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A General Synthesis of *N*-Vinyl Nitrones

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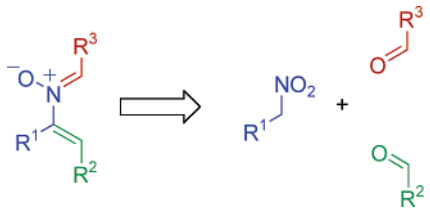
Received May 10, 2006

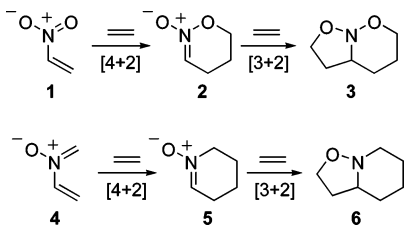


A general synthesis of a new type of heterodiene, the *N*-vinyl nitrone, is described. The synthetic sequence begins with the conjugate addition of benzeneselenol to nitroalkenes (in turn derived from Henry reaction of an aldehyde and a nitroalkane) to provide 2-selenenylnitroalkenes. These selenonitroalkanes are reduced to the corresponding hydroxylamines which are combined with aldehydes to form nitrones. The phenylselenenyl-containing nitrones are then oxidized to selenoxides which undergo *syn*-selenoxide elimination to provide *N*-vinyl nitrones. Three X-ray crystal structures of substituted *N*-vinyl nitrones were obtained. In addition, the first [4+2] cycloaddition of an *N*-vinyl nitrone is reported.

Introduction

Over the last 20 years, the tandem [4+2]/[3+2] cycloaddition of nitroalkenes (Scheme 1) has been developed in these laboratories as a powerful tool for the construction of nitrogen-containing heterocycles.[1] In this sequence, a Lewis acid promoted, inverse electron demand [4+2] cycloaddition of a nitroalkene **1** with an olefin provides a cyclic nitronate **2**, which can be further functionalized through a normal electron demand [3+2] cycloaddition[2] to provide a nitroso acetal **3**. Nitroso acetals can be converted to a variety of synthetically useful structures by hydrogenolysis. A natural consequence of the 1,5-difunctional relationship of the heteroatoms in the isoxazine portion of the nitroso acetal **3** is the general accessibility of pyrrolidine containing structures through hydrogenolysis and ring closure. Indeed, a host of pyrrolidine-containing natural and nonnatural products have been synthesized by this approach.[2] Our interest in expanding the power and scope of the tandem cycloaddition sequence to directly access piperidines[3] led us to consider the development of a new heterodiene that incorporates an additional carbon atom in place of the oxygen atom of the nitro group. The resulting structure in its simplest form is an *N*-vinyl nitrone **4**; [4+2] cycloaddition of which with a suitable dienophile would provide nitrone **5**. This nitrone could be further elaborated through various transformations including the [3+2] nitrone dipolar cycloaddition to give hexahydroisoxazolopyridine **6**. In contrast to the tandem cycloaddition of nitroalkenes, for which additional synthetic manipulations are required to form six-membered, nitrogen-containing rings,[3,4] the [4+2] cycloaddition of *N*-vinyl nitrones would provide a direct route to these heterocycles. A multitude of substituted isoxazolopyridine structures should be possible through various combinations of inter- and intramolecularity for each cycloaddition. Moreover, with an additional substitution point at the nitrone carbon of an *N*-vinyl nitrone, even more opportunities for diversification exist than in the tandem nitroalkene cycloaddition, in which the nitro group oxygen cannot serve as a tether attachment point.

SCHEME 1



(1) Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306−1307. (b) Denmark, S. E.; Thorarensen, *A. Chem. Rev.* **1996**, *96*, 137−165. (c) Denmark, S. E.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2005**, *44*, 3732−3736.

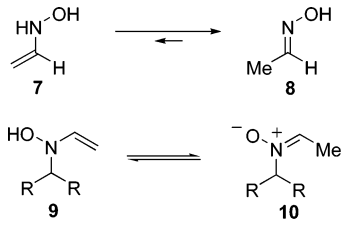
(2) Denmark, S. E.; Cottell, J. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2003.

(3) (a) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046−3056. (b) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593−605.

10.1021/jo060975n CCC: $33.50
Published on Web 07/08/2006

Before the cycloaddition chemistry of *N*-vinyl nitrones can be investigated, a practical synthesis of these compounds is needed. Unfortunately, traditional methods of nitrone synthesis,[5] namely the condensation of a hydroxylamine and a carbonyl compound or oxidation of a secondary hydroxylamine, do not provide a general route to *N*-vinyl nitrones because the required vinylhydroxylamine precursors usually exist in undesired forms. As illustrated in Scheme 2, vinylhydroxylamine **7** exists primarily as its oxime tautomer **8** and a vinylhydroxylamine **9** can convert to nitrone **10** through a 1,4 H-shift.

SCHEME 2



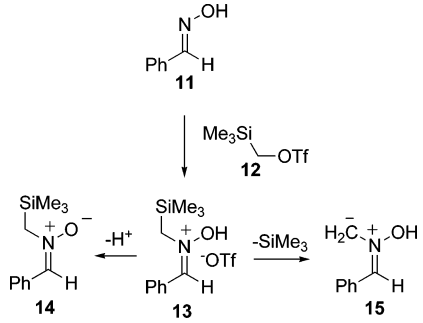
A number of *N*-vinyl nitrones have appeared in the literature, but these were formed as unexpected products[6] or were proposed as reaction intermediates,[7] and none of the reported syntheses are amenable to the creation of structurally diverse *N*-vinyl nitrones needed for our studies. Furthermore, Heaney and coworkers[8] attempted the synthesis and isolation of *N*-vinyl nitrones via intermolecular addition of oximes to activated alkynes and allenes. Unfortunately, only products arising from *O*-addition or other undesired pathways were isolated, and no *N*-vinyl nitrones were observed. Finally, a theoretical study of conformational analysis of the parent compound, *N*-vinyl nitrone **4**, and its 2,2-dichlorovinyl analogue finds that the C−N rotational barrier for **4** is about 24 kJ/mol, but no conclusions about the isolability and reactivity of **4** could be drawn.[9]

Because so little was known about the formation and stability of *N*-vinyl nitrones and their reactivity had not been investigated, a great opportunity for advancement in this area was apparent. We hoped to develop a general and synthetically useful route to *N*-vinyl nitrones beginning from readily available starting materials. In the process, knowledge about the substitution requirements for stability of *N*-vinyl nitrones would be garnered. In addition, the reactivity of *N*-vinyl nitrones in the [4+2] cycloaddition would be examined. Because an *N*-vinyl nitrone still retains the nitrone moiety, promoting the [4+2] cycloaddition against a competing [3+2] dipolar cycloaddition would be essential. It was proposed that the use of Lewis acids might promote the [4+2] pathway through electronic activation while decelerating the [3+2] process through both steric and electronic interactions. By investigating cycloadditions of *N*-vinyl nitrones, additional insights about the electronic requirements and scope of this type of cycloaddition would emerge. Finally, the reactivity of nitrones formed through [4+2] cycloadditions of *N*-vinyl nitrones would be investigated, perhaps leading to a tandem [4+2]/[3+2] cycloaddition of *N*-vinyl nitrones. This report discloses the results of our studies including the development of a general synthesis of *N*-vinyl nitrones and the first intramolecular [4+2] cycloaddition of this new type of heterodiene.

