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Structural and Synthetic Insights into Pyridine Homocouplings Mediated by a β-Diketiminato Magnesium Amide Complex

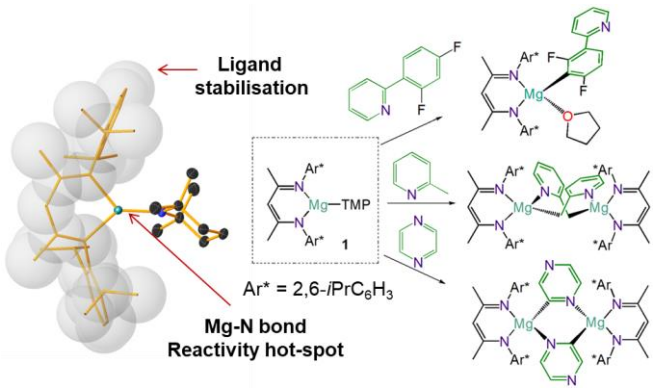
Laia Davin,[a] William Clegg,[b] Alan R. Kennedy,[a] Michael R. Probert,[b] Ross McLellan*[a] and Eva Hevia*[a]

Abstract: Reaction of [(^{Dipp}Nacnac)Mg(TMP)] (**1**) with 4-subtituted pyridines proceeds via sequential regioselective metalation and 1,2-addition to furnish a range of symmetric 4,4'R_2-2,2'-bipyridines in good yield, representing a new entry into bipyridine synthesis. Interestingly, the reaction with of **1** with 2-OMe-pyridine led to formation of asymmetric bipyridine **6**, resulting from the C6-magnesiation of the heterocycle followed by a C-C coupling step by addition to the C2 position of a second, non-metallated molecule, and subsequent elimination of [^{Dipp}NacnacMgOMe]$_2$ (**7**). Synthesis combined with spectroscopic and structural analysis help rationalise the underlying processes resulting in the observed reactivity, and elucidates the key role of the sterically encumbered β-diketiminate ligand plays in determining regioselectivity.

Introduction

Since its discovery by Anderson in 1849,[1] pyridine and related derivatives have assumed privileged positions in active pharmaceutical ingredients, wherein pyridine scaffolds are the second most popular N-heterocyclic motif.[2] Thus, the continued synthesis and regioselective modification of such prevalent entities is paramount. Entry points into substituted pyridines include the classical Knoevenagel synthesis from aldehydes, hydroxylamines and β-keto esters,[3] and the related Hantzsch synthesis, forming a dihydropyridine before oxidation.[4] Pyridines are, by the presence of a nitrogen atom in the aromatic ring, intrinsically Lewis basic and electron deficient, and modification of pyridines has a long and illustrious history. Electrophilic nitration or halogenation of pyridine occurs selectively at the 3-position, albeit at high temperatures.[5] The Chichibabin reaction between pyridine and sodium amide, affords 2-aminopyridine selectively.[6] This nucleophilic substitution can be rationalised by considering pyridine resonance forms, which render the two and four positions electrophilic and therefore amenable to nucleophilic attack by a wide range of nucleophiles. Reaction of organolithium reagents afford 2-organopyridines after work-up,[7] or alternatively the dihydropyridine intermediate, via 1,2-addition, which can be isolated and harnessed in catalytic processes.[8] Therefore, regioselective C-H functionalisation has a variety of reaction pathways available, such as nucleophilic substitution; radical reactions; metal catalysis; and deprotonative metalation. In this regard, the regioselective metalation of pyridines has been described by Schlosser as a "tightrope walk", due largely to the tendency of these molecules to undergo competing nucleophilic addition processes.[9] Mongin has recently reported a correlation between the regioselectivities observed for the metalation of a wide range of substituted pyridines and their computed C-H acidities,[10] revealing that judicious choice of the organometallic reagent and the reaction conditions are key to control selectivity.[11] Thus, several mono- and bimetallic systems have been reported that can execute the metalation of pyridines under certain reaction conditions (typically at low temperature).[12-15] In most cases, metalation products are isolated after quenching with an electrophile, with little structural information on the organometallic intermediates involved in these processes. Interestingly, when pyridine reacts with *n*BuLi and N,N'-dimethyl-2-ethanol (2 equivalents of each), and no electrophile is added, 2,2-bipyridine formation occurs in high yield, albeit as a mixture with 2-butyl-2,5-dihydropyridine.[16]

