JOC Article

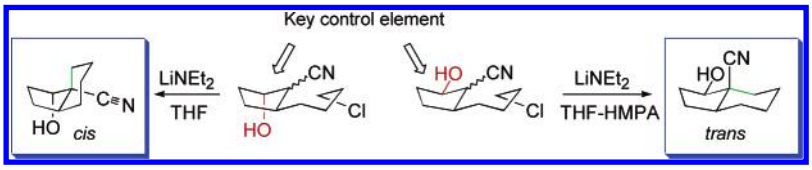
Metalated Nitriles: Chelation-Controlled Cyclizations to *cis* and *trans* Hydrindanes and Decalins

Fraser F. Fleming,* Viet Anh Vu, Brian C. Shook, Moshfiqur Rahman, and Omar W. Steward

Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282-1530

flemingf@duq.edu

Received November 2, 2006



Chelation provides a powerful means of stereocontrol in alkylations of metalated nitriles. Doubly deprotonating a series of cyclic β-hydroxynitriles triggers cyclizations that implicate metalated nitrile intermediates having configurations imposed by chelation with an adjacent, chiral lithium alkoxide. Identifying chelation as a general stereocontrol element explains several previously anomalous alkylations of metalated nitriles and provides a potential solution to the long-standing difficulty of synthesizing *trans*-hydrindanes. Employing chelation to control the metalated nitrile geometry permits selective cyclizations to *cis* and *trans* hydrindanes and decalins and provides key insight into the geometrical requirements of these demanding cyclizations.

Introduction

Metalated nitriles are exceptional nucleophiles for a diverse range of electrophilic alkylations.[1] The excellent nucleophilicity stems from the nitriles' powerful inductive stabilization of an adjacent negative charge, resulting in significant electron density remaining on the nucleophilic carbon.[2] The nucleophilicity is further enhanced by the compact,[3] cylindrical diameter of the π-system, 3.6 Å for the C≡N unit,[4] making metalated nitriles ideal for alkylations of sterically congested stereocenters.[5] Synthetically, the high nucleophilicity and small steric demand of metalated nitriles is suited for installing hindered quaternary centers, traits that have been exploited in the cyclization of medium-sized and strained carbocycles.[1,5]

Inductive stabilization of metalated nitriles creates two potential metal coordination sites: *N*-metalation at the nitrile nitrogen and *C*-metalation at the adjacent anionic carbon (Figure 1, compare **1** and **3**). Metalated nitriles are most commonly

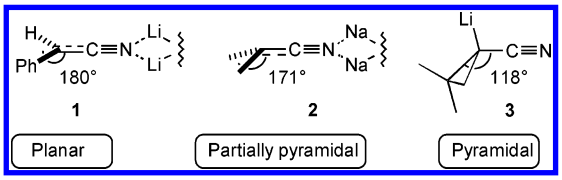


FIGURE 1. Partial solid-state structures of metalated nitriles.

generated by deprotonating alkanenitriles with lithium amide bases which predominantly afford *N*-lithiated nitriles in solution[6] and in the solid state.[1a,7] Greater structural diversity is encountered in metalated nitriles having transition metal counterions which exhibit roughly equal frequency for *N*-[8] or *C*-metalation.[9] Experimentally, the site of metal coordination depends intimately on the nature of the metal, the temperature, the presence of chelating ligands, and the solvent, allowing considerable control over the nature and reactivity of metalated nitriles.[10]

The combination of diverse metal coordination modes and inductive charge stabilization leads to a range of solid-state metalated nitrile geometries that vary from planar to pyramidal

(1) (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.

(2) (a) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715. (b) Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035. (c) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.

(3) The steric demand of a nitrile group exerts a minuscule *A* value of only 0.2 kcal mol^{-1}: Eliel, Ernest L.; Wilen, Samuel H.; Mander, Lewis N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−7.

(4) Sheppard, W. A. In *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Interscience Publishers: New York, 1970; Chapter 5.

(5) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.

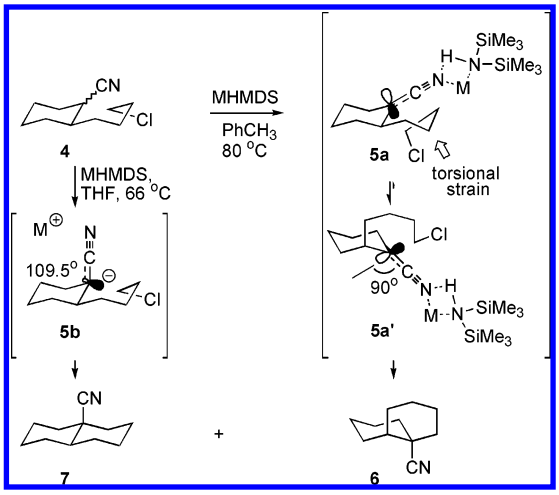
(6) (a) Carlier, P. R.; Lo, C. W.-S. *J. Am. Chem. Soc.* **2000**, *122*, 12819. (b) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.

