obtained from 25 machine-centered reflections. Three standard reflections measured every hour showed no trend in intensity during data collection. The raw step-scan data were converted to intensities by using the Lehman-Larsen[17a] method and then corrected for Lorentz, polarization, and absorption factors, the latter computed by the empirical method of Walker and Stuart[17b] since face indexating was not possible. The structure was solved by using MULTAN.[17c] After refinement of heavy atoms, difference Fourier maps revealed maxima of electron density close to the positions expected for hydrogen atoms. These atoms were introduced into structure-factor calculations by their computed coordinated (C-H = 0.95 Å) and isotropic factors such that $B(H) = 1 + B_{eqv}(C)$ Å^2. No hydrogen atom parameters was allowed to vary during full-matrix least-squares refinements minimizing $\sum w(|F_o| - |F_c|)^2$. The unit-weight observation in Table II is for $p = 0.08$ in $\sigma^2(F^2) = \sigma^2$ counts + $(pI)^2$. A final difference map showed no significant maxima. All computations were done on a MicroVaxII computer using the SDP/VAX[17d] package. The scattering factors were from ref 17e and 17f, respectively.

(17) (a) Lehman, M. S.; Larsen, F. K. *Acta Crystallogr.* **1974**, *A30*, 580. (b) Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 158. (c) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr.* **1971**, *A27*, 368. (d) Frenz, B. A.; The Enraf-Nonius CAD-4-SPD In *Computing in crystallography*; Schenk, H., Olthof-Hezekamp, R., Van Koningsveld, H., Bassi, G. C., Eds.; Delf University Press: Delf, The Netherlands, 1978; p64. (e) Cromer, D. T.; Waber, J. T. *International* Tables *for X-Ray Crystallography*, Vol. IV; The Kynoch Press: Birmingham, England, 1974; Table 2.2b. (f) Cromer, D. T. *International* Tables *for X-Ray Crystallography*, Vol. IV; The Kynoch Press: Birmingham, England, 1974; Table 2.3.1.

Acknowledgment. Thanks are due to the Fond der Chemischen Industrie for granting a Liebig-Stipendium (H.G.) and the CNRS (GRECO bases coordinences) for support of this research.

Supplementary Material Available: Table of general displacement parameter Expression-U's and hydrogen atom parameters (3 pages); observed and calculated structure factor amplitudes for all observed reflections (*10) (8 pages). Ordering information is given on any current masthead page.

Silyl Group Transfer in the Cycloaddition Reactions of Silyl Iminium Salts Derived from Aryl-Substituted Oximes

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Reaction of the iminium salt derived from benzaldehyde oxime and (trimethylsilyl)methyl triflate with cesium fluoride gives rise to azomethine ylides. Dipolar cycloaddition proceeded with complete stereospecificity with dimethyl fumarate and maleate. In sharp contrast, reaction of the salt with alkynes produces dipolar cycloadducts derived from nitrones. The different products encountered result from the operation of several competing reactions which depend on the nature of the added dipolarophile. The initial step in all cases involves removal of the OH proton by cesium fluoride to give a nitrone intermediate. Cycloaddition occurs rapidly with activated alkynes to give isoxazolines. In the presence of the slower reacting alkene, a 1,3-silicon shift to the oxygen atom occurs, giving rise to an azomethine ylide intermediate, which subsequently cycloadds to the alkene. Supporting evidence for the postulated mechanism comes from the reaction of the iminium salt with sodium hydride and also by carrying out the cycloaddition in methanol.

Organosilicon reagents have been found to play an important role in organic synthesis.[1-4] Reports from several laboratories have disclosed that the fluoride ion induced cleavage of carbon-silicon bonds represents a useful tool for the generation of carbanion equivalents.[5-13] In light of the remarkable versatility and broad synthetic utility of silicon chemistry, it is not surprising that the desilylation reactions of α-trimethylsilyl oxonium salts are becoming an increasingly popular method for 1,3-dipole generation.[14-19] In many cases, these studies have demonstrated

(1) For a review, see: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1.

(2) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981.

(3) (a) Hayashi, T.; Ito, H.; Kumada, M. *Tetrahedron Lett.* **1982**, 4605. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963. (c) Hayashi, T.; Konishi, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 281. (d) Hayashi, T.; Kabeta.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, 2865. Sakurai, H. *Pure Appl. Chem.* **1985**, *57*, 1759. (e) Yatagai, Y.; Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 4548. (f) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. (g) Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 774. (h) Maruyama, K.; Ishihara, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1981**, 4135. (i) Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1297. (j) Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1981**, 1299. (k) Keck, G. E.; Duain, E. A.; Boden, E. P.; Einholm, E. J. *Tetrahedron Lett.* **1984**, 3927. (l) Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45.

(4) (a) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (b) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinback, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989. (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, 719. (d) Heathcock, C. H.; Kiyooka, S. I.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. (e) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, 265. (f) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, 1879. (g) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, 1883.

(5) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265.

(6) Kuwajima, I.; Shimizu, M. *J. Am. Chem. Soc.* **1975**, *97*, 3257.

(7) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2348.

(8) Tamao, K.; Yoshida, J.; Masatada, T.; Yamamoto, H.; Kakui, T.; Matsumoto, H.; Kurita, A.; Kumada, M. *J. Am. Chem. Soc.* **1978**, *100*, 290.

(9) Cunico, R. F.; Dexheimer, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 2868.

(10) Chan, T. H.; Ong, B. S. *J. Org. Chem.* **1978**, *43*, 2994.

(11) Majetich, G.; Desmond, R.; Soria, J. *J. Org. Chem.* **1986**, *51*, 1753.

(12) Schinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308.

(13) Molander, G. A.; Andrews, S. W. *Tetrahedron* **1988**, *44*, 3869.

(14) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452. Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773. Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993. Vedejs, E.; Larsen, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2170.

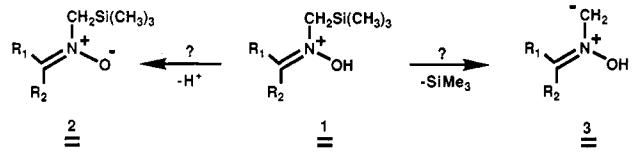
(15) Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554; *J. Chem. Soc., Chem. Commun.* **1983**, 210.

(16) Chen, S. F.; Ullrich, J. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1983**, *105*, 6160.

(17) Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Tanenaka, S. *Chem. Lett.* **1984**, 279. Tsuge, O.; Kanemasa, S.; Kuraoka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1570. Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Tanenaka, S. *Chem. Lett.* **1984**, 281. Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1985**, 1411. Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Chem. Lett.* **1984**, 801. Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *Heterocycles* **1985**, *23*, 2489.

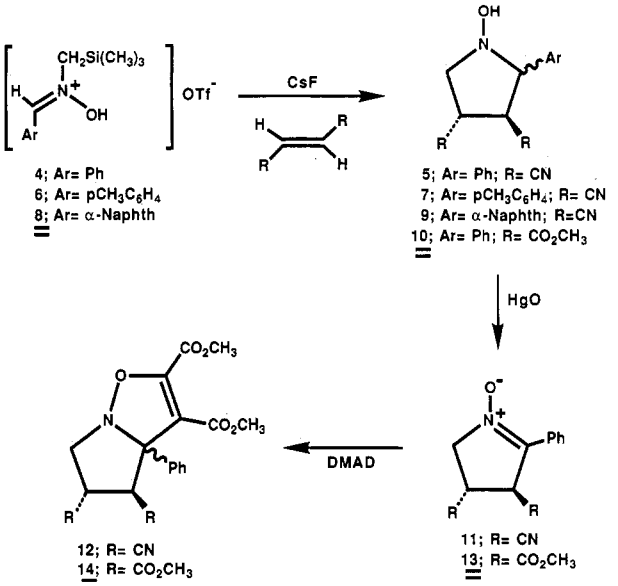
0022-3263/89/1954-4430$01.50/0

significant advantages over other methods for dipole formation. The early pioneering work by Vedejs and Martinez[14] demonstrated that α-silyl iminium salts can be prepared by imine alkylation using methyl fluorosulfonate. Desilylation with a fluoride ion source in the presence of a trapping agent produced the cycloadduct derived from an azomethine ylide dipole.[20] Continuing our own investigations in this area,[21] it occurred to us that the reaction of (trimethylsilyl)methyl triflate with oximes should give rise to iminium salts **1**, which could serve as a common precursor for both azomethine ylides and nitrones. These two species represent the most frequently used classes of 1,3-dipoles in total synthesis.[22] In this paper we report the results of these studies.[23]

