Tetrahedron Letters 56 (2015) 3216–3219

Contents lists available at ScienceDirect

Tetrahedron Letters

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Metalated nitriles: S_Ni' cyclizations with a propargylic electrophile

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ARTICLE INFO

Article history:
Received 25 November 2014
Revised 22 December 2014
Accepted 2 January 2015
Available online 12 January 2015

Keywords:
S_Ni' cyclization
Metalated nitriles
5-*exo*-Dig
Hydrindane

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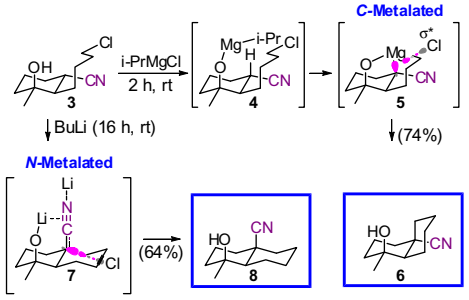
Metalated nitriles are nucleophilic chameleons that change the precise geometry of the highly nucleophilic,[1] formal carbanion in response to the solvent, temperature, substitution, and the metal cation.[2] The structures are partitioned into two distinct types, *N*- and *C*-metalated nitriles (Fig.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



Figure 1. *N*- and *C*-metalated nitrile structures.

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 interaction[5] between the electron-rich nitrile π-electrons[6] and the adjacent lithium alkoxide anchors the nitrile in an axial orientation for cyclization to the *trans*-decalin **8**.

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 sp^3 hybridization of the electrophile while harnessing the



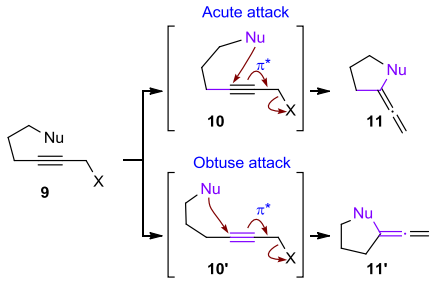
Scheme 1. Cation-controlled decalin cyclizations.

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).

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° and 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.

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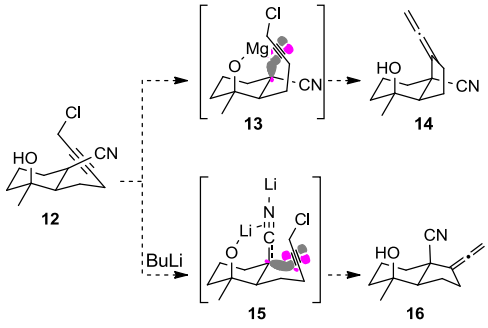
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0040-4039/Published by Elsevier Ltd.



Scheme 2. S_Ni' displacement trajectories.

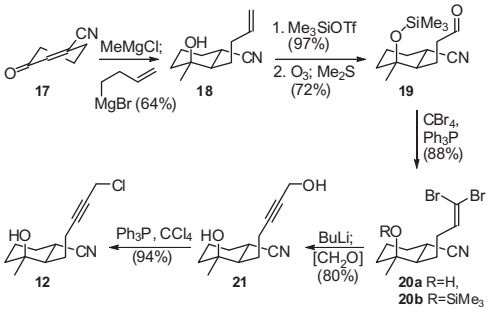
S_Ni' displacements with propargylic electrophiles are rare,[10] in large part because of the difficulty in generating anionic nucleophiles in the presence of reactive propargylic electrophiles. Metalated nitriles, although not used previously for S_Ni' displacements, are ideal because of their facile formation through deprotonation,[11] halogen-metal,[12] sulfoxide-metal,[13] and sulfide-metal[14] 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.[5b] *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**).[5b,15] 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 Letter 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.

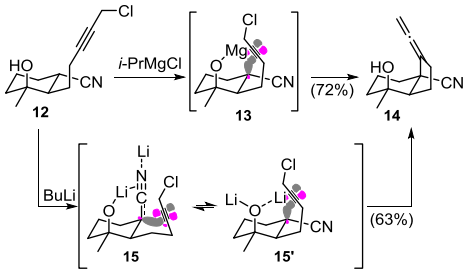
Rapid access to the cyclization precursor **12** was predicated on an efficient 1,2-1,4-double addition to oxonitrile **17** (Scheme 4).[16] Sequential addition of MeMgCl and 3-butenylmagnesium bromide to oxonitrile **17**[17] smoothly provided the substituted cyclohexanecarbonitrile **18**. Silyl protection of the tertiary hydroxyl group followed by ozonolysis[18] provided aldehyde **19**. Exposing **19** to dibromomethylene–triphenylphosphorane triggered dibromoolefination[19] accompanied by extensive cleavage of the silyl ether to afford **20a** (50%) and the silyl ether **20b** (38%). Brief exposure of **20b** to Bu_4NF quantitatively afforded **20a**. Subsequent treatment of **20a** with excess BuLi and interception of the intermediate