(7) Boche, G. *Angew. Chem., Int. Ed.* **1989**, *28*, 277.

10.1021/jo062270r CCC: $37.00
Published on Web 01/24/2007

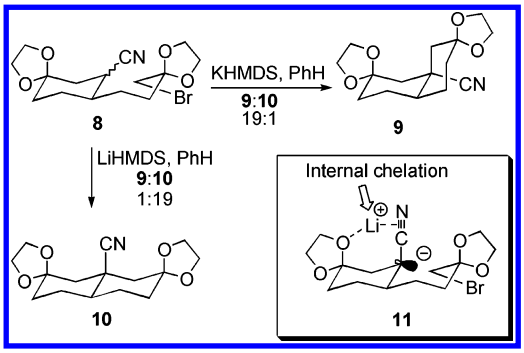
(Figure 1).[11] In solution metalated nitriles exhibit stereoselectivities consistent with a similar range of geometries, implicating a configurational lability of the nucleophilic carbon analogous to that hinted at by the continuum of solid-state geometries.[12] For example, deprotonating either diastereomer of the cyclic nitrile **4** causes cyclization to the same ratio of *cis*- and *trans*-decalins regardless of the starting nitrile configuration (Scheme 1).[13] In these cyclizations the stereochemistry is consistent with the solvent-determined formation of either the planar, sp^2-type *N*-metalated nitrile **5a**/**5a′** or the pyramidal, sp^3-type nitrile anion **5b**. Deprotonating **4** in toluene with KHMDS favors cyclization to the *cis*-decalin **6** via the planar *N*-metalated nitrile conformer **5a′**, which avoids the tortional strain imposed by twisting of the electrophilic tether for cyclization via conformer **5a**. Alternatively, cyclizing **4** with KHMDS in refluxing THF proceeds via the pyramidal ion pair **5b** where the increased attack angle (**5b** vs **5a′**) ideally orients the nucleophilic orbital for an S_N2 displacement to the *trans*-decalin **7**.

SCHEME 1. Solvent-Dependent Cyclizations of Metalated Nitriles



The *solvent*-dependent cyclizations of the parent nitrile **4** contrast with the *metal*-dependent cyclizations of the analogous ketal-containing nitrile **8** (Scheme 2). Unlike **4** where *both* LiHMDS and KHMDS in toluene preferentially cyclize to the *cis*-decalin **6** (Scheme 1), the cyclizations of **8** in benzene depend intimately on the identity of the metal counterion: KHMDS affords the *cis*-decalin **9**, as anticipated for a planar *N*-metalated nitrile (cf. **5a′** Scheme 1), whereas LiHMDS unexpectedly affords the *trans*-decalin **10**. Although arguments were advanced to explain the stereoselectivity on the basis of early and late contact distances,[14] a more compelling rationale is to envisage a structural change of the metalated nitrile induced by chelation of the electrophilic lithium cation with the π-system of the nitrile[15] (see inset **11**, Scheme 2).

SCHEME 2. Metal-Dependent Cyclizations of a Cyclic Nitrile



Complexation of metals, particularly lithium,[16] with the π-electrons of a nitrile[17] provides a particularly effective method of stereocontrol in a diverse range of reactions.[18] In the case of nitrile **8**, deprotonating with a lithium base in benzene is anticipated to favor tight association of the lithium cation with the nitrile π-electrons and the proximal acetal oxygen leading

(8) (a) Tanabe, Y.; Seino, H.; Ishii, Y.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 1690. (b) Murahashi, S.-I.; Take, K.; Naota, T.; Takaya, H. *Synlett* **2000**, 1016−1018. (c) Triki, S.; Pala, J. S.; Decoster, M.; Molinié, P.; Toupet, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 113. (d) Hirano, M.; Takenaka, A.; Mizuho, Y.; Hiraoka, M.; Komiya, S. *J. Chem. Soc., Dalton Trans.* **1999**, 3209. (e) Yates, M. L.; Arif, A. M.; Manson, J. L.; Kalm, B. A.; Burkhart, B. M.; Miller, J. S. *Inorg. Chem.* **1998**, *37*, 840. (f) Jäger, L.; Tretner, C.; Hartung, H.; Biedermann, M. *Chem. Ber.* **1997**, *130*, 1007. (g) Zhao, H.; Heintz, R. A.; Dunbar, K. R.; Rogers, R. D. *J. Am. Chem. Soc.* **1996**, *118*, 12844. (h) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (i) Hirano, M.; Ito, Y.; Hirai, M.; Fukuoka, A.; Komiya, S. *Chem. Lett.* **1993**, 2057. (j) Mizuho, Y.; Kasuga, N.; Komiya, S. *Chem. Lett.* **1991**, 2127. (k) Schlodder, R.; Ibers, J. A. *Inorg. Chem. Soc.* **1974**, *13*, 2870. (l) Ricci, J. S.; Ibers, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 2391.