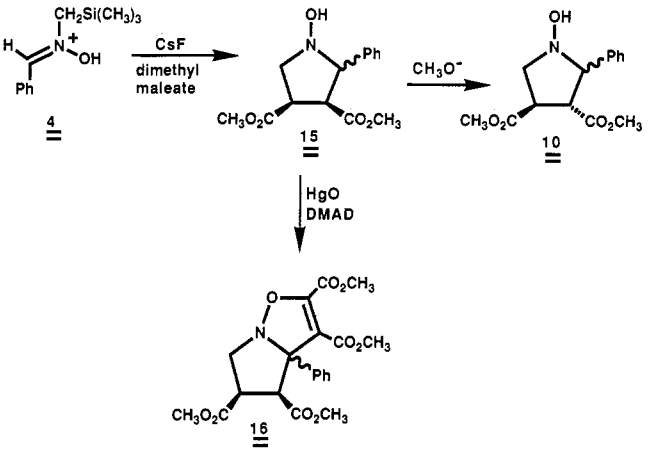


Results and Discussion

Silyl iminium salt **4** was conveniently prepared by treating benzaldehyde oxime with (trimethylsilyl)methyl triflate. The resulting solid was suspended in dimethoxyethane and treated with cesium fluoride in the presence of fumaronitrile. The two compounds isolated in near quantitative yield corresponded to a 1:1 mixture of (2*R*,3*S*,4*S*)- and (2*S*,3*S*,4*S*)-*N*-hydroxy-2-phenyl-3,4-dicyanopyrrolidine (**5a** and **5b**, respectively). The structure of **5** was supported by mercuric oxide oxidation to nitrone **11**, which undergoes ready reaction with dimethyl acetylenedicarboxylate to give the expected isoxazoline **12** derived from the double cycloaddition sequence. A related set of cycloadditions also occurred when we used the triflate salt derived from *p*-tolualdehyde oxime (**6**) as well as 1-naphthaldehyde oxime (**8**) with fumaronitrile.



In order to ascertain the stereospecificity of the reaction, we studied the cycloaddition of **4** with both dimethyl fumarate and maleate. The reaction proceeded with complete retention of olefin geometry, affording the trans (**10**) and cis (**15**) cycloadducts as the exclusive products. This result provides good support for the intermediacy of an azomethine ylide dipole since all octet-stabilized 1,3-dipoles are known to undergo stereospecific cis addition.[22] Cycloadduct **15** was readily isomerized to the thermodynamically more stable fumarate adduct **10** on treatment with sodium methoxide in methanol. Mercuric oxide oxidation of **15** followed by cycloaddition with DMAD gave isoxazoline **16** in good yield.



We have also examined the cycloaddition behavior of **4** using benzaldehyde as the trapping dipolarophile and find that nitrone **18** is produced as the major product (72%). The structure of this material was supported by its spectral properties and by its cycloaddition with DMAD to give isoxazoline **19**. The formation of **18** can be rationalized by assuming that the initially formed dipolar cycloadduct **17** undergoes ring opening followed by a subsequent proton transfer. The formation of **18** could also be the result of a stepwise HF-catalyzed imino aldol like addition. Further work is necessary to distinguish between these two possibilities.

(18) Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167. Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213. Achiwa, K.; Motoyama, T.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 3939. Achiwa, K.; Sekiya, M. *Heterocycles* **1983**, *20*, 167. Achiwa, K.; Imai, N.; Inaoka, T.; Sekiya, M. *Chem. Pharm. Bull.* **1984**, *32*, 2878. Imai, N.; Terao, Y.; Achiwa, K. *Heterocycles* **1985**, *23*, 1107. Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1982**, *23*, 2589. Achiwa, K.; Imai, N.; Motoyama, T.; Sekiya, M. *Chem. Lett.* **1984**, 2041. Imai, N.; Terao, Y.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1984**, *25*, 1579.

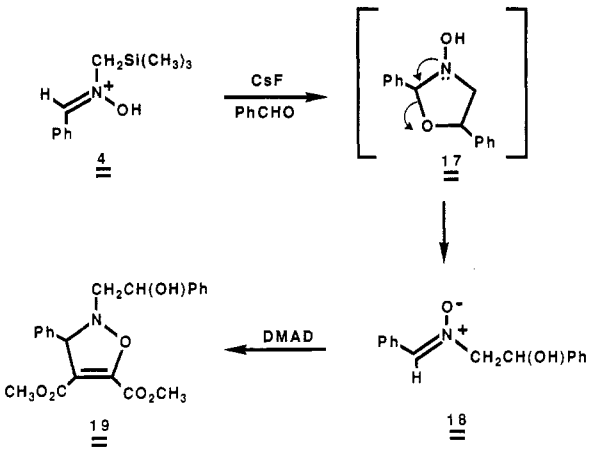
(19) Miki, Y.; Hachiken, H.; Takemura, S.; Ikeda, M. *Heterocycles* **1984**, *22*, 701.

(20) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941. Vedejs, E. In *Advances in Dipolar Cycloaddition Chemistry*; Curran, D. Ed.; JAI: Greenwich, CT, 1988.

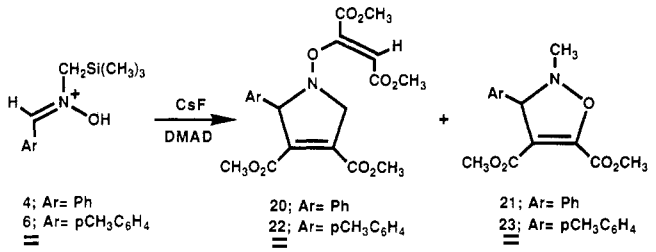
(21) Padwa, A.; Chen, Y. Y.; Koehler, K. F.; Tomas, M. *Bull. Soc. Chim. Belg.* **1983**, *92*, 811. Padwa, A.; Haffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, 4303. Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314. Padwa, A.; Chiacchio, U.; Venkatramanan, M. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1108. Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235. Padwa, A.; Chen, Y. Y. *Tetrahedron Lett.* **1983**, 3447. Padwa, A.; Chen, Y. Y.; Dent, W.; Nimmesgern, H. *J. Org. Chem.* **1985**, *50*, 4006. Padwa, A.; Dent, W.; Parker, K. A.; Cohen, I. D. *Tetrahedron Lett.* **1984**, 4917. Padwa, A.; Chen, Y. Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529. Padwa, A.; Dent, W.; Tomas, M.; Chen, Y. Y.; Chiacchio, U. *J. Heterocycl. Chem.* **1985**, *22*, 21. Padwa, A.; Gasdaska, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 1104.

(22) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, NY, 1984.

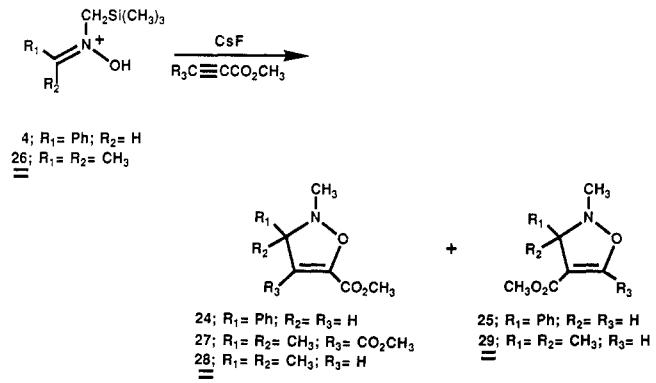
(23) For a preliminary report, see: Padwa, A.; Dent, W.; Yeske, P. E. *J. Org. Chem.* **1987**, *52*, 3946.



Since we were interested in the synthetic utility of these iminium salts, we undertook a systematic study of the cycloaddition with a number of related dipolarophiles. Interestingly, the reaction of **4** with DMAD under the standard conditions afforded cycloadduct **20** (80%) as well as the dipolar cycloadduct **21** (20%) formally derived from *N*-methyl-*C*-phenylnitrone. This structure was verified by comparison with an authentic sample.[24] An analogous set of results was obtained by using iminium salt **6** derived from *p*-tolualdehyde oxime.

