR spectrometers and use the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, brm = broad multiplet, brs = broad singlet. HRMS spectra were acquired using an MS spectrometer with Q-TOF mass analyzer. Flash chromatography was carried out with F60, 40−63 mm, 60 Å silica gel and EMD silica 60 F254 glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit, and were evaporated using a standard rotovapor and high vacuum. All reactions were carried out in oven-dried glassware, under an Ar atmosphere. All enals were distilled freshly before use. Reactions were cooled to -30ºC and below using a ThermoFisher Scientific EK90 cryocooler. Crystallographic data obtained by William W. Brennessel of the University of Rochester Department of Chemistry X-ray Crystallographic Facility.

Preparation of enals (1d-g), and *p*-nitronitrosobenzene (6b). Enals **1d**,[1] **1e**,[1] **1f**,[2] and **1g**,[3] and nitrosobenzene **6b**[4] were prepared using known procedures.

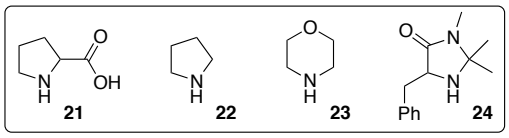
Reaction Optimization

A catalyst screen revealed that no reaction occurred in the presence of proline (entry 2, Table S1). While pyrrolidine's reactivity was comparable to that of catalyst **2b**, the former furnished the desired nitrone in lower yield (entry 3 vs. 1). Finally, morpholine and an imidazolidinone catalyst were less reactive than catalyst **2b** (entries 4-5 vs. 1).

Table S1. Catalyst screen.[a]



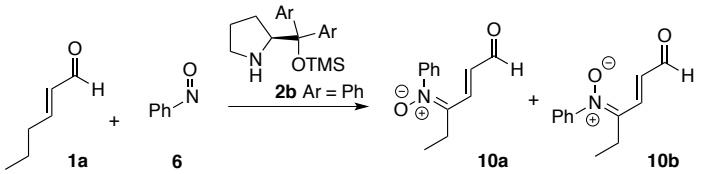
entry	cat.	time (h)	yield[b-c] (%)	dr[d] (**10a**:**10b**)
1	**2b**	1	31 (7)	3:1
2	**21**	168	--	--
3	**22**	1	21 (8)	3:1
4	**23**	23	11 (40)	100:0
5	**24**	20	21 (56)	4:1



[a] Reaction conditions: **1a**, **6** (2 equiv.), cat. (0.1 equiv), $PhCO_2H$ (0.1 equiv), toluene (1M), rt. [b] Determined by ^1H NMR using 1,4-dioxane or cyclohexene as internal standard. [c] Number in parentheses is percentage of unreacted **1a** remaining. [d] Determined by ^1H NMR.

THF and toluene afforded the nitrone products in the highest yield at rt (entries 1-6, Table S2). At lower temperatures, however, toluene was the superior solvent (entries 7-8). Ultimately, as discussed in the text, 1,4-dioxane was identified as the optimal solvent for this transformation. Finally, while use of >2 equivalents of nitrosobenzene proved fruitful (see text), use of <2 equivalents, not surprisingly, resulted in complete consumption of nitrosobenzene but reduced yields of nitrone (entries 9-10).

Table S2. Solvent screen.[a]



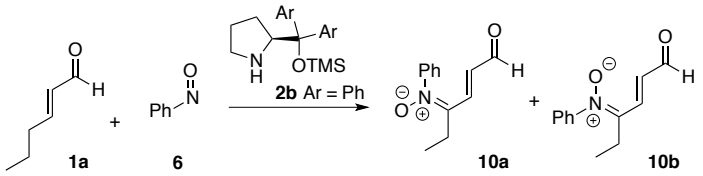
1a **6** **10a** **10b**

entry	solvent	time (h)	temp (°C)	yield[b-c] (%)	dr[d] (**10a**:**10b**)
1	toluene	4.25	rt	29	3:1
2	CH_2Cl_2	1	rt	22	2:1
3	MeOH	18.75	rt	11	nd
4	THF	18.75	rt	35	2:1
5	DMSO	18.75	rt	26	6:1
6	MeCN	3.25	rt	15	4:1
7[e-f]	toluene	14.5	-30	42	4:1
8[e-f]	THF	48	-30	trace	nd
9[e]	toluene	65.5	-30	42	3:1
10[g]	toluene	7	-30	20 (0)	2:1

[a] Reaction conditions: **1a**, **6** (1 equiv.), **2b** (0.1 equiv), $PhCO_2H$ (0.1 equiv), solvent (1M). [b] Determined by ^1H NMR using 1,4-dioxane or cyclohexene as internal standard. [c] Number in parenthesis is % of **6** remaining. [d] Determined by ^1H NMR. [e] 2 equiv of **6** used. [f] AcOH used instead of $PhCO_2H$. [g] 0.5 equiv of **6** used.

An investigation into the effect of additives revealed that acidic additives were more effective than basic additives (entries 1, 8, and 11 vs. 2-4, Table S3). Specifically, basic additives slowed down the reaction dramatically at -30 °C, and did not outperform acidic additives even at rt (entries 5-7).

