Metalated nitriles: S_Ni' cyclizations with a propargylic electrophile

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ABSTRACT

A rare 5-exo-dig S_Ni' cyclization with magnesiated and lithiated nitriles affords a *cis*-fused hydrindane bearing an exocyclic allene. The cyclization of the dilithiated nitrile pits a stereoelectronic preference for a *trans*-hydrindane against a cyclization through a less strained transition structure to the corresponding *cis*-hydrindane. Computational modeling suggests that the dilithiated nitrile cyclizes to a *cis*-hydrindane because the preferred transition structure positions the lithium cation in a cone of electron density that bridges the nitrile-bearing carbon, an alkoxide, and an electron-rich alkyne functionality.

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Metalated nitriles are nucleophilic chameleons that change the precise geometry of the highly nucleophilic,¹ formal carbanion in response to the solvent, temperature, substitution, and the metal cation.² The structures are partitioned into two distinct types, *N*- and *C*-metalated nitriles (Figure 1), depending on whether the metal is coordinated to the nitrile nitrogen or the nucleophilic carbon, **1** and **2**, respectively.³

The differing geometries at the nucleophilic carbon can be harnessed to direct cyclizations selectively to *cis*- and *trans*-decalins through selective access to *N*-lithiated and *C*-magnesiated nitriles (Scheme 1).⁴ Deprotonating **3** with *i*-PrMgCl triggers an internally directed deprotonation **4** → **5** and an S_Ni displacement via the *C*-magnesiated nitrile **5** to the *cis*-decalin **6**. Employing BuLi to deprotonate **3** affords the *N*-lithiated nitrile **7** in which the strong lithium-π interaction⁵ between the electron-rich nitrile π-electrons⁶ and the adjacent lithium alkoxide anchors the nitrile in an axial orientation for cyclization to the *trans*-decalin **8**.

Scheme 1. Cation-controlled decalin cyclizations

The tunable geometry of metalated nitriles is ideal for probing subtle stereoelectronic differences in intramolecular cyclizations. The stereodivergent cyclizations of **3** → **6** and **3** → **8** maintain the same sp³ hybridization of the electrophile while harnessing the tunable geometry of the nucleophilic carbon to control the S_Ni displacement. More subtle is the electrophile hybridization which can profoundly influence the course of S_Ni and S_Ni' displacements.⁷ As originally formulated, the nucleophilic S_Ni' attack angle on an sp hybridized carbon, Nu-C≡C, was postulated to be acute (Scheme 2, **9** → **10**), maintaining a trajectory with the propargylic substituent close to the 120° angle in the forming allene (atoms highlighted in purple).

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Scheme 2. S_Ni' displacement trajectories.

Calculations,⁸ and accumulating experimental evidence,⁹ suggest that S_Ni' displacements on propargylic electrophiles actually involve an obtuse attack angle (Scheme 2, **10'** → **11'**). Estimates of the attack angle vary between 115–130° depending on the extent of bond formation in the TS. Simplistically, an obtuse attack avoids the electronic repulsion between the nucleophilic electron pair and the π -electrons of the alkyne that occurs in an acute attack.

S_Ni' displacements with propargylic electrophiles are rare,¹⁰ in large part because of the difficulty in generating anionic nucleophiles in the presence of reactive propargylic electrophiles. Metalated nitriles, although not used previously for S_Ni' displacements, are ideal because of their facile formation through deprotonation,¹¹ halogen-metal,¹² sulfoxide-metal,¹³ and sulfide-metal¹⁴ exchange and because their formation is highly tolerant of delicate functionality. In addition, the tunable nucleophile geometry, through metal counter-ion selection,² allows control over developing bond angles for stereoselective cyclization.

Tuning the stereochemistry of a metalated nitrile in an S_Ni' displacement provides a potential solution to the long-standing difficulty in synthesizing hydrindanes.¹⁵ *trans*-hydrindanes are prevalent in natural products, but are more difficult to synthesize than their generally more stable *cis*-counterparts (Scheme 3, compare **14** and **16**).^{15,16} Conceptually, deprotonating **12** with excess *i*-PrMgCl should generate the *C*-magnesiated nitrile **13** that would cyclize to the *cis*-hydrindane **14**. Cyclization of the corresponding lithiated nitrile **15** having complexation between the alkoxy lithium and the nitrile π -electrons, should lead to the *trans*-hydrindane **16**. The cyclization of **15** pits a stereoelectronic preference for an obtuse attack against torsional strain inherent in the structure of a *trans*-hydrindane. Described in this report is the synthesis of the cyclization precursor **12**, the cyclizations of **12** with *i*-PrMgCl and BuLi, and a computational analysis of the dilithiated nitrile derived from **12**.

Scheme 3. Stereodivergent hydrindanes cyclizations.

