Face Selection in Thermal Cycloaddition and -reversion

Haifang Li,† Jack E. Silver,† William H. Watson,*,‡ Ram P. Kashyap,‡ and William J. le Noble*,†

Departments of Chemistry, State University of New York, Stony Brook, New York 11794-3400 and Box 32908, Texas Christian University, Fort Worth, Texas 76129

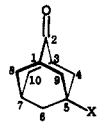
Received March 26, 1991

The isomer distribution has been determined in several cycloaddition reactions involving 5-fluoro- and 5-phenyladamantane derivatives in which C_2 serves as one of the trigonal termini. The reactions include a [2 + 2] cycloaddition with dichloroketene, a nucleophilic addition followed by cyclization, a [2 + 2] cycloreversion of a β-lactone, and two Diels–Alder reactions; in the latter case, the adamantane moiety was incorporated in the diene in one instance and in the dienophile in the other. In all these reactions, the reagent attacking the adamantane substrate was found to do so preferentially at the zu face, by modest but clear margins. This observation is in accord with the concept of transition-state hyperconjugation. This explanation is extended to several literature examples involving substrates with faces that are not isosteric because the polarizing group is placed closer to the site of attack; the ratios are substantial and in favor of the more hindered product in many of these examples.

Introduction

The Woodward–Hoffmann rules brought us an enormous step forward in our understanding of the stereochemistry of concerted cycloaddition reactions, permitting chemists to anticipate with much confidence when the termini of both partners would become bound suprafacially and when those of one of them might do so in an antarafacial mode.[1] The rules do not specify which of two faces in either π system will become the site of attack, leaving unexplored territory which has inspired active research in substituent effects on face selection. In some instances, the outcome is controlled by obvious geometric features such as the strain factor in intramolecular reactions, and steric hindrance in cycloadditions involving crowded molecules. Electronic substituent effects have proved to be much more difficult to comprehend, although some generalizations such as the Alder rule are known[2] and possibly understood.[3] Efforts to make progress by means of theoretical and/or computational approaches have been made,[4] but to date no widely accepted, simple rules have emerged that allow predictions to be made regarding electronic effects on face selection in cycloadditions.

Our active interest in this matter originated with the finding, then quite unexpected, that the ethynylation of 5-phenyladamantan-2-one (1-Ph) occurs preferentially at the zu face, by a substantial margin.[5] It will be noted that



1-X

the two carbonyl faces are sterically equivalent in this molecule and that this fact is not obscured by conformational uncertainty. Subsequent work revealed that attack of nucleophiles always occurs at the zu face if X is an electron-withdrawing group[6] and at the en face if it is a donor.[7] We interpreted these observations in terms of transition-state hyperconjugation, a concept first proposed by Cieplak[8] to account for the axial attack of many nucleophiles on cyclohexanones (see Discussion). We and others have since then contended that the same type of experimental approach and the same concept can be used to account for the stereochemistry of capture[6a,9] and production[10] of carbocations, the capture of radicals,[11] and the reaction of olefins with electrophiles.[12] Cycloadditions were included in the list in a preliminary communication;[13] we presently elaborate our findings in this area.

Results

A literature search turned up only three examples of [2 + 2] cycloadditions to alkylideneadamantanes. One of these is the low-yield addition of chlorosulfonyl isocyanate to vinylideneadamantane;[14] the others are the reactions of *N*-methyltriazolinedione[15a] and of singlet oxygen[15b] with adamantylideneadamantanes. The latter reaction proceeds in good yield and has the additional advantage that the product dioxetanes are also useful for our purpose, as they readily undergo the well-known chemiluminescent cycloreversion process to form excited adamantanones.[16] Since this chemistry was apparently under investigation elsewhere (see Discussion), we searched for new examples. The cycloaddition of dichloroketene to 4-*tert*-butyl-1-methylidenecyclohexane is known,[17] and this became the

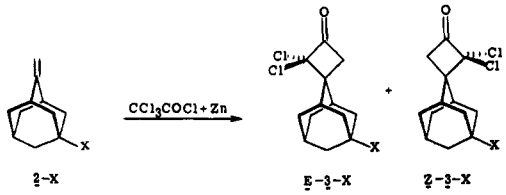
† State University of New York.
‡ Texas Christian University.

(1) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press, New York, 1971.
(2) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.
(3) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 4388. (b) Fox, M. A.; Cardona, R.; Kiwiet, N. J. *J. Org. Chem.* **1987**, *52*, 1469.
(4) Examples include: (a) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 32. (b) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663. (c) Houk, K. N. *Pure Appl. Chem.* **1989**, *61*, 643. (d) Chao, T. M.; Baker, J.; Hehre, W. J.; Kahn, S. D. *Pure Appl. Chem.* **1991**, *63*, 283.
(5) le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3244.
(6) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598; **1987**, *109*, 7239. (b) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, *31*, 4391.
(7) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836.
(8) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(9) Lin, M.-h., Cheung, C. K.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 6562.
(10) (a) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3839. (b) Adcock, W.; Cope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411.
(11) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.
(12) (a) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. (b) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875.
(13) Chung, W.-S.; Turro, N. S.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882.
(14) Sasaki, T.; Eguchi, S.; Hirako, Y. *Tetrahedron Lett.* **1976**, 541.
(15) (a) Cheng, C.-C., Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910. (b) Wierenga, J. H.; Strating, J.; Wynberg, H.; Adam, W. *Tetrahedron Lett.* **1972**, 169.
(16) Meyer, E. W.; Wynberg, H. *J. Chem. Educ.* **1982**, *59*, 1071.
(17) (a) Dunkelblum, E. *Tetrahedron* **1978**, *32*, 975. (b) Picard, P.; Moulines, J.; Lecoustre, M. *Bull. Chem. Soc. Fr.* **1984**, II-65.

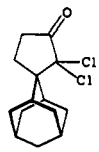
0022-3263/91/1956-5932$02.50/0

basis for our first study in this area.

When trichloroacetyl chloride is treated with activated zinc[18] in the presence of methyleneadamantane (2-H), a high yield of adducts 3-H is obtained.[19] The regiochemistry of cycloaddition is obvious from the facts that the base peak in the mass spectrum represents loss of CH_2CO (ketene) and that dechlorination gives the C_{2v} symmetrical ketone (seven ^{13}C NMR signals). The use of 2-



methylene-5-phenyladamantane (2-Ph) gave a mixture of (*E*)- and (*Z*)-3-Ph; integration of the two cyclobutanone signals showed the ratio to be 56:44. Assignment of the ^{13}C NMR signals in the parent compound 3-H was made on the basis of our experience that in adamantanes with an electronegative substituent singly bound at C_2, the *syn* methylene carbons directly below it are shielded compared to the *anti* pair even as the axial hydrogen atoms bound to them are shifted downfield; we presume that polarization of the axial C–H bonds is responsible.[20] In support of this assignment, the parent compound 3-H was converted, by means of a reaction with diazomethane,[21] into the α,α-dichlorocyclopentanone homologue 4. As would

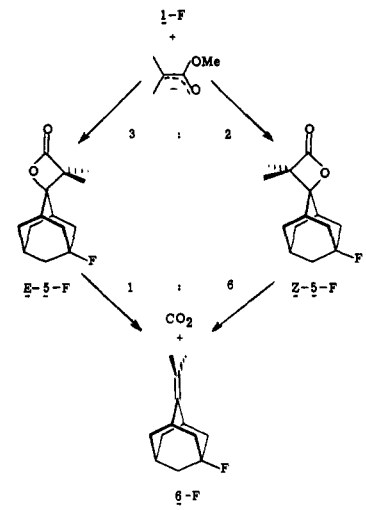


4

be expected from the change in bond angles, the chlorine atoms are now in a better position to polarize the C–H bonds, and, indeed, the C_{4-9} carbons are shielded further. It was also found that $Eu(fod)_3$ shifts these carbons downfield about twice as much as $C_{8,10}$. After partial separation of the isomers, the final assignment of (*E*)- and (*Z*)-3-Ph is then made by means of additivity calculations,[20] in which the ^{13}C shifts of both isomers are compared with sets computed on the basis of both the correct and the incorrect assumption of the stereochemistry. The *Z* isomer was in this way found to be the major product; in other words, the dichloroketene preferentially attacks the zu face of 2-Ph.

