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Complimentary Reactivity from C- And N-Metalated Nitriles

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COMPLIMENTARY REACTIVITY FROM *C*- AND *N*- METALATED NITRILES

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By

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ABSTRACT

COMPLIMENTARY REACTIVITY FROM *C*- AND *N*- METALATED NITRILES

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Thesis supervised by Dr. Fraser Fleming

Two different strategies examine intramolecular cyclizations of chiral, metalated nitriles. Cyclizations onto allylic electrophiles through competitive S_N2 or S_N2' displacements have different trajectories reflecting the different conformations within the forming ring. Deuterium labeling with allylic electrophiles reveals an inherent preference for S_N2 displacements reflecting the optimal orbital overlap for the two different geometries.

A second metalated nitrile cyclization is designed to compare stereoselectivity differences for attack on electrophilic sp and sp^3 in forming hydrindanes. Despite 5-exo-tet and 5-exo-dig having distinctly different trajectories for nucleophilic attack, the cyclizations of lithiated and magnesiated nitriles each cyclize to *cis*-fused hydrindanes.

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1. Introduction

Metalated nitriles are nucleophilic chameleons whose precise structural integrity is determined by solvent, cation and temperature.[1] X-ray crystallographic analyses of metalated nitriles[2] reveal the precise structural differences of the two main structural classes: *N*-metalated nitriles in which the metal coordinates to the nitrile nitrogen,[3] and *C*-metalated nitriles[4] in which the metal is bound to the formally anionic carbon (Figure 1, 2 and 3, respectively). NMR analysis shows essentially the same structural characteristics are maintained in solution for *N*- and *C*-metalated nitriles.[5] Formally regarded as nitrile anions, these structures represent one extreme of a continuum with *N*- and *C*-metalated nitriles in the middle and *N*-metalated ketenimines at the other.

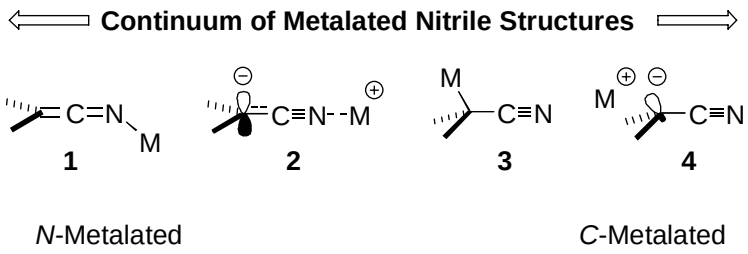
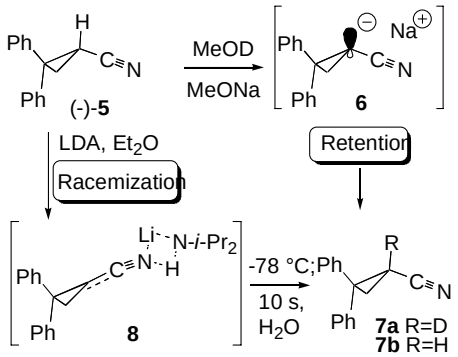


Figure 1. Continuum of Metalated Nitrile Structures

Historically the first indication of different reactivities for different metalated nitrile structures were found during the quest for a chiral metalated nitrile. Pioneering deuterations of the chiral cyclopropanecarbonitrile **5** in MeONa-MeOD proceed with greater than 99.9% stereochemical retention in generating **7a**.[6] In this polar solvent a transient ion pair **6** is generated that rapidly abstracts deuterium from the adjacent

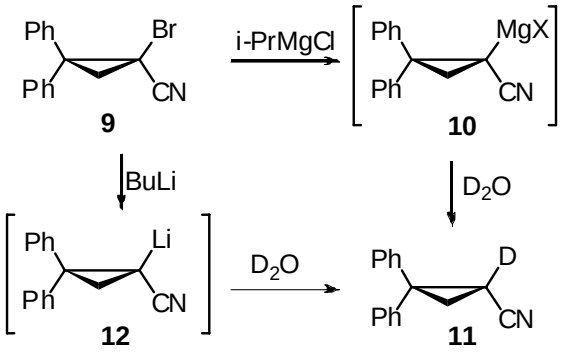
solvation sphere. In contrast, sequential deprotonation-reprotonation with LDA causes complete racemization (**5** → **7b**) via the putative *N*-lithiated nitrile **8** (Scheme 1). Subsequent reinvestigation with LDA, LiHMDS and KHMDS demonstrated racemization at temperatures as low as -135 °C.[7]

Scheme 1. Stereochemical Integrity of *C*- and *N*-Metalated Nitriles



Through a series of intricate mechanistic experiments distinct differences were demonstrated for the *C*- and *N*-metalated cyclopropanecarbonitriles **10** and **12** (Scheme 2).[7] Bromine-magnesium exchange of bromonitrile **9** proceeds with 95% retention of stereochemistry to afford *C*-magnesiated nitrile **10**. The exchange is therefore not stereospecific with the partial stereochemical erosion ascribed to competitive electron transfer processes operating during the exchange. The magnesiated nitrile **10**, a synthetically accessable chiral *C*-metalated nitrile, slowly racemizes with a $t_{1/2}$ = 11.4 h at -100 °C.

Scheme 2. Divergent Stereoselectivities of *N*- and *C*-Metalated Nitriles

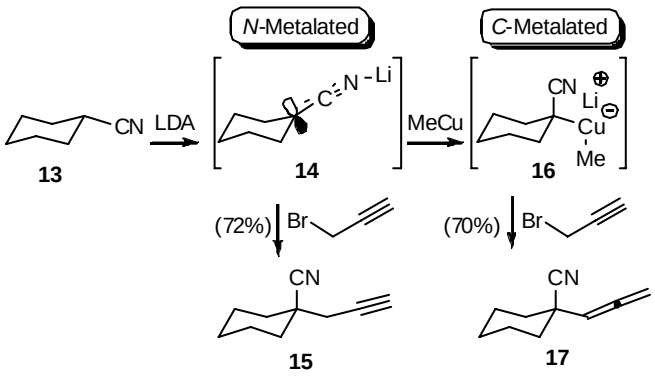


The fate of the corresponding lithiated nitrile **12** is more obscure. Lithium-bromine exchange of **9** with BuLi results in rapid racemization. Whether this is because of rapid carbon to nitrogen conducted tour equilibration, equilibration through a triple ion generated from **9** and **11**, or a coordination of both is currently an open question. The experimental significance of these experiments lie in demonstrating the viability of accessing chiral *C*-metalated nitriles. The rapid loss of configuration with lithiated nitriles is particularly significant as lithium is the most commonly used counter-ion and is consistent with relatively modest levels of asymmetric induction through the addition of chiral ligands. [8]

C- and *N*-metalated nitriles were first demonstrated to react differently in alkylations with metalated cyclohexanecarbonitrile **13** of propargyl bromide (Scheme 3).[9] Deprotonating cylohexanecarbonitrile **13** with LDA generates an *N*-lithiated nitrile **14** which alkylates propargyl bromide to afford the alkyne **15**. Adding methylcopper prior to the alkylation effectively transforms the *N*-lithiated nitrile **14** into the *C*-cuprated nitrile **16** which

intercepts propargyl bromide to afford the allene **17**. The S_N2' displacement is consistent with the reactivity of a *C*-cuprated nitrile and of cuprates in general.[10]

Scheme 3. Regiodivergent Alkylations of *N*- and *C*-Metalated Nitriles



A more subtle reactivity difference is seen between the *N*- and *C*-palladated nitriles **18** and **19** (Figure 2).[11] Although the phosphine ligand and the aryl group are different in these two complexes the greatest structural difference lies in the coordination of the nitrile with the palladium center. Reductive elimination from the *N*-palladated nitrile **18** is ten times faster than for the analogous *C*-palladated nitrile **19**.

