Nitrile Anions: Solvent-Dependent Cyclizations

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Extensive cyclizations in hydrocarbon and polar solvents demonstrate a profound solvent sensitivity for intramolecular nitrile anion alkylations. S_Ni cyclizations enforce very precise steric constraints in the transition state, allowing correlation of the cyclization stereochemistry with the orbital orientation of the nitrile anion. Collectively the cyclizations suggest a continuum of nitrile anion transition states, varying from planar to fully pyramidal, that selectively cyclize to *cis*- and *trans*-decalins, respectively.

Introduction

Nitrile anions are exceptional nucleophiles[1] with equally exceptional structural characteristics.[2] The X-ray structures of nitrile anions[3] show only a modest shortening of the carbanion−carbon bond, with the C≡N bond length (1.15−1.20 Å)[3] being virtually identical to C≡N bond lengths (1.14 Å)[4] in nonmetalated nitriles. Further insight into the structure of nitrile anions is gleaned from the X-ray structure of sodiated isobutyronitrile (**1**),[5] an aliphatic nitrile anion whose two β-substituents reveal a distortion of the anion from planarity (see inset **2**, Figure 1). The surprising 9° distortion demonstrates a partial pyramidalization[6] that may be a key feature in reactions of aliphatic nitrile anions.

Solution ^{6}Li NMR,[2f] IR,[7] and Raman[2b,c] spectra of arylacetonitrile anions in nonpolar solvents are consistent with the aggregate structures observed in the solid state.[8] Changing the solvent to HMPA or DMSO results in a solvent-separated ion pair[2a] that, for phenylacetonitrile anion, is planar and delocalized[9] *though not delocalized into the nitrile group but rather into the aromatic ring!*

Solvent was first found to profoundly influence the stereoselectivity of nitrile anion cyclizations almost 30 years ago.[10] Under otherwise identical conditions, the nitrile anion **4** preferentially cyclizes to the *trans*-decalin **5** in benzene (Scheme 1) whereas THF reverses the selectivity in favor of the *cis*-decalin **6**. The remarkable solvent-dependent cyclizations of **3** demonstrate an acute transition-state sensitivity, reflecting very precise steric constraints and orbital alignments for intramolecular cyclizations of nitrile anions.[11] Relating the cyclization stereochemistry to the structure of the transition state provides a unique structural probe that complements previous spectroscopic analyses of nitrile anions by divulging information precisely at the bond-forming event.

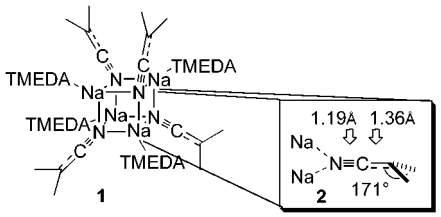
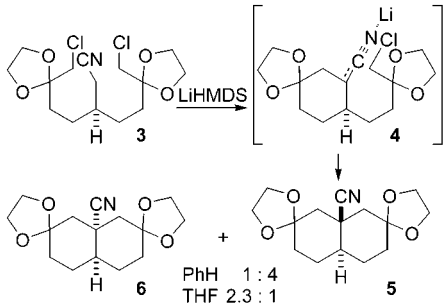


Figure 1. X-ray structure of sodiated isobutyronitrile.

Scheme 1



Results

Nitrile **8** (eq 1) is an ideal structural probe since cyclization generates the key decalin skeleton while avoiding chelation effects that complicate analyses with **3**.[12] The requisite nitrile **8** is readily available by dehy-

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(3) Boche, G. *Angew. Chem.* **1989**, *28*, 277.

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(5) Barker, J.; Barnet, N. D. R.; Barr, D.; Clegg, W.; Mulvey, R. E.; O'Neil, P. A. *Angew. Chem.* **1993**, *32*, 1366.

(6) Pyramidalization is conveniently monitored by comparing the deformation angles, defined as the C_N–C−X angle, where X is the midpoint between the two substituents at the anionic carbon (Figure 1 inset): ref 2e.

(7) Croisant, D.; Seyden-Penne, Strzalko, T.; Wartski, L.; Corset, J.; Froment, F. *J. Org. Chem.* **1992**, *57*, 6435.

(8) Carlier, P. R.; Lo, K. M. *J. Org. Chem.* **1994**, *59*, 4053.

(9) Bradamante, S.; Pagini, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035.