Results

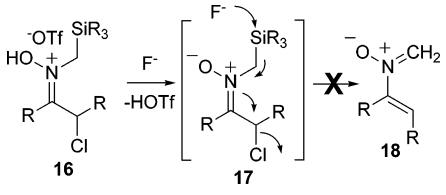
Initial Routes to *N*-Vinyl Nitrones. In the early 1980s, Padwa described how oximes can serve as 1,3-dipole "chameleons" (Scheme 3).[10] Reaction of benzaldehyde oxime (**11**) with trimethylsilylmethyl trifluoromethanesulfonate (**12**) provides silyl iminium salt **13**, which can be converted to either nitrone **14** or azomethine ylide **15** (depending on the reaction conditions) and employed in [3+2] dipolar cycloadditions.

SCHEME 3



Modification of this sequence could provide a rapid route to *N*-vinyl nitrones (Scheme 4). Alkylation of an α-chloro-substituted oxime with trimethylsilylmethyl trifluoromethanesulfonate should provide silyl iminium salts **16**. A fluoride-promoted 1,4-elimination from **16** could induce the formation of *N*-vinyl nitrones **18**. Thus, a number of structurally diverse silyl iminium salts **16** were synthesized and treated with various fluoride sources; however, only the formation of undesired products or extensive decomposition was observed. Unfortunately, it was not clear whether *N*-vinyl nitrones such as **18** did not form under these conditions or, if once formed, *N*-vinyl nitrones containing a methyl nitrone moiety are simply not stable under the reaction conditions employed.

SCHEME 4

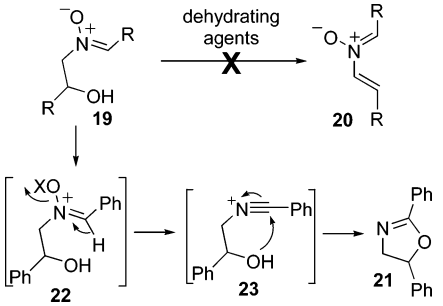


Although the formation of both of the *N*-vinyl nitrone double bonds in one step would have been direct, the initial model investigated proved to be too complex to obtain a clear understanding of what was preventing the productive elimination reaction. The system needed to be simplified to determine where the hypothesis was failing.

(4) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887−2896.
(5) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473−495.
(6) (a) Singh, P.; Berlinguet, L. *Can. J. Chem.* **1964**, *42*, 1901−1905. (b) Schenk, C.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 18−21. (c) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; Van Hummel, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 7570−7571. (d) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816−1823.
(7) (a) Singh, G. S. *Ind. J. Chem. Sect. B* **1991**, *30*, 527−528. (b) Grigg, R.; Perrior, T. R.; Sexton, G. J.; Surendrakumar, S.; Suzuki, T. *J. Chem. Soc., Chem. Commun.* **1993**, 372−374.
(8) Heaney, F.; Kelly, B. M.; Bourke, S.; Rooney, O.; Cunningham, D.; McArdle, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 143−148.
(9) Badawi, H. M.; Ali, S. A. *THEOCHEM* **2002**, *589*, 393−404.
(10) (a) Padwa, A.; Dent, W.; Yeske, P. E. *J. Org. Chem.* **1987**, *52*, 3944−3946. (b) Padwa, A.; Dent, W. H.; Schoffstall, A. M.; Yeske, P. E. *J. Org. Chem.* **1989**, *54*, 4430−4437.

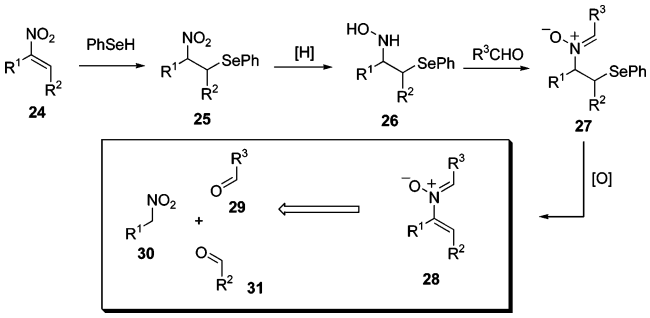
An alternate route to *N*-vinyl nitrones can be envisioned wherein the vinyl C−C double bond is installed after the nitrone is already in place. This system should allow for the synthesis of more stabilized *N*-vinyl nitrones because the nitrone moiety can be substituted. The obvious first choice for installing the required unsaturation is the elimination of water. The known nitrone **19**[11] (Scheme 5, R = Ph) was treated with a number of common dehydrating agents (triflic anhydride/DMAP, mesyl chloride, Burgess reagent,[12] Martin sulfurane[13]) to synthesize an *N*-vinyl nitrone of type **20**, but only the formation of dihydrooxazole **21** was observed. Presumably, the nitrone was dehydrated (**22**) preferentially to provide nitrilium ion **23**, which underwent ring closure leading to dihydrooxazole **21**. Clearly, an elimination that does not require competition between two nucleophilic functional groups would be more appropriate for the synthesis of *N*-vinyl nitrones.

SCHEME 5



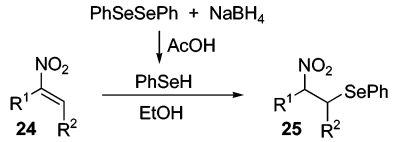
2. Generation of *N*-Vinyl Nitrones through Selenoxide Elimination. 2.1. Research Plan. Because selenoxide eliminations represent a mild and general synthesis of alkenes,[14] we decided to apply this process to the synthesis of *N*-vinyl nitrones. A general and flexible route to *N*-vinyl nitrones (Scheme 6) was planned beginning from nitroalkenes **24**, substrates that are easily prepared by the Henry reaction and that are also abundant in our laboratories because of their use in the tandem [4+2]/[3+2] cycloaddition. Conjugate addition of benzeneselenol should give 2-selenenyl nitroalkanes **25** in a temporary protection of the double bond, thus avoiding undesirable tautomerization in the next step; namely, reduction of the nitro group to the corresponding hydroxylamine **26**.[15] Reaction of **26** with aldehydes should provide nitrones **27** without complications. Oxidation of the selenide and *syn*-selenoxide elimination should result in the formation of *N*-vinyl nitrones **28**. In the retrosynthetic sense, one can see how the completed *N*-vinyl nitrones **28** would be constructed from two aldehydes and a nitroalkane (where nitroalkenes **24** are available from aldehydes **29** and nitroalkanes **30**). Although this construction of *N*-vinyl nitrones requires a number of synthetic transformations, it allows for excellent substrate variability and commences with readily available starting materials. These traits greatly increase synthetic utility over previous *N*-vinyl nitrone syntheses that have appeared in the literature.

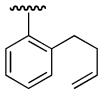
SCHEME 6



Conjugate Addition of Benzeneselenol to Nitroalkenes. In 1987, Ono reported a method for converting (*E*)-trisubstituted nitroalkenes to (*Z*)-trisubstituted nitroalkenes via 2-nitroselenides.[16] Conjugate addition of sodium benzeneselenolate to nitroalkenes followed by protonation at low temperature provided *syn*-2-nitroselenides selectively. When this reaction was performed with nitrostyrene **24b** (Table 1), only polymerization took place, and none of the desired nitro selenide **25b** was formed. To carry out the addition under milder conditions, nitrostyrene **24b** was combined with freshly prepared benzeneselenol,[17] and clean conversion to the desired product **25b** was observed. Gratifyingly, the conjugate addition takes place without the addition of a base. However, because of the sensitivity of benzeneselenol to oxidation and its strong odor, a method of generating the reagent in situ was desired. Accordingly, diphenyl diselenide was reduced with sodium borohydride in ethanol to sodium benzeneselenolate, which was protonated with an excess of acetic acid at 0 °C. The benzeneselenol thus formed was treated with nitrostyrene **24b** directly, resulting in the formation of selenide **25b** in 88% yield after purification. These reaction conditions were extended to the conjugate addition of benzeneselenol to a number of nitroalkenes with good yields. In cases where diastereomeric products were formed, the selectivity was poor, but moderate selectivity for the syn isomer could be achieved by returning to the previously reported conditions[16] for trisubstituted nitroalkenes as in the conversion of nitroalkene **24f** to nitro selenide **25f** (4.6:1 dr).