Table S3. Additive screen.[a]

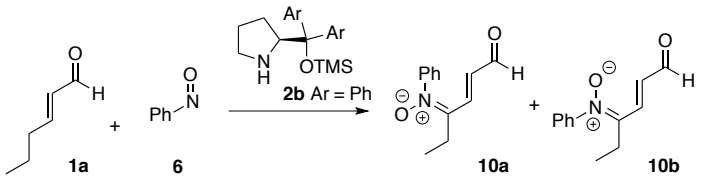


entry	additive	time (h)	yield[b-c] (%)	dr[d] (**10a**:**10b**)
1	AcOH	14.5	42	4:1
2	Et_3N	46.25	2 (77)	100:0
3	K_2CO_3	17.25	0.5 (99)	100:0
4	NaOAc	17.25	4 (97)	3:1
5[e]	Et_3N	63	23	10:1
6[e]	K_2CO_3	88	16	7:1
7[e]	NaOAc	38.75	27	8:1
8	CF_3CH_2OH	45.5	38	4:1
9	pTsOH	19.5	2	100:1
10	Cl_3CCO_2H	18.5	7	1:1
11	pNBA	18.5	28	3:1
12	H_3PO_4	26	17	3:1
13	NH_4Cl	25.75	4	4:1

[a] Reaction conditions: **1a**, **6** (2 equiv), **2b** (0.1 equiv), additive (0.1 equiv), toluene (1M), -30° C. [b] Determined by ^{1}H NMR using 1,4-dioxane or cyclohexene as internal standard. [c] Number in parentheses is percentage of unreacted **1a** remaining. [d] Determined by ^{1}H NMR. [e] Reaction run at rt.

With AcOH identified as a suitable additive, further optimizations ensued (Table S4). Reaction temperatures lower than -30 °C, even when run at higher concentration, were detrimental to reaction yield (entries 1-3). While increasing the catalyst loading proved beneficial (see text), decreasing the loading of catalyst **2b** and AcOH cocatalyst was not beneficial (entries 4). Running the reaction at higher temperature, but lower concentration, was also not fruitful (entry 5). The use of hydrogen bonding solvents to activate PhNO was unproductive (entries 6-7). Finally, the use of stoichiometric quantities of catalyst **2b** and AcOH cocatalyst resulted in lower product yields (entries 8-10).

Table S4. Optimizations with AcOH.[a]

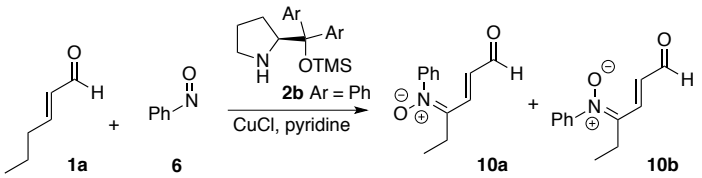


entry	equiv AcOH	solvent	time (h)	temp (° C)	yield[b] (%)	dr[c] (**10a**:**10b**)
1	0.1	toluene	89	-78	3	2:1
2[d]	0.1	toluene	63	-78	3	2:1
3	0.1	toluene	39	-50	40	3:1
4[e]	0.05	toluene	68.25	-30	38	4:1
5[f]	0.1	toluene	17	rt	34	10:1
6	0.1	EtOH	16.5	-30	17	7:1
7	0.5	TFE	>96	-30	nr	--
8[g]	1	toluene	1	-30	14	2:1
9[g]	1	toluene	2	-50	15	1:1
10[g]	1	toluene	67	-78	13	100:1

[a] Reaction conditions: **1a**, **6** (2 equiv.), **2b** (0.1 equiv), AcOH, solvent (1M). [b] Determined by ^{1}H NMR using 1,4-dioxane or cyclohexene as internal standard. [c] Determined by ^{1}H NMR. [d] Reaction concentration = 2M. [e] 0.05 equivalents of **2b** used. [f] Reaction concentration = 0.25M. [g] 1 equivalent of **2b** used.

Efforts to reoxidize the *N*-phenylhydroxylamine byproduct in situ are summarized in Table S5. Starting with the optimal loading of CuCl and temperature initially reported for oxidation of hydroxylamines,[5] the yield of nitrone product was very low (entries 1-2). At lower temperatures, the yield of nitrone product increased, especially at longer time points (entries 3-6). In each case, however, the longer time point marked the point at which **1a** was completely consumed (entries 4 and 6). In the absence of AcOH, the reaction was exceedingly sluggish and the reaction yield did not increase (entry 7). Read de Alaniz and coworkers reported that the oxidation of hydroxylamines to nitrosocompounds using catalytic CuCl and air proceeds without the pyridine additive, but is substantially slower.[refa] This may account for why we observe higher yields in the presence of pyridine (entry 3 vs. 5, entry 4 vs. 8). Use of 20 mol % CuCl and 5 mol % pyridine, the conditions reported specifically for the oxidation of N-phenyhydroxylamine,[6] did not further augment the yield of nitrone product (entry 9). In summary, in all cases, formation of **17** was completely suppressed, however the yields of **10a** and **10b** were not improved over reactions run under inert conditions and in the absence of catalytic CuCl and pyridine.

Table S5. Efforts to reoxidize *N*-phenylhydroxylamine in situ.

