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Magnesiation of Indoles | *Very Important Paper* |

Atom Efficient Magnesiation of *N*-Substituted Alkyl Indoles with a Mixed Sodium-Magnesium Base

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Abstract: This study presents the alkali metal mediated magnesiation (AMM*Mg*) of three *N*-alkylated indoles with the mixed Na/Mg base [(TMEDA)Na(TMP)$_2$Mg(CH$_2$SiMe$_3$)] **1** (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMP = 2,2,6,6-tetramethylpiperidine). All three magnesiated indoles have been successfully characterised by single-crystal X-ray diffraction and solution state NMR studies, whereas iodolysis and Pd-catalysed cross coupling have been investigated. The steric nature of the *N*-alkyl group changes the reactivity and efficiency of **1** to give either atom efficient disodium tetraindol-2-ylmagnesiates [(Na-TMEDA)$_2$Mg(α-C$_9$H$_8$N)$_4$] **2** and [(Na-TMEDA)$_2$Mg(α-C$_{10}$H$_{11}$N)$_4$] **3**, or [(TMEDA)Na(TMP)(α-C$_{11}$H$_{12}$N)Mg(TMP)] **4**, whereby only one indole molecule is selectively deprotonated.

Introduction

Indoles and their derivatives play a prominent role in a large number of biologically active compounds, as well as in many diverse products across the entire chemical industry.[1] It is considered a "privileged structural scaffold"[2] present in many important natural products (such as serotonin, tryptamine, tryptophan),[1] pharmaceuticals (such as Sumatriptan and Rizatriptan),[3] agrochemicals (such as auxins and Amisulbrom)[4] and pigments and dyes (indigoid and cyanine).[4] With the majority (88 %)[5] of active pharmaceutical drugs on the market containing aromatic heterocyclic components dominated by N-heterocyclic compounds, the synthesis and functionalisation of indoles and their derivatives is of significant interest to both synthetic and medicinal chemists.[6]

Metalation reactions have proven indispensable in the conversion of simple indole containing synthons into complex functionalised indole-based products.[7] This has predominately been achieved through the use of alkyllithium reagents through direct metalation or metathesis and/or lithium secondary-amides. However, these methods commonly require low temperatures, long reaction times and reagent excess to be employed to ensure selectivity.

In the last fifteen years, numerous research groups have developed mixed metal reagents as new tools to deprotometallate sensitive aromatic compounds.[8] In the context of indoles, Uchiyama et al. have studied both the direct *ortho*-cupration and -alumination of *N*-boc-indoles using the lithium cuprate [MeCu(TMP)(CN)Li$_2$][9] and lithium aluminate [*i*Bu$_3$Al(TMP)Li] reagents achieving C2-selective outcomes.[10] However, both mixed metal reagents required sub-ambient temperatures (–40 °C or –78 °C) and/or an excess of metalating reagent.

Recent studies by Mongin et al. focused on the room temperature metalation of a diverse range of functionalised indole and pyrrole species using a mixture of ZnCl$_2$•TMEDA/LiTMP in various ratios,[11,12] which report, after subsequent iodolysis, predominately 2-iodo derivatives in excellent yields.

Mulvey and Hevia et al. also reported the direct magnesiation and zincation of *N*-methylindole using the sodium magnesiate and zincate reagents [(TMEDA)$_2$Na$_2$MgBu$_4$] and [(TMEDA)Na(*t*Bu)(TMP)Zn(*t*Bu)] at room temperature[13] revealing the first structurally characterised C-magnesiated [(Na-TMEDA)$_2$Mg(α-C$_9$H$_8$N)$_4$] and C-zincated [(TMEDA)Zn(α-C$_9$H$_8$N)$_2$] examples of N-heterocyclic compounds.

In this study, we report the room temperature magnesiation of a range of *N*-alkyl functionalised indoles (*N*-alkyl = Me, Et and *i*Pr) with the sodium magnesium base [(TMEDA)Na-(TMP)(CH$_2$SiMe$_3$)Mg(TMP)][14] **1**. Rapid reaction times (under 20 min) and atom-efficient metalation are defined by the steric bulk of the *N*-alkyl substituent with X-ray crystallography and solution NMR studies revealing different complex architectures.

