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### Metalated Nitriles: Organolithium, -magnesium, and -copper Exchange of α-Halonitriles

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 $\alpha$ -Halonitriles react with alkyllithium, organomagnesium, and lithium dimethylcuprate reagents generating reactive, metalated nitriles. The rapid halogen-metal exchange with alkyllithium and Grignard reagents allows selective exchange in the presence of reactive carbonyl electrophiles, including aldehydes, providing a high-yielding alkylation protocol. Lithiated and magnesiated nitriles react with propargyl bromide by  $S_N 2$  displacement whereas organocopper nitriles react by  $S_N 2'$  displacement, correlating with the formation of a *C*-metalated nitrile.

#### Introduction

 $\alpha$ -Metalated nitriles are powerful nucleophiles, ideally suited for sterically demanding alkylations.<sup>1</sup> The exceptional nucleophilicity stems from the powerful inductive stabilization<sup>2</sup> of metalated nitriles that localizes negative charge density on carbon to the virtual exclusion of *N*-alkylation.<sup>3</sup> Augmenting the nucleophilicity of metalated nitriles is the extremely small steric demand of the CN unit, with an *A*-value of only 0.2 kcal mol<sup>-1.4</sup> Collectively, the exceptional nucleophilicity of metalated nitriles,<sup>1</sup> the facile installation of hindered centers,<sup>5</sup> and the conversion of nitriles into a range of functional groups<sup>6</sup> have resulted in the extensive use of metalated nitriles in synthesis.

Metalated nitriles are typically synthesized by deprotonating the parent nitriles with metal amides.<sup>1</sup> Com-

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putationally, deprotonating acetonitrile with lithium amide leads directly to *N*-lithiated acetonitrile,<sup>7</sup> which correlates with numerous X-ray<sup>8</sup> (1, 2) and solution<sup>9</sup> structures (2, 3) of metalated nitriles (Figure 1). Remarkably, X-ray analyses<sup>8</sup> consistently show metalated nitriles as having partial double bond character for the C==CN bond and only slight weakening of the C==N triple bond (1.15-1.20 Å), relative to the C==N bond length of neutral nitriles (1.14 Å)!<sup>10</sup> Another characteristic feature of



**FIGURE 1.** Prototypical solution and X-ray structures of metalated nitriles.

metalated nitriles is the persistent coordination of amide<sup>11</sup> or amine ligands<sup>12</sup> in X-ray and solution structures, which feature in both *N*- and *C*-coordinated complexes as gauged by the rapid equilibration between **3a** and **3b** in Et<sub>2</sub>O at -100 °C.<sup>13</sup>

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C-Metalated nitriles were experimentally inferred<sup>14</sup> during pioneering deuterations of the chiral cyclopropanecarbonitrile 4.<sup>15</sup> MeONa-MeOD deuteration proceeds with greater than 99.9% stereochemical retention in generating **6a**, presumably through the intermediacy of the transient ion pair 5.<sup>16</sup> In contrast, sequential deprotonation-protonation with LDA causes complete racemization ( $\mathbf{4} \rightarrow \mathbf{6b}$ ) of the putative<sup>9b,c</sup> intermediate *N*-metalated nitrile **7** (Scheme 1).

SCHEME 1. Stereochemical Integrity of C- and N-Metalated Nitriles



The absence of lithium as the counterion may facilitate maintaining the stereochemical integrity since almost  $all^{17}$  subsequent examples of *C*-metalated nitriles are

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with alkaline earth or transition metals.<sup>18</sup> For example, solution NMR of the magnesiated nitrile  $8^{19}$  and the zincated nitrile  $9^{20}$  (Figure 2) imply metalation on carbon in a trend that is maintained within numerous crystal structures of transition metal complexes.<sup>18</sup> Particularly dramatic are the seminal heat-induced interconversions of the crystalline ruthenium *C*- and *N*-phenylsulfonylacetonitriles **10** and **11**, in which the preference for *C*- or *N*-coordination depends on the phosphine ligand.<sup>21</sup>



