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Regioselective magnesiation of N-heterocyclic molecules: securing insecure cyclic anions by a β-diketiminate-magnesium clamp

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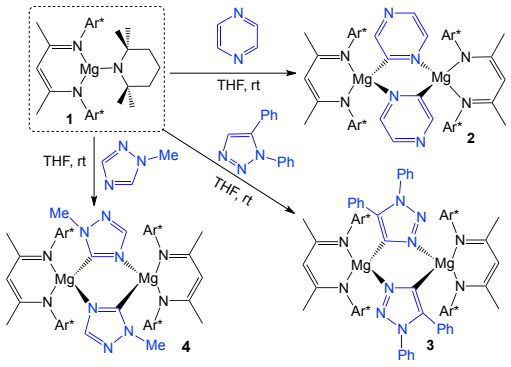
Laia Davin,[a] Ross McLellan,[a] Alberto Hernán-Gómez,[a] William Clegg,[b] Alan R. Kennedy,[a] Maria Mertens,[a] Iain Stepek,[a] and Eva Hevia*[a]

Using a specially designed magnesium metallating manifold, combining kinetically activated TMP amide base with a sterically amplified β-diketiminate ligand, this study has established a new regioselective strategy for magnesiation of challenging N-heterocyclic molecules. The broad scope of the approach is illustrated through reactions of pyrazine, triazoles and substituted pyridines by isolation and structural elucidation of their magnesiated intermediates.

N-heterocyclic aromatic molecules such as diazines, triazoles and pyridines are essential fundamental building blocks in synthesis, present in a multitude of pharmaceutically relevant and biologically active molecules.[1] Deprotonative metallation constitutes one of the most powerful methodologies for installing these ring systems into more complex molecular frameworks.[2] Lithium bases such as LiTMP (TMP= 2,2,6,6-tetramethylpiperidide) are the classical reagents of choice, but their use imposes severe limitations. This includes the need for extremely low temperatures (-78°C), large excesses of the lithium base and *in situ* electrophilic interceptions in order to cut down side reactions, such as fragmentation or addition processes, arising from the instability of the involved highly reactive heteroaryl lithium intermediates.[3] Bimetallic combinations, which pair Li with a softer metal such as Zn, Al or Ga in different ligand sets have shown greater promise, improving the stabilities of the organometallic intermediates, allowing these synergistic metallations to be performed under milder conditions.[4] Contrastingly, magnesium reagents have shown little promise, as their limited polarity leads to a limited reactivity, insufficient to produce metallation of weakly acidic C-H bonds, though some progress has been made using kinetically activated alkali-metal magnesiates.[5] Notwithstanding, even when using the LiCl-powered Mg amide $Mg(TMP)_2.2LiCl$, the additional presence of $ZnCl_2$ is critical for the success of the reaction, as it facilitates the *in situ* formation of heteroarylzinc species, which are significantly more stabilised (due to the lower polarity of their metal-carbon bonds) than corresponding magnesiated intermediates.[6] The synergistic character of these systems therefore involves three distinct metals.

Recently we have shown that it is possible to promote direct Mg-H exchange reactions of 1,3-benzoazoles using bespoke monomeric amide [(^{Dipp}Nacnac)Mg(TMP)] (**1**) (^{Dipp}Nacnac= Ar*NC(Me)CHC(Me)NAr*; Ar* = 2,6-$^{i}Pr_2$-C_6H_3) which combines a basic and kinetically activated TMP group with a sterically amplified innocent β-diketiminate ligand.[7]

Introducing a new synthetic application of β-diketiminate stabilised magnesium complexes, here we extend this approach into a more taxing territory. Thus we describe the successful regioselective magnesiation of challenging synthetically relevant N-heterocyclic substrates, disclosing the ability of these magnesium systems to generate, stabilise and entrap sensitive anions of the retained ring systems.



Scheme 1 Regioselective alpha-magnesiation of N-heterocyclic substrates by **1**.

