

Structurally-defined direct C-magnesiumation and C-zincation of N-heterocyclic aromatic compounds using alkali-metal-mediated metallation†

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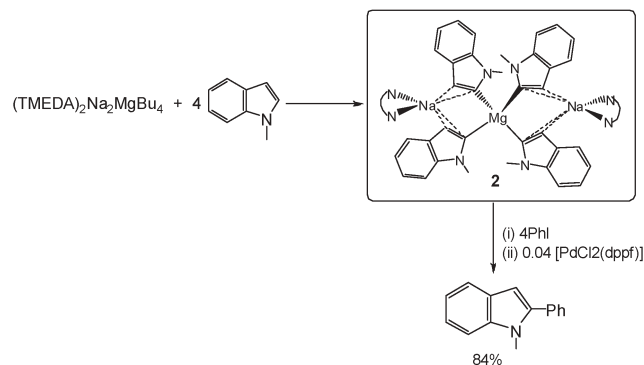
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Demonstrating direct synergic “low polarity metallation”, 1-methylindole is C-magnesiumated by $(\text{TMEDA})_2 \cdot \text{Na}_2\text{MgBu}_4$ and C-zincated by $(\text{TMEDA}) \cdot \text{Na}(\text{tBu})(\text{TMP})\text{Zn}(\text{tBu})$, and 1-methylpyrrole is C-zincated by the same reagent, with all three metal products successfully crystallographically characterised.

As vehicles for effecting C-metallation of aromatic compounds, magnesium and zinc reagents are definitely in the slow lane due to their low polarity and low reactivity power. Racing in the fast lane and undisputed champions of metallation are the high polarity, highly reactive lithium reagents which depending on the degree of difficulty of the specific lithium–hydrogen exchange manoeuvre can be administered in the form of LICKOR (alkyllithium compounds co-complexed with potassium *tert*-butoxide) super-bases, pure alkyllithium compounds, or lithium amides.¹ To access C-magnesiumated or C-zincated aromatic compounds one would normally have to prepare C-lithiated intermediates beforehand then carry out a second reaction (a metathesis) with a metal halide (commonly RMgX or ZnX_2) or some other salt. While this metathetical approach has been successful over a broad range of aromatic substrates it does nonetheless suffer from certain severe limitations. Most incapacitating is the intolerance of the method to many functional groups (esters, ketones, nitriles, *etc.*) caused by the strong basicity of lithium reagents and/or the high instability of the generated aryllithiums. Another complication is that the use of ionic salts often restricts the range of solvents available for such reactions with cheap hydrocarbons and arenes forsaken in favour of more expensive polar substitutes (commonly THF). Direct one-step magnesiumation and zincation methods avoiding indirect two-step metathesis reactions would therefore be advantageous. In that regard Knochel and co-workers have recently pioneered the use of bases of empirical formula “ $\text{R}_2\text{NMgCl} \cdot \text{LiCl}$ ” (these could be labelled “Turbo” Hauser bases²) which can directly magnesiumate various aromatic and heteroaromatic compounds in THF solution.^{3,4} We have recently also introduced the concepts of alkali-metal-mediated magnesiumation (AMMM) and zincation (AMMZ).⁵ Here the alkali metal is a passenger (albeit an essential one), while the magnesium or zinc atoms, under anionic ‘ate activation, occupies the driver’s seat as these metallations are strictly Mg–H or Zn–H exchange reactions. Spectacular

demonstrations of the power of AMMM have come with metallocenes (ferrocene can be fourfold magnesiumated⁶) and of AMMZ with anilines (*N,N*-dimethylaniline undergoes zincation selectively at the *meta* site⁷). In this communication we report the application of AMMM and AMMZ towards *N*-heterocyclic aromatic compounds and in doing so reveal the first directly C-magnesiumated indole and C-zincated indole and pyrrole.