The second study involved the β-lactones (*E*)- and (*Z*)-5-F, chosen because both their relative ease of formation and decomposition were of interest to us. The parent compound 5-H is formed when the lithium enolate of methyl isobutyrate is allowed to react with adamantanone.[22] The reaction probably occurs in two steps: nucleophilic addition followed by ring closure with displacement. The $C_{4,9}$ and $C_{8,10}$ signals in the ^{13}C NMR spectrum were assigned on the basis of the polarization effect by the singly bound oxygen. The use of 5-fluoroadamantanone (1-F) gave rise to a mixture of (*E*)- and (*Z*)-5-F, which was analyzed by means of integration of the methyl proton signals and separated chromatographically. The ^{13}C NMR spectra were measured and calculated on the basis of additivity. The net result of these experiments is that the ratio of the isomers is 3:2, in favor of the *E* isomer; in this experiment also, the reagent attacks the zu face.

Scheme I



The decarboxylation of (*E*)- and (*Z*)-5-F to give the common olefin 6-F must be studied kinetically if one wishes to determine the face selected preferentially. The methyl proton peaks in the lactone and olefin are sufficiently widely separated to allow their use in following the rates, which were measured in acetonitrile-d_3 at 80 °C. Under those conditions, the first-order rate constants of 5-H and (*E*)- and (*Z*)-5-F were found to be 130, 2.58, and 16.5×10^{-6} s^{-1}, respectively. The minor isomer decomposes 6.3 times faster than the major, showing that *departure* from the zu face is faster as well as approach to it (see Scheme I).

Our data allow several comments on the mechanism of the decarboxylation. The retention of configuration observed by Adam[22] in this reaction suggests that it is concerted; the contrast in activation volume (−20 cm^3/mol) and reaction volume (+50 cm^3/mol) led Isaacs[23] to propose a zwitterionic intermediate. The rate-decelerating effect of the fluorine we observe is about 1 order of magnitude, substantial but much smaller than that for the solvolysis of 2-(5-fluoroadamantyl) tosylate.[10a] It appears that the breaking C–O bond has developed a large dipole moment in the transition state but has not completely heterolyzed. To study this matter further, we prepared specifically labeled 5-H from adamantanone-^{17}O and found that the oxygen atoms do not scramble at all during the decarboxylation. We conclude that if the zwitterion is an intermediate, either its formation is irreversible or it is too short-lived to permit rotation of the C–CO_2^- bond.

An attempted extension of our studies to the ene reaction also deserves mention in passing. Heating mixtures of 6-H and maleic anhydride did not produce the expected ene product 7 and instead gave rearranged compound 8. Even though efforts to demonstrate the presence of 7 as

(18) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879.

(19) Since our work was completed, the parent 3-H has also been reported by Farcasiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D. B.; Sevin, A. *J. Am. Chem. Soc.* **1989**, *111*, 8466. These workers used dichloroacetyl chlorine and triethylamine to generate the ketene, as recommended by Brady, W. T. *Synthesis* **1971**, 415. In our hands, Brady's method gave low yields with 5-fluoro- and 5-phenyl-2-methyleneadamantanes, probably because the slower cycloaddition cannot compete with a side reaction involving the amine and ketene.

(20) Srivastava, S.; Cheung, C. K.; le Noble, W. J. *Magn. Reson. Chem.* **1985**, *23*, 232; **1989**, *27*(6), II.

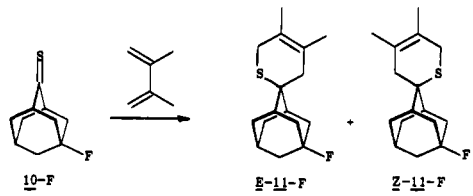
(21) The methylene insertion occurs in the CH_2–CO bond, as witness the fact that the methylene singlet in 3-H gives way to a pair of triplets. See also: Greene, A. E.; Depres, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 4003.

(22) Adam, W.; Encarnacion, L. A. A. *Chem. Ber.* **1982**, *115*, 2592.

(23) Isaacs, N. S.; Laila, A. H. *Tetrahedron Lett.* **1983**, *24*, 2897.

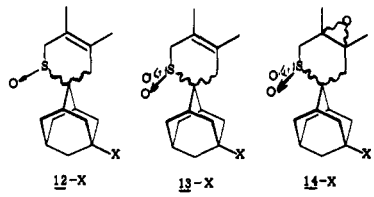
an intermediate at any stage failed, it seems probable that it is formed but is subject to a facile 1,3-shift, perhaps via ion pair 9 (Scheme II).

As noted in our initial report,[13] the Diels–Alder reaction of adamantanethione 10-F with 2,3-dimethyl-1,3-butadiene gives a 2:1 mixture (GC) of *E* and *Z* adducts 11-F, respectively. Both products are stable to the reaction conditions. The assignment of configuration of the epimers 11-F was difficult, in part because we were at first unaware that several of the literature assignments[24] of the ^1H NMR signals of the parent adduct 11-H were incorrect. The



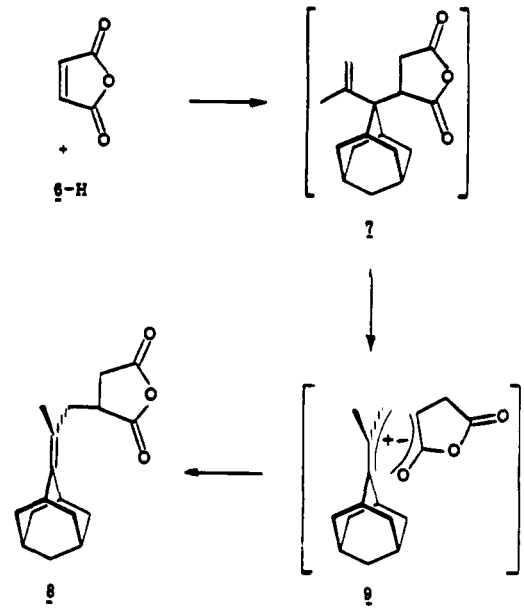
misassignments of $H_{1,3}$ as $H_{5,7}$ and vice versa were identified quickly by means of a carbon–hydrogen correlation experiment, but the reversal of the crucial $H_{4,9}$ and $H_{8,10}$ (both axial and equatorial) signals was not obvious. Indeed, although the shielding effect of the heteroatom directly "above" one pair of these C–H bonds cannot be very strong in the case of sulfur, the small difference observed (0.7 ppm) did seem to confirm Sasaki's assignment. The proton assignment carries over into the ^{13}C NMR spectrum, and application of our usual calculation[20] of expected ^{13}C NMR spectra of the fluoro derivatives then inexorably leads to the conclusion that the diene preferentially attacks the en face of the fluoro thione. In order to assess the correctness of this tentative conclusion, we sought to make use of a shift reagent study.

Sulfides themselves are too weakly basic for such studies.[25] Gentle oxidation by means of oxone of sulfides 11 gave the corresponding sulfoxides 12 in high yield (vigorous conditions lead to concurrent epoxidation of double bonds present[26]). However, this did not solve the problem. The



pyramidal sulfoxide groups lead to chiral molecules with diastereotopic $C_{4,9}$ and $C_{8,10}$ pairs, and the addition of the shift reagent $Eu(fod)_3$ did not permit a reliable identification of the signals of these atoms. More vigorous oxone treatment converted the sulfides into mixtures of the corresponding sulfones 13 and sulfone–epoxides 14, which could be separated chromatographically. In sulfone 13-H, the methylene carbons in question are readily distinguished by the fact that the distal pair is less than half as much deshielded by the shift reagent as the proximal pair (see Figure 1). The sulfone derived from the minor isomer of 11-F showed that the carbon pair much more strongly deshielded by the shift reagent is also the pair that is strongly coupled to the ^{19}F. The major isomer is thus identified as (*E*)-11-F. We note here in passing that the polarizing effect of the sulfur on the axial CH bonds "underneath", so weak as to be misleading in the sulfides,

Scheme II



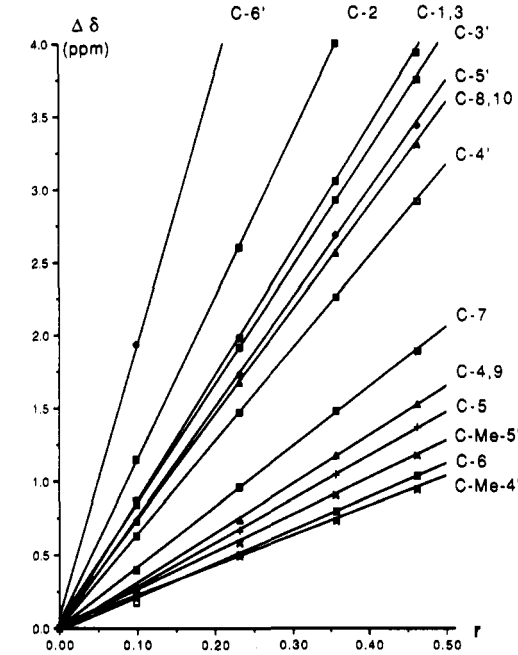


Figure 1. Effect of added $Eu(fod)_3$ (*r* equiv) on the chemical shifts of the ^{13}C NMR signals in 13-H.

is stronger and in the usual direction in the sulfones (see Experimental Section). Our NMR study of 14-H proved to be educational in another respect: although the ^1H spectrum was hopelessly complex and could not be analyzed even at 300 MHz, a 600-MHz spectrum had a first-order appearance (see supplementary material).

