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Chemoselective Alkylations with *N*- and *C*-Metalated Nitriles

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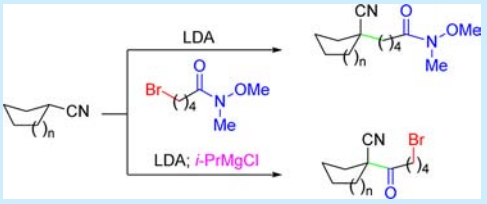
Supporting Information

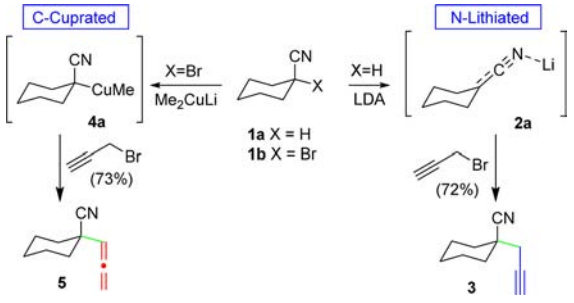
ABSTRACT: Metalated nitriles exhibit complementary chemoselectivities in electrophilic alkylations. *N*-Lithiated or *C*-magnesiated nitriles can be prepared from the same nitrile precursor and selectively reacted with a 1:1 mixture of methyl cyanoformate and benzyl bromide or bifunctional electrophiles through chemoselective attack onto either an alkyl halide or a carbonyl electrophile. A mechanistic explanation for the chemoselectivity preferences is provided that rests on the structural and complexation differences between *N*- and *C*-metalated nitriles.



Chemoselectivity is one of the greatest challenges to efficient complex molecule synthesis.[1] The "preferential reaction of a chemical reagent with one of two or more different functional groups"[2] allows bond construction with increased synthetic efficiency because functional group protection and oxidation adjustment is unnecessary.[3] Precise functionalization is particularly advantageous in the late stages of complex syntheses where the targets are functionally rich natural products or pharmaceuticals.[4]

Buried within the copious reactions of metalated nitriles are sporadic examples of chemoselective alkylations.[5] Selective electrophile attack roughly correlates with the two *N*- and *C*-metalated nitrile structures[6] in which the metal is coordinated to the nitrile nitrogen or the nucleophilic carbon, respectively (Scheme 1). Alkylations of the *N*-lithiated and *C*-cuprated

Scheme 1. Divergent Metalated Nitrile Alkylations

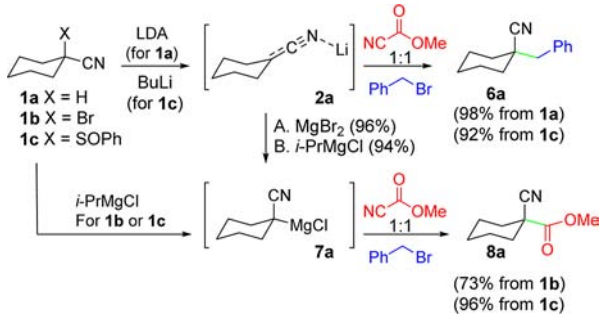


cyclohexanecarbonitriles **2a** and **4a**,[6] respectively, with propargyl bromide illustrate the different electrophile preferences; the *N*-lithiated nitrile **2a** affords alkynenitrile **3**, whereas the *C*-cuprated nitrile **4a** affords allene nitrile **5** (Scheme 1).[7] The reactions illustrate the potential to generate different *N*- and *C*-metalated nitrile structures, from the same precursor, for divergent, chemoselective alkylations.

Scouting experiments to probe chemoselectivity differences between *N*- and *C*-metalated nitriles were performed with metalated nitriles derived from cyclohexanecarbonitrile (**1a**). Metalated cyclohexanecarbonitriles are ideal prototypes because *N*- and *C*-metalated nitriles are readily prepared,[8] the stereoselectivity trends and the *N*- and *C*- coordination preferences for lithiated, magnesiated, and cuprated cyclohexanecarbonitriles are well established,[9] and the cyclohexanecarbonitrile core is a prevalent motif in pharmaceuticals.[10]

Exploratory chemoselective alkylations employed the *N*-lithiated nitrile **2a** and a 1:1 ratio of methyl cyanoformate and benzyl bromide (Scheme 2). Despite a high reactivity of both

Scheme 2. Cyclohexanecarbonitrile Alkylations



electrophiles, the benzylated nitrile **6a** was formed exclusively. An alternative preparation of the *N*-lithiated nitrile **2a**, through a sulfinyl−lithium exchange (**1c** → **2a**, Scheme 2),[8] followed by addition of a 1:1 ratio of methyl cyanoformate and benzyl bromide afforded the benzyl nitrile **6a** in essentially the same yield as from the LDA-initiated deprotonation. Collectively, these alkylations imply that the diisopropylamine formed during the deprotonation, which typically coordinates to lithiated nitriles,[11] does not play a role in determining the chemoselectivity.

