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# *C*-Metalated Nitriles: Electrophile-Dependent Alkylations and Acylations

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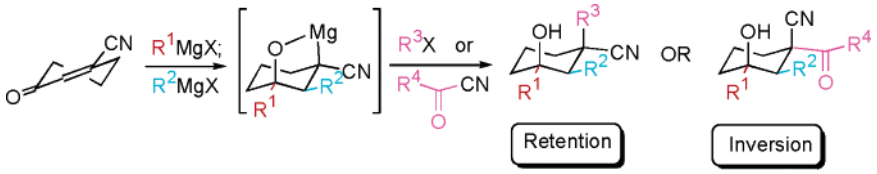


Sequential carbonyl addition−conjugate addition of Grignard reagents to 3-oxocyclohex-1-ene-1-carbonitrile generates *C*-magnesiated nitriles whose alkylation stereoselectivities intimately depend on the nature of the electrophile. The alkylation of these *C*-magnesiated nitriles with alkyl halides, sulfonates, and unstrained ketones occurs with the retention of the C−Mg configuration, whereas aldehyde and acyl cyanide acylations proceed with inversion of the stereochemistry. Mechanistic probes indicate that the stereoselectivity is controlled by stereoelectronic effects for most electrophiles, except allylic, benzylic, and cyclopropyl halides where single-electron-transfer processes intervene. Screening numerous alkylations of *C*-magnesiated nitriles with a diverse range of electrophiles reveals the reaction scope and delineates the fundamental stereoelectronic effects responsible for the highly unusual electrophile-dependent alkylations.

## Introduction

Metalated nitriles are powerful nucleophiles that are broadly effective in a diverse range of alkylations.[1] The exceptional nucleophilicity stems from the inductively stabilized[2] negative charge density localized on the formally anionic carbon. Inductive stabilization[2] of metalated nitriles, rather than resonance delocalization, is conspicuous from nucleophilicity trends,[3] acidity measurements,[4] and NMR analyses[5] and is clearly manifest in the bond distances of metalated nitriles in the solid state.[6] Particularly significant is the C≡N bond length (1.14−1.20 Å, Figure 1) of metalated nitriles, which is virtually identical to the C≡N bond length of neutral nitriles (1.14 Å).[7] Correspondingly, the C−CN bond length (1.36−1.45 Å) is appreciably contracted relative to a C−C single bond, reflecting the electrostatic attraction between the negatively charged "carbanion" and the strongly[2] electron-withdrawing nitrile group.

(1) (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Organic Reactions: Addition and Substitution Reactions of Nitrile-stabilized Carbanions*; Wiley: New York, 1984.

(2) (a) Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035. (b) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.

(3) Bug, T.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 12980.

(4) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715.

(5) Bradamante, S.; Pagani, G. A. *Adv. Carbanion Chem.* **1996**, *2*, 189.

(6) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

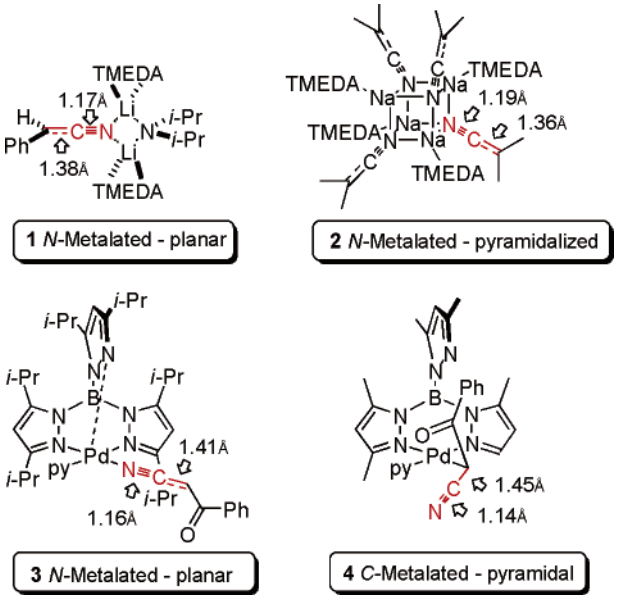


**FIGURE 1.** X-ray structures of *N*- and *C*-metalated nitriles.

Inductive stabilization of metalated nitriles creates two potential metal-coordination sites: at the nitrile nitrogen and at the adjacent anionic carbon (Figure 1, compare **3** and **4**).