(9) (a) Naota, T.; Tannna, A.; Kamuro, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2002**, *124*, 6842. (b) Naota, T.; Tannna, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2000**, *122*, 2960. (c) Alburquerque, P. R.; Pinhas, A. R.; Krause, Bauer, J. A. *Inorg. Chim. Acta* **2000**, *298*, 239. (d) Ruiz, J.; Rodríguez, V.; López, G.; Casabó, J.; Molins, E.; Miravitlles, C. *Organometallics* **1999**, *18*, 1177. (e) Ragaini, F.; Porta, F.; Fumagalli, A.; Demartin, F *Organometallics* **1991**, *10*, 3785. (f) Porta, F.; Ragaini, F.; Cenini, S.; Demartin, F. *Organometallics* **1990**, *9*, 929. (g) Ko, J. J.; Bockman, T. M.; Kochi, J. K. *Organometallics* **1990**, *9*, 1833. (h) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750. (i) Chopra, S. K.; Cunningham, D.; Kavanagh, S.; McArdle, P.; Moran, G. *J. Chem. Soc., Dalton Trans.* **1987**, 2927. (j) Del Pra, A.; Forsellini, E.; Bombieri, G.; Michelin, R. A.; Ros, R. *J. Chem. Soc., Dalton Trans.* **1979**, 1862. (k) Lenarda, M.; Pahor, N. B.; Calligaris, M.; Graziani, M.; Randaccio, L. *J. Chem. Soc., Chem. Commun.* **1978**, 279. (l) Schlodder, R.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Am. Chem. Soc.* **1974**, *96*, 6893. (m) Yarrow, D. J.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Organomet. Chem.* **1974**, *70*, 133.

(10) Fluxional mixtures of *N*- and *C*-metalated nitriles are observed in some instances: Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798.

(11) 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: Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327.

(12) For a discussion of the inversion barrier and mechanism see: Carlier, P. R. *Chirality* **2003**, *15*, 340.

(13) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.

(14) (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.

(15) Chelation of nitriles by lithium cations is directly analagous to the chelation of organolithiums with proximal alkenes and aromatic π systems: (a) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434. (b) Rölle, T.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1953. (c) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720.

(16) (a) Davis, F. A.; Mohanty, P. K. *J. Org. Chem.* **2002**, *67*, 1290. (b) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901. (c) Schrader, T.; Kirsten, C.; Herm, M. *Phosphorous, Sulfur, Silicon* **1999**, *161*, 144−146. (d) Gmeiner, P.; Hummel, E.; Haubmann, C. *Liebigs Ann.* **1995**, 1987. (e) Murray, A. W.; Murray, N. D.; Reid, R. G. *J. Chem. Soc., Chem. Commun.* **1986**, 1230.

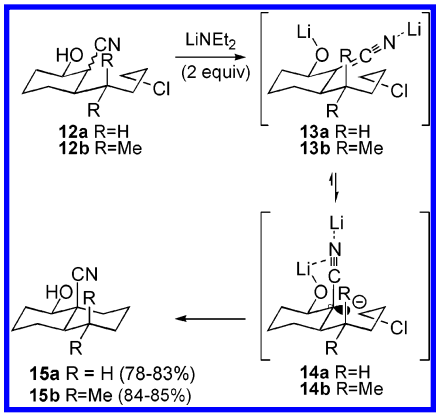
(17) Michelin, R. A.; Mozzon, M.; Bertani, R. *Coord. Chem. Rev.* **1996**, *147*, 299.

(18) (a) Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083. (b) Henbest, H. B.; Nicholls, B. *J. Chem. Soc.* **1959**, 227. For a related interaction between fluorine and the nitrile π-electrons see: Nishide, K.; Hagimoto, Y.; Hasegawa, H.; Shiro, M.; Node, M. *Chem. Commun.* **2001**, 2394.

to the pyramidal nitrile **11** (Scheme 2). Lithium chelation effectively overrides the normal preference for a planar, *N*-lithiated nitrile in favor of the pyramidal metalated nitrile **11**, in which the nucleophilic orbital is ideally oriented for an S_Ni cyclization to the *trans*-decalin **10**. Lithium complexation with the nitrile π-electrons effectively explains why the metal-dependent cyclization of **8** is not observed in THF where solvation of the lithium cation disrupts the internal chelation.[19]

Identifying internal chelation as a powerful stereocontrol element for metalated nitriles not only explains the stereoselectivity differences between the cyclizations of **4** and **8**, but provides insight into the cyclizations of hydroxynitriles **12a** and **12b** which *exclusively* afford the *trans*-decalins **15a** and **15b** (Scheme 3).[20] Deprotonating **12a**, or **12b**, with excess $LiNEt_2$ is anticipated to initially generate the *N*-lithiated nitrile **13**[21] that rapidly equilibrates to the internally chelated nitrile **14**[22] (Scheme 3). Lithium chelation with the nitrile effectively locks the lithiated nitrile **14** in a pyramidal geometry ideal for cyclization to the *trans*-decalins **15a** and **15b** (Scheme 3). In comparison, deprotonating the parent *des*-hydroxy nitrile **4** favors cyclization to the *trans*-decalin **7** (Scheme 1) for geometric reasons,[13] but less selectively because of the absence of the beneficial chelation.