Results and Discussion

Reaction of **1** with either *N*-methyl or *N*-ethyl-indole resulted in the deposition of a yellow precipitate, which when re-crystallised from *n*-hexane or toluene respectively afforded X-ray quality single crystals, identified as the disodium tetraindol-2-ylmagnesiates [(Na-TMEDA)$_2$Mg(α-C$_9$H$_8$N)$_4$][13] **2** and [(Na-TMEDA)$_2$Mg(α-C$_{10}$H$_{11}$N)$_4$] **3** (Figure 1).

Using a different metalation route, complex **2** has been previously reported in the literature[13] and will not be discussed in detail (see Supporting Information). Essentially isostructural to **2**, complex **3** contains a central distorted tetrahedral (mean 109.34°) magnesium atom [Mg(1)] bonded to four separate α-

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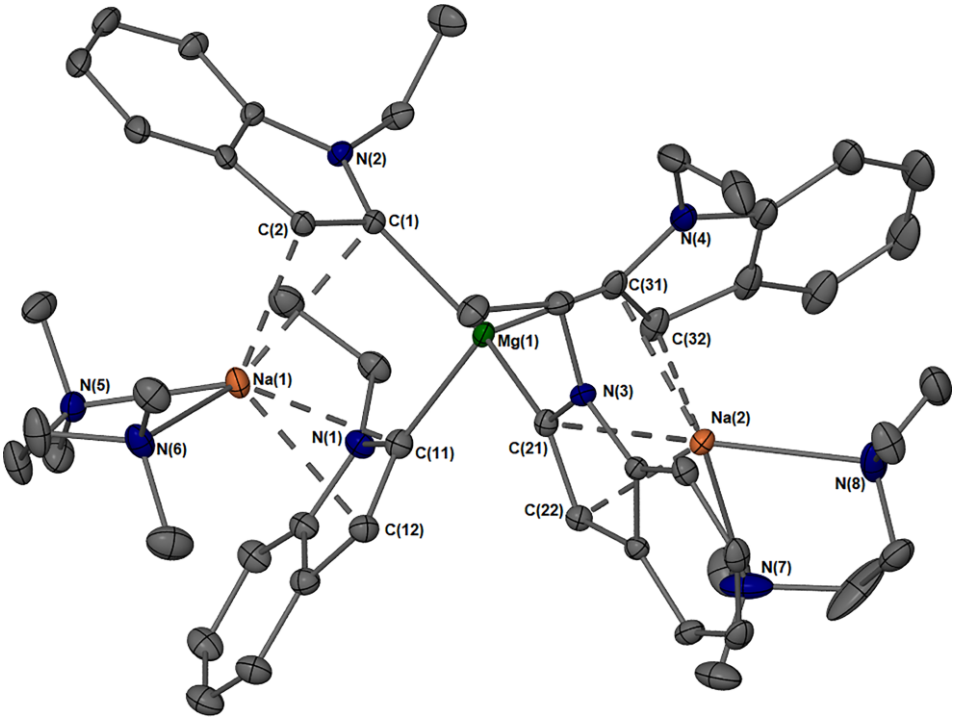


