was prepared at −78 °C, allowed to warm to 25 °C, and stirred for 12 h. No reaction occurred. At this point, trimethylsilyl triflate (0.2 equiv) was added and the reaction mixture was stirred for 12 h. Workup gave 25% of **5** and 24% of **6**.[9,10] The isolation of **6** adds substantial support to the hypothesis that **3** is the reactive intermediate in the path from **1** to **5**.

The reactions described constitute a low-temperature path to formal Diels–Alder adducts between ethyl acrylate and 1,3-dienes. It is clear that the 1,1-diethoxyallyl cation is an extremely powerful dienophile in comparison to ethyl acrylate, even when the ethyl acrylate is used in the presence of triflic acid. This low-temperature process offers a unique method for production of the described adducts under very mild conditions.

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[9] ^{1}H NMR (CDCl$_3$): δ 6.33 (t, 1 H, J = 7 Hz), 6.26 (t, 1 H, J = 7 Hz), 3.62 (m, 4 H), 2.69 (br s, 1 H), 2.58 (m, 1 H), 2.22 (t, 1 H, J = 7 Hz), 1.73 (ddd, 1 H, J = 13 Hz, J = 9.9 Hz, J = 3.1 Hz), 1.52–1.16 (m, 5 H), 1.24 (t, 3 H, J = 7 Hz), 1.19 (t, 3 H, J = 7 Hz). ^{13}C NMR (CDCl$_3$): δ 134.71 (d), 131.65 (d), 116.03 (s), 102.16 (s), 59.56 (t), 59.43 (t), 43.43 (d), 30.26 (t), 29.93 (d), 29.62 (d), 27.49 (t), 23.39 (t), 14.93 (q), 14.87 (q). IR (neat): 2230 cm^{-1}.

[10] While this experiment was carried out at 25 °C, slightly lower yields of the same products were obtained at −78 °C followed by warming to 0 °C.

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Double Diastereoselectivity in Addition of Metalated Propionitrile to Enones

Summary: Metalated propionitrile undergoes diminished selectivity for axial attack with cyclohexanones compared to metalated acetonitrile. Nevertheless, this more hindered nucleophile shows as high, or even higher, axial selectivity with cyclohexenones. Also, the newly created stereogenic center α to the nitrile is created with good diastereoselectivity as well.

Sir: The previous tenant that the stereochemistry of addition to six-membered ring ketones intrinsically favors an equatorial attack has come under increasing challenge experimentally.[1-3] An explanation for an intrinsic preference for axial attack pits torsional strain, which favors axial attack, against steric strain, which favors equatorial attack.[4,5] Recent calculations have suggested that the axial preference increases from 1.2 kcal in the case of cyclohexanones to 2.0 kcal for cyclohexenones.[5] In order to probe the magnitude of this preference, we examined the diastereoselectivity of addition of a more sterically demanding nucleophile, propionitrile anion. We report that, quite surprisingly, not only does this nucleophile maintain a high preference for axial selectivity with cyclohexenones but that there is also a high diastereoselectivity at the newly created stereogenic center α to the nitrile. The studies provide further experimental support for the proposal that the competition between torsional and steric strain accounts for the stereoselectivity of addition and suggest that metalated nitriles have a highly ordered transition state in carbonyl additions.

We initially studied the addition of metalated propionitrile to 4-*tert*-butylcyclohexanone (eq 1, Scheme I). While the preference for axial attack deteriorated (**1**[6]:**2**[7] 1.3:1 for M$^+$ = Li$^+$, 2.5:1 for M$^+$ = K$^+$) it still dominated. Use of the aluminum modifier MAD,[8] which gives rise to enhanced axial attack with nonstabilized nucleophiles, led to a predominance of equatorial attack (1:2, 1:1.8). Assignment of configuration derived from our previously established ^{13}C NMR chemical shift correlations.[3a] The signal for the methine carbon atom of the propionitrile side chain appears at higher field for the axial isomer (**1**, δ 30.8) than for the equatorial isomer (**2**, δ 38.2) as a result of steric compression. In addition, the carbinol carbon appears at lower field for an equatorial hydroxyl group (**1**, δ 71.4) than for an axial hydroxyl group (**2**, δ 70.9).[9]

Repeating the reaction of the lithiated propionitrile with 4-*tert*-butylcyclohexenone led to four products according to capillary gas chromatography in a ratio of 2.5:1:44:7.4 (order of increasing retention time) in 75% yield.[10] Flash chromatography separated the last two compounds from the first two. Hydrogenation (H$_2$, PtO$_2$, HOAc, room temperature, 3 atm) of mixtures of these latter two compounds ranging from 1:1.3 to 10.1:1 gave only **1**—a fact that allowed us to assign the latter two compounds as **3**[6] and **4**.[7] Therefore, the ratio of axial to equatorial attack in this case was 14.7:1. Furthermore, a surprisingly 6:1 ratio of the two isomers epimeric at the carbon bearing the methyl group was produced. The assignment of the major diastereomer as **3** derived from analogy (vide infra).

