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Cyclic Metalated Nitriles: Stereoselective Cyclizations to *cis*- and *trans*-Hydrindanes, Decalins, and Bicyclo[4.3.0]undecanes

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Metalated nitriles are nucleophilic chameleons whose precise identity is determined by the nature of the metal, the solvent, the temperature, and the structure of the nitrile. The review surveys the different structural types and their cyclization trajectories to show how to selectively tune the metalated nitrile geometry for stereoselective cyclizations to a variety of *cis* or *trans* hydrindanes, decalins, and bicyclo[4.3.0]-undecanes.

1. Introduction

Cyclic metalated nitriles are powerful nucleophiles.[1] Key to the exceptional nucleophilicity is the extremely small steric demand of the CN unit. Compared with carbonyl groups, the compact, cylindrical nature of the C≡N unit (3.6 Å cylindrical diameter of the π-system)[2] results in one of the smallest electron-withdrawing groups. A steric comparison is provided from the respective *A* values of carbonyl groups that are typically in excess of 1.0 kcal mol^{-1} whereas a nitrile group is a mere 0.2 kcal mol^{-1}![3]

The nitrile's minimal steric demand is ideal for alkylations in sterically demanding environments. In fact, alkylations of cyclic metalated nitriles necessarily install a quaternary center, a synthetic feature that has been critical in several natural product syntheses.[4] Typically cyclic metalated nitriles participate in alkylations by positioning the small nitrile in the more sterically congested environment which allows for a more favourable electrophilic trajectory.

Deprotonating cyclic nitriles create powerful nucleophiles.[5] Compared with other electron-withdrawing groups, metalated nitriles are up to 100 times more reactive[6] which on occasion allows carbon–carbon bond formations that cannot be achieved with carbonyl analogs.[7] In addition to the small size of the CN unit, the unusual inductive stabilization[8] localizes significant charge density

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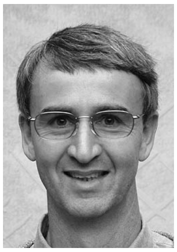

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on carbon to create a small, electron rich nucleophile. Synthetically these features relay into a high propensity for *C*-alkylation of cyclic metalated nitriles. Reactive silyl[9] and acyl[10] chlorides are among the few electrophiles with a propensity for alkylation on nitrogen.

1.1 The Structure of Metalated Nitriles

Metalated nitriles are nucleophilic chameleons. Formally regarded as "nitrile anions", these exceptional nucleophiles exist as a variety of structural types[11] whose precise identity is determined by the nature of the metal, the solvent, the temperature, and the structure of the nitrile. On one extreme are metalated ketenimines **1**[12] while on the other end of the continuum are solvent separated nitrile anions **4**[8a] (Figure 1). Sandwiched between these extremes are *N*-metalated nitriles **2** and *C*-metalated nitriles **3**.

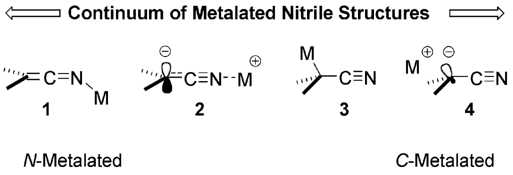


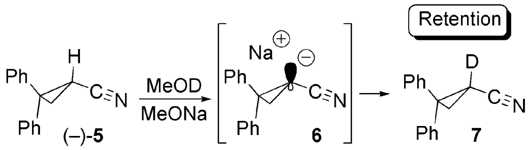
Figure 1. Continuum of metalated nitrile structures.

Although only a few examples exist at the extremes of the continuum, an analysis of their molecular features is very revealing. The best[13] crystallographically characterized metalated ketenimine structure is only favored with a sterically demanding ligand which prevents the palladium from accessing the hindered carbon center.[12] Compared to solid-state structures **2** and **3** the palladated ketenimine is differentiated by a longer C=N bond and a bent C–N–M geometry. These structural features are consistent with sp^2 hybridization of a ketenimine nitrogen.

N-Metalated nitriles **2** are the most commonly encountered metalated nitrile because they are readily generated by deprotonating the parent alkanenitrile with a lithium amide base. *N*-lithiation is favored by the electrophilic lithium which coordinates to the more electron rich nitrile nitrogen.[14] Electron deficient transition metals exhibit a similar preference for *N*-metalatation in the solid state,[15] particularly with Lewis acidic metals in a high oxidation state.

C-Metalated nitriles are favored by less electropositive transition metals.[16] Platinum, palladium, cobalt, and gold exhibit a pronounced tendency for *C*-metalation which is only perturbed by strong ligand effects. Of the non-transition metals boron,[17] magnesium,[18] germanium,[19] and zinc[20] adopt *C*-metalated nitrile structures **3**. Coordination of the metal to carbon necessarily generates a tetrahedral nucleophilic carbon with potential for being chiral.

The first evidence for a "chiral nitrile anion" was achieved in pioneering deuterations of cyclopropanecarbonitrile **5** (Scheme 1).[21] Exposing the chiral cyclopropanecarbonitrile **5** to MeONa-MeOD causes greater than 99.9% stereochemical retention in generating **7**,[22] presumably through the intermediacy of the transient ion pair **6**.[23] Stereochemical retention is favoured by rapid interception of the pyramidal carbanion **6** by proximal, deuterated methanol. In contrast, deprotonating **5** with LDA, which likely generates an *N*-lithiated nitrile, followed by protonation leads to complete racemization (**5** → **7**).