SCHEME 3. Metal-Dependent Cyclizations of Metalated Nitriles

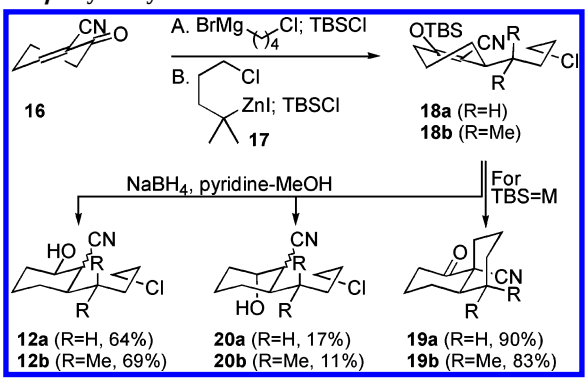


The exceptionally selective cyclizations of several oxygen-containing nitriles implicates chelation as a powerful stereocontrol element in metalated nitrile alkylations. Using chelation to relay the chirality of a lithium alkoxide to an adjacent, pyramidal metalated nitrile is shown to permit the selective cyclization of a series of cyclic β-hydroxy nitriles to *cis* and *trans* hydrindanes and decalins. Collectively, these cyclizations address the long-standing difficulty of synthesizing *trans*-fused hydrindanes,[23] demonstrate the dramatic influence of chelation in metalated nitrile alkylations, and provide key insight into the geometric requirements of these demanding cyclizations.

Results and Discussion

Several β-hydroxy nitriles ideally suited for chelation-controlled cyclizations were fortuitously synthesized during a comparative series of enolate and metalated nitrile cyclizations (Scheme 4). Conjugate addition of 4-chlorobutylmagnesium bromide,[24] or the organozinc reagent **17**,[25] to oxoalkenenitrile **16**[26] affords an intermediate enolate **18** (TBS = M) that readily cyclizes to the *cis*-decalin **19** upon warming. Alternatively, intercepting the enolate with TBSCl at low temperatures prevents premature cyclization to provide the corresponding β-siloxyalkenenitriles **18**. Reducing these β-siloxyalkenenitriles with excess $NaBH_4$ triggers a cascade in which catalytic methoxide[27] cleaves the silyl ether to temporarily unmask a ketone before further reduction to the corresponding β-hydroxynitriles **12** and **20**. Cyclizing the major equatorial β-hydroxynitriles **12a** and **12b** affords *trans*-decalins (Scheme 3) whereas the cyclization of the axial β-hydroxynitriles **20a** and **20b** has not previously been probed.[28]

SCHEME 4. Conjugate Addition−Reduction Route to Cyclic β-Hydroxynitriles



Cyclizing the β-hydroxynitrile **20b** provides an ideal probe into the strength of a lithium alkoxide−nitrile interaction. Specifically, the *gem*-dimethyl substituent constrains the cyclohexane ring to essentially one chair conformation since access to conformer **21a** (Scheme 5) is precluded by the severe steric compression with the axial *tert*-butyl-like substituent. Deprotonating **20b** with excess $LiNEt_2$ generates a dilithiated nitrile that can cyclize to *cis*- and *trans*-decalins via **21b** or **21c**, respectively. From a steric perspective **21b** is destabilized by three syn-axial type interactions[29] ($\sim$2.6 kcal mol^{-1})[3] but benefits from chelation between the nitrile and the lithium alkoxide and a potential $\sigma-\sigma^*$ stereoelectronic stabilization.[30]

(19) Cyclizing **8** in THF at room temperature with LiHMDS gives a 4:1 ratio in favor of the *cis*-decalin **9**. THF is a much stronger donor solvent that likely dissociates complex **11** in favor of an *N*-lithiated nitrile[6] that preferentially cyclizes to the *cis*-decalin **9** for geometric reasons (cf. **4** → **5a′** → **6**, Scheme 1).

(20) (a) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Tetrahedron* **2003**, *59*, 737. (b) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Org. Lett.* **1999**, *1*, 1547.

(21) Conceptually, the deprotonation may lead directly to the internally chelated nitrile **14** in contrast to nonchelated nitriles where computational analysis indicates that deprotonation with $LiNH_2$ leads directly to *N*-metalated nitriles: Koch, R.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523.

(22) Chelation in THF is favored because the lithium is maintained in close proximity by the strong oxygen−lithium bond whereas the weaker Lewis acid interaction observed in **11** requires the less coordinating solvent benzene to be effective.

(23) Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071.

(24) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.

