Mechanistic Aspects of the Boron Trifluoride Catalyzed, Intermolecular Diels-Alder Cycloaddition of an Unactivated 2-Aza 1,3-Diene with Electron-Donating-Substituted Dienophiles

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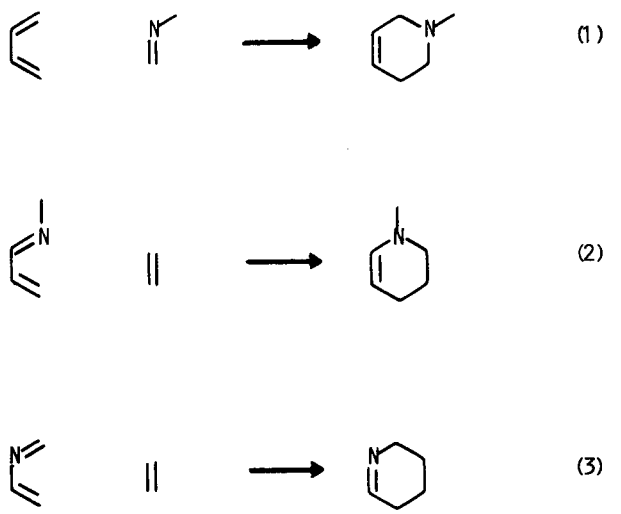
The boron trifluoride etherate catalyzed, intermolecular cycloaddition reactions of (1*E*,3*E*)- and (1*E*,3*Z*)-phenyl-2-aza-1,3-pentadiene (**13E** and **13Z**) with various dienophiles including *n*-butyl vinyl ether, benzyl vinyl ether, tetrahydropyran, 1-(trimethylsiloxy)cyclohexene, *cis*-propenyl benzyl ether, *trans*-propenyl benzyl ether, and 1-morpholinocyclopentene have been explored. All reactions were carried out at 25 °C in benzene solutions and were followed by reductive workup with sodium borohydride. The piperidine products **18–25**, along with the reduced aza diene, *N*-propyl-*N*-benzylamine (**16**), and the aza diene dimers **17**, were separated and characterized by use of a combination of spectroscopic and X-ray crystallographic methods. The yields of cycloadduct **18–25** formation range from 5 to 39% while those for amine **16** and aza diene dimer **17** production are 10–50% and 5–15%, respectively. Only the 1(*E*),3(*E*) stereoisomer **13E** is reactive under these conditions. All piperidine products were found to possess the *cis*-2-phenyl-5-methyl relative stereochemistry. The *all-cis*-2-phenyl-4-alkoxy-5-methyl stereoisomers **18** and **19** are produced exclusively in reactions of **13** with *n*-butyl and benzyl vinyl ether. Reactions of **13** with *cis*- and *trans*-propenyl benzyl ether give the corresponding *cis*- and *trans*-3-methyl-4-(benzyloxy)piperidines, **22** and **23**, respectively. No noncyclic products resulting from addition of 1-(trimethylsiloxy)cyclohexene to the imine function of **13** have been detected. In addition, this enol ether fails to undergo boron trifluoride catalyzed addition to *N*-propylbenzaldimine. Electronically neutral and electron-poor dienophiles including cyclohexene and dimethyl acetylenedicarboxylate do not cycloadd to **13** under these Lewis acid catalysis conditions. The cycloaddition stereochemistry and regiochemistry, the lack of 1(*E*),3(*Z*) aza diene **13Z** reactivity, the role of secondary interactions in controlling endo vs. exo preferences, as well as other features are discussed in terms of concerted reaction mechanisms via $\pi 2s + \pi 4s$ pericyclic transition states for these cycloaddition reactions.

The increased interest in the synthetic application of Diels–Alder cycloaddition chemistry during the past decade has been stimulated by the recognition of several features of this process. For example, the entropic driving force associated with intramolecular 4 + 2 cycloadditions often eliminates the need for incorporation of functionality which is required to drive reaction in intermolecular systems. As a result of this and other factors, the intramolecular Diels–Alder process have been used advantageously in the development of new, convergent methods for polycyclic ring construction.[1] The discovery of novel, oxygenated dienophiles[2] and of interesting procedures for in situ generation of highly reactive dienes and dienophiles[3] has contributed to the synthetic versatility of this process. In addition, the recent disclosure of numerous examples of Diels–Alder cycloaddition reactions of heteroatom containing diene and dienophile systems has had a great impact on the areas of heterocycle and natural product synthesis.[4-7] In this regard, the monoaza Diels–Alder reactions, summarized in Scheme I, comprise a family of cycloadditions which serve as useful methods for tetrahydropyridine ring construction. Two of these, the imino (eq 1) and 1-aza diene (eq 2) Diels–Alder processes, have been vigorously explored in recent years.[6,7] Principally through the elegantly conceived efforts of Weinreb[8] and Fowler,[9] these reactions have been applied in unique methods for preparing nitrogen heterocyclic ring systems as part of a number of important synthetic studies.

Scheme I



(1) See, for example: Ciganek, E. *Org. React. (N.Y.)* **1984**, *32*, 1. Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183 for recent thorough reviews of intramolecular Diels–Alder reactions.

(2) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

(3) See, for example: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. Kametani, T.; Fukumoto, J. *Heterocycles* **1975**, *3*, 29. Oppolzer, W. *Synthesis* **1978**, 793.

(4) For recent publications summarizing the Lewis acid catalyzed cycloadditions with aldehydes see: Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *Ibid.* **1985**, *107*, 1256. Danishefsky, S. J.; Maring, C. J., **1985**, *107*, 1269. Danishefsky, S. J.: Larson, E.; Springer, J. P. *Ibid.* **1985**, *107*, 1274. Danishefsky, S. J.; Pearson, W. H.; Segmuller, b. E. *Ibid.* **1985**, *107*, 1280. Danishefsky, S. J.; Uang, B. J.; Quallich, G. *Ibid.* **1985**, *107*, 1285.

(5) For a recent review of Diels–Alder cycloadditions with heterodienophiles see: Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(6) For a review of Diels–Alder reactions with heteroaromatic compounds see: Needleman, S. B.; Kuo, M. C. C. *Chem. Rev.* **1962**, *62*, 405.

(7) For a recent review of Diels–Alder reactions of aza dienes see: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

(8) Some general examples of the use of imines in Diels–Alder cycloaddition processes as part of natural product synthetic approaches see: Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T. T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962. Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Weinreb, S. M. *Ibid.* **1982**, *104*, 536. Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *Ibid.* **1979**, *101*, 5073. Schmitthener, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. Khatri, N. A.; Schmitthener, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387.

(9) For examples of the use of 1-aza diene Diels–Alder cycloaddition reactions in synthesis see: Cheng, Y. S.; Fowler, F. W.; Lupo, A. T. *J. Am. Chem. Soc.* **1981**, *103*, 2090. Cheng, Y. S.; Lupo, A. T.; Fowler, F. W. *Ibid.* **1983**, *105*, 7696.

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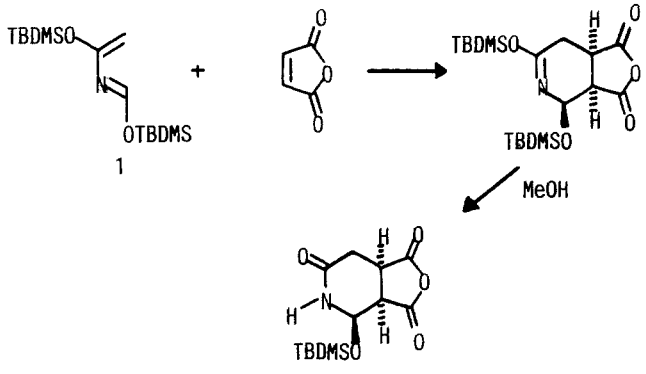
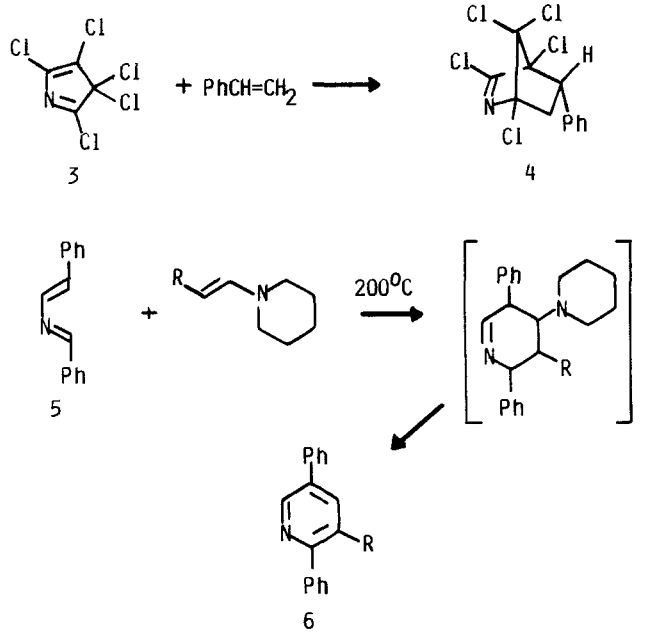
The third member of the family of aza Diels–Alder processes is represented by cycloadditions of 2-aza 1,3-dienes which lead to formation of 3,4,5,6-tetrahydropyridine products (eq 3). Studies in this area have uncovered a number of seemingly disconnected examples of this reaction. For example, Ghosez and others[10] have found that 2-aza 1,3-dienes with appended electron-donating oxy or amino substituents undergo smooth, intermolecular Diels–Alder cycloadditions with electron-poor dienophiles to generate piperidines or products derived from these species (e.g., 1 → 2).[10a] In contrast, electron-



