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γ-Hydroxynitrile Alkylations: Electrophile-Dependent Stereoselectivity†

Robert J. Mycka, Omar W. Steward, and Fraser F. Fleming*

Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282-1530

flemingf@duq.edu

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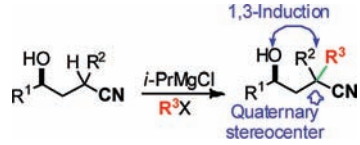
ABSTRACT



Quaternary centers are efficiently installed in chelation-controlled alkylations of acyclic hydroxynitriles. Intriguingly, the stereoselectivity is determined by the nature of the electrophile *and* the structure of the Grignard used for the deprotonation. The alkylation strategy addresses the long-standing difficulty of performing diastereoselective alkylations with conformationally mobile, acyclic nitriles.

Stereoselective alkylations of *acyclic*, metalated nitriles are particularly challenging.[1] The difficulty stems from three different features of acyclic, metalated nitriles: the rapid epimerization of C-metalated nitriles;[2] the structure of the CN unit which precludes direct attachment of a chiral auxiliary[3] and positions chiral lithium-complexing ligands remote from the nucleophilic carbon;[4] and the inherent flexibility of rotatable single bonds in metalated alkanenitriles.[5] Restricting the conformational mobility of acyclic nitriles through the influence of allylic strain can allow highly stereoselective alkylations with metalated nitriles bearing an adjacent chiral center.[6] However, positioning the chiral center on the more remote γ-carbon lowers the diastereoselectivity into the range of 3−5:1.[5]

Temporary internal chelation appeared to be an ideal strategy[7] for diastereoselectively alkylating acyclic metalated nitriles because transiently forming a cyclic chelate between the metalated carbon and a substituent on the γ-carbon would limit conformational mobility during the alkylation event and return an alkylated, acyclic nitrile. Experimentally, the chelation-controlled deprotonation of several hydroxynitriles **1** with 5 equiv of RMgCl provides competent nucleophiles that efficiently intercept alkylhalides (Table 1). Alkylating the metalated nitriles derived from **1a**−**1c** with propyl iodide as a probe shows an increasing stereoselectivity as the steric demand increases at the γ-carbinol center (Table 1, entries 1−3). Alkylating hydroxynitrile **1d** with MeI, in which the α-substituent of the nitrile and the alkyl group of the electrophile are interposed relative to **1c** (Table 1, entry 3), affords nitrile **2d**, the diastereomer of **2c** (Table 1, entry 4).

† Dedicated to friend and chemist Louis DeSimone.

(1) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.

(2) (a) Carlier, P. R.; Zhang, Y. *Org. Lett.* **2007**, *9*, 1319. (b) Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845.

(3) For chiral auxiliaries bearing an adjacent nitrile group, see: (a) Partogyan-Halim, K.; Besson, L.; Aitken, D. J.; Husson, H.-P. *Eur. J. Org. Chem.* **2003**, 268. (b) Cativiela, C.; Diaz-de-Villegas, D. M.; Galvez, A. J.; Lapena, Y. *Tetrahedron* **1995**, *51*, 5921. (c) Cativiela, C.; Diaz-de-Villegas, D. M.; Galvez, A. J. *J. Org. Chem.* **1994**, *59*, 2497. (d) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463. (e) Maigrot, N.; Mazaleyrat, J.-P.; Welvart, Z. *J. Org. Chem.* **1985**, *50*, 3916.

(4) (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147. (b) Carlier, P. R.; Lam, F. W.; Wan, C. N.; Williams, D. I. *Angew. Chem., Int. Ed* **1998**, *37*, 2252. (c) Brunner, H.; Zintl, H. *Monatsh. Chem.* **1991**, *122*, 841. (d) Mi, Q. A.; Wang, Y. Z.; Jiang, Z. Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1957. (e) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677. (f) Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3371.

(5) Fleming, F. F.; Liu, W. *Eur. J. Org. Chem.* **2009**, 699.

(6) Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 2803.

(7) Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917.

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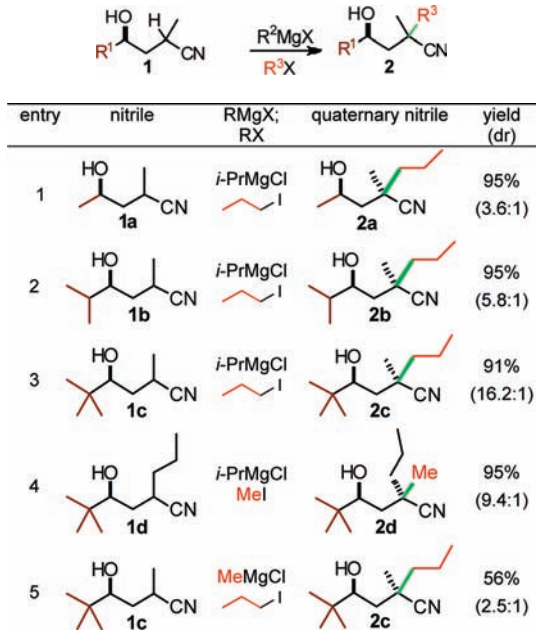
Table 1. Diastereoselective Alkylations of γ-Hydroxynitriles[a]



[a] All alkylations were performed in THF with excess Grignard and electrophile at −78 °C followed by warming to rt.