TABLE 1. Conjugate Addition of Benzeneselenol to Nitroalkenes



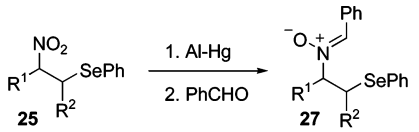
24/25	R^1	R^2	yield, %	*dr* (major)[a]
a	Me	H	80	NA
b	H	Ph	88	NA
c	Me	Ph	95	1.3:1[b] (*syn*)
d	CO_2Me	Ph	75[c]	1.4:1 (*syn*)
e			66[d]	2.3:1 (*trans*)
f	Me		89	4.6:1[e] (*syn*)

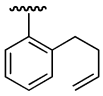
[a] Determined by ^{1}H NMR analysis of the crude product mixture. [b] *syn*-**25c** can be selectively crystallized from the product mixture. [c] Nitro selenide is ~87% pure mixed with **24d** that forms upon purification. [d] Yield of trans only. [e] PhSeNa addition with protonation at −78 °C.

(11) Kliegel, W. *Chem. Ber.* **1969**, *102*, 1776−1777.
(12) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224−5226.
(13) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 4997−5003.
(14) *Organoselenium Chemistry: A Practical Approach*; Back, T., Ed.; Oxford University Press: Oxford, 1999.
(15) Shinmon, N.; Cava, M. P.; Brown, R. F. C. *J. Chem. Soc., Chem. Commun.* **1980**, 1020−1021.

2.3. Reduction of the Nitro Group and Nitrone Formation. On the basis of literature precedent,[15] aluminum amalgam was chosen to reduce 2-selenenylnitroalkanes to the corresponding hydroxylamines. We were pleased to find the rapid conversion of **25** to **26,** but the hydroxylamines were difficult to isolate and purify. Therefore, they were combined directly with benzaldehyde to form the required nitrones in a two-step procedure with a single purification. In this way, a number of 2-selenenylnitroalkanes **25** (Table 2) were converted to nitrones **27** in modest to good yields.

TABLE 2. Reduction and Nitrone Formation

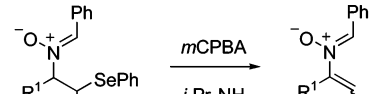


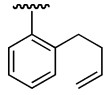
25/27	*syn:anti*[a]	R^1	R^2	yield, %
a	NA	Me	H	76
b	NA	H	Ph	43
c	1.6:1	Me	Ph	66
d	2.0:1	CO_2Me	Ph	32[b]
e	*trans* only			69
f	4.3:1	Me 		75[c]

[a] Syn/anti ratio of starting material **25**. [b] Starting material was only ~87% pure. Yield of recrystallized *syn*-**27d** that precipitates during the reaction. Additional material is available upon chromatography, but it contains an inseparable mixture of diastereomers and decomposition products. [c] Yield of recrystallized syn isomer only.

2.4. *N*-Vinyl Nitrone Formation. Various reagents were investigated for the oxidation of nitrone selenides **27** (Table 3) to selenoxides, which were predicted to undergo spontaneous *syn*-elimination to provide *N*-vinyl nitrones **28**. Oxidations with hydrogen peroxide or *m*-chloroperoxybenzoic acid (*m*-CPBA) alone provided complex mixtures of decomposition products. However, by carrying out the oxidation in the presence of a base to scavenge the benzeneselenenic acid formed during the elimination, low yields of *N*-vinyl nitrones could be obtained. The use of sodium metaperiodate in the presence of sodium bicarbonate was also successful. However, with an excess of oxidant (H_2O_2 or $NaIO_4$), the reactions were quite messy, probably due to overoxidation. In the end, nitrone selenides **27** were treated with a slight excess of phosphate-buffer-washed *m*-CPBA (1.2−1.3 equiv) at low temperature (−78 °C), where no elimination takes place. Next, diisopropylamine was added, and the mixture was allowed to warm to room temperature. In most cases, elimination took place below 25 °C to provide good to excellent yields of *N*-vinyl nitrones **28**. The selenoxide precursor to *N*-vinyl nitrone **28a** proved to be stable even at room temperature. Fortunately, heating the crude material in the presence of diisopropylamine in refluxing benzene afforded clean conversion to **28a**. The formation of *N*-vinyl nitrone **28f** also required heating (60 °C) to complete the elimination step. In all cases, diastereomerically homogeneous nitrone selenides **27** led to a single isomer of *N*-vinyl nitrones **28**, and when a mixture of diastereomers of **27c** was submitted to the reaction conditions, a corresponding selectivity was observed upon isolation of *N*-vinyl nitrones (*Z*)- and (*E*)-**27c**.

TABLE 3. Synthesis of *N*-Vinyl Nitrones



27/28	*syn:anti*[a]	R^1	R^2	yield, %	config.[b]
a	NA	Me	H	59[c]	NA
b	NA	H	Ph	64	*E*
c	1.6:1	Me	Ph	62[d]	1.6:1 *Z*:*E*
d	*syn* only	CO_2Me	Ph	93	*Z*
e	*trans* only			90	*E*
f	*syn* only	Me 		89[c]	*Z*

[a] Syn/anti ratio of purified starting material. [b] Alkene double bond configuration. [c] Heating was required for complete elimination. [d] 38% *Z* and 24% *E* separated by silica gel column chromatography.

A number of *N*-vinyl nitrones listed in Table 3 were crystalline solids, and X-ray crystal structures of (*Z*)-**28c**, **28d**, and **28e** were obtained (see the Discussion). The configuration of **28f** was assigned on the basis of ^{1}H NMR chemical shift correlation to (*Z*)-**28c** (Figure 1). Finally, the (*E*)-configuration of the vinyl group in **28b** was assigned on the basis of the large vicinal coupling constant between the two vinyl protons (J = 13.2 Hz).

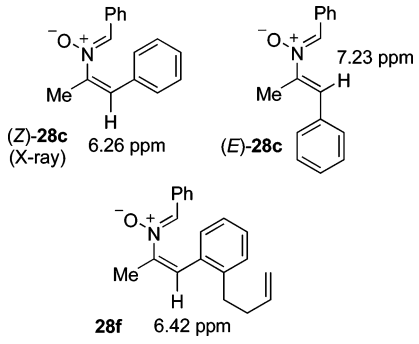


FIGURE 1. ^{1}H NMR shifts of HC(4) in *N*-vinyl nitrones.

2.5. [4+2] Cycloadditions of *N*-Vinyl Nitrones: Frontier Molecular Orbital Calculations. The frontier molecular orbitals (FMOs)[18] for nitroethylene **1** and *N*-vinyl nitrone **4** have been calculated[19] at the PM3 level (Table 4). Both heterodienes were constrained to have a planar, *s*-*cis*-diene system. Direct comparison of the FMOs of nitroethylene **1** and *N*-vinyl nitrone **4**

(16) Ono, N.; Kamimura, A.; Kawai, T.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1550−1551.
(17) Reich, H. J.; Cohen, M. L. *J. Org. Chem.* **1979**, *44*, 3148−3151.
(18) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976.
(19) CAChe WorkSystem Pro Version 6.1.12.33; Fujitsu Ltd., 2004.