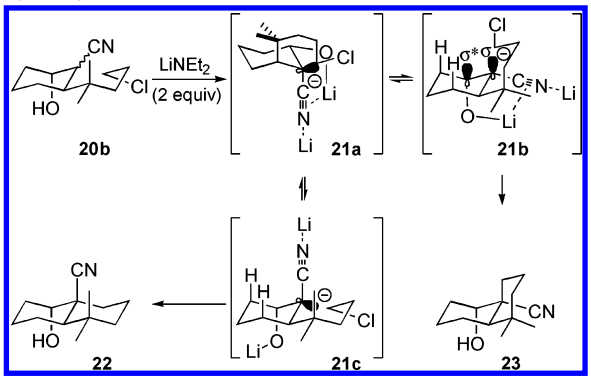
(25) Prepared from 5-chloro-2-pentanone by sequential methylation with MeLi, iodination with $MeSiCl_3$-NaI,[a−c] and zincation:[d] (a) Olah, G. A.; Husain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667. (b) Olah, G. A.; Gupta, B. G. B.; Malhotra, R.; Narang, S. C. *J. Org. Chem.* **1980**, *45*, 1638. (c) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247. (d) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

(26) Fleming, F. F.; Shook, B. C. *Org. Synth.* **2001**, *77*, 254.

(27) Hurst, D. T.; McInnes, A. G. *Can. J. Chem.* **1965**, *43*, 2004.

(28) Although the axial β-hydroxynitriles are the minor components in this sequence, several strategies exist for selectively reducing the oxonitrile precursor into either diastereomer: Fleming, F. F.; Iyer, P. S. *Synthesis* **2006**, 893.

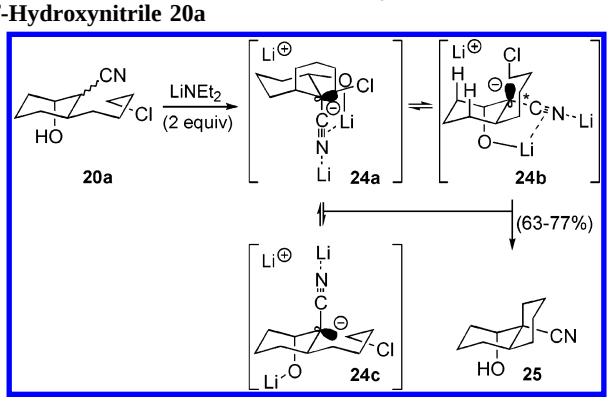
SCHEME 5. Chelation-Controlled Cyclizations of Axial β-Hydroxynitrile 20b



The alternative conformation **21c** has one CH_3-H (0.85 kcal mol^{-1})[3] and two, considerably smaller, CN−H syn-axial interactions (0.2 kcal mol^{-1})[3] but lacks lithium complexation with the nitrile because the substituents are trans-diaxial.[31] Cyclizing **20b** with excess $LiNEt_2$[32] in THF affords identical amounts of *trans*- and *cis*-decalins **22** and **23** (80%, Scheme 5)[33] which, assuming that **21b** and **21c** cyclize at equal rates, implies that the stabilization gained by chelation in **21b** offsets the inherent steric destablization. Enhancing the influence of chelation in **21b**, by performing the cyclization in benzene, results in the exclusive formation of the *cis*-decalin **23** (95%).

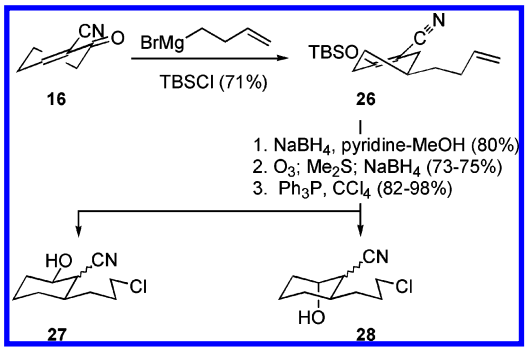
Chelation similarly dominates the analogous cyclizations of the *des*-methyl analogue **20a** (Scheme 6).[34] Deprotonating **20a** with $LiNEt_2$ in THF leads exclusively to the *cis*-decalin **25**,[35] which requires that no cyclization occurs through the uncomplexed nitrile **24c** in contrast to the analogous cyclization of **20b** (cf. **21c**, Scheme 5). Presumably, the less sterically demanding chlorobutyl side chain permits cyclization via the axial conformation **24a** in which the lithium alkoxide is complexed to the adjacent nitrile. Cyclization via **24a**, which is unavailable to the *gem*-dimethyl analogue (Scheme 5, **21a**), provides an additional reaction pathway to the *cis*-decalin **25** that complements the cyclization via **24b** and likely contributes to the exclusive formation of *cis*-decalin **25**.