1 2

rich dienophiles participate in 4 + 2 cycloaddition reactions with polyhalogen-substituted 2-aza dienes[11] (e.g., 3 → 4).[11a] Although examples exist in which electronically neutral 2-aza dienes have been shown to participate in both inter-[12] and intramolecular[13] Diels–Alder reactions, these processes normally require high temperature (e.g., 5 → 6).[12] The



3 4 5 6

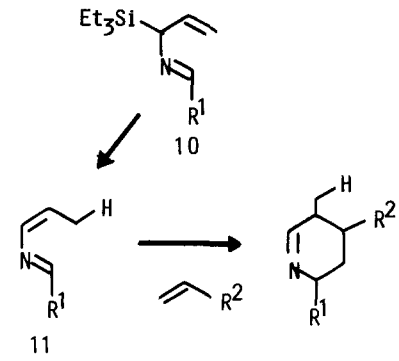
(10) (a) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428. (b) Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409. Gompper, R.; Heinemann, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 217. Nomura, Y.; Takeuchi, Y.; Tomada, S.; Ito, M. M. *Chem. Lett.* **1979**, 187; *Bull, Chem. Soc. Jpn.* **1981**, *54*, 2779. Aue, D. H.; Thomas, D. *J. Org. Chem.* **1975**, *40*, 1349.

(11) (a) Daniels, P. H.; Wong, J. L. *J. Org. Chem.* **1980**, *45*, 435. (b) Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862. Barlow, M. g.; Brown, D. E.; Haszeldine, R. N. *J. Chem. Soc., Chem. Commun.* **1977**, 669; *J. Chem. Soc., Perkin Trans. 1*, **1978**, 363. Barlow, M. G.; Brown, D. E.; Haszeldine, R. N.; Langridge, J. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 129. Brooke, G. M.; Matthews, R. S.; Robson, N. S., *Ibid.* **1980**, 102.

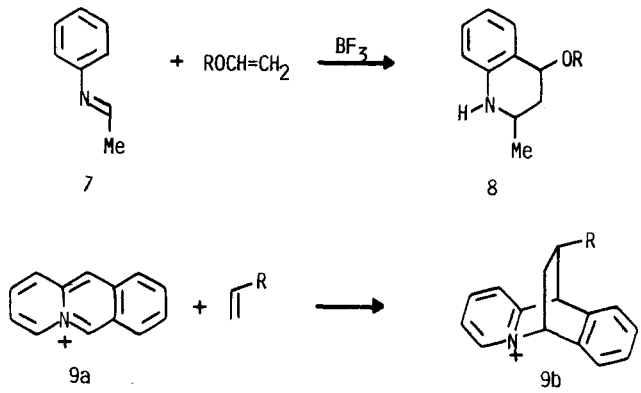
(12) Komatsu, M.; Takamatsu, S.; Uesaka, M. Yamamono, S.; Ohshio, Y.; Agawa, T., *J. Org. Chem.* **1984**, *49*, 2691.

(13) Hasan, H.; Fowler, F. W. *J. Am. Chem. Soc.* **1978**, *100*, 6696.

Scheme II



groups of Povarov[14] and Orahovats[15] through investigations of the cycloaddition chemistry of various aniline aldimines have found that Diels–Alder cycloadditions of electronically neutral 2-aza dienes can be catalyzed by Lewis acids. Accordingly, the acetaldehyde anilide–boron trifluoride complex of **7** is transformed to the tetrahydroquinolines **8** through cycloaddition with enol ether dienophiles.[14a] A larger group of cycloadditions, closely related to the Lewis acid catalyzed processes, are found in the chemistry of azonium salts investigated principally by Bradsher and his co-workers.[16,17] For example, the 2-aza diene grouping within the acridizinium salt **9a** is responsible for the 4 + 2 cycloaddition reactions which occur in the presence of a variety of dienophiles to produce the bicyclic pyridinium salts **9b**.[16a]



7 8 9a 9b

Our interest in the area of 2-aza 1,3-diene Diels–Alder chemistry has been stimulated recently by the recognition that sequences involving 2-aza diene **11** generation by protodesilylation from the corresponding *N*-(triethylsilyl)allyl imines **10**[18] followed by inter- or intramolecular cycloaddition (Scheme II) could serve as a potentially

(14) (a) Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 2221. (b) Povarov, L. S., Grigos, V. I.; Karakhanov, R. A.; Mikhailov, B. M. *Ibid.* **1964**, 179; **1963**, 2039.

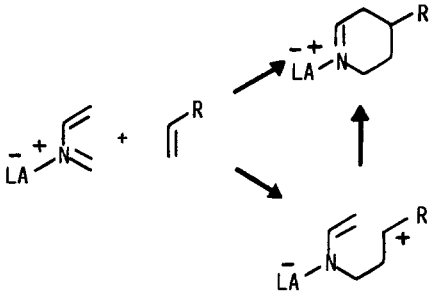
(15) Trifonov, L. S.; Orahovats, A. S. *Heterocycles* **1984**, *22*, 355.

(16) (a) Bradsher, C. K.; Solomons, T. W. G. *J. Am. Chem. Soc.* **1958**, *80*, 933. (b) Bradsher, C. K.; Stone, J. A. *J. Org. Chem.* **1968**, *33*, 519; **1969**, *34*, 1700. Westerman, I. J.; Bradsher, C. K. *Ibid.* **1971**, *36*, 969. Porter, N. A.; Westerman, I. J.; Wallis, T. G., Bradsher, C. K. *J. Am. Chem. Soc.* **1974**, *96*, 5104. Fields, D. L.; Regan, T. H.; Dignan, J. C. *J. Org. Chem.* **1968**, *33*, 320. Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1985**, 293. Stevens, R. V.; Pruitt, J. R. *J. Chem. Soc., Chem. Commun.* **1983**, 1425.

(17) (a) For intramolecular examples of azonium salt intramolecular Diels–Alder reactions see: Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Chem. Commun.* **1976**, 367. Grisby, G. P.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc. Perkin Trans. 1* **1982**, 249. (b) For closely related examples of 2-aza diene salt cycloaddition processes see Hajicek, J.; Trojanek, J. *Tetrahedron Lett.* **1981**, 1823. Shono, T.; Matsumura, Y.; Inoue, K.; Ohmiza, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753. Swan, G. A. *J. Chem. Soc., Chem. Commun.* **1969**, 20. Hess, K. A. *Justus Liebigs Ann. Chem.* **1970**, *741*, 117.

(18) Chen, S. F.; Mariano, P. S. *Tetrahedron Lett.* **1985**, 47.

useful methodology for nitrogen heterocyclic ring construction.[19] Through an analysis of frontier orbital interactions and based upon the precedent found in the early Russian work,[14,15] we anticipated that cycloadditions of electronically neutral 2-aza dienes with electron-rich dienophiles could be facilitated by Lewis acid catalysis. Reversible complexation with Lewis acids would render the 2-aza diene system more reactive in a concerted Diels–Alder process since this should result in a decrease in the LUMO (aza diene)–HOMO (dienophile) energy gap. Of course, cycloadditions catalyzed in this fashion could also occur through a nonconcerted pathway involving the intermediacy of the zwitterion **12**. Cycloaddition by either concerted or nonconcerted mechanisms in these cases should follow the same regiochemical course. The question of reaction mechanism raised here about the Lewis acid catalyzed 2-aza diene cycloaddition process is reminiscent of the unresolved controversy associated with studies of the analogous acridizinium Diels–Alder reactions.[20]



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The investigations described below were designed to address the issues of feasibility and mechanism regarding the intermolecular,[21] Lewis acid catalyzed cycloaddition reactions of electronically neutral 2-aza 1,3-dienes with electron-rich dienophiles. For these purposes, we have explored the boron trifluoride etherate catalyzed reactions of the easily prepared[22] 1-phenyl-4-methyl-2-aza 1,3-diene **13** with a variety of potential dienophiles. The olefin substrates employed in this study were selected on the basis of their ability to reveal information about reaction mechanism and other features including the electronic requirements of the dienophile and the stereochemical and regiochemical preferences governed by electronic and steric factors. No attempt has been made in these initial efforts to probe the scope of this process by varying either the azadiene system or the nature of the Lewis acid or other catalysts. These limited studies, however, have demonstrated that the boron trifluoride catalyzed, intermolecular Diels–Alder reaction of **13** is a viable process when electron-rich olefins such as enol ethers and enamines are used as dienophiles and that the cycloadditions follow concerted $\pi 2s + \pi 4s$ pathways via transition states in which endo/exo preferences are governed by electronic and steric factors.