Scheme 1. Stereochemical integrity of a nitrile anion.

Seminal insight into the structure of metalated nitriles began in the late 1980's as X-ray crystallography of these reactive organometallics identified the position of the metal and provided precise bond lengths.[14] Solid state structures show a continuum of geometries for the metalated carbon, ranging from planar through partially pyramidal to tetrahedral (Figure 2, **8**,[24]**9**,[25] **10**[26] respectively). In each case the crystallographic structures exhibit short C–CN bonds (1.36–1.45 Å, Figure 2), consistent with an electrostatic contraction between the formal carbanion and the adjacent electron deficient nitrile.[8] Minimal elongation of the C≡N bond is typical in metalated nitriles, with the bond length (1.15–1.19 Å) being only slightly elongated when compared to the average C≡N bond length in neutral nitriles (1.14 Å).[27] Even in the palladated ketenimine **1** the C=N bond length is only 1.20 Å. The nitrile carbon of metalated nitriles therefore exhibits an apparent preference for a bond order greater than four because of the ylide-type stabilization between the "anionic" and nitrile carbon atoms and the persistence of the C≡N triple bond.

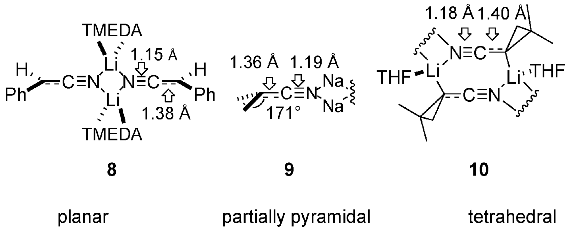
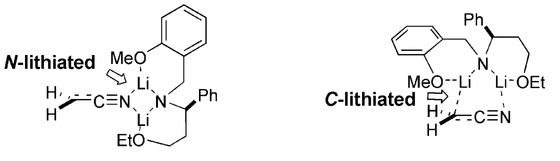


Figure 2. Partial X-ray structures of metalated nitriles.

1.2 Equilibration Between *N*- and *C*-Metalated Nitriles

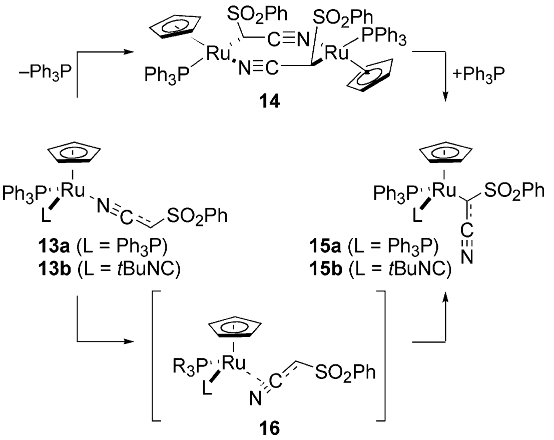
Solution NMR analysis of metalated nitriles closely correlate the range of structures identified by X-ray crystallography.[28] ^{6}Li-^{15}N NMR coupling in lithiated phenylacetonitrile is consistant with a solution structure essentially identical to that of the solid-state structure (cf. **8**, Figure 2). Complicating the structural analysis in solution are the presence of monomers and dimers whose precise constituency is strongly influenced by solvation.[28] The dramatic influence of solvation is encapsulated in the complexed lithioacetonitriles **11** and **12** (Figure 3). A fluxional mixture of rapidly equilibrating *N*- and *C*-coordinated nitriles is observed in ether at –100 °C whereas only the *N*-lithiated nitrile **11** is detected in THF (Figure 3).[29]



11 **12**

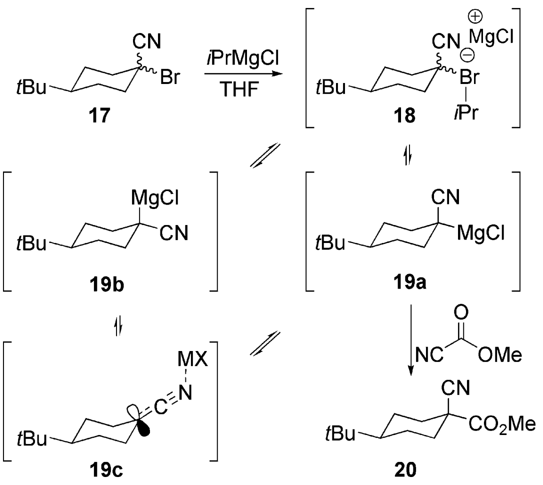
Figure 3. Solution structures of metalated nitriles.

Analogous fluxionality between *N*- and *C*-ruthenated (phenylsulfonyl)acetonitriles provides seminal insight into the equilibration mechanism (Scheme 2). Kinetic studies with the bis(triphenylphosphane) complex **13a** indicate an isomerization to **15a** by an intermolecular association. Remarkably, the putative dimeric intermediate **14** was isolated and succumbed to characterization by X-ray diffraction.[16a–16c,30] When an isocyanide ligand is substituted for one of the triphenylphosphane ligands, the resulting ruthenium complex **13b** isomerizes by an *intramolecular* mechanism! Metal dissociation from **13b** and slippage along the π-C–C–N surface of **16** has some parallel in the diversity of coordination modes of cyanide to transition metals.[31]



Scheme 2. *C*- to *N*-Metalated nitrile isomerization mechanisms.