SCHEME 6. Chelation-Controlled Cyclizations of Axial β-Hydroxynitrile 20a



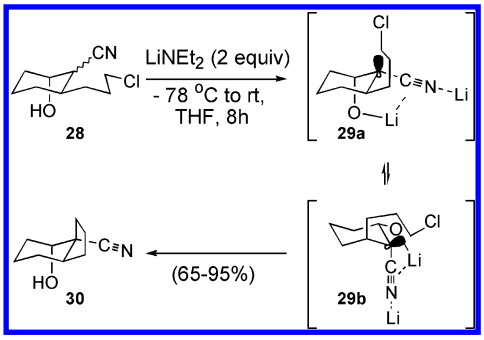
Conceptually, the chelation-controlled decalin cyclizations provide an enticing precedent for analogous metalated nitrile cyclizations to *cis*- and *trans*-hydrindanes. Access to the requisite cyclization precursors containing a three-carbon tether connected to a cyclohexanecarbonitrile was readily achieved through a conjugate addition−silylation sequence employing 3-butenylmagnesium bromide and oxoalkenenitrile **16**[26] (Scheme 7). Desilylation−reduction of the resulting β-siloxyalkenenitrile **26** affords a 2:1 ratio of equatorial and axial β-hydroxynitriles that were individually processed through an ozonolysis, reduction, chlorination sequence to access the truncated alkyl chlorides **27** and **28**.[36]

SCHEME 7. Synthesis of β-Hydroxynitriles for Hydrindane Cyclizations



Cyclizing the axial β-hydroxy nitrile **28** exclusively affords the *cis*-fused hydrindane **30** (Scheme 8).[36] Deprotonating **28** is anticipated to afford an equilibrium mixture of metalated nitriles **29a** and **29b** since the respective steric demands are similar, as is chelation between the lithium alkoxide and the nitrile. Cyclization from **29a** and **29b** leads to the same *cis*-fused hydrindane **30** since chelation effectively positions the nucleophilic orbital and the electrophilic tether on the same side of the cyclohexane ring in each case. The ensuing cyclization is facile because there is considerable flexibility in this *cis*-hydrindane precursor unlike the corresponding cyclization to the *trans*-hydrindane.

SCHEME 8. Metalated Nitrile Cyclizations to *cis*-Hydrindanes



Cyclizing the analogous equatorial hydroxynitrile **27** incurs greater torsional strain in the tether during formation of the *trans*-hydrindane ring system (Scheme 9). Addition of excess

(29) The two syn axial interactions with the forming methylene carbon are probably less than the assigned 0.85 kcal mol^{-1} since the transition state for nitrile anion alkylations is early: Bare, T. H.; Hershey, N. D.; House, H. O.; Swain, C. G. *J. Org. Chem.* **1972**, *37*, 997.

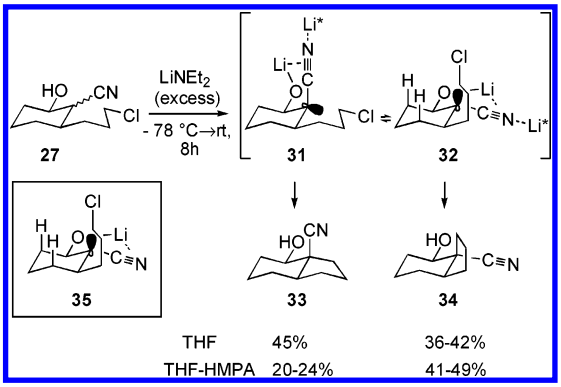
(30) Stereoelectronic effects are purported to be more influential in the transition state and particularly in nonpolar solvents (vide infra): Chandrasekhar, S. *ARKIVOC* **2005**, *13*, 37.

(31) The syn-axial interactions of the nitrile and alkoxide groups in **21b** and **21c** are identical in this comparative analysis.

(32) $LiNEt_2$ is often a more effective base than LiN-*i*-Pr_2 for deprotonating hindered, cyclic nitriles.[5] Deprotonating **20b** with a combination of $LiNEt_2$ (1 equiv) and NaH (1 equiv) or MeMgCl (2.1 equiv) causes elimination to the cyclic alkenenitrile: (a) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 3668. (b) Fleming, F. F.; Shook, B. C. *Tetrahedron Lett.* **2000**, *41*, 8847.

$LiNEt_2$ to **27** does afford the *trans*-hydrindane **33** although accompanied by an approximately equal amount of the *cis*-hydrindane **34**.[36,37] Sterically, there is a significant steric compression in conformation **32**, leading to the *cis*-hydrindane, by virtue of the axial-type methylene groups, whereas in conformer **31** the steric interactions are relieved because the small nitrile group lies in the axial orientation.[38] Despite a greater conformational preference for **31** the cyclization rate might be retarded, relative to **32**, because of the twisting required of the three-carbon tether in the S_Ni displacement.

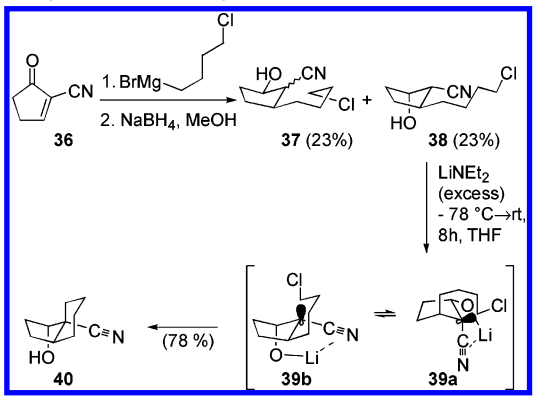
SCHEME 9. Metalated Nitrile Cyclizations to *trans*-Hydrindanes