We also wished to study the nature of the substituent effect in the Diels–Alder reaction with an example in which the adamantane moiety is incorporated in the diene. Paquette has reported[27] that this reaction is sluggish or gives other products when a simple propenylidene is grafted onto C_7 of a benzonorbornane system, presumably in part because of the surely preferred s-trans conformation, and we suspected that our difficulties with an analogous adamantane-based structure would be even greater because of the additional presence of two axial

(24) Katada, T.; Eguchi, S.; Sasaki, T. *J. Org. Chem.* **1986**, *51*, 314.
(25) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553.
(26) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(27) Paquette, L. A.; Klinger, F. *J. Org. Chem.* **1982**, *47*, 272.

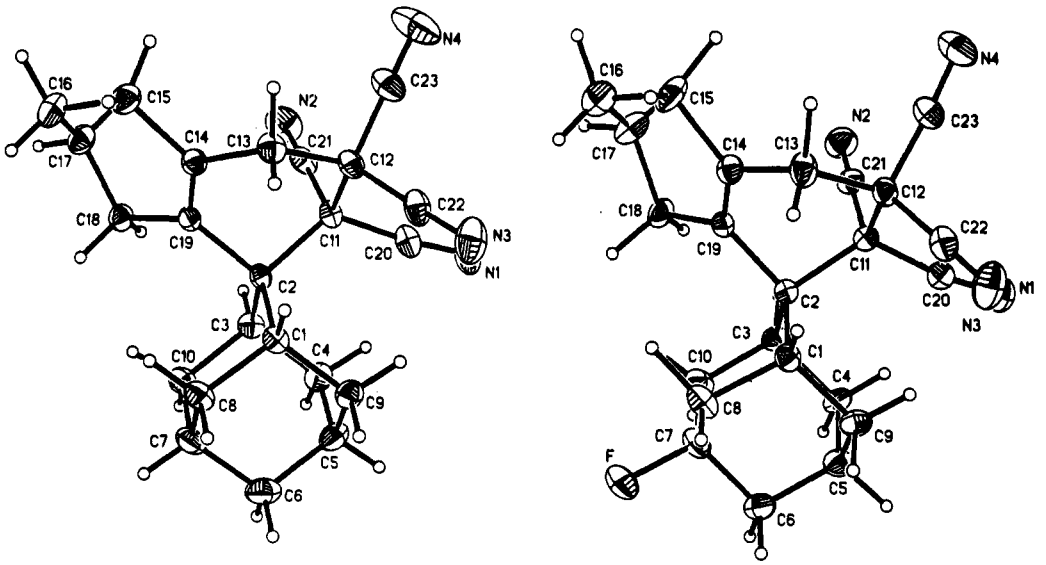


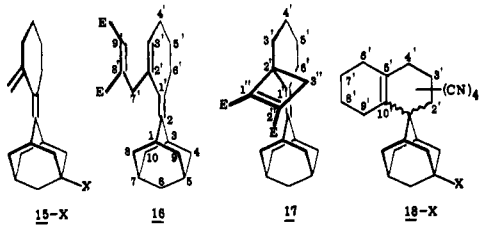
Figure 2. ORTEP representations of 18-H and *E*-18-F.

Table I. Bond Distances[a] (in Å) of 18-H and 18-F

bond	18-H	18-F	bond	18-H	18-F
1–2	1.547	1.553	14–15	1.510	1.512
2–3	1.563	1.563	15–16	1.511	1.514
1–8	1.534	1.540	16–17	1.507	1.509
3–10	1.546	1.545	17–18	1.520	1.524
1–9	1.533	1.536	18–19	1.515	1.517
3–4	1.537	1.542	13–14	1.493	1.495
7–8[b]	1.530	1.511	12–13	1.561	1.566
7–10[b]	1.521	1.509	11–12	1.603	1.604
4–5	1.525	1.528	12–22	1.475	1.480
5–9	1.521	1.522	12–23	1.481	1.479
6–7[b]	1.523	1.513	11–20	1.492	1.489
5–6	1.527	1.526	11–21	1.483	1.482
2–19	1.563	1.562	20–N	1.133	1.137
2–11	1.603	1.608	21–N	1.133	1.137
14–19	1.332	1.331	22–N	1.133	1.134
7–F[b]		1.417	23–N	1.129	1.132

[a] Numbering system: see Figure 2 (not the same as in the text). [b] These bonds are not included in one comparison in the text.

hydrogen atoms on each side. We therefore settled on the structure **15**-X, in which the s-cis conformation is enforced.



15-X **16** **17** **18**-X

This compound was still available from an earlier study. Initially, we had little success; thus, dimethyl acetylenedicarboxylate reacted only sluggishly, and the results were ene product **16** and [2 + 2] cycloaddition product **17** rather than the hoped-for Diels–Alder adduct (E is carbomethoxy).

Tetracyanoethylene (TCNE) was found to undergo a smooth reaction with **15**-H to give adduct **18**-H. The structure could not be proved by means of NMR, however. Close inspection showed that several of the peaks in both the ^{13}C and ^{1}H NMR spectra seemed suspiciously broad, and, indeed, when the proton spectrum was recorded at temperatures varied from −40 to +55 °C, coalescence was plainly visible. Inversion of cyclohexene rings is generally expected to be quite facile; however, in octalins such as **18** two cyclohexene rings have the double bond in common,

Table II. Bond Angles[a] (in degrees) of 18-H and 18-F

angle	18-H	18-F	angle	18-H	18-F
1–2–3	105.7	105.4	2–19–14	119.5	119.1
2–1–8	108.5	108.3	13–14–19	122.8	121.7
2–3–10	110.9	110.4	12–13–14	112.9	112.0
2–1–9	112.6	112.7	11–12–13	112.9	112.7
8–1–9	108.4	108.6	2–11–12	111.3	110.8
4–3–10	105.0	104.9	2–19–18	121.7	121.6
2–3–4	112.8	113.2	14–19–18	118.5	118.9
1–8–7[b]	110.3	108.9	15–14–19	124.8	125.1
3–10–7[b]	110.0	109.4	13–14–15	112.4	113.2
1–9–5	110.4	110.5	17–18–19	112.2	112.6
3–4–5	110.5	110.4	16–17–18	109.8	109.7
8–7–10[b]	108.5	110.0	15–16–17	109.8	109.3
4–5–9	109.8	109.1	14–15–16	114.7	113.5
6–7–8[b]	110.2	111.3	2–11–20	120.2	120.3
6–7–10[b]	110.0	110.6	2–11–21	106.1	106.2
6–5–9	109.0	108.7	12–11–20	104.8	105.2
4–5–6	109.6	110.2	12–11–21	109.1	109.9
5–6–7[b]	108.4	107.7	11–12–22	110.3	110.3
6–7–F[b]		108.7	11–12–23	107.6	109.4
8–7–F[b]		108.3	13–12–22	109.2	108.7
10–7–F[b]		107.9	13–12–23	110.6	108.4
1–2–19	112.4	113.4	20–11–21	104.9	104.1
3–2–19	114.6	114.3	22–12–23	105.9	107.3
1–2–11	112.4	112.2	11–20–N[b]	172.8	171.8
3–2–11	111.6	111.9	11–21–N[b]	177.1	175.8
11–2–19	100.3	100.0	12–22–N[b]	177.6	177.7
			12–23–N[b]	178.3	175.7

[a] As in Table I. [b] These angles are not included in one comparison in the text.

and the high degree of substitution in one of them makes it seem reasonable that inversion—probably involving both rings at once—could be much slower than normal.[28] Fortunately, it was not difficult to grow good quality crystals, and the X-ray structure was clearly confirmed as that of **18**-H. The highly puckered shape of the octalin rings can be seen at a glance (Figure 2). Furthermore, the presence of several unusually long CC bonds attests to the strain: the lengths of the C_2–C_{11} and C_{11}–C_{12} bonds are both 1.603 Å, and angles $C_1C_2C_{11}$, $C_1C_2C_{14}$, and $C_{13}C_{14}C_{15}$ all equal 122.4°.

Fluoro analogue **15**-F reacted similarly with TCNE, and two adducts were obtained in a 58:42 ratio as determined

(28) (a) Anet, F. A. L. In *The Conformational Analysis of Cyclohexanes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH: 1989; Chapter 1. (b) Lipkowitz, K. B. *ibid.*, ref 28a, Chapter 7.

