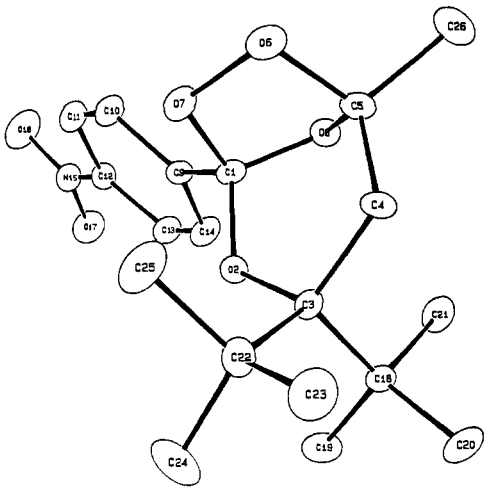
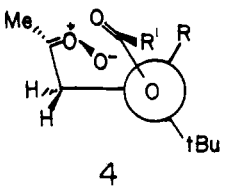



Figure 1, X-ray structure of **2a**. Hydrogen atoms have been omitted for clarity. Selected bond distances (in angstroms): C1–O2 = 1.378 (2), C3–O2 = 1.478 (2), C1–O7 = 1.434 (2), O6–O7 = 1.465 (2), O6–C5 = 1.449 (2). Bond angles: C1–O2–C3 = 119.9 (1)°, C18–C3–C22 = 117.9 (1)°.




4

Figure 2. Conformation of **4**, viewed in Newman projection along the ester oxygen–alkyl bond. When R = Me, a clockwise rotation about this bond is favorable, removing the ester C=O from proximity to the carbonyl oxide.

the dioxane ring of **2a** exists in an envelope conformation with O8 lying 0.81 Å out of the least-squares plane calculated for C1–O2–C3–C4–C5. The flattened ring minimizes transannular interactions of the *gem*-di-*tert*-butyl system with the epoxy or peroxy bridges. The five-membered ring adopts a half-chair conformation with C5 situated 0.26 Å below, and O8 0.46 Å above, the C1–O7–O6 plane. At C1, the axial peroxy bridge sets up an anomeric effect with O2. Indeed, strong differentiation of bond lengths to this center (C1–O2, 1.378 (2) Å, C3–O2, 1.478 (2) Å) confirm this interaction, as established for alkyl pyranosides.[6]

The formation of **2a** is considered to involve cycloaddition of the carbonyl oxide moiety with the ester group within **4a** (Figure 2), which is produced on fragmentation of the primary ozonide of **1a**. Thus, ozonolysis of **1a**, followed by addition of dimethyl sulfide at −70 °C, leads to a 1:1 mixture of **2a** and **3a** in essentially quantitative yield. Since **2a** does not react with dimethyl sulfide, this result requires reductive diversion of a percursor of **2a** to give **3a**. From the Criegee mechanism, only the carbonyl oxide **4a** satisfies this role. Examination of molecular models indicates that only the syn geometry of carbonyl oxide **4** is suitably disposed for intramolecular cycloaddition. Moreover, it is clear that the steric effect of the *gem*-di-*tert*-butyl segment operates to enforce a conformation of **4a** which places the reactive groups in close proximity. In this light, it was of interest to examine a less sterically biased analogue. Ozonolysis of **1b** gave none of the ozonide **2b**. Instead, subsequent reduction ($Me_2S$) of the crude reaction mixture led to ketone **3b** as the only isolable product. Apparently, replacement of a *tert*-butyl group by methyl allows greater conformational flexibility in the carbonyl oxide **4b**, so that intramolecular cyclization is no longer favored. Indeed, rotation about the ester alkyl oxygen bond (toward R = $CH_3$ in Figure 2) moves the ester group out of alignment with the carbonyl oxide, so that intermolecular reaction of the carbonyl oxide with, for example, the cognate formaldehyde, can compete successfully.