**FIGURE 2.** Solution and X-ray structures of *C*- and *N*-metalated nitriles.

Selective formation of C- and N-metalated nitriles offers the possibility for controlling regio- and stereoselective alkylations in previously undeveloped ways. Precedent for divergent reactivity of C- and N-metalated nitriles stems from metal-dependent cyclization<sup>22</sup> and carbonyl addition<sup>23</sup> stereoselectivities, and metal-dependent alkylation chemoselectivities.<sup>24</sup> Efforts to harness reactivity differences between C- and N-metalated nitriles stimulated a general route to metalated nitriles having a variety of metal counterions, that, indeed, exhibit reactivities which complement metal amide deprotonation-electrophilic alkylation of nitriles.<sup>25</sup>

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#### **Results and Discussion**

Despite extensive halogen-metal exchange<sup>26</sup> of functionalized organometallics, only recently has halogenmetal exchange been achieved with  $\alpha$ -halonitriles.<sup>25,27</sup> Historically,  $\alpha$ -chloronitriles were serendipitously subjected to chlorine-lithium exchange with BuLi,<sup>28</sup> or LDA,<sup>29</sup> during the previously perplexing oxidative conversion to ketones. Presumably the perceived difficulty<sup>30</sup> in performing chlorine-metal exchange prevented the reaction mechanism from being identified. The requisite  $\alpha$ -halonitriles are readily synthesized by brominating (PBr<sub>3</sub>, Br<sub>2</sub>)<sup>31</sup> or chlorinating (PCl<sub>5</sub>, pyridine)<sup>32</sup> the parent nitriles, through organomercury conjugate additions to  $\alpha$ -chloroacrylonitrile,<sup>33</sup> and through Diels-Alder cycloadditions with  $\alpha$ -chloroacrylonitrile.<sup>34</sup>

Exploratory reactions of bromonitrile **12a** with *i*-PrMgBr demonstrated the viability of accessing magnesiated nitriles through bromine-magnesium exchange (Scheme 2). Initial optimization was complicated by the

# SCHEME 2. Prototypical Bromine-Magnesium Exchange



competitive formation of a dimeric material (vide infra), which led to dramatically reducing the time before addition of the electrophile. Sequential addition of *i*-PrMgBr to **12a** followed, 1 min later, by the electrophile causes rapid alkylation, implying a fast brominemagnesium exchange at -78 °C. A rapid exchange correlates with the immediate color change that occurs upon addition of the Grignard reagent, although the yellow color may potentially be due to formation of the bromate complex **13a**.<sup>35</sup> Fragmentation<sup>35</sup> of the bromate complex **13a** generates *i*-PrBr and the magnesiated nitrile **14a**, which then reacts with the electrophile to furnish the alkylated nitrile **15a**.

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TABLE 1.	Halogen-Magnesium and -Lithium
Exchange-A	Alkylations of α-Halonitriles

avenar	ige-Aikylatio	ons of u-maior	numes			
entry	$\alpha$ -halonitrile	reaction	nitrile	yie	eldª	
				А	В	
1		/-PrMgBr,				
	10-B	ы	$\Box$	72%		
	12a*		15a			
2	Br	<i>i</i> -PrMgBr,				
	Ph <sup>CN</sup>				710%	
	12a <sup>b</sup>		CN CN		/170	
			Ú 15b			
3		i-PrMgBr,	CN CN			
	$\bigcirc$	Br	$\square$	62%	82%	
	<sup>∼</sup> 12b					
4	Br_CN	<i>i</i> -PrMgBr,	°			
	$\square$	Ĵ	MeO-CN	58%	80%	
	12b	MeO´ `CN	$\bigcup_{i=1}^{n}$	2070	0070	
			150			
5		<i>i</i> -PrMgBr, O	→ L, CN			
	U	→ L ci	· ^	52%	70%	
	120	I				
6	Br_CN	i-PrMgBr,	он			
	$\cap$	0 L	C5H11 CN		65%	
	12b	°C <sub>5</sub> H <sub>11</sub>				
			151			
7		/-PrMgBr,				
	U_12b	<0	$\neg$		73%	
	120		15g			
8	Br_CN	i-PrMgBr,	Ph CN			
	$\square$	Ph Br			70%	
	12b		15h			
0	Br. CN	<i>i-</i> PrMgBr,				
,	$\square$	Br	<i>"</i>		63%	
	12b	~	15		0570	
10	~	DMaR	- 04			
10	1 CN 12c				79%	
			15j			
11	Br CN	<i>i</i> -PrMgBr,	ОН			
	12d	<o< td=""><td></td><td></td><td>60%°</td><td></td></o<>			60%°	
		<u> </u>	15j			
12		BuLi,	<u>∽_</u> CN			
	$\bigcirc$	Br' 🗸	$\bigcirc$	72%		
	12e		∑15c			
13		BuLi,	N CN			
	$\bigcirc$	<u> </u>	$\mathcal{T}$	54%		
	- 12e		↓			
14	·	n-BuLi	— ОН			
14	17 CN 12c		(CN		51%	