An important structural component in many pharmaceutical agents, the indole ring system is probably the most widely distributed heterocycle in nature.⁸ Since the parent compound, indole, has an acidic N–H bond which can be readily converted to N–metal, we selected the *N*-substituted indole, 1-methylindole, **1**, for an attempt at C-magnesiumation using AMMM.⁹ Significantly, Sakamoto and co-workers had previously reported that **1** fails to react with the magnesium amide base “ $\text{Mg}(\text{NPr}^i)_2$ ” at elevated temperature though success was more forthcoming with the activated 1-phenylsulfonylindole.¹⁰ In our attempt (Scheme 1), **1** was subjected to the TMEDA-activated “highly coordinated” sodium tetraalkylmagnesiates “ $(\text{TMEDA})_2 \cdot \text{Na}_2\text{Mg}(\text{Bu})_4$ ”¹¹ in hexane solution (see ESI†). As this ‘ate has four (potentially) basic limbs, the indole : base stoichiometry employed was 4 : 1. This stoichiometry proved to be ideal as the crystalline product of the reaction in an (isolated) yield of 68% was the disodium tetraindol-2-ylmagnesiates **2**, as determined by solution NMR spectroscopy and X-ray crystallography. From the NMR data (see ESI†), metallation at the 2-position of the indole ring was established by the absence of a 2-CH ¹H resonance (found at 6.46 ppm in the starting indole) and the large downfield chemical shift of the 2-C ¹³C resonance (from 129.05 ppm in the starting indole to 181.11 ppm in **2**). The molecular structure of **2**† (Fig. 1) confirmed



Scheme 1 Synthesis of tetraindol-2-ylmagnesiates **2** and its cross-coupling reaction with iodobenzene.

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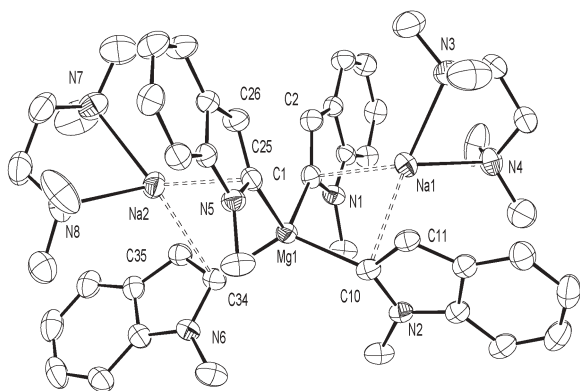
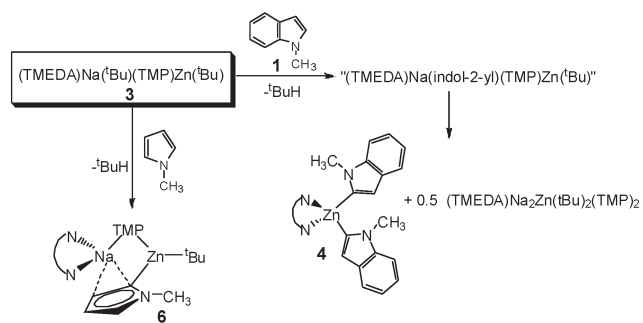


Fig. 1 Molecular structure of **2** with hydrogen atoms omitted for clarity, showing Na $\cdots\pi$ -C interactions as dashed lines. In all figures, ellipsoids are drawn at the 50% probability level.

that the metallation was a magnesiation with Mg(1) occupying the 2-positions [C(1), C(10), C(25), C(34)] of the four indolyl rings (mean Mg–C bond length, 2.216 Å) and like the outgoing H atoms, lying essentially co-planar with the aryl planes. This is achieved with a modest distortion of the central MgC₄ tetrahedron [range of CMgC bond angles, 103.58(8)–127.08(8)°; mean, 109.32°]. In contrast to the predominately covalent, σ -nature of these Mg–C bonds, the Na atoms engage in more electrostatic cation– π interactions with the indolyl system. Sitting well outside of the indolyl planes (at distances of 2.570(2), 2.576(2), 2.595(2) and 2.532(2) Å) each Na interacts in a η^2 -manner with the (deprotonated) 2-C and (proton-bearing) 3-C atoms of two indolyl ligands [range of lengths: 2.587(2)–2.856(2) Å]. Interestingly, some Na–3-C contacts are shorter than their 2-C counterparts [e.g. Na(2)–C(35), 2.662(2) Å; Na(2)–C(34), 2.854(2) Å], a mark of the Na atoms engaging more with the π -surface than with the 2-C lone pair. Bidentate TMEDA ligands complete the Na coordination spheres [range of Na–N bond lengths: 2.416(2)–2.489(2) Å]. The Na $\cdots\pi$ interactions must contribute significantly to the non-linearity of the Na \cdots Mg \cdots Na vector [130.85(3) Å]. Though new for indolyl, the Na \cdots Mg \cdots Na motif is known for other ligand systems including enolato in [(TMEDA)₂Na₂Mg{OC(=CH₂)Mes}₄],¹² where it is much closer to linearity (167.70°). There are no precedents for C-magnesiated indole structures and only one C-lithiated, [3-iodo-2-lithio-1-methylindole-(THF)₂],¹³ which exhibits a dimeric (Li–2-C)₂ ring arrangement markedly different from that of **2**. Mongin and co-workers recently reported¹⁴ the first transition metal catalysed cross-coupling reactions of lithium arylmagnesiates, that provide good access to heteroarylquinolines. Using a similar approach, we reacted (Scheme 1) the tetraindol-2-ylmagnesiante **2** with iodobenzene under palladium catalysis using [PdCl₂(dppf)] [dppf is 1,1'-bis(diphenylphosphino)ferrocene]. This produced 2-phenyl-1-methylindole in a high isolated yield of 84% (ESI†).