Preliminary studies indicate a strong electronic influence on the cyclization. Ozonolysis of benzoate ester **1c** gave quite cleanly the ketone **3c**—no ozonide product was detected. Since **4c** is subject to the same steric constraints as **4a**, the change in products reflects the decreased dipolarophilicity of the benzoate carbonyl group as compared to the *p*-nitrobenzoate.[7] Activation by an electron-withdrawing group is again manifested in **1d**, which leads to a 1:1 mixture of **2d**[4] and **3d**. The reaction of trifluoroacetate **1e** gives a complex mixture of products, from which **2e**[4] can be isolated in 18% yield. Thus, these early experiments establish rather strict steric and electronic requirements for the intramolecular carbonyl oxide–ester cycloaddition.

**Acknowledgment.** W.B. thanks the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

**Supplementary Material Available:** Tables of positional parameters, thermal parameters, interatomic distances, interatomic angles, and dihedral angles for non-hydrogen atoms (7 pages). Ordering information is given on any current masthead page.

(5) Data were collected from a 0.3 × 0.3 × 0.4 mm crystal with an Enraf-Nonius CAD4 diffractometer. $C_{19}H_{27}NO_6$ crystallizes from methanol in space group $P2_1/c$, $a$ = 7.624 (1) Å, $b$ = 12.778 (3) Å, $c$ = 19.210 (7) Å, $\beta$ = 92.50 (2)°, $V$ = 1869 (2) Å$^3$, $z$ = 4, $d_{calcd}$ = 1.296. The structure was solved (1881 reflections, $I > 2\sigma$) by direct methods and refined to $R$ = 0.042 ($R_w$ = 0.056).

(6) (a) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373. (b) Moews, P. C.; Knox, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 6628.

(7) Electron-withdrawing groups are known to increase the dipolarophilicity of carbonyl groups toward carbonyl oxides. See ref 2.

## An Example of Axial Selectivity in Nucleophilic Additions to Cyclohexanones and Cyclohexenones

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Controlling the stereochemistry of additions of carbanions to cyclic ketones remains an important contemporary problem. The concept that steric effects control such reactions leads to the normal introduction of nucleophiles in an equatorial orientation in the case of six-membered ring ketones.[1,2] A recent interesting variation using a bulky aluminum alkyl directed the nucleophile in an axial fashion due to the preference to place the even bulkier aluminum alkoxide equatorially.[3] On the other hand, orbital distortion arguments[4] and consideration of torsional effects[5] associated with the addition suggest that there may exist an intrinsic bias for axial attack—a bias which is frequently overwhelmed by

(1) For some recent examples of enhancing equatorial attack, see: Mac Donald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. Weidmann, B.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1552. Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.

(2) For an exception in the case of a 1,3-dioxan-5-one, see: Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* **1978**, *111*, 3442.

(3) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

(4) Klein, J. *Tetrahedron Lett.* **1973**, *4307*; *Tetrahedron*, **1974**, *30*, 3349; Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(5) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. Cherest, M. *Tetrahedron* **1980**, *36*, 1593. Wu, Y. D.; Houk, K. N., unpublished results. We thank Professor Houk for sending a preprint prior to publication.

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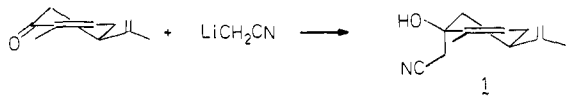
**Table I.** Effect of Metal Counterion on Diastereofacial Selectivity[a]

| | Axial/Equatorial Attack | | | |
|---|---|---|---|---|
| metal | **2** | yield | **3** | yield |
| $Li^{+b}$ | 5.5:1 | 87 | 23:1 | 94 |
| $K^{+c}$ | 5.5:1 | 72 | 20:1 | 95 |
| $Mg^{+d}$ | 1.8:1 | 81 | 6.8:1 | 79 |
| $Zn^{+e}$ | 2.5:1 | 66 | | |
| $Al^{3+f}$ | 1:2.3 | 89 | 1.6:1 | 67 |

[a] All reactions performed in THF at −78 °C unless otherwise noted. [b] Generated by treating acetonitrile with lithium hexamethyldisilazide. [c] Generated by treating acetonitrile with potassium hexamethyldisilazide. [d] Generated by addition of magnesium bromide to the lithium derivative. [e] Generated by addition of zinc chloride to the lithium derivative. Reaction allowed to warm to room temperature before quenching. [f] Generated by adding methylaluminum bis(2,6-di-*tert*-butyl-4-phenoxide) to the lithium derivative.

