DOI: 10.1002/ange.201103275

Mixed-Metal Chemistry

Magnesium-Mediated Benzothiazole Activation: A Room-Temperature Cascade of C−H Deprotonation, C−C Coupling, Ring-Opening, and Nucleophilic Addition Reactions**

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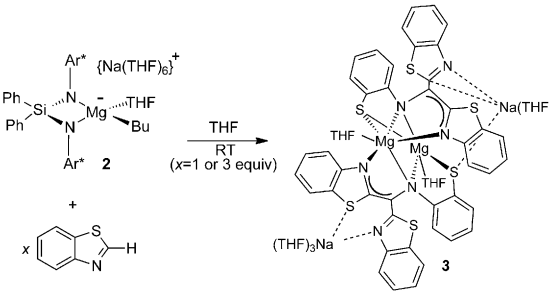
Five-membered ring aromatic heterocycles, in particular 1,3-azoles, are common building blocks for the synthesis of a multitude of natural products, pharmaceuticals, and other biologically active molecules.[1] An invaluable synthetic tool which facilitates the incorporation of these heterocyclic rings into more complex organic scaffoldings is deprotonative metalation.[2] Thus, 1–3 azoles can be readily deprotonated at the C2 position using conventional organometallics such as organolithium or Grignard reagents,[3] as well as by more sophisticated magnesiate[4] and zincate[5] systems. NMR and solid-state structural studies have shown that while C2-lithiated and magnesiated oxazoles undergo rapid isomerization to the more stable ring-opened 2-(isocyano)enolate forms,[4,6] metalated thiazoles are much more stable and do not suffer such rearrangements.[6b] Thus C2-deprotonated thiazoles can be efficiently prepared using magnesium-based reagents such as Hauser bases[7] or Turbo Grignard reagents,[8] and have been intercepted with electrophiles in high yields. This methodology can also be used in large-scale reactions, as shown by the 10 kg scale synthesis of argininylbenzo[d]thiazole (an intermediate to the trytapse inhibitor RWJ-56423) for which deprotonation of benzothiazole by EtMgCl is a key step.[9]

In contrast with these reports which provide evidence of the relatively straightforward C2 magnesiation of these heterocycles, herein we report our findings on the remarkable reactivity of new magnesium compounds supported by the bulky chelating bis(silylamido) ligand $\{Ph_2Si(NAr^*)_2\}^{2-}$ ($Ar^* = 2,6\text{-}i\mathrm{Pr}_2\text{-}C_6H_3$) with benzothiazole (btz), which discloses an unprecedented type of activation promoted by a main-group metal. Thus, isolation and structural identification of key reaction intermediates suggest that the initial deprotonation (magnesiation) of benzothiazole by sodium magnesiate $[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(Bu)(THF)\}^-]$ (**2**; for structure see Scheme 1 and Supporting Information) initiates a domino reaction of C−H deprotonation, C−C coupling, ring opening, nucleophilic addition, and intramolecular deprotonation.

Despite increasing interest in the synthesis of magnesium compounds supported by highly bulky ligands, which have been key to recent breakthroughs in magnesium chemistry,[10] the effects that such ligands may have in the reactivity/structure of alkali-metal magnesiates still remains largely unknown. Our studies started by reacting sodium magnesiate $[NaMgBu_3]$[11] with one equivalent of bis(silyl)amine $\{Ph_2Si(NHAr^*)_2\}$ (**1**),[12] which produced solvent-separated sodium magnesiate $[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(Bu)(THF)\}^-]$ (**2**) in an 89 % yield (see the Supporting Information for full characterization). Building on our previous studies showing that sodium magnesiates are regioselective bases enabling direct magnesiation (alkali-metal-mediated) of a wide range of aromatic molecules,[13] we decided to probe the ability of **2** as a base towards btz. The room temperature 1:1 reaction formed a deep red solution which deposited a crop of red crystals of **3** in 28 % yield; this yield increased to 89 % upon using three equivalents of btz (Scheme 1).



Scheme 1. Reaction of sodium magnesiate **2** with benzothiazole. THF = tetrahydrofuran.

X-ray crystallographic studies unveiled the complex molecular assembly of **3** (Figure 1) that features two similar magnesium centers (each solvated by THF) connected by the two newly generated trianionic fragments **A** (Figure 2), with two negative charges localized on an S and N atom, and a third one delocalized over the central sp^2 C and the C=N bonds of the two neighboring benzothiazolyl rings. The contacted-ion pair magnesiate **3** is completed by two THF-solvated Na atoms.