Turning to AMMZ, on account of its exceptional zincating properties the heteroleptic alkylamido reagent [(TMEDA)·Na(μ-^tBu)(μ-TMP)Zn(^tBu)],¹⁵ **3**, was employed as the base in a reaction with 1-methylindole (Scheme 2). Direct zincation was easily achieved under mild conditions in hexane solution, but manifested not in a mixed-metal ‘ate (akin to magnesiante **2**), but in the neutral bis-indol-2-yl zinc complex **4** (isolated crystalline yield, 34%, see



Scheme 2 Synthesis of neutral zincindole **4** and pyrro-2-ylzincate **6**.

ESI†). The detection of the coproduct “(TMEDA)Na₂Zn(^tBu)₂(TMP)₂” in solution from NMR spectra (ESI†), signifies the reaction is an auto-dismutation (maximum yield of **4** possible is thus 50%) of a type seen before in related lithium TMP–zincate reactions with ferrocene.¹⁶ NMR spectra of **4** (ESI†) show similar features to those of **2** with an absent 2-C¹H resonance and a large downfield chemical shift of the (zincated) 2-¹³C resonance (at 177.23 ppm: 3.88 ppm less downfield than the corresponding magnesiated resonance in **2**). Lacking Na atoms, the molecular structure of **4** (Fig. 2) simplifies in comparison to that of **2**, being mononuclear with a tetrahedrally-(N × 2; C × 2)-coordinated zinc centre. The narrow bite of TMEDA [N(3)–Zn(1)–N(4), 84.26(7)°] and the requirement to keep the indolyl rings wide apart [C(1)–Zn(1)–C(10), 129.68(8)°] cause this tetrahedron to distort (mean bond angle at Zn, 107.91°). There are no C-zincated indole structures available for a direct comparison with **4**, but comparing its mean Zn–C bond length (2.003 Å) with that of its Mg–C counterpart in **2** (2.216 Å) reveals a significant difference of 0.213 Å. This shortened, strengthened metal–C bond in the case of Zn may, in combination with bulky TMP and ^tBu ligands, be a key factor in the dismutation of the putative intermediate “[(TMEDA)·Na(μ-indol-2-yl)(μ-TMP)Zn(^tBu)]”. Again as in **2**, the Zn centre in **4** sits in the same plane as the aromatic rings. Interestingly when we mixed together 1-methylindole, ^tBu₂Zn, and TMEDA in hexane solution but omitted NaTMP, no reaction with the indole was observed. This implies that although product **4** is a single metal complex, a mixed-metal synergy is required for its formation.

To ascertain whether the steric bulk of bicyclic 1-methylindole contributes to the said dismutation process we repeated the AMMZ reaction with monocyclic 1-methylpyrrole, **5** (Scheme 2).

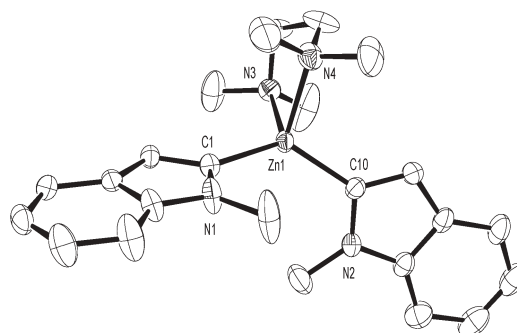


Fig. 2 Molecular structure of **4** with minor disorder component of TMEDA ligand and hydrogen atoms omitted for clarity.