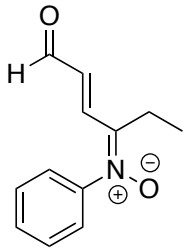


entry	equiv CuCl	equiv pyridine	time (h)	temp (° C)	yield[b] (%)
1	0.1	0	19	rt	13
2	0.1	0.025	27	rt	19
3	0.1	0	19	0	11
4	0.1	0	25	0	21
5	0.1	0.025	19	0	23
6	0.1	0.025	42	0	34
7[c]	0.1	0.025	120	0	33
8	0.1	0.05	24	0	30
9	0.2	0.05	72	0	33

[a] Reaction conditions: **1a**, **6** (2 equiv.), **2b** (0.1 equiv), AcOH (0.1 equiv), CuCl, pyridine, toluene (1M). Reaction run open to air. [b] Determined by ^{1}H NMR using 1,4-dioxane or cyclohexene as internal standard. [c] Reaction run without AcOH.

General Procedure for formation of nitrone enals 10.

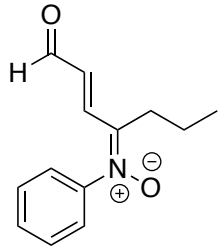
To a solution of catalyst **2b** (16.3 mg, 0.05 mmol) in 1,4-dioxane (0.25 mL), was added acetic acid (2.9 µL, 0.05 mmol) and the solution stirred for 5 minutes. Freshly distilled enal **1** (0.25 mmol) was added, the reaction stirred for 10 minutes, then nitrosobenzene **6a** (107.1 mg, 1.0 mmol) was added. The reaction was stirred at rt until complete consumption of enal, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (20% EtOAc:petroleum ether). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure nitrone **10**.



(*E*)-*N*-((*E*)-6-oxohex-4-en-3-ylidene)aniline oxide (**10a**).

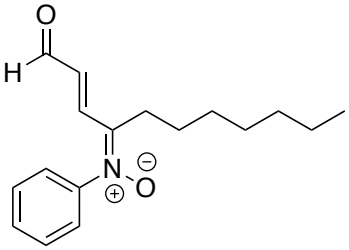
Yellow solid (27 mg, 53%): mp 90-92 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, J = 7.5 Hz, 1H), 7.53-7.52 (m, 3H), 7.37-7.36 (m, 2H), 7.02 (d, J = 15.5 Hz, 1H), 6.31 (dd, J = 15.5, 7.5 Hz, 1H), 2.90 (q, J = 7.5 Hz, 2H),

1.25 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 151.2, 145.5, 140.6, 130.5, 129.8, 129.0, 124.4, 20.4, 9.7 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{14}NO_2]$ 204.1025, found 204.1022.



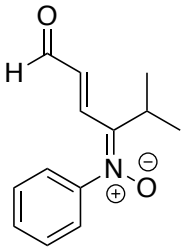
(*E*)-*N*-((*E*)-1-oxohept-2-en-4-ylidene)aniline oxide (**10b**).

Yellow oil (26 mg, 48%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, J = 7.5 Hz, 1H), 7.52-7.51 (m, 3H), 7.36-7.35 (m, 2H), 7.04 (d, J = 15.5 Hz, 1H), 6.31 (dd, J = 15.5, 7.5 Hz, 1H), 2.85 (t, J = 7.5 Hz, 2H), 1.73-1.69 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 150.2, 145.6, 141.2, 130.5, 129.8, 129.1, 124.4, 28.8, 18.9, 14.3 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{16}NO_2]$ 218.1181, found 218.1174.



(*E*)-*N*-((*E*)-1-oxoundec-2-en-4-ylidene)aniline oxide (**10c**).

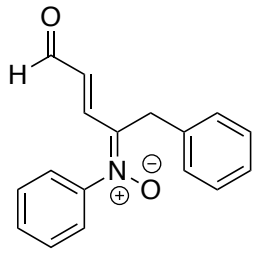
Yellow oil (29 mg, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, J = 7.5 Hz, 1H), 7.51 (m, 3H), 7.35 (m, 2H), 7.03 (d, J = 16.0 Hz, 1H), 6.30 (dd, J = 15.5, 7.5 Hz, 1H), 2.85 (t, J = 8.0 Hz, 2H), 1.66-1.62 (m, 2H), 1.46-1.41 (m, 2H), 1.37-1.25 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 150.3, 145.6, 141.1, 130.4, 129.8, 129.0, 124.4, 31.8, 29.9, 29.2, 27.0, 25.4, 22.7, 14.2 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{24}NO_2]$ 274.1807, found 274.1802.



(*E*)-*N*-((*E*)-2-methyl-6-oxohex-4-en-3-ylidene)aniline oxide (**10d**).

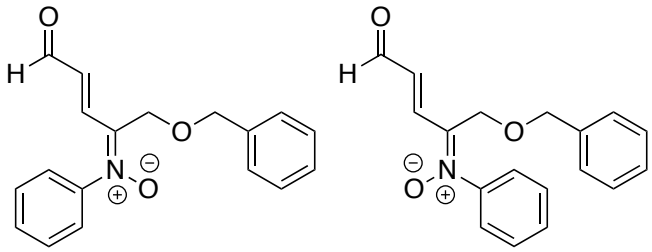
Yellow oil (32 mg, 59%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, J = 7.0 Hz, 1H), 7.51-7.50 (m, 3H), 7.34-7.33 (m, 2H), 6.95 (d, J = 16.0 Hz, 1H), 6.39 (dd, J = 16.0, 7.5 Hz, 1H), 3.64 (septet, J = 7.0 Hz, 1H), 1.42 (d, J =

7.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 153.0, 146.3, 141.4, 130.4, 129.8, 128.4, 124.3, 27.9, 17.6 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{16}NO_2]$ 218.1181, found 218.1181.