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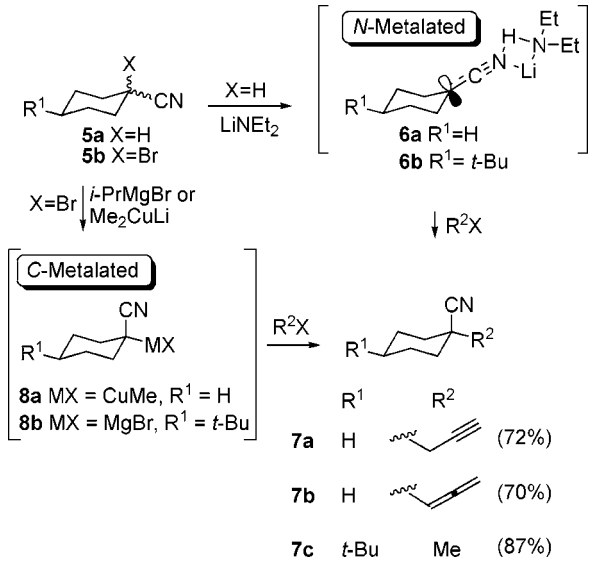
Extensive solid state[6] and solution[8] analyses reveal that lithiated nitriles exhibit a distinct preference for *N* coordination with a planar geometry at the formally anionic carbon (**1**, Figure 1).[9] In contrast, the sodiated nitrile **2** is *N*-metalated and partially pyramidal, typifying the range of solid-state structures observed for metalated nitriles.[10] Metalated nitriles with transition-metal counterions show an almost equal propensity for *C* and *N* coordination[11] with several *N*-metalated nitriles having ruthenium[12] or palladium[13] counterions, such as **3**, being converted to their thermodynamically more stable *C*-metalated counterparts, **4**, upon heating. The geometry and coordination of synthetically valuable magnesiated[14] and zincated nitriles[15] remain to be determined by crystallography, although NMR and IR analyses indicate *C* metalation in both cases.[14−16]

Distinctly different regio- and stereoselectivity preferences emanate from *N*- and *C*-metalated nitriles. For example, intercepting the putative[8] *N*-lithiated nitrile **6a** with propargyl bromide affords alkynenitrile **7a** through an $S_N2$ displacement (Scheme 1), whereas alkylation of the analogous *C*-cuprated nitrile **8a** with propargyl bromide gives the $S_N2'$ allenylnitrile **7b**.[14a] Similarly, alkylations of the *N*-lithiated, conformationally locked nitrile **6b** are only modestly diastereoselective, with preferential equatorial methylation affording **7c** in a 2.8:1 ratio (86%).[17] In contrast, alkylation of the putative *C*-magnesiated nitrile **8b** affords **7c**, exclusively, under otherwise identical conditions (Scheme 1).[14b]

**SCHEME 1. Divergent Regio- and Stereoselectivities of *N*- and *C*-Metalated Nitriles**




The excellent alkylation stereoselectivities of *C*-metalated nitriles highlights the potential of configurationally stable, chiral, *C*-metalated nitriles. Experimentally, overcoming the difficulty of synthesizing *C*-magnesiated nitriles is possible by employing internal coordination to favor formation of pyramidal, *C*-magnesiated nitriles.[18] Remarkably, the resulting *C*-magnesiated nitriles exhibit electrophile-dependent alkylation stereoselectivities previously unprecedented in alkylations of metalated nitriles.[19] Comprehensively surveying the alkylations of cyclic *C*-magnesiated nitriles establishes key electrophile-dependent alkylation trends, reveals the scope of the reaction, and delineates the fundamental stereoelectronic effects responsible for the unusual stereoselectivity preferences.

## Results and Discussion

The synthesis of an asymmetric, *C*-magnesiated nitrile was probed by deprotonating a cyclohexanecarbonitrile capable of strong internal coordination. Direct formation of magnesiated nitriles is challenging because magnesium amides do not effectively deprotonate aliphatic nitriles,[20] whereas Grignard reagents typically[21] add to, as well as deprotonate, unactivated nitriles.[22] Conceptually, selective deprotonation of nitriles with Grignard reagents is possible by rapidly forming an alkylmag-

(7) Le Questel, J.-Y.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2000**, *13*, 347. The bond length is the mean of the CN distance obtained from 5059 nitriles in the Cambridge Structural Database.

(8) (a) Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798. (b) Carlier, P. R.; Lo, C. W.-S. *J. Am. Chem. Soc.* **2000**, *122*, 12819. (c) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.

(9) The sole exception is a structurally biased lithiated cyclopropanecarbonitrile, where *N* and *C* coordination occur in a polymeric ladder structure: Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925.