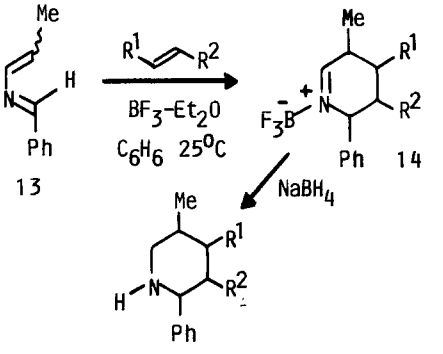
Results

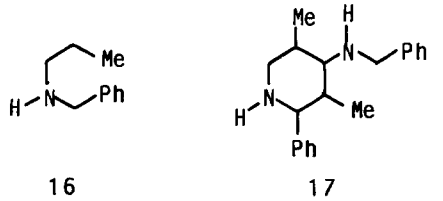
Cycloadditions of 2-Aza Diene 13. Cycloaddition reactions of 1-phenyl-4-methyl-2-aza 1,3-diene **13** with a variety of dienophiles, including enol ethers, enamines, simple olefins, and acetylenic esters, were conducted at 25 °C in benzene solutions containing boron trifluoride ethereate. In each case, a fixed mole ratio of reactants and catalyst, consisting of 2 equiv of azadiene, 1 equiv of dienophile, and 2 equiv of BF_3·Et_2O, was employed. For the purposes of synthetic convenience,[22] the aza diene **13** used in these studies was a 3:1 mixture of *E*:*Z* C=C π-bond isomers, both of which possess (>95%) *E* stereochemistry about the C=N π-bond. Following a 2 h reaction time, the reaction mixtures were cooled to 0 °C and quenched by the addition of an ethanol solution containing excess sodium borohydride. This reduction was performed to convert the initially formed BF_3–tetrahydropyridine complexes **14** to the more easily handled piperidines **15**. Silica gel chromatography was then used to separate the reduced, Diels–Alder adducts **15**, the reduction product **16** derived from unreacted azadiene, and the reduced aza diene dimers **17**. The results of these cycloaddition reactions are presented in Table I.

Table I. Results of the BF_3-Catalyzed Cycloadditions of 2-Aza Diene 13 with Various Dienophiles

dienophile	piperidine adduct (yield,[a] %)	yield, % amine **16**[b]	yield, % dimers **17**[b]
n-butyl vinyl ether	**18** (27%)	10	5
benzyl vinyl ether	**19** (30%)	10	
dihydropyran	**20** (5%)	50	10
1-(trimethylsiloxy)cyclohexene	**21** (26%)	10	15
cis-propenyl benzyl ether	**22** (27%)	30	
trans-propenyl benzyl ether	**23** (33%)	15	
1-morpholinocyclopentene	**24** (31%) **25** (8%)		

[a] Yields are based upon the amounts of dienophile used. [b] Yields are based upon the amounts of 2-aza diene **13** used.





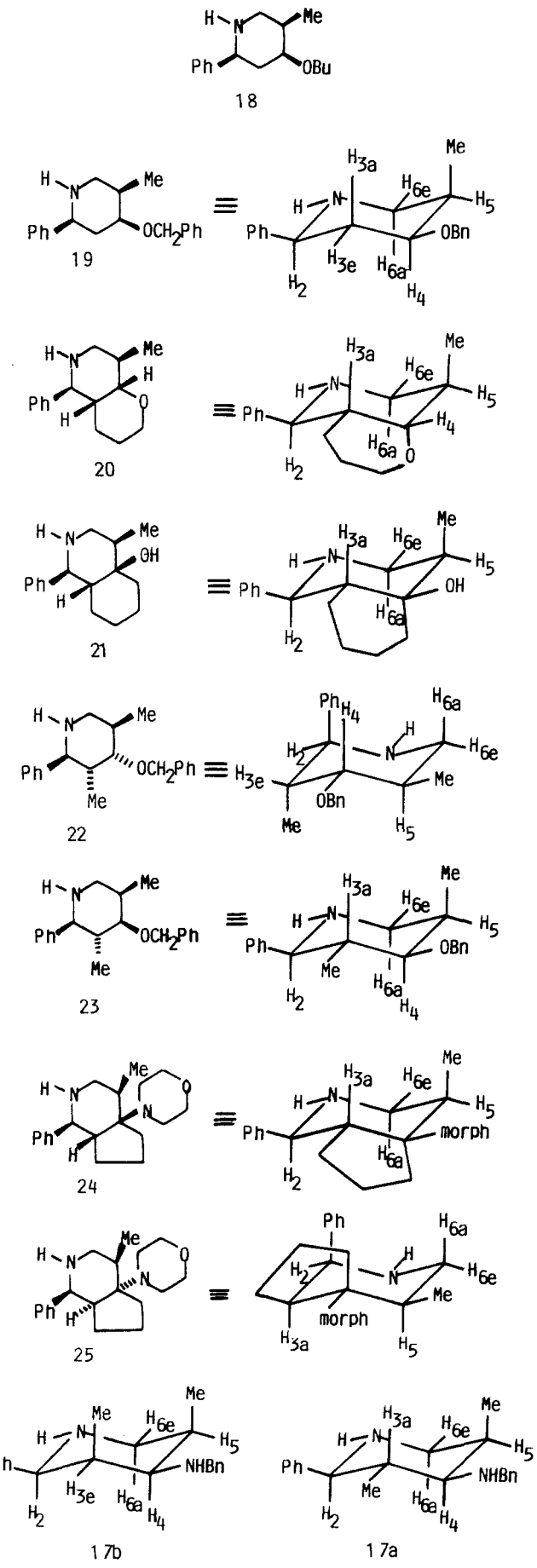
Structure and Stereochemical Assignments. The structural and stereochemical assignments to the piperidine cycloadducts **18–25** and aza diene dimers **17** are based on complete spectroscopic data. Characteristic ^1H NMR spectroscopic parameters for these substances in conjunction with X-ray crystallographic analysis of the crystalline adduct **23** (mp 76.5–78 °C), arising from reaction of aza diene **13** with *trans*-propenyl benzyl ether, has facilitated the assignment of relative stereochemistry at the chiral centers in these multisubstituted, conformationally

(19) A preliminary report of this work has been presented: 188th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 1984; American Chemical Society: Washington, D.C., 1984; ORGN 8.

(20) Bradsher, C. K. *Adv. Heeterocycl. Chem.* **1974**, *16*, 289.

(21) Preliminary results from current studies in our laboratory have demonstrated that intramolecular analogues of this process occur with high efficiency.

(22) (a) Worley, S. D.; Taylor, G. K.; Venugopalan, B.; Clark, M. S. *Tetrahedron* **1978**, *34*, 833. (b) Wender, P. A.; Schaus, J. M. *J. Org. Chem.* **1978**, *43*, 782. (c) Reference 18 above.



rigid piperidines. For example, the X-ray structure of **23** (Figure 1) clearly depicts the existence of a chair conformation for this trans,trans,cis-tetrasubstituted piperidine

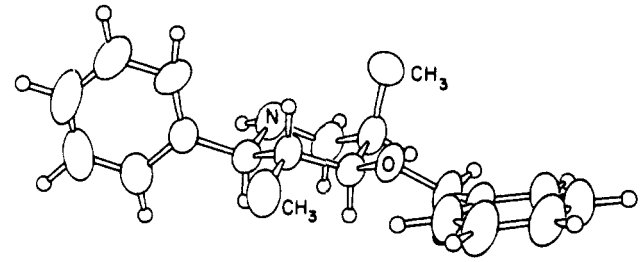


Figure 1. ORTEP drawing of the structure of piperidine **23**, obtained from an X-ray crystallographic determination.

with ring protons residing in clear axial and equatorial orientations. This feature along with the presence of a fortuitous functionality array leads to an ^1H NMR spectrum of **23** with distinctive sets of proton resonances at chemical shifts and with coupling constants which clearly reflect relative stereochemistry. Accordingly, the trans relationship between the C-2 phenyl and C-3 methyl substituents is mirrored in the appearance of H-2 as a doublet at 3.16 ppm with the large axial–axial coupling constant of 10.3 Hz and of H-4 as a doublet of doublets at 3.21 ppm resulting from the large (10.4 Hz) H-4–H-3a axial–axial and small (5.0 Hz) H-4–H-5 axial–equatorial coupling between vicinally disposed protons (see Table II). The small value for J_{4-5} is consistent with the equatorial disposition of the C-4 benzyloxy substituent. In addition, the small J_{5-6a} and J_{5-6e} values (2.9 and 2.4 Hz, respectively), dissected from the ABM pattern associated with protons H-6a, H-6e, and H-5, are in accord with the equatorial disposition of H-5 and, thus, the cis relationship between the C-2 phenyl and C-5 methyl groups.

