mmol) in THF (10 mL) with stirring under argon at -78 °C. After 30 min at that temperature, the solution was stirred at -50 °C for 10 h, and then an excess of a saturated aqueous solution of ammonium chloride was added. Hydrochloric acid (10 N) was added dropwise until pH 3 was reached. The aqueous phase was extracted with diethyl ether (4 × 30 mL), and the collected organic phases were dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure and flash chromatography of the residue afforded 67 mg (67% yield) of pure (3*S*,4*R*)-**1** with physical and spectral data identical with those reported above and 14 mg (14% recovery) of starting lactone (3*S*,4*R*)-**9**.

When (3*R*,4*R*)-**9** (108 mg, 0.45 mmol) was similarly reacted, (3*R*,4*R*)-**2** was isolated in 71% yield along with a 18% of starting lactone (3*R*,4*R*)-**9**.

(2*S*,3*S*)-3-Fluoro-1-[(4-methylphenyl)sulfenyl]-5-hexen-2-ol (10) and (2*S*,3*R*)-10. Trifluoroacetic anhydride (0.35 mL, 2.50 mmol) was added to a mixture of (2*S*,3*S*,R_S)-**5** (128 mg, 0.50 mmol) and of sodium iodide (240 mg, 1.60 mmol) in acetone (15 mL) with stirring at -40 °C under argon. After 10 min at the same temperature the reaction was quenched with an excess of a saturated aqueous solution of sodium sulfite and of a saturated aqueous solution of sodium hydrogen carbonate. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl ether (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was removed to give (2*S*,3*S*)-**10** as a pure compound in 96% yield. An analytical sample was obtained through flash chromatography (*n*-hexane/diethyl ether 85:25); $[\alpha]^{20}_D$ +46° (*c* 0.62, $CHCl_3$); ^1H NMR (250 MHz) δ 2.48 (m, 2 H, CH_2CF), 2.90 (dd, $^2J_{H,H}$ = 14 Hz, $^3J_{H,H}$ = 9 Hz, $^4J_{H,F}$ = 1.0 Hz, CHS), 3.30 (ddd, 1 H, CHS), 3.71 (m, $^3J_{H,F}$ = 10.5, $^3J_{H,H}$ = 6.0 Hz, 1 H, CHO), 4.47 (m, 1 H, CHF), 5.13 (m, 2 H, CH=CH_2), 5.82 (m, 1 H, CH=CH_2). Anal. Calcd for $C_{13}H_{17}FOS$: C, 64.96; H, 7.13. Found: C, 65.14; H, 7.32.

When (2*S*,3*R*,R_S)-**5** was similarly reacted, the sulfenyl alcohol (2*S*,3*R*)-**10** was obtained in 94% yield through flash chromatography (*n*-hexanediethyl ether 85:25); $[\alpha]^{20}_D$ +17.7° (*c* 0.61, $CHCl_3$); ^1H NMR (250 MHz) δ 2.52 (m, 2 H, CH_2CF), 3.04, 3.09 (m, 2 H, CH_2S), 3.66 (m, $^3J_{H,F}$ = 22.0 Hz, $^3J_{H,H}$ = 2.9 Hz, 1 H, CHO), 4.60 (m, $^2J_{H,F}$ = 47.4 Hz, 1 H, CHF), 5.14 (m, 2 H, CH=CH_2), 5.80 (m, 1 H, CH=CH_2). Anal. Calcd for $C_{13}H_{17}FOS$: C, 64.96; H, 7.13. Found: C, 65.03; H, 7.24.