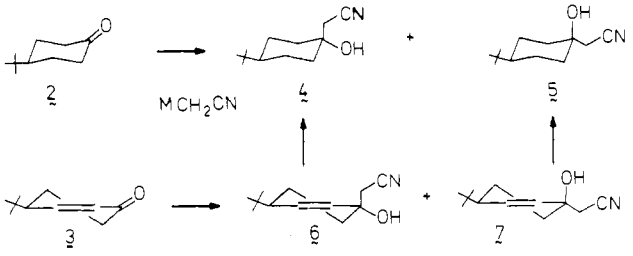
nonbonded interactions. A corollary to this argument is that if a sufficiently nonsterically demanding nucleophile can be found, axial attack may become the preferred course.[6] In conjunction with a natural product synthesis, we required addition of an acetaldehyde fragment onto a cyclohexenone in an axial fashion. We wish to report that additions of acetonitrile anion[7] to both cyclohexanones and cyclohexenones is generally highly axial selective.

Carvone represented the pertinent case for our ultimate synthetic objective and was therefore examined first. A single adduct was obtained which subsequent correlation allowed us to assign as the product from axial attack, i.e., **1**. In order to determine




**1**

whether the effect was associated with an enone as has been suggested in other cases,[6d,g] the saturated and unsaturated pair of six-membered ring ketones **2** and **3** was examined. The saturated ketone forms the two adducts **4** and **5** in a 5.5:1 ratio (as



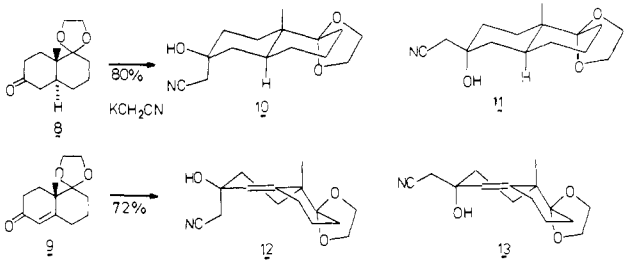

**2** **4** **5** **3** **6** **7**

determined by capillary VPC) with either the potassium or the lithium derivatives (see Table I) in excellent yields.[8,9] Assignment of the stereochemistry depicted in **4** for the major adduct derives from the single-crystal X-ray analysis. The enone **3** also reacts smoothly to give **6**[9] and **7**[9] in a ratio of 20–23:1 (Table I). Catalytic hydrogenation (3 atm of $H_2$, $PtO_2$, HOAc, room temperature) converts adduct **6** into **4**—establishing that both have the same stereochemistry. *Thus, the preference for axial attack is independent of the unsaturated nature of the ketone although the magnitude of the preference is enhanced in going from the saturated to the unsaturated acceptor.*

An examination of Table I reveals that the effect of metal on the stereochemistry may be profound. More covalent metals decrease axial attack. In contrast to the work of Yamamoto with nonstabilized anions, employment of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) increases the propensity for equatorial attack. The effective steric bulk of the reagent may account for these observations. Theoretical studies suggest that the lithium and sodium (and, by inference, potassium) salts of acetonitrile both prefer to place the metal close to nitrogen in a partially bridged bent ketenimine structure—then minimizing the effective steric bulk of the attacking nucleophile.[10] The more covalent metals such as magnesium appear to increase the covalency with carbon. The resulting increased steric demands of the attacking nucleophile then lead to enhanced nonbonded interactions between the reaction partners with the result of axial attack becoming less favored. Of course, aggregation effects as a result of the metal must not be ignored.[11]

$^{13}C$ NMR data also proves useful in assigning stereochemistry. The signal for the methylene group of the acetonitrile side chain appears at *higher* field for the *axial* isomer than for the equatorial isomer due to steric compression; in addition, the carbinol carbon appears at lower fields for an equatorial hydroxyl group (see Table II).[12]