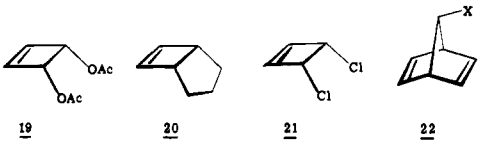
by means of ^{19}F NMR. After separation of the isomers, coalescence was once again observed in both of them, and configurational assignment by means of NMR was ruled out. Once again, we had recourse to X-ray diffraction; the minor isomer was shown to be (*E*)-18-F. Tables I and II record the bond lengths and angles describing the adamantane parts of molecules 18-H and *E*-18-F.

Discussion

In summary of these results, it can be said that bond formation (cleavage) occurred in each of the cycloaddition (-reversion) reactions at that face which is *anti* to the more electron-rich carbon–carbon bond, in agreement with expectations based on the notion of transition-state hyperconjugation. The availability of the crystal data just mentioned allows us to make an initial comment on the possibility that the presence of a strongly polarizing group such as 5-fluoro might cause significant distortions in the supposedly rigid adamantane framework and thus cause unsuspected steric differences between the two faces at C_2. Previous attempts to study this question with 5-bromo-, 5-fluoro-, and 5-phenyladamantanone had all failed because of disordered single crystals. Inspection of Tables I and II does not reveal significant distortions. The average absolute difference in bond length is 0.005 Å, with a range of 0 to 0.019 Å. Short FC–C bonds are in any case expected, and, if they are left out of the picture, the average is only 0.002 Å with a range of 0 to 0.006 Å. This is comparable to the average absolute difference in bond length in the octalin portion of the molecule (0.003 Å, range of 0–0.005 Å). The bond angles tell a similar story (average if C(FC)C and (FC)CCC angles are omitted: 20′ arc, range 0–40′; octalin portion if cyano group angles are excluded: average 40′, range 0–1.2°).

It may be pointed out that there are several additional instances in the literature that support transition-state hyperconjugation as a basis for stereochemical results. Thus, the cycloaddition of dichloroketene to 4-*tert*-butyl-1-methylenecyclohexane occurs predominantly (4:1) at the zu (axial) face[17] even though this preference is contrasteric. The aforementioned singlet oxygen reactions also furnish remarkable examples. Wynberg and Hummelen[29] reported that the presence of a 4-equatorial *N*-amido group in adamantylideneadamantane leads to a 3:2 preference of *syn* attack by $^1O_2$, and Nelsen found that the 4-equatorial chloro derivative can be oxidized to a radical cation[30] in which the preference for *syn* attack by $^1O_2$ is as much as 25:1.[31] Neither group offered an explanation for these results. The large ratio in Nelsen's case is an indication of the increased need for hyperconjugation to delocalize the positive charge, in our opinion.

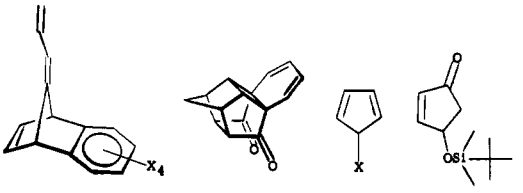
There are also a few reports concerning substituent effects on the stereochemistry of 1,3-dipolar cycloaddition. Since none are free from steric complications,[32] we emphasize the apparently contrasteric examples. Thus, Gandolfi and Rastelli[33] found that *cis*-3,4-diacetoxycyclobutene (**19**) reacts with 1,3-dipoles virtually exclusively on the *syn* side, but bicyclo[3.2.0]hept-6-ene (**20**) reacts with the same dipoles to give 100% *anti* products. Martin found that *cis*-3,4-dichlorocyclobutene (**21**) is attacked at the *syn* face by monosubstituted diazomethanes (to give products with R *exo*) and at the *anti* face with disubstituted diazomethanes.[34] Houk et al.[35] reported the relative



19 **20** **21** **22**

yields of all four products resulting from the cycloaddition of mesitylenenitrile oxide to 7-substituted norbornadienes **22**. The *anti* products, which should be less affected by strain and/or chelation considerations than the *syn* isomers, exhibit a higher exo/endo ratio when X is carbon than when it is oxygen. With the exception of the latter data, all these findings can be viewed as supporting transition-state hyperconjugation, though none of the authors of these reports discussed them in those terms.

Further information is available in the area of Diels–Alder reactions. Thus, results that were or could have been anticipated from our point of view include the facts that while **23**-H_4 is unselective in the capture of dienophiles,



23-X_4 **24** **25**-X **26**

23-F_4 suffers attack primarily at the zu face,[27] that diketone **24** reacts with dienophiles at the zu face,[36] that *syn* approach to **25**-X is favored if X is an electronegative atom[37] but *anti* approach when it is sulfur,[38] silicon,[39] or iodine,[40] and that 1,3-butadienes attack the zu face of **26**.[41] Further examples can be found in the literature just quoted. On the other hand, Houk's results with hexachlorocyclopentadiene and 7-substituted norbornadienes[42] are not readily comprehensible in this way. It is hoped that further investigations will shed light on the question of whether any of the present theories[4,43] can account for the available data better and more comprehensively than the

(29) Hummelen, J. C. Thesis, University of Groningen, 1985, p 76.
(30) Gerson, F.; Lopez, J.; Akaba, R.; Nelsen, S. F. *J. Am. Chem. Soc.* **1981**, *103*, 6716.
(31) Nelsen, S. F.; Kapp, D. L.; Akaba, R.; Evans, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6863.
(32) Two of these involve adamantanethione and can potentially be studied with 10-F. See: (a) Huisgen, R.; Mloston, G. *Tetrahedron Lett.* **1985**, *26*, 1049. (b) Mloston, G.; Skrzypek, Z. *Bull. Soc. Chim. Belg.* **1990**, *99*, 167.
(33) Burdisso, M.; Gandolfi, R.; Lucchi, M.; Rastelli, A. *J. Org. Chem.* **1988**, *53*, 2125.
(34) Landen, H.; Margraf, B.; Martin, H.-D. *Tetrahedron Lett.* **1988**, *29*, 6593.
(35) Bo, L. D.; De Amici, M.; De Micheli, C.; Gandolfi, R.; Houk, K. N. *Tetrahedron Lett.* **1989**, *30*, 807.
(36) (a) Coxon, J. M.; O'Connell, M. J.; Steel, P. J. *J. Org. Chem.* **1987**, *52*, 4726. (b) Pandey, B.; Zope, U. R.; Ayyangar, N. R. *Synth. Commun.* **1989**, *19*, 585.
(37) (a) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1988**, *110*, 4074. See also: (b) Gillard, J. R.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1439. (c) Naperstkow, A. M.; Macaulay, J. B.; Newlands, M. J.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 5077.
(38) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136.
(39) Fleming, I.; Williams, R. V. *J. Chem. Soc., Perkin Trans I* **1981**, 684.
(40) Breslow, R.; Hoffman, J. M. H.; Perchonock, C. *Tetrahedron Lett.* **1973**, *38*, 3723.
(41) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387.
(42) Houk, K. N.; Mueller, P. H.; Wu, Y.-D.; Mazzocchi, P. H.; Shook, D.; Khachik, F. *Tetrahedron Lett.* **1990**, *31*, 7285.
(43) (a) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980. (b) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257. (c) Angel, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642. (d) Mahaim, C.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 866.

simple notion of transition-state hyperconjugation.

Experimental Section

^1H and ^{13}C NMR spectra are recorded in $CDCl_3$ solution, the former at 300 MHz and the latter at 75 MHz, unless otherwise noted. The purity of all new compounds is estimated to be 95%, as established by ^{13}C NMR; all carbons were located and, with two minor exceptions, no extraneous signals were observed at signal-to-noise ratios of 20–100.

Cycloaddition of Dichloroketene and 2-Methyleneadamantane (2-H). Method A. Trichloroacetyl chloride (130.2 mg, 0.884 mmol) in anhydrous *n*-hexane (10 mL) was added to a refluxing solution of 2-H[44] (110.2 mg, 0.743 mmol) and triethylamine (116.2 mg, 1.15 mmol) in *n*-hexane (10 mL) by means of a syringe pump in 2 h; reflux was continued for 3 h. Water (40 mL) was added, and, after separation of the layers, the aqueous part was extracted with ether (3 × 30 mL). The combined organic solution was washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. Removal of solvent left a red-brown oil, which was flash-chromatographed (silica gel, petroleum ether–benzene) to give a solid. Recrystallization (petroleum ether) gave colorless crystals of 3-H (161 mg, 84%): mp 91–92 °C, lit.[19] mp 91.8–92.8°; MS 258 (0.6), 260 (0.3), 262 (0.1), 216 (100), 217 (12), 218 (66), 219 (8), 220 (11), 221 (1), 181 (21), 183 (7), 91 (40); ^1H NMR, see ref 19; ^{13}C NMR δ 194.75 (C=O), 91.88 (CCl_2), 53.24 (CH_2CO), 52.29 (C_2), 36.87 (C_6), 34.91 ($C_{8,10}$), 34.72 ($C_{1,3}$), 34.14 ($C_{4,9}$), 26.44 (C_7), 26.20 (C_5).