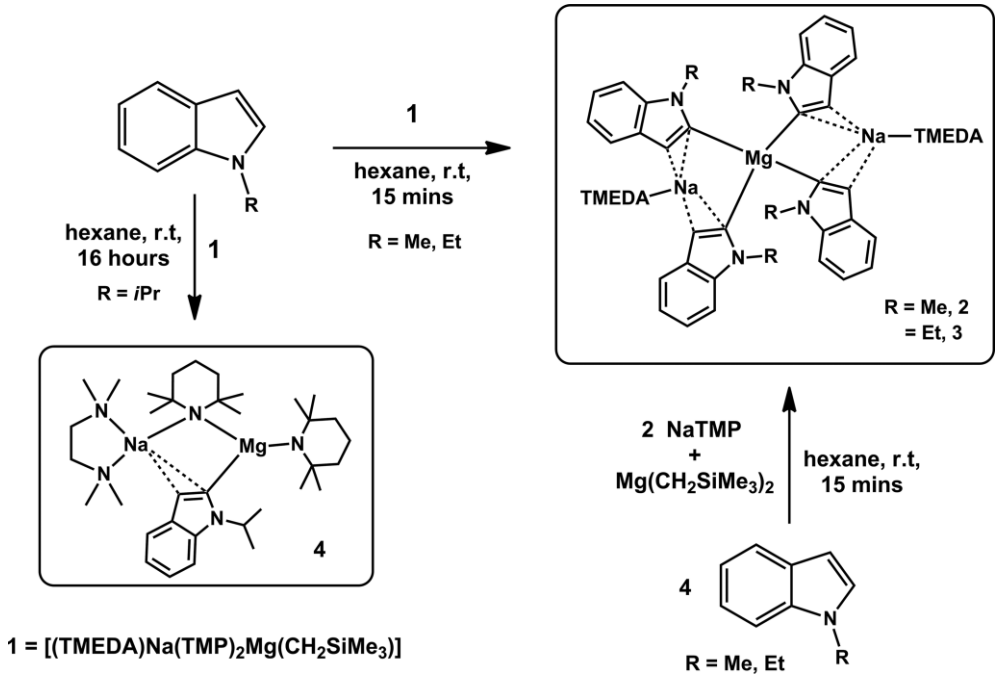
Figure 1. Molecular structure of $[(Na\text{-}TMEDA)_2Mg(\alpha\text{-}C_{10}H_{10}N)_4]$ (**3**) with thermal ellipsoids at 40 % probability. Hydrogen atoms and one disordered TMEDA molecule have been omitted for clarity. Selected bond lengths [Å]: Mg(1)–C(1), 2.2086(16); Mg(1)–C(11), 2.2120(18); Mg(1)–C(21), 2.2331(16); Mg(1)–C(31), 2.2377(17); Na(1)–C(1), 2.9184(17); Na(1)–C(2), 2.6993(17), Na(1)–C(11), 2.6905(18); Na(1)–C(12), 2.7420(18); Na(2)–C(21), 2.8580(17); Na(2)–C(22), 2.6159(17); Na(2)–C(31), 2.6492(18); Na(2)–C(32), 2.7225(18); C(1)–Mg(1)–C(11), 102.76(6); C(1)–Mg(1)–C(21), 119.67(6); C(1)–Mg(1)–C(31), 116.16(6); C(11)–Mg(1)–C(21), 102.00(6); C(11)–Mg(1)–C(31), 112.06(7); C(21)–Mg(1)–C(31), 103.46(6).

metalated indole substituents [C(1), C(11), C(21) and C(31)] with an average Mg–C bond length of 2.222 Å (mean 2.216 Å in **2**[13]). Each sodium atom in **3** makes electrostatic η^2-interactions with the 2-C and 3-C atoms of each deprotonated indole unit [range of lengths Na–C: 2.6159(17)–2.9184(17) Å]. Its coordination sphere is completed by a complexed bidentate molecule of TMEDA making the Na atoms overall six coordinate.

The rational synthesis of both **2** and **3** was achieved by reacting NaTMP, $Mg(CH_2SiMe_3)_2$, and TMEDA in a 2:1:2 ratio with four equivalents of the respective indole (Scheme 1). In both cases the desired product was isolated in a high crystalline yield (unoptimised 81 % and 72 % respectively). The original synthesis is likely to occur by a disproportionation reaction similar to that which has been previously reported for **1** with thiophene[15] and the mixed zincate bases [(TMEDA)Na(*t*Bu)$_2$Zn(TMP)] and [Li(*n*Bu)$_2$Zn(TMP)(TMEDA)] and their reactivity towards indoles and ferrocene respectively.[13,16]

Reaction of **1** with the more sterically encumbered *N*-isopropylindole substrate at room temperature resulted in the deposition of a yellow precipitate, which when recrystallised from *n*-hexane afforded X-ray quality single crystals. These were identified as $[(TMEDA)Na(TMP)(\alpha\text{-}C_{11}H_{12}N)Mg(TMP)]$ **4** (Scheme 1 and Figure 2). Complex **4** adopts a familiar structural motif,[17–20] whereby **1** has exhibited overall alkyl basicity, losing the CH_2SiMe_3 group and replacing it with an α-deprotonated *N*-isopropylindole unit. The molecular structure of **4** contains a central trigonal planar magnesium atom, bonding to a bridging and terminal TMP molecule and an α-deprotonated *N*-isopropylindole [C(1)–Mg(1), 2.192(4) Å]. Similar to **3**, the sodium atom is interacting electrostatically with both the C(1) and C(2) atoms of the *N*-isopropylindole in a η^2-manner, as indicated by the Na–C bond lengths of 2.857(4) and 2.646(4) Å respectively.

