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Cyclic Nitriles: Diastereoselective Alkylations

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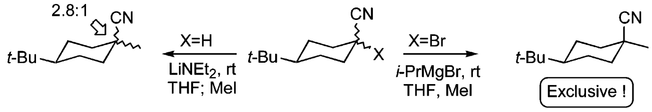

Diastereoselective alkylations of metalated conformationally locked 4-*tert*-butylcyclohexanecarbonitrile are highly diastereoselective with magnesium and copper counterions but only modestly diastereoselective with lithium as the counterion. Selective generation of diverse metalated nitriles is readily achieved through bromine−magnesium, −copper, and −lithium exchange reactions of the corresponding bromonitrile or, for lithium, by deprotonating the parent nitrile with lithium diethylamide. Collectively, high alkylation stereoselectivities correlate with the retentive alkylations of *C*-metalated nitriles, whereas *N*-lithiated nitriles alkylate with modest selectivity, reflecting minimal steric differences in the corresponding axial and equatorial electrophile trajectories.

α-Metalated nitriles are exceptional nucleophiles, ideally suited for stereoselective alkylations.[1] Alkylation stereoselectivities are governed by the powerful inductive stabilization[2] of metalated nitriles, which minimizes *N*-alkylation[3] and often leads to stereoselectivities complimentary to those achieved with resonance-stabilized enolates.[4] Inductive stabilization is evident from the X-ray[5] structures of metalated nitriles that consistently exhibit short C−CN bonds (1.36−1.45 Å, Figure 1), resulting from an electrostatic contraction between the formal carbanion and the adjacent electron-deficient nitrile. Analogously, minimal elongation of the C≡N bond is observed in numerous metalated nitriles, with the bond length being only slightly elongated when compared to the C≡N bond length in neutral nitriles (1.15−1.20 and 1.14 Å, respectively).

The X-ray structures of metalated nitriles show a continuum of geometries for the metalated carbon. Geometries of the metalated carbon range from planar in the *N*-metalated nitrile **1**[6] to pyramidal in the *C*-metalated nitriles **2**[7] and **4**,[8] with considerable variation in the degree of pyramidalization, depending on the nature of the metal and the presence or absence of adjacent aromatic substituents.[9] Lithiated nitriles exhibit exclusive *N*-lithiation,[10] whereas transition metals coordinate to nitrogen or carbon with roughly equal fre-

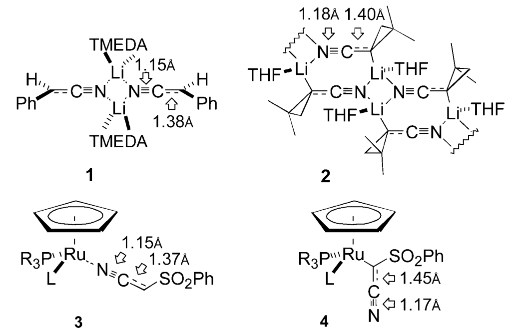

FIGURE 1. X-ray structures of metalated nitriles.

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[10] Lithiated cyclopropanenitrile **2** is unique in having *N*- and *C*-coordination.

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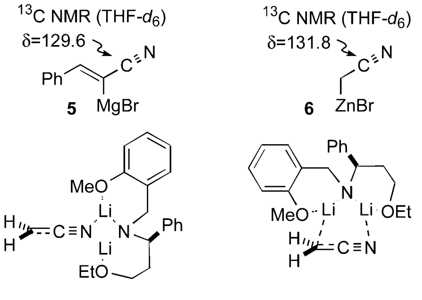
quency.[11] This coordination promiscuity is encapsulated in the thermally induced interconversion of the *N*- and *C*-phenylsulfonylacetonitriles **3** and **4** (Figure 1).[12]

Extensive NMR analyses of the metalated nitriles identify the predominant solution structures as being essentially identical to those observed in the solid state.[13] ^{6}Li-^{15}N NMR coupling confirms the preference for the *N*-lithiated dimer **1** in ether−toluene solvent mixtures,[14] whereas the transition-metal-containing nitriles **3** and **4** exhibit solution-^{13}C chemical shifts for the nitrile carbon, indicative of the corresponding *N*- and *C*-metalated nitriles ($\delta = 140-155$ and $110-125$, respectively).[15] Diagnostic ^{13}C NMR shifts for the nitrile carbons of **5**[16] and **6**,[17] which are only slightly shifted from those of the parent neutral nitriles similarly suggest *C*-metalated nitrile solution structures (Figure 2). Resident within this continuum of *N*- and *C*-metalated nitriles is the complexed lithioacetonitrile (**7**), which exists as a rapidly equilibrating mixture of *N*- and *C*-coordinated nitriles in ether at −100 °C.[18]