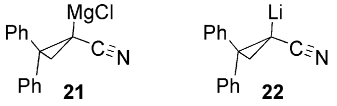
Cyclic metalated nitriles can rapidly equilibrate to one of three different structures; an *N*-metalated nitrile or two diastereomeric *C*-metalated nitriles (Scheme 3). Insight into this equilibration was provided by the metalation and alkylation of the bromonitriles **17**.[18b] Addition of *i*PrMgBr to a –78 °C, THF solution containing methyl cyanoformate and *either* diastereomeric bromonitrile **17** preferentially affords the same ester nitrile **20** (>12:1). Alkylations of analogous planar ester enolates are less selective,[32] implying that the ester nitrile **20** is generated through a retentive alkylation of **19a**. Rapid equilibration to **19a** is favoured by positioning the small nitrile group in the less sterically demanding axial orientation and the larger solvated metal in the equatorial orientation. Initial formation of the bromate **18**[33] could trigger direct fragmentation to the *C*-metalated nitrile **19a** potentially admixed with the diastereomer **19b**, or **18** could fragment to the *N*-metalated nitrile **19c**. Equilibration of **19b** to **19a** is presumed to occur through **19c** by metal migration from carbon to nitrogen and then back again on the opposite face. This "conducted tour equilibration"[34] must be particularly facile[35] because the in situ exchange-alkylation of the individual diastereomeric bromonitriles **17** affords essentially the same acylated nitrile **20**.



Scheme 3. Stereochemical integrity of a nitrile anion.

1.3 Quests for a Chiral Metalated Nitrile

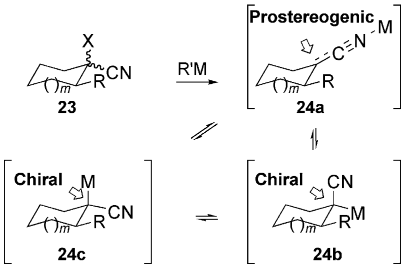
Quests to generate chiral nitrile anions[36] have been complicated by the facile equilibration of metalated nitriles.[34,37] Seminal configurational analyses of the magnesiated and lithiated nitriles **21** and **22** calculate an inversion barrier of 14 kcal mol^{-1} for the magnesiated nitrile **21** in diethyl ether at –100 °C.[22] The lithiated nitrile **22** is considerably less stable with rapid racemization only providing an upper limit of 11.1 kcal mol^{-1} for the inversion barrier (Figure 4).



21 **22**

Figure 4. Solution structures of chiral metalated mitriles.

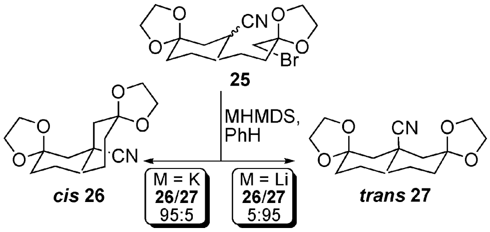
An alternative strategy for generating chiral, cyclic metalated nitriles is to desymmetrize the carbocyclic ring. Introducing a ring substituent effectively transforms the nucleophilic carbon into a prostereogenic centre for a planar *N*-metalated nitrile, or into a chiral nucleophilic carbon if *C*-metalated (Scheme 4). Selective access to the *N*-metalated nitrile **24a** is conceptually possible through judicious metal selection whereas selectively forming **24b** over **24c** is anticipated on steric grounds. Employing a substituent R bearing a pendant electrophile creates the potential for stereodivergent cyclizations to *cis*- and *trans*-fused bicyclic nitriles with the stereochemistry being controlled simply by tuning the geometry of the metalated nitrile.



Scheme 4. Equilibration route to chiral metalated nitriles.

2. Metalated Nitrile Cyclizations

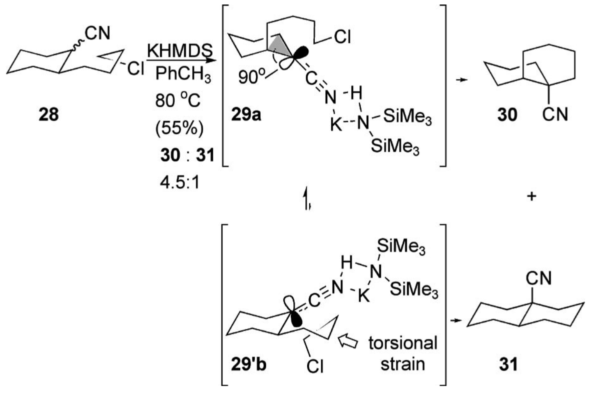
Metalated nitriles have a rich history in cyclization reactions.[38] Deprotonating cyclic nitriles generates reactive nucleophiles that efficiently alkylate pendant electrophiles to form the ubiquitous hydrindane[39] and decalin scaffolds.[40] A landmark discovery[41] was the metal-dependent stereodivergent cyclization of the ketal-containing nitrile **25** to *cis*- and *trans*-decalins **26** and **27**, respectively (Scheme 5). The significance lies in the simple means of stereocontrol combined with addressing the challenge[42] in generating decalins that avoid the sometimes troublesome cyclization-equilibration strategies of ketone enolates.



Scheme 5. Stereodivergent metalated nitrile cyclizations.