To examine the generality of this double diastereoselectivity, we added lithiated propionitrile to the enones **7**, **8**, and **9** as summarized in eq 3–5, Scheme II. X-ray crystallography established the stereochemistry of **10**[6] as depicted. ^{13}C NMR shifts showed the normal trends. The

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[1] For acetylide additions, see: Hennion, G. F.; O'Shea, F. X. *J. Am. Chem. Soc.* **1958**, *80*, 614. Akhrem, A. A.; Kamernitskii, A. V.; Prohoda, A. M. *Zh. Org. Khim.* **1967**, *3*, 50. Rocquet, F.; Battioni, J. P.; Capmau, M.-L.; Chodkiewicz, W. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *26B*, 1449. Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887. Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975. Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99.

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[3] (a) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613. (b) Also see: Bellassoued, M.; Dardoize, F.; Gaudemar-Bardone, F.; Gaudemar, M.; Goasdoue, N. *Tetrahedron* **1979**, *32*, 2713. Irdiss, N.; Perry, M.; Maroni-Bernaud, Y.; Roux-Schmitt, M.-C.; Seyden-Penn, J. *J. Chem. Res. Synop.* **1978**, 128.

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[6] This compound has been fully characterized spectroscopically and elemental composition established by high resolution mass spectroscopy or combustion analysis.

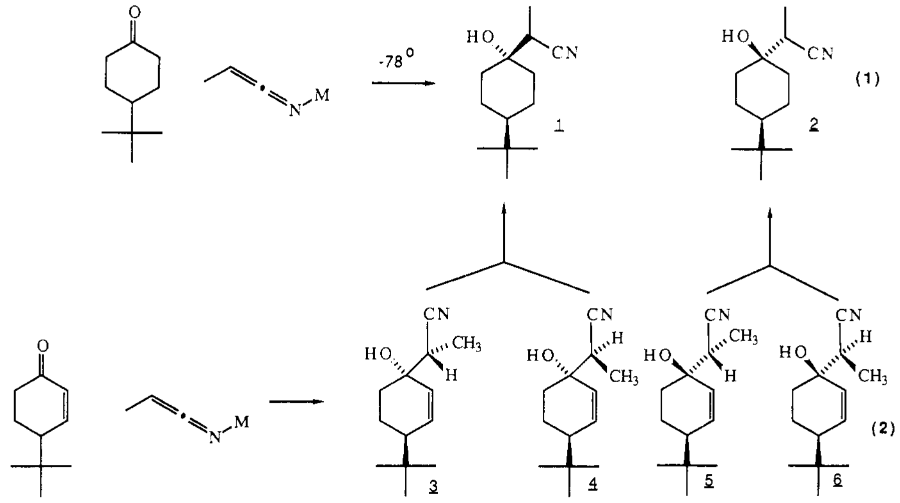
[7] This compound has been characterized spectroscopically.

[8] MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). See: Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