(10) For computed structural differences in the extent of *C* and *N* coordination for lithiated, sodiated, and magnesiated acetonitrile, see: Kaneti, J.; Schleyer, P. V. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Andrade, J. G.; Moffat, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 1481.

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(12) For an analogous interconversion of ruthenium complexes, see: Naota, T.; Tannna, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2000**, *122*, 2960.

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(14) (a) Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845. (b) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200. (c) Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787. (d) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319.

(15) Orsini, F. *Synthesis* **1985**, 500.

(16) Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1972**, *39*, 17.

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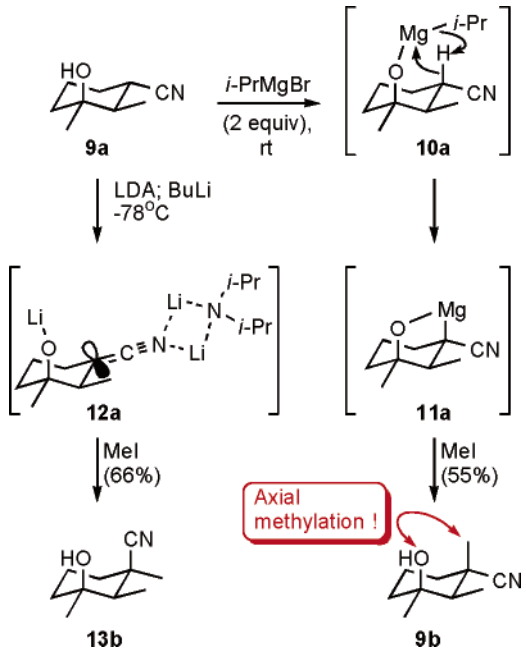
(18) For a preliminary account, see: Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *Org. Lett.* **2005**, *7*, 447.

(19) For an excellent discussion of electrophile-dependent alkylations of chiral organolithiums, see: Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, The Netherlands, 2002; Chapter 6.

**SCHEME 2. Stereodivergent Alkylations of *N*- and *C*-Magnesiated Nitriles**

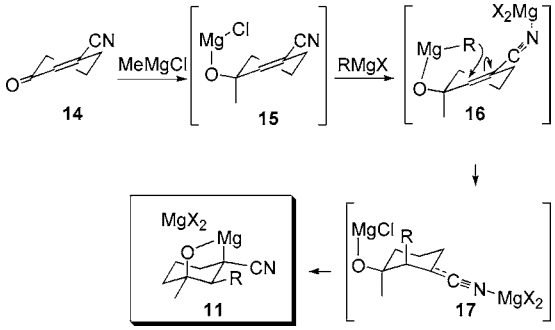



nesium alkoxide[23] in which coordination directs internal proton abstraction *and* geometrically prevents internal alkyl delivery to the electrophilic nitrile group (**9a** → **10a**, Scheme 2). In practice, sequential addition of *i*-PrMgBr and methyl iodide to hydroxy nitrile **9a**[24] affords exclusively the *axially* methylated nitrile **9b**, which is in direct contrast to the usual[25] equatorial alkylation of *N*-lithiated cyclohexanecarbonitriles (compare with Scheme 1).

The remarkable installation of a 1,3-diaxial interaction, overriding typical steric preferences,[25] implies that stereoelectronic effects direct the retentive alkylation via the *C*-magnesiated nitrile **11a**. Support for the intermediacy of the *C*-magnesiated nitrile **11a** stems from the stereodivergent methylation of the corresponding *N*-lithiated nitrile **12a**, where steric effects are the sole determinant of the alkylation stereochemistry. Deprotonating **9a** with LDA, followed by the addition of BuLi to prevent internal proton return,[26] generates the *N*-lithiated nitrile **12a**[8] that alkylates methyl iodide exclusively[27] from the sterically more accessible equatorial direction to afford **13b** (Scheme 2). The stereodivergent alkylations of the *C*- and *N*-metalated nitriles **11a** and **12a** stimulated a comprehensive series of alkylations of *C*-magnesiated nitriles with an array of electrophiles.

***C*-Magnesiated Nitrile Alkylations with Alkyl Halides.** Rapid access to different *C*-magnesiated nitriles was conveniently achieved through sequential 1,2−1,4 Grignard additions[28] to 3-oxocyclohex-1-ene-1-carbonitrile (**14**,[29] Scheme 3). The addition of methylmagnesium chloride to **14** generates the halomagnesium alkoxide **15**, which exchanges[23a] with a second Grignard reagent to afford **16** that, in turn, triggers a conjugate addition[30] to the alkenenitrile functionality. The resulting bismagnesiated nitrile **17** is conformationally destabilized by the two axial alkyl substituents, favoring equilibration to the *C*-magnesiated nitrile **11** (cf. **11a**, Scheme 2).

