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### Sulfone–Metal Exchange– Alkylation of SulfonyInitriles

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**Abstract:** The first general sulfone-metal exchange is described. Treating substituted 2-pyridylsulfonylacetonitriles with BuLi or Bu<sub>3</sub>MgLi generates metalated nitriles that alkylate a variety of electrophiles to efficiently install quaternary centers. The 2pyridylsulfone is critical for the sulfone-metal exchange, anchoring the organometallic proximal to the electrophilic, tetrasubstituted sulfone to override complex-induced deprotonation. Alkylating commercial 2pyridinesulfonylacetonitrile with mild bases, K<sub>2</sub>CO<sub>3</sub> or DBU, followed by sulfone-metal exchange-alkylation rapidly assembles quaternary nitriles through three alkylations, only one of which requires an organometallic reagent.

Metalation strategies lie at the core of organic synthesis.<sup>[1]</sup> Formation of metalated nitriles is illustrative of the different metalation strategies used to generate organometallics: traditional base-promoted deprotonation  $(1 \rightarrow 2 \text{ or } 3)$ , <sup>[2]</sup> halogenmetal exchange  $(5 \rightarrow 2 \text{ or } 3)$ , <sup>[3]</sup> sulfoxide-metal exchange  $(6 \rightarrow 2/3)$ , <sup>[4]</sup> and sulfide-metal exchange  $(7 \rightarrow 2 \text{ or } 3)$ , Scheme 1).<sup>[5]</sup> Each strategy has distinct advantages by providing selective access to *C*-metalated (2) or *N*-metalated nitriles (3) that intrinsically control alkylation chemo-,<sup>[6]</sup> and stereoselectivity.<sup>[7]</sup> Conspicuously absent from the types of exchangeable functionality are sulfones such as 8.<sup>[8]</sup>

Traditional deprotonation



Scheme 1. Nitrile-based metalation-alkylation strategies.

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Conceptually, a sulfone-metal exchange would converge the exceptionally rich chemistry of sulfones  $^{[I]} \circ ^{]}$  with the diverse alkylation potential of organometallics while providing a versatile alternative to reductive desulfonylation.  $^{[I]}$  For substituted sulfonyl acetonitriles such as 10, an additional advantage lies in using mild base for the alkylation of commercially available sulfonyl acetonitrile  $^{[I]} (9 \rightarrow 10$ , Scheme 2); the sequence obviates the need for two equivalents of a strong base typically required in nitrile alkylations.  $^{[2]}$ 



Scheme 2. Sulfone-directed metalation vs exchange.

Developing a sulfone-metal exchange requires overcoming the excellent directing group ability of sulfones<sup>[12]</sup> which channels organometallics to complex-directed ortho deprotonation<sup>[13]</sup> (**11**) rather than attack at the tetra-substituted sulphur (**12**). Indeed, attempted sulfone-metal exchange with BuLi on the phenylsulfone **10** afforded the imine **13**, presumably by complexation, ortho-deprotonation (**11**), and attack of the resultant aryllithium on the nitrile.

Overcoming the deprotonation by replacing the phenylsulfone with a 2-pyridylsulfone ( $14 \rightarrow 15a$ , Scheme 3) was predicated on the strong chelation of organometallics with 2-pyridines<sup>[14]</sup> to anchor the nucleophilic alkyl group proximal to the electrophilic, but tetrasubstituted, sulfur (16a). Although no exchange occurred on addition of *i*-PrMgCl to 15a, the more nucleophilic Bu<sub>3</sub>MgLi triggered a smooth sulfone-magnesium exchange between -15 °C and -5 °C [ $_{15}$ ] ( $15a \rightarrow 16a \rightarrow 17a$ , Scheme 3). Trapping the magnesiated nitrile 17a with BnBr as a test electrophile efficiently afforded the quarternary nitrile 4a. Alternatively, the exchange was equally efficacious with BuLi (5 min, -78 °C) to afford a lithiated nitrile that was benzylated to afford 4a (Scheme 2). In each case, butyl-2-pyridylsulfone was generated in high yield.<sup>[16]</sup>



Scheme 3. 2-Pyridylsulfone exchange-alkylation.

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The successful exchange-alkylation stimulated the development of a method to sequentially alkylate commercially available 2-pyridylsulfonylacetonitrile (14) with two different electrophiles.<sup>[17]</sup> DBU was found to perform admirably (Scheme 3);<sup>[18]</sup> sequential addition of DBU and two different electrophiles provided an efficient synthesis of unsymmetrical sulfonylnitriles (15).

The sulfone-metal exchange-alkylation is effective with diverse electrophiles across a variety of different cyclic and acyclic scaffolds (Table 1, entries 1-10 and 11-15, respectively). Alkylations are efficient with activated (entries 1-2, 7, and 9-14) and unactivated alkyl halides (entries 3 and 15), diphenyl disulphide (entry 4), methyl cyanoformate (entries 5, 8) and 2-chloropyridine (entry 6), a challenging electrophile for metalated nitrile arylation.<sup>[19]</sup> Allylation of the conformationally constrained cyclohexanecarbonitrile **15**c<sup>[20]</sup> afforded an 11.3:1 ratio of axial to equatorial nitriles (**4h**, Table 1, entry 7), a stereochemical outcome consistent with alkylation via an equatorial magnesiate.<sup>[21]</sup>





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<sup>[a]</sup> Performing the exchange with BuLi afforded **4c** in 82% yield. <sup>[b]</sup> Obtained as an 11.3.1 ratio of axial to equatorial nitrile diastereomers. <sup>[c]</sup> BuLi was used because MgBu<sub>3</sub>Li leads to butyl displacement of the allyllic chloride.