Focussing first on the classical naked diazine, pyrazine, whose metallation is particularly difficult due to its tendency to undergo competitive nucleophilic addition,[3] we examined its reaction with equimolar amounts of **1** at room temperature

[a] WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1XL, UK; e-mail: eva.hevia@strath.ac.uk.
[b] School of Chemistry, Newcastle University, Newcastle upon Tyne, UK, NE1 7RU, UK

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which rapidly produced a dark green solution. Cooling this solution afforded light brown crystals of [{(^{Dipp}Nacnac)Mg($C_4H_3N_2$)}$_2$] (**2**) (isolated yield 51%, note NMR analysis of the reaction filtrate showed **2** is obtained quantitatively) resulting from selective C2 metallation of pyrazine (Scheme 1). NMR experiments of **2** in C_6D_6 established the regioselectivity of the reaction, as indicated by the appearance of three resonances at 9.28, 8.77 and 7.95 ppm in the ^{1}H NMR spectrum, consistent with the lack of symmetry in the pyrazinyl fragment. Determined by X-ray crystallography, the centrosymmetric dimeric structure of **2** (Fig 1) confirmed the C2-magnesiation of the N-heterocycle, with the metallated pyrazinyl rings acting as asymmetric bridges via their N and C2 atoms (i.e. N3 and C33 in Fig 1a) between two {(^{Dip}Nacnac)Mg} fragments.

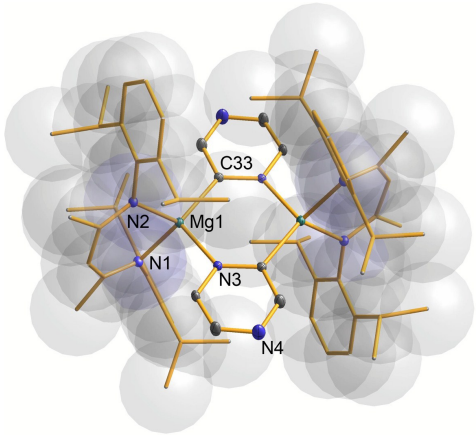


Fig 1 Molecular structure of **2**. Displacement ellipsoids are displayed at the 35% probability level and hydrogen atoms are omitted for clarity. Carbon atoms of ^{Dipp}NacNac framework are pictured as capped sticks with translucent space-filling van der Waals surfaces for a probe of 1.5 Å radius.

The room temperature, stoichiometric regioselective control of this reaction contrasts sharply with previous lithiation studies where even using a 4 molar equivalent excess of LiTMP at -75^{o}C, the relevant 2-substituted derivatives are obtained only in modest yields (39-65%) mixed in some cases with 2,5-disubstituted product.[8] Even more surprisingly, highlighting the inherent lack of stability of diazinyl magnesiated intermediates, Knochel has shown that when related quinoxaline is treated with Mg(TMP)$_2$.2LiCl only traces of C2 metallation are observed along with the formation of homocoupled product.[6] In **2**, the emerging insecure pyrazinyl anion can be trapped in its crystalline form at room temperature and secured by the low-coordinate {(^{Dipp}Nacnac)Mg} fragment, where the β-diketiminate ligand acts as a protective shelter towards the newly generated Mg-C bonds (Fig 1). Furthermore, as revealed by the structural studies, the unique dimeric motif of **2**, with the α-nitrogen of the pyrazinyl anion forming a stabilizing dative Mg-N interaction with a Mg centre of a neighbouring unit, facilitating further stabilization, minimizing electronic repulsion between the N lone pair and the negative charge of the new carbanion. Charge density investigations have quantified the contribution of related Mg-N interactions in the bonding present in [Mg[(pz*)$_3$C}$_2$] (pz*=3,5-dimethylpyrazolyl).[9]

Interestingly, illustrating the kinetic resilience of Mg-C vs Mg-N bonds, it should be noted that, when pyrazine was treated with the related butyl base [(^{Dipp}Nacnac)Mg(Bu)(THF)], the formation of **2** is not observed, affording instead donor adduct [(^{Dipp}Nacnac)Mg(Bu)($C_4H_4N_2$)]. This runs counter to the normal pattern of reactivity exhibited by conventional bases, as for example BuLi, which is a much stronger base than LiTMP.[10]