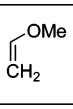
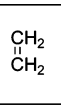
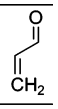
reveals that both the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of nitroethylene **1** are lower in energy than those for *N*-vinyl nitrone **4** (HOMO is 2.46 eV lower, LUMO is 0.34 eV lower). This change would be expected intuitively because nitroethylene contains a second electronegative oxygen atom that should lower the energy of all of the molecular orbitals.

TABLE 4. FMOs of Nitroethylene 1 and *N*-Vinyl Nitrone 4

energy (PM3) (eV)	 1	 4
HOMO	-12.03	-9.57
LUMO	-0.97	-0.63

It is well-known that nitroalkene [4+2] cycloadditions proceed under inverse electron demand (LUMO of nitroalkene interacts with the HOMO of the dienophile).[1b] Therefore, reactions with electron-rich dienophiles (such as vinyl ethers) should be more facile than those with electron-poor dienophiles (Table 5). Because the LUMO of *N*-vinyl nitrone **4** is so close in energy to that of nitroethylene **1** (Δ0.34 eV), similar reactivity would be expected. Namely, *N*-vinyl nitrone should undergo inverse electron demand [4+2] cycloadditions with electron-rich dieneophiles. In addition, Lewis acid coordination to the nitrone oxygen in *N*-vinyl nitrones should further decrease the energy gap by lowering the LUMO of the heterodiene. As a result, promotion of [4+2] cycloadditions of *N*-vinyl nitrones by Lewis acids should be possible, as is the case for the corresponding nitroalkenes.[1b]

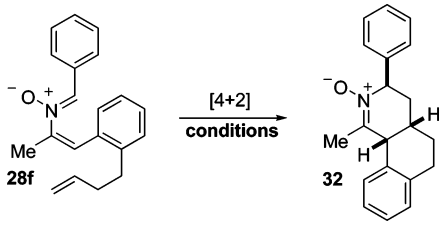
TABLE 5. Energy Differences for Normal and Inverse Electron Demand Cycloadditions[a]

ΔE (eV)				
 1	NED	13.33	13.26	11.85
	IED	8.55	9.68	9.73
 4	NED	10.87	10.80	11.85
	IED	8.89	10.01	9.73

[a] NED (normal electron demand) = $E_{LUMO\_dienophile} - E_{HOMO\_diene}$. IED (inverse electron demand) = $E_{LUMO\_diene} - E_{HOMO\_dieneophile}$.

2.6. [4+2] Cycloaddition of *N*-Vinyl Nitrone 28f. *N*-Vinyl nitrone **28f**, which contains a tethered dienophile, was synthesized to investigate an *intra*molecular [4+2] cycloaddition. Toward this end, **28f** (Table 6) was heated in xylenes to 140 °C, but only slight decomposition of the *N*-vinyl nitrone was observed. The relatively weak Lewis acids Ti(O-*i*-Pr)$_2$Cl$_2$ and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) led to similar results. However, the strong Lewis acids tin tetrachloride and titanium tetrachloride led to reaction. On a 1.27 mmol scale, treatment of *N*-vinyl nitrone **28f** with 3.0 equiv of $SnCl_4$ provided an 86% yield of tetrahydropyridine *N*-oxide **32**, representing the first [4+2] cycloaddition of an *N*-vinyl nitrone. Nitrone **32** proved to be unstable upon storage and was isolated with about 90% purity. The impurity could be either decomposition products or a minor diastereomer.

TABLE 6. First [4+2] Cycloaddition of an *N*-Vinyl Nitrone



conditions	yield (%)
xylenes, 140 °C	no reaction
Ti(O-*i*-Pr)$_2$Cl$_2$, −78 °C to rt	no reaction
MAD, −78 °C to rt	no reaction
$SnCl_4$, −78 °C to rt	86
$TiCl_4$, −78 °C to rt	73

2.7. Assignment of Configuration of Cycloadduct 32. The stereostructure of cycloadduct **32** was assigned on the basis of observed coupling constants and nuclear Overhauser (NOE) experiments (Figure 2). The coupling constant observed for the two protons at the *cis*-fused ring fusion (H^1 and H^2, J = 5.4 Hz) was too small to indicate a trans fusion. The assignment of the relative configuration of the remaining stereogenic center was carried out via NOE experiments. No NOE enhancements were observed between the ring fusion protons (H^1 and H^2) and the proton attached to the carbon bearing the phenyl group (H^3), suggesting that these nuclei were on opposite sides of the six-membered tetrahydropyridine *N*-oxide ring. However, a small (0.5%) NOE was observed between H^3 and H^4. Although these two protons are quite far apart in space in the global-minimized energy structure, another local minimized energy structure exists (+10.2 kJ/mol) where the protons are only 3.35 Å apart, which could explain the observed NOE.

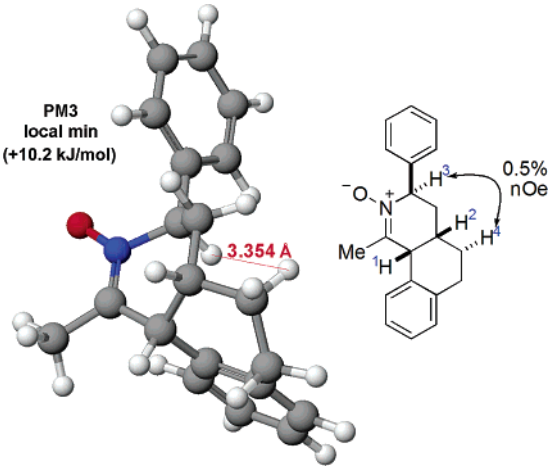


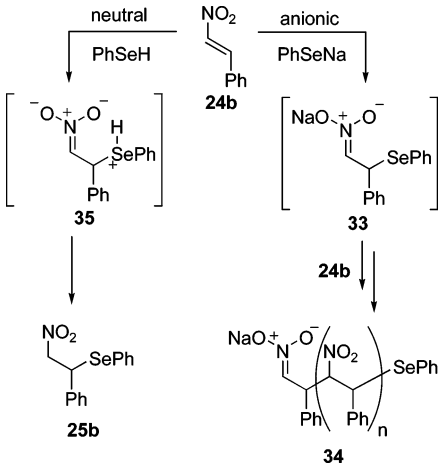
FIGURE 2. PM3 local minimum for **32** and observed NOE.

Discussion

1. Conjugate Addition of Benzeneselenol. 1.1. Reaction Conditions. The conjugate addition of benzeneselenol to nitroalkenes proceeded under neutral (freshly prepared PhSeH) or acidic (in situ generated PhSeH in the presence of AcOH) conditions to provide 2-phenylselenenyl nitroalkanes **25** in good yield. Although the diastereoselectivity was poor, in cases where

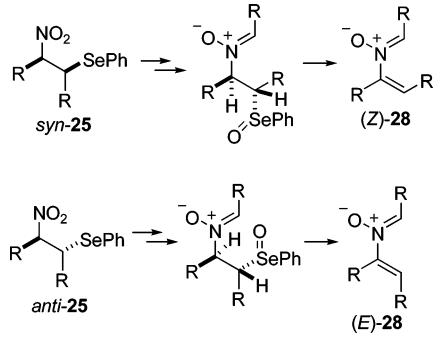
selectivity is not an issue, or when the anti diastereomer is desired, the procedure is a marked improvement over that reported in the literature,[16] where anionic polymerization is a problem for disubstituted nitroalkenes (Scheme 7). When sodium benzeneselenolate added to a disubstituted nitroalkene such as nitrostyrene **24b**, the resulting anion **33** was reactive enough to induce polymerization to **34**. Fortunately, benzeneselenol is nucleophilic enough to add to nitrostyrene **24b** without activation, generating another neutral intermediate (**35**) which can undergo inter- or intramolecular proton transfer to provide 2-phenylselenenylnitroalkane **25b**.