When comparing complexes **2** and **3** to **4**, although the overall regioselectivity of **1** does not change, different complex architectures are uncovered. The α-magnesiation of both *N*-methyl and *N*-ethyl indole results in **1** or "$[(TMEDA)_2Na(TMP)_2Mg(CH_2SiMe_3)_2]$" replacing all the available (potentially) basic arms with α-magnesiated indole units, whereas in **4**, only one basic (CH_2SiMe_3) arm is lost. This makes **2** and **3** the products of a more atom efficient process. Complexes **2** and **3** are obtained swiftly under ambient conditions (quantitative at room temperature, 15 min), with no cooling or reflux conditions (cf. lithiation of *N*-methylindole[21]) required to retain selectivity, whereas **4** needs longer reaction times to achieve quantitation (16 h). Attempts to force **4** to be more atom-efficient and react faster unfortunately failed, even when an excess of *N*-isopropylindole was employed under both room temperature and reflux conditions. It would therefore appear that the added steric bulk of the *N*-isopropyl group in **4** inhibits the formation of a structural motif similar to **2** or **3**. Examining the space filling diagram of **3** (Figure 3) demonstrates the steric congestion already present around the metal centres when an ethyl group is present, most likely hindering the isolation of an isopropyl analogue. To the best of our knowledge, structurally characterised



Scheme 1. Reaction of **1** with methyl, ethyl and isopropyl *N*-alkyl indoles.

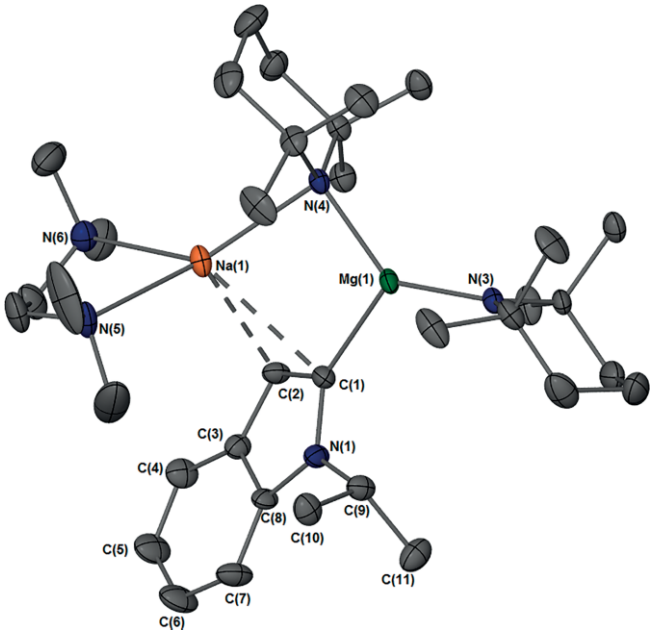


Figure 2. Molecular structure of [(TMEDA)Na(TMP)(α-$C_{11}H_{12}N$)Mg(TMP)] (**4**) with thermal ellipsoids at 40 % probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Mg(1)–C(1), 2.192(4); Mg(1)–N(4), 2.070(3); Mg(1)–N(3), 2.009(3); Na(1)–N(4), 2.464(3); Na(1)–N(5), 2.499(4); Na(1)–N(6), 2.457(4); Na(1)–C(1), 2.857(4); Na(1)–C(2), 2.646(4); C(1)–Mg(1)–N(3), 121.72(15); N(3)–Mg(1)–N(4), 133.32(14); N(4)–Mg(1)C(1), 104.94(15).