Method B. Activated zinc[18] (134 mg, 2.05 mmol) was suspended in a solution of 2-H (101 mg, 0.68 mmol) in ether (10 mL). A solution of trichloroacetyl chloride (407 mg, 2.24 mmol) and $POCl_3$ (329 mg, 2.15 mmol) in ether (10 mL) was added at room temperature by means of a syringe pump in 4 h. The solution was warmed to reflux (4 h), cooled, and filtered; the filtrate was diluted with ether (50 mL), washed with water (3 × 50 mL), dilute NaOH (0.1 N, 50 mL), and water (3 × 50 mL), dried over $MgSO_4$, and concentrated to small volume. The resulting solid was crystallized as in method A; yield 135 mg, 76%.

Cycloaddition of Dichloroketene with 2-F and 2-Ph. Neither methods A or B worked satisfactorily with 2-F,[12a] but method B worked well with 2-Ph:[11] a colorless solid adduct mixture 3-Ph was obtained in 97% yield. The product ratio was obtained by integration of the two CH_2CO signals at δ 3.154 and 3.118 (57.2:42.8, respectively). Fractional crystallization gave small amounts of the major adduct in pure form. **(*Z*)-3-Ph**: ^1H NMR δ 1.5–2.6 (m, 13 H), 3.154 (s, 2 H), 7.0–7.6 (m, 5 H); ^{13}C NMR δ 27.21 (C_7), 34.16 ($C_{8,10}$), 34.80 (C_5), 35.53 ($C_{1,3}$), 39.62 ($C_{4,9}$), 42.59 (C_6), 51.53 (C_2), 52.78 ($C_{4'}$), 91.76 ($C_{2'}$), 124.78 (C_o), 125.99 (C_p), 128.35 (C_m), 149.57 (C_i), 194.31 ($C_{3'}$). **(*E*)-3-Ph**: ^1H NMR δ 1.5–2.6 (m, 13 H), 3.118 (s, 2 H), 7.0–7.6 (m, 5 H); ^{13}C NMR δ 26.92 (C_7), 33.39 ($C_{8,10}$), 35.09 (C_5), 35.59 ($C_{1,3}$), 40.28 ($C_{4,9}$), 43.00 (C_6), 51.84 (C_2), 53.32 ($C_{4'}$), 91.76 ($C_{2'}$), 124.70 (C_o), 126.09 (C_p), 128.29 (C_m), 149.12 (C_i), 194.31 ($C_{3'}$).

Dechlorination of 2-H. Zinc powder (45 mg) was added to a solution of 2-H (26.8 mg) in acetic acid (2 mL). The mixture was stirred at 70 °C for 2 h. The mixtured was filtered, the filtrate was diluted with CH_2Cl_2 (15 mL), and the mixture was washed with aqueous NaOH (2 N, 15 mL), water (3 × 15 mL), and brine (15 mL), and dried over $MgSO_4$. Removal of solvent and chromatography (silica gel, 10–15% ethyl acetate in hexane) gave the white solid spirocyclobutanone (16.1 mg, 82%); physical characteristics are as in ref 19.

Ring Expansion of 3-H. A dry ethereal solution of diazomethane (2 mmol, prepared from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine[45] 10 mL) was added dropwise to a solution of 3-H in ether (10 mL) at 0 °C. After 2 h and quenching with acetic acid, the solution was worked up in the usual way to give the colorless solid 2',2'-dichlorospiro[adamantane-2,1'-cyclopentan-3'-one], which was crystallized from hexane (53 mg, 90%): mp 93–93.5 °C; MS 276 (2.3), 274 (12.8), 272 (18.3), 91 (100); ^1H NMR δ 2.808 (2 H, d, J = 13.5 Hz, $H_{4,9}$ ax), 2.436 (2 H, t, J = 7.7 Hz, $H_{4'}$), 2.234 (2 H, t, J = 7.7 Hz, $H_{5'}$), 2.070 (2 H, d, J = 12.9 Hz, $H_{8,10}$ ax), 2.038 (2 H, bs, $H_{1,3}$), 1.973 (1 H, s, H_5), 1.927 (1 H, d, s, H_7), 1.752 (2 H, s, H_6), 1.702 (2 H, d, J = 12.9 Hz, $H_{8,10}$ eq), 1.614 (2 H, d, J = 13.5 Hz, $H_{4,9}$ eq); ^{13}C NMR δ 27.23 ($C_{5,7}$), 28.97 ($C_{4'}$), 29.09 ($C_{5'}$), 32.44 ($C_{4,9}$), 32.76 ($C_{1,3}$), 34.76 ($C_{8,10}$), 39.42 (C_6), 54.20 (C_2), 95.58 ($C_{2'}$), 201.81 ($C_{3'}$). The $C_{4'}$ and $C_{5'}$ signals were confirmed by means of a 2D carbon–hydrogen correlation experiment and a shift reagent study.

Cycloaddition of Methyl Isobutyrate Enolate Anion to Adamantanones. Methyl isobutyrate (181 mg, 1.77 mmol) was added dropwise and with stirring to a solution of lithium diisopropylamide (LDA, 246 mg, 2.30 mmol) in dry THF (10 mL) under nitrogen at −78 °C. Adamantanone (270 mg, 1.80 mmol) in dry THF (5 mL) was added after 1 h. After continued stirring for 4 h at −78 °C, the solvent was removed at room temperature by rotary evaporation, the residue was dissolved in ether and washed with water, the aqueous layer was extracted with ether (3 × 10 mL), the combined ether extracts were dried over Na_2SO_4, and the solvent was removed to yield a light yellow solid, which was chromatographed (silica gel, hexane–ether 4:1 v/v): yield of 5-H, 317 mg (80%); mp 110 °C dec, lit.[22] mp 110.5–112 °C; ^{13}C NMR (O *anti* to C_5) δ 18.09 (Me), 25.97 (C_5), 26.25 (C_7), 33.48 ($C_{8,10}$), 33.64 ($C_{1,3}$), 35.16 ($C_{4,9}$), 36.40 (C_6), 53.83 ($C_{3'}$), 89.55 (C_2), 176.20 ($C_{4'}$).

A similar experiment with 5-fluoroadamantanone (100 mg, 0.42 mmol; methyl isobutyrate, 45 mg, 0.44 mmol; LDA, 58 mg, 0.54 mmol) led to a crude mixture of the two β-lactones (*E*)- and (*Z*)-5-F, which was analyzed by means of ^1H NMR integration (SYNCAP program). Chromatography (under the same conditions as the parent compound) led to samples of the pure, separate isomers, which were crystallized from hexane. **((*E*)-3',3'-Dimethylspiro[5-fluoroadamantane-2,2'-oxetan-4'-one] ((*E*)-5-F)**: mp 115 °C dec; ^1H NMR δ 1.42 (6 H, s), 1.5–2.3 (11 H, m), 2.48 (2 H, bs); ^{13}C NMR δ 17.99 (Me), 29.53 (C_7, J_{CF} = 10.35 Hz), 32.01 ($C_{8,10}$), 36.05 ($C_{1,3}$, J_{CF} = 10.31 Hz), 39.74 ($C_{4,9}$, J_{CF} = 19.91 Hz), 41.81 (C_6, J_{CF} = 18.26 Hz), 54.27 ($C_{3'}$), 87.25 (C_2), 90.52 (C_5, J_{CF} = 194.5 Hz), 175.0 ($C_{4'}$). **(*Z*)-5-F**: mp 109 °C dec; ^1H NMR δ 1.40 (6 H, s), 1.58–2.26 (11 H, m), 2.52 (2 H, bs); ^{13}C NMR δ 18.48 (6 H, s), 29.11 (C_7, J_{CF} = 10.64 Hz), 33.58 ($C_{8,10}$), 36.87 ($C_{1,3}$, J_{CF} = 10.95 Hz), 38.18 ($C_{4,9}$, J_{CF} = 20.00 Hz), 41.57 (C_6, J_{CF} = 19.84 Hz), 53.66 ($C_{3'}$), 86.94 (C_2), 90.50 (C_5, J_{CF} = 195.5 Hz), 175.2 ($C_{4'}$).