Identification of the product arising from cycloaddition of *cis*-propenyl benzyl ether to aza diene **13** as the trans,cis,trans piperidine stereoisomer **22** follows nicely from its characteristic ^1H NMR spectroscopic parameters. Accordingly, the equatorial location of H-2 (3.80 ppm) is reflected in the H-2–H-3 coupling constant of 3.0 Hz. Similarly, the respective axial, equatorial, and equatorial disposition of the methyl and benzyloxy substituents at C-3, C-4, and C-5 are demonstrated by the coupling constants J_{3e-4}, J_{4-5}, and J_{5-6a} recorded in Table II. Additional information about the stereochemistry and preferred solution-phase conformation of **22** comes from the chemical shifts for H-6a in the piperidines **22** and **23**. Specifically, H-6a in **22** resonates ca. 0.7 ppm upfield of the corresponding proton in **23**, reflecting the shielding effect of the axial phenyl group in **22**.

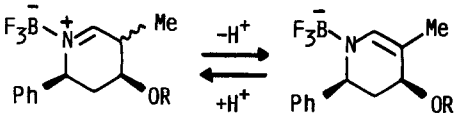
The stereochemical and conformational assignments to the cycloadducts arising from reaction of aza diene **13** with other dienophiles and itself are based on chemical shift and coupling constant correlations similar to those described above.

Additional Observations. Additional observations have been made in these investigations which pertain to the mechanism and scope of the Lewis acid catalyzed cycloaddition reactions of the electronically neutral aza diene **13**. The first of these is related to the azadiene conformational requirements for cycloaddition. The exclusive formation of piperidine products possessing the *cis*-2-phenyl-5-methyl relative stereochemistry (see Table I) suggests an important source of stereocontrol for this process. It appears unlikely that this stereochemical result can be easily rationalized in terms of a non-concerted mechanism in which both the 3(*E*) and 3(*Z*) aza diene stereoisomers undergo cycloaddition to generate the 2,5-cis-disubstituted cycloadducts. No pattern could be discerned by inspection of the transition states for the C4–C5 bond-forming step in a nonconcerted pathway which would

Table II. Characteristic ^{1}H NMR Spectroscopic Data for the Cycloadducts 19–25

	chem shifts (ppm relative to Me_4Si)					coupling consts, Hz						
piperidine	H-2	H-3a	H-3e	H-6a	H-6e	J_{2-3a}	J_{2-3e}	J_{4-3a}	J_{4-3e}	J_{4-5}	J_{5-6a}	J_{5-6e}
19	3.68	1.70	1.90	2.89	3.00	12	4	12	5	5	3	2.4
20	4.10			2.69	3.28	11		1.5		1.5	3	4
21	3.80	1.95		2.81	3.20	11					3	5
22	3.80		2.40	2.40	3.20		3		5	11	12	5
23	3.16	1.95		2.93	3.03	10.3		10.4		5	2.9	2.4
24	3.30			2.75	3.09	13					3	4
25	3.15	1.35		3.16	3.95	3					10	4
17a	3.19			2.86	2.98	11		12		5	2	3
17b	4.25			2.80	3.25		3		4.3	4.3	4.5	5

be consistent with this uniform stereochemical outcome. Likewise, reaction stereochemistry, established through equilibration at C5 via an iminium salt–enamine equilibrium (e.g., **26** → **27**) would not be consistent with selective generation of products such as **18** and **19** which do not represent the thermodynamically most stable C5 epimers.



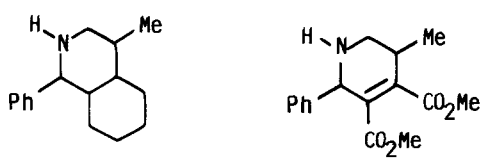
26 **27**

However, the observed C2–C5 stereochemistry would be understandable in terms of a stereospecific cycloaddition process in which only the 3(*E*) aza diene stereoisomer **13E** is reactive. Indeed, this proposal was verified by observations which indicate that the 3(*Z*) aza diene **13Z** does

13Z **13E**

not participate in cycloaddition with benzyl vinyl ether. Separation of **13Z** from the mixture of aza diene stereoisomers is accomplished by the gas chromatographic methods described earlier by Worley and his co-workers[22a] or by HPLC on a Partisil M9 column (30% hexane–chloroform). The spectroscopic properties of **13Z** are equivalent to those previously reported.[22a] Reaction of the 3-(*Z*)-aza diene with benzyl vinyl ether at 25 °C in benzene solution containing boron trifluoride etherate followed by borohydride reduction leads to exclusive (85%) generation of *N*-propyl-*N*-benzylamine (**16**). No trace of cycloadducts related to **19** could be detected in the product mixture by use of ^{1}H NMR or chromatographic methods.

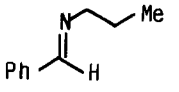
In order to probe the electronic requirements for dienophiles in these Lewis acid catalyzed cycloadditions, reactions of azadiene **13** with olefins other than vinyl ethers and enamines were investigated. Boron trifluoride catalyzed reaction of aza diene **13** with cyclohexene or dimethyl acetylenedicarboxylate does not provide after reductive work detectable quantities of the cycloadducts **28** or **29** nor



28 **29**

does it form products which could have derived from these substances. In each case, the aza diene reduction product **16** and dimers **17** are the only products generated under these conditions. Thus, it appears that simple alkyl or electron-withdrawing group substituted olefins do not participate in this intermolecular cycloaddition process.

Additional information about the mechanism for the aza diene, Lewis acid catalyzed cycloaddition reactions has come from observations made in studies with the *N*-propylbenzaldimine (**30**), a substance prepared by condensation of *N*-propylamine with benzaldehyde. We felt that imine **30** would serve as a good model with which to test the feasibility of the first step of a nonconcerted mechanism for the aza diene cycloaddition process. Accordingly, if a nonconcerted pathway were followed, we expected that the model imine **30** would also participate in addition reactions with electron-rich olefins, such as the siloxycyclohexane **31**, under the conditions used for the cycloaddition processes. However, borohydride workup of the mixture, obtained by reacting imine **30** with the silyl enol ether **31** at 25 °C in benzene solution containing boron trifluoride etherate, leads to high yielding (85%) generation of *N*-propyl-*N*-benzylamine (**16**). No products arising from addition of **31** to **30** (e.g., **32**) could be detected in the product mixture. Indeed, the Mukaiyama[23] type addition process does occur when titanium tetrachloride is employed as catalyst for this reaction.



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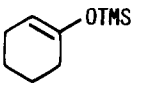

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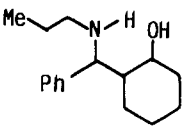
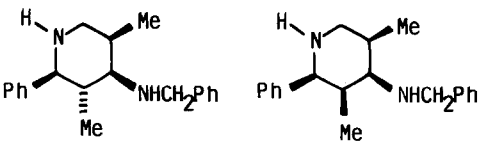


32

Finally, the reduced dimers **17**, arising by cycloadditions in which the aza diene **13** serves as both the diene and dienophile component, are formed in varying but small quantities in each of these reactions. The isolation of these substances was restricted, however, to only a few cases (see Table I). ^{1}H NMR analysis of the dimer mixture indicates that four stereoisomers are generated. The major stereoisomers present in these mixtures have been fully characterized on the basis of spectroscopic data and demonstrated to have the trans,trans,cis and cis,cis,cis stereochemistries represented by **17a** and **17b**. As such, the



17a **17b**

major isomers, if derived by a stereospecific concerted Diels–Alder process, would be produced by cycloaddition

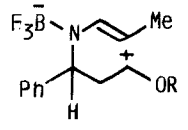
(23) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

of the 1(*E*),3(*E*) aza diene stereoisomer, **13E** as the diene component with either **13E** or **13Z** as dienophiles.