(*E*)-*N*-((*E*)-5-oxo-1-phenylpent-3-en-2-ylidene)aniline oxide (10e).

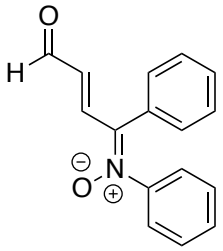
Yellow oil (31 mg, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, J = 7.0 Hz, 1H), 7.55 (m, 3H), 7.42-7.41 (m, 2H), 7.36-7.33 (m, 4H), 7.29-7.26 (m, 1H), 7.14 (d, J = 15.5 Hz, 1H), 6.41 (dd, J = 15.5, 7.5 Hz, 1H), 4.28 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 148.6, 145.4, 140.9, 135.9, 130.6, 129.9, 129.5, 129.0, 128.6, 127.2, 124.4, 32.4 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{16}NO_2]$ 266.1181, found 266.1178.



(2*Z*,3*E*)-1-(benzyloxy)-5-oxo-*N*-phenylpent-3-en-2-imine

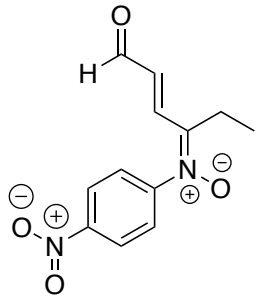
(2*E*,3*E*)-1-(benzyloxy)-5-oxo-*N*-phenylpent-3-en-2-imine oxide (10f).

Yellow oil (32 mg, 43%): ^{1}H NMR (500 MHz, $CDCl_3$) δ Z-isomer: 9.36 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 15.5 Hz, 1H), 6.63 (dd, J = 16.0, 7.5 Hz, 1H), 4.84 (s, 2H), 4.69 (s, 2H) E-isomer: 9.79 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 16.5 Hz, 1H), 6.74 (dd, J = 16.5, 8.0 Hz, 1H), 4.44 (s, 2H), 4.19 (s, 2H) Both: 7.55-7.49 (m, 6H), 7.45 (d, J = 7.0 Hz, 2H), 7.40-7.37 (m, 4H), 7.34-7.32 (m, 6H), 7.25 (d, J = 6.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 192.7, 146.4, 146.0, 145.3, 143.3, 140.0, 139.9, 137.4, 136.5, 133.9, 130.7, 130.6, 130.0, 129.8, 129.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.7, 124.1, 123.4, 73.9, 73.3, 65.1, 63.5 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{18}NO_3]$ 296.1287, found 296.1280.



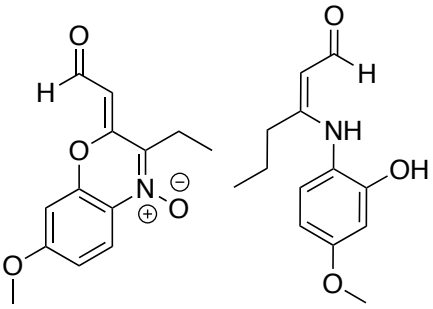
(*E*)-*N*-((*E*)-4-oxo-1-phenylbut-2-en-1-ylidene)aniline oxide (10g').

Dark yellow oil (15 mg, 23%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 16.0 Hz, 1H), 7.30-7.25 (m, 8H), 7.13-7.12 (m, 2H), 6.26 (dd, J = 16.0, 7.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 147.9, 147.2, 142.2, 136.3, 131.7, 130.6, 129.8, 129.7, 129.0, 128.9, 124.7 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{16}H_{14}NO_2]$ 252.1025, found 252.1023.



(*E*)-4-nitro-*N*-((*E*)-6-oxohex-4-en-3-ylidene)aniline oxide (10h).

Yellow solid (28 mg, 45%): mp 107-d ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 15.0 Hz, 1H), 4.88 (dd, J = 15.5, 7.0 Hz, 1H), 2.91 (q, J = 7.5 Hz, 2H), 1.26, (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 152.3, 149.4, 148.6, 138.7, 130.0, 125.8, 125.5, 20.5, 9.6 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{13}N_2O_4]$ 249.0875, found 249.0867.



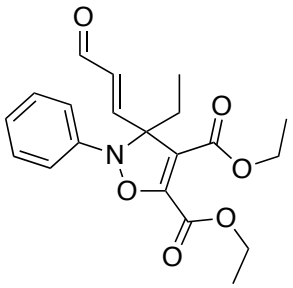
Procedure for formation of (*Z*)-3-ethyl-7-methoxy-2-(2-oxoethylidene)-2*H*-benzo[*b*][1,4]oxazine 4-oxide (10i) and (*Z*)-3-((2-hydroxy-4-methoxyphenyl)amino)hex-2-enal (11).

To a solution of catalyst **2b** (32.6 mg, 0.1 mmol) in chloroform (2.0 mL), was added freshly distilled enal **1a** (58.0 μL, 0.5 mmol). The reaction was stirred for 10 minutes, then 2-nitrosoresorcinol monomethyl ether (153.1

mg, 1.0 mmol) was added. The reaction was stirred at rt until complete consumption of enal, as observed by ^{1}H NMR.