Decarboxylation of β-Lactones. Parent β-lactone 5-H (8.1 mg) was dissolved in molecular-sieve-dried toluene-d_8 (0.34 mL), and the solution was degassed and sealed in an NMR tube. The decarboxylation was studied at 80 °C; 16 acquisitions were taken every 20 min for 6 h. The methyl signals of the olefin and lactone were integrated by means of a GENCAP program and compared to allow calculation of the first-order rate constant. A similar run was made with CD_3CN. Kinetics of (*E*)- and (*Z*)-5-F were studied in CD_3CN at 80 °C also, data being taken every 40 min for 12 h. These reactions produced the common olefin 6-F, which was not characterized further.

Oxygen Scrambling Study. To ^{17}O NMR signals for natural abundance 5-H were found to be at 322 (carbonyl oxygen) and 267 ppm (ether oxygen) relative to water; the assignment was made in analogy to that common in esters.[46] Adamantanone-^{17}O was prepared from natural ketone (120 mg, 0.80 mmol), $H_2{}^{17}O$ (10%, 0.1 mL), and THF (0.5 mL) in a sealed tube heated to 80 °C for 7 d. After sublimation, a strong ^{17}O signal was observed at 518 ppm. The labeled β-lactone was prepared in the same way as the natural abundance material; the 267 ppm signal was strongly enhanced. After this lactone was heated to 80 °C in CH_3CN solution for 1 decarboxylation half-life, the remaining fraction was examined for evidence of scrambling by means of its ^{17}O NMR spectrum. No scrambling was detected.

Reaction of 6-H with Maleic Anhydride. Olefin 6-H (100 mg, 0.57 mmol) and maleic anhydride (crystallized from benzene) were sealed together under vacuum and heated to 145 °C overnight. The product was crystallized from ether and identified as 8: ^1H NMR δ 1.64–2.0 (m, 16 H), 2.6–2.7 (m, 2 H), 2.79 (m, 1 H), 2.9–3.0 (m, 1 H), 3.24 (m, 1 H), no ^1H signal was observed in the vinyl region; ^{13}C NMR δ 16.83, 25.75, 32.97, 33.20, 33.36, 33.99, 36.78, 38.61, 38.69, 39.10, 39.35, 39.55, 115.1, 145.4, 170.3, 173.9. Interruption of the reaction before completion did not lead

(44) Olah, G. A.; Krishnamurthy, V. V. *J. Am. Chem. Soc.* **1982**, *104*, 3987.

(45) Black, T. H. *Aldrichimica Acta* **1983**, *16*(*1*), 3.

(46) Orsini, F.; Ricca, G. S. *Org. Magn. Reson.* **1984**, *22*, 653.

to reaction mixtures in which a vinyl ^1H signal could be seen.

4',5'-Dimethylspiro[adamantane-2,2'-thiacyclohex-4'-ene] (11-H). The parent adduct was prepared from **10-H**[47] as described by Sasaki:[24] ^1H NMR (S anti to C_5) δ 1.572 (2 H, d, $H_{8,10}$ eq), 1.666 (2 H, d, $H_{4,9}$ eq), 1.697 (8 H, s, H_6, H_{Me}), 1.775 (2 H, s, $H_{1,3}$), 1.860 (1 H, s, H_5), 1.903 (1 H, s, H_7), 2.044 (2 H, d, $H_{4,9}$ ax) 2.472 (2 H, d, $H_{8,10}$ ax), 2.491 (2 H, s, $H_{3'}$), 2.983 (2 H, s, $H_{6'}$); ^{13}C NMR δ 16.86 and 20.87 (CH_3), 27.68 (C_5), 27.98 (C_7), 29.43 ($C_{6'}$), 33.07 ($C_{4,9}$), 33.74 ($C_{8,10}$), 35.13 ($C_{1,3}$), 39.17 (C_6), 42.48 ($C_{3'}$), 50.62 (C_2), 122.45 and 126.11 ($C_{4',5'}$).

5-Fluoroadamantane-2-thione (10-F). P_4S_{10} (122 mg, 0.274 mmol) was added in small portions to a solution of 5-fluoroadamantanone[6a] in anhydrous pyridine (10 mL) at 90 °C within 10 min. Heating was continued for 11 h; the mixture was cooled and diluted with petroleum ether (75 mL). The resulting red solution was washed with water (4 × 50 mL), hydrochloric acid (2 M, 2 × 50 mL), water (to pH 6), and brine (50 mL) and dried over $MgSO_4$. Evaporation of solvent gave 333 mg of a red solid (93%). GC indicated the presence of less than 1% of the fluoro ketone. **10-F**: MS 184 (M^+); ^1H NMR δ 1.8–2.4 (11 H, m), 3.49 (2 H, bs, $H_{1,3}$); ^{13}C NMR δ 30.72 (C_7, J_{CF} = 8.35 Hz), 39.85 ($C_{8,10}$), 41.73 (C_6, J_{CF} = 17.81 Hz), 43.22 ($C_{4,9}$, J_{CF} = 18.23 Hz), 57.78 ($C_{1,3}$, J_{CF} = 12.36 Hz), 90.12 (C_5, J_{CF} = 185.54 Hz), 264.96 (C_2). This compound dimerizes rapidly even in solution to the colorless solid dimer; hence purification was not attempted.

5-Fluoro-4',5'-dimethylspiro[adamantane-2,2'-thiocyclohex-4'-ene] (11-F). Thione **10-F** (378 mg, 2.05 mmol), hydroquinone (11.7 mg, 0.11 mmol), and 2,3-dimethylbuta-1,3-diene (1.74 g, 21.2 mmol) were dissolved in toluene (15 mL), and the solution was heated to reflux for 50 h at which time it had become colorless. GC analysis indicated a product ratio of 1.99:1; ^1H NMR integration of the $H_{8,10(ax)}$ signals gave a ratio of 2.33:1. Repeated chromatography (silica gel, petroleum ether–0–40% benzene) led to partial separation (228 mg, (*E*)-**11-F**, 153 mg mixture, 61 mg (*Z*)-**11-F**; overall, 83%). **(*E*)-11-F**: mp 75.5–76 °C (MeOH); MS 266 (33, M^+), 184 (100); ^1H NMR δ 1.425 (2 H, d, $H_{8,10}$ eq), 1.695 (6 H, Me), 1.755 (2 H, d, $H_{4,9}$ eq), 1.863 (2 H, s, H_6), 2.066 (2 H, s, $H_{1,3}$), 2.19 (3, H, m, $H_{7,4,9}$ ax), 2.390 (2 H, d, $H_{8,10}$ ax), 2.467 (2 H, s, $H_{3'}$), 2.977 (2 H, s, $H_{6'}$); ^{13}C NMR δ 18.83 and 20.89 (Me), 29.58 ($C_{5'}$), 30.91 (C_7, J_{CF} = 9.65 Hz), 32.02 ($C_{8,10}$), 37.92 ($C_{4,9}$, J_{CF} = 18.04 Hz), 38.19 ($C_{1,3}$, J_{CF} = 9.79 Hz), 42.36 ($C_{3'}$), 44.05 (C_6, J_{CF} = 16.86 Hz), 48.77 (C_2), 91.95 (C_5, J_{CF} = 184.47 Hz), 122.58 and 125.82 ($C_{4',5'}$). **(*Z*)-11-F**: mp 93–95 °C (MeOH); MS 266 (37, M^+), 184 (100); ^1H NMR δ 1.516 (2 H, d, $H_{8,10}$ eq), 1.695 (6 H, s, Me), 1.681 (2 H, d, $H_{4,9}$ eq), 1.858 (2 H, s, H_6), 1.948 (2 H, d, $H_{8,10}$ ax), 2.068 (2 H, s, $H_{1,3}$), 2.211 (1 H, s, H_7), 2.67 (2 H, m, $H_{4,9}$ ax), 2.999 (2 H, s, $H_{6'}$), 3.438 (2 H, s, $H_{3'}$); ^{13}C NMR δ 18.85 and 20.86 (Me), 29.40 ($C_{5'}$), 30.45 (C_7, J_{CF} = 9.79 Hz), 31.39 ($C_{8,10}$), 38.22 ($C_{1,3}$, J_{CF} = 10.37 Hz), 38.49 ($C_{4,9}$, J_{CF} = 18.77 Hz), 41.43 ($C_{3'}$), 43.94 (C_6, J_{CF} = 17.42 Hz), 48.72 (C_2), 92.14 (C_5, J_{CF} = 184.74 Hz), 122.57 and 125.98 ($C_{4',5'}$).