In contrast to the alkylations of lithiated nitrile **2a**, magnesiated cyclohexanecarbonitrile 7a exhibits a complemen-

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tary chemoselectivity preference for methyl cyanoformate (Scheme 2). Preparation of the *C*-magnesiated nitrile **7a** by bromine− or sulfinyl−magnesium exchange reactions (**1b** → **7a** and **1c** → **7a**, respectively),[8] and addition of a 1:1 mixture of benzyl bromide and methyl cyanoformate afforded only the cyanoester **8a** in 73% from **1b** and in 96% yield from **1c**.[12] Alternatively, sequential deprotonation of **1a** with LDA, transmetalation with $MgBr_2$ to form the *C*-magnesiated nitrile **7a**, and addition of a 1:1 mixture of benzyl bromide and methyl cyanoformate exclusively afforded the ester nitrile **8a** (96%).[12] Operationally, the same outcome was achieved by sequential deprotonation of **1a** with LDA, addition of *i*-PrMgCl, and then addition of a 1:1 mixture of electrophiles which afforded **8a** in 94%. The latter procedure is simple and uses a readily available Grignard reagent to effect transmetalation.

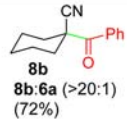
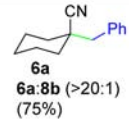
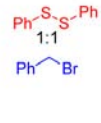
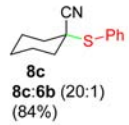
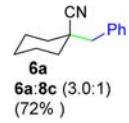
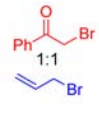
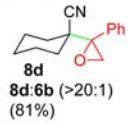
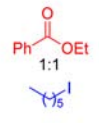
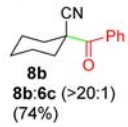
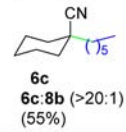
The analogous alkylations of cuprated and zincated cyclohexanecarbonitriles were performed to determine if the divergent chemoselectivity preferences were uniquely correlated with the metal or with the *C*- or *N*-metalated nitrile structures (Scheme 3). Formation of the *C*-cuprated nitrile **4a**, prepared through a

Scheme 3. *C*-Metalated Carbonitrile Alkylations

copper−bromine exchange with **1b**,[7] and exposure to a 1:1 mixture of methyl cyanoformate and benzyl bromide only afforded cyanoester **8a**.[12] Treating the sulfinylnitrile **1c** with lithium butyldiethylzincate[13] afforded a zincated nitrile, tentatively formulated with zinc coordinated to carbon (**7b**), which selectively reacted with the electrophile pair to only afford cyanoester **8a**.[12] The preference of the *C*-magnesiated, *C*-cuprated, and *C*-zincated nitriles to react with methyl cyanoformate suggests that the chemoselectivity is determined by the metal coordination site.

Having discovered the chemoselective alkylations of *N*- and *C*-metalated nitriles with an equimolar mixture of methyl cyanoformate and benzyl bromide, additional pairs of electrophiles were screened for chemoselective alkylations. Early forays indicated a general preference of the magnesiated nitrile **7a** for a range of oxygenated electrophiles whereas the lithiated nitrile **2a** had a more limited preference for alkyl halides. Exposure of the lithiated nitrile **2a** to a 1:1 mixture of benzyl bromide and benzoyl chloride afforded only the benzylated nitrile **6a** whereas the magnesiated nitrile **7a** reacted selectively with benzoyl chloride to afford **8b** (Table 1, entry 1). Addition of a 1:1 mixture of BnBr and PhSSPh to the lithiated nitrile **2a** led to a 3.0:1 preference for alkylation with BnBr while the magnesiated nitrile **7a** exhibited a 20.0:1 preference for sulfenylation (Table 1, entry 2). Efforts to identify additional electrophiles that react preferentially with the *N*-lithiated nitrile **2a** led to a selective reaction with a 1:1 mixture of allyl bromide and bromoacetophenone; the lithiated nitrile exhibited a 5.0:1 preference for allyl bromide over bromoacetophenone, whereas the magnesiated nitrile **7a** reacted exclusively with bromoacetophenone to afford epoxide **8d** (Table 1, entry 3). Selective alkylation of the lithiated nitrile **2a** with an aliphatic iodide was achieved with iodohexane and ethyl benzoate (Table 1, entry 4).