Discussion

The results presented above demonstrate that intermolecular, Diels–Alder cycloaddition reactions of the electronically neutral 2-aza 1,3-diene **13** with electron-rich dienophiles, including enol ethers and enamines, can be facilitated by use of the Lewis acid catalyst, boron trifluoride. The processes occur in only low to moderate yields as a result, in part, of competitive cyclodimerization reactions of the 2-aza dienes. These Lewis acid catalyzed cycloadditions appear to be limited to 2-aza dienes which can adopt low energy s-cis conformations (see below) and to electron-donating group substituted olefins.[24] However, the low temperatures and short reaction times required suggest that they may find application in the area of N-heterocycle synthesis. Indeed, future studies of this process probing the relationships between reaction efficiency and natures of the Lewis acid catalyst, the aza diene system, the dienophile and the reaction molecularity (inter vs. intra) should provide useful information on this point.

Reaction Mechanism. An important purpose of the current study was to explore the mechanism of these catalyzed Diels–Alder reactions. The electronic character of both the BF_3-complexed aza diene and electron-rich olefins appear compatible with either concerted or stepwise mechanisms for these processes. Our studies have generated results that allow distinction between these alternatives. Perhaps the most significant observations relating to mechanism concern the reaction stereochemistry. The fact that the C=N and C=C π-bond stereochemistry of the reactive aza diene **13E** is retained in these cycloaddition processes suggests the operation of a concerted mechanism. This conclusion is confirmed by results obtained from investigations of the cycloadditions with *cis*- and *trans*-propenyl benzyl ether which demonstrate that the process possesses an exceptionally high degree of dienophile stereospecificity. Thus, these stereochemical results are in full accord with a concerted mechanism for the catalyzed cycloadditions proceeding through $\pi 2s + \pi 4s$ transition states. Of course, as is true in the case of most pericyclic processes, the stereochemical information is insufficient to exclude the operation of nonconcerted pathways via the intermediacy of short-lived zwitterions **33** and where the rate of bond formation exceeds that of bond rotation. It is worth noting that the regiochemical course of the enol ether and enamine cycloadditions to **13** parallels that predicted on the basis of FMO analysis for a concerted pathway. Accordingly, the LUMO aza diene and HOMO dienophile coefficients, depicted qualitatively in structures **34** and **35**, indicate that transition states involving bonding of the dienophile β-carbon to C-1 of the complexed aza diene should be favored.



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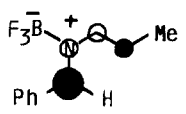
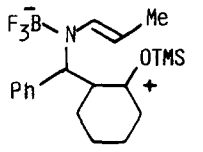


34

35

Another feature signaling the concerted nature of these Diels–Alder reactions is the apparent dependence of reactivity on factors affecting aza diene conformation. The reluctance of 1(*E*)-phenyl-4(*Z*)-methyl-2-aza 1,3-diene **13Z** to cycloadd to benzyl vinyl ether would be difficult to rationalize if a non-concerted pathway were followed in which the first step was rate limiting. However, the presence of the cis methyl substituent in **13Z** is expected to have an effect upon the rate of concerted 2 + 4 cycloadditions in which transition states with the s-cis aza diene conformation are required. This phenomenon would parallel those associated with thermally induced Diels–Alder cycloadditions of all carbon dienes.

A final aspect pertaining to the issue of mechanism for these reactions relates to observation arising from studies with 1-(trimethylsiloxy)cyclohexene (**31**) and the model imine **30**. A zwitterion **36**, if present in the pathway for cycloaddition between **31** and aza diene **13**, would have the potential of undergoing rapid desilylation to form the ketoenamine **37** whose existence would have been revealed by isolation of the amino alcohol **38** in the product mixture



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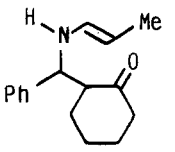

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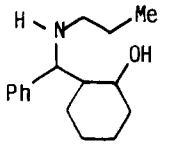

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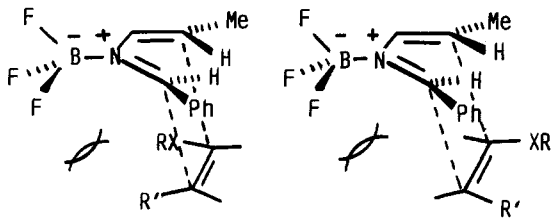
formed upon reductive workup. This acyclic adduct, prepared independently by titanium tetrachloride catalyzed addition of **31** to the imine **30** (CH_2Cl_2, −78 °C) followed by borohydride reduction, was not detected in the Diels–Alder reaction mixture. In addition, the fact that the silyl enol ether **31** does not undergo boron trifluoride catalyzed addition to the benzaldimine **30** under conditions identical with those used in the cycloaddition reaction with aza diene **13** further indicates that the first step in a nonconcerted route is energetically less favorable than $\pi 2s + \pi 4s$ cycloaddition.

Endo vs. Exo Stereochemical Preferences. As discussed above, the stereochemical course of the boron trifluoride catalyzed, intermolecular Diels–Alder reactions of aza diene **13E** appears to be governed by the facial specificities which reflect the $\pi 2s + \pi 4s$ nature of the processes. The relative stereochemistries at C-2 and C-5 and at C-3 and C-4 of the formed piperidines are controlled by this feature. In addition, these cycloaddition reactions also display a high degree of stereoselectivity which is manifested in the relative stereochemistry at the C-2 and C-3 and at the C-4 and C-5 centers.[25] The latter stereochemical feature is related to preferences for endo XR vs. exo XR **40** transition states for concerted cycloaddition. By inspection of the results presented above, an interesting pattern interconnecting the nature of the dienophile and transition-state selection can be uncovered. It appears that cycloadditions with dienophiles which lack a cis alkyl substituent at the β-carbon, such as *n*-butyl and benzyl

(24) This restriction is removed in intramolecular examples[21] where the yields are generally higher.

(25) We have assumed that the observed stereochemical preferences are a result of kinetic rather than thermodynamic factors although no information about the potential reversibility of these cycloadditions is available at the current time.

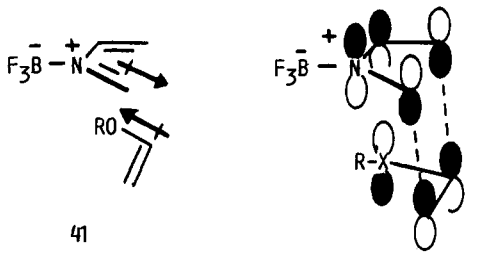


39 endo-XR 40 exo-XR

vinyl ether, 1-(trimethylsiloxy)cyclohexene and *trans*-propenyl benzyl ether, proceed via endo XR transition states selectively. On the other hand, exo XR transition states are involved in cycloadditions of aza diene **13E** with dihydropyran and *cis*-propenyl benzyl ether, both of which have cis alkyl substituents β to the alkoxy group. The enamine, 1-morpholinocyclopentene, would fit into the former group of dienophiles and, as such, produces a product stereoisomer mixture reflecting predominant (ca. 4:1) reaction through an endo XR transition state.

The endo vs. exo selectivities summarized above appear to be the result of two counteracting effects. In those cases where a cis β-alkyl group is present in the dienophile, a high-energy steric interaction between this substituent (R') and the BF_3 grouping exists in the endo XR transition-state **39** for cycloaddition. A similar steric crowding can develop when the XR group of the dienophile is excessively large. This might very well serve as the source of the low stereoselectivity observed for reaction of **13E** with 1-morpholinocyclopentene.[38]

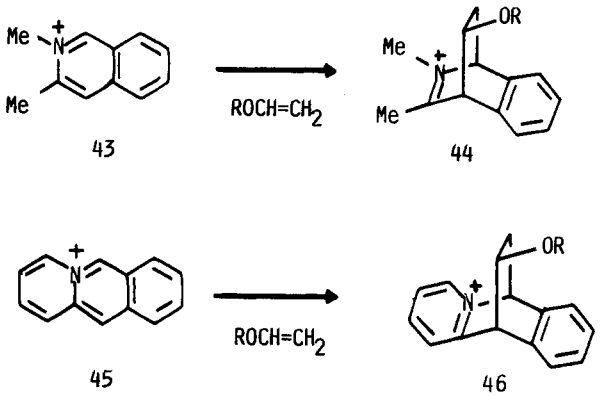
Perhaps of greater interest is the factor(s) which controls preference for the endo XR cycloaddition transition-state **39** when steric effects associated with the dienophile are absent. One possible source of this control might reside in transition-state stabilization arising as a result of the near anti-parallel alignment of the dipoles associated with the endo alkoxy and iminium cation functions.[26] This favorable interaction is depicted in the transition-state representation **41**. Secondary orbital interactions might



41 42

also contribute to the observed endo XR selectivities. As shown in the transition-state representation **42**, perturbations resulting from interactions between the enol ether oxygen (or enamine nitrogen) and nitrogen or C-3 of the complexed aza diene in the dominant frontier orbitals (aza diene LUMO and dienophile HOMO) will lead to stabilization of the endo XR transition states.