2-Phenylpropionic Esters 12 of (2*S*,3*S*)-10 and of (2*S*,3*R*)-10. 4-(Dimethylamino)pyridine (1.2 mg, 0.01 mmol) was added to a dichloromethane solution (0.5 mL) containing the sulfenyl alcohol (2*S*,3*S*)-**10** (24 mg, 0.10 mmol), the (+)-(*S*)-2-phenylpropionic acid (**11**, 17 mg, 0.11 mmol), and dicyclohexylcarbodiimide (25 mg, 0.12 mmol). After 4 h at room temperature the dicyclohexylurea was removed by filtration and washed with *n*-hexane. The collected organic phases were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (*n*-hexane/diethyl ether 98:2) to give the desired (*S*)-2-phenylpropionate **12** of the alcohol (2*S*,3*S*)-**10**: ^1H NMR (250 MHz) δ 1.51 (d, 3 H, CH_3CH), 2.30 (s, 3 H, $CH_3C_6H_4$), 2.28 (m, 2 H, CH_2CHF), 3.02, 3.07 (m, 2 H, CH_2S), 3.72 (q, 1 H, $CHCH_3$), 4.66 (m, 1 H, CHF), 5.0-5.1 (m, 3 H, CHO and CH=CH_2), 5.72 (m, 1 H, CH=CH_2). Similarly, by use of (-)-(*R*)-**11** and (2*S*,3*S*)-**10** the corresponding (*R*)-2-phenylpropionate **12** of the alcohol (2*S*,3*S*)-**10** was obtained: ^1H NMR (250 MHz) δ 1.37 (d, 3 H, CH_3CH), 1.96 (m, 2 H, CH_2CHF), 2.26 (s, 3 H, $CH_3C_6H_4$), 3.02, 3.14 (m, 2 H, CH_2S), 3.41 (q, 1 H, $CHCH_3$), 4.47 (m, 1 H, CHF), 4.7-5.0 (m, 3 H, CHO and CH=CH_2), 5.53 (m, 1 H, CH=CH_2). When (2*S*,3*R*)-**10** was esterifyied with (+)-(*S*)-**11**, the obtained ester **12** showed the following spectrum: ^1H NMR (250 MHz) δ 1.53 (d, 3 H, CH_3CH), 2.25 (m, 2 H, CH_2CF), 2.30 (s, 3 H, $CH_3C_6H_4$), 3.01 (d, 2 H, CH_2S), 3.78 (q, 1 H, $CHCH_3$), 4.80-4.95 (m, 2 H, CHFCHO), 5.01, 5.06 (m, 2 H, CH=CH_2), 5.70 (m, 1 H, CH=CH_2). Similarly the ester **12** obtained from (-)-(*R*)-**11** and the alcohol (2*S*,3*R*)-**10** showed the following spectrum: ^1H NMR (250 MHz) δ 1.52 (d, 3 H, CH_3CH); 1.99 (m, 2 H, CH_2CF), 2.31 (s, 3 H, $CH_3C_6H_4$), 3.09, 3.18 (m, 2 H, CH_2S), 3.71 (q, 1 H, $CHCH_3$), 4.73 (m, 1 H, CHF), 4.7-5.0 (m, 3 H, CHO and CH=CH_2), 5.53 (m, 1 H, CH=CH_2).

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Registry No. α-(3*S*,4*R*)-**1**, 122333-24-8; β-(3*S*,4*R*)-**1**, 122333-25-9; α-(3*R*,4*R*)-**2**, 122333-26-0; β-(3*R*,4*R*)-**2**, 122333-27-1; (*R*)-**3**, 105984-80-3; (3*R*,R_s)-**4**, 121911-10-2; (3*S*,R_s)-**4**, 121911-11-3; (2*S*,3*R*,R_s)-**5**, 121911-13-5; (2*S*,3*S*,R_s)-**5**, 121961-08-8; (2*S*,3*R*,R_s)-**6**, 122406-16-0; (2*S*,3*S*,R_s)-**6**, 122333-15-7; (2*R*,3*R*)-**7**, 122333-16-8; (2*R*,3*S*)-**7**, 122356-68-7; (2*R*,3*R*)-**8**, 122333-18-0; (2*R*,3*S*)-**8**, 122333-17-9; (3*R*,4*R*)-**9**, 122333-22-6; (3*R*,4*R*)-**9** ring opened acid deriv), 122333-21-5; (3*S*,4*R*)-**9**, 122333-20-4; (3*S*,4*R*)-**9** (ring opened acid deriv), 122333-19-1; (2*S*,3*R*)-**10**, 121911-12-4; (2*S*,3*S*)-**10**, 12233-28-2; (*R*)-**11**, 7782-26-5; (*S*)-**11**, 7782-24-3; (2*S*,2′*R*,3*R*)-**12**, 122406-19-3; (2*S*,2′*R*,3*S*)-**12**, 122406-17-1; (2*S*,2′*S*,3*R*)-**12**, 122406-18-2; (2*S*,2′*S*,3*S*)-**12**, 122333-29-3; allyl bromide, 106-95-6; (3*S*,4*R*)-5-(benzoyloxy)-4-(benzyloxy)-3-fluoropentanal, 122333-23-7.

Notes

On the Synthesis of Diarylnitrones

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Compounds containing the imine *N*-oxide moiety are most commonly called nitrones and were first described nearly 100 years ago.[1] Interest in nitrones stems from their photochemical reactivity,[2] as well as from their utility in the synthesis of heterocycles by 1,3-dipolar cycloaddition reactions.[3] Nitrones are also well-known as radical spin-trapping reagents,[4] which has led to their use as antioxidants.[5] Our own interest in nitrones grew out of a new imaging technology we recently introduced for the field of microlithography.[6]

We required for our microlithography programs diarylnitrones with absorption maxima above 400 nm. Nitrones with substituent combinations that provided the requisite absorption maxima proved difficult to synthesize by conventional techniques. In fact few such compounds

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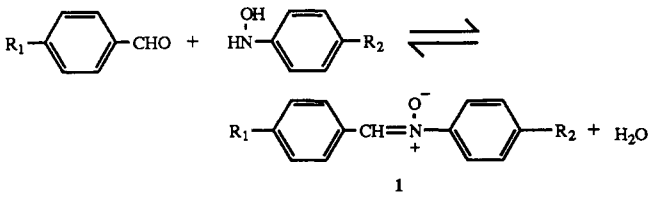
Scheme I



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have been previously described in the literature. We wish to report that acid catalysis can be used to great advantage in the preparation of diarylnitrones, particularly those whose synthesis is otherwise impeded by electronic effects.