Intricate NMR studies demonstrate that the addition of HMPA to lithiated nitriles efficiently sequesters lithium cations.[6a] Reasoning that HMPA might selectively abstract the Lewis acidic lithium (Li*) complexed to nitrogen rather than the more tightly bound lithium alkoxide, the cyclization of **27** was repeated in a 9:1 THF−HMPA solvent mixture (Scheme 9). Although the modestly increased preference for the *cis*-hydrindane **34** might be caused by numerous factors, the change is consistent with increased alkylation from the more reactive metalated nitrile **35** (see inset in Scheme 9). Sequestering the less-tightly bound N-coordinated lithium is anticipated to generate a more reactive nucleophile with cyclization from **35** being faster than the monolithiated counterpart of **31**. Despite being speculative, this analysis implies that the primary difficulty in forming the *trans*-hydrindane is the twisting of the tether required for correct S_Ni alignment and suggests a potential solution: cyclization of a *ring-contracted* 5-membered cyclic nitrile bearing a *methylene-expanded* 4-carbon tether.

Rapid entry to the requisite 5-membered β-hydroxynitriles **37** and **38** was provided by conjugate addition of chlorobutylmagnesium bromide to 3-oxo-1-cyclopentene-1-carbonitrile (**36**)[39] followed by reduction (Scheme 10). Each hydroxynitrile diastereomer **37** and **38**[40] is separable allowing cyclization of the individual alcohol epimers.[41] Deprotonating the pseudoaxial β-hydroxynitrile **38** generates a single *cis*-hydrindane **40**[42] as expected for metalated nitriles **39a** and **39b** in which the nucleophilic orbital of the metalated nitrile and electrophilic side chain are constrained into a *cis* geometry through chelation.

SCHEME 10. Cyclizations of 5-Membered β-Hydroxynitriles to *cis*-Hydrindanes



Cyclizing the pseudoequatorial β-hydroxynitrile **37** provides key insight into the geometric requirements for intramolecular displacements leading to *trans*-hydrindanes. Deprotonating **37** (Scheme 11) with $LiNEt_2$ in THF preferentially affords the *trans*- and *cis*-hydrindanes **43** and **44** in a 1.5:1 ratio, respectively.[43] The increased preference for the *trans*-hydrindane, relative to **27** (Scheme 9), is consistent with cyclization from conformation **41** in which the four-carbon tether more readily aligns the electrophilic chloromethylene carbon with the nucleophilic orbital oriented trans to the chlorobutyl side chain (cf. **41** in Scheme 11 with **31** in Scheme 9). Conformationally, the pyramidal metalated nitrile **41** incorporates the chelate within a *cis*-hydrindane ring whereas the diastereomeric counterpart **42** contains the chelate within a less-stable[44] *trans*-fused hydrindane ring system. Assuming that increased complexation between the lithium alkoxide and the π-electrons of the nitrile would be more readily accommodated in the *cis*-fused chelate **41** than in the *trans*-fused chelate **42**, the cyclization was

(33) The ring junction stereochemistry was assigned by Jones oxidation of **22** and **23** to the corresponding *trans* and *cis* ketones **i** and **19b** whose stereochemistries were previously determined by X-ray crystallography (CCDC nos. 183548 and 183550, respectively).[20a]

(34) Nitrile **20a** cyclizes exclusively to the *cis*-decalin **25** regardless of the stereochemistry of the nitrile bearing carbon.

(35) The ring junction stereochemistry of **25** was assigned by Jones oxidation to the corresponding *cis* ketone **19a** whose stereochemistry was previously determined by X-ray crystallography (CCDC 139957).[20b]

(36) The range in yield reflects differences in reaction efficiencies from diastereomeric nitrile precursors.

(37) Jones oxidation of **34** and **33** afforded two diastereomeric hydrindanones **ix** and **x** with the former being identical with that obtained by Jones oxidation of **30**.

(38) Essentially **31** has only two minimal CN-H *syn*-axial interactions (2×0.1 kcal mol^{-1}) whereas **32** experiences three CH_2-H *syn*-axial type interactions (3×0.85 kcal mol^{-1}).[3]

(39) Zhu, J.-L.; Shia, K.-S.; Liu, H.-J. *Chem. Commun.* **2000**, 1599.

(40) The stereochemistry was determined by conversion to the corresponding *p*-nitrobezoate **xii** whose stereochemistry was determined by X-ray crystallography. The authors have deposited the crystallographic data for **xii** with the Cambridge Crystallographic Data Center (CCDC 626356). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(41) The stereochemistry of the diastereomeric nitriles **37** were assigned from diagnostic ^{13}C NMR shifts: Dehli, J. R.; Gotor, V. *J. Org. Chem.* **2002**, *67*, 6816.