We are particularly interested in harnessing main group organometallic bases to achieve metal-hydrogen exchange with a variety of synthetically and biologically important molecules, including challenging N-heterocyclic substrates. Recently we reported the synthesis and applications of specially designed β-diketiminate stabilized mononuclear Mg systems [(^{Dipp}Nacnac)Mg(TMP)] (**1**) (TMP = 2,2,6,6-tetramethylpiperidide; ^{Dipp}Nacnac = Ar*NC(Me)CHC(Me)NAr*; Ar* = 2,6-*i*Pr$_2$-C$_6$H$_3$) and [(^{Dipp}Nacnac)Mg(*n*Bu)·THF] (**2**). Exploiting ligand-ligand cooperation, by combining a sterically operative β-diketiminate ligand with a kinetically-activated basic TMP amide group, **1** functions as a regioselective base capable of promoting the room temperature direct Mg-H exchange of a range of pharmaceutically relevant and challenging N-heterocyclic substrates and fluoroarenes.[17-19] While the β-diketiminate ligand acts as a spectator in these reactions, it plays a major role facilitating the trapping and stabilization of the newly formed sensitive anions as illustrated in Scheme 1.



Scheme 1. LHS: Space-filling representation of ^{DIPP}Nacnac ligand in **1** showing the protected Mg-N reactivity site. RHS: reactivity of **1** with N-heterocyclic substrates 2-(2,4-difluorophenyl)-pyridine, 2-picoline and pyrazine.

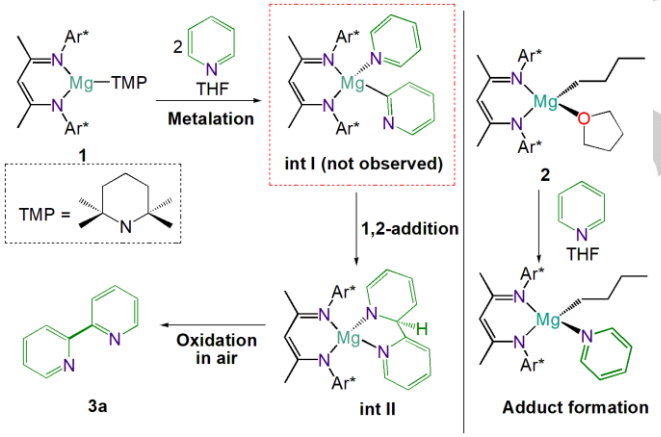
[a] Dr. L. Davin, Dr. A. R. Kennedy, Dr. R. McLellan, Prof. E. Hevia, WestCHEM, Department of Pure and Applied Chemistry University of Strathclyde Glasgow G1 1XL (UK) E-mail: ross.mclellan@strath.ac.uk eva.hevia@strath.ac.uk
[b] Prof. W. Clegg, Dr. M. R. Probert School of Chemistry, Newcastle University, Newcastle Upon Tyne, Ne1 7RU, UK

Thus **1** promotes high-yielding lateral metalation of the 2-substituted pyridines 2-picoline and 2-(2,4-difluorophenyl)-pyridine at the methyl and fluoroaryl substituent respectively.[18,19] Contrastingly, when reacted with the non-substituted diazine pyrazine regioselective C2-magnesiation occurs (RHS Scheme 1).[18] These studies also reveal that **2** has significantly reduced kinetically basicity, in failing to metallate these N-heterocyclic molecules, affording only Lewis acid-base coordination adducts.

Building upon this work, here we investigate the metalation of pyridine using **1** or **2**, before extending our observations to a range of 2-, and 4- substituted derivatives, mapping out their reactivity patterns with these bespoke metalating agents.

Results and Discussion

We started our investigation by reacting equimolar amounts of **1** and pyridine in d_8-thf solution. ^{1}H NMR monitoring of the reaction revealed several new resonances extending from the aliphatic to the aromatic region, suggesting, at least in part, reduced pyridine aromaticity. This includes a clear set of seven resonances of equal intensity prompting a tentative assignment as a magnesium-bound dihydrobipyridine species (**int II** in Scheme 2). The reaction was repeated in a Schlenk flask using a 2:1, pyridine:**1** ratio. After stirring in THF solution for two hours, and oxidation in air, the solution colour changed from dark red to pale yellow. After a standard organic workup and flash column chromatography (EtOAc:*n*hexane, 1:20), 2,2-bipyridine (**3a**) was isolated in a 73% yield (Scheme 2).