15i

The sulfone-metal exchange of **15h** and **15i** are an intriguing pair (Table 1, entries 14 and 15). Exposure of **15h** to BuLi afforded a lithiated nitrile that alkylated benzyl bromide rather than engaging in a 4-exo-tet cyclization, presumably because of the unfavourable trajectory involved in forming a methylene cyclobutane (Entry 14).<sup>[22]</sup> In contrast, a sulfone-magnesium exchange with **15i** triggered a facile 5-exo-tet cyclization to afford the cyclopentylcarbonitrile **4p** (entry 15).

The sulfone-magnesium exchange was paired with a conjugate addition to install contiguous tertiary-quaternary centers (Scheme 4). Condensing pyridylsulfonylacetonitrile (14) with benzaldehyde afforded alkenesulfonylnitrile 18. Unlike most alkenenitriles<sup>[23]</sup> 18 engaged in a facile conjugate addition upon addition of PhLi (Scheme 4). The efficacy of the conjugate addition likely stems from chelation with the sulfone<sup>[12]</sup> and pyridine,<sup>[14]</sup> allowing conjugate addition through the sixmembered complex 19. The resultant lithiated nitrile was

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efficiently trapped with methyl iodide to afford the sulfonyl nitrile **15j**, a  $\beta$ ,  $\beta$ -disubstituted nitrile. Standard sulfone-magnesium exchange of **15j** followed by methylation afforded the quaternary nitrile **4q** (82% yield).



Scheme 4. Conjugate Addition-Exchange Alkylation

Metalated nitriles are powerful nucleophiles capable of challenging alkylations that fail with enolates.<sup>[24]</sup> The exceptional nucleophilicity suggested that the sulfone-metal exchange might allow the displacement of allylic ethers<sup>[25]</sup> thereby extending the range of available electrophiles for carbon-carbon bond formation. Exploratory experiments with the magnesiated or lithiated nitriles derived from **15a** and allyl methyl ether (**20a**, 10 equiv) afforded the allyl nitrile **4c** in low yield (Figure 1). Pairing BuLi for the exchange with the glycol ether **20b** afforded the allylated nitrile **4c** in 53% yield. <sup>[26]</sup> Although speculative, the successful allylation may involve activation of the olefin through a lithium complex **21**<sup>[27]</sup> which is consistent with the lack of allylation with the glycol **20c**. Allylation of the seven-membered nitrile **15d** with **20b** gave **4k** in 51% yield.

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Figure 1. Lithiated nitrile alkylations of allylic ethers.

2-Pyridylsulfonylacetonitriles engage Bu<sub>3</sub>MgLi or BuLi in the first sulfone-metal exchange. The sulfone-metal exchange offers complementary advantages to existing routes to metalated nitriles: substituted sulfones are readily prepared from commercially available 2-pyridinesulfonylacetonitrile, alkylations of 2-pyridinesulfonylacetonitrile only require K<sub>2</sub>CO<sub>3</sub> or DBU thereby avoiding the use of two equivalents of strong base, and sulfonylnitriles are typically stable, crystalline solids. The sulfone-metal exchange-alkylation is remarkably facile across a range of cyclic and acylic substrates affording quaternary nitriles even through alkylation with allylic ethers.

#### Acknowledgements

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<sup>[15]</sup> Determined by monitoring a THF-*d8* solution by <sup>1</sup>H NMR which shows the rapid formation of butyl-2-pyridylsulfone.

<sup>[16]</sup> The exchange with Bu<sub>3</sub>MgLi afforded butyl-2pyridylsulfone in 93%. The metalated nitrile does not appear to deprotonate the sulfone (for a related example see: Lovinger, G. J.; Aparece, M. D.; Morken, J. P. *J. Am. Chem. Soc.* **2017**, *139*, 3153–3160.

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 $[_{20}]$  The configuration of **15c** was determined by crystallographic analysis. The authors have deposited the crystallographic data for **15c** with the Cambridge Crystallographic Data Center (CCDC# 1517980 and 1517981). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

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 $[_{26}]$  Critical to the success of the alkylation is the rapid addition of the allyl glycol ether within one minute of the addition of butyllithium. Allylation with **20a** and the lithiated cyclohexanecarbonitriles derived by LDA deprotonation, lithium-sulfide exchange, and lithium-sulfoxide exchange afforded less than 25% yield of allyl nitrile **4c**. Possibly the allylation with **20b** proceeds through a ten-electron sulfuranylide prior to generating a lithiated nitrile.

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Three makes a hat-trick! Sulfone-metal exchange of pyridylsulfonylacetonitriles demonstrates that all three oxidat states of sulphur can function as latent organometallics throu exchange processes.



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