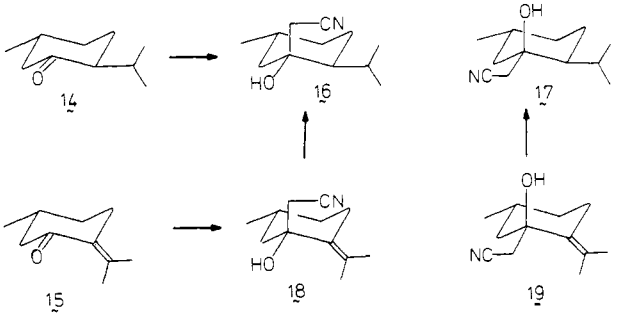
Similar results are obtained for the saturated–unsaturated ketone pair **8** and **9**. Using the potassium anion derived from acetonitrile, the saturated ketone **8** gives a 6:1 ratio of **10**[9]:**11**,[9] and the unsaturated ketone **9** gives a 10:1 ratio of **12**[9]:**13**.[9]




**8** **10** **11**

**9** **12** **13**

Examination of the menthone (**14**)–pulegone (**15**) pair reveals the limitations to the preference for axial attack. Menthone reacts with lithiated acetonitrile to give a 20:1 ratio of the two adducts;[9] pulegone under the same conditions gives a 22:1 ratio of its adducts.[9] Examination of the $^{13}C$ data for the menthone adducts indicates the major isomer is the product of equatorial attack, **17**, not of axial attack, **16**, whereas, the same data support the preference for axial attack in the case of pulegone. Verification




**14** **16** **17**

**15** **18** **19**

that the major isomer from pulegone corresponds to the minor isomer from menthone arises by catalytic hydrogenation ($H_2$, $PtO_2$, 3 atm, HOAc, room temperature). Confirmation of the assignments of **16** and **17** is also obtained by conversion of the nitriles to the known esters.[14] In this way, the major product from

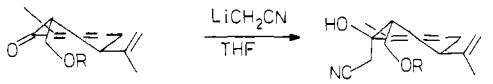
**Table II.** Relevant $^{13}C$ Shifts for Stereochemical Assignment[a]

| | saturated ketone adducts | | | | | unsaturated ketone adducts | | | |
|---|---|---|---|---|---|---|---|---|---|
| | axial | | equatorial | | | axial | | equatorial | |
| ketone | $CH_2CN$ | HO–C–$CH_2CN$ | $CH_2CN$ | HO–C–$CH_2CN$ | ketone | $CH_2CN$ | HO–C–$CH_2CN$ | $CH_2CN$ | HO–C–$CH_2CN$ |
| **2** | 27.3 | 70.8 | 33.0 | 31.6 | **3** | 30.2 | 69.0 | 31.6 | 67.3 |
| **8** | 28.2 | 71.2 | 32.8 | 69.9 | **9** | 30.2 | 69.1 | 31.4 | 67.6 |
| **14** | 24.2 | 73.4 | 30.2 | 73.8 | **15** | 28.7 | 75.2 | ND[b] | 72.3 |

[a] See ref 13. [b] Not detected.

menthone is assigned as the equatorial isomer **17** and that from pulegone as the axial isomer **18**. The change in stereochemistry of attack on menthone presumably derives from the combinatorial effects of the 2-isopropyl substituent and the $\beta$-axial hydrogens making the nonbonded interactions dominate over the intrinsic bias for axial attack.

We attribute the ability of the acetonitrile salts to reflect the intrinsic bias of six-membered ring ketones to suffer axial attack to the small steric bulk associated with the attacking end of these ketenimine-type structures. Indeed, the decreasing order of axial selectivity in going from $Li^+$ to $Mg^{2+}$ agrees with the recent calculations suggesting greater bonding of $Mg^{2+}$ to the carbon, thereby increasing its effective steric bulk. Furthermore, the results also seem to be more in accord with torsional effects rather then orbital distortion as the major contributor to the intrinsic axial bias in nucleophilic addition to six-membered ring ketones. In contrast to the results of Yamamoto, use of the bulky aluminum reagent *decreased* the axial selectivity. The difference may reside in the fact that our nucleophile is a stabilized anion, whereas his were not. The versatility of the nitrile for further structural elaboration makes this method for formation of an axial C–C bond quite synthetically useful. For example, DIBAL-H reduction converts the acetonitrile side chain to an axial acetaldehyde side chain which cannot derive from a crossed aldol condensation. While, at first glance, the case of menthone seems to be a limitation, synthetically, the axial isomer is available by the expedient of employing the unsaturated analogue followed by hydrogenation of its adduct **18** to give the axial isomer **16**. The effect of an $\alpha$-substituent to disfavor axial attack needs not dominate. In the case of the substrate **20** which bears an $\alpha$-substituent that hinders axial attack, axial attack still dominated. It appears that by designing an appropriate nucleophile, axial rather than equatorial attack may be more generally available.