2.1 *N*-Metalated Nitrile Cyclizations

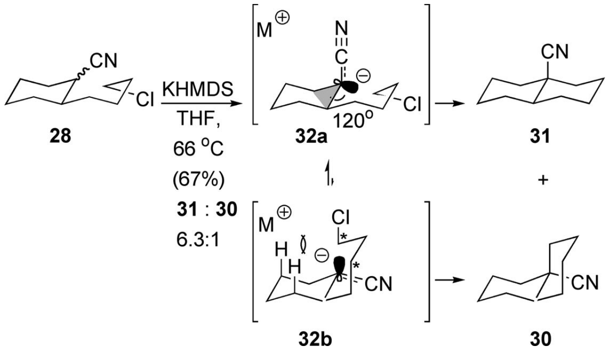
Insight into the stereodivergent cyclizations of metalated nitriles was provided through an extensive series of cyclizations correlating stereoselectivity with solvent, cation, and temperature.[43] The trajectory-based analysis provides insight into the nature of the metalated nitrile by using the diastereomeric product ratio as an indirect probe of the nucleophilic carbon geometry during the alkylation. Cyclizations of the parent carbonitrile **28** under conditions favoring *N*-metalation, such as KHMDS in toluene, favor the *cis*-decalin **30** over the *trans*-decalin **31**. The stereoselectivity is consistent with preferential cyclization through the planar *N*-metalated nitrile conformer **29a** (Scheme 6) which avoids the tortional strain imposed by twisting of the electrophilic tether attending cyclization via **29b** to the *trans*-decalin **31**.



Scheme 6. *N*-Metalated nitrile cyclization to a *cis*-decalin.

2.2 Nitrile Anion Cyclizations

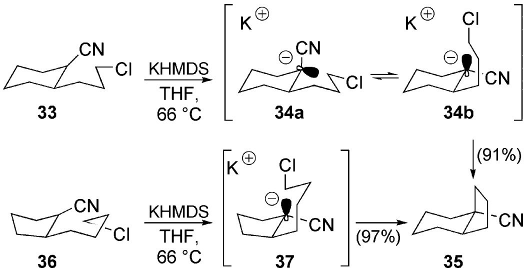
Cyclizations of the probe nitrile **28** under conditions favoring a nitrile anion revealed fundamental differences compared with cyclizations of the *N*-metalated nitrile **29**. As an immediate point of departure, cyclizing **28** in refluxing THF preferentially affords the *trans*-decalin **31** (Scheme 7).[43] No significant selectivity change occurs in the presence of 18-C-6, supporting the intermediacy of a solvent separated ion pair. The selectivity is consistent with preferential cyclization of the pyramidal nitrile anion **32a** in which the small nitrile adopts the axial orientation with an equatorial nucleophilic anion ideally oriented for an S_N2 displacement. Cyclization through the diastereomeric nitrile anion **32b**, epimeric at the nitrile-bearing carbon, incurs steric compression between the synaxial protons and the chloromethylene and ring methylene (*) C atoms.



Scheme 7. Nitrile anion cyclization to a *trans*-decalin.

Comparing the *trans*-selective cyclization of **28** in refluxing THF (Scheme 7) with the *cis*-selective cyclization of **28** in toluene (Scheme 6), underscores the importance of the anion geometry in controlling the cyclization stereochemistry. The pyramidal, sp^3-hybridized nitrile anion **32a** projects toward the electrophile at an angle of 120° relative to the plane (grey) containing the adjacent three ring atoms whereas the nucleophilic *p*-orbital of the *N*-metalated nitrile **29** projects at a reduced angle of 90°. The difference in the attack angle changes the tortional strain required for cyclization to the *trans*-decalin which otherwise benefits by placing the small nitrile in the sterically more demanding axial orientation.

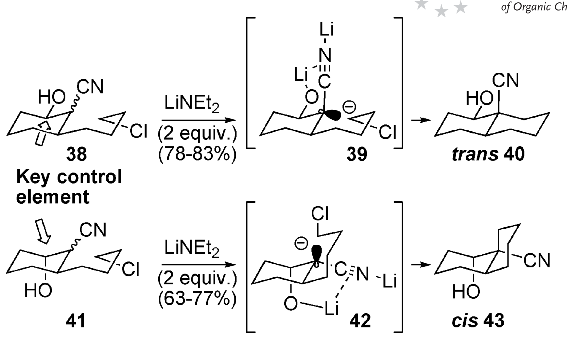
Extending the nitrile anion strategy to the synthesis of *trans*-hydrindanes is significantly more challenging because *trans*-hydrindanes, unlike their decalin counterparts,[42a] are typically thermodynamically less-stable than their *cis*-fused counterparts.[44] Two nitrile anion cyclization strategies are available for generating *trans*-hydrindanes; cyclizing a six-membered ring with a 3-carbon electrophilic tether (**33** → **35**, Scheme 8), or cyclizing a five-membered ring bearing a four-carbon electrophilic tether (**36** → **35**, Scheme 8).[45] Exploring the nitrile anion cyclization in both series leads only to the *cis*-hydrindane **35**. Presumably the torsional strain for cyclization via the pyramidal, nitrile anion **34a** is greater than the steric compression experienced in the diastereomeric anion **34b** leading to the *cis*-hydrindane **35**. Relaxing the torsional strain in the tether by increasing the length of the carbon chain, and simultaneously decreasing the ring size as in **37**, still affords only the *cis*-hydrindane **35** (Scheme 8).[46]



Scheme 8. Nitrile anion cyclizations to a *cis*-hydrindane.