Table 1. Chemoselective Alkylations with 1:1 Electrophiles

entry	electrophile	alkylated nitrile (% yield) from *N*-lithiated **2a**	alkylated nitrile (% yield) from *C*-magnesiated **7a**
1		 **8b** **8b**:**6a** (>20:1) (72%)	 **6a** **6a**:**8b** (>20:1) (75%)
2		 **8c** **8c**:**6b** (20:1) (84%)	 **6a** **6a**:**8c** (3.0:1) (72%)
3		 **8d** **8d**:**6b** (>20:1) (81%)	 **6b** **6b**:**8d** (5.0:1) (78%)
4		 **8b** **8b**:**6c** (>20:1) (74%)	 **6c** **6c**:**8b** (>20:1) (55%)

The chemoselectivity preferences of *N*-lithiated and *C*-magnesiated nitriles in alkylations with a 1:1 mixture of methyl cyanoformate and benzyl bromide is maintained in a series of structurally diverse nitriles (Table 2). In general, *C*-magnesiated nitriles exhibit higher selectivity for methyl cyanoformate than the corresponding *N*-lithiated nitrile does for benzyl bromide. Formation of the *N*-lithiated nitrile from the norbornene nitrile **1d** and exposure to methyl cyanoformate and benzyl bromide afforded only benzyl nitrile **6d**; the corresponding *C*-magnesiated nitrile generated the ester nitrile **8e** (Table 2, entry 1). The lithiated nitrile derived from cyclopentanecarbonitrile (**1e**) selectively alkylated benzyl bromide, whereas the sequential lithiation and alkylation of cycloheptanecarbonitrile (**1f**) is relatively nonselective. In contrast, both magnesiated nitriles derived from 5- and 7-membered cyclic nitriles exhibit a high preference for acylation (Table 2, entries 2 and 3, respectively). The lithiated nitrile derived from acyclic nitrile **1g** alkylates stereoselectively but not chemoselectively, whereas the lithiated nitriles obtained from acyclic nitriles **1h** and **1i**, which have a diminished steric demand relative to **1g**, exhibit a greater selectivity for benzyl bromide (Table 2, compare entries 5 and 6 with entry 4). All three acyclic magnesiated nitriles derived from **1g**, **1h**, and **1i** exhibit a high preference for acylation with methyl cyanoformate (Table 2, entries 4−6). Addition of 1 equiv of LiCl to the lithiated nitrile derived from **1i**, which contains a potential chelating γ-methoxy group,[14] renders the reaction nonselective (Table 2, entry 6), suggesting disruption of an association between the lithiated nitrile and the electrophile.

The chemoselectivity trends of electrophile pairs suggested that *C*-magnesiated and *N*-lithiated nitriles derived from the same nitrile should react with a bifunctional electrophile at different electrophilic sites.[15] Optimization led to chemoselective alkylations of metalated cyclohexanecarbonitrile with the bromoamide **9** (Scheme 4). Exposure of the lithiated nitrile derived from **1a** to bromoamide **9** led to a greater than 99:1 preference for the cyano amide **10a**, whereas intercepting the corresponding magnesiated nitrile derived from **1c** preferentially

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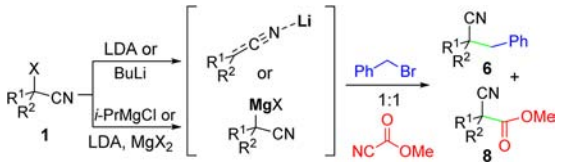
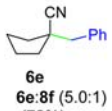
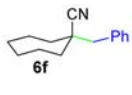
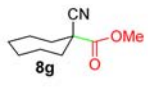
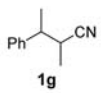
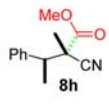
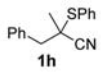
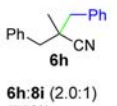
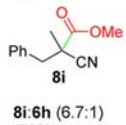
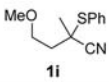
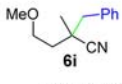
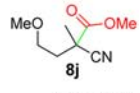
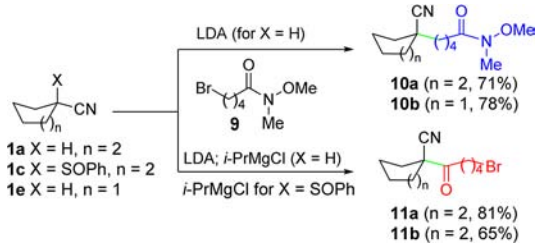
Table 2. Chemoselective Metalated Nitrile Alkylations[a]