Mg–C or Mg–N bonded indole complexes are rare with only one previously reported Mg–C indole complex [(Na-TMEDA)$_2$Mg(α-C_9H_8N)$_4$][13] and two Mg–N bonded bis-indolyl complexes [($C_{14}H_{12}SN$)$_2$Mg(THF)$_2$] and [($C_{14}H_{12}ON$)$_2$Mg(THF)$_2$] reported in the literature.[22]

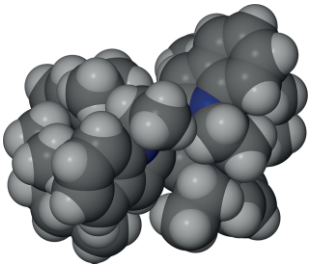
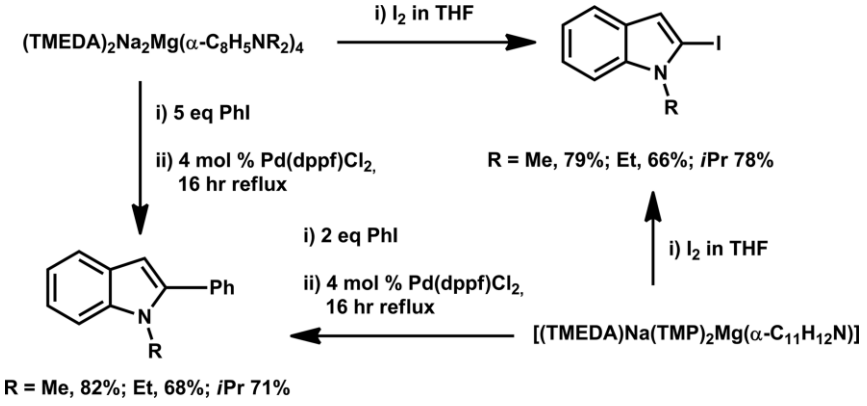


Figure 3. Space-filling diagram of compound **3**.

Crystalline **2**–**4** were dissolved in C_6D_6 and analysed by ^{1}H and ^{13}C NMR spectroscopy. The spectra indicate an α-substituted *N*-alkyl indole in a 2:1 ratio with TMEDA for **2** and **3** and a 1:1 ratio for **4**, with all three complexes preserving their solid state composition in solution. The disappearance of the two doublet signals (6.51 and 6.55 ppm for **2**; 6.54 and 6.68 ppm for **3**; 6.57 and 6.88 ppm for **4**) in the aromatic region corresponding to the parent indole, and the appearance of a singlet at δ = 6.53, 6.86 and 6.21 ppm respectively are indicative of an α-magnesiated species. Large down field chemical shifts for the 2-C ^{13}C resonance to 180.39, 181.49 and 178.79 ppm (parent indole: 129.05, 126.5 and 123.0 ppm) in **2**–**4** respectively are indicative of a magnesiation.

Utilising the Mg–C bond in complexes **2**–**4**, we examined their potential use in both in situ iodolysis and Pd-catalysed cross-coupling reactions[23] with iodobenzene. In a "one pot" procedure, all three complexes successfully gave their expected 2-iodo-1-alkylindole or 2-phenyl-1-alkylindole products in unoptimised high to moderate yields (I_2 79–66 %; cross-coupling 82–68 %, Scheme 2).



Scheme 2. In situ iodolysis and cross coupling reactions of **2**–**4**.

Conclusion

We have demonstrated that AMM*Mg* with **1** can successfully α-magnesiate three N-alkylated indoles selectively and under mild reaction conditions. We have revealed, through X-ray crystallographic and solution characterisation, that the efficiency of **1** is influenced by the steric nature of the *N*-alkyl group, leading to a less atom efficient magnesiation as steric bulk is increased. Utilising these selective indol-2-magnsiates in both in situ iodolysis and Pd-catalysed cross-coupling reactions leads to the isolation of the corresponding 2-iodo-1-alkylindole or 2-phenyl-1-alkylindole products in high to moderate yields.

Experimental Section

General Experimental Details: All reactions (unless otherwise stated) were completed under an atmosphere of dinitrogen and anhydrous conditions using standard Schlenk-line techniques. Water and oxygen were removed from *n*-hexane and diethyl ether using a MBRAUN SPS-800 solvent purification system and were stored over 4 Å molecular sieves under a dinitrogen atmosphere. TMEDA was dried by reflux over CaH_2 and stored over 4 Å molecular sieves. TMP(H) was purchased from Oakwood Chemicals and stored over 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX 400 MHz or 600 MHz Cryo spectrometers with chemical shifts internally referenced to C_6D_6 or $CDCl_3$. Microanalysis were carried out at the Science Centre, London Metropolitan University, with samples prepared in air-tight sealed glass ampules. *N*-methylindole was purchased from Aldrich and stored over 4 Å molecular sieves. *N*-ethylindole,[24] *N*-isopropylindole,[25] *n*BuNa,[26] and $Mg(CH_2SiMe_3)_2$[14] were prepared according to literature procedures.