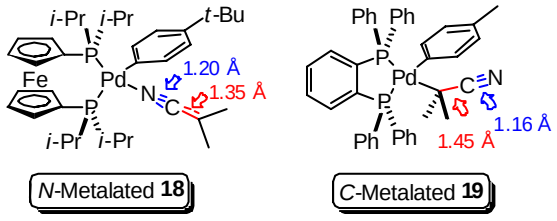
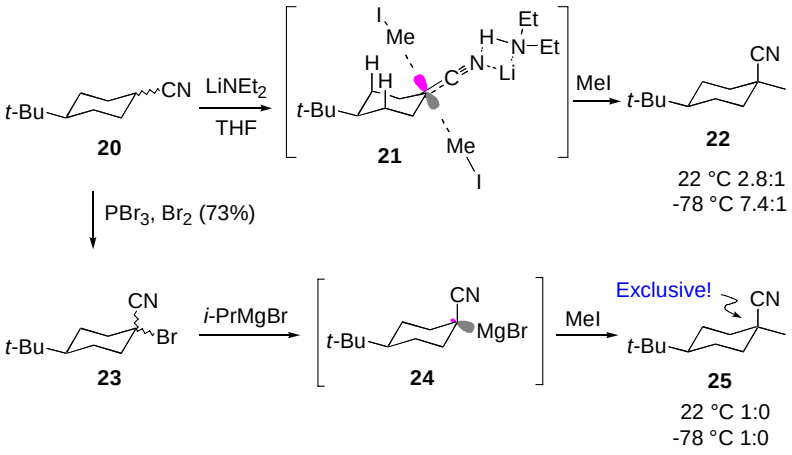


Figure 2. Pseudodiastereomeric *N*- and *C*-Palladated Nitriles

Not only are regioselectivity differences observed with different metalated nitriles but stereoselectivity of *N*- and *C*-metalated nitrile alkylations can be very different (Scheme 4). For example, lithium diethylamide deprotonation of **20** generates a planar *N*-lithiated nitrile **21** that alkylates methyl iodide with a modest preference for equatorial alkylation. In contrast, methylating the corresponding magnesiated nitrile **24**, obtained by bromine-magnesium exchange, affords the equatorial nitrile **25** exclusively even at room temperature! In contrast, lithium-halogen exchange affords an intermediate that reacts at -78 °C with MeI to afford a 3:1 ratio of diastereomers. The ratio is similar but not identical to that obtained by deprotonation (7.4:1), implying that lithiated nitriles generated in the absence of amine bases exhibit different reactivity.

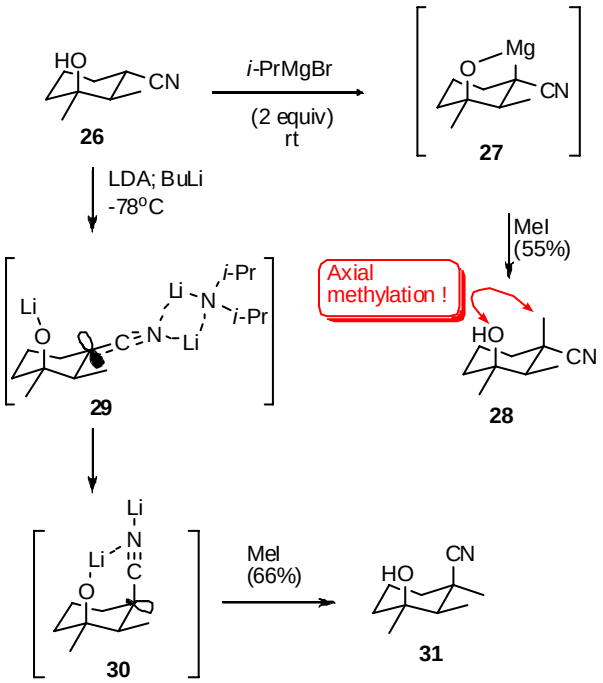
Scheme 4. Stereoselectivity of *C*- and *N*-Metalated Nitriles from Different Geometry



Stereodivergent alkylations occur in the alkylations of the hydroxy nitrile **26** depending on whether organolithium or organomagnesium bases are used for the deprotonation. Sequential addition of *i*-PrMgBr and methyl iodide to hydroxy nitrile **26** affords the axially methylated nitrile **28**, in direct contrast to the usual equatorial alkylation of *N*-

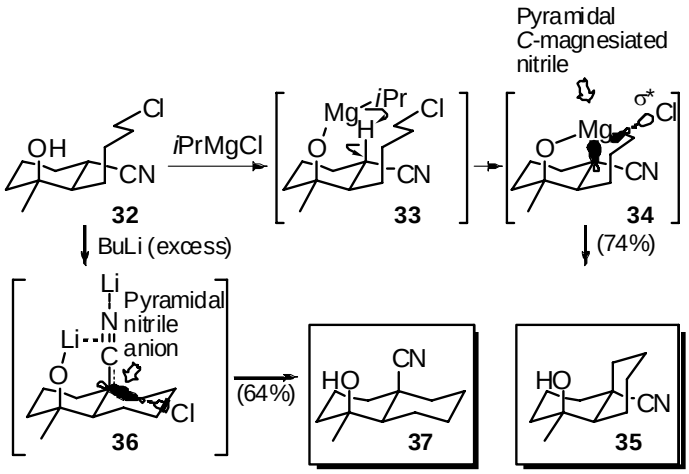
lithiated cyclohexanecarbonitriles. The remarkable installation of a methyl group having a 1,3-diaxial interaction is consistent with the retentive alkylation via the *C*-magnesiated nitrile **27**. Methylating the corresponding *N*-lithiated nitrile **29**, generated by sequential addition of LDA and BuLi, to prevent internal proton return,[12] generates the axial nitrile **31**. Although the selectivity was first rationalized as the result of a strictly directed attach on the *N*-lithiated nitrile **29**, subsequent alkylations suggest alkylation via the internally complexed *C*-lithiated nitrile **30**.[13] The electron rich π-system[14] of the *N*-lithiated nitrile provides an excellent ligand for the adjacent lithium which effectively coaxes rehybridization of the metalated nitrile to an sp^3 carbanion. The equatorial nucleophile alkylates to give the axial nitrile **31**.