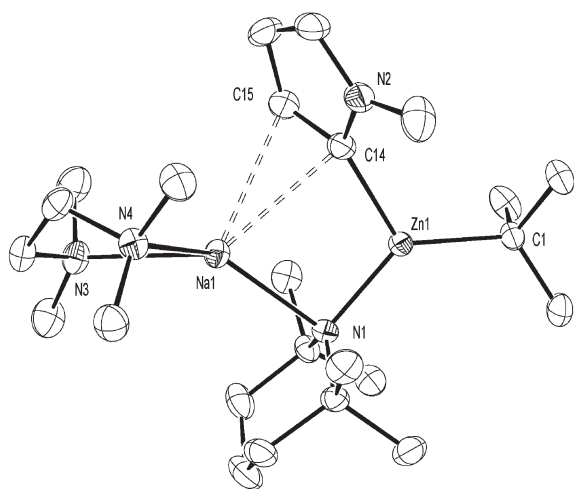


Fig. 3 Molecular structure of **6** with hydrogen atoms omitted for clarity, showing Na \cdots π -C interactions as dashed lines.

Direct regioselective (at the 2-position) C-zincation was again accomplished, manifested in the sodium heterotrianiionic zincate **6** (ESI †). NMR spectra of **6** revealed the absence of the 2-C- 1 H resonance (at 6.25 ppm in **5**) and a large downfield shift of the 2- 13 C-Zn resonance (from 109.04 ppm in **5** to 144.27 ppm in **6**) (ESI †). In the molecular structure of **6 ‡ (Fig. 3), 17 whilst collecting the pyrrol-2-yl ligand (a product of alkyl deprotonation), the Zn centre retains the bridging TMP and terminal t Bu ligands of reagent **3**, leading to a trigonal planar (1 \times N; 2 \times C) coordination overall. Reflecting the steric constraints within **6** (which would be magnified in the putative indolyl analogue), the Zn-C (pyrrolyl) bond is slightly longer than its counterparts in **4** [2.0527(18) Å vs. 2.003 Å] even though this runs counter to the Zn in **6** having a lower coordination number (*i.e.* 3 vs. 4 in **4**). Near in plane Zn-C (pyrrolyl) (0.244(4) Å removed from the plane) and out of plane Na- η^2 C(pyrrolyl) contacts [2.333(3) Å removed from the plane: Na(1)-C(14), 2.772(2) Å; Na(1)-C(15), 2.831(2) Å] are, as in **2** for the Na/Mg indolyl attachment, also present in **6**. The structure of **6** is completed by TMEDA N,N-attaching to Na.**

In conclusion, the first structurally-defined direct C-magnesiation and C-zincation reactions 18 of N-heterocyclic aromatic compounds, circumventing the need for an indirect metathetical approach, have been demonstrated.

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Notes and references

‡ Crystal data for **2**: C $_{48}$ H $_{64}$ MgN $_8$ Na $_2$, M_r = 823.36, monoclinic, space group $P2_1/a$, a = 15.8300(3), b = 16.8625(3), c = 17.9095(4) Å, β = 91.237(1) $^\circ$, V = 4779.53(16) Å 3 , Z = 4, λ = 0.71073 Å, μ = 0.096 mm $^{-1}$, T = 123 K; 90776 reflections, 9374 unique, R_{int} = 0.084; final

refinement to convergence on F^2 gave R = 0.0496 (F , 6015 obs. data only) and R_w = 0.1161 (F^2 , all data), GOF = 1.015. Crystal data for **4**: C $_{24}$ H $_{32}$ N $_4$ Zn, M_r = 441.91, orthorhombic, space group $P2_12_12_1$, a = 12.2666(2), b = 13.1709(2), c = 14.3918(2) Å, V = 2325.17(6) Å 3 , Z = 4, λ = 0.71073 Å, μ = 1.073 mm $^{-1}$, T = 123 K; 54726 reflections, 5323 unique, R_{int} = 0.064; final refinement to convergence on F^2 gave R = 0.0309 (F , 4616 obs. data only) and R_w = 0.0601 (F^2 , all data), GOF = 1.024. Flack parameter -0.019(10). The TMEDA group is modeled as disordered over two sites. Crystal data for **6**: C $_{24}$ H $_{49}$ N $_4$ NaZn, M_r = 482.03, orthorhombic, space group $P2_12_12_1$, a = 10.9318(3), b = 14.4362(4), c = 17.5664(5) Å, V = 2772.22(13) Å 3 , Z = 4, λ = 0.71073 Å, μ = 0.918 mm $^{-1}$, T = 123 K; 24509 reflections, 6275 unique, R_{int} = 0.032; final refinement to convergence on F^2 gave R = 0.0271 (F , 5631 obs. data only) and R_w = 0.0560 (F^2 , all data), GOF = 1.057. Flack parameter 0.514(8). CCDC 641398-641400. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704362g

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