To obtain **10i**: The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (5% Et_2O:dichloromethane). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **10i**. Orange solid (24 mg, 19%): mp 174-d ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 6.72 (s, 1H), 5.57 (d, J = 7.5 Hz, 1H), 3.89 (s, 3H), 2.84 (q, J = 7.5 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 162.9, 156.8, 147.9, 139.3, 123.7, 121.3, 111.7, 105.5, 100.5, 56.2, 19.5, 9.3 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{14}NO_4]$ 248.0923, found 248.0920.

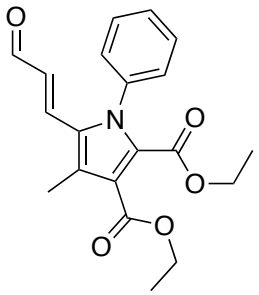
To obtain **11**: The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (20% EtOAc:petroleum ether). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **11**. Red oil (26 mg, 22%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.63 (brs, 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.42 (brs, 1H), 6.91 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.43 (dd, J = 8.5, 2.5 Hz, 1H), 5.13 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H), 2.08 (t, J = 7.5 Hz, 2H), 1.45 (q, J = 7.5 Hz, 2H), 0.84 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 170.8, 160.5, 153.8, 129.1, 117.7, 106.5, 102.7, 96.6, 55.6, 33.9, 21.1, 14.0 ppm; ^{15}N (INEPT) NMR (50 MHz, $CDCl_3$) δ 119.15 ppm HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{17}NO_3]$ 236.1287, found 236.1286.



Procedure for synthesis of (*E*)-diethyl 3-ethyl-3-(3-oxoprop-1-en-1-yl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate (**18**).

To a solution of nitrone **10a** (100.0 mg, 0.49 mmol) in toluene (2.5 mL) was added diethyl acetylenedicarboxylate (236.3 µL, 1.48 mmol) at 0 ºC. Reaction was stirred at 0 ºC for 37 hours until complete consumption of nitrone, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (15-20% Et_2O:petroleum ether gradient). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **18**. Yellow oil (99 mg, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 7.04 (d, J

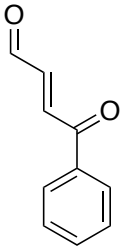
= 8.5 Hz, 2H), 6.66 (d, *J* = 16 Hz, 1H), 6.29 (dd, *J* = 16, 7.5 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.30 (sextet, *J* = 7.0 Hz, 1H), 1.99 (sextet, *J* = 7.0 Hz, 1H), 1.41 (t, *J* = 7.5 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 161.6, 158.7, 155.6, 153.0, 145.0, 133.3, 129.0, 125.4, 118.9, 108.2, 77.7, 63.2, 61.1, 27.5, 14.1, 8.3 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{24}NO_6]$ 374.1604, found 374.1596.



Procedure for synthesis of (*E*)-diethyl 4-methyl-5-(3-oxoprop-1-en-1-yl)-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**19**).

a) A solution of pure 2,3-dihydroisoxazole **18** (28.95 mg, 0.08 mmol) in toluene (390 µL) in a sealed pressure tube was heated to 80 ºC. The reaction was heated for 5 days until complete consumption of 2,3-dihydroisoxazole, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (1% Et_2O:dichloromethane). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure pyrrole **19**.

b) To a solution of nitrone **10a** (50.0 mg, 0.26 mmol) in toluene (1.2 mL) in a pressure tube, was added diethyl acetylenedicarboxylate (118.1 µL, 0.74 mmol). The reaction was heated to 50 ºC and allowed to stir for two days until complete consumption of nitrone, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (1% Et_2O:dichloromethane). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **19**. Yellow oil (15 mg, 16%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, *J* = 7.5 Hz, 1H), 7.52-7.46 (m, 3H), 7.26 (m, 2H), 7.00 (d, *J* = 16.5 Hz, 1H), 6.03 (dd, *J* = 16, 7.5 Hz, 1H), 4.35 (q, *J* = 7.5 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.46 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 164.5, 160.7, 139.2, 136.9, 131.1, 129.9, 129.6, 129.3, 128.2, 127.5, 126.4, 120.0, 61.7, 61.0, 14.3, 13.9, 11.9 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{22}NO_5]$ 356.1498, found 356.1491.



Procedure for synthesis of (*E*)-4-oxo-4-phenylbut-2-enal (20).

To a solution of nitrone **10g'**(50.0 mg, 0.20 mmol) in acetone/water (2.4 mL/0.24 mL) in a pressure tube, was added paraformaldehyde (48.4 mg, 1.61 mmol) and Amberlyst-15 (138.3 mg). The reaction was heated to 40 ºC and stirred for 21 hours until disappearance of starting material by ^{1}H NMR. Reaction was cooled to rt, loaded directly onto silica gel and purified by flash chromatography (5% EtOAc:petroleum ether). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure compound **20**. Yellow oil (20 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (d, J = 7.0 Hz, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 16.0 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.00 (dd, J = 16.0, 7.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 189.9, 142.2, 139.3, 136.4, 134.3, 129.2, 129.0 ppm; HRMS (ESI) $[M]^+$ calcd. for $[C_{10}H_8O_2]$ 160.0524, found 160.0521.