The condensation of arylhydroxylamines with benzaldehyde derivatives offers the most direct approach to the preparation of diarylnitrones (Scheme I).[7] Generally the equlibria lie in favor of the nitrones, and removal of the water of condensation is often not necessary. The electron-withdrawing and electron-donating substituents that provide the push–pull effect necessary to achieve the desired bathochromic shifts in the nitrone absorption maxima are also those that tend to make the corresponding hydroxylamines less nucleophilic and the aldehydes less electrophilic. Such substituents unfortunately can also reduce the equilibrium constant for the condensation reaction to the extent that isolation and purification of the nitrone become difficult. Removal of water by azeotropic distillation has been used in some instances to drive these condensation reactions to completion.[8] Although the elevated distillation temperatures offer the added benefit of enhanced reaction rates, side reactions can also lead to the rapid destruction of the arylhydroxylamine. It is the sensitive nature of arylhydroxylamines that makes impractical the use of forcing conditions for condensation reactions that do not otherwise proceed readily.

Arylhydroxylamines are susceptible toward oxidation, particularly in the presence of base, and are also prone toward redox disproportionation reactions. Even under neutral conditions, the oxidation of phenylhydroxylamine has been observed to be catalyzed at 35 °C by a variety of metal ions such as cupric, ferric, manganous, nickel, chromium, and cobaltous ion.[9] Zerovalent metals such as nickel, iridium, palladium, and platinum have also been reported to induce the disproportionation of phenylhydroxylamine at 55 °C into aniline and nitrosobenzene.[10] Since arylhydroxylamines are generally prepared either by dissolving metal reductions or by catalytic hydrogenations of the corresponding nitro compounds, contamination with trace metals is practically unavoidable. That arylhydroxylamines are in general difficult to prepare on a large scale is indicated by the fact that only four such compounds are listed as being offered for sale.[11] Certain arylhydroxylamines are particularly labile and have defied attempts at their isolation and purification.[12] We have found it essential, therefore, to develop reaction conditions that permit the use of arylhydroxylamines directly as obtained from the reduction of the corresponding nitro compounds without intermediate isolation and purification.

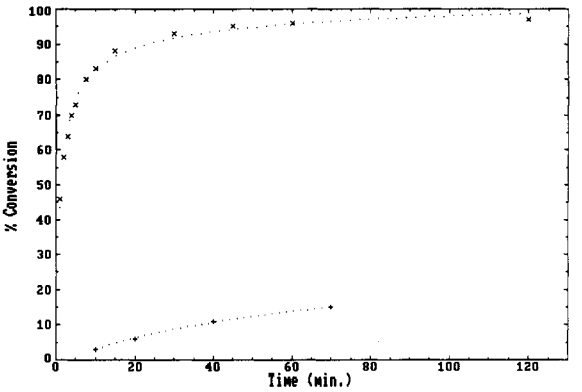

Figure 1. Comparison of reaction rates of 4-(diethylamino)-benzaldehyde with phenylhydroxylamine: (+) no acid catalyst; (×) with 15 mequiv of methanesulfonic acid.

The use of acid catalysis in the condensation of arylhydroxylamines with benzaldehydes permits such reactions to be run at or below room temperature. Furthermore, since nitrones are in many cases less soluble than either of their precursors, reaction conditions may be chosen to drive the equilibrium by selective precipitation of the product. By such strategies it is even possible to obtain high yields of diarylnitrones in the presence of large excesses of water. In view of the fact that acid catalysis has been previously studied in the formation of nitrones from alkylhydroxylamines,[13] it is surprising that acid catalysts apparently have not been employed in the synthesis of diarylnitrones. The use of phenylhydroxylamine hydrochloride was described in an early report on the synthesis of diphenylnitrone, but the salt may have been chosen for its convenience in handling due to its greater stability relative to the free hydroxylamine. Furthermore, the stoichiometric proportions used resulted in the isolation of the nitrone as the hydrochloride complex.[14] Efforts to avoid acid-catalyzed rearrangements of arylhydroxylamines to aminophenols[15] may be responsible in part for the tendency to run the condensation reactions under essentially neutral conditions. The aminophenol rearrangement is precluded for arylhydroxylamines substituted in the para position; however, acids also catalyze the redox disproportionation of arylhydroxylamines, particularly those bearing electron-donating substituents.[16] We have also observed acid-catalyzed disproportionation of arylhydroxylamines with electron-withdrawing substituents. Nevertheless, acid catalysts preferentially accelerate the condensation reactions so as to minimize losses due to any of the above side reactions.