GP1: *n*BuNa (0.08 g, 1 mmol) was suspended in 10 mL of dry *n*-hexane. To this suspension was added TMP(H) (0.34 mL, 2 mmol) dropwise, and the reaction was stirred at room temperature for at least 30 min. Next, $Mg(CH_2SiMe_3)_2$ (0.2 g, 1 mmol) was added with subsequent addition of TMEDA (0.15 mL, 1 mmol), affording a pale yellow, clear solution, which was used in situ. **GP2:** *n*BuNa (0.16 g, 2 mmol) was suspended in 10 mL of dry *n*-hexane. To this suspension was added TMP(H) (0.34 mL, 2 mmol) dropwise, and the reaction was stirred at room temperature for at least 30 min. Next $Mg(CH_2SiMe_3)_2$ (0.2 g, 1 mmol) was added with subsequent addition of TMEDA (0.3 mL, 2 mmol). The resulting pale yellow, cloudy solution was used in situ.

X-ray Data Collection, Reduction, Solution and Refinement

X-ray crystallographic data for **2** and **4** were obtained on a Bruker X8 Nonius Kappa CCD diffractometer with graphite-monochromated Mo-K_α (λ_0 = 0.71073 Å) radiation at 123 K. All single crystals were mounted on a glass fibre under oil. Data was collected and processed using the Bruker Apex2 v.2012.2.0 software; Lorentz, polarisation and absorption corrections (multi-scan – SADABS)[27] were applied. Crystallographic data of compound **3** was collected at the MX1 beamline at the Australian Synchrotron, Melbourne, Victoria, Australia (γ = 0.71070 A). All data was collected at 100 K, maintained using an open flow of nitrogen. The software used for data collection and reduction of the data were BluIce[28] and XDS.[29] Multi-scan absorption corrections (SADABS[27]) were applied. Compounds **2**, **3** and **4** were solved and refined with SHELX-2016[30] and X-seed interface[31] or Olex2.[32] Compound **2** was modelled as a two component twin (twin law −1 0 0 0 −1 0 0 0 1), BASF = 0.1492(19). Compound **3** had a disordered TMEDA molecule which was modelled as disordered across two sites.

CCDC 1578143 (for **2**), 1578142 (for **3**), and 1578141 (for **4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[(Na-TMEDA)$_2$Mg(α-C$_9$H$_8$N)$_4$] (2): *N*-Methylindole (0.13 mL, 1 mmol) was added to a stirred solution of **GP1**. A large quantity of white precipitate was observed after roughly 10–15 min, which was isolated by filtration and transferred to an argon glovebox for storage. X-ray quality crystals were obtained upon recrystallisation from *n*-hexane. Yield = 0.2 g, 24 % (max yield 25 % based on consumption of *N*-methylindole). Rational synthesis of **2** was achieved using **GP2**. *N*-methylindole (0.52 mL, 4 mmol) was added to a stirred solution of **GP2**. This resulted in the immediate formation of a clear solution. After approximately 10–20 min, a large quantity of a white precipitate was observed, which was identified by NMR as **2**. Isolated crystalline yield = 0.67 g, 81 % (quantitative by NMR). ^1H NMR (400 MHz, C_6D_6, 300 K): δ = 7.68–7.60 (m, 1 H, H3), 7.27 (m, 1 H, H6), 7.21–7.16 (m, 2 H, H4/H5), 6.94 (d, $^4J_{HH}$ = 0.9 Hz, 1 H, H2), 4.15 (s, 3 H, CH_3), 1.19 (s, 6 H, CH_3-TMEDA), 1.06 (s, 2 H, CH_2-TMEDA) ppm. ^{13}C NMR (101 MHz, C_6D_6, 300 K): δ = 180.39 (Mg-C2), 141.17, 131.79, 118.52 (C5/6), 117.97 (C4), 117.65 (C5/6), 109.71 (C3), 108.62 (C7), 55.84 (CH_2-TMEDA), 44.46 (CH_3-TMEDA), 36.57 (CH_3) ppm. $C_{48}H_{64}MgN_8Na_2$ (823.37): calcd. C 70.19, H 7.61, N 13.64; found C 69.73, H 7.65, N 13.41. Crystal data for compound **2** $C_{48}H_{64}MgN_8Na_2$: M = 823.38, colourless plates, 0.21 × 0.20 × 0.14 mm^3, monoclinic, space group $P2_1/c$, a = 17.6570(16), b = 16.8891(15), c = 15.9701(14),