**SCHEME 3. Sequential 1,2−1,4 Grignard Additions to Oxonitrile 14**




Alkylating the *C*-magnesiated nitrile **11** with an array of electrophiles reveals a remarkable electrophile-dependent stereoselectivity (Table 1).[19,31] Prior coordination between the electrophile and the magnesium atom of **11** does not appear to control the stereoselectivity,[32] because alkylation with $Me_2SO_4$, an electrophile capable of metal-directed alkylation,[33] affords exactly the same axially methylated nitrile **9b** as that obtained by alkyating with MeI (Table 1, entries 1 and 2). Intercepting **11** with the more sterically demanding propyl iodide maintains the preference for axial alkylation despite the increased steric compression relative to alkylation with MeI (Table 1, entry 3). Alternatively, increasing the steric demand in the methylation by incorporating a phenyl group adjacent to the magnesiated

(20) Unpublished results with BrMgN-*i*-$Pr_2$ and BuMgN-*i*-$Pr_2$. For deprotonations with BuMgN-*i*-$Pr_2$, see: Zhang, M.-X.; Eaton, P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169.

(21) (a) Sumrell, G. *J. Org. Chem.* **1954**, *19*, 817. (b) Hauser, C. R.; Humphlett, W. J. *J. Org. Chem.* **1950**, *15*, 359. (c) For an exception, see: Fauvarque, J.-F.; Meklati, B.; Dearing, C. *C. R. Chim.* **1968**, *267*, 1162.

(22) For the deprotonation of phenyl acetonitrile, see: (a) Ivanov, C.; Markov, P.; Arnaudov, M. *Chem. Ber.* **1967**, *100*, 690. (b) Ivanov, C.; Markov, P.; Arnaudov, M. *Chem. Ber.* **1964**, *97*, 2987.

(23) (a) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393. (b) Turova, N. Y.; Turevskaya, E. P. *J. Organomet. Chem.* **1972**, *42*, 9.

(24) Cyclic nitrile **9a** can be prepared through the conjugate addition of MeMgCl to 3-hydroxy-3-methylcyclohex-1-enecarbonitrile or, more conveniently, by sequential 1,2−1,4 addition to oxonitrile **14** (vide infra). Fleming, F. F.; Wang, Q.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* **2002**, *67*, 5953.

(25) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.

(26) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed.* **1989**, *28*, 1392. Deprotonating **9a** with LDA (2 equiv), followed by the addition of MeI, affords a mixture of **9a**, **13a**, and **13b**. Analogously, deprotonating **9a** with $ClMgNEt_2$ (2 equiv), followed by the addition of MeI, afforded mainly the nitrile **9a** with **13b** as a minor component, whereas deprotonating **9a** with $ClMgNEt_2$ (2 equiv), followed by the addition of MeMgCl (2 equiv) prior to the addition of MeI, gave **13b** (27%) and **9a** and **13a** (2.2:1, 28%), implying incomplete sequestration of the complexed $HNEt_2$.

(27) $^1$H NMR analysis of the crude reaction mixture failed to identify any of the diastereomer **9b**.

(28) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126.

(29) Fleming, F. F.; Zhang, Z.; Wei, G. *Synthesis* **2005**, 3179.

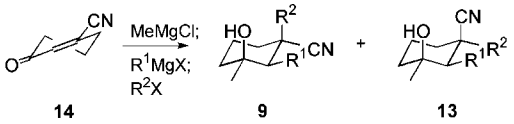
(30) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235.

(31) Electrophile-dependent alkylations are relatively rare but often occur with chiral, tertiary, benzylic and allylic organolithiums. Collectively, the occurrence of electrophile-dependent stereoselectivity implies the intermediacy of a chiral organometallic intermediate, in this case, the asymmetric *C*-magnesiated nitrile **11**. (a) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 717.