Scheme 5. Stereodivergent Alkylations of Magnesiated and Lithiated Nitriles



Selective access to structurally distinct *C*-magnesiated and *N*-lithiated nitriles was harnessed in stereodivergent cyclizations to *cis*- and *trans*-decalins and bicyclio [4,3,0] undecanes.[15] Deprotonating **32** with *i*-PrMgCl leads to the *C*-magnesiated nitrile **34** via **33**, which cyclizes to *cis*-decalin **35**. An alkoxy-directed deprotonation with BuLi generates the internally complexed nitrile anion **36** from which cyclization is directed to the *trans*-decalin **37**. This strategy of using two different metals to access different metalated nitrile geometries provides a powerful method of accessing *cis*- and *trans*-fused bicyclic nitriles.[16]

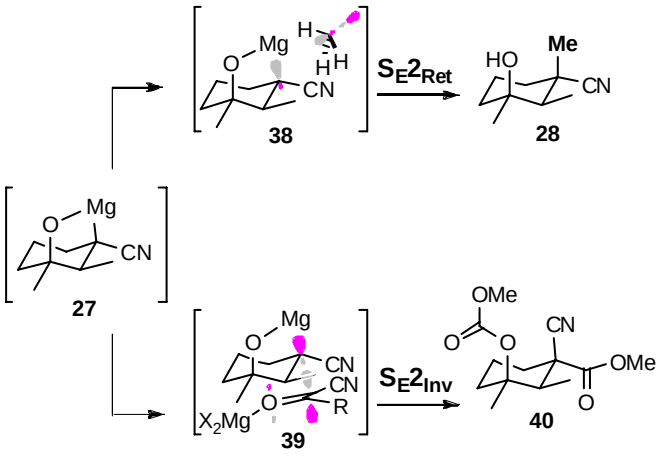
Scheme 6. Cation-Controlled Cyclizations



The most remarkable feature of *C*-magnesiated nitrile alkylations is their electrophile-dependent stereoselectivity.[17] Alkyl halide and sulfonate electrophiles alkylate **27** with retention of stereochemistry through a three-center two-electron, electrophilic retentive alkylation mechanism (S_E2_{Ret}).[18] Reactive carbonyl electrophiles alkylate with an inversion of stereochemistry reflecting the better collinear geometry of the two-electron

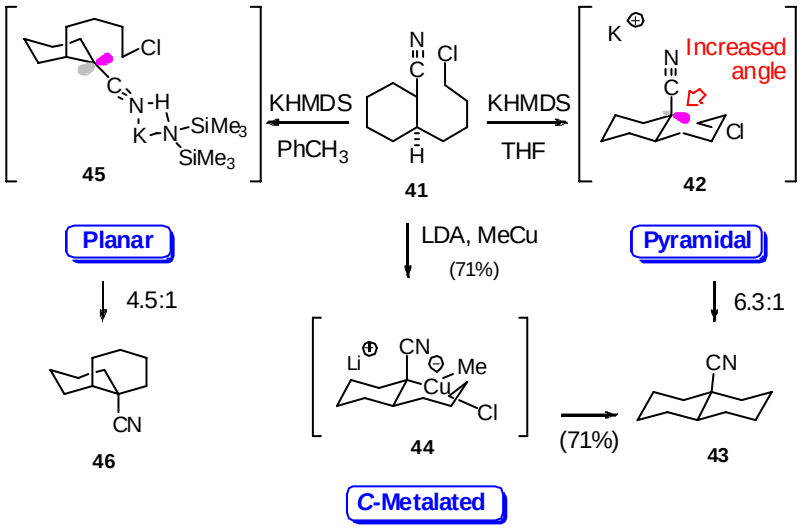
two-center transition structure **39** (Scheme 7). The stereoelectonically controlled alkylation of **27** provides another strategy for varying at the stereochemistry of the nitrile-bearing carbon in alkylations of cyclic nitriles.

Scheme 7. Electrophile Dependent Alkylations of *C*-Magnesiated Nitriles



Selective access to different metalated nitrile geometries was harnessed to direct a series of stereodivergent cyclizations (Scheme 8).[19] *cis-trans* ratios were used to correlate the preference of the metalated nitrile intermediate with the geometry of the nucleophilic center. Deprotonating **41** with KHMDS in refluxing THF, conditions favoring a solvent separated carbanion **42**, preferentially affords the *trans*-decalin **43** (6.3:1). Performing the same cyclization in toluene favors the planar, *N*-metalated nitrile **45**, which generates primarily the *cis*-decalin **46** (4.5:1). Transmetalating the lithiated nitrile to the *C*-cuprated nitrile **44** redirects the cyclization exclusively to the *trans*-fused diastereomer **43** suggesting an equatorially oriented Cu(III) intermediate **44** as the reactive species.[20]

Scheme 8. Stereodivergent Metalated Nitrile Cyclizations to *cis* and *trans*-Decalins



The advent of new reactivity from metalated nitriles rests largely on selectively accessing three structurally distinct nucleophiles; *C*-metalated nitriles, *N*-metalated nitriles and nitrile-stabilized carbanions. Alkylations with these three different species can result in different stereo- and regioselectivities. *C*-metalated nitriles are particularly versatile because, by virtue of having four bonds, these chiral nucleophiles can exhibit electrophile-dependent reactivity. Tuning the nature of the metalated nitrile, through judicious choice of metal, electrophile, temperature, and solvent, provides a powerful strategy for stereodivergent alkylations and cyclizations.

2. Results and Discussion

2.1 S_N2 vs S_N2' Displacements of *N*- and *C*-Metalated Nitriles

Metalated nitriles are exceptional nucleophiles by virtue of a miniscule steric demand[21] coupled with a high charge localization .[22] Augmenting this high nucleophilicity is accessibility of three different metalated nitrile species capable of different stereo- and regioselectivity; *N*-metalated nitriles, typically formed by lithium amide mediated deprotonation,[23] *C*-metalated nitriles, generally formed by halogen-metal exchange,[9] and nitrile-stabilized carbanions,[24] usually favored in highly polar solvents or by internal complexation (Figure 3).[25]

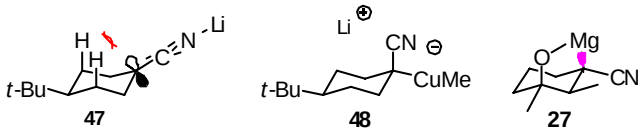
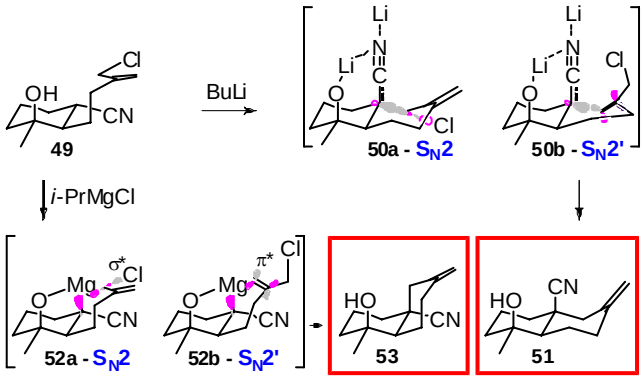


Figure 3. Three Typical Forms of Metalated Nitriles

The inherent preferences of *N*- and *C*-metalated nitriles for S_N2 and S_N2' displacements is currently an open question. Prior cyclizations of the hydroxy nitrile **49**[26] demonstrate the facility for cyclization via the *N*-lithiated nitrile anion **50** and the *C*-magnesiated nitrile **52** but mask whether the displacements proceed via S_N2, S_N2', or both displacement manifolds. Although 6-exo-tet and 6-endo-trig are favorable processes,[27] a better orbital alignment is possible in the S_N2 displacements because of the greater flexibility from incorporating rotatable single bonds within the forming cylcohexane ring. The analogous S_N2' displacements **50b** and **52b** incorporate two rigid sp^2 centers within the developing ring, restricting the tether from reaching the opposite side of the cyclohexane ring.