An example of the effect of acid on the rate of condensation is presented in Figure 1. Under neutral conditions 4-(diethylamino)benzaldehyde reacts sluggishly with phenylhydroxylamine, achieving only partial conversion to nitrone **1a** ($R_1 = Et_2N$, $R_2 = H$) even after 24 h at room temperature. Competing with the condensation reaction is the oxidation of the hydroxylamine, which in the absence of the aldehyde is completely consumed in less than 16 h. The addition of 0.015 equiv of methanesulfonic acid allows formation of **1a** to compete successfully with decomposition of the hydroxylamine since the condensation reaction is virtually complete after only 1 h. The rate-limiting step in the condensation of methylhydroxylamine with 4-chlorobenzaldehyde under neutral conditions is reported

(7) Rundel, W. In *Methoden Der Organischen Chemie*; Müller, E., Ed.; Georg Theme Verlag: Stuttgart, 1968; Vol. 10/4, pp 315–448.
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(13) (a) Reimann, J. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3973. (b) Masui, M.; Yijima, C. *J. Chem. Soc., Sect. B* **1966**, 56.
(14) Beckmann, E. *Liebigs Ann. Chem.* **1909**, *365*, 201.
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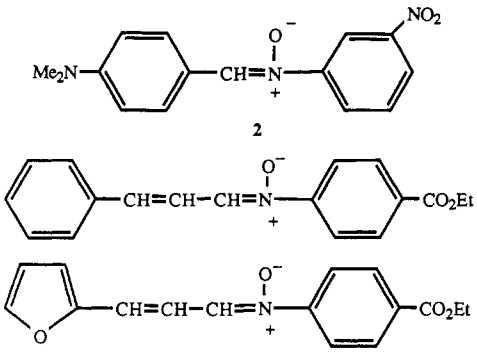
to be the dehydration of the carbinolamine intermediate.[13a] Dehydration of the carbinolamine is accelerated by protic acids, and thus nucleophilic attack of the free hydroxylamine upon the aldehyde becomes the rate-determining step under acidic conditions. The same analysis likely applies for the condensation of arylhydroxylamines with benzaldehydes, except that the relative concentration of free arylhydroxylamines is probably greater as a consequence of their lower basicity.

In the example in Figure 1, the reaction proceeded to 98% completion even without removal of the water of condensation. The condensation of 4-(diethylamino)-benzaldehyde with the much less nucleophilic (4-carbethoxyphenyl)hydroxylamine results in only 70% conversion to nitrone **1b** ($R_1 = Et_2N$, $R_2 = CO_2Et$) at equilibrium, as demonstrated in the comparison of the catalyzed and uncatalyzed processes in Figure 2. Attempts to increase yields through removal of water by azeotropic distillation afforded at best 75% conversion to the nitrone when the hydroxylamine was carefully purified but otherwise usually resulted in disproportionation of the hydroxylamine to a 2:1 mixture of 4,4′-dicarbethoxyazoxybenzene and ethyl 4-aminobenzoate. However, by simple dilution of the acid-catalyzed reaction mixture with water, nitrone **1b** could be induced to precipitate as it was formed at room temperature to give an isolated yield of 87%. In the absence of an acid catalyst, the condensation reaction proceeded slowly relative to the decomposition of the hydroxylamine, and the product tended to separate from the reaction mixture as an intractable oil.

Perhaps the best illustration of the benefits afforded by the use of acid catalysis is provided by the synthesis of the nitro-substituted nitrone **2**. The nitro substituent greatly



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reduces the nucleophilicity of the hydroxylamine in its reaction with the aldehyde whose electrophilicity is already attenuated by the dimethylamino substituent. The synthesis of nitrone **2** was first described by Splitter and Calvin, who reported having attempted "numerous" experiments to optimize its synthesis.[17a] Under their optimum conditions, a crude yield of 52% of a material exhibiting a melting range of 165–168 °C was obtained after a reaction time of over 3 days. An excess of the aldehyde was used since it was observed that the (nitrophenyl)-hydroxylamine tended to form a low-melting 1:1 complex with nitrone **2**. Purification required column chromatography followed by several recrystallizations to bring the melting point up to 172 °C.[17] A subsequent attempt to repeat the procedure of Splitter and Calvin reportedly resulted in an isolated yield of only 5%.[17b] We have been able to condense stoichiometric quantities of the aminobenzaldehyde and (nitrophenyl)hydroxylamine in the presence of a catalytic amount of methanesulfonic acid to give, after only 3 h at room temperature, a 67% yield of nitrone **2** melting at 179 °C without further purification. Although no effort was made to optimize the yield, the solvent composition could again be adjusted to cause selective precipitation of the nitrone during the course of the condensation reaction.

Finally, acid catalysis can be put to particular advantage in the synthesis of diarylnitrones by eliminating the need to isolate the arylhydroxylamine. The "one-pot" approach is particularly useful for nitrones derived from arylhydroxylamines bearing electron-donating substituents. For example, previous attempts to isolate (*p*-methoxyphenyl)hydroxylamine afforded instead a mixture of *pp*′-dimethoxyazobenzene and *p,p*′-dimethoxyazoxybenzene.[18] Our own efforts to identify conditions that would allow the selective catalytic hydrogenation of 4-nitroanisole to the hydroxylamine have likewise been unsuccessful, with overreduction to *p*-anisidine resulting instead. However, if the identical reduction is carried out in the presence of 1 equiv of 4-(diethylamino)benzaldehyde and 0.015 equiv of methanesulfonic acid, a 58% yield of nitrone **1c** can be isolated. Apparently the acid catalyst permits the hydroxylamine intermediate to be intercepted by the aldehyde before further hydrogenation to the aniline takes place.