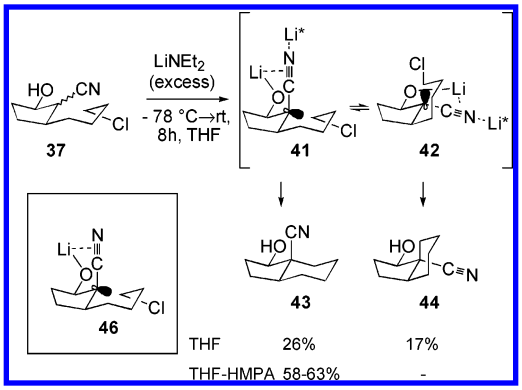
(42) The ring junction stereochemistry was determined by conversion to the corresponding *p*-nitrobezoate **xiii** whose stereochemistry was determined by X-ray crystallography. The authors have deposited the crystallographic data for **xiii** with the Cambridge Crystallographic Data Center (CCDC 626357). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(43) The 1,3-syn axial-type interactions of the ring protons with the pseudo-axial nitrile and CH_2Cl in **41** and **42** are minimal in this 5-membered ring: Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 758−762.

(44) The relative stabilities of cis and trans hydrindanes depends on temperature and substitution pattern, with angularly substituted *cis*-hydrindanes generally being more stable than their *trans*-hydrindane counterparts: Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 774−775.

repeated with excess HMPA. The expectation was that sequestering the lithium associated with the nitrile nitrogen (Li*) would increase the electron density available for complexation with the lithium alkoxide[45] resulting in a greater preference for the *trans* complex **46**. Experimentally, deprotonating **37** in a 9:1 THF−HMPA solvent mixture afforded the *trans*-hydrindane as the only isolated hydrindane.[46]

SCHEME 11. Cyclizations of Equatorial *β*-Hydroxynitriles to *cis*-Hydrindanes



Cyclizations of cyclic *β*-hydroxynitriles provide insight into the key geometrical requirements of S_Ni cyclizations to *cis* and *trans* hydindanes and decalins. Controlling the metalated nitrile geometry by chelation with an adjacent lithium alkoxide permits the selective cyclization of cyclic 6-membered *β*-hydroxynitriles to *cis*-hydrindanes but not to the *trans*-hydrindane counterparts. The difficulty lies in the twisting of the three-carbon chain required for the correct S_Ni alignment, which is better achieved through the cyclization of cyclic 5-membered *β*-hydroxynitriles bearing a more flexible electrophilic side chain having 4 carbons. Chelation-controlled cyclizations of these 5-membered *β*-hydroxynitriles provide an effective route not only to *cis*-hydrindanes but also to the synthetically more challenging *trans*-hydrindane ring system.[23]

Cyclizations of metalated nitriles to *cis*- and *trans*-decalins are equally well directed by lithium complexation. Deprotonating a series of 6-membered *β*-hydroxynitriles having an electrophilic chlorobutyl side chain gives *cis*- or *trans*-decalins where the chirality of the lithium alkoxide is relayed to the adjacent metalated nitrile. Collectively, the hydrindane and decalin cyclizations demonstrate the key influence of chelation between the electrophilic lithium cation and the *π*-electrons of the nitrile for controlling the stereochemistry of the pyramidal metalated nitrile and provide key insight into the geometric requirements of these demanding cyclizations.

Experimental Section[47]

General Cyclization Procedure. A −78 °C, THF solution of $LiNEt_2$ (1.1 equiv) was prepared by the addition of a hexanes solution of BuLi (1.1 equiv) to a −78 °C, THF solution of Et_2NH (1.2 equiv). After 20 min a THF solution of the *β*-hydroxynitrile (1 equiv) was added an, after 4 h the solution was allowed to warm slowly to room temperature. After 10 h saturated aqueous NH_4Cl was added, the aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Purification of the crude product by radial chromatography (EtOAc/hexanes) afforded the pure bicyclic nitrile.

Acknowledgment. Financial support for this research from NSF (0515715) is gratefully acknowledged as is support for the X-ray facility (CRIF 0234872).

Note Added After ASAP Publication: The author name Rahman was spelled incorrectly in the version posted ASAP January 24, 2007; it was corrected in the version posted February 2, 2007.

Supporting Information Available: Experimental procedures, ^1H NMR, and ^{13}C NMR spectra for all new compounds and CIF and ORTEPs for the structures **xiv** and **xv** determined by X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062270R

(45) Metalated nitriles are more electron rich than their neutral parent nitriles: (a) Wu, F.; Foley, S. R.; Burns, C. T.; Jordan, R. F. *J. Am. Chem. Soc.* **2005**, *127*, 1841. (b) Groux, L. F.; Weiss, T.; Reddy, D. N.; Chase, P. A.; Piers, W. E.; Ziegler, T.; Parvez, M.; Benet-Buchholz, J. *J. Am. Chem. Soc.* **2005**, *127*, 1854.

(46) Examining the crude ^1H NMR of the cyclization reaction indicated the presence of approximately 5% of the alkene resulting from elimination of the alkyl chloride making the definitive absence of any regioisomeric *cis*-hydrindane impossible. Resubjecting **43** to $LiNEt_2$ in THF without HMPA leads to full recovery of **43** indicating that the cyclization is kinetically controlled.

(47) For general experimental procedures see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.