Deuterium labelling appeared ideal for probing the preference of *C*- and *N*-metalated nitriles in S_N2 and S_N2' displacements.

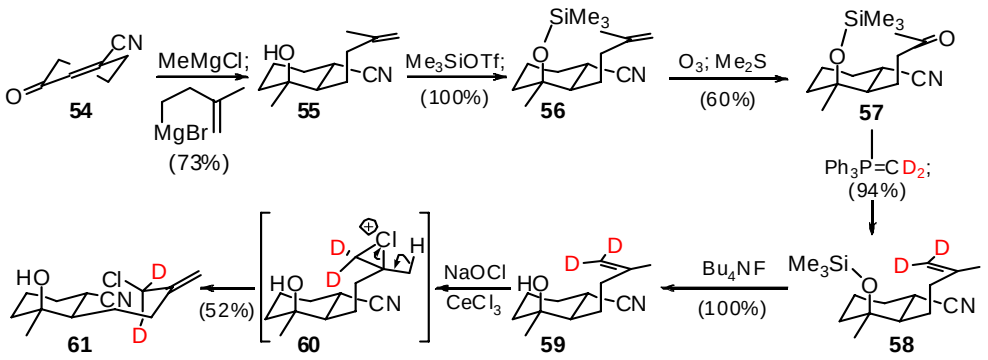
Scheme 9. Stereodivergent Cyclizations of Allylic Nitrile



Stereoelectronic principles imply an inherent bias for S_N2 displacement of lithiated nitrile **50** and magnesiated nitrile **52**. Although 6-exo-tet and 6-endo-trig are favorable processes the better orbital alignment is possible in the S_N2 displacements because of the greater flexibility from incorporating rotatable single bonds within the forming cylcohexane ring. The analogous S_N2' displacements **50b** and **52b** incorporate two rigid sp^2 centers within the developing ring, restricting the tether from reaching the opposite side of the cyclohexane ring. The subtle stereoelectronic differences controlling allylic displacements appear not to have been determined, possibilty because of the difficulty in generating chiral carbanions with pendant allylic electrophiles. Selective formation of geometrically distinct "chiral" metalated nitriles appeared ideal for testing the viability of stereoelectronically controlled S_N2 displacements as a strategy for assembling subsituted decalins.

Rapid access to the deuterated carbocyclic nitrile rests on an efficient 1,2-1,4-addition to oxonitrile **54** [28] (Scheme 10). Sequential addition of MeMgCl and (3-methyl)3-butenylmagnesium bromide to oxonitrile **54** efficiently affords alkenenitrile **55**. Excising the methylene carbon required prior protection of the free hydroxyl group (**55**→**56**), which unmasked the ketone for labeling. D_2-methylenetriphenylphosphorane readily installed the requisite deuteration to afford, after silyl ether removal, nitrile **59**. Chlorination with olefin transposition occurred smoothly on exposure to sodium hypochlorite, [29] presumably with selective abstraction of the allylic proton ensuring stereochemical fidelity en route to **61**.

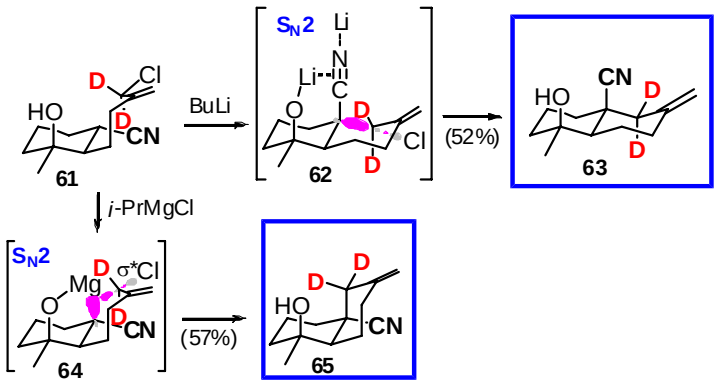
Scheme 10. Synthesis of D_2-Labelled Cyclization Precursor



Cyclizing the deuterated nitrile **61** revealed an inherent preference for S_N2 displacements of the *C*-magnesiated nitrile and the *N*-lithiated nitrile anion (Scheme 11). Deprotonating nitrile **61** with excess BuLi triggers cyclization to *trans*-decalin **63** without observable formation of positional isomers revealing an inherent preference for S_N2 displacment.[30] Cyclization of the corresponding magnesiated nitrile also proceeds through an S_N2 displacement, affording the *cis*-decalin **65**. In each case the chair-like transition structure

for S_N2 displacement is favored whereas the half-chair conformation required for the S_N2' manifold is not.

Scheme 11. Cyclization of D_2-labelled Allylic Nitrile



C-Metalated nitriles and *N*-lithiated nitrile anions exhibit a dramatic preference for S_N2 over S_N2' in intramolecular displacements. Deuterium labeling demonstrates that the influence is derived from stereoelectronic principles of orbital overlap rather than through steric effects. The powerful nucleophilicity of metalated nitriles, combined with the exquisite preference for S_N2 displacement suggest that the method is ideally suited for sterically demanding applications.

2.2 Comparative Metalated Nitrile Cyclizations at sp and sp^3 Centers

Baldwin's rules are immensely powerful for predicting the viability of intramolecular displacements.[31] Underpinning the heuristic rules is the relative ease of aligning a nucleophilic orbital with a geometrically accessible anti-bonding orbital. Essentially two broad reaction trajectories are possible: exocyclic and endocyclic processes in which the electrophilic unit lies inside or outside the developing ring, respectively (Figure 4).

Figure 4. Two Basic Cyclization Trajectories.

Endo- and exocyclic processes are sub-categorized depending on the hybridization of the acceptor carbon: sp^3 (**tet**rahedral), sp^2 (**trig**onal), or sp (**dig**onal). For the carbocyclic series of 5-exo cyclizations, all formally "allowed" processes, the nucleophilic attack on sp^3, sp^2, and sp centers involves quite different attack angles and orbital overlap. Simplistic geometric estimations of the attack angles for 5-exo carbocyclizations suggests attack angles of 132°[32] for 5-exo-tet, 106°[33] for 5-exo-trig, and 72°[34] for 5-exo-dig cyclizations. Although these different attack angles are readily accommodated by each of the three electrophiles' anti-bonding orbital geometries, the different efficiencies of orbital overlap can potentially change the cyclizations.