20 21

**Acknowledgment.** We thank the General Medical Sciences Institute of the National Institutes of Health for their generous support of our program. Josepha Florez is a Spanish Ministry of Education and Science Postdoctoral Fellow.

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(8) The much higher axial selectivity we observe than previously found may be due to the difference in solvent. Also we find that there is a deterioration of axial selectivity with increased reaction times (normally reactions are complete within 15–30 min) which apparently arises by the addition being somewhat reversible. Such a factor may also be responsible for the lower selectivity of the above report.

(9) All new compounds have been fully characterized and elemental composition established by combustion analysis and/or mass spectroscopy.

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## [6 + 3] Cycloaddition to Nine-Membered Ring Carbocycles

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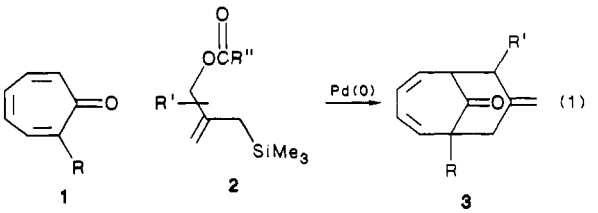
The Diels–Alder reaction continues to prove itself as the most important six-membered ring-forming reaction. In searching for alternative cycloaddition strategies for ring construction, we hoped that any such methods developed would be applicable to a variety of ring sizes. FMO theory suggests that tropones should preferentially react at C(2) and C(7) rather than C(2) and C(3).[1,2] Indeed, in cycloadditions of dienes with these acceptors, a [6 + 4] pathway may compete with and/or dominate the [4 + 2] reaction.[3] We wish to record our preliminary observations that demonstrate that 2-[(trimethylsilyl)methyl]allyl carboxylates[4] and their substituted analogues[5] not only can form five-membered rings[6] but undergo exclusive [6 + 3] nine-membered carbocycle formation in their reactions with tropones according to eq 1. To our knowledge, this reaction is the first report of a [6 + 3] cycloaddition.




1 2 3

In order to test the feasibility of [6 + 3] cycloaddition of **2**, R′ = H and R″ = $CH_3$, with tropone, we reacted a 1:1 mixture of the two in toluene at 80 °C using 2.5 mol % of a Pd(0) catalyst generated in situ by mixing palladium acetate and triisopropyl phosphite, the latter serving as both reductant and ligand.[5] A 68% yield of a single crystalline (mp 85–86 °C) adduct is formed whose spectral properties identify it as the desired [6 + 3] adduct **3**, R = R′ = H.[7] The symmetry of the adduct is clearly visible by the simplicity of the $^1H$ NMR spectrum [$\delta$ 5.80 (td, $J$ = 12.0, 3.1 Hz, 2 H), 5.42 (m, 2 H), 4.95 (appt., $J$ = 1.5 Hz, 2 H), 3.37 (appt., $J$ = 6.0 Hz, 2 H), 2.72 (ddd, $J$ = 13.0, 6.0, 1.5 Hz, 2 H), 2.43 (d, $J$ = 13.0 Hz, 2 H)].

The examples summarized in Table I attest to the generality of this reaction. To examine the role of the electrophilicity of the tropone, we placed electron-donating groups at the 2-position

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(7) All new compounds have been fully characterized and have had elemental compositions determined by combustion analysis and/or high-resolution mass spectroscopy.

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