Complimentary Reactivity from C- And N- Metalated Nitriles

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COMPLIMENTARY REACTIVITY FROM C- AND N- METALATED NITRILES

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ABSTRACT

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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.

![Continuum of Metalated Nitrile Structures](image)

**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 \(\text{MeONa-MeOD}\) 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 ($5 \to 7b$) via the putative $N$-lithiated nitrile $8$ (Scheme 1). Subsequent reinvestigation with LDA, LiHMDS and KHMDS demonstrated racemization at temperatures as low as $-135\, ^\circ\mathrm{C}$.\(^7\)

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

![Scheme 1](image)

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 accessible chiral $C$-metalated nitrile, slowly racemizes with a $t_{1/2} = 11.4\, \text{h}$ at $-100\, ^\circ\mathrm{C}$.\(^2\)
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 cyclohexanecarbonitrile 13 with LDA generates an $N$-lithiated nitrile 14 which alkylates propargyl bromide to afford the alkyne 15. Adding methylocopper 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.\textsuperscript{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).\textsuperscript{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,\(^\text{12}\) 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 alkylation suggests alkylation via the internally complexed C-lithiated nitrile 30.\(^\text{13}\) The electron rich \(\pi\)-system\(^\text{14}\) 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 bicyclo [4,3,0] 
undecanes. 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.

Scheme 6. Cation-Controlled Cyclizations

The most remarkable feature of C-magnesiated nitrile alkylations is their electrophile-
dependent stereoselectivity. Alkyl halide and sulfonate electrophiles alkylate 27 with 
retention of stereochemistry through a three-center two-electron, electrophilic retentive 
alkylation mechanism (S_{E2,Ret}). 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 stereoelectronically 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). 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
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 coupled with a high charge localization. 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, $C$-metalated nitriles, generally formed by halogen-metal exchange, and nitrile-stabilized carbanions, usually favored in highly polar solvents or by internal complexation (Figure 3).

![Figure 3. Three Typical Forms of Metalated Nitriles](image)

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 demonstrate the facility for cyclization via the $N$-lithiated nitrile anion and the $C$-magnesiated nitrile 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, a better orbital alignment is possible in the $S_N2$ displacements because of the greater flexibility from incorporating rotatable single bonds within the forming cyclohexane ring. The analogous $S_N2'$ displacements and 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 cyclohexane 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 substituted decalins.
Rapid access to the deuterated carbocyclic nitrile rests on an efficient 1,2-1,4-addition to oxonitrile 54 (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. D₂-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, presumably with selective abstraction of the allylic proton ensuring stereochemical fidelity en route to 61.

Cyclizing the deuterated nitrile 61 revealed an inherent preference for SN₂ 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 SN₂ displacement. Cyclization of the corresponding magnesiated nitrile also proceeds through an SN₂ 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<sup>3</sup> Centers

Baldwin's rules are immensely powerful for predicting the viability of intramolecular displacements.<sup>31</sup> 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.](image)

Endo- and exocyclic processes are sub-categorized depending on the hybridization of the acceptor carbon: sp<sup>3</sup> (tetrahedral), sp<sup>2</sup> (trigonal), or sp (digonal). For the carbocyclic series of 5-exo cyclizations, all formally "allowed" processes, the nucleophilic attack on sp<sup>3</sup>, sp<sup>2</sup>, 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°<sup>32</sup> for 5-exo-tet, 106°<sup>33</sup> for 5-exo-trig, and 72°<sup>34</sup> 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 chloroalkynitriles 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\textsuperscript{35} (Scheme 3).\textsuperscript{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\textsuperscript{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-hydindane 90 (Scheme 15). 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-hydindane 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. A reduction in the torsional strain is likely achieved through gentle twisting of the ring substituents which directs cyclization to the cis-hydindane 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 hydindane. Comparable attack of C-magnesiated nitriles and N-lithiated nitrile anions onto sp³ hybridized centers have similar but different reaction trajectories that favor cyclization to cis-fused hydindanes. Attack on an sp hybridized carbon involves an oblique attack angle, rather than a backside attack for and sp³ center, but the trajectory difference is not sufficient to redirect the cyclization with acetylenic electrophiles to trans-hydindanes.
3. Experimentals

3-Trimethylsilyl-oxy-3-methyl-2-(3-methylbut-3-enyl)cyclohexanecarbonitrile (56):
Neat Et₃N (84.4 mg, 0.84 mmol) and TMSOTf (135.6 mg, 0.61 mmol) were added to a 0 °C CH₂Cl₂ 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 NaHCO₃ was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₆H₂₉NOSi: [M+Na⁺] calculated 302.1911, found 302.1929.