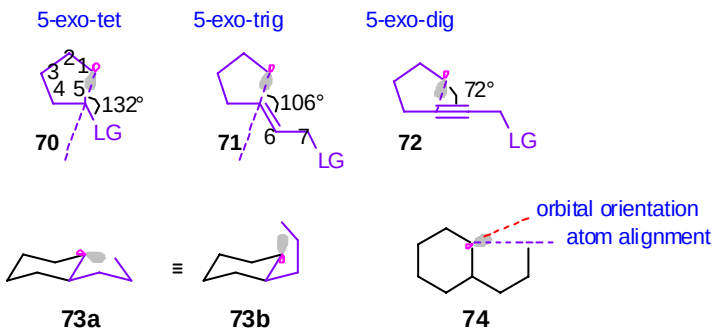


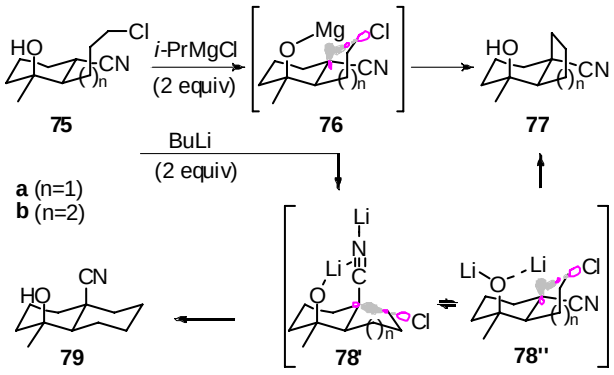
Figure 5. Different Attack Angles for sp, sp^2 and sp^3 centers

The differences in the attack angles are accentuated for cyclizations with nucleophiles embedded within rigid carbocycles. Fusing a cyclohexane ring to the nucleophile as in **73** enlarges the attack angle because of the diequatorial orientation of the nucleophile on the cyclohexane ring. The result is an imperfect alignment between the orbitals which requires twisting of the three-carbon tether to bring the centers sufficiently close for reaction. Specifically, the attack onto trigonal and digonal centers involves acute angles that seem better suited to accommodating the torsional strain when compared to an S_N2 of a tetrahedral center.

Metalated nitriles appeared ideal for probing the use of stereoelectronic effects to direct cyclizations to *trans*-hydrindanes because the geometry of the nucleophile is tunable and because a series of prior cyclizations already provides a reference point for the displacement with sp^3 hybridized electrophiles (Scheme 12). Specifically, deprotonating **75a** with *i*-PrMgCl is believed to generate the *C*-magnesiated nitrile **76a** which directs the alkylation through a three-center side on orbital overlap to the *cis*-hydrindane **77a**.

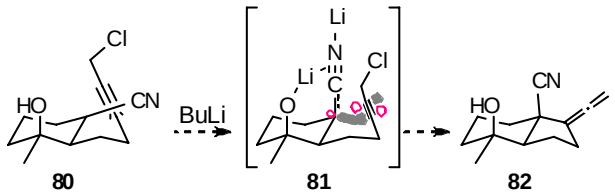
Changing the base to BuLi generates an *N*-lithiated nitrile **78'** which cyclizes to the *cis*-hydrindane **77a** presumably through **78a''** in which the torsional strain is minimized. Cyclizing the homolog **75b** with one additional carbon in the tether redirects the cyclization to the *trans*-decalin **79** because the torsional strain is reduced. This and related hydroxynitrile alkylations, are consistent with cyclization proceeding through **78b'** in which the small nitrile is held in the axial orientation through a lithium-π interaction.

Scheme 12. Stereoselective Cyclizations to *cis*-Hydrindane



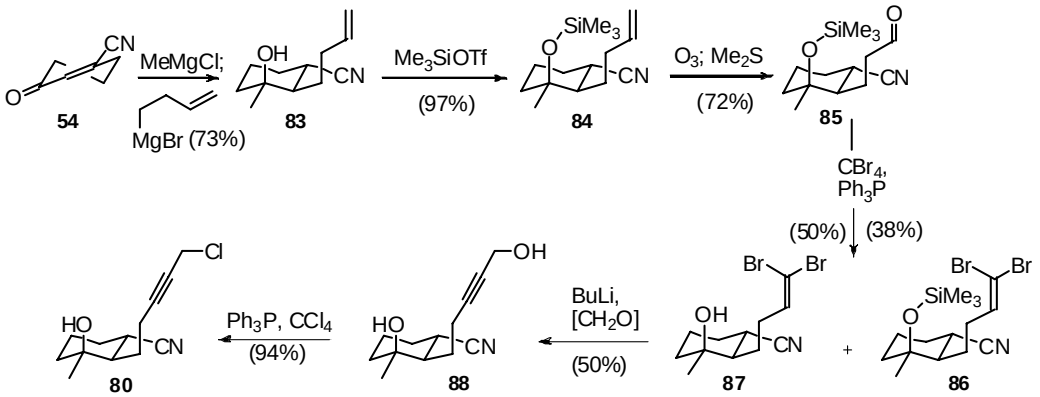
The delicately balanced cyclizations of the chloroalkylnitriles **75a** and **75b** inspired an analogous cyclization with the propargyl chloride **80** (Scheme 13). Naively the hybridization change of the electrophilic carbon was anticipated to allow an easier "oblique attack" (**81**) by the nitrile anion to favor cyclization to the *trans*-hydrindane **82**. Described below is the synthesis of the cyclization precursor **80** and the cyclizations of **80** with *i*-PrMgCl and BuLi.

Scheme 13. Stereoelectronically Controlled Cyclization?



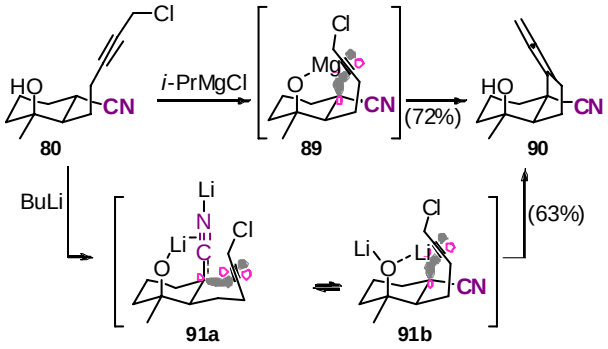
Rapid access to the cyclization precursor **80** was predicated on an efficient 1,2-1,4-double addition to oxonitrile **54**[35] (Scheme 3).[36] Sequential addition of MeMgCl and 3-butenylmagnesium bromide to oxonitrile **54** smoothly provided the substituted nitrile **83**. Silyl protection of the tertiary hydroxyl group prior to ozonolysis[37] provide the aldehyde **85** that was exposed to in situ generated dibromomethylenetriphenyl phosphorane. Under these conditions the dibromoolefin formed readily and the silyl ether was cleaved to provide the corresponding alcohol **87**. Subsequent treatment with BuLi and interception of the intermediate acetylide with gaseous formaldehyde provided the acetylenic alcohol **88** that was converted into the corresponding chloride **80**.