Scheme 2. LHS: Proposed reaction sequence accounting for 2,2'-bipyridine formation from reaction between **1** and pyridine. RHS: Adduct formation during reaction between **2** and pyridine.

These findings suggest that initial metalation has occurred at the 2-position (**int I** in Scheme 2), which is followed by nucleophilic addition at the 2-position of a second molecule of substrate (**int II** in Scheme 2). Furthermore, it is apparent that the 1,2-addition step, presumably across a pre-coordinated pyridine molecule is fast, with respect to metalation, since the metallated complex cannot be detected by NMR monitoring studies (Scheme 2). In contrast, when **2** reacts with pyridine, a coordination adduct is formed, where the solvating THF molecule is replaced by pyridine. Even after heating at 70 °C for 24 hours, no further reactivity is observed. This behavior mirrors that reported by Hill, where addition of N-heterocyclic molecules to **2** affords coordination adducts which are suitable for 1,2 or 1,4 additions.[20]

While the divergent reactivities of **1** and **2** follow the same trend we have previously described for other N-heterocyclic substrates, it is noteworthy that under the conditions of our study, it is not possible to trap the metallated intermediate (**int I**) which rapidly transforms into magnesium dihydrobypyridine **int II**. Nevertheless while self-condesation of pyridines is a typical unwanted side reaction in metallation chemistry,[9] here, by using **1** as a magnesiating agent, we can transform this side reaction into an efficient method to access synthetically useful 2,2-bipyridines under mild reaction conditions.

Being in high demand in supramolecular and macromolecular chemistry, bipyridines can be prepared using a variety of transition-metal catalyzed protocols, spanning from Stille, Negishi and Suzuki couplings employing halo-pyridines to ring-assembling reactions like the Kröhnke-type condensations.[21] Interestingly, Diaconescu has shown that group 3 benzyl complexes supported by a ferrocene bis(amide) ligand deliver dihydrobipyridyl complexes when reacted with 2-phenylpyridine, although harsh reaction conditions are required (3 days at 70°C).[22] Related Zr(II)[23] and Y(III)[24] mediated pyridine homocouplings have also been recently reported in the literature by the groups of Gade and Mashima respectively.

The reactivity of **1** towards pyridine contrasts with those reported for 2-picoline or pyrazine (Scheme 1).[18] For these substrates, even when an excess of the N-heterocycle is employed, no 1,2-addition step is observed. A possible explanation may lie in the dimeric structures of these metallated species (Scheme 1), with Mg being coordinatively saturated, precluding pre-coordination of a second equivalent of N-heterocycle to Mg, which is thought to be required to promote the nucleophilic addition step.

In order to check the generality of the formation of **3a** we next investigated the reactivity of **1** with 4-picoline. Previous studies using group 1 metal amides have shown that metalation of 4-picoline occurs preferentially at its lateral position,[25] although examples of C2-metalation have also been reported by judicious reagent choice.[26] Interestingly treating **1** with two equivalents of 4-picoline in THF at reflux for 2 hours followed by aerobic oxidation furnished 4,4'-Me_2-2,2'-bipyridine (**3b**) in a 63% yield (Scheme 3).

This is consistent with the initial magnesiation of one equivalent of 4-picoline at the C2 position. While this regioselectivity is unusual, it may be facilitated by the sterically demanding Nacnac ligand. Assuming that in the first instance, pre-coordination of 4-picoline to magnesium in **1** occurs, this should result in a reasonably congested metal atom, with the picoline methyl group pointing outwards and distant from the reactive metal-amide bond. Moreover, the bulky aryl ligands may impede a second molecule of base from reacting at the methyl

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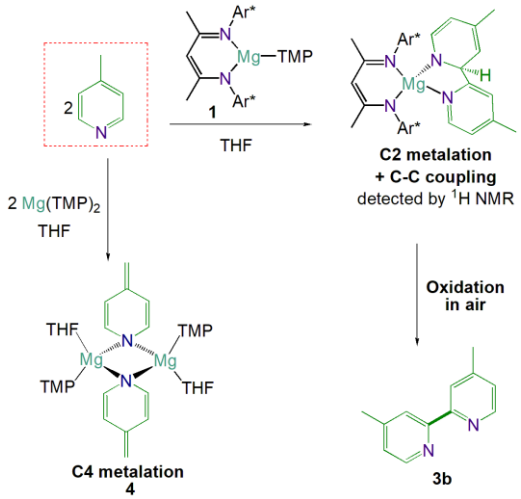
substituent. This pre-organisation primes reactivity at the α-C-H bond, leaving the methyl group intact (Scheme 3), contrasting with the reactivity described for 2-picoline with **1**, where lateral magnesiation is observed (Scheme 1). These findings emphasize the close interplay between the unique structure of **1** and the reactivity observed when confronted with heterocyclic molecules.