SCHEME 7



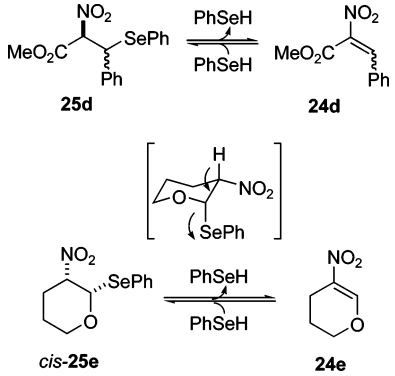
1.1. Stereochemical Consequences. Because of the stereoelectronic requirement for a *syn*-selenoxide elimination, the stereoselectivity during the protonation of the conjugate adduct eventually determines the geometry of the *N*-vinyl nitrone (Scheme 8). A syn diastereomer of **25** leads to a (*Z*)-*N*-vinyl nitrone **28**, while the anti diastereomer of **25** leads to an (*E*)-*N*-vinyl nitrone **28**. As described, selectivity for the syn isomer is possible under basic conditions. However, if the (*E*)-*N*-vinyl nitrone is desired, it is necessary to carry out the conjugate addition unselectively (neutral conditions) and then separate the diastereomers. In the case of nitro selenide **25c**, this separation can be accomplished through crystallization.

SCHEME 8



1.2. Reversibility of the Conjugate Addition. In two cases, the formation of nitroalkenes was observed upon purification of the corresponding 2-phenylselenenylnitroalkanes. Even though nitroalkene **24d** (Scheme 9) was geometrically homogeneous when added to in situ generated benzeneselenol, during the isolation of **25d**, ~13% of nitroalkene **24d** coeluted as a mixture of double bond isomers in the same diastereomeric ratio as the nitro selenides **25d**. Two explanations are possible for the reappearance of the nitroalkene. Either the selenide **25d** is extremely sensitive to air oxidation, leading to selenoxide elimination and nitroalkene formation, or the addition of benzeneselenol is reversible under the reaction and isolation conditions. Support for the reversibility of the benzeneselenol addition is provided by another example in which the selenoxide elimination is unlikely. Namely, after the formation of a 2.3:1 ratio of *trans*- and *cis*-selenides **25e**, the ^{1}H NMR spectrum of the crude reaction mixture showed no nitroalkene **24e** was present. However, upon separation of the diastereomers by silica gel column chromatography, the trans isomer was isolated in pure form, while the cis isomer coeluted as a 1.8:1 mixture of nitroalkene **24e** to selenide *cis*-**25e**. Because a *syn*-selenoxide elimination from oxidized *cis*-**25e** would require the formation of a trans double bond in a six-membered ring and would not lead to nitroalkene **24e**, it is unlikely that oxidation is responsible for the regenerated nitroalkene. However, because the favored conformer of *cis*-**25e** has the selenenyl group in an axial orientation (anomeric effect), the axial proton on the carbon bearing the nitro group is poised for anti elimination, and nitroalkene **24e** can be regenerated. Therefore, it seems that the conjugate addition of benzeneselenol to nitroalkenes is reversible on a laboratory time scale in some cases, especially in the presence of silica gel. In the case of nitro selenide **25d**, the elimination is favored due to the increased acidity of the α proton. In the case of nitro selenide **25e**, a conformational effect leads to reversibility. On silica gel, the equilibrium is probably shifted toward the nitroalkene because benzeneselenol can be trapped (and removed from the system) on the column.

SCHEME 9



2. Selenenyl Nitrone Stability. Nitrones in general are reactive molecules and are prone to hydrolysis and dimerization.[20] For this reason, they are often generated and used immediately. However, nitrones **27** proved to be relatively stable. In fact, all of the examples in Table 2 were crystalline solids that could be stored at low-temperature indefinitely. In addition, crystallization proved to be a valuable method for removing minor diastereomers as in the case of nitrones **27d** and **27f**.

3. *N*-Vinyl Nitrone X-ray Crystal Structures. To prove molecular structure and assign configuration, X-ray crystal structures for *N*-vinyl nitrones (*Z*)-**28c**, **28d**, and **28e** were obtained. *N*-Vinyl nitrone (*Z*)-**28c** produced needles suitable for X-ray analysis by recrystallization from hexane/EtOAc (Figure 3).[21] The crystal structure confirms the (*Z*)-geometry of both

(20) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173.

double bonds and allows for the assignment of its *E*-C═C isomer (*E*)-**28c**. As might be expected from analysis of molecular models and calculations, the diene system is not planar, due to minimization of steric interactions with the C(3) phenyl substituent. The dihedral angle C(1)−N(1)−C(2)−C(3) is 79.8°, making the diene system nearly orthogonal.

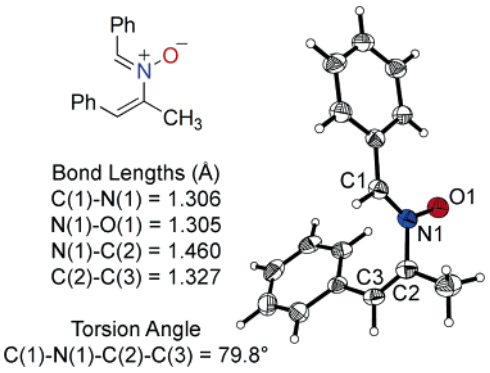


FIGURE 3. ORTEP plot of the X-ray crystal structure of (*Z*)-**28c** (30% thermal ellipsoids).

X-ray quality crystals of *N*-vinyl nitrone **28d** (Figure 4) were grown by slow evaporation of an ether solution at room temperature.[21] The (*Z*)-geometry of the olefin was confirmed, and again, **28d** exists in the solid state with a near-orthogonal diene system (C(1)−N(1)−C(2)−C(3) dihedral = −80.0°) and with an s-cis ester conformation. The bond lengths of interest are all within 0.01 Å of the corresponding bonds in (*Z*)-**28c**.

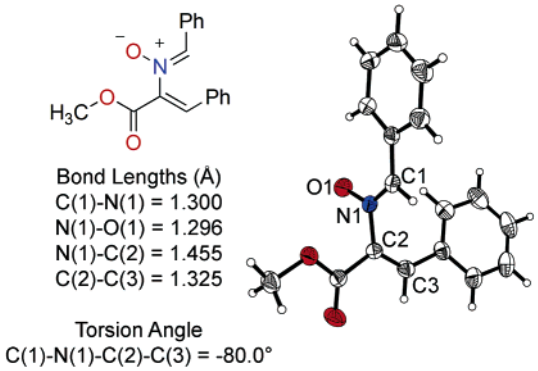


FIGURE 4. ORTEP plot of the X-ray crystal structure of **28d** (30% thermal ellipsoids).

Vapor diffusion of pentane into a solution of **28e** in ethyl acetate over a period of 3 days provided X-ray quality crystals of this *N*-vinyl nitrone (Figure 5).[21] The *E*-geometry of the vinyl ether group (constrained in a six-membered ring) allows the diene to exist close to planarity (14.4° diene dihedral angle), suggesting that conjugation between the vinyl group and the nitrone moiety is a stabilizing factor. In addition, the diene exists with s-trans geometry in the solid state. Again, the *N*-vinyl nitrone bond lengths are all within 0.01 Å of the corresponding bonds in (*Z*)-**28c** and **28d**.

