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Metalated Nitriles: Cation-Controlled Cyclizations

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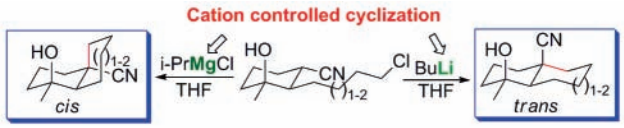
ABSTRACT



Judicious choice of cation allows the selective cyclization of substituted γ-hydroxynitriles to *trans*- or *cis*-decalins and *trans*- or *cis*-bicyclo-[5.4.0]undecanes. The stereoselectivities are consistent with deprotonations generating two distinctly different metalated nitriles: an internally coordinated nitrile anion with BuLi, and a *C*-magnesiated nitrile with *i*-PrMgCl. Employing cations to control the geometry of metalated nitriles permits stereodivergent cyclizations with complete control over the stereochemistry of the quaternary, nitrile-bearing carbon.

Stereodivergent, cation-controlled alkylations are exceptionally appealing. The appeal stems from the inherent efficiency of controlling nucleophile geometry simply by judicious cation selection. Directing a single precursor to two structurally different organometallics for stereodivergent alkylations is particularly challenging, potentially explaining why cation-controlled alkylations are relatively rare.[1]

Metalated nitriles are ideal organometallics for stereodivergent alkylations because of their chameleon-like structural preferences.[2] At least three structurally distinct metalated nitriles are selectively accessed simply through choice of solvent, temperature, and ligand. Solution and X-ray[3] analyses identify the three main metalated nitrile structures as spanning a range of geometries at the nucleophilic carbon: planar *N*-metalated nitriles **1**,[4] partially pyramidal carbanions **2**,[5] and tetrahedral *C*-metalated nitriles **3**[6] (Figure 1).

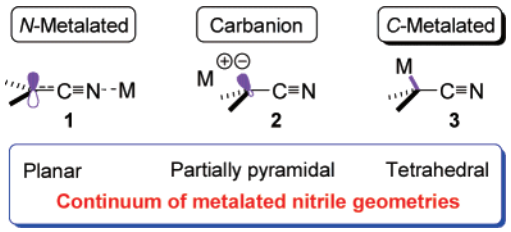


Figure 1. Structural classes of metalated nitriles.

Conceptually, two different geometries of metalated nitriles are accessible through stereodivergent deprotonations leading to a *C*-metalated nitrile and the corresponding inverted nitrile stabilized carbanion. The relatively low inversion barrier of metalated nitriles[5a] and the dramatic influence of chelation on metalated nitrile geometry[7] suggested using internal chelation with mono- or divalent cations to favor two distinct

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(2) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.

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

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(7) (a) Fleming, F. F.; Wei, G.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* In press. (b) Fleming, F. F.; Vu, V. A.; Shook, B. C.; Raman, M.; Steward, O. W. *J. Org. Chem.* **2007**, *72*, 1431.