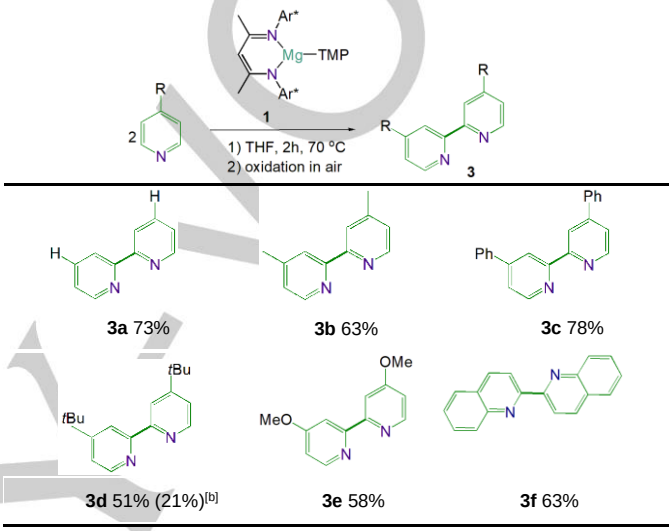


Scheme 3.: C4 metalation of 4-picoline using $Mg(TMP)_2$ affording **4**, and C2 metalation of 4-picoline using **1**, that leads to 4,4'-Me_2-2,2'-bipyridine, **3b**.

Furthermore, highlighting the key role of the ^{Dipp}Nacnac ligand, when 4-picoline was reacted with bis(amide) $Mg(TMP)_2$,[27] in a 1:1 ratio, magnesiation occurs exclusively at the methyl site. ^{1}H monitoring of this reaction revealed the formation of [(THF)Mg(TMP)(C_6H_6N)] (**4**) (Scheme 3), as evidenced by the appearance of three new informative resonances at δ 6.31, 5.38 and 2.94 ppm. These chemical shifts compare well with those of reported for a related 4-picoline complex of lithium (δ 6.34, 5.23 and 2.68 ppm), the structure of which has described as a donor supported lithium amide, rather than a carbanion.[25] ^{1}H DOSY NMR studies are consistent with the formation of a THF-solvated dimeric arrangement of complex **4**. Probing further the ability of **1** to promote bipyridine formation, we reacted other 4-substituted pyridines and quinoline with **1** in a 2:1 ratio, at reflux for 2 hours in THF prior to an organic work-up in air (Table 1). 2,2'-bipyridines **3a-f** were obtained in yields ranging from 51 to 78%. Interestingly, reaction of 4-*t*butylpyridine led to isolation of **3d** in a 51% yield along with 21% of 4,4',4''-*t*Bu_3-2,2',6,'2''-terpyridine (**3d'**) (21%). While the formation of **3d'** remains unclear, it could be due to a further addition of a third equivalent of 4-*t*butylpyridine to the proposed dihydrobipyridine intermediate. Nevertheless, using a larger excess of 4-*t*butylpyridine when reacted with **1** did not render a greater yield of **3d'**. Interestingly, reacting **1** with an equimolar mixture of pyridine and 4-methoxypyridine afforded a mixture of the homocoupled products **3a** and **3e**, without observing the formation of the unsymmetrical pyridine.

In an attempt to try isolating and structurally defining the magnesium intermediate species involved in these reactions, prior to the hydrolysis/oxidation step (Scheme 2), 4-OMe-pyridine was reacted with 0.5 equivalents of **1** in THF at room temperature followed by storage at -30 °C overnight. A crop of black crystals of [(^{Dipp}Nacnac)Mg($C_{12}H_{13}N_2O_2$)] (**5**) was obtained in a 47% isolated yield.

Table 1. [(^{Dipp}Nacnac)Mg(TMP)] (**1**) promoted 2,2'-bipyridine synthesis.[a]



[a] Isolated yields [b] isolated as an inseparable mixture with terpyridine congener (**3d'**) in a 2.5:1 ratio.