The reactivity of the aldehyde in all of the above examples was diminished by the presence of the *p*-dialkylamino substituent. It might be thought, therefore, that the function of the acid catalyst was simply to protonate the amino group and thereby render the aldehyde more electrophilic in nature. However, we have observed that acid catalysts are useful in the condensation of a broad spectrum of benzaldehydes with arylhydroxylamines. For example, the condensation between *p*-tolualdehyde and (*p*-carbethoxyphenyl)hydroxylamine in dichloromethane is facile enough so as to require only about 3 h to reach equilibrium. Nevertheless, the rate enhancement provided by the addition of a catalytic amount of methanesulfonic acid is such that the reaction is complete in less than a minute. Weak acids such as acetic acid also catalyze the condensation reactions, but rate enhancements are not as great and require more acid than with the stronger acids. Methanesulfonic acid has proven most convenient to use, although complications due to acetal formation can occur with some aldehydes. For example, attempts to catalyze the condensation between tolualdehyde and phenylhydroxylamine in methanol resulted in the immediate formation of an equilibrium mixture of approximately 50% nitrone and 50% of the dimethylacetal. Once again, the problem is easily remedied through the addition of sufficient water to hydrolyze the acetal and induce precipitation of the nitrone. We have also obtained good results with catalytic amounts of trifluoroacetic acid or hydrochloric acid (introduced as the hydroxylamine hydrochloride) as well as with polymer-bound acids, such as the Amberlyst resins manufactured by Rohm and Haas. The examples in Table I illustrate the variety of diarylnitrones that can be obtained by acid catalysis in good yields and with short reaction times.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Varian Associates EM-390 and XL-200 spectrometers were used to record 90- and 200-MHz ^1H NMR spectra, respectively, and an XL-300 instrument was used to obtain ^{13}C NMR data. All chemical shifts are

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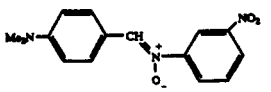
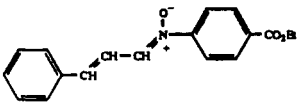
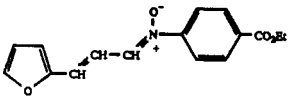
(18) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.

Table I. Diarylnitrones Prepared by Acid-Catalyzed Condensation Reactions[a]

nitrone	R_1	R_2	reaction time	yield, %
1a	Et_2N	H	1.5 h	84
1b	Et_2N	CO_2Et	2 h	88
1c	Et_2N	OCH_3	18 h	62[b]
1d	Et_2N	CH_3	5 h	66[b]
1e	Et_2N	CN	15 min	80
1f	H	CO_2Et	10 min	94
1g	CN	CO_2Et	10 min	82
1h	CH_3O	CO_2Et	15 min	94
1i	H	CN	10 min	78
1j	CH_3O	H	20 min	95
1k	CH_3	H	20 min	80
2			3 h	67
3			15 min	96
4			10 min	76

[a] Reaction conditions and yields not optimized. [b] Overall yield starting from nitro compound for one-pot reaction.

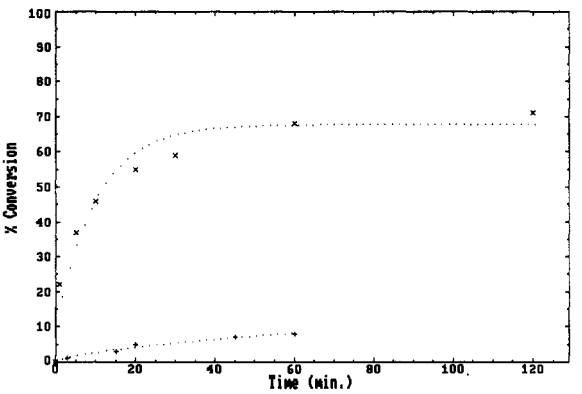


Figure 2. Comparison of reaction rates of 4-(diethylamino)-benzaldehyde with (4-carbethoxyphenyl)hydroxylamine: (+) no acid catalyst; (×) with 15 mequiv of methanesulfonic acid.

reported in parts per million (δ scale) relative to tetramethylsilane as an internal standard. UV data were obtained with either a Cary 219 or a Shimadzu UV-240 spectrophotometer. High-resolution mass spectra were obtained on a Varian-MAT 731 operating at 10 000 resolution. HPLC analyses were performed on a Waters dual-pump system with UV detection at 280 nm. Chromatographic separations were accomplished on a 25-mm Whatman Partisil 10 ODS-3 column by reverse-phase elution at 1.5 mL/min with a 15-min linear gradient program from 50% aqueous methanol to 100% methanol.