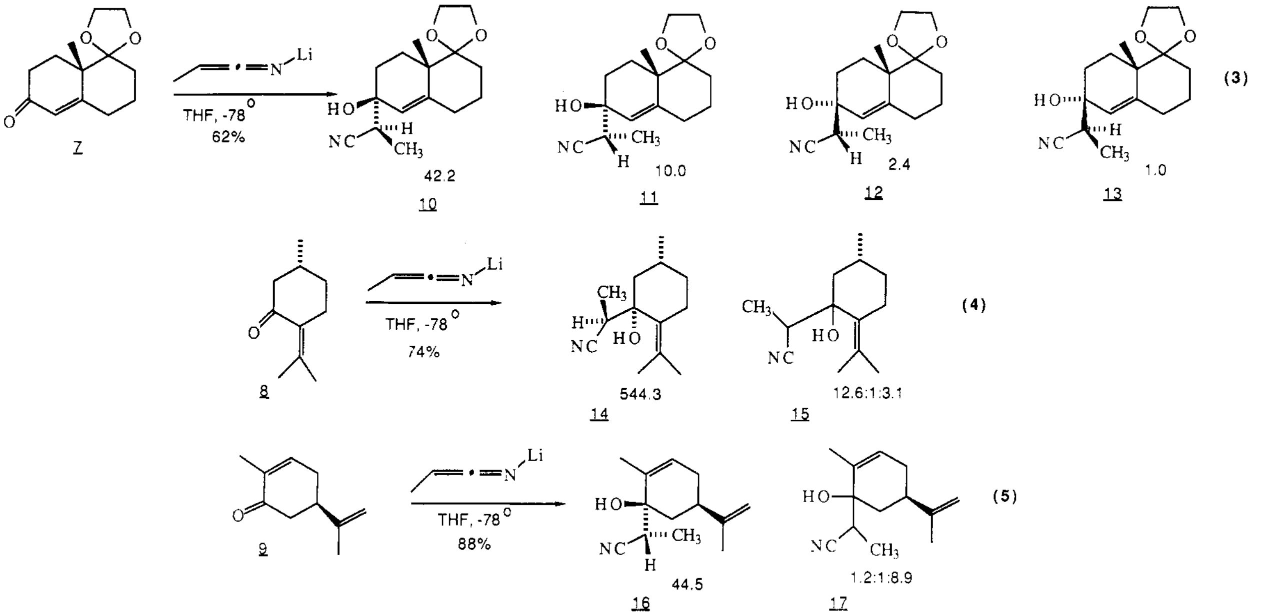
[9] Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972. Senda, Y.; Ishiyama, J.; Imaizumi, S. *Tetrahedron* **1975**, *31*, 1601.

[10] The use of the potassium salt gave a 1:1:6.8:4.4 ratio. While axial selectivity remained, albeit diminished in magnitude, facial selectivity with respect to the nitrile disappeared. The source of the difference between Li and K as a counterion may relate to differences in aggregation or structure. Such a large effect was not noted in the case of metalated acetonitrile.

Scheme I



Scheme II



signals for the methine carbon of the propionitrile side chain appeared at higher field for the axial isomers (**10**,[6] δ 36.1; **11**,[7] 36.5) than for the equatorial isomers (**12**,[7] δ 37.2; **13**,[7] δ 37.1). Reinforcement for the assignments was found in the signals for the carbinol carbon which appeared at lower field for the equatorial alcohol (**10**, δ 70.6; **11**, δ 70.3) than for an axial alcohol (**12**, δ 69.8; **13**, δ 69.6). Thus, axial selectivity of 15.3:1 was even larger than in the case of the sterically smaller metalated acetonitrile. Facial selectivity, with respect to the side chain, was also good.

Pulegone showed a dramatic increase in axial selectivity by using the sterically more demanding nucleophile—136:1 for metalated propionitrile and 22:1 for metalated acetonitrile.[3a] Furthermore, facial selectivity, with respect to the propionitrile anion was an excellent 43:1. The assignment of the major single diastereomer as depicted in **14**[6] was based upon an X-ray crystallographic analysis. The minor isomers were present in such small amounts that tentative assignments were made only on analogy to the above cases.

Carvone also showed good double diastereoselectivity to give an excellent yield of **16**[6]—axial preference of 24.3:1 and *S* side-chain preference of 5:1. Here, too, the small amounts of the minor isomers precluded their definitive assignment except by analogy.

Whereas, the axial selectivity of the additions of the more hindered nucleophile decreased with cyclohexanones, as expected, the situation is quite different for cyclohexenones where the axial selectivity with the more hindered nucleophile was as good or better. The selectivity for the above enone cases corresponds to 1–2 kcal/mol at -78 °C. A highly ordered, Zimmerman type[11] of cyclic transition state for the case of ketene iminates,[12] as depicted in eq 6 and 7, accommodates our observations. Torsional strain favors the axial attack as depicted. In the case of cyclohexanones (eq 6), this facial selectivity must encounter a severe nonbonded interaction, regardless of facial preference with respect to the ketene iminate, between the methyl substituent and at least one of the C-(3)-axial hydrogens. An increased destabilization of the axial attack arises because steric strain increases in im-

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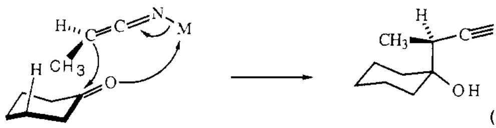
(11) Zimmerman, H. E.; Traxler, M. *J. Am. Chem. Soc.* **1957**, *79*, 1920. Also see: Dubois, J. E.; Dubois, M. *Bull. Soc. Chim. Fr.* **1969**, 3120, 3553. Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225. Heathcock, C. H. In *Comprehensive Carbanion Chemistry, Part B*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; pp 177–237.