2-(2-Acetylethyl)-3-Trimethylsilyloxy-3-methylcyclohexanecarbonitrile (57):
Gaseous ozone was passed through a -78 °C, CH₂Cl₂ 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 Me₂S (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 (Na₂SO₄), 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₅H₂₇NO₂Si: [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 Ph₃PCD₃I (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 NaHCO₃ was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na₂SO₄), 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₆H₂₇D₂NOSi: [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 Bu₄NF (0.27 mmol) was added dropwise to a rt, THF solution of 58
(51.2 mg, 0.18 mmol). After 1 h, saturated, aqueous NH₄Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na₂SO₄), 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₃H₁₉D₂NO: [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, H₂O-CH₂Cl₂ (1:1, 4 mL) biphasic mixture containing 59 (40.8 mg, 0.20 mmol) and CeCl₃·7H₂O (436 mg, 1.17 mmol). After 1 h, saturated aqueous Na₂S₂O₃ was added, the phases were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic extract was washed with brine, dried (Na₂SO₄), 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₃H₁₉D₂ClNO: [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 NH₄Cl (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 (Na₂SO₄), 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₃H₁₇D₂NO: [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·H₂O (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 (Na₂SO₄) 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; ¹H-NMR (500 MHz, CDCl₃) 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\(_3\)) \(\delta\) 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\(_2\)NO: [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 °C, 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\(_4\)Cl was added. The aqueous phase was separated, extracted with EtOAc, and then the combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)), 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\(_3\)N (191.9 mg, 1.91 mmol) and TMSOTf (311.2 mg, 1.40 mmol) were added to a 0 °C, CH\(_2\)Cl\(_2\) 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$_2$SO$_4$) 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$_2$Cl$_2$ 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$_2$S (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$_2$SO$_4$), 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$_2$Si [M+Na$^+$] calculated 290.1547, found 290.1543.
2-(4,4-Dibromo-But-3-enyl)-3-Trimethylsilyl-oxy-3-methyl-cyclohexanecarbonitrile (86): Neat CBr₄ (1.6 mmol) was added to a rt, CH₂Cl₂ solution (30 mL) of Ph₃P (3.2 mmol). After 15 min, the solution was cooled to 0 ºC and then a CH₂Cl₂ 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; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₅H₂₅Br₂NOSi: [M+Na⁺] calculated 445.9945, found 445.9955. For 87: IR 3484.5, 2237.3, 1620.3 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₂H₁₇Br₂NO: [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 Bu₄NF (0.40 mmol) was added dropwise to a rt, THF solution of 86 (115.6 mg, 0.27 mmol). After 1 h, saturated, aqueous NH₄Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic
extract was washed with brine, dried (Na₂SO₄), concentrated, and purified by radial chromatography (20:80, EtOAc/hexanes) to afford 94.5 mg (100%) of hydroxynitrile 87 as an oil spectically 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 °C, THF solution (20 mL) of 87 (140.0 mg, 0.4 mmol). After 30 min the reaction was allowed to warm to 0 °C and then formaldehyde gas was bubbled through the solution for 10 min. After 2 h an aqueous, saturated solution of NH₄Cl (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 (Na₂SO₄) 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 °C): IR 3404.6, 2237.6, cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (400 MHz, CDCl₃) 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 C₁₃H₁₉NO₂: [M+Na⁺] calculated 244.1308, found 244.1307.

2-(5-Chloro-Pent-3-ynyl)-3-hydroxy-3-methyl-cyclohexanecarbonitrile (80): Neat CCl₄ (0.06 mL, 0.54 mmol) was added to a rt, CH₂Cl₂ solution (20 mL) of Ph₃P (283.3 mg, 1.08 mmol). After 15 min, the solution was allowed to cool to 0 °C and then a CH₂Cl₂ 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$_4$Cl (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$_2$SO$_4$), 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 NH₄Cl (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 (Na₂SO₄), 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 spectrally identical to the material isolated previously.
References

7 Carlier, P. R.; Zhang Y. *Org. Lett.* 2007, 9, 1319.
20 Analogous Cu(III) species were verified as key intermediates during coupling of lithium dimethyl cuprate with halobenzenes, although the lifetime of this intermediate may be short since a Cu(III) intermediate was not detected by $^{13}$C NMR.

The cylindrical diameter of the π-system is only 3.6 Å: Sheppard, W. A. in *The Chemistry of the Cyano Group* Rappoport, Ed. 1970, Ch. 5.


³⁰ Within the limits of NMR detection there were no deuterium isomers.


³² Viewing the ring from above the electrophilic carbon appears trigonal with the C₄-C₅-LG angle appearing as 120°. Assuming the sp³ hybridized nucleophile orients directly toward the electrophilic carbon requires a bond angle for C₁-C₅-C₄ of 108°. As the angle sum at a point is 360° the remaining angle must be 132°.


³⁴ Assuming the sp³ hybridized nucleophile orients directly toward the electrophilic carbon creates an internal bond angle for C₁-C₅-C₄ of 108°. As the angle sum of a straight line is 180°, the attack angle is 72°.

Temporary protection of the alcohol was required to circumvent attack on the intermediate ozonide and dehydration to the corresponding pyran.


Equilibration between C- and N-lithiated nitriles has been detected by NMR: Sott, R.; Granander, J.; Hilmersson, G. J. Am. Chem. Soc. 2004, 126, 6798.