Arylhydroxylamines. Phenylhydroxylamine was prepared by the reduction of nitrobenzene with zinc dust as previously described.[19] (4-Carbethoxyphenyl)hydroxylamine[8] was similarly prepared from ethyl 4-nitrobenzoate in 50% aqueous ethanol: mp 75–77 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.35 (t, 3 H, J = 7 Hz), 4.28 (q, 2 H, J = 7 Hz), 6.60 (s, 1 H), 6.87 (d, 2 H, J = 8 Hz), 7.08 (s, 1 H), 7.88 (d, 2 H, J = 8 Hz).

General Procedure for the Preparation of Diarylnitrones. Unless otherwise specified, the aldehyde and hydroxylamine (10 mmol each) were combined in 95% ethanol (10 mL) and treated with methanesulfonic acid (10 μL). The nitrone usually began to precipitate after 15–30 min, but if necessary the reaction mixture was diluted with water until the nitrone began to separate from solution. The reaction mixture was then cooled, and the product collected by filtration. Most of the nitrones may be recrystallized either from aqueous ethanol or from tetrahydrofuran/cyclohexane.

α-(4-(Diethylamino)phenyl)-*N*-phenylnitrone (1a). 4-(Diethylamino)benzaldehyde (1.8 g, 10 mmol) and phenylhydroxylamine (1.1 g, 10 mmol) were stirred in glacial acetic acid (8 mL) for 1.5 h. The reaction mixture was then poured into water and extracted with ether. The ether extracts were washed with saturated aqueous sodium bicarbonate and with water. After drying and evaporation of the solvent, 2.35 g of nitrone was obtained. Recrystallization from cyclohexane/toluene afforded 2.2 g (8.4 mmol, 84%) of **1a**: mp 111–113 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (t, 6 H, J = 7 Hz), 3.43 (q, 4 H, J = 7 Hz), 6.70 (d, 2 H, J = 9 Hz), 7.42 (m, 3 H), 7.77 (s, 1 H), 7.77 (m, 1 H), 8.32 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 12.6, 44.4, 110.7, 118.2, 121.5, 128.9, 128.9, 131.6, 134.8, 148.9, 149.5; UV (EtOH) λ_{max} 390 nm (ϵ 41 000); exact mass calcd for $C_{17}H_{20}N_2O$ 268.1576, found 268.1581.

α-(4-(Diethylamino)phenyl)-*N*-(4-carbethoxyphenyl)-nitrone (1b): mp 114–116 °C; NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, 6 H, J = 7 Hz), 1.41 (t, 3 H, J = 7 Hz), 3.44 (q, 4 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.71 (d, 2 H, J = 9 Hz), 7.84 (s, 1 H), 7.87 (d, 2 H, J = 9 Hz), 8.13 (d, 2 H, J = 9 Hz), 8.34 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.2, 44.4, 61.1, 110.7, 117.6, 121.1, 130.3, 130.5, 131.9, 135.3, 149.8, 151.6, 165.5; UV (EtOH) λ_{max} 419 nm (ϵ 40 000); exact mass calcd for $C_{20}H_{24}N_2O_3$ 340.1787, found 340.1792.

α-(4-(Diethylamino)phenyl)-*N*-(4-methoxyphenyl)nitrone (1c): 4-Nitroanisole (1.53 g, 10 mmol) was stirred in ethanol (10 mL) under an atmosphere of hydrogen in the presence of 4-(diethylamino)benzaldehyde (1.77 g, 10 mmol), triphenylphosphine (0.1 g), methanesulfonic acid (10 μL), and 5% platinum on charcoal (0.05 g) until 2 equiv of hydrogen had been consumed (approximately 18 h). The catalyst was then removed by filtration and rinsed with ethanol (5 mL). The filtrate was cooled to 0 °C, whereupon a precipitate began to form. The filtrate was diluted with water (10 mL), and the precipitated nitrone was collected and rinsed with 50% aqueous ethanol to give 1.86 g (6.2 mmol) of material which was 98% pure by HPLC analysis: mp 123–125 °C; NMR ($CDCl_3$, 90 MHz) δ 1.14 (t, 6 H, J = 8 Hz), 3.37 (q, 4 H, J = 8 Hz), 3.76 (s, 3 H), 6.62 (d, 2 H, J = 9 Hz), 6.83 (d, 2 H, J = 9 Hz), 6.67 (d, 2 H, J = 9 Hz), 7.68 (s, 1 H), 8.31 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 385 nm (ϵ 46 000); exact mass calcd for $C_{18}H_{22}N_2O_2$ 298.1681, found 298.1688.

α-(4-(Diethylamino)phenyl)-*N*-(4-methylphenyl)nitrone (1d): 4-Nitrotoluene (1.37 g, 10 mmol) was stirred in ethanol (10 mL) under an atmosphere of hydrogen in the presence of 4-(diethylamino)benzaldehyde (1.6 g, 9 mmol), dimethyl sulfoxide

(19) Kamm, O. *Org. Synth., Coll. Vol. I* **1948**, pp 445–447.