Scheme 14. Synthesis of Cyclization Precursor



Exposing nitrile **80** to excess *i*-PrMgCl triggers a smooth cyclization to the *cis*-hydrindane **90** (Scheme 15).[38] Cyclizing **80** by deprotonating with BuLi, conditions which favor internal chelation of the alkoxylithium with the electron rich nitrile anion (**91a**) affords only the *cis*-hydrindane **90**. Presumably the torsional strain in **91a** prevents orbital overlap despite the presence of the sp hybridized electrophile, and instead the anion equilibrates to the *C*-lithiated nitrile **91b**.[39] A reduction in the torsional strain is likely achieved through gentle twisting of the ring substituents which directs cyclization to the *cis*-hydrindane **90**.

Scheme 15. Organometallic-Induced Cyclizations



Intramolecular displacements on a propargylic chloride by *C*-magnesiated nitriles and *N*-lithiated nitrile anions readily affords the corresponding hydrindane. Comparable attack of *C*-magnesiated nitriles and *N*-lithiated nitrile anions onto sp^3 hybridized centers have similar but different reaction trajectories that favor cyclization to *cis*-fused hydrindanes. Attack on an sp hybridized carbon involves an oblique attack angle, rather than a backside attack for and sp^3 center, but the trajectory difference is not sufficient to redirect the cyclization with acetylenic electrophiles to *trans*-hydrindanes.

3. Experimentals

3-Trimethylsilyl-oxy-3-methyl-2-(3-methylbut-3-enyl)cyclohexanecarbonitrile (56): Neat Et_3N (84.4 mg, 0.84 mmol) and TMSOTf (135.6 mg, 0.61 mmol) were added to a 0 ℃ CH_2Cl_2 solution (20 mL) of 3-hydroxy-3-methyl-2-(3-methylbut-3-enyl)cyclohexanecarbonitrile (115.3 mg, 0.557 mmol), After 2 h, saturated aqueous $NaHCO_3$ was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated and the crude product was purified by radial chromatography (5:95, EtOAc/hexanes) to afford 157 mg (100%) of nitrile **56** as an oil: IR 2236.5, 1649.8 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.23-1.33 (m, 2H), 1.29 (s, 3H), 1.44-1.69 (m, 5H), 1.76 (s, 3H), 1.82-1.91 (m, 1H), 2.03-2.11 (m, 2H), 2.28-2.36 (m, 1H), 2.66-2.73 (m, 1H), 4.71 (s, 2H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.34, 20.39, 22.37, 28.21, 28.36, 30.56, 31.37, 37.47, 39.79, 48.89, 74.29, 110.16, 123.16, 145.84; HRMS for $C_{16}H_{29}NOSi$: [M+Na^+] calculated 302.1911, found 302.1929.

2-(2-Acetylethyl)-3-Trimethylsilyloxy-3-methylcyclohexanecarbonitrile (57): Gaseous ozone was passed through a -78 ºC, CH_2Cl_2 solution (2 mL) of **56** (31.2 mg, 0.11 mmol) until the distinctive blue color of excess ozone persisted. Ozonolysis was then terminated, the solution was allowed to warm to room temperature, and then neat Me_2S (3 mL) was added dropwise. After 16 h the mixture was concentrated, the resulting oil was redissolved in EtOAc, and then washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography (10:90,

EtOAc/hexanes) to provide 19.0 mg (60%) of **57** as a white crystal (mp: 35-36 ºC): IR 2235.4, 1710.9 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.24-1.32 (m, 2H), 1.28 (s, 3H), 1.48-1.68 (m, 5H), 1.98-2.12 (m, 2H), 2.13 (s, 3H), 2.55-2.69 (m, 2H), 2.74-2.83 (m, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.33, 20.36, 23.32, 28.35, 29.89, 30.56, 30.86, 39.69, 42.48, 48.30, 74.33, 123.02, 208.28; HRMS for $C_{15}H_{27}NO_2Si$: [M+Na^+] calculated 304.1703, found 304.1697.

3-Trimethylsilyl-oxy-3-methyl-2-(3-methylbut-3-D,D-enyl) cyclohexanecarbonitrile (58): A hexanes solution of BuLi (0.12 mL, 2.9 M) was added to a -78 ºC, THF suspension of Ph_3PCD_3I (158.8 mg, 0.39 mmol). After 30 min, a THF solution (2 mL) of **57** (54.1 mg, 0.193 mmol) was added and after 1 h the reaction was allowed to warm to 0 ºC. After 3 h saturated, aqueous $NaHCO_3$ was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), concentrated and purified by radial chromatography (5:95, EtOAc/hexanes) to afford 51.2 mg (94%) of the deuteriated nitrile **58** as an oil: IR 2236.6, 1614.9 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.22-1.37 (m, 2H), 1.28 (s, 3H), 1.43-1.68 (m, 5H), 1.75 (s, 3H), 1.82-1.91 (m, 1H), 2.02-2.10 (m, 2H), 2.27-2.35 (m, 1H), 2.66-2.72 (m, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.33, 20.39, 22.27, 28.19, 28.35, 30.56, 31.37, 37.37, 39.78, 48.89, 74.29, 109.59, 123.13, 145.61; HRMS for $C_{16}H_{27}D_2NOSi$: [M+Na^+] calculated 304.2025, found 304.2026.

3-Hydroxy-3-methyl-2-(3-methylbut-3-D,D-enyl) cyclohexanecarbonitrile (59): A THF solution of Bu_4NF (0.27 mmol) was added dropwise to a rt, THF solution of **58**

(51.2 mg, 0.18 mmol). After 1 h, saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (20:80, EtOAc/hexanes) to afford 39.2 mg (100%) of hydroxynitrile **59** as an oil. IR 3488.6, 2238.4 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.35-1.44 (m, 2H), 1.50-1.70 (m, 5H), 1.76 (s. 3H), 1.84-1.93 (m, 1H), 2.08-2.16 (m, 2H), 2.30-2.38 (m, 1H), 2.73 (td, *J* = 12, 4 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 20.25, 22.30, 27.87, 29.17, 30.52, 31.48, 37.73, 39.80, 47.23, 70.96, 109.92, 122.89, 145.29; HRMS for $C_{13}H_{19}D_2NO$: [M+K^+] calculated 248.1369, found 248.1371.

2-(3-(Chloromethyl)but-3-D,D-enyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (61): An aqueous solution (0.83 mL) of NaOCl (1.17 mmol) was added dropwise to a rt, H_2O-CH_2Cl_2 (1:1, 4 mL) biphasic mixture containing **59** (40.8 mg, 0.20 mmol) and $CeCl_3 \cdot 7H_2O$ (436 mg, 1.17 mmol). After 1 h, saturated aqueous $Na_2S_2O_3$ was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried (Na_2SO_4), concentrated, and the crude chloride purified by radial chromatography (20:80, EtOAc/hexanes) to afford 21.9 mg (52%) of chloronitrile **61** as an oil: IR 3486.0, 2237.1, 1642.5 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.40-1.48 (m, 2H), 1.57-1.72 (m, 5H), 1.95-2.02 (m, 1H), 2.12-2.15 (m, 1H), 2.31-2.37 (m, 1H), 2.48-2.54 (m, 1H), 2.74-2.80 (m, 1H), 5.03 (s, 1H), 5.17 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 20.24, 27.80, 29.24, 30.47, 31.39, 32.88, 39.96, 47.33, 70.96, 115.07, 122.76, 144.69; HRMS for $C_{13}H_{18}D_2ClNO$: [M+Na^+] calculated 266.1252, found 266.1242.