(21) The crystallographic coordinates of **(***Z***)-28c**, **28d**, and **28e** have been deposited with the Cambridge Crystallographic Data Centre, deposition nos. CCDC 603732, 603733, 603734, respectively These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

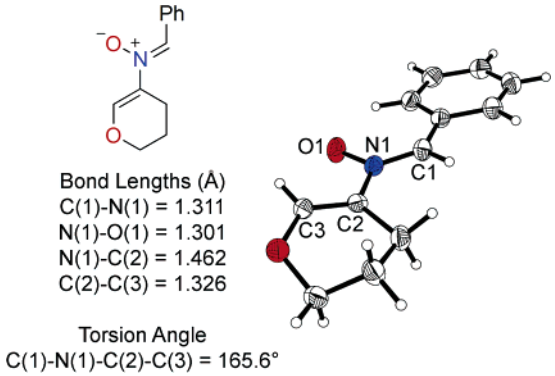


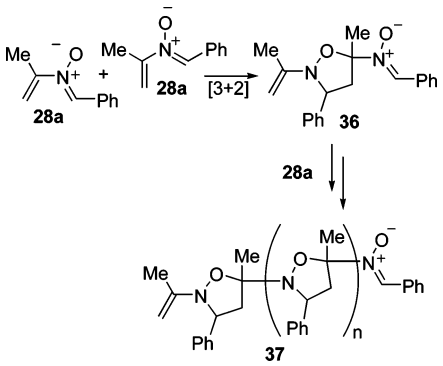
FIGURE 5. ORTEP plot of the X-ray crystal structure of **28e** (30% thermal ellipsoids).

3.1. Stability of *N*-Vinyl Nitrones 28a and 28b. Early attempts at the synthesis of **28a** consistently resulted in very low (<20%) yields because of the instability of this *N*-vinyl nitrone. The selenoxide precursor, which is stable at room temperature, could be isolated from the reaction mixture after an aqueous workup. However, simply heating the selenoxide resulted in messy reactions that only provided trace amounts of **28a**. Fortunately, heating the selenoxide in the presence of diisopropylamine led to clean conversion to **28a**, implying that the *N*-vinyl nitrone is stable under basic conditions at elevated temperature. Upon purification by silica gel column chromatography, clean **28a** was obtained. However, the isolated material soon polymerized at room temperature and to some extent at −20 °C as well. The analytical sample of **28a**, analyzed one day after submission, was within 0.4% for carbon, hydrogen, and nitrogen, proving that the composition of matter did not change. However, the sample hardened to a glass, and its ^{1}H NMR spectrum clearly showed polymerization had occurred.

N-Vinyl nitrone **28b** also proved to be somewhat unstable and slowly decomposed upon storage. Because the material is a solid, an X-ray crystal structure was desired. However, all attempts at recrystallization resulted in a cloudy solution with a precipitate that was no longer soluble in any organic solvents. Presumably, upon heating the nitrone in organic solvents, partial polymerization takes place, leading to insoluble material. In addition, **28b** is unstable in $CDCl_3$, probably due to traces of hydrogen chloride in solution. Therefore, its NMR spectra had to be measured in benzene-d_6, in which no polymerization took place.

A reasonable mechanism of polymerization involves [3+2] dipolar cycloadditions between the nitrone moiety of one molecule of *N*-vinyl nitrone and the vinyl group of another to

SCHEME 10



form **36** (Scheme 10). This polymerization would lead to material with a repeating isoxazolidine unit (**37**). Because the vinyl group in **28a** is electron poor (positively charged nitrogen substituent), it is not surprising that a normal electron demand [3+2] dipolar cycloaddition could take place. In addition, this polymerization would be hindered by steric interactions with increased vinylic substitution, which could explain why substrates such as (*E*)-**28c** are more stable.

Moreover, *N*-vinyl nitrones with a (*Z*)-trisubstituted vinyl group like (*Z*)-**28c** (Figure 6) most likely prefer an orthogonal diene system (see X-ray crystal structure discussion). As a result, steric hindrance around both faces of the dipole is present. These interactions could explain why the (*Z*)-substituted *N*-vinyl nitrones display increased stability.

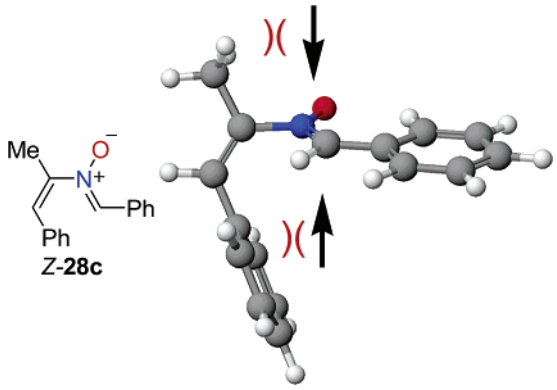


FIGURE 6. 3D representation of (*Z*)-**28c**.

Finally, the stable *N*-vinyl nitrone **28e** possesses an electron-donating substituent (oxygen) on the vinyl group along with the electron-withdrawing nitrone moiety. Although [3+2] cycloadditions can take place under conditions of normal or inverse electron demand,[20] the overall electronic nature of the vinyl group in **28e** could disfavor dipolar cycloaddition.

3.2. [4+2] Cycloaddition of *N*-Vinyl Nitrone 28f. Rationalization for Observed Stereoselectivity. If the conversion of *N*-vinyl nitrone **28f** to nitrone **32** proceeds by a concerted mechanism, the stereochemical outcome can be predicted through analysis of the possible transition structures for the [4+2] cycloaddition (Figure 7). With the methylene groups of the tether in an endo orientation, it is difficult to obtain favorable orbital overlap while maintaining reasonable bond lengths and angles. In addition, analysis of molecular models reveals the existence of a steric interaction between the tether and the methyl group on the vinyl nitrone. An endo-tether transition structure would lead to a [4+2] adduct with a trans fusion between the six-membered rings, **38**, which is not observed experimentally. On the other hand, an exo-tether transition state allows for good orbital overlap while minimizing steric interactions. In addition, this pathway leads to the observed diastereomer **32**. Finally, a nitroalkene analogue (without the aryl group in the tether) underwent smooth [4+2] cycloaddition to give a nitronate with the same relative configuration as nitrone **32**.[1a]

Conclusion

Synthetic approaches to a new type of heterodiene, the *N*-vinyl nitrone, have been developed. Benzeneselenol is added in a conjugate fashion to nitroalkenes to provide 2-selenenylnitroalkanes, which are reduced to the corresponding hydroxylamines and then combined with an aldehyde to form nitrones.

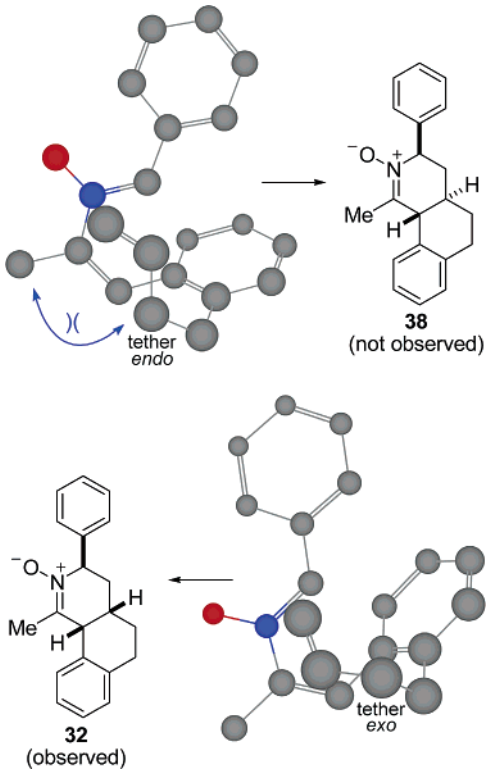


FIGURE 7. [4+2] Cycloaddition transition structures for *N*-vinyl nitrone **28f** and outcomes.