entry	electrophiles	alkylated nitrile from *N*-Li **2a**	alkylated nitrile from *C*-Mg **7a**
1	 **1d**	 **6d** **6d:8e** (>20:1) (70%)	 **8e** **8e:6d** (>20:1) (82%)
2	 **1e**	 **6e** **6e:8f** (5.0:1) (72%)	 **8f** **8f:6e** (12:1) (62%)
3	 **1f**	 **6f** **6f:8g** (1.2:1) (75%)	 **8g** **8g:6f** (33:1) (78%)
4	 **1g**	 **6g** **6g:8h** (1.1:1) (70%)	 **8h** **6g:8h** (>19:1) (55%)
5	 **1h**	 **6h** **6h:8i** (2.0:1) (75%)	 **8i** **8i:6h** (6.7:1) (72%)
6	 **1i**	 **6i** **6i:8j** (4.0:1) (75%)	 **8j** **8j:6i** (15:1) (91%)[a]

[a]Addition of LiCl (1 equiv) leads to a 1.7:1 ratio of **6i**/**8j** (88% yield).

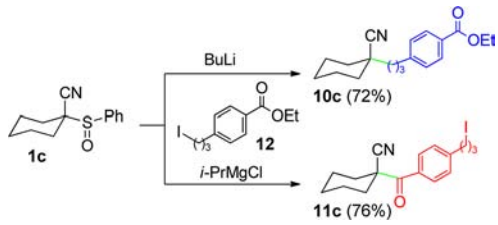
Scheme 4. Chemoselective Alkylations with a Bromoamide



afforded **11a** with trace amide **10a** (24:1 ratio). An analogous alkylation of the bromoamide **9** with cyclopentanecarbonitrile (**1e**) was even more selective.[16] Alkylation of lithiated cyclopentanecarbonitrile with **9** only afforded the amide **10b**, whereas alkylation with chloromagnesium cyclopentanecarbonitrile exclusively gave the bromoester **11b** (Scheme 4).

Using the same principle, two chemodivergent alkylations were performed with cyclohexanecarbonitrile (**1a**) and the iodoester **12** (Scheme 5). Sulfinyl−lithium exchange of **1c** with

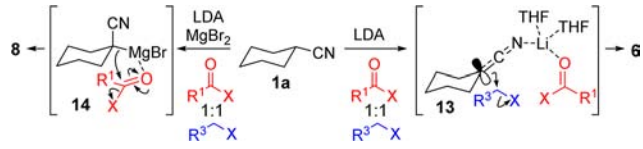
Scheme 5. Chemoselective Iodoester Alkylations



BuLi followed by addition of iodoester **12** afforded solely the cyanoester **10c** through selective iodide displacement whereas sulfinyl-magnesium exchange of nitrile **1a** with *i*-PrMgCl and alkylation with **12** afforded only the cyanoketone **11c**.[16]

The ability of the *N*- and *C*- metalated nitrile structures to direct the chemoselective alkylations suggests that associative electrophile interactions control the selectivity, a notion supported by the disruptive influence of LiCl. Addition of a mixture of electrophiles to a lithiated nitrile likely results in coordination of oxygen-containing electrophiles to the Lewis acidic lithium which serves to prevent alkylation by anchoring the electrophile remote from the nucleophilic carbon (Scheme 6, **13**). Alkyl halides, being weaker Lewis bases, may be able to directly approach the nucleophilic carbon resulting in alkylation through **13** to **6**.