The molecular structure of **5** was established by X-ray crystallographic studies (Figure 1). Exhibiting a monomeric arrangement, it shows a dihydrobipyridyl anion, resulting from the coupling of two molecules of 4-OMe-pyridine at their C2-positions, which coordinates in a chelating fashion to the cationic {(^{Dipp}Nacnac)Mg}$^+$ fragment. The newly formed C-C bond [C34-C35 1.563(4) Å] is close to that of a standard single C-C bond.

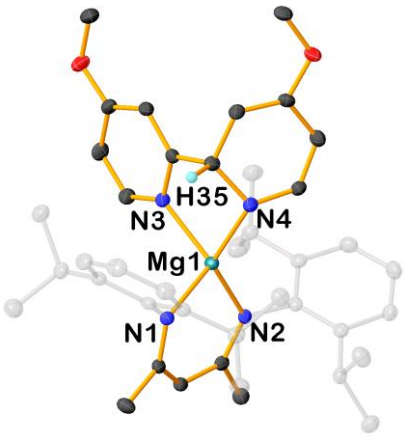


Figure 1. Structure of **5**. *i*Pr groups and all hydrogen atoms, except for the dihydrobipyridyl hydrogen atom, are omitted for clarity. Thermal ellipsoids are drawn at 30% probability. Dipp substituents drawn as transparent for clarity.

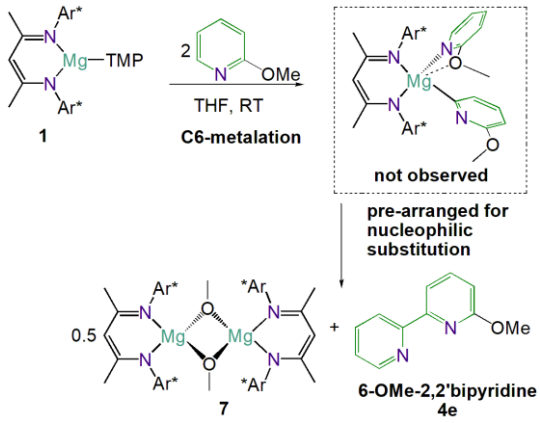
Unsurprisingly, the Mg-N distance to the dearomatised ring of the dihydrobipyridyl is shorter than the one to the aromatic ring (Mg1-N3 2.129(2) vs Mg1-N4 2.021(2) Å), reflecting the different bonding modes. Thus the aromatic ring bonds to Mg as a simple neutral Lewis donor, whereas the anionic dihydropyridyl fragment is best regarded as an amide group. For the latter, the observed Mg1-N4 distance is within the range of those reported by Hill for related 1,2-dihydropyridide derivatives of pyridine, 4-picoline and quinoline,[20] resulting from a hydride transfer into the aromatic ring of these N-heterocyclic molecules.

Confirming that **5** is a valid reaction intermediate, exposing to air a solution of isolated crystals of **5** in C_6D_6 shows its conversion to 4,4'-OMe_2-2,2'bipyridine (**3e**), with the concomitant formation of ^{Dipp}NacnacH as a coproduct. Interestingly, it should be noted that formation of **5** and **3e** involves the initial C2-magnesiation of 4-OMe-pyridine. This regioselectivity is very unusual, as in agreement with calculated pKa values,[10] deprotonation of 4-MeO-pyridine has been largely described at its C3 site.[28],[29] These results hint again at the influence of the bulky {^{Dipp}Nacnac} ligand in tuning the regioselectivity of magnesium base **1**.

At this point in our studies two main conclusions can be drawn from the reactivity of **1** with substituted pyridines: *i)* substrates bearing a substituent in the 4-position favour metalation at C2, rendering dihydrobipyridyl fragments by coupling with some unreacted substrate; and ii) substituents at the 2-position containing an acidic hydrogen, favour metalation at the substituent, rather than the pyridine ring, affording stable intermediates that do not undergo further insertion with an excess of the substrate. The latter scenario is best exemplified in our previous studies using 2-picoline and 2-(2,4-difluorophenyl)-pyridine (Scheme 1).

We next pondered the reactivity of other C2-substituted pyridines containing groups which are not susceptible to metalation and on whether C6 metalation and subsequent bipyridine formation was feasible. Thus the reactivity of **1** was tested against 2 molar equivalents of 2-R-pyridines (R =, *t*Bu, MeO).