The phenylselenenyl-containing nitrones are then oxidized to selenoxides which undergo *syn*-selenoxide elimination to provide *N*-vinyl nitrones. By starting with various aldehydes and nitroalkenes, a number of variably substituted *N*-vinyl nitrones can be synthesized. Three X-ray crystal structure analyses of substituted *N*-vinyl nitrones were obtained that demonstrate proof of structure and provide some insight into stability. In addition, the first [4+2] cycloaddition of an *N*-vinyl nitrone was documented. Extension of this method to the synthesis of other substrates and the development of a tandem [4+2]/[3+2] cycloaddition of *N*-vinyl nitrones is currently underway.

Experimental Section

General Experimental Procedures. See the Supporting Information.

(2-Nitropropyl)(phenyl)selane (25a). Diphenyl diselenide (1.17 g, 3.75 mmol, 0.75 equiv) was suspended in EtOH (20 mL) in a 100-mL, two-neck, round-bottom flask equipped with a septum, Ar inlet, and magnetic stir bar. A solution of sodium borohydride (378 mg, 10 mmol, 2.0 equiv) in EtOH (20 mL) was added dropwise via cannula to the bright yellow reaction mixture over 10 min. The addition was stopped (after ~15 mL had been added) when all of the yellow color dissipated to give a colorless solution. The reaction flask was then cooled in a 0 °C bath (ice/H_2O) for 5 min, and glacial acetic acid (1.14 mL, 20 mmol, 4.0 equiv) was added dropwise via syringe. Next, nitropropene **24a** (435 mg, 5.0 mmol) was added in EtOH (2 mL) via cannula, the reaction was stirred 5 min at 0 °C, and then the cold bath was removed. After being stirred for 2 h at room temperature, the reaction mixture was poured into H_2O (200 mL) and was extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated (25 °C, 10 mmHg) to give a yellow oil. The crude product was purified by silica gel column chromatography (30 mm × 12 cm column, gradient elution, hexanes

until diphenyl diselenide came off (bright yellow band) then hexanes/EtOAc, 9/1) to provide 981 mg (80%) of nitro selenide **25a** as a light yellow oil. A 227 mg portion was further purified via distillation (Kugelrohr, 215 °C ABT, 1.2 mmHg) to provide 220 mg (97% recovery) of an analytical sample. Data for **25a**: bp 215 °C (ABT, 1.2 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 7.54−7.57 (m, 2 H, HC(5)), 7.28−7.33 (m, 3 H, HC(6), HC(7)), 4.61 (sextet, J = 6.8, 1 H, HC(2)), 3.41 (dd, J = 13.1, 7.0, 1 H, *H*HC(1)), 3.10 (dd, J = 13.2, 6.8, 1 H, H*H*C(1)), 1.63 (d, J = 6.6, 3 H, H_3C(3)); ^{13}C NMR (126 MHz, $CDCl_3$) 134.0 (C(5)), 129.5 (C(6)), 128.2 (C(7)), 128.0 (C(4)), 82.9 (C(2)), 30.7 (C(1)), 19.4 (C(3)); IR (neat) 3072 (m), 3058 (m), 2990 (m), 2938 (m), 2899 (w), 1954 (w), 1881 (w), 1806 (w), 1578 (s), 1552 (s), 1478 (s), 1454 (m), 1438 (s), 1405 (m), 1384 (s), 1357 (s), 1301 (m), 1220 (m), 1126 (m), 1072 (m), 1022 (s), 1000 (m), 831 (m), 740 (s), 692 (s); MS (EI, 70 eV) 245 (M^+, 38), 199 (54), 172 (15), 156 (100), 117 (17), 91 (13), 77 (45), 65 (11); TLC R_f 0.25 (hexanes/EtOAc, 9/1) [silica gel, UV]. Anal. Calcd for $C_9H_{11}NO_2Se$ (244.15): C, 44.27; H, 4.54; N, 5.74; Se, 32.34. Found C, 44.40; H, 4.55; N, 5.86; Se, 33.50.

(*Z*)-*N*-Benzylidene-1-(phenylselanyl)propan-2-amine *N*-Oxide (27a). Nitro selenide **25a** (733 mg, 3.00 mmol) was dissolved in water-saturated EtOAc (9 mL) in a 50-mL, single-neck, round-bottom flask equipped with an Ar inlet and magnetic stir bar. The reaction flask was lowered into a room-temperature water bath, and aluminum amalgam (450 mg, 150 mg/mmol **25a**) was added in one portion. The cloudy, gray suspension was stirred for 15 min and then was filtered through a pad of Celite (40 mm × 1 cm) with hardened filter paper on top, eluting with EtOAc (50 mL). The filtrate was dried (Na_2SO_4) and concentrated to give crude hydroxylamine (643 mg). The residue was dissolved in EtOH (10 mL) in a 100 mL single-neck round-bottom flask equipped with a septum with an Ar inlet (needle) and a magnetic stir bar. Benzaldehyde (1.52 mL, 15.0 mmol, 5.0 equiv) was added via syringe, and the reaction mixture was stirred for 2 h at room temperature. EtOAc (20 mL) and silica gel (3.5 g) were added to the reaction flask, and the mixture was concentrated (25 °C, 10 mmHg) to give silica-bound crude **27a**. Purification by silica gel column chromatography (30 mm × 15 cm column, dry loaded, hexanes/EtOAc, 2/1) provided 725 mg (76%, two steps) of nitrone **27a** as a heavy, colorless oil that became partially crystalline upon storage. Data for **27a**: mp 54.1−55.1 °C (hexane); ^{1}H NMR (500 MHz, $CDCl_3$) 8.19−8.22 (m, 2 H, HC(6)), 7.49−7.52 (m, 2 H, HC(10)), 7.40−7.42 (m, 3 H, HC(11), HC(12)), 7.32 (s, 1 H, HC(4)), 7.24−7.26 (m, 3 H, HC(7), HC(8)), 4.05−4.15 (m, 1 H, HC(2)), 3.54 (dd, J = 13.2, 8.6, 1 H, *H*HC(1)), 3.14 (dd, J = 13.2, 4.9, 1 H, H*H*C(1)), 1.59 (d, J = 6.6, 3 H, H_3C(3)); ^{13}C NMR (126 MHz, $CDCl_3$) 133.9 (C(4)), 132.9, 130.4, 129.2, 128.8, 128.4, 127.3 (C(6), C(7), C(8), C(10), C(11), C(12)), 130.2, 129.1 (C(5), C(9)), 71.9 (C(2)), 31.3 (C(1)), 19.4 C(3)); IR (KBr plate) 3071 (w), 2978 (w), 2932 (w), 1961 (w), 1941 (w), 1582 (m), 1565 (m), 1479 (m), 1462 (m), 1437 (m), 1407 (m), 1312 (m), 1302 (m), 1144 (s), 1111 (m), 1071 (m), 1010 (m), 933 (m), 897 (m), 854 (w), 844 (m), 758 (m), 734 (s), 689 (s), 669 (m); MS (EI, 70 eV) 319 (M^+, 4), 303 (2), 198 (100), 183 (16), 156 (37), 132 (19), 117 (23), 105 (11), 91 (15), 77 (34), 65 (15); TLC R_f 0.27 (hexanes/EtOAc, 1/1) [silica gel, $KMnO_4$]. Anal. Calcd for $C_{16}H_{17}NOSe$ (318.27): C, 60.38; H, 5.38; N, 4.40. Found: C, 60.50; H, 5.32; N, 4.42.