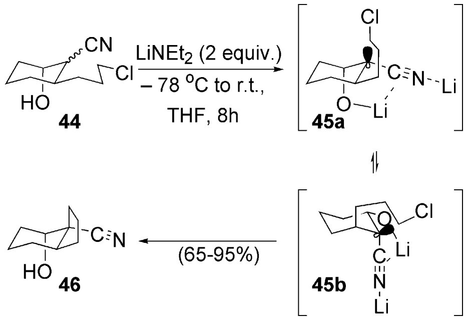
2.3 Chelated Nitrile Anion Cyclizations

Greater control over the orientation of the anionic orbital is achieved with chelated nitrile anions. The dramatic influence of chelation was demonstrated in the stereodivergent cyclizations of the diastereomeric hydroxynitriles **38** and **41** (Scheme 9).[47] Adding excess $LiNEt_2$ to **38** or **41** first deprotonates the hydroxyl group which prevents subsequent elimination on deprotonation at the adjacent nitrile-bearing carbon.[48] Complexation in the resulting dilithiated nitriles **39** and **42** between the lithium alkoxide[49] and the nitrile π-electrons[50] effectively locks the lithiated nitrile in a pyramidal geometry, the geometry of the chiral carbanion being determined by the configuration of the adjacent alkoxide.[51] For the equatorially oriented hydroxynitrile **38**, the chelate **39** with the axial nitrile is favoured which directs the cyclization exclusively to the *trans*-decalin **40**. Cyclization of the axial hydroxynitrile **41** can only proceed through chelate **42** with the nitrile in the equatorial orientation. Chelate **42** has the opposite relative configuration of the chiral carbanion compared to **39** which channels the displacement to the *cis*-decalin **43**.



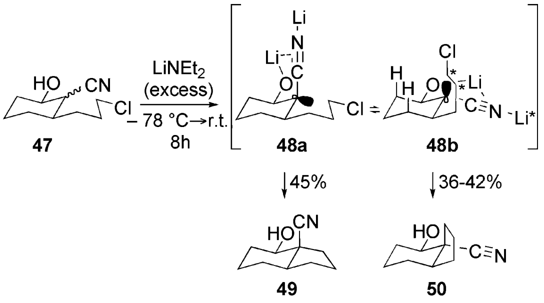
Scheme 9. Stereodivergent nitrile anion cyclizations.

The lithium-nitrile interaction is critical for controlling hydroxynitrile cyclizations to *cis*- and *trans*-hydrindanes. The combination of lithium-nitrile complexation and greater flexibility in cyclizations to *cis*-fused carbocycles allows a particularly facile cyclization of **44** (Scheme 10). Deprotonating **44** with excess $LiNEt_2$ may lead to an equilibrium mixture of metalated nitriles **45a** and **45b** because the respective steric demands are similar. Cyclization from **45a** and **45b** leads to the same *cis*-fused hydrindane **46** because chelation effectively positions the nucleophilic orbital and the electrophilic tether on the same side of the cyclohexane ring in each case.



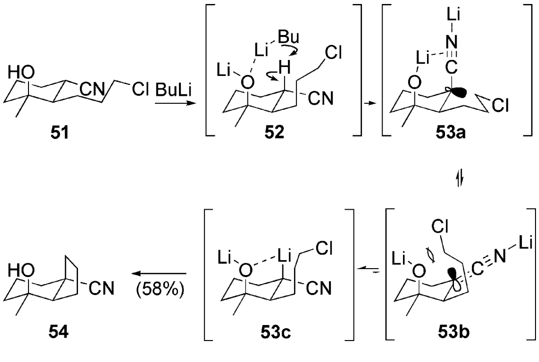
Scheme 10. *cis*-Selective alkoxide-nitrile anion cyclization.

Cyclizing the diastereomeric β-hydroxynitrile **47** to a *trans*-hydrindane is significantly more subtle. Deprotonating **47** (Scheme 11) with excess $LiNEt_2$ generates two chelates **48a** and **48b** having three significant differences; steric, torsional differences in the tether, and torsional differences in the chelate. Although steric compression is minimized in **48a** by positioning the small nitrile group in an axial orientation, the cyclization confers considerable twisting in the electrophilic tether. Twisting of the tether is relieved in the alternative chelate **48b** but with additional steric strain from the axial methylenes in the developing ring (*) *and* torsional strain in the chelate. Viewed as a five-membered chelate, the lithium-nitrile chelate in **48b** resides within a *trans*-hydrindane whereas **48a** is contained within a *cis*-hydrindane. The outcome of these competing effects is formation of approximately equal amounts of *trans*- and *cis*-hydrindanes **49** and **50**, respectively.



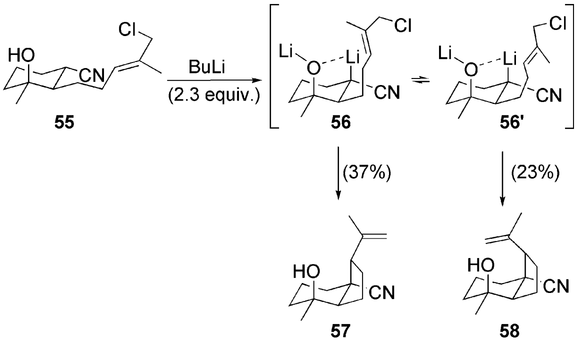
Scheme 11. Chelate-controlled hydrindane cyclizations.