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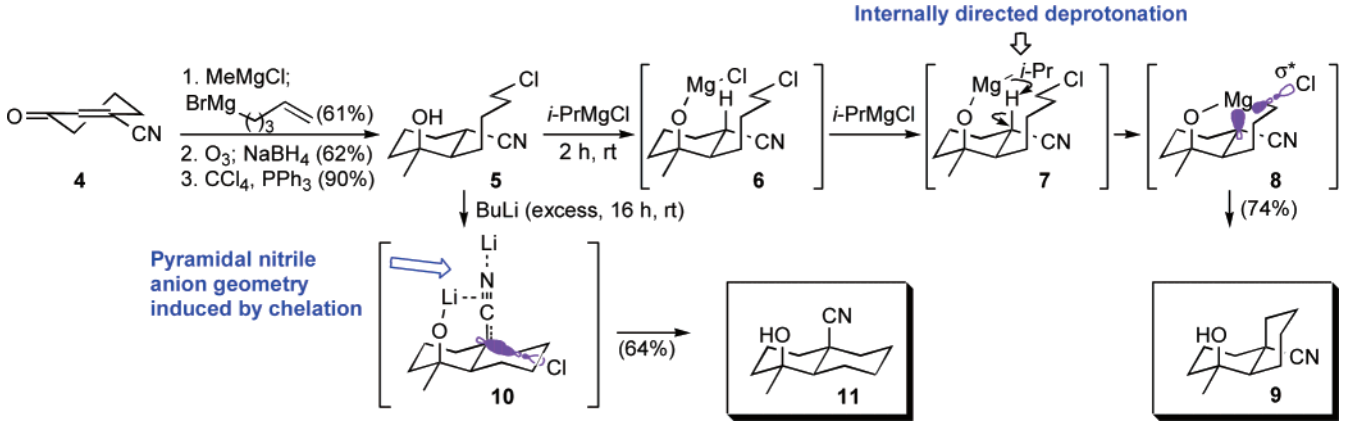
Scheme 1. Cation-Dependent Cyclizations of Pyramidal *C*-Magnesiated and *N*-Lithiated Nitriles



metalated nitrile geometries. Specifically, metalated nitriles derived from γ-hydroxy nitriles such as **5** (Scheme 1) permit two coordination modes by virtue of a metal's capacity to form one or two formal bonds. Internal coordination in the dilithiated nitrile **10** favors a pyramidal anion with an equatorial nucleophilic orbital, whereas the corresponding *C*-magnesiated nitrile **8** possesses an axial nucleophilic C−Mg bond (Scheme 1).

The facile synthesis of **5** makes this nitrile an ideal prototype for pursuing a cation-selective cyclization. Sequential addition of MeMgCl and 4-pentenylmagnesium bromide[8] to oxonitrile **4**[9] provides an alkenenitrile intermediate which, after ozonolysis, reduction, and chlorination, provides an expedient synthesis of nitrile **5** (Scheme 1). Mounting experimental evidence[10] indicates that addition of excess *i*-PrMgCl to this type of γ-hydroxynitrile (**5**) triggers deprotonation to a halomagnesium alkoxide (**6**) that subsequently engages in a halogen−alkyl exchange to afford an alkylmagnesium alkoxide (**7**).[11] Forming the axial alkylmagnesium alkoxide **7** conveniently anchors the basic isopropyl group for a directed, internal deprotonation while preventing alkyl addition to the nitrile group.

Cyclization of the resulting *C*-magnesiated nitrile **8** affords the *cis*-decalin **9**[12] as the sole stereoisomer. The stereochemistry is consistent with a retentive S_Ni displacement resulting from attack of the carbon−magnesium bond on the C−Cl σ* orbital via a 3-centered transition structure (**8**).[10]

The stereodivergent cyclization of **5** to the *trans*-decalin **11** was pursued via the putative lithiated nitrile **10** with the opposite configuration at the nitrile-bearing carbon. Extensive experimentation identified BuLi as the optimum base, with a slight excess triggering the cyclization of **5** to the diastereomeric *trans*-decalin **11**.[12] Exclusive formation of the *trans*-decalin **11** requires overlap of an equatorally oriented orbital with the σ* orbital of the C−Cl bond. The cyclization stereochemistry is consistent with forming a pyramidal nitrile anion in which internal chelation between the alkoxy lithium cation and the π-electrons of the nitrile[7b,13] defines the stereochemistry at the nitrile-bearing carbon.