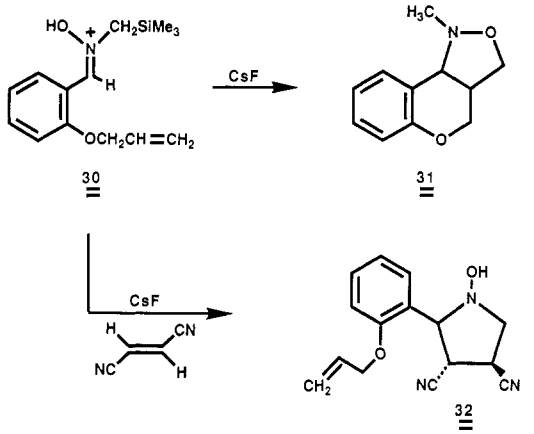


The above observation prompted us to examine the reaction between iminium salt **4** and methyl propiolate. We found that in this case the reaction only afforded isoxazolines **24** and **25** (1:2 mixture). The structures were established by comparison with independently synthesized samples.[24] It should be noted that the ratio of isoxazolines derived from the desilylation reaction of **4** corresponds to the same ratio of products obtained from the reaction of *N*-methyl-*C*-phenylnitrone and methyl propiolate.[24] This observation clearly implicates a nitrone intermediate in the desilylation reaction of **4** with the activated acetylene.



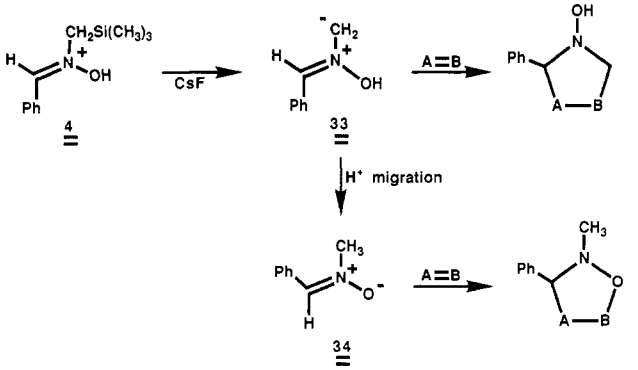
A similar cycloaddition was also found to occur when the silyl iminium salt **26** derived from acetone oxime was treated with fluoride in the presence of activated acetylenes. Thus, treatment of **26** with cesium fluoride and DMAD afforded the nitrone cycloadduct **27** in 75% yield. Formation of a 1:3.5 mixture of isoxazoline cycloadducts **28** and **29** was observed when methyl propiolate was used as the dipolarophile.

We also studied the cycloaddition reaction of the triflate salt derived from *o*-(allyloxy)benzaldehyde oxime (**30**) with cesium fluoride. The intramolecular cycloadduct isolated (85%) from the reaction (i.e., **31**) also corresponds to a product that is formally derived from an *N*-methyl-*C*-arylnitrone.[25] Most interestingly, the silyl iminium salt **30** gave cycloadduct **32** as the exclusive product when it was treated with cesium fluoride in the presence of fumaronitrile. This compound corresponds to the dipolar cycloaddition product derived from an azomethine ylide intermediate. No significant quantities of the intramolecular cycloadduct **31** could be detected in the crude reaction mixture by NMR analysis. Thus, *silyl iminium salt **30** is behaving as a 1,3-dipole chameleon: it reacts as either an azomethine ylide or a nitrone precursor, depending on the nature of the dipolarophile.*



At first glance it would appear that the bimolecular cycloaddition reactions of these silyl iminium salts proceed via an initial desilylation to give an azomethine ylide intermediate (**3**). This species could either cycloadd to the available dipolarophile or undergo proton transfer from carbon to oxygen to give *N*-methylnitrone **34**. This mechanism (path A) would require that dipolarophiles

PATH A



such as fumaronitrile or methyl fumarate cycloadd to the azomethine ylide at a much faster rate than methyl propiolate or dimethyl acetylenedicarboxylate. It is well-known that azomethine ylides prefer to react with π-bonds possessing strongly electron withdrawing groups since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap.[26] Since azomethine ylide cyclo-

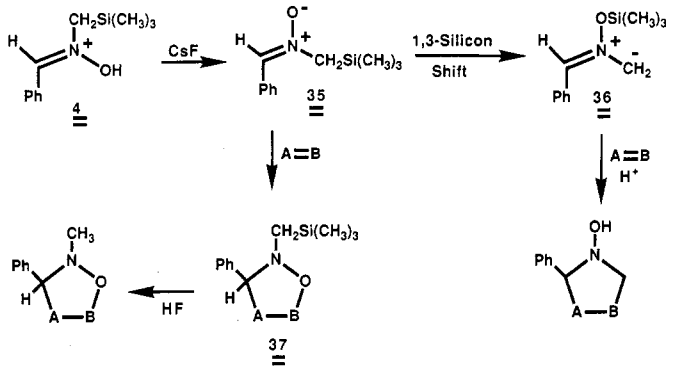
(24) Huisgen, R.; Seidl, H.; Bruning, I. *Chem. Ber.* **1969**, *102*, 1102.

(25) Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, 1117.

additions are LUMO-controlled processes,[27] the mechanism outlined in path A seems unreasonable. In fact, reaction of iminium salt **4** with a 1:1 mixture of methyl propiolate and fumaronitrile in the presence of cesium fluoride only afforded the nitrone cycloadducts **28** and **29**, thereby eliminating the above path.

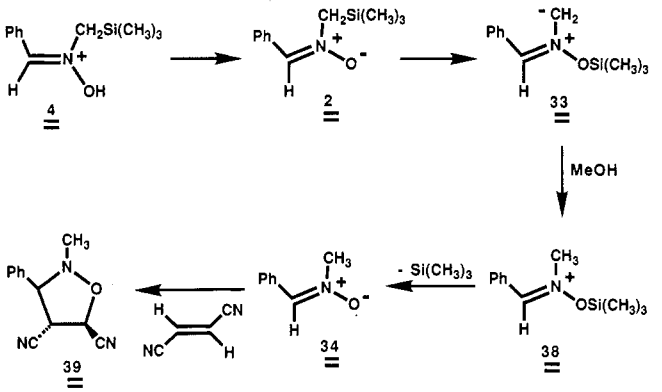
We propose that the different products encountered result from the operation of alternate paths which depend on the nature of the added dipolarophile. The initial step in all cases involves removal of the OH proton by cesium fluoride to give a nitrone intermediate. The rate of nitrone cycloaddition to electron-deficient alkynes is known to be much greater than to their alkenyl counterparts.[28] In the presence of the slower reacting alkene, a 1,3-silicon shift to the oxygen atom occurs, giving rise to azomethine ylide **36**, which undergoes a subsequent cycloaddition (path B).

PATH B

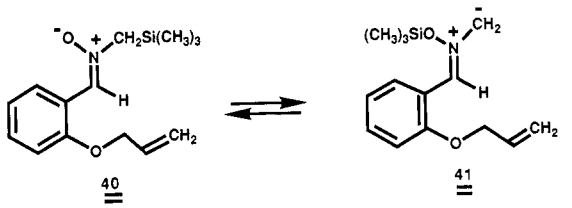


The initially formed cycloadduct **37** is readily converted to the *N*-methylnitrone adduct under the reaction conditions.[29] Undoubtedly, replacement of the weaker C–Si bond by a stronger O–Si bond provides the driving force for the rearrangement. There are a number of related anionic silyl shifts reported in the literature, thereby providing good analogy for the overall transformation.[30-41]

Supporting evidence for pathway B was obtained by treating silyl iminium salt **4** with sodium hydride in the presence of fumaronitrile. The isolation of cycloadduct **5** under these conditions provides good support for the initial proton removal step, which is then followed by the silyl shift. Interestingly, when a small amount of methanol is added to the reaction mixture using CsF, nitrone cycloadduct **39** was also formed (40%) in addition to pyrrolidine **5**. When methanol was used as the solvent, however, cycloadduct **39** was the only product isolated. The formation of **39** can be rationalized by assuming that methanol protonates the methylenic carbon atom of the azomethine ylide dipole. The resulting species (i.e., **38**) is readily desilylated to give *N*-methylnitrone **34**, which subsequently cycloadds to fumaronitrile to produce **39**.