α = 90°, β = 90.628(4)°, γ = 90°, V = 4762.2(7) Å ^{3}, Z = 4, D_c = 1.148 g/cm^3, F(000) = 1768, T = 123(2) K, 82061 reflections collected, 10691 unique (R_{int} = 0.1037), Final GooF = 1.022, $R1$ = 0.0794, $wR2$ = 0.2648, 545 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.096 mm^{-1}. Refined as a two-component twin (Twin law –1 0 0 0 –1 0 0 0 1), BASF = [0.1492(19)].

[(Na-TMEDA)$_2$Mg(α-C$_{10}$H$_{11}$N)$_4$] (3): *N*-Ethylindole (0.15 g, 1 mmol) was added dropwise to a stirred solution of **GP1**. After approximately five minutes, formation of a white precipitate was observed. The precipitate was isolated by filtration, washed with *n*-hexane and dried in vacuo, before storage in an argon glove box. X-ray quality crystals were obtained upon recrystallisation in toluene. Both the crystalline material and the powder were found to be the same product by NMR analysis. Yield = 0.2 g, 24 % (maximum yield 25 % based on consumption of *N*-ethylindole). Rational synthesis of **3**: To a stirred suspension of **GP2** was added *N*-ethylindole (0.58 g, 4 mmol) dropwise, resulting in the immediate formation of a clear solution. After approximately 10–20 min, a large quantity of a white precipitate was observed, which was identified by NMR as the title species. Isolated crystalline yield: 0.586 g, 70 % (quantitative by NMR). ^{1}H NMR (400 MHz, C_6D_6, 300 K): δ = 7.63–7.56 (m, 1 H, H4), 7.29 (m, 1 H, H7), 7.17–7.08 (m, 2 H, H5/H6), 6.86 (s, 1 H, H3), 4.70 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2), 1.44 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, CH_3), 1.28 (s, 6 H, TMEDA-CH_3), 1.21 (s, 3 H, TMEDA-CH_2) ppm. ^{13}C NMR (101 MHz, C_6D_6, 300 K): δ = 181.49 (Mg-C2), 140.45, 132.73, 119.01 (C5/6), 118.58 (C5/6), 118.23 (C4), 109.88 (C7), 109.64 (C3), 56.79 (CH_2-TMEDA), 45.25 (CH_3-TMEDA), 45.14 (CH_2), 17.31 (CH_3) ppm. Crystal data for Compound **3** $C_{52}H_{72}MgN_8Na_2$: M = 1198.37, colourless plates, 0.04 × 0.03 × 0.02 mm^3, triclinic, space group *Pbca*, a = 16.682(3), b = 16.236(3), c = 38.216(8), α = 90°, β = 90°, γ = 90°, V = 10351(4) Å^3, Z = 8, D_c = 1.129 g/cm^3, F(000) = 3792.0, T = 100(2) K, 85955 reflections collected, 12826 unique (*R*int = 0.706), Final GooF = 1.056, $R1$ = 0.0706, $wR2$ = 0.1528, 612 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.090 mm^{-1}.