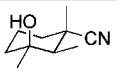
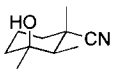
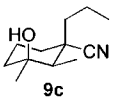
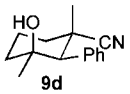
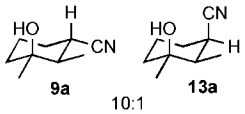
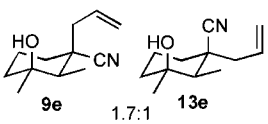
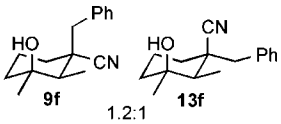
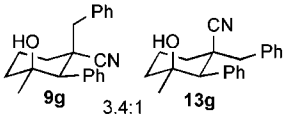
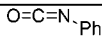
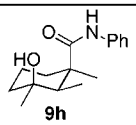
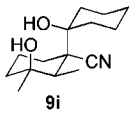
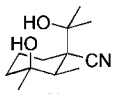
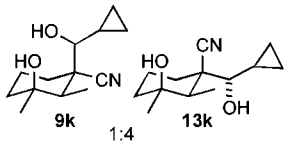
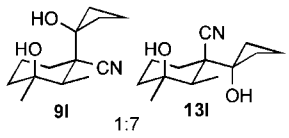
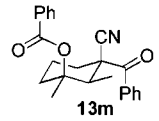
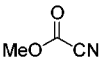
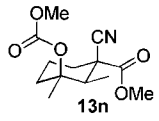
(32) The Mg−O bond exhibits considerable back-bonding, which dramatically reduces the Lewis acidity of the metal, making prior coordination with the electrophile unlikely: Richey, H. G. *Grignard Reagents: New Developments*; Wiley: New York, 2000; Chapter 1, p 4.

(33) (a) Meyers, A. I.; Knaus, G. *J. Am. Chem. Soc.* **1974**, *96*, 6508. (b) Chassaing, G.; Lett, R.; Marquet, A. *Tetrahedron Lett.* **1978**, 471. For an excellent discussion of the mechanism of these formally forbidden alkylations, see: Hill, E. A. *J. Organomet. Chem.* **1975**, *91*, 123.

**TABLE 1. Electrophile-Dependent Alkylations of *C*-Magnesiated Nitriles**




**14** **9** **13**

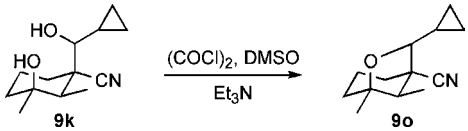
| Entry | Grignard Reagent $R^1MgX$; $R^2MgX$ | Electrophile | Nitrile[a] | Yield[b] |
|---|---|---|---|---|
| 1 | MeMgCl (excess) | MeI |  **9b** | 86% |
| 2 | MeMgCl (excess) | $Me_2SO_4$ |  **9b** | 57% |
| 3 | MeMgCl (excess) |  |  **9c** | 70% |
| 4 | MeMgCl; PhMgCl | MeI |  **9d** | 71% |
| 5 | MeMgCl (excess) | $NH_4Cl$ |  **9a** 10:1 **13a** | 90% |
| 6 | MeMgCl (excess) |  |  **9e** 1.7:1 **13e** | 71% |
| 7 | MeMgCl (excess) | BnBr |  **9f** 1.2:1 **13f** | 71% |
| 8 | MeMgCl; PhMgCl | BnBr |  **9g** 3.4:1 **13g** | 61% |
| 9 | MeMgCl (excess) |  |  **9h** | 58% |
| 10 | MeMgCl (excess) |  |  **9i** | 68% |
| 11 | MeMgCl (excess) |  |  **9j** | 64% |
| 12 | MeMgCl (excess) |  |  **9k** 1:4 **13k** | 55%[c] |
| 13 | MeMgCl (excess) |  |  **9l** 1:7 **13l** | 59%[d] |
| 14 | MeMgCl (excess) |  |  **13m** | 55% |
| 15 | MeMgCl (excess) |  |  **13n** | 61% |

[a] Unless stated otherwise, the stereochemical assignments are based on X-ray crystallographic analysis. [b] Represents the overall 3-step yield for 1,2 addition; 1,4 addition; and alkylation. [c] The cyclopropylmethyl stereochemistry was assigned by intramolecular etherification to **9o**.[34] [d] Stereochemical assignments are based on the downfield shift of an equatorial nitrile carbon in the $^{13}C$ NMR spectra.[35]

nitrile-bearing carbon still furnishes the axially methylated nitrile (Table 1, entry 4).