The chemistry encountered with silyl iminium salt **30** merits some comment. Isolation of the intramolecular cycloadduct **31** implies that the initially formed silyl-substituted nitrone undergoes cycloaddition to the adjacent π-bond. What is so surprising is that pyrrolidine **32** is the major product (60%) isolated when fumaronitrile is used as the trapping agent. This would imply that there is an equilibration between dipoles **40** and **41**. Apparently the bimolecular addition of azomethine ylide **41** with an activated alkene such as fumaronitrile is significantly faster than intramolecular cycloaddition of nitrone **40** with the unactivated alkenyl π-bond. The formation of intramolecular cycloadduct **31** is also consistent with this mechanism since azomethine ylides are generally unreactive toward simple alkenes.[27] In support of the above suggestion, it should be noted that Mora and Costa have reported that reversible 1,4-migration of a silyl group can occur from oxygen to carbon.[41] These workers have found that anions generated from trialkylsilyl ethers of methyl ketoximes (**42**) undergo anionic rearrangement with 1,4-migration of the silyl group. After protonation, the resulting α-trialkylsilyl ketoxime undergoes a subsequent rearrangement with 1,4-migration of the silyl group from carbon to oxygen. Presumably the rearrangement occurs via the intermediacy of a pentavalent silicon anion,[42,43] thus establishing an effective equilibrium between the starting carbanion and the oxymate anion.



(26) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

(27) The reactivity of azomethine ylides with simple π-bonds often depends on how the dipole is generated; see: Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235. Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554. Confalone, P. N.; Huie, E. *J. Am. Chem. Soc.* **1984**, *106*, 7175. Chastanet, J.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 2910. Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1988**, *44*, 4953.

(28) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 9.

(29) All attempts to isolate cycloadduct **37** failed. We were not able to unequivocally establish its presence in the crude NMR spectrum as a consequence of the overlap of several trimethylsilyl singlets around 0 ppm.

(30) Rucker, C. *Tetrahedron Lett.* **1984**, 4349.

(31) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371.

(32) Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1987**, 5965.

(33) Van Boeckel, C. A. A.; Van Aelst, S. F.; Beetz, T. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 415.

(34) Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1983**, *31*, 2607.

(35) Daney, M.; Lapouyade, R.; Bouas-Laurent, H. *J. Org. Chem.* **1983**, *48*, 5055.

(36) Fall, Y.; Bac, N. V.; Langlois, Y. *Tetrahedron Lett.* **1986**, 3611.

(37) Ochiai, M.; Sumi, K.; Fujita, E.; Shiro, M. *Tetrahedron Lett.* **1982**, 5419.

(38) Muchowski, J. M.; Naef, R.; Maddox, M. L. *Tetrahedron Lett.* **1985**, 5375.

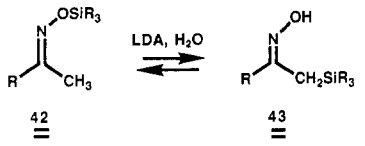
(39) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809.

(40) Green, J. R.; Majewski, M.; Alo, B. I.; Snieckus, V. *Tetrahedron Lett.* **1986**, 535.

(41) Mora, J.; Costa, A. *Tetrahedron Lett.* **1984**, 3493.

(42) Eisch, J. J.; Tsai, M. R. *J. Organomet. Chem.* **1982**, *225*, 5.

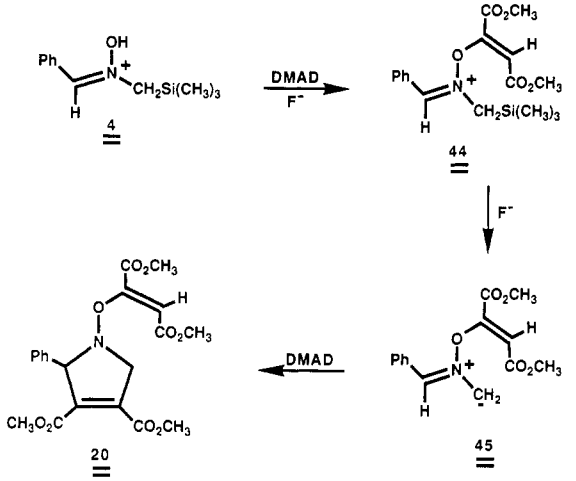
(43) Wilson, S. R.; Georgiadis, G. M. *J. Org. Chem.* **1983**, *48*, 4143.



42 43

One final point has to do with the reaction of silyl iminium salt 4 and DMAD. In this case, the major product isolated corresponds to a 2:1 cycloadduct (**20**) seemingly derived from an azomethine ylide intermediate. We believe that the formation of this material proceeds by still another pathway (i.e., path C). Most likely the salt reacts by conjugate addition onto the highly activated π-bond of DMAD to produce structure **44** as a transient species.

Path C



4 44 20 45

Desilylation affords azomethine ylide **45**, which undergoes dipolar cycloaddition with additional DMAD to give the observed 2:1 cycloadduct **20**. This result stands in contrast to the chemistry encountered with methyl propiolate, where a mixture of typical nitrone cycloadducts was produced. Apparently there is a delicate balance between dipolar cycloaddition versus conjugate addition to the acetylenic π-bond. Moreover, the competition depends on the nature of the substituent groups present on the alkyne.

In conclusion, the cesium fluoride induced desilylation of trimethylsilyl-substituted iminium salts derived from aryl oximes provides access to both *N*-hydroxy-substituted azomethine ylides and *N*-methylnitrones. The distribution of products depends on the nature of the dipolarophile used. Further studies on the scope and reactivity of trimethylsilyl iminium salts derived from oximes and the schizophrenic behavior of these dipole precursors will be reported in due course.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390, a Nicolet 360, and a General Electric QE 300 spectrometer. ^{13}C NMR spectra were recorded on a GE QE 300 spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Cycloaddition of the Triflate Salt Derived from Benzaldehyde Oxime (4) with Fumaronitrile. To 200 mg (1.65 mmol) of benzaldehyde oxime at 0 °C was added 390 mg (1.75 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 12 h. The solid that formed was diluted with 8 mL of anhydrous dimethoxyethane, and 130 mg (1.67 mmol) of fumaronitrile was added. This solution was cannulated into a flask containing 350 mg (2.30 mmol) of dry cesium fluoride in 2 mL of dimethoxyethane.[44] The mixture was stirred overnight and concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using a 25% ethyl acetate–hexane solution as the eluent. The first fraction isolated (45%) was recrystallized from ethyl acetate–hexane to give (2*R*,3*S*,4*S*)-*N*-hydroxy-2-phenyl-3,4-dicyanopyrrolidine (**5a**)[45] as a yellow solid: mp 136–137 °C; IR (KBr) 3160, 2960, 2840, 2260, 1440, 1210, 1050, 1010, 840, 750, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.5–3.6 (m, 3 H), 3.75 (d, 1 H, J = 8.3 Hz), 4.27 (d, 1 H, J = 9.5 Hz), 5.17 (br s, 1 H), and 7.43 (s, 5 H). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.50; H, 5.24; N, 19.65.

The mother liquors were concentrated under reduced pressure, and the resulting residue was subjected to flash chromatography using a 25% acetone–hexane mixture as the eluent to give (2*S*,3*S*,4*S*)-*N*-hydroxy-2-phenyl-3,4-dicyanopyrrolidine (**5b**) (40%) as a yellow crystalline solid: mp 96–97 °C; IR (KBr) 3180, 2960, 2820, 2240, 1440, 1210, 1040, 760, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.27 (dd, 1 H, J = 10.6 and 9.0 Hz), 3.54 (dd, 1 H, J = 9.0 and 8.0 Hz), 3.71 (d, 1 H, J = 8.0 Hz), 3.92 (dd, 1 H, J = 10.6 and 8.0 Hz), 4.33 (d, 1 H, J = 8.0 Hz), 5.20 (br s, 1 H), and 7.45 (s, 5 H); MS, m/e 213, 195, 194, 193, 168, 140, 135, 118 (base), and 91. Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.51; H, 5.28; N, 19.68.