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[**] We thank the EPSRC, the Royal Society (University Research Fellowship to E.H.), and the University of Strathclyde (studentship to Z.L.) for their generous sponsorship of this research.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103275.

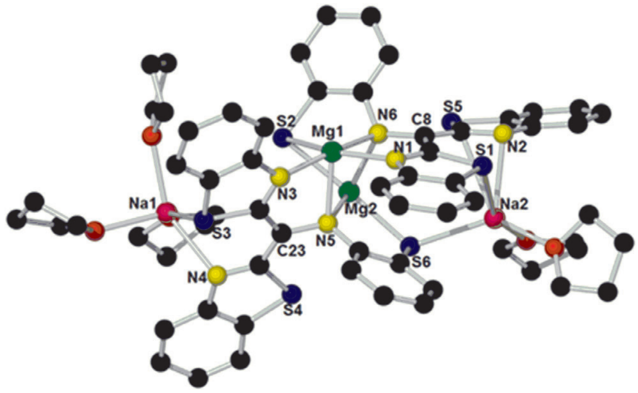


Figure 1. Molecular structure of **3** with hydrogen and THF ligands coordinated to Mg atoms omitted for clarity.

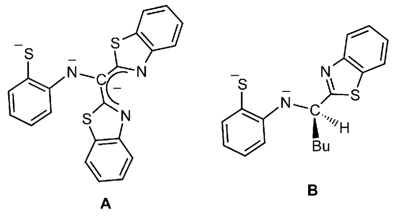
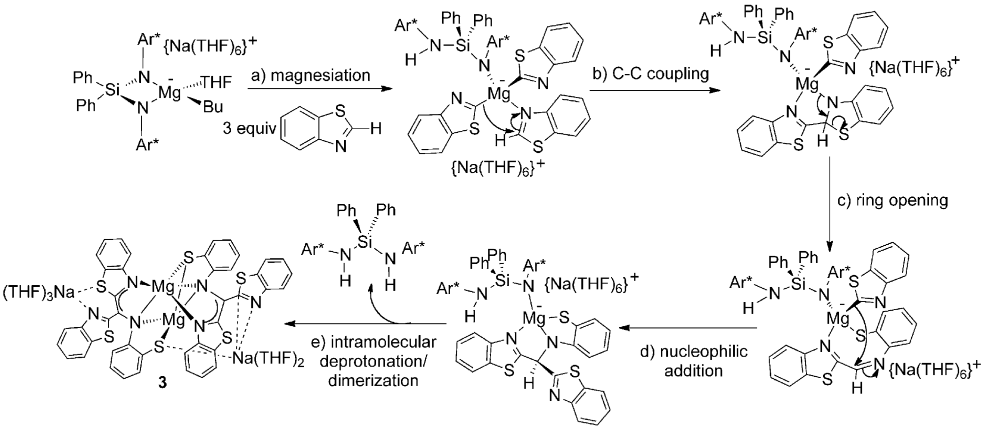


Figure 2. Representation of fragments **A** and **B** resulting from the benzothiazole activation reactions.



Scheme 2. Proposed mechanism for the formation of **3** (solvating THF molecules on Mg are omitted for clarity).