Reaction between **1** and 2-*t*Bu-pyridine (Scheme 4) in d_8-THF in a J. Young's NMR tube did not result in any change in the NMR spectrum, even after heating at 70 °C for 24 hours. This lack of reactivity could be due to the steric mismatch between **1** and this C2-substituted pyridine, which may hinder pre-coordination of the heterocyclic donor to the largely sterically congested Mg centre present in **1**.



Scheme 4. Nucleophilic aromatic substitution reactivity of **1** with 2-MeO-pyridine, giving **6** and **7**.

The reaction between **1** and 2-MeO-pyridine in a J. Young's NMR tube in d_8-THF remains similarly unchanged, via ^{1}H NMR monitoring, after reacting at room temperature for 24 hours. Upon heating at 70 °C for one hour a change results in the ^{1}H NMR spectrum, with the appearance of six new aromatic resonances that are unobscured by residual 2-MeO-pyridine, which we tentatively assign to an asymmetric bipyridine (see SI). Further, these resonances are all of equal integral and integrate in 1:3 ratio with a new resonance in the region of the ^{1}H NMR spectrum corresponding to OMe protons, hinting at the loss of a MeO^- group. Importantly, in contrast with the studies on 4-substituted pyridines (*vide supra*), no spectroscopic evidence was found for the formation of a dihydrobipyridine species. Also present in the NMR tube after this time was an insoluble white precipitate containing a few crystals, which were fortunately amenable to X-ray diffraction analysis. Structural analysis revealed [^{Dipp}NacnacMgOMe]$_2$ **7**, the result of formal cleavage of an OMe group from 2-OMe-pyridine during reaction (Figure 2).

Similar alkoxide bridged [^{Dipp}NacnacMgOR]$_2$ dimers are known in the literature, although these invariably contain bulkier substituents than methyl groups (*n*Bu, *i*Pr, *t*Bu, benzyl)[30]. Chisholm reported that the preparation of such species containing smaller alkoxides e.g., OEt and O*i*Pr (and presumably OMe), once formed are susceptible to ligand scrambling reactions, affording complexes of the type $[Mg(OR)_2]_n$ and (^{Dipp}Nacnac)$_2$Mg,[30c] therefore it is somewhat surprising that we were able to obtain structural information for **7**.

Repeating the reaction on a larger scale, and including an organic work-up resulted in isolation of 6-OMe-2,2'-bipyridine, **6** in a 47% yield.[31] Thus, as depicted in Scheme 4, it appears that while some 2-OMe-pyridine is first metallated at its C6 position, it then undergoes nucleophilic aromatic substitution with another equivalent of substrate, eliminating methoxide complex **7** and furnishing non-symmetrical bipyridine **6**. This reactivity although new in Mg chemistry, is reminiscent to those reported before for C-O bond activation in pyridines using transition-metal catalysis.[32] Related to these findings it should be noted that we have recently reported the efficient C-F bond arylation of 2-(2,4-difluorophenyl)-pyridine by [(^{Dipp}Nacnac)Mg(Ph)(THF)] via

coordination of the organic substrate to the Mg centre, which facilitates the nucleophilic aromatic substitution reaction with the concomitant formation of [^{Dipp}NacnacMgF]$_2$.[19]

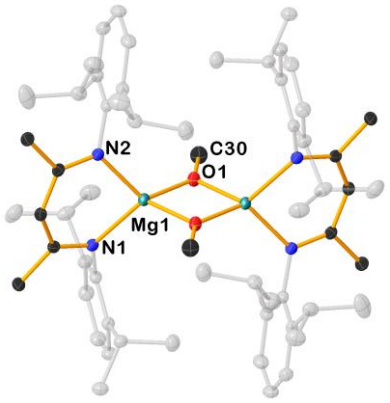


Figure 2. Molecular structure of **7**. All hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 30% probability.

Importantly, this outcome extends the chemistry of **1** into asymmetric 2,2-bypyridine systems, an area that has attracted considerable synthetic endeavours.[33] Together these reactions demonstrate the utility of **1**, in challenging C-O bond activations, alongside the more established C-H functionalisation, hinting at the potential of **1** in complex C-X bond modifications.