To a solution containing 200 mg (0.94 mmol) of **5a** in 5 mL of chloroform at −10 °C was added 710 mg (3.28 mmol) of mercuric oxide. After stirring for 3 h, 200 mg of magnesium sulfate was added and the mixture was stirred for an additional hour. The reaction mixture was filtered through a magnesium sulfate pad and concentrated under reduced pressure. The crude nitrone was dissolved in 4 mL of toluene, and 0.14 mL (1.14 mmol) of dimethyl acetylenedicarboxylate was added. The solution was heated at reflux for 12 h, then the solvent was removed under reduced pressure, and the crude residue was chromatographed on a silica gel column using a 30% acetone–hexane mixture as the eluent. The major fraction (85%) corresponded to a yellow solid, mp 55–56 °C, whose structure was assigned as (3a*R*,4*R*,5*R*)-3a,4,5,6-tetrahydro-3a-phenyl-2,3-dicarbomethoxy-4,5-dicyanopyrrolo[1,2-*b*]-isoxazole (**12**) on the basis of its spectral properties: IR (neat) 3020, 2970, 2220, 1750, 1720, 1630, 1450, 1370, 1220, 1170, 1040, and 710 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.53 (d, 1 H, J = 9.4 Hz), 3.56 (s, 3 H), 3.76 (m, 1 H), 3.78 (s, 3 H), 4.03 (m, 1 H), 4.20 (dd, 1 H, J = 10.6 and 7.4 Hz), and 7.3–7.5 (m, 5 H); UV (95% ethanol) 272 nm (ϵ 11 400). Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.32; H, 4.20; N, 11.83.

The reaction was also carried out by using methanol as the solvent. To 300 mg (2.48 mmol) of benzaldehyde oxime at 0 °C was added 590 mg (2.65 mmol) of (trimethylsilyl)methyl triflate dropwise, and the mixture was stirred for 12 h. The resulting solid was diluted with 10 mL of anhydrous methanol, and 200 mg (2.56 mmol) of fumaronitrile was added. This solution was cannulated into a flask containing 500 mg (3.29 mmol) of dry cesium fluoride in 5 mL of methanol. The solution was stirred overnight and concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using a 25% acetone–hexane solution as the eluent. The major fraction (87%) isolated from the column corresponded to *trans*-2-methyl-3-phenyl-4,5-dicyanoisoxazolidine (**39**) as a clear oil, whose structure was based on its spectral properties and by comparison to an authentic sample:[24] NMR ($CDCl_3$, 360 MHz) δ 2.72 (s, 3 H), 3.70 (dd, 1 H, J = 8.2 and 2.9 Hz), 3.74 (d, 1 H, J = 8.2 Hz), 5.06 (d, 1 H, J = 2.9 Hz), and 7.3–7.5 (m, 5 H).

Cycloaddition of the Triflate Salt Derived from *p*-Tolualdehyde Oxime (6) with Fumaronitrile. To a 279-mg (2.06 mmol) sample of *p*-tolualdehyde oxime was added 500 mg (2.25 mmol) of freshly distilled (trimethylsilyl)methyl triflate, and the

(44) An equivalent amount of sodium hydride was also used in a separate experiment, and only cycloadducts **5a** and **5b** were isolated.

(45) The *R,S* notation is used to describe diastereoselectivity and not enantioselectivity.

mixture was sonicated for 20 min under nitrogen. The solution became increasingly viscous, and after 20 min, the white triflate salt **6** appeared. The salt was dissolved in 10 mL of dimethoxyethane, and 163 mg (2.09 mmol) of fumaronitrile was added. The solution was cannulated into a flask containing 377 mg (2.48 mmol) of cesium fluoride, and the mixture was stirred overnight and then concentrated under reduced pressure. Water was added, and the solution was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and was concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 25% ethyl acetate–hexane solution as the eluent. The major fraction contained 160 mg (56%) of a yellow solid, which was recrystallized from ethyl acetate–hexane to give (2*R*,3*S*,4*S*)-*N*-hydroxy-2-*p*-tolyl-3,4-dicyanopyrrolidine (**7a**) as a yellow solid: mp 164–165 °C; IR (KBr) 3180 (br s), 2980, 2255, 1440, 1210, 1090, 1035, 1010, 810, and 770 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3 H), 3.52 (m, 3 H), 3.70 (d, 1 H, J = 10.7 Hz), 4.20 (d, 1 H, J = 10.7 Hz), 5.08 (s, 1 H), and 7.26 (m, 4 H); MS, m/e 227 (M^+), 209, 182, 122, and 105; HRMS calcd for $C_{13}H_{13}N_3O$ 227.1059, found 227.1061.

The mother liquors from the above crystallization were concentrated to a small volume under reduced pressure. The resulting residue contained a clear oil (15%), whose structure was assigned as (2*S*,3*S*,4*S*)-*N*-hydroxy-2-*p*-tolyl-3,4-dicyanopyrrolidine (**7b**); IR (KBr) 3180 (br s), 2970, 2260, 1445, 1210, 1040, 1015, 810, and 770 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3 H), 3.20 (dd, 1 H, J = 10.5 and 9.0 Hz), 3.65 (dd, 1 h, J = 9.0 and 8.5 Hz), 3.80 (m, 2 H), 4.27 (d, 1 H, J = 8.5 Hz), 5.16 (d, 1 H, J = 8.5 Hz), and 7.25 (m, 4 H); HRMS calcd for $C_{13}H_{13}N_3O$ 227.1059, found 227.1053.

Cycloaddition of the Triflate Salt Derived from 1-Naphthaldehyde Oxime (8) with Fumaronitrile. To a 353-mg (2.06 mmol) sample of 1-naphthaldehyde oxime was added 500 mg (2.25 mmol) of (trimethylsilyl)methyl triflate, and the mixture was sonicated for 1 h under nitrogen and was then stirred overnight. The resulting salt was diluted with 15 mL of anhydrous dimethoxyethane, and 163 mg (2.09 mmol) of fumaronitrile was added. The solution was cannulated into a flask containing 377 mg (2.48 mmol) of dry cesium fluoride, and the mixture was stirred overnight and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using a 35% ethyl acetate–hexane mixture as the eluent. The major fraction isolated (33%) was identified as (2*R*,3*S*,4*S*)-*N*-hydroxy-2-(1-naphthyl)-3,4-dicyanopyrrolidine (**9a**): mp 164–165 °C; IR (KBr) 3400 (br s), 2980, 2260, 1520, 940, 800, 790, and 740 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.38 (dd, 2 H, J = 14.1 and 7.2 Hz), 3.64 (m, 2 H), 4.90 (d, 1 H, J = 8.7 Hz), 5.63 (br s, 1 H), 7.44 (m, 4 H), 7.77 (t, 2 H, J = 7.0 Hz), and 8.02 (d, 1 H, J = 7.0 Hz); MS, m/e 263 (M^+), 245, 218, 168, 128, and 69; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1058, found 263.1056.

The minor product (32%) consisted of a white solid, mp 147–148 °C, whose structure was assigned as (2*S*,3*S*,4*S*)-*N*-hydroxy-2-(1-naphthyl)-3,4-dicyanopyrrolidine (**9b**): IR (KBr) 3400 (br s), 3060, 2960, 2255, 1510, 1400, 910, 780, and 730 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.20 (t, 1 H, J = 9.6 Hz), 3.33 (m, 1 H), 3.55 (m, 1 H), 3.81 (m, 1 H), 4.92 (d, 1 H, J = 8.1 Hz), 5.27 (br s, 1 H), 7.42 (m, 4 H), 7.78 (m, 2 H), and 8.03 (d, 1 H, J = 9.0 Hz); HRMS calcd for $C_{16}H_{13}N_3O$ 263.1058, found 263.1051.

Cycloaddition of the Triflate Salt Derived from Benzaldehyde Oxime (4) with Dimethyl Fumarate. To 200 mg (1.65 mmol) of benzaldehyde oxime at 0 °C was added 390 mg (1.75 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 12 h. The resulting solid was diluted with 8 mL of anhydrous dimethoxyethane, and 240 mg (1.67 mmol) of dimethyl fumarate was added. This solution was cannulated into a flask containing 350 mg (2.30 mmol) of dry cesium fluoride in 2 mL of dimethoxyethane. The mixture was stirred overnight and concentrated under reduced pressure. Water was added and the solution extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using a 20% acetone–hexane solution as the eluent. The first fraction isolated (34%) was recrystallized from ethyl acetate–hexane to give (2*R*,3*S*,4*S*)-*N*-hydroxy-2-phenyl-3,4-dicarbomethoxypyrrolidine (**10a**) as a white crystalline solid: mp 102–103 °C; IR (KBr) 3270, 3000, 2960, 2900, 1750, 1460, 1440, 1350, 1300, 1260, 1230, 1170, 1030, 1020, 920, 760, and 710 cm^{-1}; NMR ($CDCl_3$) δ 3.09 (dd, 1 H, J = 10.1 and 8.8 Hz), 3.13 (s, 3 H), 3.62–3.82 (m, 3 H), 3.75 (s, 3 H), 4.25 (d, 1 H, J = 9.7 Hz), 5.15 (s, 1 H), and 7.3–7.4 (m, 5 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.15; H, 6.18; N, 5.01.