Scheme 4. Synthesis of the cyclization precursor.

acetylide with gaseous formaldehyde provided the acetylenic alcohol **21**. Having installed the requisite carbon skeleton, alcohol **21** was chlorinated[20] to provide the cyclization precursor **12**.

Exposing hydroxynitrile **12** to excess *i*-PrMgCl triggers a smooth cyclization to the *cis*-hydrindane **14** (Scheme 5).[21] 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.[22]



Scheme 5. S_Ni' hydrindane cyclizations.

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 nitrile[5] is insufficient to achieve the orientation for cyclization through **15**. Presumably, the developing torsional strain prevents cyclization through **15** which instead occurs through **15′**.[23]

The preference of the lithiated nitrile **15** to cyclize to a *cis*-hydrindane stimulated a computational analysis[24] to gain insight into the factors controlling the cyclization. The AM1 semi-empirical quantum chemistry method,[25] incorporating the PCM continuum solvation model with THF as solvent,[26] 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 structures[27] in the dilithiated models.

Two different *cis*-transition structures were identified (Fig. 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 create 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

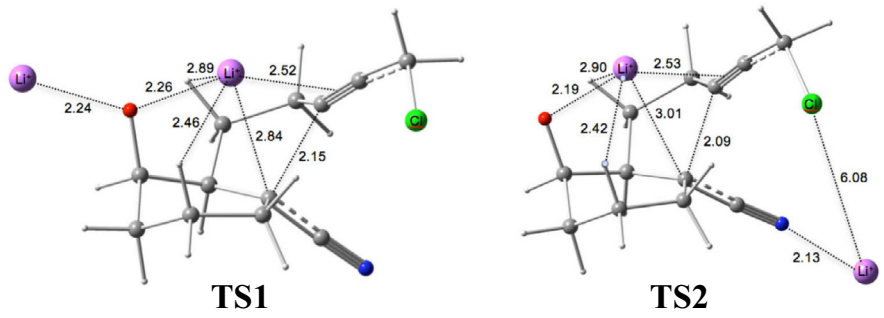


Figure 2. TS for S_Ni' cyclizations to *cis*-hydrindanes.

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**).

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**, Fig. 3). In **TS3** one lithium cation bridges the alkoxide and the nitrile nitrogen while the other associates with the alkoxide. 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′**.

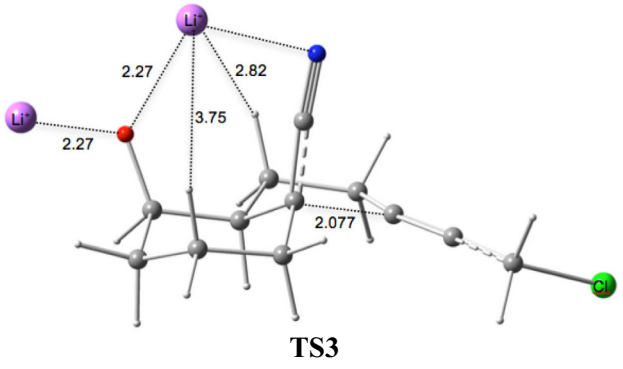


Figure 3. TS for S_Ni' cyclization to a *trans*-hydrindane.

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.

Acknowledgments

Financial support from the National Institutes of Health (2R15AI051352-03) and in part from the National Science Foundation (IRD and CHE-1126465) are gratefully acknowledged. The opinions expressed in this manuscript are those of the authors and do not necessarily reflect the views of the NSF or NIH.

Supplementary data

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://dx.doi.org/10.1016/j.tetlet.2015.01.013.