Despite significant steric compression, the *C*-magnesiated nitrile **11** consistently intercepts alkyl halides and sulfonates with an exclusive preference for axial alkylation. Axial alkylation of the *C*-magnesiated nitrile **11** requires a side-on overlap of the electrophilic $\sigma^*$ orbital with the large lobe of the metal carbon $\sigma$ bond[36] in a retentive, electrophilic substitution, $S_E2_{(ret)}$[37] (Scheme 4, **11a″**). Although the side-on orbital overlap is far from optimal, the alternative collinear approach of an $sp^3$ hybridized electrophile to the small $\sigma$ lobe of the C−Mg bond is sterically prohibitive (Scheme 4, **11a′**).[37] Reducing the side-on orbital overlap by alkylating **11a** with PrBr, having a smaller $\sigma^*$ orbital, is considerably more difficult[38] than with PrI, leading

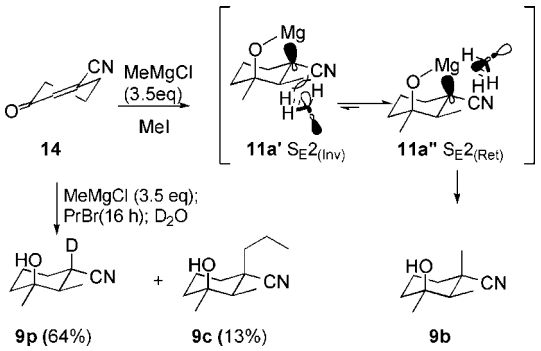
(34) The attempted oxidation of **9k** afforded the cyclic ether **9o**, presumably by the ionization of an activated cyclopropyl alcohol, followed by an internal cyclization, as shown below.




**9k** **9o**

(35) Bailey, W. F.; Cioffi, A. *Magn. Reson. Chem.* **1987**, *25*, 181.
(36) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.
(37) For an excellent overview of terms, steric constraints, and orbital overlap, see: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.

**SCHEME 4. Stereoelectronic $S_E2_{(ret)}$ Alkylations of Metalated Nitriles**

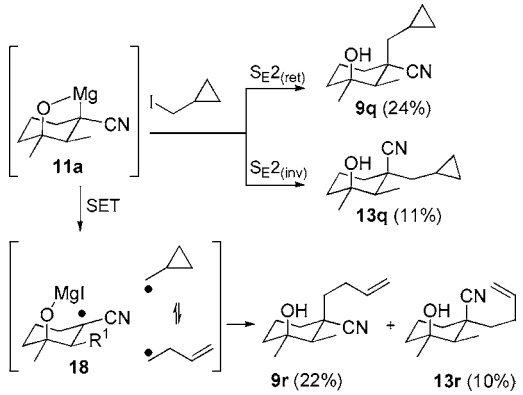



to incomplete alkylation (13% of **9c** for PrBr compared to 70% for PrI). The reactivity difference is not due to a competitive $E_2$ elimination with PrBr, because the addition of $D_2O$ results in high deuterium incorporation from the axial direction, analogous to preferential axial protonation upon the addition of aqueous $NH_4Cl$ (Table 1, entry 5).[39] Collectively, these comparative alkylations indicate that *C*-magnesiated nitriles require the more reactive alkyl iodides as electrophiles, because incomplete alkylation occurs with the less reactive alkyl bromides.

The retentive alkylations of *C*-magnesiated nitriles with alkyl halide and sulfonate electrophiles contrast with the nonselective alkylations of **11** with allyl and benzyl bromide (Table 1, entries 6−8). Conceptually, the more reactive benzylic and allylic electrophiles, having larger $\sigma^*$ orbitals, might be able to access the small lobe of the Mg−C $\sigma$ bond for alkylation through an $S_E2_{(inv)}$ mechanism, in addition to a side-on $S_E2_{(ret)}$ alkylation (cf. **11a′** and **11a″**, Scheme 4). Alternatively, a single-electron transfer (SET) from the electron-rich *C*-magnesiated nitrile **11**, formally a dianion, could generate a radical cation and an alkyl bromide radical anion.[40] Subsequent bromide ejection from the radical anion and nonselective radical−radical recombination would account for the mixture of diastereomers.

Differentiating between these mechanistic scenarios was achieved through alkylations with cyclopropylmethyl iodide (Scheme 5).[41] Cyclopropylmethyl iodide is a useful mechanistic probe;[42] cyclopropylmethyl substitution provides evidence for an ionic $S_N2$ displacement, whereas butenyl alkylation, through SET, ring opening, and radical−radical recombination (**18**), indicates radical formation (Scheme 5).[43] Experimentally, alkylating **11a** with cyclopropylmethyl iodide affords approximately equal ratios of cyclopropylmethyl carbonitriles (**9q** and **13q**) and but-3-enyl carbonitriles (**9r** and **13r**), implying that a combination of electrophilic $S_E2_{(inv)}$ and $S_E2_{(ret)}$ alkylations compete with SET processes.[44] A similar mechanistic scenario accounts for the diastereomers generated during alkylations with allyl and benzyl bromide (Table 1, entries 6−8).