The decrease in stereoselectivity between these two alkylations suggests that propyl iodide is more selective in alkylating the magnesiated nitrile than the smaller, more reactive methyl iodide. Particularly remarkable is the decreased stereoselectivity for the alkylation of **1c** with propyl iodide when the deprotonation is performed with excess MeMgCl[8] rather than *i*-PrMgCl (Table 1, entries 5 and 3, respectively).[9]

The influence of the Grignard reagent on stereoselectivity implies an unusual incorporation of the Grignard-derived alkyl group within the magnesiated nitrile structure.[10] Assuming alkylation from a C-magnesiated nitrile, hydroxynitrile **1c** was alkylated with a range of alkyl halide, sulfide, and carbonyl electrophiles because an electrophile-dependent stereoselectivity appears to be a signature for C-metalated nitriles.[11] By determining the configuration at each newly installed quaternary center,[12] the alkylations of **1c** were found to fall into three distinct categories: *syn*-selective alkylations, nonselective alkylations, and *anti*-selective alkylations (Figure 1).

Compared to the alkylation of **1c** with propyl iodide, the more reactive, but sterically similar, electrophiles allyl and propargyl bromide alkylate with the same relative stereochemical sense but with reduced selectivity (Figure 1, left column, **2e** and **2f**, respectively). Comparable sulfenylations with diphenyl disulfide and *S*-phenyl benzenethiosulfonate (Figure 1, bottom row) show disparate selectivity trends with only the former being selective.

Neither the alkylation with benzaldehyde nor the acylation with methyl cyanoformate is selective (Figure 1, central column, **2h** and **2i**, respectively). In the latter case, formation of lactone **2i** presumably results from an internal attack of the magnesium alkoxide on the intermediate ester.[13]

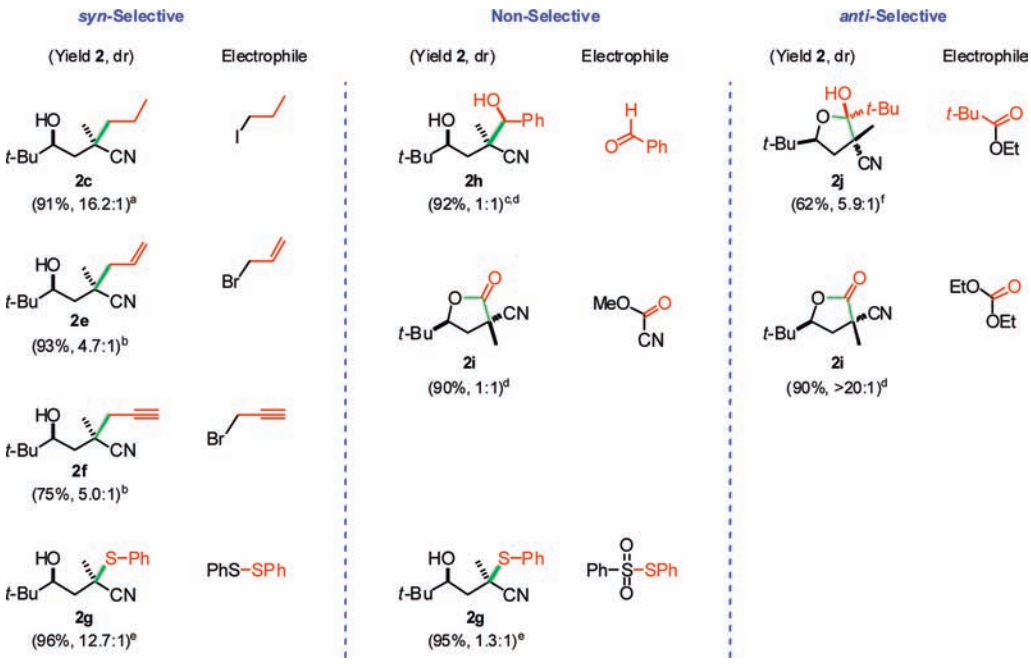
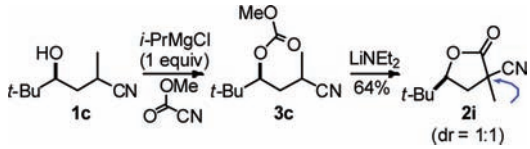


Figure 1. Electrophile-dependent alkylations of γ-hydroxynitrile **1c**. [a]Configuration determined by NOE correlations in the lactone obtained by treatment with NaHMDS (see the Supporting Information for a complete description). [b]Configuration determined by chemical correlation. [c]The diastereomer is a 1:1 mixture at the benzylic methine. [d]Configuration determined by X-ray crystallography. [e]Configuration determined by NOESY of a derivative. [f]Configuration determined by NOESY.