(0.5 mL), acetic acid (0.3 g, 5 mmol), and 5% platinum on charcoal (0.05 g) until 2 equiv of hydrogen had been consumed (approximately 5 h). The catalyst was then removed by filtration, and the filtrate was diluted with about 15 mL of water. The product first separated as an oil, which on stirring solidified. The crude nitrone was collected, rinsed with 50% ethanol, and dried to give 1.85 g (6.6 mmol, 73%) of a bright yellow powder: mp 121–124 °C; NMR ($CDCl_3$, 90 MHz) δ 1.22 (t, 6 H, J = 7 Hz), 2.39 (s, 3 H), 3.42 (q, 4 H, J = 7 Hz), 6.65 (d, 2 H, J = 9 Hz), 7.16 (d, 2 H, J = 8 Hz), 7.61 (d, 2 H, J = 8 Hz), 7.69 (s, 1 H), 8.25 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 388 nm (ϵ 44 100), exact mass calcd for $C_{18}H_{22}N_2O$ 282.1732, found 282.1744.

α-(4-(Diethylamino)phenyl)-*N*-(4-cyanophenyl)nitrone (1e): mp 206–207 °C; NMR ($CDCl_3$, 90 MHz) δ 1.23 (t, 6 H, J = 7 Hz), 3.46 (q, 4 H, J = 7 Hz), 6.68 (d, 2 H, J = 9 Hz), 7.67 (d, 2 H, J = 9 Hz), 7.83 (s, 1 H), 7.93 (d, 2 H, J = 9 Hz), 8.32 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 427 nm (ϵ 39 300); exact mass calcd for $C_{18}H_{19}N_3O$ 293.1528, found 293.1536.

α-Phenyl-*N*-(4-carbethoxyphenyl)nitrone (1f): mp 143–145 °C (lit.[8] mp 141–142 °C); NMR ($CDCl_3$, 90 MHz) δ 1.48 (t, 3 H, J = 7 Hz), 4.44 (q, 2 H, J = 7 Hz), 7.4 (m, 3 H), 7.86 (d, 2 H, J = 8 Hz), 7.99 (s, 1 H), 8.18 (d, 2 H, J = 8 Hz), 8.4 (m, 2 H); UV (EtOH) λ_{max} 324 nm (ϵ 20 000); exact mass calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1054.

α-(4-Cyanophenyl)-*N*-(4-carbethoxyphenyl)nitrone (1g): mp 185–187 °C; NMR ($CDCl_3$, 90 MHz) δ 1.46 (t, 3 H, J = 7 Hz), 4.42 (q, 2 H, J = 7 Hz), 7.72 (d, 2 H, J = 9 Hz), 7.83 (d, 2 H, J = 9 Hz), 8.03 (s, 1 H), 8.17 d, 2 H, J = 9 Hz), 8.48 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 336 nm (ϵ 29 100); exact mass calcd for $C_{17}H_{14}N_2O_3$ 294.1004, found 294.1005.

α-(4-Methoxyphenyl)-*N*-(4-carbethoxyphenyl)nitrone (1h): mp 152–154 °C; NMR ($CDCl_3$, 90 MHz) δ 1.41 (t, 3 H, J = 7 Hz), 3.89 (s, 3 H), 4.39 (q, 2 H, J = 7 Hz), 6.95 (d, 2 H, J = 9 Hz), 7.81 (d, 2 H, J = 8 Hz), 7.88 (s, 1 H), 8.11 (d, 2 H, J = 8 Hz), 8.38 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 346 nm (ϵ 26 000); exact mass calcd for $C_{17}H_{17}NO_4$ 299.1158, found 299.1163.

α-Phenyl-*N*-(4-cyanophenyl)nitrone (1i): mp 161–162 °C (lit.[20] mp 144–148 °C); NMR ($CDCl_3$, 90 MHz) δ 7.4 (m, 3 H), 7.71 (d, 2 H), 7.88 (d, 2 H), 7.89 (s, 1 H), 8.3 (m, 2 H); UV (EtOH) λ_{max} 328 nm (ϵ 21 200); exact mass calcd for $C_{14}H_{10}N_2O$ 222.0793, found 222.0797.

α-(4-Methoxyphenyl)-*N*-phenylnitrone (1j): mp 119–120 °C (lit.[21] mp 118 °C); NMR ($CDCl_3$, 90 MHz) 3.87 (s, 3 H), 6.94 (d, 2 H, J = 9 Hz), 7.3–7.5 (m, 3 H), 7.6–7.8 (m, 2 H), 7.80 (s, 1 H), 8.36 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 329 nm (ϵ 23 300); exact mass calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0937.

α-(4-Methylphenyl)-*N*-phenylnitrone (1k): mp 91–93 °C (lit.[22] mp 85–87 °C); NMR ($CDCl_3$, 90 MHz) δ 2.37 (s, 3 H), 7.12 (d, 2 H, J = 9 Hz), 7.2–7.4 (m, 3 H), 7.6–7.7 (m, 2 H), 7.79 (s, 1 H), 8.19 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 318 nm (ϵ 24 000); exact mass calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0992.