Scheme 6. Mechanistic Explanation for the Chemoselectivity



C-Magnesiated nitriles likely coordinate oxygenated electrophiles close to the nucleophilic carbon (Scheme 6, **14**). Complexation increases the carbonyl electrophilicity and the electron density on magnesium which promotes alkylation either through the *C*-magnesiated nitrile **14** or by scission of the weak C−Mg bond to form a transient *N*-magnesiated nitrile or a nitrile-stabilized carbanion. Close proximity with the activated electrophile complex would then trigger rapid alkylation to afford the nitrile **8**. The preference of *C*-magnesiated nitriles for oxygenated electrophiles does not preclude alkylations with alkyl halides. Magnesiated nitriles are configurationally labile and readily equilibrate from *C*-magnesiated to *N*-magnesiated nitriles through conducted tour or ion exchange mechanisms.[17] Consistent with this mechanistic suggestion, for alkylations of the lithiated nitrile **2a** with mixtures of benzyl bromide and methyl cyanoformate, increasing the ratio of methyl cyanoformate from 1:1 to 2:1 through 5:1 to 10:1 results in higher ratios of the ester **8a** relative to the benzyl nitrile **6a** (3.1:1, 5.0:1, and 10.1:1, respectively).

Further support for the proposed chelation-derived chemoselectivity was gleaned from alkylations with the metalated cyclopropanecarbonitriles **7c** and **7d** (Scheme 7). Generation of the *C*-lithiated nitrile **7c** and exposure to the bromoamide **15** afforded only the ketonitrile **8k** in which the carbonyl is selectively attacked. The reversed chemoselectivity preference,

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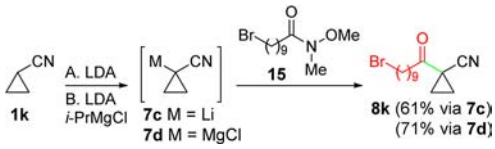
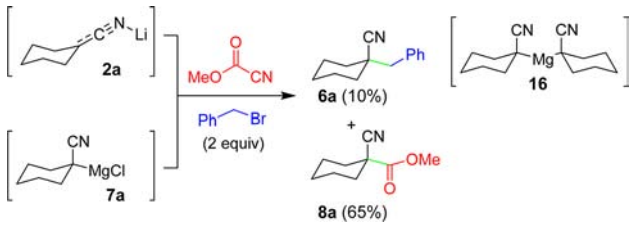
Scheme 7. Mechanistic Probe for the Chemoselectivity



compared to other lithiated nitriles (cf. Scheme 2), is consistent with the *C*-lithiated structure of cyclopropanecarbonitriles.[18] The magnesiated nitrile **7d** selectively acylated **15** to afford **8k**. These acylations, particularly of the lithiated nitrile **7c**, are congruent with the chemoselectivity arising from the metal coordination site.

The role of coordination was probed through a competition experiment with an admixture of lithiated nitrile **2a** and magnesiated nitrile **7a** (Scheme 8). Addition of a solution of

Scheme 8. Metalation Crossover Experiment



7a to lithiated nitrile **2a**, formed by sulfinyl−magnesium and sulfinyl−lithium exchange, respectively, followed by an equimolar mixture of methyl cyanoformate and benzyl bromide afforded 65% of the ester **8a** and 10% of the benzyl nitrile **6a** (**8a**:**6a** = 6.5:1). The product ratio suggests predominant alkylation via a magnesiated nitrile, possibly through transmetalation with magnesium halide released after alkylation or through a dialkylmagnesium species. Insight into the potential identity of the intermediate was gained by ^{13}C NMR analysis of the species formed by addition of the lithiated cyclohexanecarbonitrile (**2a**) to the magnesiated nitrile **7a**. The diagnostic ^{13}C chemical shift[6] of the nitrile carbon of **7a** (δ = 129.63) shifted slightly to δ = 129.10 upon addition of lithiated nitrile **2** (δ = 164.81), suggesting selective acylation via the dialkylmagnesium **16**.

In summary, chemoselective alkylations of *N*- and *C*-metalated nitriles allow preferential nucleophilic attack with different electrophiles. For comparable alkylations from the same nitrile precursor, *N*-lithiated nitriles prefer to react with alkyl halides, whereas *C*-magnesiated nitriles preferentially alkylate oxygenated electrophiles. Alkylations with bis-electrophiles allow selective attack at different electrophilic sites simply by judicious choice of the metal cation. The chemoselective alkylations of metalated nitriles offers the possibility of selective, late-stage alkylations of polyfunctional electrophiles for efficient syntheses and the creation of diverse natural-product like libraries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02481.

^{1}H NMR and ^{13}C NMR spectra and experimental procedures for all new compounds (PDF)

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Notes

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