It is interesting to contrast the endo XR selectivities for aza diene cycloadditions observed in the present study to stereochemical observations made earlier for related N-heteroaromatic salt systems. Bradsher and his co-workers[27] had noted the Diels–Alder addition of vinyl ethers to the 2,3-dimethylisoquinolinium salt **43** occurs to generate selectively the tricyclic iminium salt **44** as a result of a preferred exo OR transition state. A similar preference is seen in formation of the cycloadduct **46** by addition of enol ethers to the acridizinium salt **45**.[28] The stereochemical course of these cycloadditions appear to reflect the influence of electronic rather than steric factors. Bradsher has rationalized these results in terms of a preference for exo OR transition states resulting from the minimization of repulsion of like charges. While the foundations supporting his proposal are not obvious, it is clear that the endo vs. exo selectivities for 2 + 4 cycloadditions of N-heteroaromatic salts and the BF_3-complexed 2-aza diene **13E** differ significantly.[29-32] Finally, it is worth noting that dipolar cycloadditions of nitrones with enol ethers in some cases display high degrees of diastereofacial selectivity reflecting a preference for endo OR transition-state geometries.[33] It is possible that the dipole and secondary orbital effects discussed above for Lewis acid catalyzed Diels–Alder processes might be similar to those operating to control the stereochemistry of these dipolar cycloadditions.



43 44 45 46

Experimental Section

General Data. Nuclear Magnetic resonance spectra were recorded by using Varian EM-360 and Bruker WP-200 spectrometers. Chemical shifts are recorded in parts per million relative to tetramethylsilane. In all cases, the solvent for NMR measurements was $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 281-283 spectrometer. Mass spectrometric data were recorded at 70 eV on Hitachi RMU-6 (low-resolution) or VG-7070 (high-resolution) instruments. Melting points obtained by use of a Mel-temp apparatus are reported uncorrected. Drying of organic solutions obtained during workup of reaction mixtures was over anhydrous sodium sulfate. Preparative TLC was performed on 20 × 20 cm plates coated with E-Merck Silica gel 60 GF-254. Molecular distillations were performed at reduced pressure with a Kugelrohr apparatus. Flash chromatography was performed according to the method of Still[34] by using EM-60 silica gel (230–400 mesh). IR and mass spectrometric data are included with the supplementary material.

(26) The possible influences of polar and dipole effects on the endo–exo selectivity of Diels–Alder and dipolar cycloadditions have been discussed in: Berson, J. A.; Mueller, W. A. *Tetrahedron Lett.* **1961**, 131. Matsumoto, K.; Uchida, T.; Maruyama, K. *Chem. Lett.* **1974**, 327.

(27) Bradsher, C. K.; Day, F. H. *Tetrahedron Lett.* **1971**, 409. Bradsher, C. K.; Day, F. H.; McPhail, A. J., Wong, P. *Tetrahedron Lett.* **1971**, 4205.

(28) Bradsher, C. K.; Day, F. H.; McPhail, A. J., Wong, P. *J. Chem. Soc., Chem. Commun.*, **1973**, 156.

(29) Cycloadditions of Maleic anhydride and *N*-phenylmaleimide to **45** occur stereoselectively to generate the products of endo addition.[30] Bradsher has explained these results in terms of charge transfer between the pyridinium cation ring of **45** and the dienophiles. Alslager and Worth[31] have shown that the BF_3-catalyzed addition of 5-methyl-2,3-dihydrofuran to aniline benzaldimine[32] proceeds to generate a 1:1 mixture of cycloadducts resulting from competitive endo OR and exo OR transition states.

(30) Bradsher, C. K.; Harvan, A. I. *J. Org. Chem.* **1971**, *36*, 3778.

(31) Elslager, E. F.; Worth, D. F. *J. Heterocycl. Chem.* **1970**, *7*, 538.

(32) Pavorov, L. S. *Russ. Chem. Rev. (Engl. Trans.)* **1967**, *36*, 696.

(33) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.

(34) Still, W. C.; Kohn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

General Procedure for Diels–Alder Cycloaddition. A solution of 1-phenyl-2-aza-1,3-pentadiene (**13**)[22] (3:1 ratio of *E,E*:*E,Z* isomers) (2 molar equiv), the appropriate dienophile (1 molar equiv), and BF_3·Et_2O (2 molar equiv) in 10 mL of anhydrous benzene was stirred under a nitrogen atmosphere at 25 °C for 2 h. After this solution was cooled to 0 °C, a mixture of sodium borohydride (40 molar equiv) in 5 mL of ethanol was added and the resulting mixture was stirred for 1 h at 0 °C and 2 h at 25 °C. The reaction mixture was diluted with 1 mL of 5% aqueous sodium bicarbonate and extracted with ether. The ethereal extracts were dried and concentrated in vacuo giving a residue which was subjected to flash chromatography on silica gel. The yields of Diels–Alder adducts are based upon the amount of dienophile used while those for the aza diene dimers and reduction products are based upon the amount of aza diene used.

Cycloaddition with *n*-Butyl Vinyl Ether Giving Piperidine 18. Reaction of 232 mg of *n*-butyl vinyl ether with aza diene **13** under the conditions described above gave, after chromatographic purification (elution with 50% hexane–ether), 155 mg (27%) of *cis,cis*-2-phenyl-4-*n*-butoxy-5-methylpiperidine (**18**), 34 mg (3%) of the 2-phenyl-4-(benzylamino)-3,5-dimethylpiperidine (**17a**), and 35 mg (5%) of *N*-benzyl-*N*-propylamine (**16**).

Piperidine **18**: ^{1}H NMR δ 0.92 (3 H, t, J = 7 Hz), 1.12 (3 H, d, J = 7 Hz) 1.20–1.80 (7 H, m), 1.91 (1 H, d of t, J = 12, 3 Hz, H3 eq), 2.15 (1 H, m, H5 eq), 3.00 (2 H, AB q, H6), 3.30–3.69 (3 H, m), 7.18–7.45 (5 H, m); ^{13}C NMR δ 144.40, 128.30, 127.00, 126.50, 126.00, 78.7 (C4), 67.20 (OCH_2), 60.20 (C2), 51.10 (C6), 34.6 (C3), 32.20, 31.30 (C5), 19.40, 13.80, 10.40 (Me); high-resolution mass spectrum, m/e 247.1947 ($C_{16}H_{25}NO$ requires m/e 247.1936).

Piperidine **17a**: ^{1}H NMR δ 0.72 (3 H, d, J = 7.5 Hz, 5Me), 1.16 (3 H, J = 8 Hz, 3Me), 1.40–1.90 (2 H, m), 2.15 (1 H, m, H5), 2.45 (1 H, dd, J = 12.5, 5 Hz, H4 ax), 2.86 (1 H, dd, J = 11, 2 Hz, H6 ax), 2.98 (1 H, dd, J = 11, 3 Hz, H6 eq), 3.19 (1 H, d, J = 11 Hz, H2), 3.8 (2 H, AB q, J = 12 Hz, NCH_2Ph), 7.20–7.70 (10 H, m); ^{13}C NMR δ 144.0, 141.1, 128.4, 128.3, 128.0, 127.9, 127.2, 126.8, 126.6, 69.1 (NCH_2Ph), 63.5 (C2), 52.2 (C4), 50.7 (C6), 37.6 (C3), 30.4 (C5), 29.2 (3Me), 14.9 (5Me); high-resolution mass spectrum, m/e 294.2078 ($C_{20}H_{26}N_2$ requires m/e 294.2096).

The spectroscopic properties of *N*-benzyl-*N*-propylamine (**16**) were identical with those of a commercially available (Ames Laboratory) sample of this substance.

Cycloaddition with Benzyl Vinyl Ether Giving Piperidine 19. Reaction of 156 mg of benzyl vinyl ether[35] with aza diene **13** under the above described conditions gave, after chromatographic purification (elution with 50% hexane–ether), 95 mg (30%) of *cis,cis*-2-phenyl-4-(benzyloxy)-5-methylpiperidine (**19**): ^{1}H NMR δ 1.11 (3 H, d, J = 6.5 Hz, Me), 1.47 (1 H, m), 1.70 (1 H, q, J = 12 Hz, H3 ax), 1.91 (1 H, dt, J = 12, 4 Hz, H3 eq), 2.19 (1 H, m), 2.89 (1 H, dd, J = 12, 3 Hz, H6 ax), 3.00 (1 H, dd, J = 12, 2.4 Hz, H6 eq), 3.68 (1 H, dd, J = 12, 4 Hz, H2 ax), 3.73 (1 H, dt, J = 12, 4 Hz, H4 ax), 4.61 (2 H, AB q, J = 12 Hz, OCH_2Ph), 7.15–7.60 (10 H, m); ^{13}C NMR δ 144.4, 139.0, 128.3, 128.3, 127.6, 127.4, 127.1, 126.9, 126.6, 78.3(C4), 69.3 (OCH_2Ph), 60.8 (C2), 51.2 (C6), 35.1 (C3), 31.4 (C5), 10.6 (Me); high-resolution mass spectrum, m/e 281.1776 ($C_{19}H_{23}NO$ requires m/e 281.1476).