***Cis*-Decahydro-1-hydroxy-1-methyl-5-D,D-6-methylenenaphthalene-4a-carbonitrile (65):** A THF solution of *i*-PrMgCl (0.07 mL, 13.5 μmol) was added dropwise to a rt, THF solution (1 mL) of **61** (11 mg, 0.045 mmol). After 1.5 h, saturated, aqueous NH_4Cl (2 mL) was added, the phases were separated, the aqueous phase was extracted with EtOAc and then the combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude decalin by radial chromatography (20:80, EtOAc/hexanes) afforded 5.4 mg (57%) of **65** as a solid. IR (film) 3471.5, 2230.7, 1650.3 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.50-1.59 (m, 1H), 1.66-1.72 (m, 3H), 1.78-1.89 (m, 3H), 2.02-2.11 (m, 3H), 2.45-2.54 (m, 1H), 4.75 (s, 1H), 4.82 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 19.37, 24.16, 29.73, 30.26, 31.95, 32.18, 39.53, 46.39, 72.53, 110.93, 125.62, 143.25; HRMS for $C_{13}H_{17}D_2NO$: [M+Na^+] calculated 230.1482, found 230.1478.

***Trans*-Decahydro-1-hydroxy-1-methyl-5D,D-6-methylenenaphthalene-4a-carbonitrile (63):** A hexanes solution of BuLi (33 μL, 95 μmol) was added dropwise to a -78 °C, THF solution (2 mL) of **61** (11 mg, 45 μmol). After 2 h, the mixture was allowed to warm to room temperature and after a further 1.5 h, a THF solution (1mL) of $TsOH{\cdot}H_2O$ (25.7 mg, 0.14 mmol) was added. After 15 min, brine was added and then the mixture was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude decalin that was purified by radial chromatography (15:85, EtOAc/hexanes) to afford 4.9 mg (52%) of **63** as an oil: IR 3484.6, 2230.1, 1650.5 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.27-1.31 (m,

2H), 1.34-1.41 (m, 1H), 1.43-1.50 (m, 1H), 1.65-1.69 (m, 2H), 1.82-1.86 (m, 1H), 1.99-2.09 (m, 3H), 2.50-2.54 (m, 1H), 4.84 (s, 1H), 4.90 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 18.92, 24.16, 29.00, 34.17, 37.43, 40.20, 40.84, 46.37, 51.38, 70.34, 111.93, 122.81, 142.50; HRMS for $C_{13}H_{17}D_2NO$: [M+Na^+] calculated 230.1484, found 230.1495.

2-But-enyl-3-hydroxy-3-methyl-cyclohexanescarbonitrile (83): A THF solution (1.4 mL) of MeMgCl (3.7 mmol) was added to a -20 ºC, THF solution (15 mL) of 3-oxo-cyclohex-1-enecarbonitrile (427.3 mg, 3.5 mmol). After 2 h at -20 °C, the intermediate magnesium alkoxide was added to a 0 °C, THF solution (4 mL) of butenylmagnesium bromide. [4-Bromo-1-butene (0.5 mL, 5.3 mmol) was slowly added to a 0 °C, THF (4 mL) suspension of Mg (156.8 mg, 6.5 mmol), activated by addition of 1, 2-dibromoethane (0.1 mL, 0.7 mmol) and allowed to react at 0 °C for 1 h]. The resulting mixture was allowed to warm to room temperature and after 24 h, an aqueous, saturated solution (15 mL) of NH_4Cl was added. The aqueous phase was separated, extracted with EtOAc, and then the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the resulting crude product by radial chromatography (20:80, EtOAc/hexanes) afforded 500.0 mg (73%) of **83** as an oil spectrally identical to compound previously synthesized. (Ref: *Tet*. **2008**, *64*, 7477)

2-But-3-enyl-3-Trimethylsilyl-oxy-3-methyl-cyclohexanecarbonitrile (84): Neat Et_3N (191.9 mg, 1.91 mmol) and TMSOTf (311.2 mg, 1.40 mmol) were added to a 0 ℃, CH_2Cl_2 solution (20 mL) of **83** (245.5 mg, 1.27 mmol). After 2 h, saturated, aqueous $NaHCO_3$ was added, the phases were separated and the aqueous phase was extracted with

EtOAc. The combined organic extract was washed with $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated and the crude product was then purified by radial chromatography (5:95, EtOAc/hexanes) to afford 327.0 mg (97%) of nitrile **84** as an oil: IR 2237.1 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.25-1.33 (m, 2H), 1.29 (s, 3H), 1.42-1.63 (m, 4H), 1.67-1.71 (m, 1H), 1.79-1.87 (m, 1H), 2.05-2.08 (m, 1H), 2.13-2.21 (m, 1H), 2.32-2.38 (m, 1H), 2.66-2.72 (m, 1H), 4.98-5.07 (m, 2H), 5.80-5.88 (m, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.37, 20.41, 28.40, 29.18, 30.56, 31.50, 33.52, 39.76, 48.54, 74.26, 114.91, 123.22, 138.59; HRMS for $C_{15}H_{27}NOSi$: [M+Na^+] calculated 288.1754, found 288.1778.

2-(2-formylethyl)-3-Trimethylsilyloxy-3-methylcyclohexanecarbonitrile (85): Gaseous ozone was passed through a -78 ºC, CH_2Cl_2 solution (20 mL) of **84** (309.4 mg, 1.17 mmol) until the distinctive blue color of excess ozone persisted. Ozonolysis was then terminated, the solution was allowed to warm to room temperature, and then neat Me_2S (30 mL) was added dropwise. After 16 h the mixture was concentrated, the resulting oil was redissolved in EtOAc, and then washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by radial chromatography (20:80, EtOAc/hexanes) to provide 225 mg (72%) of **85** as an oil: IR 2720.7, 2236.3, 1723.8 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 9H), 1.27-1.34 (m, 2H), 1.32 (s, 3H), 1.50-1.63 (m, 3H), 1.69-1.77 (m, 2H), 2.06-2.14 (m, 2H), 2.58-2.66 (m, 1H), 2.68-2.73 (m, 1H), 2.73-2.79 (m, 1H), 9.79 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.37, 20.37, 21.57, 28.42, 30.52, 30.83, 39.67, 42.87, 48.31, 74.32, 122.87, 201.80; HRMS for $C_{14}H_{25}NO_2Si$ [M+Na^+] calculated 290.1547, found 290.1543.