Remarkably, alkylating the metalated nitrile derived from **1c** with ethyl pivalate affords a 5.9:1 ratio of *anti* diastereomers with the nitrile-bearing carbon having the stereochemical sense opposite to that of the alkylhalide electrophiles (**2j** Figure 1, right column)! Perhaps more unusual is the alkylation with diethylcarbonate which affords the lactone **2i** with excellent *anti* stereoselectivity in direct contrast to the nonselective acylation with methyl cyanoformate (cf. Figure 1, middle row, middle and right columns). The distinctly different ratios for acylations with methyl cyanoformate and diethyl carbonate are not compatible with O-acylation followed by an intramolecular alkylation as the two intermediate magnesiated nitriles would be expected to give the same lactone in virtually identical ratios.

As a mechanistic probe to determine the origin of the stereoselective acylations, the carbonate **3c** was prepared and cyclized (Scheme 1). Deprotonating **3c** with $LiNEt_2$[14] affords

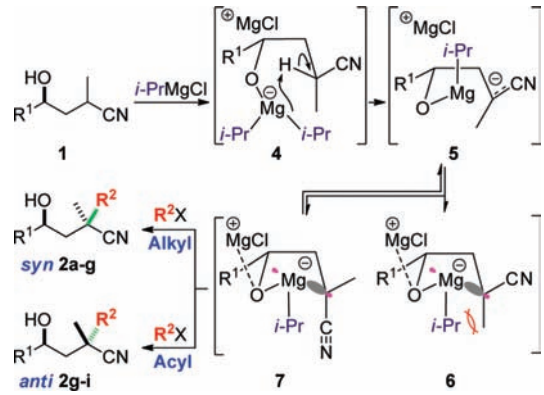
Scheme 1. Probe for a Cyclic Magnesiated Nitrile Intermediate



a 1:1 mixture of lactones **2i** implying that the stereochemistry does not arise from O-acylation and an internal attack on a conformationally biased carbamate.

The electrophile-dependent stereoselectivity has not previously been observed in alkylations of *acyclic* nitriles or even acyclic magnesiated nitriles bearing an adjacent chiral center.[15] Electrophile-dependent alkylations have only been observed once before with constrained, cyclic C-magnesiated nitriles.[11b] Furthermore, the unique influence of the Grignard reagent on the stereoselectivity implies direct attachment of magnesium to the nucleophilic carbon (Table 1, entries 1−4 vs entry 5). Formation of a C-magnesiated nitrile is further supported by the divergent selectivities for alkylations with methyl cyanoformate and diethyl carbonate (Figure 1) and the nonselective cyclization of the carbonate **3c** (Scheme 1). A working mechanism consistent with the observations is for alkylation via the cyclic magnesiated nitrile **6** or **7** (Scheme 2).

Scheme 2. Tentative Diastereoselectivity Mechanism



Experimentally, at least 4 equiv of Grignard is required to deprotonate the hydroxynitriles **1** (Scheme 2).[16] An amount of 1 equiv of *i*-PrMgCl is expended to remove the hydroxyl proton. Presumably, excess Grignard is required to access the magnesiate **4** which abstracts the proximal, acidic methine. Formation of **5** allows collapse to the isopropyl-containing C-magnesiated nitrile **6** or, with prior bond rotation, collapse to **7**.

Pinpointing the configuration of the magnesiated nitrile is difficult. Although speculative, the electron-rich alkyoxy oxygen might complex a chloromagnesium cation[17] on the face opposite the carbinol substituent R to favor **7** with an alternating substitution pattern around the five-membered chelate. Retentive alkylation and invertive acylation from **7** would relay the stereochemistry to *syn*-**2a**−**g** and *anti*-**2h**,**i**, respectively (Scheme 2).[18] Alternatively, invertive alkylation and retentive acylation from **6** translate to the same net configuration. The absence of clear alkylation trends[19] for this type of "chiral organometallic" leaves the configuration of the magnesiated nitrile **6** or **7** an open question. Particularly reactive electrophiles such as methyl cyanoformate are presumably capable of nonselectively reacting by both retentive and invertive modes.