 $^a$  Isolated yields for sequential metalation–alkylation, procedure A, and with an in situ metalation–alkylation, procedure B.  $^b$  Prepared by free radical bromination with NBS.<sup>39</sup>  $^c$  Contains 6% of the hydroxynitrile resulting from deprotonation and carbonyl addition.

15j

Diverse  $\alpha$ -halonitriles efficiently alkylate an array of electrophiles using the optimized exchange-electrophile addition procedure (Table 1, column A). Brominemagnesium exchange generates magnesiated nitriles that efficiently alkylate representative alkyl halide and carbonyl electrophiles (Table 1, entries 1–11), whereas the corresponding chloronitriles react significantly less ef-

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fectively. Chloronitriles exchange more slowly with *i*-PrMgBr resulting in considerable dimerization between the magnesiated nitrile and unreacted chloronitrile, which is conveniently avoided by performing the exchange with BuLi (Table 1, entries 12–14). The efficient lithium–chlorine exchange attests to the activation of the carbon–chlorine bond by the nitrile since chlorine–metal exchange is particularly difficult and seldom observed.<sup>30</sup>

The extremely rapid chlorine–lithium and bromine– magnesium exchanges stimulated a more daring in situ protocol where *i*-PrMgBr or BuLi is added to a solution containing the halonitrile and the electrophile.<sup>36</sup> Remarkably, the in situ protocol is successful even with particularly electrophilic functionalities such as acyl cyanide and aldehyde electrophiles. Comparing the exchange-alkylation and in situ alkylations reveals the latter to be the method of choice, affording consistently a 20% higher yield of alkylnitrile (Table 1, column B). Presumably the increased yield of the in situ procedure is partly due to rapid capture of the magnesiated nitrile with the electrophile, which effectively circumvents prior single electron transfer between the magnesiated nitrile **14** and the electrophilic halonitrile **12**.<sup>37</sup>

Key regio- and chemoselectivity preferences of magnesiated nitriles were probed with the in situ protocol. Alkylations with cinnamyl and propargyl bromide occur exclusively through  $S_N2$  alkylation, analogous to alkylations of lithiated nitriles obtained by metal amide deprotonation.<sup>1b</sup> Perhaps not surprisingly, iodine-magnesium exchange is faster than the corresponding brominemagnesium exchange as gauged by the increased yield for comparable exchange reactions of *i*-PrMgBr with iodoacetonitrile and bromoacetonitrile (Table 1, entries 10 and 11). Even for the magnesium-bromine exchange of bromoacetonitrile, only 6% of the hydroxynitrile arising from deprotonation of bromoacetonitrile is obtained, indicating that the metal-halogen exchange is faster than the competitive deprotonation.<sup>38</sup>

Dramatic advances in copper-halogen exchange<sup>40</sup> stimulated developing an analogous copper-halogen exchange with  $\alpha$ -halonitiles.<sup>41</sup> Optimization experiments with bromonitrile **12b** revealed that a facile copper-bromine exchange with Me<sub>2</sub>CuLi is complete within 1.5 h at 0 °C. Subsequent addition of allylic electrophiles generates alkylated nitriles (Table 2, entries 1–3), with complete S<sub>N</sub>2' displacement occurring for the alkylation with propargyl bromide (Table 2, entry 4).<sup>42</sup> Analogous cuprate exchange-alkylations of the bromonitrile **12f** 