2-(4,4-Dibromo-But-3-enyl)-3-Trimethylsilyl-oxy-3-methyl-cyclohexanecarbonitrile (86): Neat CBr_4 (1.6 mmol) was added to a rt, CH_2Cl_2 solution (30 mL) of Ph_3P (3.2 mmol). After 15 min, the solution was cooled to 0 ºC and then a CH_2Cl_2 solution (20 mL) of **85** (214 mg, 0.8 mmol) was added dropwise. After 1 h the mixture was concentrated and the crude dibromide separated by radial chromatography (10:90, EtOAc/hexanes) to provide 127 mg (38%) of **86** as an oil and 140.4 mg (50%) of **87** as an oil. For **86**: IR 2236.2, 1621.5 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 9H), 1.23-1.34 (m, 2H), 1.32 (s, 3H), 1.46-1.62 (m, 4H), 1.67-1.72 (m, 1H), 1.80-1.88 (m, 1H), 2.05-2.10 (m, 1H), 2.15-2.24 (m, 1H), 2.32-2.42 (m, 1H), 2.66-2.73 (m, 1H), 6.44 (t, *J* = 9 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 2.42, 20.35, 27.76, 28.41, 30.45, 31.19, 32.38, 39.62, 48.58, 74.18, 89.44, 122.90, 138.34; HRMS for $C_{15}H_{25}Br_2NOSi$: [M+Na^+] calculated 445.9945, found 445.9955. For **87**: IR 3484.5, 2237.3, 1620.3 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.34-1.39 (m, 1H), 1.42-1.47 (m, 1H), 1.50-1.70 (m, 5H), 1.86-1.95 (m, 1H), 2.09-2.13 (m, 1H), 2.20-2.30 (m, 1H), 2.36-2.46 (m, 1H), 2.70-2.77 (m, 1H), 6.45 (t, *J* = 8 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 20.20, 27.60, 29.15, 30.42, 31.34, 32.75, 39.92, 46.88, 70.87, 89.74, 122.66, 137.99; HRMS for $C_{12}H_{17}Br_2NO$: [M+Na^+] calculated 373.9549, found 373.9569.

2-(4,4-Dibromo-But-3-enyl)-3-hydroxy-3-methyl-cyclohexanecarbonitrile (87): A THF solution of Bu_4NF (0.40 mmol) was added dropwise to a rt, THF solution of **86** (115.6 mg, 0.27 mmol). After 1 h, saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic

extract was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (20:80, EtOAc/hexanes) to afford 94.5 mg (100%) of hydroxynitrile **87** as an oil spectrically identical to material isolated previously.

2-(5-Hydroxyl-Pent-3-ynyl)-3-hydroxy-3-methyl-cyclohexanecarbonitrile (88): A hexane solution of BuLi (0.48 mL, 1.2 mmol) was added dropwise to a -78 ºC, THF solution (20 mL) of **87** (140.0 mg, 0.4 mmol). After 30 min the reaction was allowed to warm to 0 ºC and then formaldehyde gas was bubbled through the solution for 10 min. After 2 h an aqueous, saturated solution of NH_4Cl (15 mL) was added, the phases were separated, and then the aqueous phase was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated and then the crude product was purified by radial chromatography (30:70, EtOAc/hexanes) to afford 44.5 mg (50%) of nitrile **88** as a white crystal (mp: 78-80 ºC): IR 3404.6, 2237.6, cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.42-1.48 (m, 1H), 1.53-1.57 (m, 1H), 1.59-1.71 (m, 5H), 2.03-2.09 (m, 1H), 2.11-2.16 (m, 1H), 2.40-2.53 (m, 2H), 2.73-2.78 (dt, J = 10, 5 Hz, 1H), 4.24 (s, 2H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 18.65, 20.17, 28.42, 29.07, 30.44, 31.51, 39.79, 46.52, 51.23, 70.80, 79.52, 85.72, 123.01; HRMS for $C_{13}H_{19}NO_2$: [M+Na^+] calculated 244.1308, found 244.1307.

2-(5-Chloro-Pent-3-ynyl)-3-hydroxy-3-methyl-cyclohexanescarbonitrile (80): Neat CCl_4 (0.06 mL, 0.54 mmol) was added to a rt, CH_2Cl_2 solution (20 mL) of Ph_3P (283.3 mg, 1.08 mmol). After 15 min, the solution was allowed to cool to 0 ºC and then a CH_2Cl_2 solution (10 mL) of **88** (59.8 mg, 0.27 mmol) was added dropwise. After 1 h the

mixture was concentrated and then the crude chloride was purified by radial chromatography (20:80, EtOAc/hexanes) to provide 60 mg (94%) of **80** as an oil: IR 3479.8, 2236.2, 688.5 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.43-1.54 (m, 2H), 1.57-1.72 (m, 5H), 2.03-2.10 (m, 1H), 2.11-2.16 (m, 1H), 2.47-2.59 (m, 2H), 2.74-2.80 (dt, *J* = 12, 4 Hz, 1H), 4.14 (s, 2H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 18.44, 20.27, 28.25, 29.21, 30.47, 31.12, 31.22, 39.90, 46.52, 70.84, 75.86, 86.98, 122.61; HRMS for $C_{13}H_{18}NOCl$: [M+Na^+] calculated 262.0969, found 262.0963.

***Cis*-Octahydro-7-hydroxy-7-methyl-3-vinylidene-1H-indene-3a-carbonitrile (90):** A THF solution of *i*-PrMgCl (mL, 0.28 mmol) was added dropwise to a rt, THF solution (2 mL) of **80** (22 mg, 0.092 mmol). After 1.5 h, saturated aqueous NH_4Cl (2 mL) was added, the phases were separated, the aqueous phase was extracted with EtOAc and then the combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude hydrindane by radial chromatography (20:80, EtOAc/hexanes) afforded 13.5 mg (72%) of **90** as a white crystal (mp: 48-51 °C): IR 3417.7, 2236.6 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 3H), 1.54-1.76 (m, 5H), 1.79-1.90 (m, 2H), 2.02-2.10 (m, 1H), 2.33-2.37 (t, *J* = 8 Hz, 1H), 2.51-2.68 (m, 2H), 4.92-4.97 (m, 1H), 5.03-5.08 (m, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 20.24, 24.94, 27.07, 29.29, 31.63, 35.56, 44.87, 54.53, 70.96, 80.49, 106.45, 123.44, 201.62; HRMS for $C_{13}H_{17}NO$: [M+Na^+] calculated 226.1202, found 226.1204.

***Cis*-Octahydro-7-hydroxy-7-methyl-3-vinylidene-1H-indene-3a-carbonitrile (90):** A hexanes solution of BuLi (0.08 mL, 0.192 mmol) was added dropwise to a -78 °C, THF

solution (2 mL) of **80** (23 mg, 0.096 mmol). After 2 h, the mixture was allowed to warm to room temperature and after a further 0.5 h, saturated aqueous NH_4Cl (2 mL) was added. The phases were separated, the aqueous phase was extracted with EtOAc, and then the combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude hydrindane by radial chromatography (20:80, EtOAc/hexanes) afforded 12.3 mg (63%) of **90** as a white crystal spectrically identical to the material isolated previously.

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