Oxidation of Adducts 11. Oxidation of 30–40 mg of adducts 11-H and (*E*)-, and (*Z*)-11-F with 50 mg of oxone (Aldrich) in a mixture of water (5 mL), methanol (10 mL), and acetone (2.5 mL) at 0 °C for 30 min followed by $NaHSO_3$ quench (10%, 5 mL), workup, and chromatography (silica gel, 25–75 ethyl acetate–hexane) gave the corresponding pure, solid sulfoxides in quantitative yield. The four C_4 and C_{8-10} signals could not be assigned with confidence even when $Eu(fod)_3$ solution was added, and hence these compounds were not studied further.[48] More vigorous oxidation at room temperature for 5 h gave in each case a mixture of two compounds, which were separated chromatographically (silica gel, EtOAc–hexane). They were characterized as the sulfone and sulfone–oxirane.

13-H: 73%, mp 102–103 °C (petroleum ether); MS 216 (64, $M^+ - SO_2$, 201 (100); ^1H NMR δ 1.6–1.8 (12 H, m, H_{Me}, H_6, $H_{4,8-10}$ eq), 1.903 (1 H, s, H_7), 1.950 (1 H, s, H_5), 2.054 (2 H, d, $H_{4,9}$ ax), 2.237 (2 H, s, $H_{1,3}$), 2.797 (2 H, s, $H_{3'}$), 2.823 (2 H, d, $H_{8,10}$ ax), 3.490 (2 H, s, $H_{6'}$); ^{13}C NMR δ 19.02 and 19.99 (C_{Me}), 27.08 (C_7), 27.22 (C_5), 31.12 ($C_{1,3}$), 33.16 ($C_{8,10}$), 33.75 ($C_{4,9}$), 39.15 (C_6), 42.32 ($C_{3'}$), 53.95 ($C_{6'}$), 65.61 (C_2), 119.56 and 125.74 ($C_{4',5'}$). **(*E*)-13-F**: 61%; ^1H NMR δ 1.494 (2 H, d, $H_{8,10}$ eq), 1.682 (3 H, s, CH_3), 1.732 (3 H, s, CH_3), 1.790 (2 H, d, $H_{4,9}$ eq), 1.919 (2 H, s, H_6), 2.205 (2 H, m, $H_{4,9}$ ax), 2.335 (1 H, s, H_7), 2.521 (2 H, s, $H_{1,3}$), 2.781 (2 H, d, $H_{8,10}$ ax), 2.805 (2 H, s, $H_{3'}$), 3.521 (2 H, s, $H_{6'}$); ^{13}C NMR δ 19.11 and 20.06 (CH_3), 29.94 (C_7, J_{CF} = 10.50 Hz), 31.53 ($C_{8,10}$), 34.33 ($C_{1,3}$, J_{CF} = 9.20 Hz), 38.45 ($C_{4,9}$, J_{CF} = 19.18 Hz), 42.26 ($C_{3'}$), 44.03 (C_6, J_{CF} = 16.60 Hz), 54.21 ($C_{6'}$), 63.77 (C_2), 91.16 (C_5, J_{CF} = 185.28 Hz), 119.65 and 125.44 ($C_{4',5'}$). **(*Z*)-13-F**: 24%; ^1H NMR δ 1.564 (2 H, d, $H_{4,9}$ eq), 1.6–2.1 (12 H, m, H_{Me}, H_6, $H_{8,10}$, ax, eq), 2.281 (1 H, s, H_7), 2.474 (2 H, s, $H_{3'}$), 2.529 (2 H, s, $H_{1,3}$), 3.06 (2 H, m, $H_{4,9}$ ax), 3.536 (2 H, s, $H_{6'}$); ^{13}C NMR δ 19.13 and 20.94 (CH_3), 29.87 (C_7, J_{CF} = 9.97 Hz), 32.12 ($C_{8,10}$), 33.92 ($C_{1,3}$, J_{CF} = 10.81 Hz), 38.17 ($C_{4,9}$, J_{CF} = 19.88 Hz), 41.29 ($C_{3'}$), 43.99 (C_6, J_{CF} = 17.66 Hz), 53.69 ($C_{6'}$), 63.64 (C_2), 90.94 (C_5, J_{CF} = 184.53 Hz), 119.86 and 125.72 ($C_{4',5'}$). The three corresponding oxiranes were obtained in yields of 20, 16, and 43%, respectively. **14-H**: mp 112–113 °C; MS, M^+ not observed, 217 (38, $M^+ - SO_2 - CH_3$), 91 (100). The ^1H NMR spectrum at 600 MHz and the ^{13}C NMR spectrum at 150 MHz were analyzed and the signals assigned by means of 2D C–H correlation; for details, see ref 48.

Shift Reagent Study of 13-H and (*E*)-13-F. Small incremental amounts of a standard solution of $Eu(fod)_3$ in $CDCl_3$ were added to a solution of the substrate in an NMR tube, the volume was reduced to the original value, and the ^{13}C NMR was measured; six–eight spectra were collected. The chemical shifts were plotted against the amounts of $Eu(fod)_3$ added. The plots were essentially linear with $r > 0.995$. The slopes in arbitrary units are as follows: **13-H**: 4'-CH_3, 1.92; C_6, 2.41; 5'-CH_3 2.41; C_5, 2.83; $C_{4,9}$, 3.19; C_7, 3.89; $C_{4'}$, 5.95; $C_{8,10}$, 6.69; $C_{5'}$, 7.07; $C_{3'}$, 7.26; $C_{1,3}$, 9.09; C_2, 10.50; $C_{6'}$, 17.36. **(*E*)-13-F**: 4'-CH_3, 2.71; 5'-CH_3, 3.55; C_6, 3.57; C_5, 4.49; $C_{4,9}$, 4.95; C_7, 6.12; $C_{4'}$, 8.91; $C_{8,10}$, 10.21; $C_{5'}$, 10.68; $C_{3'}$, 11.46; $C_{1,3}$, 12.14; C_2, 15.30; $C_{6'}$, 25.85. The assignments rest on attached proton tests, slopes, and CF coupling constants. The ^{13}C NMR spectra of (*E*)- and (*Z*)-**13-F** could be calculated from those of adamantane, 1-fluoroadamantane, and **13-H** to good precision.[20]

Cycloaddition of Dimethyl Acetylenedicarboxylate to 15-H. 1-(2-Adamantylidene)-2-methylenecyclohexane was available from earlier investigations.[49] A solution of this diene (190 mg) and dimethyl acetylenedicarboxylate (1.16 g) in toluene (20 mL) was heated to reflux; progress of the reaction was monitored by GC. Two major products and several minor ones were formed. After 120 h, the solvent was stripped off; the residue was chromatographed (silica gel, 0–20% ethyl acetate–hexane) to give 41 mg (13%) of an oil identified as **16**: ^1H NMR δ 1.6–2.0 (14 H, m), 2.17 (4 H, m, $H_{4',6'}$), 2.72 (1 H, s, H_3), 2.88 (1 H, s, H_1), 3.23 (2 H, s, $H_{7'}$), 3.70 and 3.78 (6 H, s, OMe), 5.55 (1 H, t, $H_{3'}$), 5.79 (1 H, s, $H_{9'}$); ^{13}C NMR δ 24.48 ($C_{5'}$), 26.17 ($C_{6'}$), 27.66 ($C_{4'}$), 27.98 ($C_{5,7}$), 33.63 (C_3), 35.31 (C_1), 36.91 (C_6), 38.99 and 39.13 $C_{4,8-10}$), 41.85 ($C_{7'}$), 51.74 and 52.14 (OCH_3), 119.09 ($C_{9'}$), 131.28 ($C_{3'}$), 124.87, 133.69, 142.46 and 150.78 ($C_{1',2',2,8'}$), 165.61 and 169.27 (C=O). Also isolated was 89 mg (29%) of solid **17**: mp 169–171 °C (recrystallized from hexane); ^1H NMR δ 1.0–2.6 (22 H, m), 2.66 (1 H, d, J = 20.4 Hz) and 3.08 (1 H, d, J = 20.4 Hz, $H_{3''}$), 3.71 (3 H, s, OMe) and 3.73 (3 H, s, OMe); ^{13}C NMR δ 22.82 and 24.33 ($C_{4',5'}$), 26.83 and 27.07 ($C_{5,7}$), 30.92, 31.61, 31.76, 34.02, 35.07 ($C_{3''}$), 35.13 (2C), 35.56, 35.76, 38.72, 51.91 (OMe), 52.04 (OMe), 52.12 ($C_{2'}$), 131.13, 132.28, 141.07, 152.53 ($C_{1',1'',2,2''}$), 167.90 (C=O), 170.21 (C=O).