The dramatic influence of the lithium-nitrile π interaction is starkly illustrated by comparing the cyclization of **47** (Scheme 11) with the analogous *des*-hydroxynitrile cyclization (Scheme 8). In the absence of chelation **33** cyclizes exclusively to the *cis*-hydrindane **35** (Scheme 8). Moving the lithium alkoxide one carbon further from the nitrile is thought to reduce the interaction because the dilithiated nitrile **53**[52] cyclizes only to the *cis*-hydrindane **54** (Scheme 12). Deprotonating the γ-hydroxynitrile **51** with BuLi is thought to proceed via an oxygen assisted deprotonation[53] of the alkoxide **52** because alkyllithiums are otherwise prone to attack nitriles.[54] The resulting dilithiated nitrile **53a** cyclizes to the *cis*-hydrindane **54** which suggests that cyclization via the chelated nitrile anion **53a** is unfavorable relative to the *N*- or *C*-lithiated nitriles **53b** or **53c**. Presumably the greater distance between the lithium alkoxide and the nitrile in **53a** reduces the lithium-nitrile interaction which insufficiently compensates for the torsional strain in the tether. Although tentative, cyclization might occur through the *C*-lithiated nitrile **53c** which is structurally analogous to internally chelated organolithiums.[53]



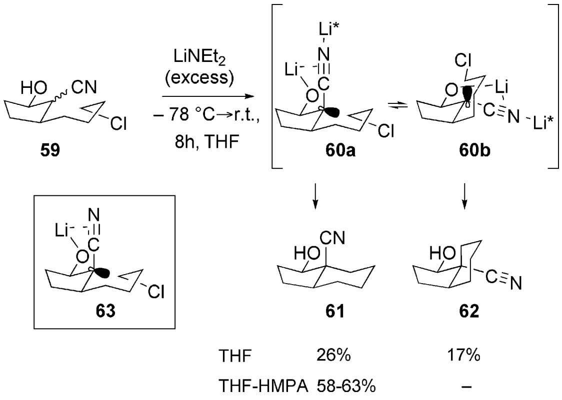
Scheme 12. Cyclization of a γ-chelated nitrile anion.

The same preference for a *cis*-hydrindane persists in the analogous S_N2' displacement of the γ-hydroxynitrile **55** bearing an allylic electrophile (Scheme 13).[52] Addition of excess BuLi to **55** generates two *cis*-hydrindanes **57** and **58** that correlate with cyclization through internally coordinated *C*-lithiated nitriles **56** and **56′**, respectively. Forming the two *cis*-hydrindanes **57** and **58** in roughly equal amounts likely reflects similar energetics for the nucleophilic attack on the diastereotopic faces of the allylic chloride.



Scheme 13. S_N2' cyclization of a γ-chelated nitrile anion.

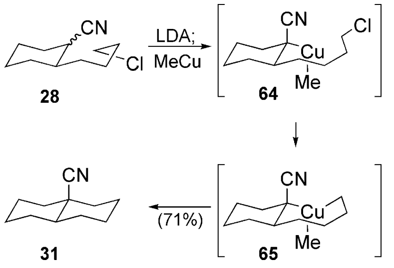
Preferential cyclization of a chelated nitrile anion to a *trans*-hydrindane requires positioning the chelate adjacent to the nitrile and cyclizing a pre-existing five-membered ring onto a 4-carbon tether (Scheme 14). Deprotonating **59** with excess LiNEt$_2$ leads to two pyramidal metalated nitriles in which optimal chelation is achieved with the *cis*-fused chelate **60a** rather than with a less stable *trans*-fused chelate in **60b**. In THF cyclization affords primarily the *trans*-hydrindane **61** and less of the *cis*-hydrindane **62**. Repeating the cyclization with excess HMPA, to sequester the less-tightly associated Li*, affords only the *trans*-hydrindane **61**, consistent with greater complexation between the remaining lithium and the more electron rich nitrile π-system (see inset **63**, Scheme 14).



Scheme 14. Chelation-controlled cyclizations to *cis*- and *trans*-hydrindanes.

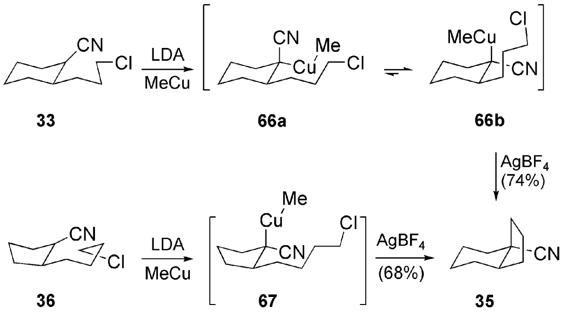
2.4 *C*-Cuprated Nitrile Cyclizations

Alkylations with *C*-metalated nitriles are relatively poorly explored. Comparable alkylations of *C*-metalated nitriles exhibit distinctly different reactivity and stereoselectivity preferences compared to their *N*-lithiated and anion counterparts.[18a,18b] In contrast to lithium, copper and magnesium prefer to coordinate to the carbon atom of metalated nitriles. Forming the *C*-cuprated nitrile **64** from **28** is readily achieved by sequential deprotonation and addition of MeCu (Scheme 15), employing low temperatures to prevent premature cyclization of the *N*-lithiated nitrile intermediate (cf. Scheme 6). Exclusive cyclization to the *trans*-decalin **31** implies formation of an equatorially orientated organocopper **64** which inserts into the proximal C–Cl bond to form the copper(III) intermediate **65**.[55] Subsequent reductive elimination with retention of the C–Cu configuration affords the *trans*-decalin **31**. For comparison, cyclizing the nitrile anion derived from **28** affords the *trans*-decalin **31** and the corresponding *cis*-decalin in a 6.3:1 ratio (Scheme 7).[43]



Scheme 15. Cyclization of a *C*-cuprated nitrile to a *trans*-decalin.