(10) (a) Stork, G.; Gardner, J. O.; Boeckman, R. K., Jr.; Parker, K. A. *J. Am. Chem. Soc.* **1973**, *95*, 2014. (b) Stork, G.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 2016.

(11) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Org. Lett.* **1999**, *1*, 1547.

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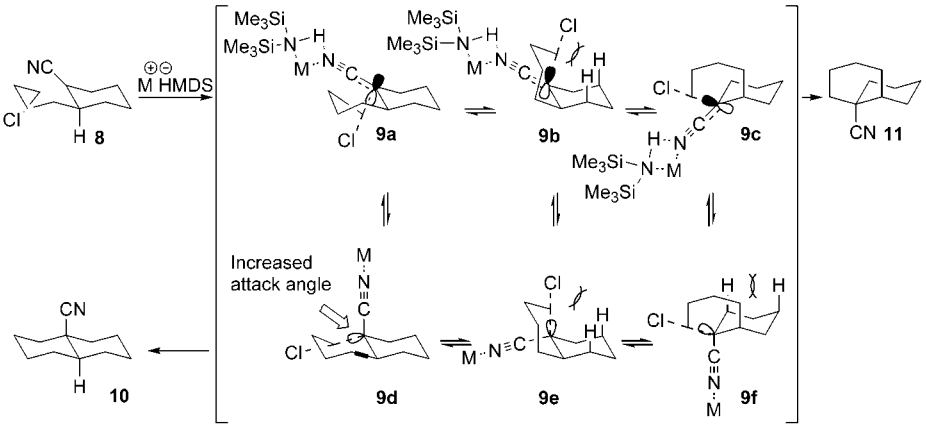
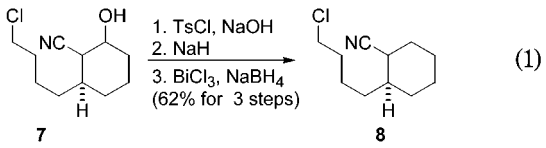
Scheme 2



drating the diastereomeric β-hydroxy nitriles **7**[13] via the corresponding tosylates,[14] converging the mixture to a single unsaturated nitrile. Subsequent reduction to **8** requires the bismuth boride species obtained from $BiCl_3$ and $NaBH_4$[15] since no reduction occurs with the more conventional reagents.[16]



(1)

KHMDS-induced cyclization of a 1:1 mixture of diastereomeric nitriles 8, in toluene, affords predominantly the *cis*-decalin **11**[17] (Scheme 2). Conceptually, the *cis*-decalin must be formed through cyclization of either the planar[18] or pyramidal[19] nitrile anion transition states **9b** and **9c** or **9e** and **9f**, respectively. Despite difficulties in correlating solution structures with transition states,[20] an appealing rationale is to assume that the early transition state[21] favors cyclization through a planar, complexed, nitrile anion analogous to structures identified by X-ray crystallography and solution NMR (**12**[22a] and **13**,[2f] Figure 2).[23] Optimal orbital alignment for S_Ni cyclization through transition state **9b** engenders allylic strain and requires an oblique trajectory that exacerbates the *syn*−axial interactions, whereas transition state **9c** avoids allylic strain, and has an excellent orbital alignment. Formation of the minor *trans*-decalin isomer must proceed through the pyramidal anion **9d** since analogous cyclizations of planar ester enolates[24] afford exclusively *cis*-decalins. Analysis of molecular models reveals that transition state **9a** is severely compromised by allylic strain and by a considerable twisting of the electrophilic tether required to accommodate the oblique 90° attack angle enforced by the planar nitrile anion.

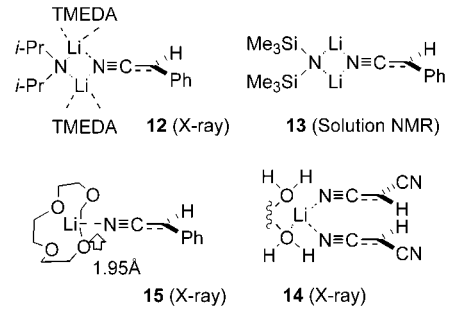
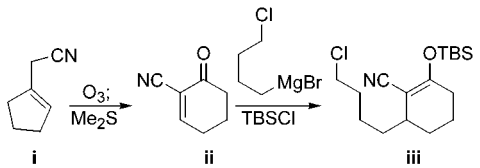


Figure 2. Nitrile anion complexation.