α-(4-(Dimethylamino)phenyl)-*N*-(3-nitrophenyl)nitrone (2): mp 179–181 °C (lit.[17] mp 172 °C; NMR ($CDCl_3$, 90 MHz) δ 3.12 (s, 3 H), 6.69 (d, 2 H, J = 8 Hz), 7.5–8.7 (m, 4 H), 7.83 (s, 1 H), 8.31 (d, 2 H, J = 8 Hz); UV (EtOH) λ_{max} 400 nm (ϵ 40 200); exact mass calcd for $C_{15}H_{15}N_3O_3$ 285.1113, found 285.1130.

α-Styryl-*N*-(4-carbethoxyphenyl)nitrone (3): mp 149–150 °C; NMR ($CDCl_3$, 90 MHz) δ 1.43 (t, 3 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 7–8 (m, 7 H), 7.80 (d, 2 H, J = 8 Hz), 7.87 (s, 1 H), 8.12 (d, 2 H, J = 8 Hz); UV (EtOH) λ_{max} 392 nm (ϵ 45 500); exact mass calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1221.

α-[2-(2-Furyl)ethenyl]-*N*-(4-carbethoxyphenyl)nitrone (4): mp 164–166 °C; NMR ($CDCl_3$, 90 MHz) δ 1.43 (t, 3 H, J = 7 Hz), 4.39 (q, 2 H, J = 7 Hz), 6.4–6.5 (m, 1 H), 6.57 (d, 1 H, J = 3 Hz), 7.0–7.6 (m, 3 H), 7.79 (d, 2 H, J = 9 Hz), 7.81 (d, 2 H, J = 8 Hz), 8.12 (d, 2 H, J = 9 Hz); UV (EtOH) λ_{max} 388 nm (ϵ 34 900); exact mass calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1002.

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A Novel Synthesis of Spironolactone. An Application of the Hydroformylation Reaction

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Spironolactone (1), an aldosterone antagonist introduced in the late 1950s is a high-volume diuretic and belongs to a growing class of steroidal spirolactones.[1] Our interest in this class of lactones has lead us to develop a new approach to spironolactone from the readily available acetylene adduct **2**. We thought that hydroformylation[2] of ethisterone **2** would lead to the lactol **3**, which would give lactone **8** upon oxidation. Initial attempts at hydroformylating ethisterone were successful but with the caveat that the 4,5 olefin was also reduced. However, we felt that if the alkene could be deconjugated by ketal formation the now isolated alkene would be less susceptible to reduction and the reaction would proceed in the desired sense. Indeed, when the derived ketal **5** was hydroformylated, a clean reaction ensued, giving lactol **6** as the primary product in 90% yield without over-reduction. The reaction can be carried out with as little as 0.01% catalyst in the form of $Rh_2(OAc)_4$, but reaction times at our standard 15 bar operating pressure tend to extend beyond 48 h. The best results were achieved with 0.1 mol % $Rh_2(OAc)_4$, 0.5 mol % triphenylphosphine in ethyl acetate at 80 °C, and 15 bar pressure of a 1:1 mixture of carbon monoxide/hydrogen. Triphenylphosphine was necessary to achieve clean conversions since its omission lead to much lower yields.

Oxidation of lactol **6** to the lactone **7** proceeded quantitatively with $Ru(Ph_3P)_3Cl_2$ and anhydrous *N*-methylmorpholine *N*-oxide.[3] If anhydrous NMO is not used the reaction fails to go to completion. Other oxidants such as PDC[4] and PCC[5] are also successful. Hydrolysis of the ketal proceeds smoothly, giving enone **8** in 97% overall yield. In general the intermediate ketal was not isolated but hydrolized to afford enone **8** directly. Introduction of the 5,6-alkene is the most troublesome step in the sequence. The best method is through chloranil oxidation,[6] which gives a 70–80% yield of product. Other methods give lower yields or are multiple-step processes that result in an overall lower yield.

Introduction of the thioacetate could be accomplished by traditional acid catalysis,[7] but this inevitably resulted in a thermodynamic mixture of α and β isomers **1** and **10** (ratios vary from 6:1 to 8:1). After exploring a number of unsuccessful approaches to achieving better diastereoselectity in the addition we found that 30 mol % TMSOTf catalizes the reaction to give a >50:1 ratio of α and β isomers.[8] However, when the catalyst concentration is

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(7) Dodson, R. M.; Tweit, R. C. *J. Am. Chem. Soc.* **1959**, *81*, 1224. Cella, J. A.; Tweit, R. C. *J. Org. Chem.* **1959**, *24*, 1109.
(8) Schering AG has found (Patent DE 3,544,661) that BF_3·Et_2O/iPrOH catalyzes the addition of thioacetic acid to diene **9** to give excellent diastereoselectivity. We have found that the reaction also proceeds with aqueous HF in iPrOH to give a >30:1 ratio of the α and β isomers.

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