(*Z*)-*N*-Benzylidene-1-propen-2-amine Oxide (28a). Nitrone **27a** (318 mg, 1.00 mmol) was dissolved in CH_2Cl_2 (2 mL) in a 25-mL, single-neck, round-bottom flask equipped with a septum with an Ar inlet (needle) and a magnetic stir bar. The reaction flask was cooled in a −78 °C cold bath (CO_2(s)/*i*-PrOH) for 10 min, and *m*-chloroperoxybenzoic acid (207 mg, 1.20 mmol, 1.2 equiv) was added in CH_2Cl_2 (3 mL) dropwise via cannula over 5 min. The reaction mixture was stirred for 5 min, and diisopropylamine (182 μL, 1.30 mmol, 1.3 equiv) was added via syringe. Then, the cold bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 30 min. Next, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (25 °C, 10 mmHg) to give crude selenoxide. The residue was dissolved in benzene (10 mL) in a 25-mL, conical flask, and diisopropylamine (182 μL, 1.30 mmol, 1.3 equiv) was added. The resulting solution was transferred dropwise via cannula to a 25-mL, round-bottom flask equipped with a reflux condenser containing 1 mL of refluxing benzene (85 °C oil bath). The reaction mixture was heated to reflux for 30 min and then was concentrated (25 °C, 10 mmHg). The residue was purified by silica gel column chromatography (20 mm × 12 cm column, EtOAc/hexane, 3/1) to provide 95.4 mg (59%) of **28a** as a yellow oil. **28a** was not stable to prolonged storage. Data for **28a**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.32 (dd, J = 7.1, 3.7, 2 H, HC(6)), 7.68 (s, 1 H, HC(4)), 7.42−7.45 (m, 3 H, HC(7), HC(8)), 5.67 (s, 1 H, *H*HC(1)), 5.07 (s, 1 H, H*H*C(1)), 2.25 (s, 3 H, H_3C(3)); ^{13}C NMR (126 MHz, $CDCl_3$) 151.1 (C(2)), 133.3 (C(4)), 130.8 (C(8)), 130.4 (C(5)), 129.2 (C(6)), 128.5 (C(7)), 109.4 (C(1)), 18.2 (C(3)); IR (neat) 3134 (w), 3057 (m), 3026 (w), 2993 (w), 2927 (w), 1962 (w), 1896 (w), 1817 (w), 1657 (m), 1575 (m), 1550 (m), 1493 (m), 1445 (s), 1409 (s), 1369 (s), 1322 (m), 1304 (m), 1260 (m), 1205 (m), 1158 (m), 1125 (s), 941 (m), 910 (m), 755 (s), 692 (s); MS (EI, 70 eV) 161 (M^+, 52), 144 (20), 130 (4), 120 (7), 104 (30), 89 (18), 77 (50), 65 (13), 55 (100); TLC R_f 0.22 (EtOAc/hexanes, 3/1) [silica gel, UV]. Anal. Calcd for $C_{10}H_{11}NO$ (161.2): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.19; H, 6.85; N, 8.50.

1-Methyl-3-phenyl-3,4,4a,5,6,10b-hexahydrobenzo[*h*]isoquinoline 2-*N*-Oxide (32). *N*-Vinyl nitrone **28f** (370 mg, 1.27 mmol) was dissolved in CH_2Cl_2 (12.7 mL) in a 100-mL, two-neck, round-bottom flask equipped with a septum, Ar inlet, and a magnetic stir bar. The reaction flask was cooled in a −78 °C cold bath (CO_2(s)/*i*-PrOH) over 5 min, and tin(IV) tetrachloride (446 μL, 3.81 mmol, 3.0 equiv) was added dropwise via syringe. The solution turned bright yellow. The reaction mixture was stirred for 5 min at −78 °C, and then the cold bath was removed and the reaction mixture was allowed to warm to room temperature and stir for 2 h. Then, saturated aqueous sodium bicarbonate solution (20 mL) was added slowly to quench the reaction, and the entire mixture was poured into saturated aqueous sodium bicarbonate solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give **32**. The crude material was purified by silica gel column chromatography (20 mm × 10 cm column, acetone) to provide 317 mg (86%) of nitrone **32** as a foamy solid. ^{1}H NMR analysis showed the product to be ∼90% pure. The contaminant was either another diastereomer or decomposition products. Nitrone **32** was not stable to storage in the freezer under Ar. Data for **32**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (t, J = 7.2, 2 H, HC(8)), 7.29 (tt, J = 7.5, <1, 1 H, HC(9)), 7.18−7.25 (m, 4 H, HC(7), HC(14), HC(15)), 7.17 (dd, J = 5.8, 3.0, 1 H, HC(16)), 7.12 (dd, J = 5.8, 2.8, 1 H, HC(13)), 5.09 (s (br), 1 H, HC(5)), 3.75 (d, J = 5.4, 1 H, HC(2)), 2.72 (dt, J = 15.4, 5.1, 1 H, *H*HC(11)), 2.64 (ddd, J = 15.0, 11.2, 5.6, 1 H, H*H*C(11)), 2.40−2.48 (m, 1 H, HC(3)), 2.42 (s, 3 H, H_3C(18)), 2.08 (dddd, J = 13.5, 8.0, 5.6, 4.1, 1 H, *H*HC(10)), 2.03 (ddd, J = 13.9, 10.5, 5.8, 1 H, *H*HC(4)), 1.94 (dt, J = 14.2, 3.0, 1 H, H*H*C(4)), 1.16 (dddd, J = 13.0, 11.0, 7.0, 5.5, 1 H, H*H*C(10)); ^{13}C NMR (126 MHz, $CDCl_3$) 148.8 (C(1)), 140.0 (C(17)), 138.9 (C(12)), 135.5 (C(6)), 128.6 (C(8)), 127.8, 127.7 (C(13), C(16)), 127.4 (C(9)), 127.1 (C(7)), 126.33, 126.27 (C(14), C(15)), 70.7 (C(5)), 44.2 (C(2)), 36.2 (C(4)), 27.8 (C(11)), 27.0 (C(10)), 25.5 (C(18)), 20.2 (C(3)); IR (neat) 3045 (s), 3031 (s), 2934 (s), 2869 (s), 1962 (w), 1884 (w), 1817 (w), 1591 (s), 1574 (m), 1480 (m), 1451 (s), 1375 (m), 1222 (s), 1195 (m), 1152 (s), 1077 (m), 1036 (m), 973 (m), 928 (m), 834 (m), 806 (w), 752 (s), 703 (s), 678 (s), 622 (s); MS (EI, 70 eV) 291 (M^+, 2), 275 (54), 260 (14), 198 (5), 170 (35), 157 (4), 146 (15), 130 (100), 115 (15), 104 (6), 91 (13),

77 (7); TLC R_f 0.13 (acetone) [silica gel, $KMnO_4$ or UV]; HRMS calcd for $C_{20}H_{21}NO$ 291.1623, found 291.1618.

Acknowledgment. We are grateful to the National Institutes of Health (GM30938) for generous financial support. J.I.M. thanks the Procter & Gamble Company, Abbott Laboratories, and Johnson & Johnson for graduate fellowships. We thank Scott R. Wilson and Teresa Prussak-Wieckowska of the UIUC George L. Clark X-ray Facility for collection and interpretation of X-ray data.

Supporting Information Available: Full characterization of all products, detailed experimental procedures, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO060975N