(12) Cf. Kaneti, J.; Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Andrade, J. G.; Moffatt, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 1481. Also see: Kruger, C. *J. Organomet. Chem.* **1967**, *9*, 125. Boche, G.; Marech, M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 373. Das, R.; Wilkie, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 4555.



(6)

(7)

portance relative to torsional strain. Since equatorial attack does not lead to as large an increase in nonbonded interactions, enhanced addition from the equatorial direction occurs.

As eq 7 reveals, enones offer a relief of this increased steric strain in the axial attack mode by allowing the methyl group to find an empty pocket by placing itself over the double bond—an orientation we may refer to as a syn mode. Indeed, X-ray analysis confirms precisely this stereochemistry in two cases. By analogy, the axial syn stereochemistry is assigned to the major diastereomer for all the cases.

The results suggest that the preference for axial attack in enones is surprisingly insensitive to an increased steric bulk of the approaching nucleophile. It may derive, in part, from the planar nature of the attacking nucleophile. However, most importantly, the reacting system finds a way to steer the nucleophile to minimize steric strain, even at a cost of increased entropy of activation. From a synthetic viewpoint, this approach appears to be an excellent strategy to introduce side chains onto ring systems with excellent double diastereoselectivity.

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Supplementary Material Available: X-ray crystallographic analysis of adducts 10 and 14 (14 pages). Ordering information is given on any current masthead page.

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Deuterium Isotope Effects and the Mechanism of Kinetic Enolate Formation. A Correction[1]

Sir: Contrary to a previous report from this laboratory that the deuterium isotope effect in the reaction of 2-methyl-3-pentanone at the 4-position with LDA in THF is negligibly small (k_H/k_D = 0.9 ± 0.1 at 0 °C),[2] independent rechecks by three of the undersigned (H.P.B., L.X., and D.J.M.) have convinced us that there are substantial isotope effects at *both* the 4-position (k_H/k_D = 3.3) and the 2-position (k_H/k_D = 3.8), and this pattern holds for a variety of solvent–base combinations. Details will follow in a full paper.

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[3] Sherman Clarke Fellow.

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Tandem Cycloaddition/Radical Cyclization, a Widely Applicable Strategy for the Rapid Assembly of Polycyclic Systems

Summary: By treating a diene (or 1,3-dipole) that contains an appropriately located potential radical site successively with a dienophile (or dipolarophile) and a radical source one can construct a variety of polycyclic systems in two steps.

Sir: The construction of polycyclic systems using a minimum number of synthetic manipulations remains a challenging problem. Cycloaddition[1] and radical cyclization[2] are two frequently used reactions for ring construction. Here we report a versatile synthetic strategy that uses these reaction types in a tandem mode, thus permitting the rapid construction of a variety of polycyclic systems, often with considerable regio- and stereocontrol. The double bond generated in the cycloaddition step serves as the trap for the radical generated in the cyclization step.

The primary building block is a diene (or 1,3-dipole) which contains the functionality needed for generating a radical at an appropriate site. A simple example is diene **1**, which has the advantage of being cisoid and in which the bromine is located on a carbon atom appropriately situated from C2 of the diene moiety. Diene **1** was readily prepared from 2-lithiofuran (**2**) and 2-bromobenzyl bromide (**3**) (Scheme I). Treatment of **1** with benzyne (generated from benzenediazonium carboxylate) gave cycloadduct **4** (50%) which, on heating with 1 equiv of Bu_3SnH (AIBN, benzene, reflux) gave a single cyclized product (**5**), mp 104–108 °C (67%). The carbon framework of **5** was established by dehydration to the known[3] benzo[*a*]fluorene (**6**). Although the ^1H NMR spectrum showed **5** to be a single stereoisomer, the stereochemistry could not be definitively assigned. An X-ray structure[4] of the naphtho analogue **7** (prepared analogously, using 2,3-naphthyne in place of benzyne) established the exo geometry of the new C–C bond formed in the radical cyclization step.[5] The

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