Conclusions

Advancing the synthetic applications of magnesium reagents supported by bulky β-diketiminate ligands, **1** is found to be an efficient regioselective reagent at promoting the synthesis of 4-substituted 4,4'-R$_2$-2,2'-bipyridines. These reactions follow a pathway involving regioselective C-2 metalation and rapid 1,2-addition, indicated by spectroscopic and structural studies. Interestingly, the β-diketiminate ligand plays a key role in directing the Mg-H exchange reaction to the C2 position in the heterocyclic substrate as illustrated by reaction of unsupported Mg(TMP)$_2$ which deprotonates 4-picoline at its lateral methyl group, whereas **1** leaves that position intact.

Conversely, 2-substituted pyridines will normally only undergo metalation with **1** when the 2-substituent contains an acidic hydrogen. One key divergence is with 2-MeO-pyridine, where regioselective metalation occurs at the C6 position and the resulting transient species participates in nucleophilic substitution with a MeO of a second molecule of substrate, activating a strong C-O bond, and providing access to an asymmetric bipyridine. This work further extends the metallation chemistry of **1** and illustrates the importance of ligand effects on the ensuing reactivity.

Ongoing work in our group with this, and related systems, aims to further harness and elucidate the metal-ligand cooperativity in a range of challenging transformations including further tandem metalation/addition and metalation/C-X bond activation processes.

Experimental Section

All reactions and manipulations were conducted under a protective argon atmosphere using either standard Schlenk techniques or an MBraun glove box fitted with a gas purification and recirculation unit. NMR experiments were conducted in J. Young's NMR tubes oven dried and flushed with Argon prior to use. Solvents were dried by heating to reflux over sodium benzophenone ketyl and then distilled under nitrogen prior to use. All other reagents were purchased commercially from Sigma-Aldrich and used as received. NMR spectra were recorded on a Bruker AV3 or AV 400 MHz spectrometer operating at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C. All ^{13}C spectra were proton decoupled. ^{1}H and ^{13}C NMR spectra were referenced against the appropriate solvent signal. X-ray Crystallography Crystallographic data were collected on Oxford Diffraction instruments with Cu Kα radiation (λ = 1.54184 Å), or at the diamond beam line synchrotron source (λ = 0.6889 Å). Structures were solved using SHELXS-97[34] or OLEX2,[35] while refinement was carried out on F^2 against all independent reflections by the full matrix least-squares method using the SHELXL-97 program or by the GaussNewton algorithm using OLEX2. All non-hydrogen atoms were refined using anisotropic thermal parameters. Selected crystallographic details and refinement details are provided in table S1. CCDC 1849547-1849548 contains the supplementary crystallographic data for these structures. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of [(^{Dipp}Nacnac)Mg($C_{12}H_{13}N_2O_2$)] 5: To a solution of **1** (0.28 g, 0.5 mmol) in THF (5 mL), 4-methoxypyridine (0.105 mL, 1 mmol) was added. The solution turned to dark red and was stirred for 3 hours at room temperature. The solvent was removed and a mixture of 2 mL of hexane and 2 mL of toluene was added and was placed at -30 °C. After 48 hours a crop of black crystals were isolated, washed with hexane and placed in a glove box (0.154 g, 47%). **^{1}H NMR (400.13 MHz, C_6D_6, 298 K)** δ 8.79-7.78 [d, 1H, *J* = 6.2 Hz, $C_{12}H_{13}N_2O_2$], 7.13-7.00 [br. m, 6H, Ar* of ^{Dipp}Nacnac], 6.94-6.93 [d, 1H, *J* = 6.1 Hz, $C_{12}H_{13}N_2O_2$], 6.57-6.56 [d, 1H, *J* = 2.5 Hz, $C_{12}H_{13}N_2O_2$], 6.26-6.23 [dd, 1H, *J* = 6.2 Hz, *J* = 2.6 Hz, $C_{12}H_{13}N_2O_2$], 5.24-5.22 [dd, 1H, *J* = 6.3 Hz, *J* = 2.2 Hz, $C_{12}H_{13}N_2O_2$], 4.97-4.96 [d, 1H, *J* = 2.8 Hz, $C_{12}H_{13}N_2O_2$], 4.93 [s, 1H, C*H* of ^{Dipp}Nacnac], 3.62-3.47 [br. m, 1H, C*H*, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 3.47-3.37 [br. m, 1H, C*H*, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 3.35 [s, 3H, C*H*$_3$ OMe of $C_{12}H_{13}N_2O_2$], 3.35 [br m, 3H, C*H*$_3$ OMe of $C_{12}H_{13}N_2O_2$ + 1H, C*H* of $C_{12}H_{13}N_2O_2$], 3.30-3.08 [br. m, 2H, C*H*, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 2.84 [s, 3H, C*H*$_3$ OMe of $C_{12}H_{13}N_2O_2$], 1.73 [s, 6H, C*H*$_3$ of ^{Dipp}Nacnac], 1.50-1.34 [br. d, 6 H, C*H*$_3$, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 1.31-1.30 [br. d, 12H, C*H*$_3$, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 0.83-0.72 [br. d, 3HC*H*$_3$, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 0.67-0.53 [br. d, 3HC*H*$_3$, ^{i}Pr, Ar* of ^{Dipp}Nacnac]. **^{13}C NMR {^{1}H} (100.61 MHz, C_6D_6, 298 K)** δ 172.3 [C$_q$], 169.5 [C$_q$], 168.1 [C$_q$], 161.2 [C$_q$], 150.4 [*C*H, $C_{12}H_{13}N_2O_2$], 147.1 [*C*H, $C_{12}H_{13}N_2O_2$], 144.8 [C$_q$], 142.8 [C$_q$], 142.1 [C$_q$], 124.2 [CH, Ar* of ^{Dipp}Nacnac], 123.6 [C$_q$, Ar* of ^{Dipp}Nacnac], 110.7 [*C*H, $C_{12}H_{13}N_2O_2$], 106.5 [*C*H, $C_{12}H_{13}N_2O_2$], 94.9 [*C*H of ^{Dipp}Nacnac], 91.6 [CH, $C_{12}H_{13}N_2O_2$], 72.9 [CH, $C_{12}H_{13}N_2O_2$], 63.0 [*C*H, $C_{12}H_{13}N_2O_2$], 54.8 [O*C*H$_3$, $C_{12}H_{13}N_2O_2$], 53.4 [O*C*H$_3$, $C_{12}H_{13}N_2O_2$], 29.2 [CH, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 29.0 [*C*H, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 28.2 [CH, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 28.1 [*C*H, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 25.4 [CH$_3$, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 24.5 [CH$_3$, ^{i}Pr, Ar* of ^{Dipp}Nacnac], 24.4 [CH$_3$ of ^{Dipp}Nacnac], 24.1 [CH$_3$ of ^{Dipp}Nacnac]. **Elemental analysis:** ($C_{41}H_{54}MgN_4O_2$) *Calculated:* C: 74.70 % H: 8.26 % N: 8.50 %. *Found:* C: 75.02 % H: 8.07 % N: 8.01 %.