(12) A detailed series of cyclizations reveals that hydroxyl groups, and ketals such as those in **5**, chelate with adjacent nitrile anions to significantly alter cyclization selectivities: Shook, B. C. Ph.D. Thesis, Duquesne University, Pittsburgh, 2001. See also: Murray, A. W.; Murray, N. D.; Reid, R. G. *J. Chem. Soc., Chem. Commun.* **1986**, 1230.

(13) Prepared by sequential conjugate addition−silylation with **ii** (Fleming, F. F.; Shook, B. C. *Org. Synth.* **2001**, *78*, 254) followed by reduction of **iii** with $NaBH_4$.



(14) Laxmi, Y. R. S.; Iyengar, D. S. *Synthesis* **1996**, 594.

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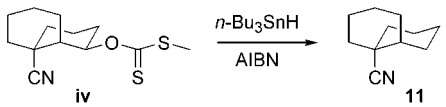
(17) ^{1}H NMR readily allows stereochemical assignment since the conformationally mobile *cis*-decalin **11** exhibits broad signals whereas the rigid *trans*-decalin **10** is well resolved and exhibits a ^{13}C spectrum with only seven signals, consistent with a symmetrical *trans*-decalin structure. Chemical correlation of **11**, by deoxygenating the X-ray diffracting xanthate **iv**, corroborates the NMR assignments. The atomic coordinates of the structure of xanthate **iv** have been submitted to the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Rd., Cambridge CB2 1EZ, U.K.



(18) The terms "planar nitrile anion" and "pyramidalized nitrile anion" are used to avoid the term "keteniminate" that inaccurately reflects the unusual bond order typically observed in X-ray structures. Collectively, the structures are referred to as nitrile anions, realizing that in most cases the actual species are most likely metalated nitriles.

(19) Experimentally, pyramidal nitrile anions were first implicated during the deprotonation of chiral cyclopropane carbonitriles: Walborsky, H. M.; Motes, J. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445.

(20) Sun, X.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039.

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(22) (a) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem.* **1989**, *28*, 1392. (b) Boche, G.; Langlotz, I.; Marsch, M.; Harms, K.; Frenking, G. *Angew. Chem.* **1989**, *28*, 1171.

(23) Recent computational analyses strongly support correlating the X-ray and solution structures of nitrile anions: Carlier, P.; Madura, J. *J. Org. Chem.*, submitted for publication.

(24) (a) Bilyard, K. G.; Garrat, P. J.; Zahler, R. *Synthesis* **1980**, 389. (b) For an additional enolate cyclization to a *cis*-decalin see ref 10a.

Table 1. Cyclizations of 9 in $PhCH_3$, Dioxane, and Et_2O

entry	base	solvent	*T* (°C)	**10:11** (*trans*:*cis*)	yield (%)
1	KHMDS	$PhCH_3$	80	1:4.5	55
2	KHMDS	ether	33	1:2.9	67
3	CsHMDS	$PhCH_3$	80	1:2.6	56
4	LiHMDS	$PhCH_3$	80	1:1.2	69
5	KH	ether	33	1:1.1	62
6	KH	PhH	80	1.2:1	74
7	KHMDS	dioxane	80	1.4:1	74
8	LiHMDS	ether	33	1.8:1	69
9	KHMDS 18-C-6	$PhCH_3$	80	2.5:1	60
10	LiHMDS 12-C-4	$PhCH_3$	80	2.7:1	67

Table 2. Cyclizations of 8 in THF and HMPA

entry	base	solvent	*T* (°C)	**10:11** (*trans*: *cis*)	yield (%)
1	KHMDS	THF	66	6.3:1	67
2	KHMDS 18-C-6	THF	66	6.0:1	69
3	KHMDS	HMPA	25	4.9:1	44
4	KHMDS 18-C-6	THF	25	4.6:1	65
5	LiHMDS 12-C-4	THF	66	3.8:1	74
6	KHMDS	THF	25	3.2:1	65
7	LiHMDS	THF	66	3.2:1	77
8	CsHMDS	THF	66	1.6:1	68
9	KHMDS	HMPA	80	1.2:1	52