Rapid access to the cyclization precursor **12** was predicated on an efficient 1,2-1,4-double addition to oxonitrile **17** (Scheme 4).¹⁷ Sequential addition of MeMgCl and 3-butenylmagnesium bromide to oxonitrile **17**¹⁸ smoothly provided the substituted cyclohexanecarbonitrile **18**. Silyl protection of the tertiary hydroxyl group followed by ozonolysis¹⁹ provided aldehyde **19**. Exposing **19** to dibromomethylene-triphenylphosphorane triggered dibromo-olefination²⁰ accompanied by extensive cleavage of the silyl ether to afford **20a** (50%) and the silyl ether **20b** (38%). Brief exposure of **20b** to Bu₄NF quantitatively afforded **20a**. Subsequent treatment of **20a** with excess BuLi and interception of the intermediate acetylide with gaseous formaldehyde provided the acetylenic alcohol **21**. Having installed the requisite carbon skeleton, alcohol **21** was chlorinated²¹ to provide the cyclization precursor **12**.

Scheme 4. Synthesis of the Cyclization Precursor

Exposing hydroxynitrile **12** to excess *i*-PrMgCl triggers a smooth cyclization to the *cis*-hydrindane **14** (Scheme 5).²² Forming the *cis*-hydrindane **14** is consistent with cyclization through a three-centered *C*-magnesiated nitrile **13** having a side-on overlap in the $S_E2_{(Ret)}$ displacement.²³

Cyclizing **12** by deprotonating with BuLi affords the same *cis*-hydrindane **14** (Scheme 5). The absence of any *trans*-hydrindane indicates that the internal coordination between the alkoxy lithium and the electron rich nitrile⁵ is insufficient to achieve the orientation for cyclization through **15**. Presumably, the developing torsional strain prevents cyclization through **15** which instead occurs through **15'**.²⁴

Scheme 4. S_Ni' hydrindane cyclizations.

The preference of the lithiated nitrile **15** to cyclize to a *cis*-hydrindane stimulated a computational analysis²⁵ to gain insight into the factors controlling the cyclization. The AM1 semi-empirical quantum chemistry method,²⁶ incorporating the PCM continuum solvation model with THF as solvent,²⁷ was used to analyze the structural and activation enthalpy differences between the transition structures. Frequency analysis was used to confirm all stationary points as transition structures²⁸ in the dilithiated models.

Two different *cis*-transition structures were identified (Figure 2). The two transition structures **TS1** and **TS2** both contain a centrally located lithium cation that bridges the nitrile-bearing carbon and the alkoxide. In addition, the lithium cation interacts with the electron-rich alkyne functionality and maintains two C–H interactions that creates an ideally oriented cone of electron density for the lithium cation to reside in. **TS1** and **TS2** differ in the coordination of the second lithium atom; in **TS1** lithium coordinates to the alkoxide whereas in **TS2** lithium coordinates to the nitrile nitrogen. **TS1**, formally a *C*-lithiated nitrile, is computed to be 8.4 kcal/mol higher in energy than **TS2** which is both *C*- and *N*-lithiated. Coordination of lithium to the nitrile nitrogen in **TS2** removes electron density from the nucleophilic carbon which stabilizes the transition structure; the breaking/forming bond of **TS2** (2.09 Å) is significantly shorter than that of **TS1** (2.15 Å). The lithium cation bridging the alkoxide and the nucleophilic carbon has a shorter Li–O bond in **TS2** (2.19 Å) compared with **TS1** (2.26 Å) and a longer Li–C interaction with the nucleophilic α -carbon of the nitrile (3.01 Å for **TS2** compared with 2.84 Å for **TS1**).

Figure 2. TS for S_Ni' cyclizations to *cis*-hydrindanes

Several transition structures analogous to **TS1** and **TS2** were explored for cyclization to the corresponding *trans*-hydrindane. Despite extensive optimization, only one transition structure was located that would afford a *trans*-hydrindane (**TS3**, Figure 3). In **TS3** one lithium cation bridges the alkoxide and the nitrile nitrogen while the other associates with the alkyne. The computed energy of **TS3** is 1.9 kcal/mol and 6.4 kcal/mol higher in energy than **TS1** and **TS2**, respectively. Of the three

computationally identified transition structures, the lowest energy transition structure **TS2** is stabilized by lithium encapsulation through a series of interactions with electron rich contacts that serve to guide the cyclization to the *cis*-hydrindane **14**. The computational identification of transition structure **TS2** as the low energy structure reveals a dual *C*- and *N*-lithiation not captured in the simplistic representation **15'**.

Figure 3. TS for S_Ni' cyclization to a *trans*-hydrindane.

The cyclizations of **12** are the first S_Ni' displacements of a propargylic electrophile by metalated nitriles. Formation of the *C*-magnesiated nitrile sets the stereochemistry of the nucleophilic C–Mg bond which directs cyclization to the *cis*-hydrindane **14**. Cyclization via the corresponding lithiated nitrile pits internal complexation between lithium and the nitrile π -electrons in the developing *trans*-hydrindane against cyclization to a more flexible *cis*-hydrindane. Computational modeling indicates that the *cis*-hydrindane **14** is favored because of an unusual encapsulation of one lithium cation through coordination to a series of electron rich contact points accompanied by a favorable coordination of the second lithium to the nitrile nitrogen. Collectively, the cyclizations are the first S_Ni' displacements of metalated nitriles with propargylic electrophiles, a test of lithium–nitrile π -coordination in cyclizations of small rings, and identify an unusual encapsulation of lithium in an S_Ni' displacement.

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Supplementary Material

Supplementary data (experimental procedures, characterization data, proton and carbon spectra of all compounds and computational information) associated with this article can be found, in the online version, at <http://>

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