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TABLE 2.  $Me_2CuLi$ -Induced Exchange-Alkylations of  $\alpha$ -Bromonitriles

ontru		alaatrophila	nitrilo	wield
entry	α-bromonitrile	electrophile	mune	yleid
1	Br CN	<i>S</i> r → Br	CN 15c	69%
2	Br CN	PhBr	Ph CN 15h	54%
3	Br CN	CO <sub>2</sub> Et	EtO <sub>2</sub> C 15k	70%
4	Br CN	Br	CN 151	73%
5	CN 105 Br 12f	Br	CN ()5 15m	85%
6	CN M5 Br 12f	Br	CN ()5 15n	77%
7	CN ()5 Br 12f	CO <sub>2</sub> Et Br	CN CO <sub>2</sub> Et	78%
8	CN M5 Br 12f	NCOMe	CN OMe 15p	87%

proceed without any observable deprotonation, affording high yields of the alkylated nitriles with allylic and carbonyl electrophiles (Table 2, entries 5–8).

Key mechanistic insight was gleaned from copperhalogen exchange reactions with the bromonitrile 12a(Scheme 3). Me<sub>2</sub>CuLi-induced exchange of 12a generates

# SCHEME 3. Organocopper Exchange of Bromonitrile 12a



the dimer  $16^{43}$  (26%) and dimethylphenylacetonitrile (17, 42%), even when the exchange was performed with an electrophile in situ at -78 °C. Presumably<sup>35</sup> Me<sub>2</sub>CuLi reacts with 12a to generate the bromate 13a that

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(43) Obtained as a mixture of dl and meso isomers

fragments to the *C*-cuprated nitrile **18a**.<sup>44</sup> Reductive elimination of **18a** leads to **17** whereas competitive alkylation of **18a** with the electrophilic bromonitrile **12a**, through single electron transfer, affords **16**.<sup>37,39,45</sup> Bromine-copper exchange of **12a** with the less reactive MeCu<sup>46</sup> affords **16** (62%), but without the formation of **17** since collapse of the bromate **13a** leads to an organocopper species and not a cuprate.<sup>47</sup>

Formation of dimethylphenylacetonitrile (17) by reductive elimination identifies *C*-cuprated nitriles as the key intermediates resulting from Me<sub>2</sub>CuLi exchange. The formation of *C*-cuprated nitrile 18b (Scheme 4) is consistent with the  $S_N2'$  displacement of propargyl bromide and difficult to rationalize if copper were coordinated to nitrogen (19).<sup>48</sup> Halogen-magnesium exchange of bromonitrile 12b through an ate complex may initially lead to the *C*-magnesiated nitrile 14b, although progression to an *N*-metalated nitrile is equally conceivable. The ambiguity is not resolved during alkylation with propargyl bromide since *N*- and *C*-magnesiated nitriles are both anticipated to react by  $S_N2$  alkylation,<sup>1b</sup> leaving the site of magnesium coordination an open question (Scheme 4).



Lithiated nitriles are, almost without exception,<sup>17</sup> *N*-coordinated.<sup>9b,c</sup> Alkylation of the, presumed, *N*-lithiated nitrile **19b** with propargyl bromide causes exclusive  $S_N 2$ displacement (Scheme 5). The preference of the cuprate **18b** for  $S_N 2'$  alkylation (Scheme 4) stimulated an intriguing  $N \rightarrow C$  transmetalation of the lithiated nitrile **19b** with MeCu. Sequential LDA deprotonation of **20** and addition of MeCu generates the putative *C*-cuprated nitrile **18b**, which reacts with propargyl bromide to give exclusively the  $S_N 2'$  allenylnitrile **15l**. Collectively, these alkylations indicate a high propensity of copper for coordination on carbon.

(47) The absence of 17 requires that no alkylation occurs between the organocopper and organocuprate 18a, with the bromomethane generated from fragmentation of the bromate 13a.