***N*-Tosylamide Derivative of Piperidine 19.** A solution of 25 mg (0.089 mmol) of the piperidine **19**, 25 mg (0.13 mmol) of *p*-toluenesulfonyl chloride, and triethylamine (14 mg, 0.13 mmol) in 2 mL of methylene chloride was stirred at reflux for 3 days cooled to 25 °C, washed with 5% aqueous sodium bicarbonate, dried, and concentrated in vacuo to give a crystalline solid. Recrystallization from 50% hexane–ether gave pure 1-*p*-tosyl-2-phenyl-4-(benzyloxy)-5-methylpiperidine: mp 133–134 °C; ^{1}H NMR 0.84 (3 H, d, J = 8 Hz, Me), 1.70 (1 H, m, H5), 1.82 (1 H, ddd, J = 15.7, 5, 2.9 Hz, H3 ax), 2.39 (3 H, s, $MePhSO_2$), 2.61 (1 H, dt, J = 15.7, 2.0 Hz, H3 eq), 3.32 (1 H, dd, J = 15, 12 Hz, H6 ax), 3.43 (1 H, t, J = 2 Hz, H4), 3.67 (1 H, dd, J = 15, 5.7 Hz, H6 eq), 4.10 (2 H, AB q, J = 13 Hz, OCH_2Ph), 5.26 (1 H, d, J = 5 Hz, H2), 6.8–7.60 (9 H, m, aromatic); mass spectrum, m/e (relative intensity) 435 (M^+, 0.1), 280 (34), 279 (13), 114 (21), 111 (37), 91 (100), 82 (15); high-resolution mass spectrum, m/e 435.1868 ($C_{26}H_{29}NO_3S$ requires m/e 435.1863).

(35) Julia, S.; Julia, M.; Linares, H.; Blondel, J. C., *Bull. Soc. Chim. Fr.* **1962**, 1947. Schilling, C. L. *J. Organomet. Chem.* **1971**, *29*, 93.

Cycloaddition with 2,3-Dihydropyran Giving the 2-Aza-5-oxadecalin 20. Reaction of 145 mg of 2,3-dihydropyran with aza diene **13** under the above described conditions gave, after chromatographic purification (elution with 10% hexane–ether), 20 mg (5%) of *all-cis*-1-phenyl-4-methyl-2-aza-5-oxadecalin (**20**), 124 mg (50%) of *N*-benzyl-*N*-propylamine (**16**), and 51 mg (5%) of a mixture of aza diene dimers **17**. Spectroscopic data for **20**: ^{1}H NMR δ 0.72–1.40 (4 H, m), 1.24 (3 H, d, J = 8.5 Hz, Me), 1.55 (1 H, m), 1.75 (1 H, m), 2.69 (1 H, dd, J = 13, 3 Hz, H3 ax), 3.28 (1 H, dd, J = 12, 4 Hz, H3 eq), 3.45 (1 H, t, J = 1.5 Hz, H9), 3.45–3.70 (2 H, m), 4.10 (1 H, d, J = 11 Hz, H1), 7.15–7.45 (5 H, m, aromatic); ^{13}C NMR δ 143.7, 128.3, 128.1, 127.6, 126.6, 78.0 (C9), 69.0 (C6), 59.4 (C1), 47.5 (C3), 36.7 (C10), 34.4 (C4), 25.6 (C7), 21.9 (C8), 16.0 (Me); high-resolution mass spectrum, m/e 231.1599 ($C_{15}H_{21}NO$ requires m/e 231.1575).

Cycloaddition with 1-(Trimethylsiloxy)cyclohexene Giving the 2-Azadecalin 21. Reaction of 340 mg of 1-(trimethylsiloxy)cyclohexene with aza diene **13** under the conditions described above followed by chromatographic separation (elution with 50% hexane–ether) gave 150 mg (26%) of the *all-cis*-1-phenyl-4-methyl-10-hydroxy-2-azadecalin **21**, 88 mg (8%) of the aza diene dimer **17b**, and 28 mg (5%) of *N*-benzyl-*N*-propylamine (**16**). Spectroscopic data for **21**: ^{1}H NMR δ 1.21 (3 H, d, J = 8 Hz, Me), 1.40–1.79 (9 H, m), 1.91 (1 H, dt, J = 10.5, 5 Hz, H9), 2.20 (1 H, dd, J = 11.5, 4 Hz), 2.81 (1 H, dd, J = 12, 3 Hz, H3 ax), 3.20 (1 H, dd, J = 12, 5 Hz, H3 eq), 3.75 (2 H, d, J = 11 Hz, H1), 7.16–7.59 (5 H, m, aromatic); ^{13}C NMR δ 143.8, 128.5, 127.5, 127.4, 76.0 (C10), 72.5 (C1), 62.9 (C3), 44.9 (C9), 33.5 (C4), 23.9 (C6), 22.0 (C7), 21.7 (C8), 13.2 (Me); high-resolution mass spectrum, m/e 245.1775 ($C_{16}H_{23}NO$ requires m/e 245.1735).

Spectroscopic data for **17b**: ^{1}H NMR δ 0.81 (3 H, d, J = 9 Hz, 5Me), 1.20 (3 H, d, J = 9 Hz, 3Me), 1.76 (1 H, m, H5), 2.00 (1H, m, H3), 2.65 (1 H, t, J = 4.3 Hz, H4), 2.81 (1 H, dd, J = 13, 5 Hz, H6 ax), 3.25 (1 H, dd, J = 13, 4.5 Hz, H6 eq), 3.87 (2 H, s, NCH_2Ph), 4.25 (1 H, d, J = 3 Hz, H2), 7.23–7.45 (10 H, m, aromatic); ^{13}C NMR δ 143.6, 141.1, 128.4, 128.2, 128.1, 127.2, 126.9, 126.4, 63.8 (C2), 59.8 (C4), 51.8 (NCH_2Ph), 48.5 (C6), 39.2 (C3 or C5), 34.1 (C5 or C3), 18.2 (3Me), 14.8 (5Me); high-resolution mass spectrum m/e 294.2082 ($C_{20}H_{26}N_2$ requires m/e 294.2096).

Cycloaddition with *cis*-Propenyl Benzyl Ether Giving Piperidine 22. Reaction of 27 mg of *cis*-propenyl benzyl ether[35] with aza diene **13** under the above described conditions followed by chromatographic separation (elution with 50% ether–hexane) gave 15 mg (27%) of *trans,cis,trans*-2-phenyl-3,5-dimethyl-4-(benzyloxy)piperidine (**22**) and 8 mg (15%) of *N*-benzyl-*N*-propylamine (**16**).

Spectroscopic data for **22**: ^{1}H NMR δ 0.75 (3 H, d, J = 8.5 Hz, 3Me), 1.01 (3 H, d, J = 8.5 Hz, 5Me), 1.56 (1 H, NH), 1.95 (1 H, m, H5), 2.38 (1 H, m, H3), 2.45 (1 H, t, J = 11.8 Hz, H6 ax), 3.15 (1 H, dd, J = 11.8, 4.5 Hz, H6 eq), 3.20 (1 H, dd, J = 11, 5 Hz, H4), 3.85 (2 H, d, J = 3 Hz, H2), 4.59 (2 H, AB q, J = 11.5 Hz, OCH_2Ph), 7.15–7.56 (10 H, m, aromatic); ^{13}C NMR 143.0, 138.8, 128.3, 128.1, 127.7, 127.5, 126.6, 126.5, 85.5 (C4), 70.0 (OCH_2Ph), 63.4 (C2), 53.4 (C6), 37.3 (C3), 31.6 (C5), 15.9 (3Me), 6.07 (5Me); high-resolution mass spectrum, m/e 295.1930 ($C_{20}H_{25}NO$ requires m/e 295.1936).

Cycloaddition with *trans*-Propenyl Benzyl Ether Giving Piperidine 23. Reaction of 103 mg of *trans*-propenyl benzyl ether[35] with aza diene **13** under the reaction conditions described above followed by chromatographic separation (elution with 2% methanol–chloroform) gave 68 mg (33%) of the crystalline *trans,trans,cis*-2-phenyl-3,5-dimethyl-4-(benzyloxy)piperidine (**23**), mp 76.5–78 °C (Et_2O), and 16 mg (8%) of *N*-benzyl-*N*-propylamine (**16**).