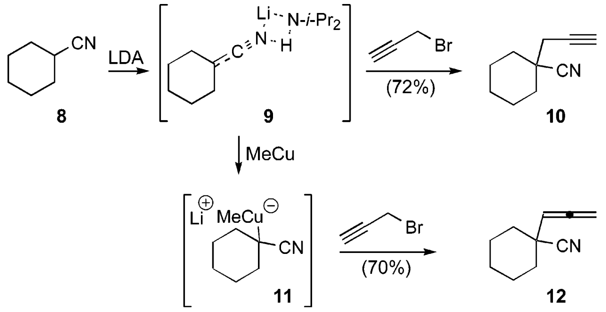


5 **6** **7a** **7b**

FIGURE 2. Solution structures of metalated nitriles.

Several intriguing alkylations with metalated nitriles imply that the metal coordination site profoundly influences the reactivity of metalated nitriles.[19] For example, intercepting the putative[14,20] *N*-lithiated nitrile **9** with propargyl bromide causes exclusive S_N2 displacement, whereas conversion to the *C*-metalated nitrile **11** and alkylation with propargyl bromide gives the S_N2' allenylnitrile **12** exclusively (Scheme 1).[21] Related regiodivergent alkylations in polar and nonpolar solvents may result from analogous preferential formation of *N*- or *C*-metalated nitriles.[22]

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



8 **9** **10** **11** **12**

Even more intriguing are *stereodivergent* alkylations of *N*- and *C*-metalated nitriles that are subtly inferred from stereoselectivity trends in cyclopropanecarbonitrile deuterations,[23] solvent-selective cyclizations to *cis*- and *trans*-decalins,[24] and alkylations of cylohexanecarbonitriles.[4] The modest selectivity for the deprotonation−methylation of the conformationally locked nitrile **13** and the completely stereoselective methylation of the corresponding magnesiated nitrile similarly imply selective formation of *N*- and *C*-metalated nitrile intermediates (Scheme 2).[25] The potential for complementary stereoselectivities in alkylations of *N*- and *C*-metalated nitriles stimulated a comprehensive series of alkylations. Alky-

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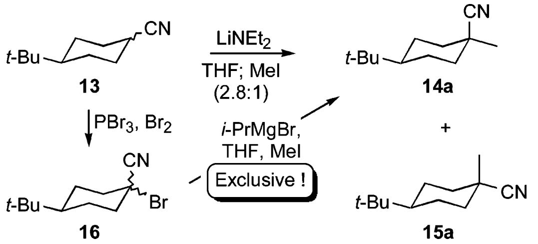
SCHEME 2. Stereoselective Methylations of Metalated Nitriles

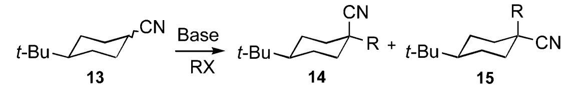


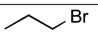
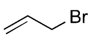
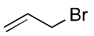
lations with a conformationally constrained *N*-lithiated nitrile were probed to establish the fundamental dependence of the solvent, the temperature, and the electrophile on the stereoselectivity and to allow subsequent comparison with *C*-metalated nitriles having magnesium and copper counterions. Collectively, modest stereoselectivities correlate with sterically controlled alkylations of *N*-lithiated nitriles, whereas the corresponding *C*-metalated nitriles alkylate with high selectivities.

Results and Discussion

Pioneering[26] isotope labeling identified an early transition state for alkylations of lithiated 4-*tert*-butylcyclohexanecarbonitrile. Deprotonating **13** with lithium diethylamide in DME is presumed to generate a planar *N*-lithiated nitrile[27] with only a slight steric bias for an electrophile approach along an equatorial trajectory (Table 1, entry 6).[28] Repeating the benchmark deprotonation−methylation of nitrile **13** in THF, DME, and toluene at varying temperatures and with different electrophiles (Table 1) provides a crucial reference point for comparing the stereoselective alkylations of diverse metalated nitriles. Not surprisingly, the stereoselectivity is virtually identical in THF and DME, with modestly improved selectivity at low temperatures and minimal selectivity at or above room temperature (Table 1, compare entries 6 and 7 with entries 3 and 4 and entries 8−10, respectively).