Consistent with the mechanistic proposal is the acylation of **1c** with ethyl isobutyrate (Scheme 3). Intercepting the putative C-magnesitated nitrile **8** with ethyl isobutyrate affords solely[20] the dihydroxynitrile **10c** whose configuration

(8) The same diastereoselectivity was observed with MeMgBr indicating that there is no influence from the halide. This implies that the halide is not contained within the magnesiated nitrile nucleophile.

(9) Attempts to enhance the selectivity by using *t*-BuMgCl (5 equiv) or combinations of *t*-BuMgCl and *i*-PrMgCl were plagued by incomplete deprotonation.

(10) Intercepting the magnesiated nitrile derived from **1c** with ethyl isobutyrate generates dihydroxynitrile **10c** through a stereoselective reduction that similarly implies incorporation of an isopropyl group within the metalated nitrile (Scheme 3).

(11) Although organolithiums[a] can exhibit electrophile-dependent stereoselectivity, only one case with a conformationally constrained magnesiated nitrile exhibits this type of stereoselectivity.[b] (a) For an excellent discussion of related alkylations with chiral organolithiums, see: Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002; *Ch.6*. (b) Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430.

(12) The stereochemistry for each product was determined by X-ray crystallography (**2h**, **2i**), NOESY (**2g**, **2j**), NOE (**2c**), or chemical correlations (**2e**, **2f**) as described in the Supporting Information.

(13) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351.

(14) Unfortunately, methods do not currently exist for generating the magnesiated nitrile from **3c** for a direct comparison.

(15) Presumably, the strong steric shielding in these systems overides an electrophile-dependent stereoselectivity.[6]

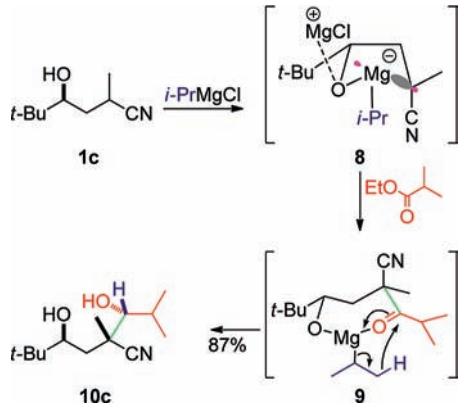
(16) Incomplete deprotonation was observed with combinations of RLi or R_2NLi and RMgX.

(17) (a) Layfield, R. A.; Bullock, T. H.; Garcia, F.; Humphrey, S. M.; Schueler, P. *Chem. Commun.* **2006**, 2039. (b) Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* **2001**, *3*, 1793.

(18) For an excellent overview of terms, steric constraints, and orbital overlap, see: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.

(19) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.

Scheme 3. Sequential Alkylation−Reduction with an Ester



was determined by crystallographic analysis (Figure 2). Acylation of **8** positions an electrophilic ketone in close proximity to the Grignard-derived isopropyl group (**9**). Internal hydride delivery[21] to the hindered ketone is presumably constrained by chelation which very selectively directs reduction from the *re* face. The reduction further supports the putative incorporation of a Grignard-derived alkyl group within the magnesiated nitrile.

Magnesiated nitriles are emerging as highly unusual nucleophiles. C-Magnesiated nitriles derived from γ-hydroxynitriles appear to behave essentially as chiral organometallics with the bridging magnesium atom incorporating an additional alkyl ligand from exogenous RMgCl. The alkylation stereoselectivities of these magnesiated nitriles are

(20) No diastereomers were discernable in the ^{1}H NMR spectrum of the crude reaction mixture.

(21) Dunn, G. E.; Warkentin, J. *Can. J. Chem.* **1956**, *34*, 75.

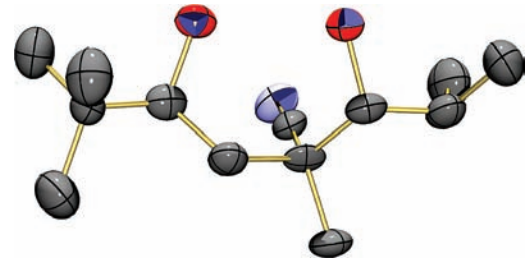


Figure 2. ORTEP of dihydroxynitrile **10c**.

dictated by the structure of the electrophile: alkyl halides afford *syn*-diastereomers, reactive carbonyl electrophiles alkylate nonselectively, whereas less reactive ester and carbonate electrophiles alkylate to afford *anti*-diastereomers. Collectively, these alkylations represent the first electrophile-dependent alkylations of *acyclic* nitriles, involve a highly unusual incorporation of a Grignard-derived alkyl group within the magnesiated nitrile, and address the challenge of installing quaternary centers in conformationally mobile, acyclic nitriles.

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Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all new compounds and ORTEPs of crystalline derivatives synthesized for configurational determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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