Extending the cation-controlled cyclization strategy to the synthesis of *cis*- and *trans*-bicyclo[5.4.0]undecanes is surprisingly challenging (Scheme 2). Related cyclizations of ω-haloalkylnitriles are remarkably difficult for 7-membered carbocycles relative to corresponding ring closures of the 3−6-membered analogues.[14] Consistent with this difficulty, sequential addition of MeMgCl and 5-chloropentylmagnesium iodide[15] to oxonitrile **4** generates the chloroalkylnitrile **13** without premature cyclization of the intermediate *C*-metalated nitrile **12**. Regenerating **12**, through addition of *i*-PrMgCl to **13**, fails to induce *any* cyclization even in refluxing THF! Coaxing the cyclization requires prior conversion to the corresponding iodide **14**, with cyclization of the *C*-magnesiated nitrile **15** requiring heating in refluxing THF to afford the cis-fused[16] nitrile **16**.[17]

Diverting the cyclization manifold through the use of BuLi results in a slow, but relatively efficient, cyclization of **13** to the *trans*-lactone **19** (Scheme 2). Installation of the trans-ring junction stereochemistry is consistent with cyclization via the pyramidal, internally coordinated nitrile **17**. Presumably this "dianion" is more reactive than the corresponding

(8) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126.
(9) Fleming, F. F.; Zhang, Z.; Wei, G. *Synthesis* **2005**, 3179.
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(12) The stereochemical assignments of **9** (ref 8) and **11** (Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 7646) are made by comparison with previously identified material. No trace of the diastereomer was observable in ^{1}H NMR spectra of the crude reaction mixture.
(13) (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**, *144−146*, 161. (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.
(14) Larcheveque, M.; Mulot, P.; Cuvigny, T. *J. Organomet. Chem.* **1973**, *57*, C33.
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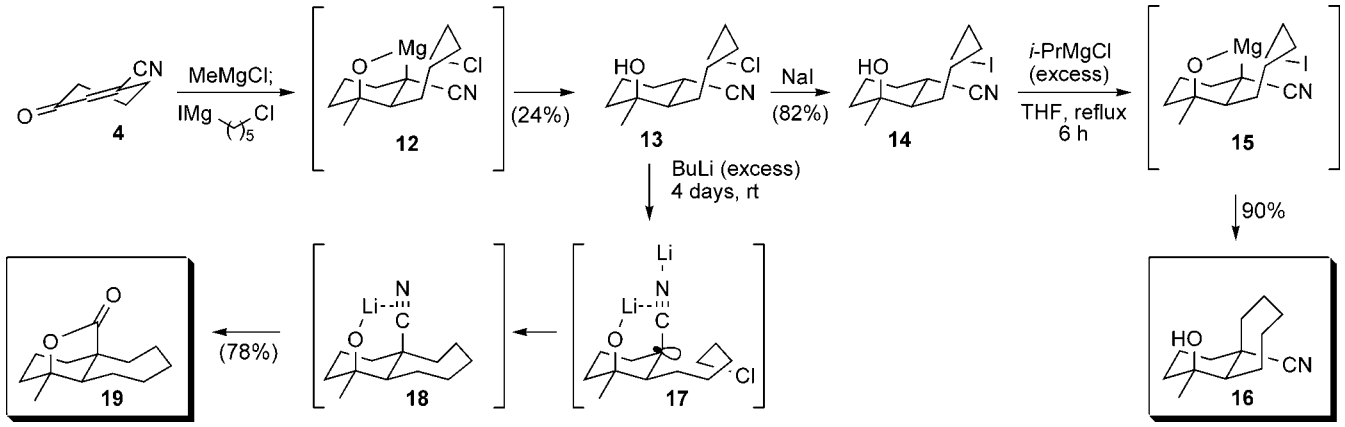
(16) The stereochemical assignment is based on the characteristic ^{13}C shift of the equatorial nitrile carbon: Bailey, W. F.; Cioffi, A. *Magn. Reson. Chem.* **1987**, *25*, 181.
(17) No cyclization is observed after 1 day at room temperature.