Configuration Determination

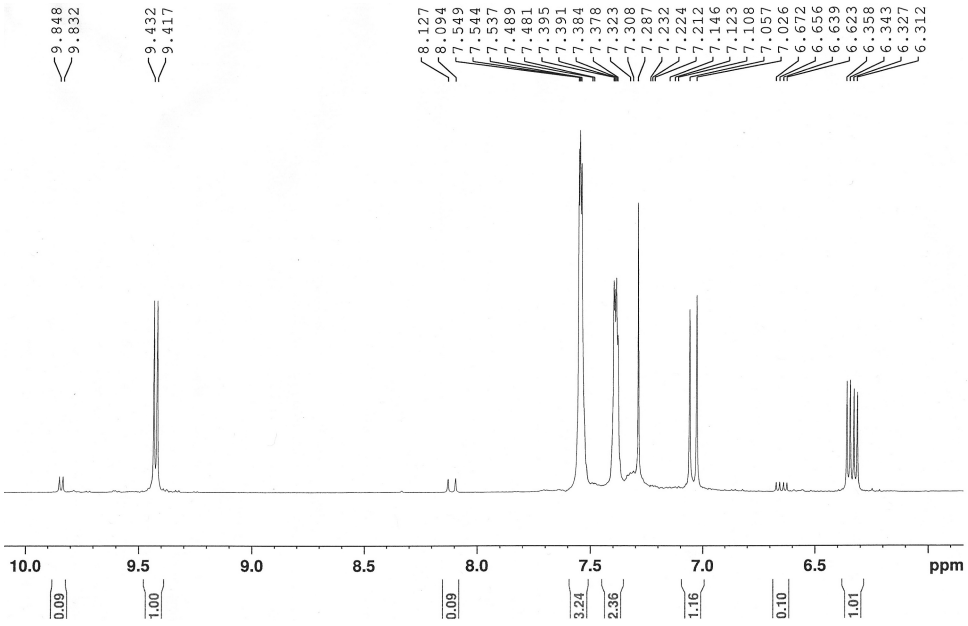


Figure S1: Zoom of ^{1}H NMR spectrum **10a**

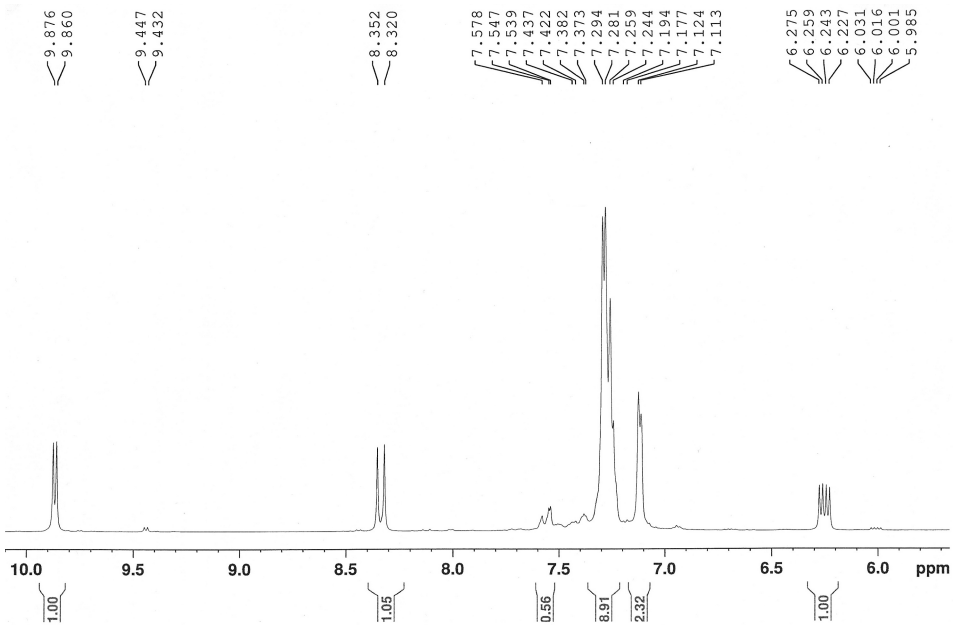


Figure S2: Zoom of ^{1}H NMR spectrum **10g'**

The presence of the two isomers was confirmed by comparing the ^{1}H NMR spectra (*Figures S1 & S2*) and HRMS data fror nitrone products **10a** and **10g'**. The ^{1}H NMR spectrum of **10a** shows the aldehyde major isomer as a doublet (J = 7.5 Hz) at 9.42 ppm and the minor isomer further downfield as a doublet (J = 8.0 Hz) at 9.84 ppm, which can be compared to the major isomer of **10g'**, which is a doublet (J = 8.0 Hz) at 9.87 ppm and the minor isomer, which is an upfield doublet (J = 7.5 Hz) at 9.44 ppm. The major alkene peaks of **10a** were a doublet (J = 15.5 Hz) at 7.04 ppm and a doublet of doublets (J = 15.5, 7.5 Hz) at 6.34 ppm and the minor peaks were a doublet (J = 16.5 Hz) at 8.11 ppm and a doublet of doublets (J = 16.5, 8.0 Hz) at 6.65 ppm. The major peaks of **10g'** compare to the minor peaks of **10a** with a doublet (J = 16.0 Hz) at 8.34 ppm and a doublet of doublets (J = 16.0, 8.0 Hz) at 6.25 ppm, the major doublet of doublets of **10a** compares to the minor doublet of doublets (J = 15.0, 7.5 Hz) at 6.01 ppm of **10g'**. The J-couplings between the alkene peaks, ranging from 15.0 Hz to 16.5 Hz, confirm the *E*-stereochemistry in both the major and minor isomers for **10a** and **10g'**. The HRMS (ESI) data confirmed that these were indeed different isomers of the corresponding nitrone with **10a** $[M+H]^+$ calculated for $C_{12}H_{14}NO_2$ as 204.1025, found to be 204.1022; and **10g'** $[M+H]^+$ calculated for $C_{16}H_{14}NO_2$ as 252.1025, found to be 252.1023.