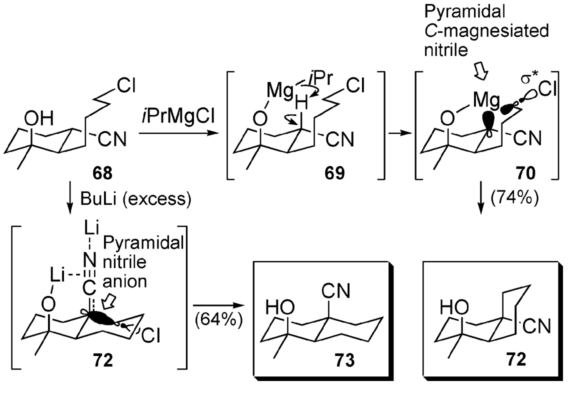
C-cuprated nitriles are significantly less reactive than their lithiated and magnesiated counterparts. Refluxing the *C*-cuprated nitrile derived from **33** (Scheme 16) fails to generate any of the hydrindane **35**! The cyclization of **66** requires the addition of silver tetrafluoroborate to coax displacement of the pendant electrophile to the *cis*-hydrindane **35**.[45] Exclusive formation of the *cis*-hydrindane **35** implies cyclization through conformer **66b** in which the large methyl copper is axial despite the steric preference for positioning the smaller nitrile in the more sterically demanding axial orientation.[56] Presumably a greater torsional strain in the tether occurs for cyclization from conformer **66a** which is relieved in conformer **66b** leading to the *cis*-hydrindane. Relaxing the steric constraints by incorporating an additional carbon in the tether and using a methylene contracted cyclopentane still results in cyclization to a *cis*-hydrindane (Scheme 16, **36** → **67** → **35**).



Scheme 16. *C*-cuprated nitrile cyclizations to a *cis*-hydrindane.

2.5 Stereodivergent Metal-Dependent Nitrile Cyclizations

Tuning the stereochemistry of metalated nitriles by solvent diverts the cyclization to *cis*- or *trans*-decalins (Scheme 6 and Scheme 7). Greater selectivity in stereodivergent cyclizations is achieved in the cation-controlled cyclizations of γ-hydroxynitriles.[52] Deprotonating γ-hydroxy nitriles such as **68** (Scheme 17) permits two coordination modes by virtue of a metal's capacity to form one or two formal bonds. Addition of excess *i*PrMgCl to the γ-hydroxynitrile **68** triggers sequential deprotonation of the hydroxyl proton and a halogen–alkyl exchange to afford the alkylmagnesium alkoxide **69**.[57] Forming the axial alkylmagnesium alkoxide **69** conveniently anchors the basic isopropyl group for a directed, internal deprotonation leading to the *C*-magnesiated nitrile **70**. Although the side-on orbital overlap between the C-Mg nucleophilic orbital and the σ^* C-Cl orbital is far from optimal (**70**), the alternative colinear approach of an sp^3 hybridized electrophile to the small σ lobe of the C–Mg bond is sterically prohibited. The cyclization through **70** to the *cis*-decalin **72** is therefore stereoelectronically controlled.

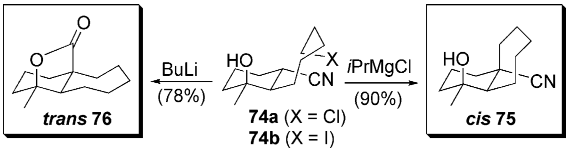


Scheme 17. Stereodivergent cation-controlled cyclizations.

Deprotonating the same γ-hydroxyalkenenitrile **68** with BuLi generates the diastereomeric *trans*-decalin **73** consistent with cyclization through the pyramidal nitrile anion **72** (Scheme 17). Internal coordination of the alkoxide lithium with the nitrile π-system generates an equatorially oriented nucleophile within **72** that is ideally positioned for an S_N2 displacement through a chair-chair conformation. The monovalent character of the metal therefore directs the cyclization of **72** to the *trans*-decalin **73** whereas the divalent magnesium counterion in **70** directs cyclization to the *cis*-decalin **72**.

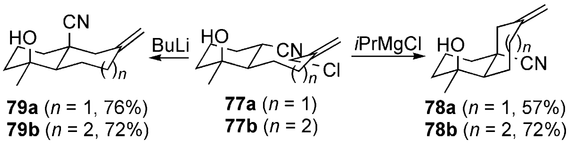
The stereodivergent metal-based cyclization strategy is equally effective for generating *cis*- and *trans*-bicyclo[5.4.0]-undecanes although cyclizing the seven-membered ring is surprisingly more difficult. *i*PrMgCl-induced cyclization of the nitrile **74a** (Scheme 18) requires converting the chloride to the corresponding iodide **74b** and heating of the reaction to reflux. Essentially no cyclization of the chloride or iodide occurs at room temperature, conditions under which the corresponding decalin is formed (Scheme 17). Cyclization with BuLi is most effective with the chloride **74a** but the cyclization requires two days for full conversion. The extended reaction time allows for the first-formed alkoxide to internally attack the proximal axial nitrile leading to the *trans*-lactone **76** after an aqueous workup.