From the constitution of **A**, it appears that three molecules of btz have been activated, with one undergoing ring opening (resulting from a C–S bond cleavage) and coupling with two other benzothiazolyl units. Furthermore, the lack of H atoms at the original C2 positions of the three btz molecules, suggests that all three (two amido and one alkyl) potential basic arms of magnesiate **2** are used in forming **3**.[14] This was supported by ^{1}H NMR analysis of the reaction filtrate, which confirmed the presence of bis(silyl)amine {$Ph_2Si(NHAr^*)_2$} (**1**) as a major co-product. Contrasting with previous reports that btz can be quantitatively magnesiated at the C2 position by the Knochel base (TMP)MgCl.LiCl, these results seem more related to the reactivity exhibited by d^0f^n metal alkyl complexes (M = Sc, Y, Lu, U) supported by 1,1′-ferrocenylene bis(amide).[15] Elegant mechanistic studies by Diaconescu reveal that these compounds can promote ring-opening reactions of methyl imidazole, involving C–H activation of the heterocycle and subsequent C–C coupling reactions, with the bis(amide) ancillary ligand playing an important role in stabilizing/trapping reaction intermediates involved.[15a] Based on these earlier studies, and considering the similarities recently noted between the chemistry of lanthanides and alkaline earth metal complexes,[16] a tentative mechanism to rationalize the formation of **3** can be proposed (Scheme 2). Thus, initially sodium magnesiate **2** mediates the deprotonation of two btz molecules, while the third btz acts as a neutral N-donor ligand to Mg (step a, Scheme 2).[17] This coordination would favor the intramolecular nucleophilic attack of one benzothiazolyl unit onto the C2 position of the btz molecule, thus bringing about dearomatization of the latter and forming a new C–C bond (step b, Scheme 2).[17] This putative intermediate can then undergo ring opening of the nonaromatic ring, through C–S cleavage, to form an electrophilic C=N bond (step c, Scheme 2) which in turn can react with the remaining benzothiazolyl to generate a dianionic organic fragment resulting from coupling three initial btz molecules (step d, Scheme 2). Finally, this intermediate can be internally deprotonated at the remaining aliphatic sp^3 CH by the remaining basic arm of **2**, thereby generating the sodium magnesiate containing the trianionic fragment **A** (which can then dimerize to yield **3**) along with the concomitant formation of bis(amide) **1** (detected by ^{1}H NMR spectroscopy).

Unlike the f-block imidazole activation studies, where reactions had to be thermally induced ($T = 85–100$ °C, 2–3 days),[15a,b] the reaction of **2** with btz to yield **3** appears much faster, occurring almost instantaneously at room temperature as evidenced by ^{1}H NMR monitoring. To detect some possible reaction intermediates, the reaction was performed at 0 °C, producing novel sodium magnesiate **4** as an orange crystalline solid along with traces of **3** (Figure 3).

X-ray crystallographic studies established the molecular structure of **4**, with its 4:3 Na/Mg ratio which implies that it is formed through a disproportionation process. Remarkably **4** also contains two units of the same trianionic fragment **A** that is present in **3**, but its coordination mode differs significantly to that in **3** (Figure 3). Surprisingly, the structure also contains two of the novel dianionic fragment **B**.

Featuring two negative charges localized at S and N atoms, **B** has been formed by the activation of two btz molecules which have coupled with a Bu group from the

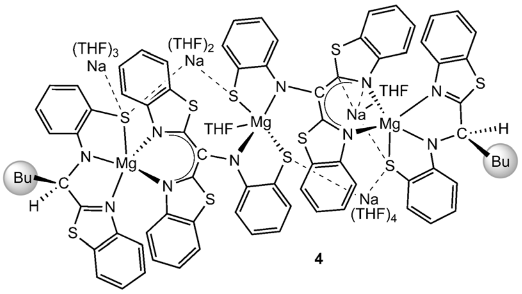
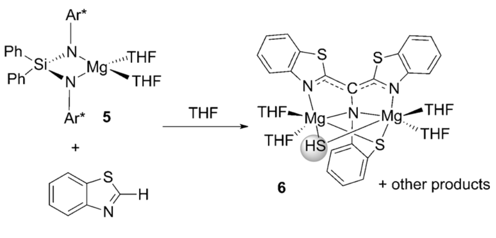


Figure 3. Representation of **4**.

sodium magnesiate **2**. Unlike **A**, only one btz molecule has been deprotonated whereas the other one that has undergone ring opening retains its hydrogen atom;[18] this structure therefore supports steps b and c in Scheme 2, thus implying that it is a non-deprotonated heterocyclic molecule that experiences dearomatization with a subsequent ring-opening reaction. Furthermore, the presence of a Bu group in **B** suggests that deprotonation appears to be the rate-determining step of this process. The formation of **B** can be rationalized similarly as proposed for **A** (Scheme 2), where now as a result of the lower temperature, a single btz molecule is deprotonated (with **2** acting as a mono-amido base, leaving the Bu group bonded to Mg)[19] with a subsequent similar fast C–C coupling and intramolecular ring-opening reaction that is then terminated by the Bu nucleophilic addition to the C=N bond (see Scheme S1 in the Supporting Information). In this case, the intramolecular deprotonation (step e, Scheme 2) does not occur, probably because it would generate a highly unstable carbanion with a negative charge α to an amido nitrogen atom.[20,21] The fact that even at low temperature compounds **3** and **4** can be obtained, highlights that these activation processes generating **A** and **B** are genuine examples of cascade chemistry, which once initiated (by magnesiation of one of two btz molecules), are followed by an unstoppable, unique sequence of fast intramolecular reactions.