Diastereomeric Ratio Determination

The dr was determined by using the ^{1}H NMR integrations of the major and minor aldehyde peaks when NMR yield was obtained.

Crystallography

The crystal structure of **10a** (CCDC=1451744) was used along with HRMS data to confirm the presence of a nitrone versus an imine, as well as determine the stereochemistry of the major isomer, confirming both the C=C and C=N as *E*. This, along with the previously discussed ^{1}H NMR data, allowed for extrapolation to the stereostructure of the major isomer of **10g'**, with the C=C as *E*, and the C=N as *Z*.

Mechanistic Studies

HRMS evidence to support the proposed mechanism for the formation of nitrone **10** was obtained by dilution of an aliquot of the reaction mixture to 20μM in dichloromethane after two hours of reactivity. This solution was injected onto a Bruker Apex-ultra 70 hybrid FTMS by ESI and the masses for our proposed mechanistic intermediates were compared to the output.

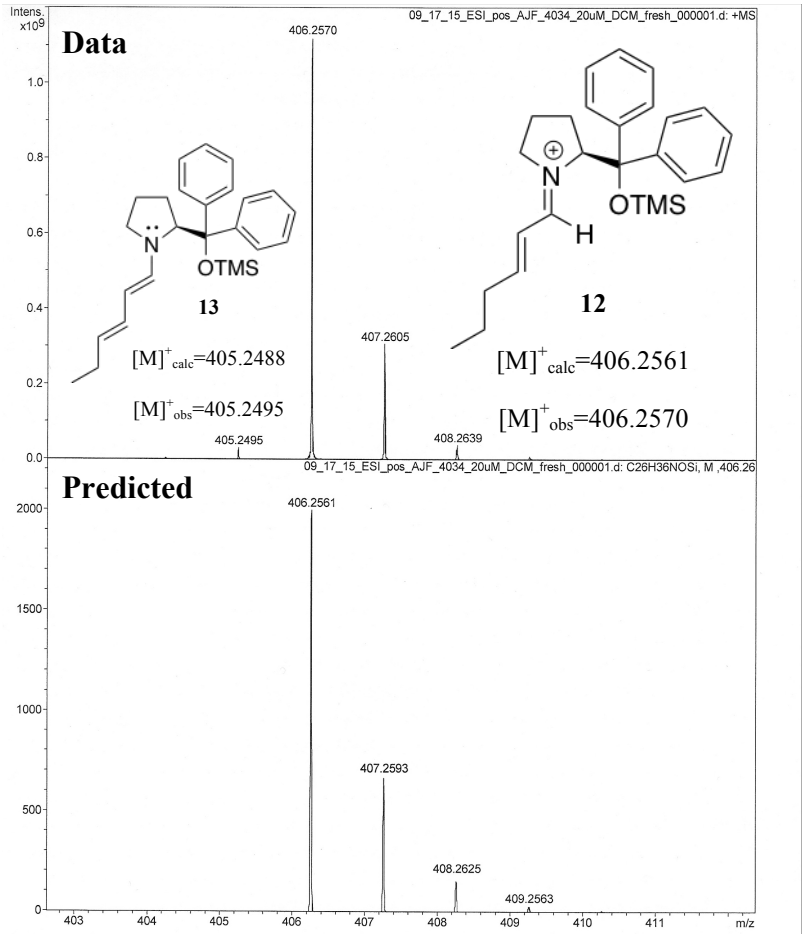


Figure S3: HRMS data-iminium ion **12** and dienamine **13**

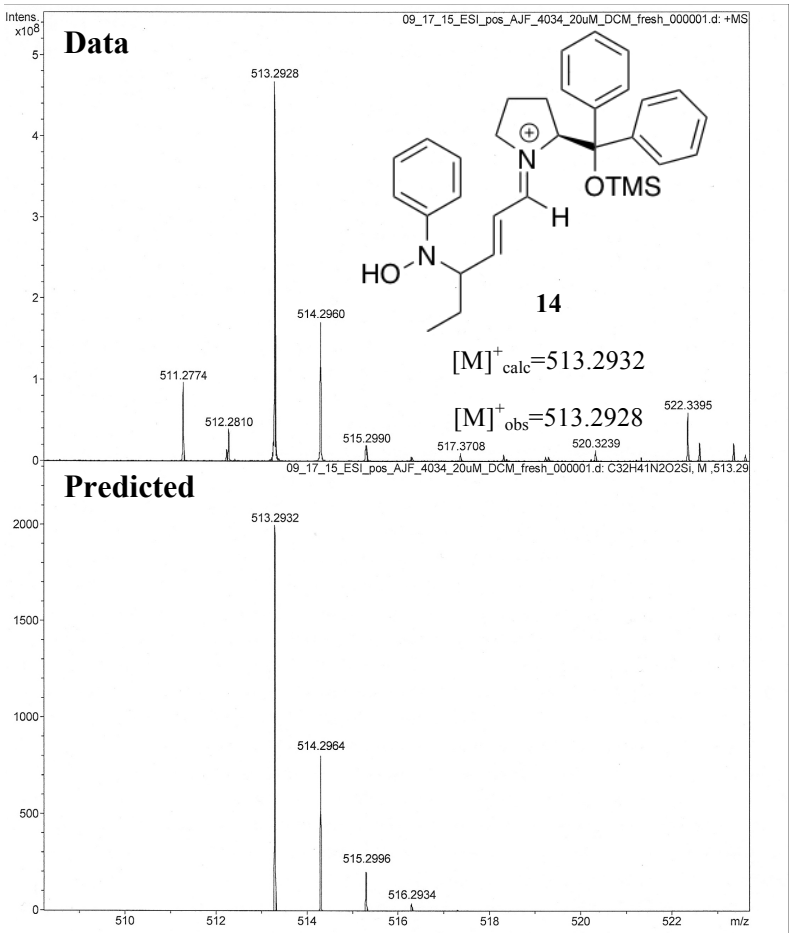


Figure S4: HRMS data-γ-oxyaminated iminium ion **14**

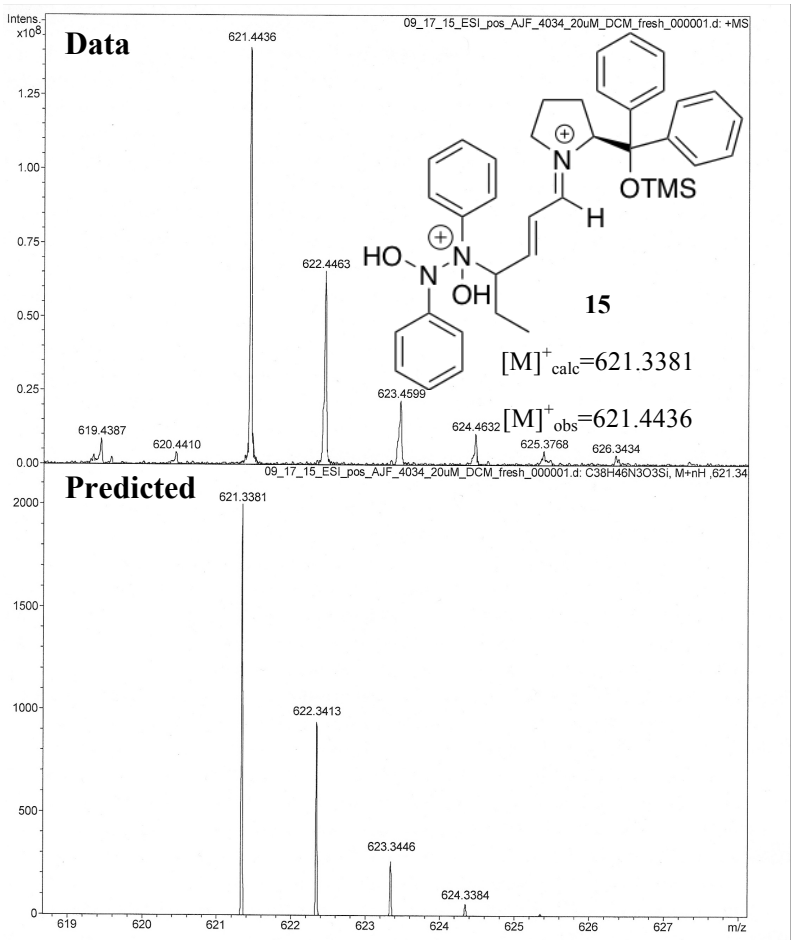
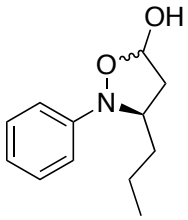