Cycloaddition of TCNE to 15-H and 15-F. A solution of **15-H** (115 mg) and TCNE (77.6 mg, 1.25 equiv) in CH_3CN (15 mL) was heated at 65 °C for 3 d. Removal of solvent and column chromatography (silica gel, EtOAc–hexane) afforded solid **18-H** (159 mg, 90%): mp > 200 °C dec; ^1H NMR δ 1.2–2.6 (m), 3.20 (bs, $h_{1/2}$ = 170 Hz); ^{13}C NMR δ 22.14, 23.00, 26.21, 26.45, 31.67, 32.87 (b, $h_{1/2}$ = 33 Hz), 33.10, 33.47 (2 C), 36.33 (b, $h_{1/2}$ = 33 Hz), 38.19 (2 C), 40.02 and 49.38 ($C_{2',3'}$), 57.05 (C_2), 113.32, 129.56, 140.80. Single crystals were obtained by slow evaporation of a solution of **18-H** in ethyl acetate–hexane (1:4).

The same conditions were applied to a solution of **15-F** (101 mg) and TCNE (95.4 mg) in CH_3CN (15 mL). ^{19}F NMR integration gave a ratio of the isomers as 42:58. Chromatography gave 62.2 mg of the minor isomer and 85.5 mg of the major isomer (96% overall). Major isomer ((*Z*)-**18-F**): mp > 200 °C dec; ^1H NMR δ 1.0–2.6 (m), 3.1 (bs); ^{19}F (CF_3COOH, 282 MHz) δ –61.70. Minor

(47) Greidanus, J. W. *Can. J. Chem.* **1970**, *48*, 3530.

(48) Spectral details may be found in Li, H. Ph.D. Thesis, State University of New York, Stony Brook, NY, 1991.

(49) (a) Mukherjee, A.; Venter, E.; le Noble, W. J. (b) Boyd, M.; Lin, M.-H.; Mukherjee, A.; le Noble, W. J. Manuscripts in preparation.

isomer ((*E*)-18-F): mp > 200 °C dec: ^{1}H NMR δ 1.0–2.6 (m), 3.1 (bs); ^{19}F NMR (CF_3COOH, 282 MHz) δ −60.06. Single crystals were obtained by slow evaporation of a solution in ethyl acetate–hexane (1:4). A ^{13}C NMR spectrum could not be obtained for either epimer because of poor solubility.

X-ray Diffraction Studies. For the parent compound 18-H, a colorless crystal of dimensions 0.33 × 0.25 × 0.23 mm was mounted on a R3m/μ update of a Nicolet $P2_1$ diffractometer. Unit cell dimensions were obtained from a least-squares refinement of 25 reflections. Crystal data: $C_{23}H_{24}N_4$, M_r = 356.48, monoclinic; $P2_1/c$; a = 14.710 (3), b = 10.597 (2), and c = 13.151 (2) Å, β = 114.63 (1)°; V = 1863.4 (6) Å^3; Z = 4, D_x = 1.270 g cm^{-3}; μ = 0.72 cm^{-1}; $F(000)$ = 760. Intensity data were collected by the ω-scan technique ($3 \le 2\theta \le 55°$) with a variable scan rate (4 to 29.3° min^{-1}) using graphite-monochromated radiation (Mo Kα, λ = 0.71073 Å). A total of 5733 reflections were collected of which 4290 were independent (R_{int} = 0.008), yielding 3137 with intensities greater than $3\sigma(I)$. Lorentz and polarization corrections and a ω-scan based absorption correction were applied. The structure was solved by direct methods and refined by a block-cascade least-squares technique. The structure was refined to R = 0.0561 and R_ω = 0.0794 with 341 parameters and 3137 reflections giving S = 1.597, $(\lambda/\sigma)_{max}$ = 0.022 and the largest peaks in a final difference map of −0.28 and 0.26 e Å^{-3}. The function $\sum w(|F_o| - |F_c|)^2$ was minimized with $w = [\sigma^2(F_o) + 0.00017F_o]^{-1}$. All programs supplied by Nicolet Instrument Corp. for Desktop 30 Microeclipse and Nova 4/C configuration with atomic scattering factors and anomalous dispersion corrections from *International Tables for X-ray Crystallography*.

Similarly, for (*E*)-18-F ($C_{23}H_{23}N_4F$), M_r = 374.50, monoclinic; $P2_1/c$; a = 9.529 (2), b = 16.523 (4), and c = 12.516 (2) Å, β = 105.81 (1)°; V = 1896.0 Å^3; z = 4, D_x = 1.310 g cm^{-3}; μ = 0.81 cm^{-1}; $F(000)$ = 792; 2522 reflections R = 0.0520.

Acknowledgment. W. le Noble is pleased to acknowledge NSF support for this investigation and for NIH and NSF support for the purchase of a 600-MHz NMR spectrometer.

Supplementary Material Available: X-ray data for 18-H and 18-F, ^{13}C NMR spectra of (*Z*)-3-Ph, 10-F, (*E*)- and (*Z*)-11-F, 13-H, (*E*)- and (*Z*)-13-F, 17, and 18-H, and ^{1}H NMR spectra of (*E*)- and (*Z*)-11-F and 14-H (at 600 MHz) (25 pages). Ordering information is given on any current masthead page.

Notes

Regioalternating Selectivity in the Metal Salt Catalyzed Aminolysis of Styrene Oxide

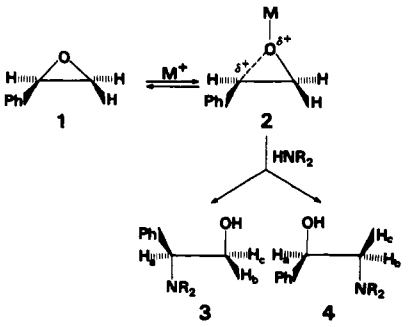
Marco Chini, Paolo Crotti,* and Franco Macchia

Dipartimento di Chimica Bioorganica, Università di Pisa, via Bonanno 33, 56126 Pisa, Italy

Received December 11, 1990

β-Amino alcohols are an important class of organic compounds[1] of considerable use in medicinal chemistry.[2] The most practical and widely used route to the synthesis of these compounds is the direct aminolysis of 1,2-epoxides;[1] however, these reactions, which are usually carried out with a large excess of ammonia or amines in protic solvents at elevated temperatures, often fail when poorly nucleophilic amines or highly substituted epoxides are concerned.[1] Recently, we discovered[3] a new, mild, and efficient method for the aminolysis of 1,2-epoxides in nonprotic solvents through the catalytic assistance of metal ion salts (Li^+, Na^+, Mg^{2+}, Ca^{2+}, Zn^{2+}). Besides the nature of the amine and epoxide, the reaction rate also depends on the type of the metal ion of the catalyst salt.[3] For example, in the alkaline metal ion series, the reactivity slows down dramatically on passing from lithium- to potassium-based salts.[3] The efficiency of this simple catalysis is confirmed by the fact that under appropriate conditions it is possible to obtain, in fair yield, the reaction of cyclohexene oxide with the poorly nucleophilic, sterically hindered diisopropylamine,[3] a reaction not previously accomplished. The stereoselectivity observed in these reactions[3] is complete inversion of configuration. Unsymmetrical epoxides[3] undergo regioselective addition of the nucleophile to the less substituted carbon. The exception is styrene oxide (1) in which an almost equimolar mixture of the two regioisomeric phenyl-substituted β-amino alcohols 3 and 4, (Scheme I) was obtained (see reaction with diethylamine in the presence of lithium perchlorate, entry 11, Table I). In view of the particular interest in phenylethanolamines in medicinal chemistry,[2] we wanted to study the regiochemical behavior of these new metal salt catalysts in the aminolysis of 1 in order to verify whether the regioselectivity could be appreciably modified depending on the amine and/or the catalyst in such a way as to direct the regiochemistry of these reactions selectively.

Scheme I



Results and Discussion

Table I reports the regioselectivity of the ring-opening reactions of 1 with several amines using $LiClO_4$ as the catalyst, (entries 1–12) together with the results obtained in the aminolysis reaction of 1 with a representative amine (diethylamine), using different metal salts as catalysts (entries 13–16). For the sake of comparison, the result of the opening reaction of 1 with diethylamine, carried out in the classic way without any metal catalyst in a protic solvent (EtOH)[1] is also reported (entry 17). The yields of

(1) (a) Möller, F. *Methoden der Organische Chemie (Houben-Weyl)*, 4th ed.; Müller, E., Ed.; Thieme Verlag: Stuttgart, 1957; Vol. 11/1, p 311–326. (b) Mousseron, M.; Jullien, J.; Jolchine, Y. *Bull. Soc. Chim. Fr.* **1952**, 757.

(2) Triggle, D. J. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley-Interscience; New York, 1981; p 225.

(3) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661.

0022-3263/91/1956-5939$02.50/0