#### Conclusion

Halogen-metal exchange of  $\alpha$ -halonitriles with organometallics generates diverse metalated nitriles. Grignard and alkyllithium reagents trigger the rapid metalhalogen exchange of  $\alpha$ -halonitriles whereas the exchange with lithium dimethylcuprate is considerably slower. An array of electrophiles efficiently intercept the intermediate metalated nitriles either through sequential addition of the electrophile to the metalated nitrile or by performing the exchange in the presence of the electrophile. The reactivities of organocopper- and halomagnesium-substituted nitriles imply C-metalated nitrile intermediates, at least in the former instance, with complementary regioselectivity preferences in comparable alkylations with propargyl bromide. Synthetically, the organocoppersubstituted nitriles are efficiently accessed by sequential deprotonation followed by the addition of MeCu. Collectively the metal-halogen exchange allows tuning of the metal coordination site with N- and C-metalated nitriles exhibiting reactivity trends complementary to those of metalated nitriles obtained through deprotonation with metal amide bases.

#### **Experimental Section**

**General Nitrile Bromination Procedure.** Neat bromine and nitrile were sequentially added to ice-cooled PBr<sub>3</sub>. After the addition, the ice bath was removed and the reaction was heated at 60 °C. After 5 h the mixture was poured onto ice and extracted with ether  $(3\times)$ , and then the crude extracts were washed with NaHCO<sub>3</sub>  $(3\times)$  and water and then dried (MgSO<sub>4</sub>). Concentration and purification of the crude product by radial chromatography afforded analytically pure material.

**General Alkylation Procedure A.** A THF solution of *i*-PrMgBr (1.05 equiv) was added to a -78 °C, THF solution of the bromonitrile (1.0 equiv) and, after 1 min, neat electrophile (1.05 equiv) was added. After 2 h saturated, aqueous NH<sub>4</sub>Cl solution was added, and the crude product was extracted with EtOAc, dried (MgSO<sub>4</sub>), concentrated, and purified by radial chromatography to afford analytically pure material.

**General in Situ Alkylation Procedure B.** A THF solution of *i*-PrMgBr (1.05 equiv) was added to a -78 °C, THF solution of the bromonitrile (1.0 equiv) and the electrophile (1.05 equiv). After 2 h saturated, aqueous NH<sub>4</sub>Cl solution was added, and the crude product was extracted with EtOAc, dried (MgSO<sub>4</sub>), concentrated, and purified by radial chromatography to afford analytically pure material.

General Bromine-Copper Exchange Procedure. A THF solution of the bromonitrile was added to a 0 °C, ether solution of Me<sub>2</sub>CuLi [generated by adding methyllithium (2.2 equiv) to copper iodide (1.2 equiv)]. After 1 h, neat electrophile (1.30 equiv) was added and, after a further 2 h at 0 °C,

<sup>(44)</sup> For the synthesis of C-cuprated nitriles see: (a) Kondo, J.; Ito, Y.; Shinokubo, H.; Oshima, K. Angew. Chem., Int. Ed. **2004**, 43, 106. (b) Tsuda, T.; Nakatsuka, T.; Hirayama, T.; Saegusa, T. J. Chem. Soc., Chem. Commun. **1974**, 557. (c) Corey, E. J.; Kuwajima, I. Tetrahedron Lett. **1972**, 487.

<sup>(45)</sup> Aryl- and  $\alpha$ -aminomethyl cuprates couple in the presence of electrophiles: (a) Dieter, R. K.; Li, S. J.; Chen, N. J. Org. Chem. 2004, 69, 2867. (b) Kronenburg, C. M. P.; Amijs, C. H. M.; Wijkens, P.; Jastrzebski, J. T. B. H.; van Koten, G. Tetrahedron Lett. 2002, 43, 1113. (c) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. Angew. Chem., Int. Ed. Engl. 1994, 33, 1842. (d) Lipshutz, B. H.; Siegmann, K.; Garcia, E. J. Am. Chem. Soc. 1991, 113, 8161.

<sup>(46)</sup> MeCu does not cause bromine-copper exchange with 12b.

<sup>(48)</sup> Potentially, the transition state for reductive elimination could arise from either an *N*- or *C*-cuprated nitrile ground state.

saturated, aqueous  $NH_4Cl$  solution was then added. The mixture was stirred vigorously with exposure to air for 30 min, and the crude product was then extracted with ethyl ether and dried (MgSO<sub>4</sub>). Concentration of the crude product and purification by radial chromatography afforded analytically pure material.

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**Supporting Information Available:** Experimental procedures and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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