Extensive cyclizations in toluene, ether, and dioxane reveal an unusual solvent-dependent stereoselectivity (Table 1). Cyclizations with KHMDS and CsHMDS[25] in toluene and ether (Table 1, entries 1−3) are selective for the *cis*-decalin **11**, whereas cyclizations with KH in benzene and ether are not selective (Table 1, entries 5−6). The selectivity difference implies a complexation[26] between hexamethyldisilazane and the nitrile anion, analogous to complexation observed in the solid state[22] and in solution[2f] (Figure 2, **12** and **13**, respectively.). Further support for amine complexation stems from cyclizations in the presence of crown ethers (Table 1, entries 9 and 10) where a striking reversal in stereoselectivity[27] occurs (Table 1, compare entries 1 and 4 with entries 9 and 10). Association between the amine and nitrile is favored by similar acidities[28] of HMDS and the parent nitrile, and is analogous to an unusual complexation between water and malononitrile anion (**14**, Figure 2) that is maintained in solution and in the solid state.[29] Although modest, the stereoselectivity reversal, with crown ethers in toluene, requires the presence of two structurally distinct transition states—presumably corresponding to planar and pyramidal nitrile anions.

LiHMDS manifests exactly the same cyclization trends as for KHMDS. LiHMDS alone modestly favors *cis*-decalin **11** (Table 1, entry 4), while addition of 12-C-4 reverses the stereoselectivity in favor of *trans*-decalin **10** (Table 1, entry 10), in virtually the same ratio as with KHMDS and 18-C-6 (Table 1, entry 9). In the solid-state, crown ether sequestration disrupts the usual bismetal chelate by forming singly metalated complexes,[30] typified by **15**[31] (compare **12** and **13** with **15**, Figure 2), where the crown-encapsulated metal maintains coordination with the nitrile. An analogous complexation in solution[23] reasonably accounts for the observed stereoselectivity change, assuming that complexation causes enhanced pyramidalization,[32] and promotes cyclization through transition state **9d** (Scheme 2). Collectively, the cyclizations in Table 1 correlate with hydrocarbon solvents favoring amine-complexed, planar transition states, whereas crown ethers favor cyclization through a pyramidalized nitrile anion transition state.

Insight into the cyclization selectivity in THF and HMPA was gleaned from a series of cyclizations with **8** and hexamethyldisilazide bases (Table 2). In direct contrast to the *cis*-selective cyclizations in toluene (1:4.5), THF favors cyclization to the *trans*-decalin **10** (6.3:1). Preferential formation of *trans*-decalin **10** requires cyclization from the pyramidal transition state **9d** (Scheme 2) and is consistent with a preferred cyclization through the least sterically congested conformation.[33] Cyclizations with KHMDS in refluxing THF are not significantly affected by the addition of 18-crown-6 (Table 2, entries 1 and 2), whereas the cyclization becomes *less selective* as the temperature is reduced to 25 °C (Table 2, entry 6). The *decreased* selectivity at ambient temperature suggests partial amine complexation that is presumably favored by the reduced molecular motion at lower temperatures. In agreement with this rationale, the addition of 18-C-6 at ambient temperature increases the preference for *trans*-decalin **10** (Table 2, compare entries 4 and 6). Exactly the same trends are evident in the cyclizations with LiHMDS (Table 2, entries 5 and 7).

Formation of a pyramidal, solvent-separated, nitrile anion is anticipated for cyclizations in HMPA.[34] The cyclization of **8** in neat HMPA, at a comparable temperature, results in a rapid, unselective cyclization (Table 2, entry 9), suggesting that the free nitrile anion is too reactive to discriminate among conformations **9d**, **9e**, and **9f** (Scheme 2). Importantly, reducing the temperature to 25 °C restores the selectivity for the *trans*-decalin **10** (Table 2, entry 3), consistent with the intermediacy of a pyramidalized nitrile anion.

(25) (a) Neander, S.; Behrens, U. *Z. Anorg. Allg. Chem.* **1999**, *625*, 1429. (b) Edelmann, F. T.; Pauer, F.; Wedler, M.; Stalke, D. *Inorg. Chem.* **1992**, *31*, 4143.

(26) The complexes **9a**−**c** are depicted as bridged monomers since nitrile anions favor monomeric structures in dilute solutions (0.025 M) whereas solvated aggregates form at higher concentrations (0.25 M): (a) Reference 8. (b) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972. (c) Reference 7.

(27) ^{1}H NMR and GC analyses of the crude reaction mixture show that the ratio remains invariant before and after purification while repetitive cyclizations consistently reproduce the *cis*:*trans* ratios.