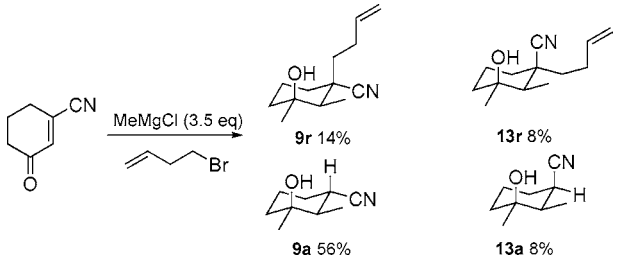
**SCHEME 5. Mechanistic Probe for *C*-Metalated Nitrile Alkylations**




***C*-Magnesiated Nitrile Alkylations with Carbonyl Electrophiles.** Carbonyl electrophiles exhibit an extremely delicate stereoselectivity dependence in alkylations with the *C*-magnesiated nitrile **11** (Table 1, entries 9−15).[45] Alkylations with phenyl isocyanate, cyclohexanone, and acetone proceed with exclusive retention of configuration (Table 1, entries 9−11), whereas cyclopropanecarboxaldehyde and cyclobutanone afford primarily the nitriles resulting from equatorial alkylation (Table 1, entries 12 and 13).[46] In contrast, magnesiated nitrile **11a** reacts with excess methyl cyanoformate and benzoyl cyanide to afford bisacylated nitriles in which *C* acylation occurs only from the equatorial direction (Table 1, entries 14 and 15).

A tentative explanation for the stereoselectivity differences exhibited in alkylations of **11** with carbonyl electrophiles emerges by comparing the reactivity of the $\pi^*$ orbitals. Particularly reactive carbonyl electrophiles with large, diffuse $\pi^*$ orbitals, such as methyl cyanoformate and benzoyl cyanide, exert a sufficiently small steric demand to permit a collinear approach to the small $\sigma$ lobe of the C−Mg bond (**11a‴**, Figure 2). The collinear trajectory, while more hindered than the side-on axial approach, benefits from a more favorable orbital overlap. Carbonyl electrophiles with a large steric demand, such

(38) An analogous alkylation of **11a** with 4-bromobutene similarly affords only 22% of the corresponding alkylated nitriles **9r** and **13r**, with the protonated nitriles **9a** and **13a** predominating.




(39) The minor equatorial protonation isomer, **13b**, may arise through a sterically accessible $S_E2_{(inv)}$ attack (cf. **11a′**).

(40) For SET reactions of metalated nitriles, see: (a) Werry, J.; Stamm, H.; Sommer, A. *Chem. Ber.* **1990**, *123*, 1553. (b) Roux-Schmitt, M.-C.; Pettit, A.; Sevin, A.; Seyden-Penne, J.; Anh, N. T. *Tetrahedron* **1990**, *46*, 1263. (c) Chauffaille, J.; Hebert, E.; Welvart, Z. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1645. For SET reactions of Grignard reagents, see: (d) Hill, E. A. In *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, England, 2000; Chapter 1, pp 43−45.

(41) No alkylation of **11a** is observed with the less reactive, but commercially available, cyclopropylmethyl bromide.

(42) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.

(43) Butenyl alkylation is, in some cases, possible through $S_N2''$ alkylation: Alnajjar, M. S.; Smith, G. F.; Kuivila, H. G. *J. Org. Chem.* **1984**, *49*, 1271.

(44) Numerous alkylations of **11a** with cyclopropylmethyl iodide identified a distinct mechanistic dependence on the quality of the MeMgCl employed in the 1,2−1,4 addition. In preliminary studies,[18] the use of low titre MeMgCl afforded almost exclusively the cyclopropylnitriles **9q** and **13q** (53%) and only a trace amount of the butenylnitriles **9r** and **13r**. Presumably, the presence of alkoxide species causes a change in the nature of the reactive magnesiated nitrile, which has minimal propensity toward SET.

(45) No alkylation was observed between **11a** and DMF, methyl benzoate, or dimethyl carbonate.