Intrigued by the unusual activity of the bulky bis(amido) ligand in these reactions, contrasting with previous reports where related ligands acts as steric stabilizers for low oxidation state zinc and lanthanide complexes,[22] we studied the reaction of the Mg bis(amide) complex [(Ph$_2$Si-(NAr*)$_2$)Mg(THF)$_2$] (**5**) with two equivalents of btz. Being homometallic, **5** is expected to be much less basic than its magnesiate analogue **2**. However a reaction did occur producing complex **6** (yield upon isolation: 9%) which was analyzed by NMR spectroscopy and X-ray crystallography (Scheme 3 and see the Supporting Information).



Scheme 3. Reaction of homometallic magnesium bis(amide) **5** with benzothiazole

Dimeric **6** contains the trianionic fragment **A** bridging two Mg centers, thus demonstrating that even in the absence of the alkali metal, Mg ligated by {Ph$_2$Si(NAr*)$_2$}$^{2-}$ can promote the same type of btz activation (albeit in a less clean and lower yielding reaction), but more surprising is the presence of a bridging SH$^-$ ligand, which presumably results from the cleavage of two C–S bonds of a btz ring. Although sulfur extrusion processes have been previously reported for substituted thiazoles and related thiazolium salts,[23] to our knowledge this Mg-mediated bond-cleavage reaction has no precedent though it shares some features with the recent bimetallic-induced fragmentation of THF reported by Mulvey et al. In this report a Na magnesiate simultaneously cleaves two C–O bonds from THF, thus generating an oxo-dianion which is trapped in the core of an inverse crown.[24] We should cautiously mention that **6** is obtained as a minor product, and no other organometallic species from the reaction could be identified. However formation of **6** indicates that the bis(amido) ligand coordinated to Mg can initiate (to a certain extent) a related cascade of reactions to that observed for sodium magnesiate **2**.

In summary, where previous organomagnesium reagents simply deprotonate btz, this new ate modification, its key constituent being a bulky bis(amido) ligand, initiates a remarkable cascade process with btz comprising at least five distinct reaction types.

Experimental Section

Full experimental details and characterization of compounds **2–6** are included in the Supporting Information. CCDC 822041 (**2**), 822042 (**3**), 822043 (**4**), and 822044 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: May 12, 2011

Keywords: cascade reactions · heterocylces · magnesium · metalation · mixed-metal chemistry

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[17] Step a in Scheme 2 shows sodium magnesiate **2** acting as a dual alkyl/amido base, although the possibility of it acting as a bis(amido)base cannot be ruled out. However, in this regard we found that when the related mixed-metal diphenylamido species $[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(NPh_2)(THF)\}^-]$ reacts with 3 equivalents of btz **3** (or a related compound containing fragment **A**) was not observed and instead 2,2′-dibenzothiazole could be isolated as colorless crystals (presumably resulting from oxidation of the coupling product of a benzothiazole molecule with a C2-magnesiated benzothiazolyl unit). These findings not only suggest that the butyl group present in **2** is crucial to promote deprotonation of the two btz molecules shown in step a but also supports the C−C coupling process proposed in step b.

[18] The ^{1}H NMR spectrum of **3** in [D$_8$]THF exhibited an indicative multiplet at 4.30 ppm for this CH group which contrasts with the chemical shift observed for the hydrogen bonded to C2 in benzothiazole in the same deuterated solvent at 9.10 ppm.

[19] A study of a bis(amido)alkyl potassium magnesiate has demonstrated that it reacts kinetically through its amide, generating a metalated intermediate and concomitant amine, which is then deprotonated by its alkyl ligand to yield the thermodynamic final metalation product. This second step is slowed down by performing the deprotonation at 0 °C. W. Clegg, B. Conway, P. Garcia-Alvarez, A. R. Kennedy, R. E. Mulvey, L. Russo, J. Sassmannshausen, T. Tuttle, *Chem. Eur. J.* **2009**, *15*, 10702.

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[21] Contrastingly in **A**, there are two benzothiazolyl units bonded to the related carboanionic unit, thus enabling effective delocalization/stabilization of its negative charge across the $N{=}C{-}C{-}C{=}N$ junction.

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