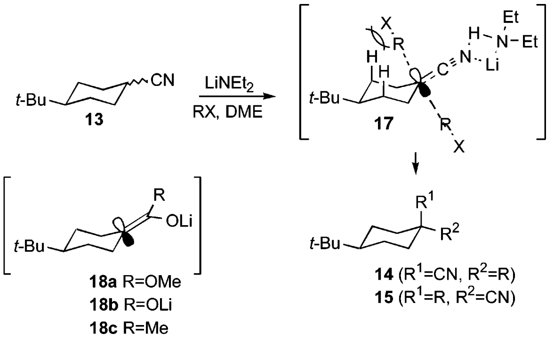
TABLE 1. LiNEt$_2$ Deprotonation−Alkylation of 4-*tert*-Butylcyclohexanecarbonitrile



entry	base	solvent	T (°C)	electrophile	**14**:**15**[a]		yield
1	LiNEt$_2$	THF	-78	 Br	**14b**:**15b**	1:0	71%
2	LiNEt$_2$	THF	-78	 Br	**14c**:**15c**	7.9:1	74%
3	LiNEt$_2$	DME	-60	MeI	**14a**:**15a**	7.7:1	86%
4	LiNEt$_2$	THF	-78	MeI	**14a**:**15a**	7.4:1	85%
5	LiNEt$_2$	DME	22	 Br	**14c**:**15c**	7.3:1	75%[b]
6	LiNEt$_2$	DME	22	MeI	**14a**:**15a**	2.8:1	86%[c]
7	LiNEt$_2$	THF	22	MeI	**14a**:**15a**	2.8:1	86%
8	LiNEt$_2$	THF	66	MeI	**14a**:**15a**	1.9:1	90%
9	KHMDS	PhCH$_3$	22	MeI	**14a**:**15a**	1.6:1	84%
10	KHMDS	PhCH$_3$	80	MeI	**14a**:**15a**	1:1	71%

[a] Ratios determined by 500 MHz ^{1}H NMR integration of the axial and equatorial diastereomers.[29] [b] Reference 29c. [c] Reference 26. Repetition under the original conditions afforded a 3.6:1 ratio (85%), which compares favorably with the methylation ratio (3.1:1) of the corresponding lithiated nitrile generated by fragmentation of a methyldiazine carboxylate.[30]

SCHEME 3. Stereoselective Alkylations of an *N*-Lithiated Nitrile



Alkylations of **13** are consistent with the formation of a planar *N*-lithiated nitrile[20] (**17**) upon deprotonation (Scheme 3). Specifically, the planar lithiated nitrile **17** exhibits a 2.8:1 preference for equatorial methylation at room temperature, which is very similar to the methylation selectivities of the planar enolates **18a**, **18b**, and **18c** (1.8:1,[31] 5.3:1,[31] and 5.7:1,[28] respectively). An axial electrophile trajectory to the nucleophilic orbital of **17** is modestly disfavored by 1,3-*syn*-axial interactions,[32] which are exacerbated by sterically demanding electrophiles.[33] For example, alkylations with allyl bromide are modestly more selective than alkylations with the smaller electrophile, methyl iodide (Table 1, compare entries 5 and 6). Comparative alkylations of allyl- and propyl bromide, having virtually identical steric demands, are completely stereoselective in the latter case, presumably reflecting better steric discrimination from the less-reactive electrophile in a later transition state (Table 1, compare entries 1 and 2).

Alkylations of copper- and magnesium-derived metalated nitriles exhibit dramatically improved stereoselectivities. Metalated nitriles having different metal cations are readily generated by halogen−metal exchange[34] of

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[29] The stereochemical assignments for **14a**/**15a**[28,a] and **14c**/**15c**[b] are based on ^{13}C NMR shift comparisons with known values, whereas the stereochemistry of **15b** rests on the diagnostic ^{13}C NMR shift for the axial nitrile group[a] (δ_{CN} 124.4, 123.7, 123.2 for **14a**−**c**, respectively). (a) Bailey, W.; Cioffi, A. *Magn. Reson. Chem.* **1987**, *25*, 181. (b) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86.