The mother liquors were concentrated under reduced pressure, and the resulting residue was recrystallized from ethyl acetate–hexane to yield (2*S*,3*S*,4*S*)-*N*-hydroxy-2-phenyl-3,4-dicarbomethoxypyrrolidine (**10b**) (32%) as a white crystalline solid: mp 77–78 °C; IR (KBr) 3150, 2960, 1750, 1440, 1390, 1330, 1250, 1210, 1180, 1020, 770, and 710 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.29 (t, 1 H, J = 9.8 Hz), 3.48 (m, 1 H), 3.7–3.8 (m, 2 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 4.05 (d, 1 H, J = 9.8 Hz), 4.85 (br s, 1 H), and 7.3–7.5 (m, 5 H); MS, m/e 279, 262, 248, 230, 202, 201, 177, 170, 143, 127, 118 (base), 99, and 91. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.09; H, 6.19; N, 5.00.

To a solution containing 470 mg (1.68 mmol) of **10a** in 6 mL of chloroform at −10 °C was added 880 mg (4.06 mmol) of mercuric oxide. After stirring for 3 h, 200 mg of magnesium sulfate was added and the mixture was stirred for an additional hour. The reaction mixture was filtered through a magnesium sulfate pad and concentrated under reduced pressure. The crude nitrone was dissolved in 7 mL of toluene, and 0.21 mL (1.71 mmol) of dimethyl acetylenedicarboxylate was added. The mixture was heated at reflux for 12 h, then the solvent was removed under reduced pressure, and the crude residue was chromatographed on a silica gel column using a 20% acetone–hexane mixture as the eluent. The gummy yellow solid was recrystallized from ether to give 95 mg (60%) of (3a*R*,4*R*,5*R*)-3a,4,5,6-tetrahydro-3a-phenyl-2,3,4,5-tetracarbomethoxypyrrolo[1,2-*b*]isoxazole (**14**) as a white crystalline solid: mp 104–105 °C; IR (KBr) 3000, 2960, 1750, 1720, 1660, 1440, 1350, 1310, 1230, 1210, 1170, 1140, 1100, 980, 760, and 710 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.24 (s, 3 H), 3.57 (ddd, 1 H, J = 8.6, 6.9, and 6.8 Hz), 3.68 (dd, 1 H, J = 11.0 and 8.6 Hz), 3.73 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.14 (dd, 1 H, J = 11.0 and 6.9 Hz), 4.56 (d, 1 H, J = 6.8 Hz), and 7.2–7.6 (m, 5 H); UV (95% ethanol) 266 (ϵ 4230). Anal. Calcd for $C_{20}H_{21}NO_9$: C, 57.28; H, 5.05; N, 3.34. Found: C, 57.25; H, 5.11; N, 3.29.

Cycloaddition of the Triflate Salt Derived from Benzaldehyde Oxime (4) with Dimethyl Maleate. To 200 mg (1.65 mmol) of benzaldehyde oxime at 0 °C was added 390 mg (1.75 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 12 h. The resulting solid was diluted with 8 mL of anhydrous dimethoxymethane, and 240 mg (1.67 mmol) of dimethyl maleate was added. This solution was cannulated into a flask containing 350 mg (3.29 mmol) of dry cesium fluoride in 2 mL of dimethoxyethane. The reaction mixture was stirred overnight and concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using a 25% acetone–hexane solution as the eluent. The major fraction (75%) was recrystallized from ethyl acetate–hexane to give (2*R*,3*R*,4*S*)-*N*-hydroxy-2-phenyl-3,4-dicarbomethoxypyrrolidine (**15**) as a white crystalline solid: mp 120–121 °C; IR (KBr) 3210, 2940, 1750, 1440, 1360, 1305, 1270, 1200, 1180, 950, 760, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.42 (t, 1 H, J = 9.8 Hz), 3.51 (m, 1 H), 3.6–3.8 (m, 2 H), 3.63 (s, 3 H), 3.71 (s, 3 H), 4.31 (d, 1 H, J = 9.8 Hz), 4.78 (br s, 1 H), and 7.3–7.5 (m, 5 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.07; H, 6.15; N, 5.02.

To a solution containing 210 mg (0.75 mmol) of **15** in 3 mL of chloroform at −10 °C was added 400 mg (1.85 mmol) of mercuric oxide. After stirring for 3 h, 200 mg of magnesium sulfate was added and the mixture was stirred for an additional hour. The reaction mixture was filtered through a magnesium sulfate pad and concentrated under reduced pressure. The crude nitrone was dissolved in 4 mL of toluene, and 0.10 mL (0.81 mmol) of dimethyl acetylenedicarboxylate was added. The mixture was heated at reflux for 12 h, then the solvent was removed under reduced pressure, and the crude residue was chromatographed on a silica gel column using a 25% acetone–hexane mixture as the eluent. The major fraction (60%) corresponded to a yellow oil, whose structure was assigned as (3a*R*,4*R*,5*S*)-3a,4,5,6-tetrahydro-3a-phenyl-2,3,4,5-tetracarbomethoxypyrrolo[1,2-*b*]isoxazole (**16**) on the basis of its spectral properties: IR (neat) 3000, 2960, 1740, 1440, 1300, 1210, 1170, 1040, 920, 730, and 710 cm^{-1}; NMR ($CDCl_3$,

360 MHz) δ 3.68 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 4.10 (dd, 1 H, J = 13.6 and 1.6 Hz), 4.29 (dd, 1 H, J = 13.6 and 9.5 Hz), 4.50 (dd, 1 H, J = 8.5 and 1.6 Hz), 4.86 (d, 1 H, J = 9.5 Hz), and 7.2–7.4 (m, 5 H); UV (95% ethanol) 270 nm (ε 2500). Anal. Calcd for $C_{20}H_{21}NO_9$: C, 57.28; H, 5.05; N, 3.34. Found: C, 57.09; H, 5.06; N, 3.29.

Cycloaddition of the Triflate Salt of Benzaldehyde Oxime (4) with Benzaldehyde. To 180 mg (1.49 mmol) of benzaldehyde oxime at 0 °C was added 350 mg (1.57 mmol) of (trimethylsilyl)methyl triflate, and the mixture was stirred for 10 h. The crude triflate salt was dissolved in 3 mL of anhydrous dimethoxymethane, and 0.15 mL (1.49 mmol) of benzaldehyde was added. This solution was cannulated into a flask containing 300 mg (1.97 mmol) of dry cesium fluoride in 1 mL of dimethoxyethane, and the mixture was stirred at room temperture for 12 h. The solvent was removed under reduced pressure, and the crude residue was diluted with water and extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 20% acetone–hexane mixture as the eluent to give 180 mg (55%) of a white solid, mp 160–161 °C, whose structure was assigned as *N*-(2-hydroxy-2-phenylethyl)-*C*-phenylnitrone (**18**) on the basis of its spectral properties: IR (KBr) 3300–3000, 1600, 1490, 1450, 1420, 1330, 1150, 1070, 950, 750, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 4.08 (dd, 1 H, J = 12.6 and 8.4 Hz), 4.17 (dd, 1 H, J = 12.6 and 2.6 Hz), 5.26 (d, 1 H, J = 3.0 Hz), 5.36 (ddd, 1 H, J = 8.4, 3.0, and 2.6 Hz), 7.3–7.8 (m, 9 H), 8.24 (d, 1 H, J = 7.7 Hz), and 8.25 (d, 1 H, J = 5.5 Hz); UV (95% ethanol) 296 nm (ε 19300); MS, m/e 241, 221, 206, 196, 165, 135, 122, 118 (base), 105, 91, and 77. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.59; H, 6.33; N, 5.76.