Moving on to five-membered heterocyclic triazoles, which are widely used in medicinal chemistry, their lithiation can be accomplished by strict control of the temperature, followed by electrophilic interception.[11] Contrastingly, at room temperature these intermediates tend to undergo fragmentation, eliminating nitrogen, affording instead N-phenylalkynamide lithium complexes, as for example in the case of 1,4-diphenyl-1,2,3-triazole.[12] Taking this substrate as a case study, we reacted it at room temperature with one molar equivalent of **1** in THF, which resulted in the formation of **3**, where the triazole has been magnesiated at its C5 position (isolated crystalline yield: 45%). This approach also works well for 1-methyl-1,2,4-triazole, a substrate furnishing **4** as a crystalline solid in a 66% yield (Scheme 1). We previously reported the metallation of 1-methyl-1,2,4-triazole using ate-activated base [(PMDETA)$_2$K$_2$Mg(CH_2SiMe_3)$_4$] followed by electrophilic interception with I_2; however, attempts to isolate or characterize the organometallic intermediate proved unsuccessful.[13] The molecular structures of **3** and **4** mimic many of the features of **2**, possessing dimeric arrangements where the triazolyl anions connect the Mg centres through their C=N junction, giving rise to a six-membered {MgNCMgNC} ring, with each Mg clamped by a β-diketiminate ligand. As discussed for **2**, these dual sigma Mg-C/dative Mg-N bonding modes must significantly contribute to the entrapment and stabilization of these sensitive anions, which despite their synthetic relevance, as far as we are aware, their structures have remained elusive.

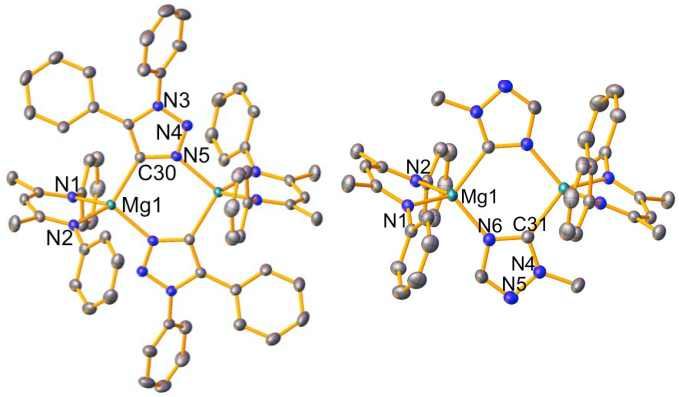
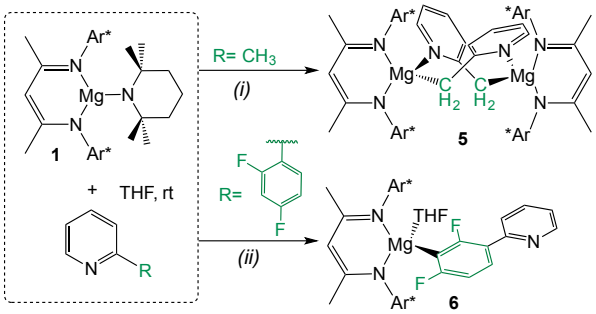


Fig 2. Molecular structure of **3** (left) and **4** (right) with 50% probability displacement ellipsoids (in both figures hydrogen atoms and ^{i}Pr groups have been omitted for clarity).

While **2-4** are products of alpha-magnesiation, with the C atom experiencing the metallation adjacent to a N atom which in turn engages with a neighbouring unit via N…Mg dative interactions, studies on C2-substituted pyridines revealed that **1** can promote regioselective lateral metallation of these N-heterocyclic substrates (Scheme 2). Thus reactions with 2-

picoline and 2-(2,4-difluorophenyl)pyridine (ppf), under the same conditions previously described for the synthesis of **2-4**, led to the isolation of **5** and **6** in 67 and 68% crystalline yield, respectively. ^{1}H NMR monitoring of these reactions in deuterated THF demonstrated that formation of **5** (resulting from the magnesiation of the methyl group in 2-picoline) and **6** (where ppf is metallated at the C3 position of the fluoroaromatic ring), occurs quantitatively, without observing other regioisomers in solution.