General procedure for bipyridine synthesis: **1** (140 mg, 0.25 mmol) was dissolved in 5 mL THF and the relevant 4-R-pyridine or quinoline (2 equivalents 0.5 mmol) was added dropwise at room temperature. On addition, in all cases, the yellow solution became deep red. After stirring at reflux temperature the reaction was cooled to room temperature before

oxidation in air and an organic workup. 4,4'-R2-2,2'-bipyridines were isolated using flash column chromatography, eluting with EtOAc:Hexane.

Full experimental details are given in the accompanying supplementary material.

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We thank the European Research Council (ERC StG, MixMetApps) and the EPSRC (EP/N011384/1) for their generous sponsorship of this research. and to Diamond Light Source for access to beamline I19 (award MT11145). Data supporting this research are openly available from http://dx.doi.org/10.15129/ac1fc5bb-2588-433f-8d25-ce36d1389d82

Keywords: magnesium • metalation • pyridines • C-C coupling • β-diketiminate

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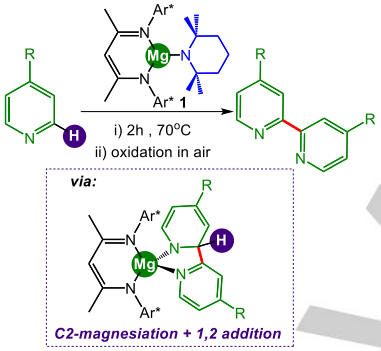
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Two for one! β-Diketiminate stabilised magnesium amide **1** promotes the regioselective homocoupling of 4-substituted pyridines via a sequence of C2-metalation and1-2 addition steps.



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Structural and Synthetic Insights into Pyridine Homocouplings Mediated by a β-Diketiminato Magnesium Amide Complex