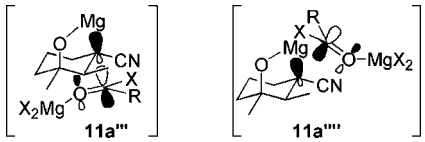
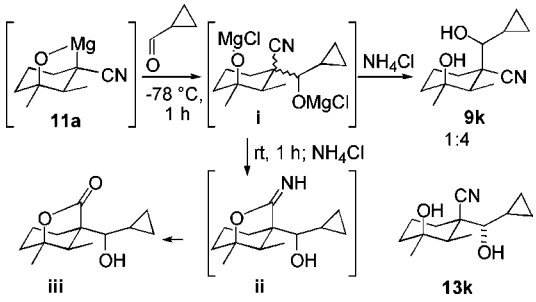



**FIGURE 2.** Stereoelectronic control with carbonyl electrophiles.

as cyclohexanone, are unable to achieve sufficient proximity for overlap in a collinear equatorial approach and preferentially alkylate by side-on overlap (**11a⁗**, Figure 2).

The difference in the sizes of the $\pi^*$ orbitals effectively explains the rather perplexing 7:1 preference for the equatorial alkylation with cyclobutanone and the axial alkylation with acetone (Table 1, entries 13 and 11, respectively). The larger $\pi^*$ orbital of cyclobutanone[47] permits a more facile $S_E2_{(inv)}$ by more effectively interacting with the small $\sigma$ lobe in **11a⁗** than acetone, which has a similar steric demand but a smaller $\pi^*$ orbital and, therefore, preferentially alkylates only from the axial orientation. Acylations with methyl cyanoformate and benzoyl cyanide, particularly electron deficient electrophiles with large $\pi^*$ orbitals, similarly react through $S_E2_{(inv)}$ processes.[45]

(46) Control experiments, in which the temperature was raised to room temperature, cause equilibration of the intermediate alkoxy nitrile, whereas quenching the reaction at −78 °C retains the stereochemical integrity of the first-formed alkoxy nitriles: Carlier, P. R.; Lo, C. W.-S.; Lo, M. M.-C.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443. For example, in the alkylation of **11a** with cyclopropanecarboxaldehyde, elevating the reaction to ambient temperature causes an equilibration to a mixture of nitriles **9k** and **13k** and two diastereomeric lactones, **iii**. Presumably, higher temperatures facilitate not only retro-aldol fragmentation but also attack of the adjacent magnesium alkoxide onto the nitrile to generate **ii**, which hydrolyzes to **iii**.




(47) An indication of the difference is provided by the stretching frequency of cyclobutanone, 1775 $cm^{-1}$, and acetone, 1715 $cm^{-1}$: Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989; p I125.

## Conclusion

Alkylations of *C*-magnesiated nitriles exhibit an unprecedented stereoselectivity dependence on the nature of the electrophile. *C*-Magnesiated nitriles efficiently alkylate alkyl iodides and sulfonates with retention of stereochemistry, whereas acylations with aldehyde and acyl cyanide electrophiles occur with inversion of stereochemistry. Mechanistic probes indicate that the alkylations of *C*-magnesiated nitriles are primarily controlled by stereoelectronic effects, depending intimately on the size of the antibonding $\sigma^*$ or $\pi^*$ orbital. Allyl and benzyl bromide and cyclopropylmethyl iodide are exceptions in which SET processes compete with substitution reactions.

The stereoelectronically controlled alkylations of *C*-magnesiated nitriles are stereochemically complementary to the sterically controlled alkylations of *N*-metalated nitriles. Synthetically, these two divergent strategies permit selective installation of diastereomeric quaternary centers from a single metalated nitrile.

## Experimental Section[48]

**General Grignard Addition−Alkylation Procedure.** A THF solution of the Grignard reagent (2 equiv) was added to a −78 °C THF solution (0.1 M) of 3-oxocyclohex-1-ene-1-carbonitrile (**14**).[29] After 1 h at −78 °C, a THF solution of the second Grignard reagent (1.5 equiv) was added, or for reactions with only one Grignard reagent, 3.5 equiv was added initially. The mixture was stirred at −78 °C for 10 min and then warmed to room temperature. After 1.5 h, the electrophile (3 equiv) was added neat, either at room temperature or with prior cooling to −78 °C. A subsequent addition of saturated $NH_4Cl$ and an extraction with EtOAc afforded a crude product that was washed with brine and dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford the pure nitrile.

**Acknowledgment.** Financial support of this research from NSF and, in part, NIH is gratefully acknowledged. Support for the X-ray facility from NSF (CRIF 0234872) is gratefully acknowledged, as is assistance from Dr. Charles Campana in solving the X-ray structure of **9h**.

**Supporting Information Available:** Experimental procedures, $^1H$ NMR and $^{13}C$ NMR spectra for all new compounds, and CIF and ORTEPs for all structures assigned by X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052102J

(48) For general experimental procedures, see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.