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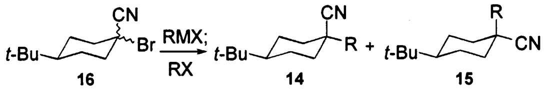
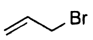
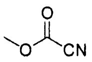
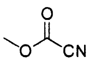
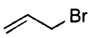
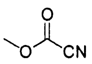
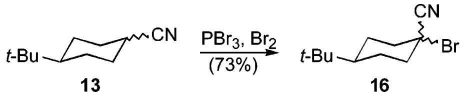
TABLE 2. Diastereoselective Halogen−Metal Exchange Alkylations



entry	RM	T (°C)	electrophile	14:15[a]		yield
1	n-BuLi	-78°C	MeI	**14a**:**15a**	3:1	56%
2	i-PrMgBr	-78°C	MeI	**14a**:**15a**	1:0	61%
3	i-PrMgBr	0°C	MeI	**14a**:**15a**	1:0	75%
4	i-PrMgBr	rt	MeI	**14a**:**15a**	1:0	87%
5	i-PrMgBr	-78°C		**14c**:**15c**	22:1	77%
6	i-PrMgBr[b]	-78°C		**14d**[c]:**15d**	12:1	62%
7	i-PrMgBr[d]	-78°C		**14d**[c]:**15d**	17:1	73%
8	Me_2CuLi	-78°C		**14c**:**15c**	1:0	92%
9	Me_2CuLi	-78°C		**14d**[c]:**15d**	17:1	73%

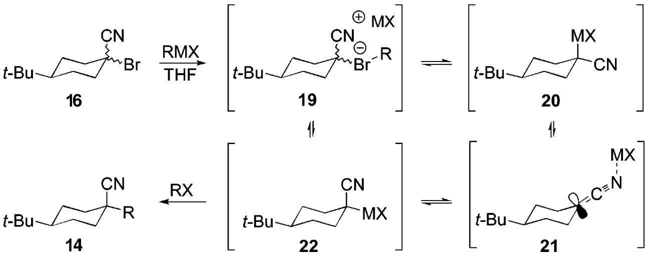
[a] A diastereomeric mixture of bromonitriles was employed unless otherwise specified. Ratios are based on isolated yields of diastereomeric nitriles. [b] A single diastereomeric bromonitrile was employed. [c] The stereochemistry of **14d** was assigned by reduction and X-ray crystallography of the corresponding alcohol (**i**).[36] [d] A single bromonitrile diastereomeric to that in entry 6 was employed.

the corresponding bromonitriles,[21] which, in the case of **16**, is readily prepared by bromination of **13** with PBr_3, Br_2 (eq 1).[35] Exploratory bromine−magnesium exchange in the presence of methyl iodide affords the equatorially



methylated nitrile **14a** as the sole diastereomer (Table 2, entry 2), which is in direct contrast to comparable methylations of the corresponding lithiated nitrile (Table 2, entry 1 and Table 1, entry 4). Probing the effect of temperature on the magnesium exchange methylation proved to be particularly revealing. Remarkably, the exclusive preference for equatorial methylation is maintained for i-PrMgBr exchange alkylations at 0 °C and at room temperature, which is in direct contrast to lithium diethylamide deprotonation methylations (compare Table 2, entries 2−4 with Table 1, entries 4 and 7). Analogous i-PrMgBr exchange alkylations with more reactive electrophiles, such as allyl bromide and methyl cyanoformate, selectively generate the corresponding equatorially alkylated nitriles (Table 2, entries 5−7). Sequential bromine−copper exchange and alkylation with allyl bromide or methyl cyanoformate is even more selective than the comparable i-PrMgBr exchange alkylations (Table 2, compare entries 8 and 9 with entries 5−7). The highly selective alkylations with i-PrMgBr and Me_2CuLi directly contrast with the BuLi exchange methylation, in which the modest selectivity (Table 2, entry 1) more closely parallels the deprotonation−methylation of **13** with $LiNEt_2$ (Table 1).

SCHEME 4. Equilibration of C-Metalated Nitriles



The divergent alkylation stereoselectivities of metalated nitriles with magnesium and copper counterions, as opposed to lithium, require the formation of distinctly different metalated nitriles (compare, in particular, Table 2, entry 4 with Table 1, entry 7 and Table 2, entry 8 with Table 1, entry 2).[37] Identifying the lithiated nitrile as a planar N-lithiated nitrile structure (Table 1 and Table 2, entry 1) is consistent with the prior alkylation preferences of planar enolates[28,31] and NMR[14] and X-ray structural studies,[5] suggesting that magnesium and copper counterions preferentially form C-metalated nitriles. Mechanistically, addition of i-PrMgBr or Me_2CuLi to the bromonitrile **16** is presumed to generate the bromate **19**[38] (Scheme 4) that fragments to directly generate the C-metalated nitriles **20** or **22** or the corresponding N-metalated nitrile **21**. In either case, rapid[39] conducted tour equilibration[40] to one predominant metalated nitrile is consistent with the qualitatively identical ratios[41] of acylated nitriles **14d** and **15d** (Table 2, entries 6 and 7) upon addition of i-PrMgBr to a −78 °C, THF solution containing methyl cyanoformate and diastereomerically pure cis- or trans-bromonitrile **16**. Similarly, probing the configurational stability through the in situ methylation of a 1−2:1 diastereomeric mixture of bromonitriles **16** leads exclusively to the equatorially methylated nitrile **14a** (Table 2, entries 2−4).