Spectroscopic data for **23**: ^{1}H NMR δ 0.78 (3 H, d, J = 7 Hz, 5Me), 1.23 (3 H, d, J = 7 Hz, 3Me), 1.95 (1 H, m, H3), 2.37 (1H, m, H5), 2.93 (1 H, dd, J = 2.9, 12 Hz, H6 ax), 3.03 (1 H, dd, J = 2.4, 12 Hz, H6 eq), 3.17 (1H, d, J = 10.3 Hz, H2), 3.21 (1H, dd, J = 5.0, 10.4 Hz, H4), 4.53 (2 H, AB q, J = 11.6 Hz, OCH_2Ph), 7.0–7.6 (10 H, m, aromatic); ^{13}C NMR δ 143.1, 138.8, 128.3, 128.1, 127.8, 127.4, 127.3, 126.4, 84.1 (C4), 70.0 (OCH_2Ph), 68.5C2), 51.0 (C6), 37.7 (C3), 30.7 (C5), 14.6 (3Me), 11.3 (5Me); high-resolution mass spectrum, m/e 295.1923 ($C_{20}H_{25}NO$ requires m/e 295.1936).

Cycloaddition with 1-Cyclopentenylmorpholine Giving the 2-Azaindans 24 and 25. Reaction of 380 mg of 1-cyclopentylmorpholine with aza diene **13** under the conditions described

above followed by chromatographic separation (elution with 50% ether–hexane) gave 234 mg (31%) of the 1-phenyl-4-methyl-9-morpholino-2-azaindan (**24**) and 58 mg (8%) of the stereoisomeric azaindan **25**.

Spectroscopic data for **24**: ^{1}H NMR 1.27 (3 H, d, J = 8 Hz, Me), 1.36–1.86 (7 H, m), 1.86–2.11 (1 H, m), 2.21 (1 H, dd, J = 10, 5 Hz, H8), 2.75 (1 H, dd, J = 16, 3 Hz, H3 ax), 2.79 (4 H, quintet, J = 5 Hz, CH_2OCH_2), 3.09 (1 H, dd, J = 16, 4 Hz, H3 eq), 3.31 (1 H, d, J = 13 Hz, H1), 3.55 (4 H, t, J = 6 Hz, CH_2NCH_2), 7.18–7.50 (5 H, m, aromatic); ^{13}C NMR δ 144.0, 128.1, 127.4, 69.9, 66.0 (CH_2OCH_2), 68.7 (C1), 64.2 (C9), 45.9 (C3), 77.0 (C8), 34.5 (C4), 52.0 and 52.2 (CH_2NCH_2), 31.4 (C7), 25.7 (C6), 20.2 (C5), 18.1 (Me); high-resolution mass spectrum, m/e 300.2265 ($C_{16}H_{28}N_2O$ requires m/e 300.2202).

Spectroscopic data for **25**: ^{1}H NMR δ 0.96 (3 H, d, J = 9 Hz, Me), 1.17–1.45 (2 H, m), 1.28–1.50 (5 H, m), 2.35 (1 H, dt, J = 11, 2 Hz, H8), 2.61 (4 H, m), 3.15 (1 H, d, J = 3 Hz, H1), 3.16 (1 H, dd, J = 16, 10 Hz, H3 ax), 3.74 (4 H, m), 3.95 (1 H, dd, J = 16, 4 Hz, H3 eq), 7.10–7.45 (5 H, m, aromatic); ^{13}C NMR δ 139.0, 128., 128.3, 127.7, 126.2, 68.2, 65.8 (CH_2OCH_2), 67.7 (C1), 65.5 (C9), 52.9 and 43.6 (CH_2NCH_2), 46.4 (C3), 31.4 (C8), 29.8 (C4), 27.0 (C6), 24.5 (C7), 15.3 (C5), 10.2 (Me); high-resolution mass spectrum, m/e 300.2193 ($C_{19}H_{28}N_2O$ requires m/e 300.2184).

Attempted Cycloaddition Reaction of Pure (1*E*,3*Z*)-1-Phenyl-2-aza-1,3-pentadiene (13Z) with Benzyl Vinyl Ether. Reaction of the *E,Z* aza diene **13Z** (45 mg) with benzyl vinyl ether (43 mg) was conducted under the normal conditions described above. Inspection of the crude reaction mixture by ^{1}H NMR spectroscopy showed that it contained (85%) of *N*-benzyl-*N*-propylamine (**16**). This, along with TLC analysis demonstrated that no Diels–Alder adduct had been produced in this reaction.

Attempted Addition of 1-(Trimethylsiloxy)cyclohexene to *N*-Propylbenzaldimine (30). A mixture of 1-(trimethylsiloxy)cyclohexene (**31**; 170 mg, 1.0 mmol), *N*-propylbenzaldimine (**30**; 147 mg, 1.0 mmol) and boron trifluoride etherate (125 mL) in 5 mL of benzene was stirred under an N_2 atmosphere at 25 °C for 2 h. The reaction mixture was cooled to 0 °C and mixed with a solution of 0.45 g of sodium borohydride in 10 mL of ethanol. The resulting solution of 0.45 g of sodium borohydride in 10 mL of ethanol. The resulting solution was stirred at 25 °C for 2 h and subjected to the same workup and chromatographic (5% MeOH–$CHCl_3$) separation procedure used in the Diels–Alder cycloaddition processes. This afforded 127 mg (85%) of *N*-benzyl-*N*-propylamine (**16**). No products resulting from addition of the silyl enol ether to the imine **30** were detected in the crude reaction mixture or after separation.

Crystallographic Study of the Piperidine 23. Crystals were obtained from an ethereal solution of the cycloadduct **23**. A 0.2 × 0.2 × 0.3 mm specimen was used for all X-ray measurements. Data were collected on a Picker FACS-I diffractometer with graphite-monochromated Cu radiation (λ (Cu Kα) = 1.5418 A). Lattice parameters were obtained by least squares from 15 reflections automatically centered at $\pm 2\theta$. Crystal data: $C_{20}H_{25}NO$; M_r 295.4; triclinic, $P\bar{1}$, a = 6.660 (1) Å, b = 11.268 (3) Å, c = 12.012 (3) Å, α = 77.99 (2)°, δ = 89.68 (2)°, γ = 77.19 (2)°; D_{calcd} = 1.141 g cm^{-3} for Z = 2.

Intensity data were collected to 2θ maximum of 126° with 2θ–θ scan geometry at 2° min^{-1} and with 10-s backgrounds. Four standards were measured at 100 reflection intervals. The average intensity decline was 4%. A total of 3173 data were measured and gave 2772 unique data and 2223 data with $I \geq 3\sigma(I)$. The structure was solved with the MULTAN-80 system of programs.[36] The other crytallographic calculations were carried out with the XRAY 76 system[37,38] on a UNIVAC 1100/82 computer. The least-squares structure refinement minimized $\sum w(F_o - F_c)^2 gw = 1/\sigma^2(F_o)$. Anisotropic temperature factors were used for carbon, nitrogen, and oxygen.

The framework hydrogen atoms linked to carbon were placed at calculated positions with C–H = 1 Å; methyl hydrogen atoms were not placed; the N–H hydrogen atom was located from a difference map; these atoms were included in the structure refinement with isotropic B values of 10 Å but were not varied. The final R $\sum(1F_o - F_c)/\sum F_o$) and weighted R ($[\sum w(F_o - F_c)^2/\sum wF_o^2]^2$) are 0.076 and 0.096. Tables of atomic coordinates and temperature factors are included with the supplementary material.

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Registry No. (1*E*,3*E*)-**13**, 68003-58-7; (1*E*,3*Z*)-**13**, 97290-59-0; **16**, 2032-33-9; **17a**, 99398-24-0; **17b**, 99398-25-1; **18**, 99398-26-2; **19**, 99398-27-3; **19** *N*-tosylamide derivative, 99398-28-4; **20**, 99398-29-5; **21**, 99398-30-8; **22**, 99398-31-9; **23**, 99398-32-0; **24**, 99398-33-1; **25**, 99398-34-2; $BuOCH{=}CH_2$, 111-34-2; $PhCH_2OCH{=}CH_2$, 935-04-6; (*Z*)-$CH_3CH{=}CHOCH_2Ph$, 32426-80-5; (*E*)-$CH_3CH{=}CHOCH_2Ph$, 32426-79-2; 3,4-dihydro-2*H*-pyran, 110-87-2; 1-(trimethylsiloxy)cyclohexene, 6651-36-1; 1-morpholinocyclopentene, 936-52-7.

Supplementary Material Available: IR and mass spectroscopic data for products **17–25** and tables of atomic fractional coordinates and atomic parameters (4 pages). Ordering information is given on any current masthead page.

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(38) A reviewer has thoughtfully suggested that the lower degree of endo selectivity observed in cycloaddition of 1-morpholinocyclopentene as compared to, for example, that displayed by 1-(trimethylsiloxy)cyclohexene might also reflect the lesser dipole of the C–N vs. C–O bond.