To a solution containing 200 mg (0.83 mmol) of *N*-(2-hydroxy-2-phenylethyl)-*C*-phenylnitrone (**18**) in 7 mL of toluene was added 0.1 mL (0.81 mmol) of dimethyl acetylenedicarboxylate, and the mixture was heated at reflux for 24 h. The solvent was concentrated under reduced pressure, and the residue was chromatographed on a silica gel column using a 20% acetone–hexane solution as the eluent. The major fraction (70%) obtained was recrystallized from methylene chloride–hexane to give 4,5-dicarbomethoxy-3-phenyl-*N*-(2-hydroxy-2-phenylethyl)isoxazoline (**19**) as a yellow solid: mp 78–79 °C; IR (KBr) 3300–3000, 1750, 1720, 1660, 1490, 1450, 1150, 1070, 970, 750, and 710 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.97 (dd, 1 H, J = 12.6 and 8.4 Hz), 3.25 (dd, 1 H, J = 12.5 and 2.5 Hz), 3.73 (s, 3 H), 3.83 (s, 3 H), 4.30 (s, 1 H), 5.09 (dd, 1 H, J = 8.4 and 2.5 Hz), and 7.2–7.4 (m, 10 H). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.69; H, 5.49; N, 3.63.

Cycloaddition of the Triflate Salt of Benzaldehyde Oxime (4) with Dimethyl Acetylenedicarboxylate. To 436 mg (3.60 mmol) of benzaldehyde oxime at 0 °C was added 870 mg (3.91 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 12 h. The crude triflate salt was diluted with 15 mL of anhydrous dimethoxymethane, and 0.88 mL (7.18 mol) of dimethyl acetylenedicarboxylate was added. This solution was cannulated into a flask containing 650 mg (4.28 mmol) of dry cesium fluoride in 5 mL of dimethoxyethane. The reaction mixture was stirred overnight and concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 25% ethyl acetate–hexane solution as the eluent. The first fraction (80%) contained a yellow oil, whose structure was assigned as 3,4-dicarbomethoxy-1-[(1,2-dicarbomethoxyvinyl)oxy]-2-phenylpyrroline (**20**): IR (neat) 3050, 2975, 1730, 1605, 1435, 1270, 730 and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.54 (s, 3 H), 3.57 (s, 3 H), 3.64 (s, 3 H), 3.79 (s, 3 H), 3.94 (d, 1 H, J = 17.0 Hz), 4.15 (d, 1 H, J = 17.0 Hz), 5.14 (s, 1 H), 5.67 (s, 1 H), and 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.3, 51.3, 52.5, 52.7, 52.9, 80.3, 93.3, 128.4, 128.5, 129.0, 129.6, 134.0, 138.9, 151.4, 163.3, 164.1, 165.3, and 166.2; MS, m/e 419 (M^+), 388, 327, 259, 228, and 105; HRMS calcd for $C_{20}H_{21}NO_9$ 419.1216, found 419.1215.

The second fraction (20%) contained a colorless oil, whose structure was assigned as 4,5-dicarbomethoxy-3-phenyl-*N*-methylisoxazoline (**21**) on the basis of its spectral properties: NMR ($CDCl_3$, 360 MHz) δ 3.00 (s, 3 H), 3.66 (s, 3 H), 3.95 (s, 3 H), 5.05 (s, 1 H), and 7.3–7.5 (m, 5 H). The structure of this latter material was verified by comparison with an independently synthesized material.[24] A solution containing 0.86 mL (7.04 mmol) of dimethyl acetylenedicarboxylate and 900 mg (6.65 mmol) of *N*-methyl-*C*-phenylnitrone (**34**) in 150 mL of benzene was heated at 50 °C for 10 h. Removal of the solvent left an oily residue, which was chromatographed on silica gel to give a colorless oil, whose structure was identical in every detail with a sample obtained from the cycloaddition of the triflate salt of benzaldehyde oxime with dimethyl acetylenedicarboxylate.

Cycloaddition of the Triflate Salt of *p*-Tolualdehyde Oxime (6) with Dimethyl Acetylenedicarboxylate. To a 1.35-g (10.0 mmol) sample of *p*-tolualdehyde oxime was added 2.48 g (11.1 mmol) of (trimethylsilyl)methyl triflate dropwise under a nitrogen atmosphere, and the mixture was sonicated for 20 min at 25 °C until the white triflate salt **6** had formed. The triflate salt could be stored under nitrogen for periods up to 3 days without significant decomposition. The salt was dissolved in 35 mL of dimethoxyethane, and 1.23 mL (10.0 mmol) of dimethyl acetylenedicarboxylate was added. The solution was cannulated into a flask containing 1.52 g (10.0 mmol) of dry cesium fluoride, and the mixture was stirred overnight at 25 °C and then concentrated under reduced pressure. Water was added, and the solution was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using a 25% ethyl acetate–hexane solution as the eluent, to give 840 mg (40%) of a pale yellow oil, whose structure was assigned as 3,4-dicarbomethoxy-1-[(1,2-dicarbomethoxyvinyl)oxy]-2-*p*-tolylpyrroline (**22**): IR (neat) 3050, 2975, 1725, 1610, 1440, 1270, 815, and 680 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3 H), 3.50 (s, 3 H), 3.52 (s, 3 H), 3.61 (s, 3 H), 3.73 (s, 3 H), 3.91 (d, 1 H, J = 17.0 Hz), 4.13 (d, 1 H, J = 17.0 Hz), 5.10 (s, 1 H), 5.62 (s, 1 H), and 7.10 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 47.2, 51.1, 52.3, 52.6, 52.8, 80.0, 92.9, 128.0, 128.9, 129.0, 131.0, 138.9, 139.4, 151.5, 163.3, 164.0, 165.3, and 166.2; MS, m/e 433 (M^+), 341, 273, 242, 201, 169, and 119; HRMS calcd for $C_{21}H_{23}NO_9$ 433.1373, found 433.1371.

The minor fraction (20%) was obtained from the silica gel column by using an ethyl acetate–hexane mixture and consisted of a clear oil, whose structure was assigned as 4,5-dicarbomethoxy-3-*p*-tolyl-*N*-methylisoxazoline (**23**): NMR ($CDCl_3$, 90 MHz) δ 2.30 (s, 3 H), 2.95 (s, 3 H), 3.62 (s, 3 H), 3.90 (s, 3 H), 4.96 (s, 1 H), and 7.20 (m, 4 H). The structure of this material was verified by comparison with an independently synthesized sample. A solution containing 0.37 mL (3.0 mmol) of dimethyl acetylenedicarboxylate and 447 mg (3.0 mmol) of *N*-methyl-*C*-*p*-tolylnitrone in 25 mL of tetrahydrofuran was stirred for 6 h at room temperature under a nitrogen atmosphere. Removal of the solvent under reduced pressure left an oily residue, which was chromatographed on silica gel to give a colorless oil, whose structure was identical in every detail with a sample of isoxazoline **23** obtained from the cycloaddition of the triflate salt of *p*-tolualdoxime with dimethyl acetylenedicarboxylate.

Cycloaddition of the Triflate Salt of Benzaldehyde Oxime (4) with Methyl Propiolate. To 1.0 g (8.25 mmol) of benzaldehyde oxime at 0 °C was added 1.95 g (8.77 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 12 h. The crude triflate salt was diluted with 25 mL of anhydrous dimethoxyethane, and 0.74 mL (8.32 mmol) of methyl propiolate was added. This solution was cannulated into a flask containing 1.26 g (8.29 mmol) of dry cesium fluoride in 5 mL of dimethoxyethane. The reaction mixture was stirred overnight and concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 20% acetone–hexane solution as the eluent. The first material isolated was a colorless oil (60%), whose structure was assigned as 4-carbomethoxy-*N*-methyl-3-phenylisoxazoline (**24**) on the basis of its spectral properties: NMR ($CDCl_3$, 360 MHz) δ 2.98 (s, 3 H), 3.67 (s, 3 H), 4.88 (s, 1 H), and 7.2–7.5 (m, 6 H). The second material isolated (30%) was a clear oil, whose structure was assigned as 5-carbomethoxy-*N*-methyl-3-phenylisoxazoline (**25**) on the basis of its spectral

properties: NMR ($CDCl_3$, 360 MHz) δ 2.98 (s, 3 H), 3.86 (s, 3 H), 4.85 (d, 1 H, J = 3.0 Hz), 5.84 (d, 1 H, J = 3.0 Hz), and 7.2–7.4 (m, 5 H).