References and notes

1. (a) Bug, T.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 12980.
2. (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1; (b) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.
3. Fleming, F. F.; Wei, Y.; Liu, W.; Zhang, Z. *Tetrahedron* **2008**, *64*, 7477.
4. (a) Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008**, 5365; (b) Fleming, F F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.
5. (a) Sasaki, M.; Shirakawa, Y.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Chem. Eur. J.* **2009**, *15*, 3363; (b) Fleming, F. F.; Vu, V. A.; Shook, B. C.; Raman, M.; Steward, O. W. *J. Org. Chem.* **2007**, *72*, 1431; (c) Davis, F. A.; Mohanty, P. K. *J. Org. Chem.* **2002**, *67*, 1290; (d) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901; (e) Schrader, T.; Kirsten, C.; Herm, M. *Phosphorous Sulfur Silicon* **1999**, *144–146*, 161; (f) Gmeiner, P.; Hummel, E.; Haubmann, C. *Liebigs Ann.* **1987**, *1995*, 5; (g) Murray, A. W.; Murray, N. D.; Reid, R. G. *J. Chem. Soc. Chem. Commun.* **1986**, 1230
6. Metalated nitriles are more electron rich than their neutral parent nitriles: (a) Wu, F.; Foley, S. R.; Burns, C. T.; Jordan, R. F. *J. Am. Chem. Soc.* **1841**, *2005*, 127; (b) Groux, L. F.; Weiss, T.; Reddy, D. N.; Chase, P. A.; Piers, W. E.; Ziegler, T.; Parvez, M.; Benet-Buchholz, J. *J. Am. Chem. Soc.* **1854**, *2005*, 127.
7. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734
8. (a) Strozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340; (b) Houk, K. N.; Strozier, R. W.; Rozeboom, M. D.; Nagaze, S. *J. Am. Chem. Soc.* **1982**, *104*, 323.
9. (a) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513; (b) Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014; (c) Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175.
10. Devambatla, R. K. V.; Velagaleti, R.; Yarravarapu, N.; Fleming, F. F. *Tetrahedron* **2012**, *68*, 2925.
11. Watt, D. S.; Arseniyadis, S.; Kyler, K. S. *Org. React.* **1984**, *31*, 1.
12. (a) Pitta, B. R.; Fleming, F. F. *Org. Lett.* **2010**, *12*, 2810; (b) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200; (c) Fleming, F. F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, *6*, 501.
13. Nath, D.; Fleming, F. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11790.
14. Nath, D.; Skilbeck, M.; Coldham, I.; Fleming, F. F. *Org. Lett.* **2014**, *16*, 62.
15. Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071.
16. (a) Fleming, F. F.; Wei, G.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* **2007**, *72*, 5270; (b) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126.
17. (a) Lujan-Montelongo, J. A.; Fleming, F. F.; Hughes, D. *Org. Synth.* **2013**, *90*, 229; (b) Fleming, F. F.; Zhang, Z.; Wei, G. *Synthesis* **2005**, 3179.

18. Temporary protection of the alcohol was required to circumvent attack on the intermediate ozonide and dehydration to the corresponding pyran.
19. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769
20. Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801.
21. The ^{13}C chemical shift of the nitrile carbon provides a reliable, and diagnostic means of assigning stereochemistry: Fleming, F. F.; Wei, G. *J. Org. Chem.* **2009**, *74*, 3551.
22. Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.
23. 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.
24. The Gaussian 09 quantum chemistry package[a] was used with the computational resources at the Center for Computational Sciences.[b] (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T., ; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision D.01*; Gaussian: Wallingford CT, 2009
(b) Center for Computational Sciences at Duquesne University Supported by National Science Foundation: CHE-0723109 and CHE-1126465 and United States Department of Education: P116Z080180 and P116Z050331.
25. Thiel, Walter *WIREs: Comput. Mol. Sci.* **2014**, *4*, 145–157.
26. (a) Morao, I.; McNamara, J. P.; Hillier, I. H. *J. Am. Chem. Soc.* **2003**, *125*, 628; (b) Iron, M. A.; Martin, J. M. L.; van der Boom, M. E. *J. Am. Chem. Soc.* **2003**, *125*, 11702; (c) Freccero, M.; Di Valentin, C.; Sarzi-Amade, M. *J. Am. Chem. Soc.* **2003**, *125*, 3544.
27. Acevedo, O.; Evanseck, J. D. Transition States and Transition Structures. In *Computational Medicinal Chemistry for Drug Discovery*; Bultinck, P., De Winter, H., Langenaeker, W., Tollenaere, J. P., Dekker, M., Eds.; Marcel and Dekker: New York, 2004; p 323.