(28) The pK_a of HMDS, estimated at 25.8[28a] in THF, and therefore in DMSO,[28b] is less than the pK_a of acetonitrile (29−31)[28c,d] in DMSO. Presumably the favorable deprotonation of alkylnitriles by metalated HMDS[1b] reflects the profound influence of solvation and aggregation on the pK_a of HMDS.[28e] (a) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. (b) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288. (c) Bordwell, F. G.; Bartmess, J. E.; Drucker, G. E.; Margolin, Z.; Mathews, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 3226. (d) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715. (e) Grimm, J. E.; Grimm, D. T. *J. Am. Chem. Soc.* **1992**, *114*, 1227.

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(31) Langlotz, I.; Marsch, M.; Harms, K.; Boche, G. *Z. Kristallogr.* **1999**, *214*, 509.

(32) For a related rationalization of planar and pyramidal effects see: (a) For lithiated carbamates, Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (b) For nitriles, ref 1a.

(33) Cyclization through conformation **9d** is favored by the extremely small steric demand of the nitrile group, the *A* value is 0.2 kcal mol^{-1},[33a] which minimizes the *syn*−axial interactions. The alternative cyclizations through **9e** and **9f** have good orbital alignments but are destabilized by three, more severe, *syn*−axial CH_2–H interactions (2.6 kcal mol^{-1}).[33b] (a) Eliel, Ernest L.; Wilen, Samuel H.; Mander, Lewis N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−7. (b) The *syn*−axial interactions between the nitrile and the axial protons in the forming ring are the same in all three conformations and are therefore ignored in this comparative analysis.

(34) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728.

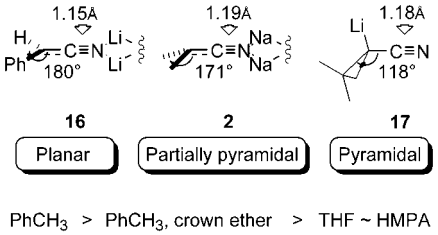

Figure 3. X-ray continuum of partial nitrile anion structures.

The emerging structure of nitrile anion transition states is a continuum varying between planar and pyramidal extremes. Intuitively the continuum of structures parallels the X-ray structures of planar phenylacetonitrile anion **16**, partially pyramidalized aliphatic nitrile anion **2**, and the pyramidal cyclopropanecarbonitrile anion **17** (Figure 3). The large deformation angle observed with the cyclopropyl carbanion **17** is expected with the biased cyclopropane ring, whereas the modest deformation of **2** is more significant since simplistic resonance ideas predict this type of nitrile anion to be planar. Molecular modeling[35] of numerous nitrile anions consistently reproduces the pyramidalization observed in the X-ray structure of the anion of isobutyronitrile (**2**). The striking bond length consistency, for what are otherwise vastly different structures (Figure 3), argues for a common inductive[36] stabilization over a continuum of nitrile anions.

Conclusion

Nitrile anion S_Ni cyclizations are acutely sensitive to solvent. Extensive cyclizations correlate with the transition states exhibiting varying degrees of pyramidalization as observed in the crystal structures of a diverse range of nitrile anions. Complexation of nitrile anions with amines in hydrocarbon solvents favors a planar transition state, whereas pyramidalization occurs upon crown ether chelation, and in THF, or HMPA. The selectivity reversal with crown ethers, or the use of KH as a nonamide base, implicates amine complexation as a key element in controlling cyclization stereoselectivity. Knowledge of the pyramidalization and complexation of nitrile anions allows tuning of S_Ni cyclizations to selectively generate a *cis*- or *trans*-decalin simply by the addition of a crown ether or through judicious choice of solvent.