Analogous cyclizations of the γ-hydroxynitriles **77a** and **77b** bearing allylic electrophiles provide modestly functionalized *cis*- and *trans*-decalins and bicyclo[5.4.0]undecanes



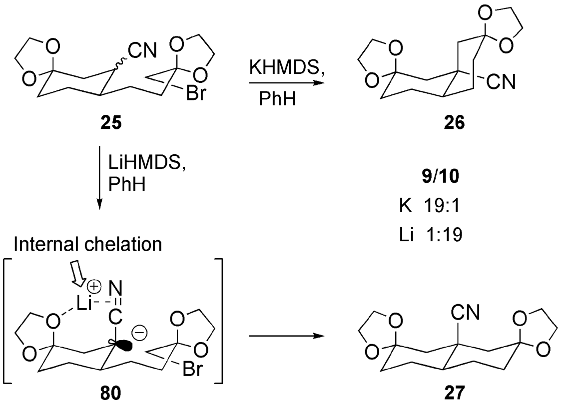
Scheme 18. Stereodivergent bicyclo[5.4.0]undecane cyclizations.

(Scheme 19). *i*-MgCl-induced cyclizations of **77a** and **77b** lead exclusively to the *cis*-fused decalin **78a** and *cis*-undecane **78b**. Standard addition of BuLi to **77a** or **77b** triggers two facile *trans*-selective cyclizations to **79a** and **79b** without lactone formation.



Scheme 19. Stereodivergent cyclizations of γ-hydroxynitriles bearing allylic electrophiles.

Understanding the intricacies of metalated nitrile cyclizations allows a reinterpretation of the first stereodivergent cation-controlled cyclization (Scheme 20).[41] Although the original argument was based on early and late contact distances, a more compelling rationale is a cation controlled cyclization. The potassium counterion likely favors cyclization to the *cis*-decalin **26** through a planar *N*-metalated nitrile (cf. **29** Scheme 6) whereas the lithium ion complexes with the ketal and the nitrile π electrons to channel cyclization through the pyramidal anion **80**. In support of this complexation, the selectivity is reduced in THF which likely better competes as a ligand for the lithium cation.



Scheme 20. Stereodivergent metalated nitrile cyclizations.

Conclusions

Metalated nitriles are outstanding nucleophiles for cyclization reactions. Judicious choice of solvent, temperature, and cation allows excellent control over the geometry of the nucleophilic nitrile-stabilized carbon (Figure 5). The most common metalated nitriles **82**, generated by deprotonating with a lithium amide base, cyclize with a modest preference for *cis*-fused carbocycles. Better stereoselectivity is possible with the internally coordinated *C*-magnesiated counterpart **81** which cyclizes exclusively to *cis*-fused bicyclic nitriles.

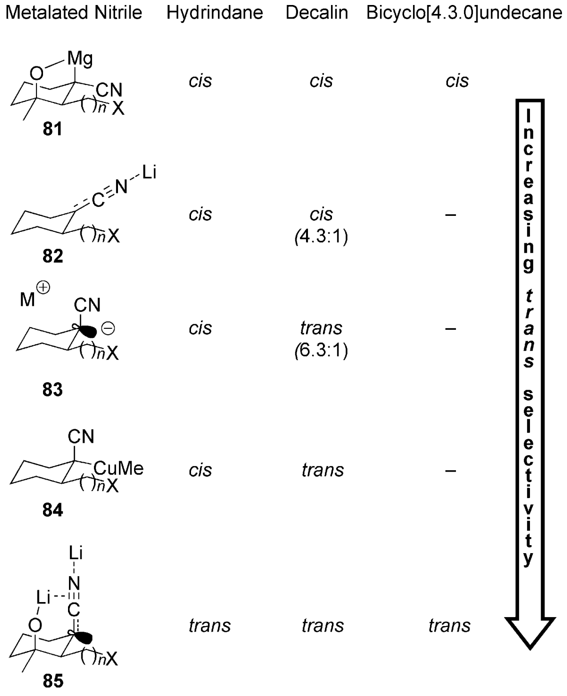


Figure 5. Metalated nitrile cyclization selectivities.

Solvent-separated nitrile anions **83** preferentially cyclize to *trans*-fused bicyclic nitriles when the tether containing the electrophile has four carbons. Fewer carbons in the electrophilic tether engenders too much strain for cyclization to a *trans*-hydrindane and favors cyclization to the *cis*-hydrindane. The difficulty stems from twisting of the tether containing the electrophilic chloromethylene carbon required for the correct S_Ni alignment. Improved selectivity for the *trans*-decalin is achieved in cyclizations of the *C*-metalated nitrile **84**. Greatest selectivity for *trans*-fused bicyclic nitriles is accomplished with dilithiated nitrile anions **85** in which the pyramidal geometry of the nucleophile is defined by precise internal coordination.

Metalated nitrile cyclizations assemble carbocycles with excellent control at the quaternary ring junction carbon. Tuning of the metalated nitrile geometry allows facile, stereodivergent syntheses of *cis*- and *trans*-hydrindanes, decalins, and bicyclo[4.3.0]undecanes. Collectively, these cyclizations demonstrate the key influence of solvent, metal, and chelation in controlling the geometry at the nucleophilic nitrile-bearing carbon. The facile, stereodivergent metalated nitrile cyclizations are ideal for assembling complex molecular architectures required in natural product synthesis.

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