Figure S5: HRMS data-iminium ion γ-hydroxylamine dimer **15**



2-phenyl-3-propylisoxazolidin-5-ol (**17**).

Yellow oil (104 mg, 50%): $[\alpha]_D^{23}$ = -87.07 (*c* = 1.0 in $CHCl_3$ for 54% ee, 1.5:1 dr); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 5H), 7.15-7.12 (m, 5H), 7.07 (t, *J* = 7.0 Hz, 1H), 6.97 (t, *J* = 7.0 Hz, 1H), 5.76 (m, 1H), 5.71 (m, 1H), 3.88-3.85 (m, 1H), 3.72 (brs, 1H), 3.47-3.45 (m, 1H), 3.29 (brs, 1H), 2.56-2.54 (m, 1H), 2.46 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.23-2.20 (m, 1H), 2.02 (d, *J* = 12.0 Hz, 1H), 1.91-1.90 (m, 1H), 1.84-1.79 (m, 1H), 1.65-1.63 (m, 1H), 1.56-1.44 (m, 3H), 0.99 (t, *J* = 13.5 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 151.1, 128.9, 128.7, 123.6, 121.8, 117.5, 115.5, 98.2, 97.0, 67.4, 64.0, 42.0, 41.7, 37.2, 36.2, 20.4, 20.0, 14.2, 14.1 ppm; HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 90:10), 0.5 mL/min; major diastereomer: major

enantiomer t_R = 19.4 min, minor enantiomer t_R = 15.2 min; minor diastereomer: major enantiomer t_R = 17.4 min, minor enantiomer t_R = 16.6 min; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{18}NO_2]$ 208.1338, found 208.1331.

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