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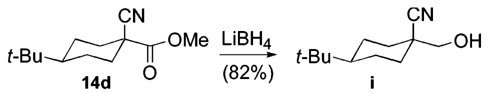
(35) Stevens, C. L.; Coffield, T. H. *J. Am. Chem. Soc.* **1951**, *73*, 103.

(36)



The supplementary crystallographic data for **i**, CCDC no. 259789, can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033; or deposit@ccdc.cam.ac.uk.).

(37) Attempts to access the magnesiated nitrile **22** (MX = MgBr) by deprotonating **13** with $BrMgNEt_2$ afforded the corresponding amidine.

(38) (a) Hoffmann, R. W.; Brönstrup, M.; Muller, M. *Org. Lett.* **2003**, *5*, 313. (b) Schulze, V.; Brönstrup, M.; Böhm, V. P. W.; Schwerdtfeger, P.; Schimeczek, M.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 824. (c) Reich, H. J.; Green, D. P.; Phillips, N. H.; Borst, J. P.; Reich, I. L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *67*, 83.

(39) For a related equilibration see: Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003.

(40) Carlier, P. R. *Chirality* **2003**, *15*, 340.

(41) The ratios of **14b** and **15b** were essentially identical as determined by integration of the crude ^1H NMR spectra. The variable ratios observed in Table 2, entries 6 and 7, most likely reflect the small quantities isolated for the minor isomer.

The high, or exclusive, equatorial alkylation preferences with magnesium and copper counterions are consistent with the retentive alkylation[42] of equatorial *C*-metalated nitriles (**22**, Scheme 4). The exceptionally small steric demand of the nitrile group, a mere 0.2 kcal mol,[43] is anticipated to favor diastereomer **22** over **20**, in which the larger, solvated metal adopts the axial orientation. Detecting the minor conformer **20** through alkylation is facilitated with particularly reactive electrophiles[44] and may account for the formation of trace acylated and allylated nitriles **15c** and **15d** in alkylations with allyl bromide and methyl cyanoformate (Table 2, entries 5−7). As expected, the less-reactive cuprated nitrile exhibits greater discrimination in alkylations with allyl bromide and methyl cyanoformate (compare Table 2, entries 5−7 with entries 8 and 9).

N- and *C*-metalated conformationally locked nitriles alkylate electrophiles with divergent and diagnostic stereoselectivity preferences. Alkylations of *N*-lithiated nitriles, generated by lithium diethylamide deprotonation or bromine−lithium exchange, exhibit a modest sterically controlled preference for equatorial alkylation. Sequential bromine−magnesium or bromine−copper exchange alkylations are consistent with the formation of equatorial *C*-metalated nitriles, which exhibit a high, or exclusive, preference for retentive alkylation. Selectively forming *N*- or *C*-metalated nitriles provides complementary stereocontrol manifolds for overcoming the long-standing difficulty of achieving highly selective alkylations with sterically unbiased cyclohexanecarbonitriles.

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Note Added after ASAP Publication. There was an error in the structure numbers of reference 44 in the version published ASAP April 14, 2005; the corrected version was published ASAP April 18, 2005.

Supporting Information Available: Experimental procedures, ^{1}H NMR, and ^{13}C NMR spectra for all new compounds, and an ORTEP for **i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(42) For an excellent overview see: Clayden, J. In *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002; Chapter 6. For retentive alkylation of a chiral organocopper reagent see: Hoffmann, R. W.; Hölzer, B. *J. Am. Chem. Soc.* **2002**, *124*, 4204.

(43) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: NY, 1994; pp 696−697.

(44) The analysis assumes similar reactivities of the transition states for alkylations of **20** and **22**, which may be a reasonable assumption given the early transition state for alkylations of *N*-lithiated nitriles.[26]