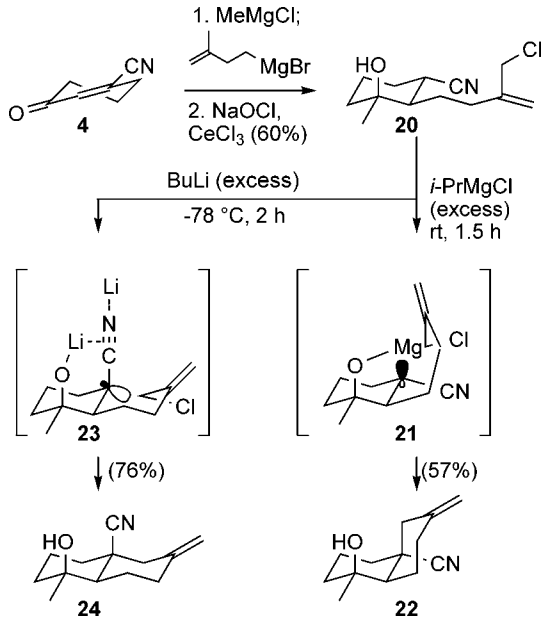
Scheme 2. Stereodivergent Cyclizations of Pyramidal *C*-Magnesiated and *N*-Lithiated Nitriles to Bicyclo[5.4.0]undecanes



C-magnesiated nitrile **12** since cyclization does not require heating or the more electrophilic iodide leaving group. Complete cyclization at room temperature requires 4 days, during which the alkoxide **18** resulting from cyclization attacks the proximal nitrile to afford the lactone **19** after hydrolysis.

The stereodivergent decalin and bicyclo[5.4.0]undecane cyclizations stimulated an analogous cyclization with an allylic electrophile to introduce an *exo*-methylene substituent as a potential handle for subsequent synthetic ventures (Scheme 3). Access to the cyclization precursor **20** was readily achieved through sequential addition of MeMgCl and 3-methyl-3-butenylmagnesium bromide to oxonitrile **4** followed by selective chlorination[18] in the presence of the unprotected tertiary alcohol. Addition of excess *i*-PrMgCl to nitrile **20** initiates a deprotonation cascade leading to the *cis*-decalin **22** whose stereochemistry was secured by X-ray crystallography (Figure 2).

Scheme 3. Stereodivergent Allyl Chloride Cyclizations



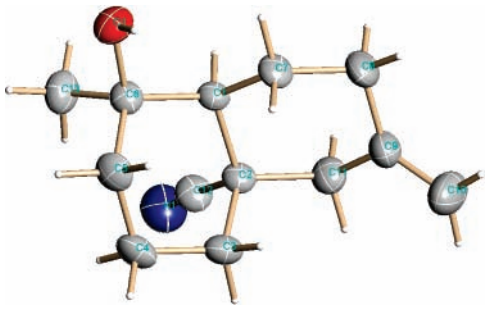


Figure 2. ORTEP diagram of *cis*-decalin **22**.

Employing BuLi for the deprotonation of **20** triggers a particularly facile cyclization to the *trans*-decalin **24**. In contrast to the room temperature S_Ni displacement of the alkylchloride **10** (Scheme 1), cyclization of the putative dilithiated nitrile **23** (Scheme 3) proceeds at −78 °C and was complete within 2 h. The facility of metalated nitrile cyclizations with allylic electrophiles suggests a possible extension of this strategy in sterically demanding cyclizations.

Stereodivergent cyclizations of γ-hydroxynitriles are readily achieved by judicious choice of mono- or divalent cations in the intermediate metalated nitriles. Hydroxyl directed deprotonations with Grignard or organolithium reagents provides an expedient entry to two putative metalated nitriles that differ primarily in the geometry at the nitrile-bearing carbon. Cyclizations initiated with *i*-PrMgCl consistently afford cis-fused decalins or bicyclo[5.4.0]undecanes whereas BuLi affords the trans-fused diastereomers. In each instance the stereoselectivies are consistent with generating *C*-magnesiated nitriles through *i*-PrMgCl deprotonation and an internally coordinated nitrile anion by deprotonating with

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BuLi. Synthetically, the stereodivergent cyclizations provide an effective method for diverting a single precursor to *cis*- and *trans*-bicyclic nitriles through stereoselective alkylation at the quaternary, ring junction stereochemistry.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds and the CIF files for **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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