Experimental Section

2-(4-Chlorobutyl)cyclohexanecarbonitrile (8). Solid *p*-toluenesulfonyl chloride (854 mg, 4.48 mmol) and NaOH (286 mg, 6.16 mmol) were added successively to a cold, 0 °C, THF solution (20 mL) of **7**[11] (768 mg, 3.57 mmol). After 3 h the mixture was poured into a beaker of ice−water, and the aqueous phase was extracted with EtOAc. The organic extracts were combined and washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated to afford 1.20 g (91%) of a yellow oil that was used without further purification. Solid NaH (99 mg, 3.90 mmol) was added to a cold (0 °C) THF solution (20 mL) of the tosylates (1.20 g, 3.25 mmol) and the reaction mixture allowed to warm to rt. After 21 h saturated, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$), concentrated, and purified by radial chromatography (2 mm plate, 1:19 EtOAc/hexanes) to afford 456 mg (71%; 65% for two steps) of 6-(4-chlorobutyl)-cyclohex-1-enecarbonitrile as a colorless oil: IR (film) 3035, 2215, 1633 cm^{-1}; ^1H NMR δ 1.15−2.23 (m, 9H), 1.42 (t, J = 7.1 Hz, 1H), 2.48−2.58 (m, 3H), 3.82 (t, J = 6 Hz, 2H), 6.81−6.84 (m, 1H); ^{13}C NMR δ 19.0, 23.7, 25.8, 26.3, 32.3, 32.8, 35.2, 44.7, 117.2, 119.0, 145.7; MS *m/e* 198 (M + H).

Solid $NaBH_4$ (178 mg, 4.70 mmol) was added to a cold (0 °C) EtOH (95%) solution of 6-(4-chlorobutyl)cyclohex-1-enecarbonitrile (185 mg, 0.94 mmol) and $BiCl_3$ (148 mg, 0.47 mmol). The resulting black solution was allowed to warm to rt and stirred for an additional 12 h. The mixture was then vacuum filtered through filter paper, neutralized with 1 M HCl, and concentrated. Water (5 mL) was added, and the aqueous phase was extracted with EtOAc. The extracts were combined, washed with brine, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1 mm plate, 1:9 EtOAc/hexanes) to afford 177 mg (95%) of **8** as a 1:1 ratio of epimeric axial and equatorial nitriles. Repetitive chromatography provided a sample of the axially oriented nitrile as a colorless oil: IR (film) 2237 cm^{-1}; ^1H NMR δ 1.16−1.32 (m, 1H), 1.48−2.44 (m, 14H), 3.12 (br s, 1H), 3.76−3.83 (m, 2H); MS *m/e* 198 (M − H).

Data for 5-(Methylthiothioxomethoxy)bicyclo[4.4.0]-decanecarbonitrile (iv):[37] IR (film) 2230 cm^{-1}; ^1H NMR δ 1.24−1.98 (m, 15H), 2.55 (s, 3H), 5.95−6.00 (m, 1H); ^{13}C NMR δ 19.0, 20.3, 20.6, 21.0, 24.5, 24.7, 27.0, 35.8, 38.2, 41.0, 81.5, 124.1, 214.5; MS *m/e* 237 (M). Neat *n*-Bu_3SnH (4.1 mg, 15.2 μmol) was added to a xylene solution (2 mL) of the xanthate (2.5 mg, 9.3 μmol) followed by heating at 80 °C for 16 h. The solution was then cooled to rt, aqueous HCl (3 mL, 3 vol %) was added, and the mixture was extracted with ether, dried (Na_2SO_4), and concentrated. The resulting material exhibited a ^1H NMR spectrum corresponding to *cis*-decalin **11** and was further correlated through GC/MS co-injections with **11** and **10** obtained from cyclizations of **8**.

General Cyclization Procedure. A solution of **8** (1.0 equiv), as a 1:1 mixture of nitrile epimers, in the appropriate solvent was added to a rt solution of the appropriate base (1.5 equiv) to afford a solution with a final concentration, in **8**, of 0.025 M. After 3 h (4 days for Table 2, entries 3 and 4, and 2 days for Table 3, entry 6), saturated, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The extracts were combined, washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1 mm plate, 1:19 EtOAc/hexanes) to afford a mixture of **10** and **11**. The ratio **10**:**11** was routinely determined by GC after being verified by ^1H NMR analysis.

Data for *trans-Bicyclo[4.4.0]decanecarbonitrile (10)*: IR (film) 2228 cm^{-1}; ^1H NMR δ 1.12−1.43 (m, 7H), 1.49−1.57 (m, 2H), 1.65−1.94 (m, 8H); ^{13}C NMR δ 23.2, 25.8, 30.4, 37.3, 42.7, 44.8, 122.5; MS *m/e* 162 (M − H).

Data for *cis-Bicyclo[4.4.0]decanecarbonitrile (11)*: IR (film) 2228 cm^{-1}; ^1H NMR δ 1.24−1.93 (m, 17H); MS *m/e* 162 (M − H).

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds and an ORTEP diagram for **iv**. This material is available free of charge via the Internet at http://pubs.acs.org.

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