The structures of these materials were verified by comparison with independently synthesized materials.[24] A solution containing 0.70 mL (7.85 mmol) of methyl propiolate and 1.0 g (7.40 mmol) of *N*-methyl-*C*-phenylnitrone in 30 mL of benzene was heated at 50 °C for 10 h. Removal of the solvent left an oily residue, which was chromatographed on silica gel to give a 2:1 mixture of regioisomers, whose structures were identical in every detail with the samples obtained from the cycloaddition of the triflate salt of benzaldehyde oxime with methyl propiolate.

Cycloaddition of the Triflate Salt of Acetone Oxime (26) with Dimethyl Acetylenedicarboxylate. To 500 mg (6.84 mmol) of acetone oxime at 0 °C was added 1.62 g (7.29 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 3 h. The crude triflate salt was diluted with 3 mL of anhydrous dimethoxyethane, and 0.84 mL (6.83 mmol) of dimethyl acetylenedicarboxylate was added. This solution was cannulated into a flask containing 1.05 g (6.91 mmol) of dry cesium fluoride in 2 mL of dimethoxyethane. The reaction mixture was stirred overnight and then concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 25% ethyl acetate–hexane solution as the eluent, to give a colorless oil (75%), whose structure was assigned as 4,5-dicarbomethoxy-3,3-dimethyl-*N*-methylisoxazoline (**27**) on the basis of its spectral properties: NMR ($CDCl_3$, 360 MHz) δ 1.40 (s, 6 H), 2.79 (s, 3 H), 3.76 (s, 3 H) and 3.89 (s, 3 H).

The structure of this material was verified by comparison with an independently synthesized material. A solution containing 0.86 mL (7.04 mmol) of dimethyl acetylenedicarboxylate and 0.5 g (5.74 mmol) of *N*-methyl-*C*,*C*-dimethylnitrone in 150 mL of benzene was heated at 50 °C for 10 h. Removal of the solvent left an oily residue, which was chromatographed on silica gel to give a colorless oil, whose structure was identical in every detail with a sample of **27** obtained from the cycloaddition of the triflate salt of acetone oxime with dimethyl acetylenedicarboxylate.

Cycloaddition of the Triflate Salt of Acetone Oxime (26) with Methyl Propiolate. To 1.0 g (13.7 mmol) of acetone oxime at 0 °C was added 3.23 g (14.5 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 3 h. The crude triflate salt was diluted with 55 mL of anhydrous dimethoxyethane, and 1.22 mL (13.7 mmol) of methyl propiolate was added. This solution was cannulated into a flask containing 2.6 g (17.1 mmol) of dry cesium fluoride in 5 mL of dimethoxyethane. The reaction mixture was stirred overnight and then concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 20% acetone–hexane solution as the eluent. The first material isolated was a colorless oil (70%), whose structure was assigned as 4-carbomethoxy-3,3-dimethyl-*N*-methylisoxazoline (**28**) on the basis of its spectral properties: NMR ($CDCl_3$, 90 MHz) δ 1.38 (s, 6 H), 2.75 (s, 3 H), 3.72 (s, 3 H), and 7.26 (s, 1 H). The second material isolated from the column was a clear oil (20%), whose structure was assigned as 5-carbomethoxy-3,3-dimethyl-*N*-methylisoxazoline (**29**) on the basis of its spectral properties: NMR ($CDCl_3$, 90 MHz) δ 1.28 (s, 6 H), 2.63 (s, 3 H), 3.82 (s, 3 H), and 5.80 (s, 1 H). The structure of the above cycloadducts was verified by comparison with independently synthesized samples. A solution containing 1.0 mL (11.2 mmol) of methyl propiolate and 1.0 g (11.5 mmol) of *N*-methyl-*C*,*C*-dimethylnitrone in 30 mL of benzene was heated at 50 °C for 10 h. Removal of the solvent left an oily residue, which was chromatographed on silica gel by using a 20% acetone–hexane mixture as the eluent, to give a 3.5:1 mixture of regioisomers, whose structures were identical in every detail with the compounds obtained from the cycloaddition of the triflate salt of acetone oxime **26** with methyl propiolate.

Cycloaddition Reactions of the Triflate Salt of *o*-(Allyloxy)benzaldehyde Oxime (30). To a solution containing 200 mg (1.13 mmol) of *o*-(allyloxy)benzaldehyde oxime in 4 mL of anhydrous dichloromethane at 0 °C was added 270 mg (1.21 mmol) of (trimethylsilyl)methyl triflate, and the mixture was stirred for 10 h. The solvent was removed under reduced pressure, and the residue was dissolved in 2 mL of dimethoxyethane. This solution was cannulated into a flask containing 220 mg (1.45 mmol) of anhydrous cesium fluoride in 2 mL of dimethoxyethane, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in 5 mL of benzene and heated at reflux for 24 h. The solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography using a 10% acetone–hexane mixture as the eluent. The major fraction isolated (75%) contained a clear oil, whose structure was assigned as *cis*-1-methyl-1,3a,4,9b-tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole (**31**) on the basis of its spectral properties: NMR ($CDCl_3$, 360 MHz) δ 2.87 (s, 3 H), 3.01 (m, 1 H), 3.61 (d, 1 H, J = 5.2 Hz), 3.72 (dd, 1 H, J = 8.6 and 4.3 Hz), 4.09 (d, 1 H, J = 11.0 Hz), 4.14 (d, 1 H, J = 11.0 Hz), 4.17 (dd, 1 H, J = 11.0 and 5.0 Hz), 4.28 (t, 1 H, J = 8.0 Hz), 6.9–7.0 (m, 2 H), and 7.2–7.3 (m, 2 H). The spectral data obtained are identical with those reported for a pure sample of this compound.[25]

To 200 mg (1.13 mmol) of *o*-(allyloxy)benzaldehyde oxime at 0 °C was added 270 mg (1.21 mmol) of (trimethylsilyl)methyl triflate dropwise, and the reaction mixture was stirred for 12 h. The resulting solid was diluted with 5 mL of anhydrous dimethoxyethane, and 90 mg (1.15 mmol) of fumaronitrile was added. This solution was cannulated into a flask containing 220 mg (1.45 mmol) of dry cesium fluoride in 2 mL of dimethoxyethane. The reaction mixture was stirred overnight and then concentrated under reduced pressure. Water was added, and the solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography using a 30% acetone–hexane solution as the eluent. The major fraction isolated (75%) was recrystallized from ethyl acetate–hexane to yield *trans*-3,4-dicyano-*N*-hydroxy-2-[*o*-(allyloxy)phenyl]-pyrrolidine (**32**) as a yellow solid: mp 109–110 °C; IR (KBr) 3290, 2980, 2240, 2200, 1610, 1590, 1570, 1510, 1490, 1460, 1310, 1260, 1210, 1050, 780, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.26 (t, 1 H, J = 9.2 Hz), 3.43 (m, 1 H), 3.66 (d, 1 H, J = 8.5 Hz), 3.89 (m, 1 H), 4.62 (m, 2 H), 4.84 (d, 1 H, J = 8.5 Hz), 5.3–5.5 (m, 2 H), 5.70 (s, 1 H), 6.0–6.2 (m, 1 H), and 6.9–7.5 (m, 4 H); UV (95% ethanol) 230 (ε 8500) and 310 nm (16 000). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.97; H, 5.58; N, 15.51.

Competitive Rate Study between Fumaronitrile and Methyl Propiolate with the Triflate Salt of Benzaldehyde Oxime. To a 218-mg (1.80 mmol) sample of benzaldehyde oxime was added 440 mg (1.98 mmol) of (trimethylsilyl)methyl triflate, and the solution was stirred for 12 h under nitrogen. The triflate salt **4** was dissolved in 10 mL of dimethoxyethane that contained 0.15 mL (1.67 mmol) of methyl propiolate and 140 mg (1.79 mmol) of fumaronitrile. This solution was cannulated into a flask containing 330 mg (2.17 mmol) of dry cesium fluoride, and the reaction mixture was stirred for 12 h and concentrated under reduced pressure. Water was added, and the solution was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The 300-MHz NMR spectrum of the crude material showed isoxazolines **28** and **29** as the major products.

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