Scheme 2. Lateral magnesiation of 2-substituted pyridines by **1**

Synchrotron X-ray crystallographic studies confirmed the lateral deprotonation of these heterocyclic substrates (Fig 3). Picoline derivative **5** displays a dimeric motif, reminiscent of those described above for **2-4**, where two Mg centres are connected by two newly formed 2-picolyl anions, using their CH_2 and N groups, generating an internal eight-membered {MgCCNMgCCN} ring which adopts a pseudo-boat conformation. In this case, both picolyl anions point upwards in a splayed open arrangement [dihedral angle between the pyridine rings is 73.38(7)^{o}], rather than lying approximately coplanar as seen in **2-4**. This alternative geometry appears to be imposed by the picolyl anion bonding mode, with the N atom bound to one Mg while the CH_2 binds to the other Mg. Previous structural and theoretical studies have uncovered the diversity of feasible electronic situations in 2-picolyl anions resulting from the delocalisation of the negative charge into the ring from the carbanion, giving rise to different bonding modes to metal.[14] For example 2-picolyllithium complexes form dimeric structures where the anions act as aza-allyl ligands (simultaneously forming Li-C and Li-N bonds)[15] whereas lithium derivatives of Cα-substituted picolines have shown both aza-allyl and enamido bonding modes,[16] with the latter using exclusively its N atom to bond to Li. Interestingly, a close inspection of the geometrical parameters of **5** revealed that picolyl anions can be best described as carbanionic ligands, although some degree of delocalisation of the negative charge over the N atom is also evident as indicated by the relatively short Mg-N bond distances [mean value 2.1226 Å], when compared to that found by Hill for the coordination adduct [(^{Dip}Nacnac)Mg(Bu)(2-picoline)] [Mg-N, 2.216 (4) Å].[17]
Interestingly, magnesiation of ppf, a molecule that finds several applications in materials science as a precursor for organic light emitting diodes (OLEDs),[18] affords monomeric **6**. In **6** the position previously occupied by a H atom at the C3 atom in the fluorinated ring [i.e. C34 in Fig 3] is now filled by a {(^{Dip}Nacnac)Mg} fragment, the Mg of which is also solvated by a THF molecule. In this case, the remote location of the pyridyl N precludes the formation of dimers. The regioselectivity observed is consistent with metallation at the most acidic site of the molecule, leaving the pyridine ring untouched. Although this regioselectivity has been previously described for organolithium bases (which have to be employed at low temperatures to avoid LiF elimination and benzyne formation),[19] **6** constitutes the first example where this anion has been isolated and structurally characterized. This reactivity contrasts with those reported for transition metals such as Ir where ppf undergoes cyclometallation, removing the H at the C5 position of the fluorinated ring in ppf.[20] These findings show the potential of **1** to act as a regioselective base not only for N-heterocyclic substrates but also for substituted benzene and related ring systems.

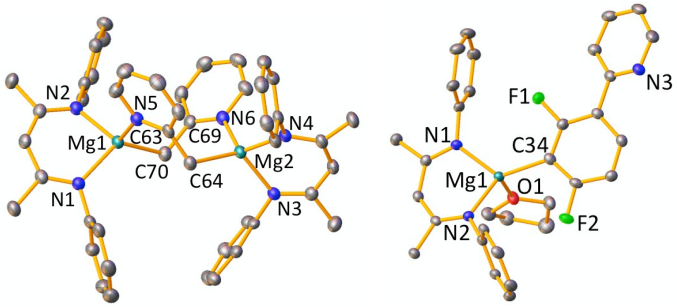


Fig 3 Molecular structure of **5** (left) and **6** (right) with 50% probability displacement ellipsoids (in both figures hydrogen atoms and ^{i}Pr groups have been omitted for clarity).

Initial reactivity studies of **6** with iodine and deuterated water demonstrated that the new C-Mg bonds in these systems are accessible to electrophiles, affording products **7** and **8** in yields of 65 and 72% respectively (see ESI for full details), as a result of the incorporation of iodine or deuterium at the C3 position of the phenyl ring in ppf
In summary, a new improved strategy for the regioselective metallation of challenging N-heterocycilc molecules is described. Designed for enhanced reactivity through a single Mg-TMP bond and for exceptional selectivity through a β-diketiminato-shielded Mg centre, monomeric base **1** allows the trapping and structural elucidation of the newly generated N-heterocyclic anions. These findings provide the first structural insight into their constitution, which correlates well with their unprecedented stability at room temperature.

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