[(TMEDA)Na(TMP)(α-C$_{11}$H$_{12}$N)Mg(TMP)] (4): *N*-Isopropylindole (0.16 g, 1 mmol) was added dropwise to a stirred solution of **GP1**. After stirring overnight, a white precipitate was observed and collected via filtration, washed with *n*-hexane and dried in vacuo, before storage in a glovebox. X-ray quality single crystals were obtained upon recrystallisation from *n*-hexane. Both the crystalline material and the powder were found to be the same product by NMR analysis. Yield: 0.35 g, 58 %. ^{1}H NMR (400 MHz, C_6D_6, 300 K): δ = 7.49 (m, 2 H, H3/6), 7.1–7.2 (m, 2 H, H4/5), 6.21 (d, $^4J_{HH}$ = 0.8 Hz, 1 H, H_2), 5.16 (septet, $^3J_{HH}$ = 6.8 Hz, 1 H, CH), 1.69 (d, $^3J_{HH}$ = 6.8 Hz, 6 H, CH_3), 1.88 (m, 4 H, γ-CH_2 TMP), 1.59 [s (br), 24 H, CH_3 TMP], 1.46 [s (br), 12 H, CH_3, TMEDA], 1.44 [s (br), 4 H, CH_2, TMEDA], 1.39 [s (br), 6 H, β-CH_2 TMP] ppm. ^{13}C NMR (100 MHz, C_6D_6, 300 K): δ = 178.79 (Mg-C2), 138.0, 133.4, 118.4 (C4), 117.8 (C7), 117.7 (C5), 111.1 (C6), 106.4 (C3), 56.4 (CH_2 TMEDA), 54.1 (CH-isopropyl), 52.2 (TMP-quaternary), 45.2 (CH_3 TMEDA), 41.8 (β-CH_2 TMP), 35.7 (CH_3 TMP), 22.3 (CH_3 isopropyl), 20.0 (γ-CH_2 TMP) ppm. $C_{70}H_{122}Mg_2N_{10}Na$ (1175.40): calcd. C 69.80, H 10.71, N 11.63; found C 69.88, H 9.96, N 11.45. Crystal data for compound **4** $C_{70}H_{122}Mg_2N_{10}Na_2$: M = 1198.37, colourless plates, 0.18 × 0.16 × 0.10 mm^3, triclinic, space group $P\bar{1}$, a = 11.5469(4), b = 16.3939(6), c = 20.4362(8), α = 81.102(2)°, β = 85.116(2)°, γ = 72.647(2)°, V = 3644.9(2) Å^3, Z = 2, D_c = 1.092 g/cm^3, F(000) = 1316, T = 123(2) K, 49988 reflections collected, 14416 unique (*R*int = 0.1065), Final GooF = 1.038, $R1$ = 0.0794, $wR2$ = 0.2291, 783 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.090 mm^{-1}.

Iodolysis Protocol: To a stirred solution of **2**, **3** or **4**, was added a 1 M solution of iodine in THF (10 mL for **2** and **3**, 5 mL for **4**) dropwise at room temperature. The resulting solution was stirred overnight and quenched with saturated $Na_2S_2O_3$ sodium thiosulfate (20 mL). The solution was diluted with CH_2Cl_2, dried with $MgSO_4$ and the solvent removed in vacuo. *N*-methyl-2-iodoindole was isolated as a crystalline solid. *N*-ethyl-2-iodoindole and *N*-isopropyl-2-iodoindole were isolated as pale yellow oils following purification by flash chromatography (silica gel, *n*-hexane). ***N*-methyl-2-iodoindole**: 0.81 g, 79 %: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 7.57 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, H3), 7.34 (d, $^3J_{HH}$ = 8.3 Hz, 1 H, H6), 7.19 (d, $^3J_{HH}$ = 7.4 Hz, 1 H, H5), 7.11 (t, $^3J_{HH}$ = 7.4 Hz, 1 H, H4), 6.84 (s, 1 H, H2), 3.79 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ = 138.19, 129.74, 121.96 (C4), 119.93 (C5), 119.62 (C6), 111.94 (C2), 109.82 (C7), 84.10 (C1), 34.19 (CH_3) ppm. ***N*-ethyl-2-iodoindole**: 0.72 g, 66 %: ^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ = 7.53 (dt, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0 Hz, 1 H, H3), 7.33 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 0.9 Hz, 1 H, H6), 7.15 (ddd, $^3J_{HH}$ = 8.3, 7.1, $^4J_{HH}$ = 1.2 Hz, 1 H, H5), 7.06 (ddd, $^3J_{HH}$ = 7.9, 7.1, $^4J_{HH}$ = 1.0 Hz, 1 H, H4), 6.78 (d, $^4J_{HH}$ = 0.8 Hz, 1 H, H2), 4.23 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2), 1.35 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 300 K): δ = 137.01, 130.08, 121.87 (C5), 119.89 (C4), 119.76 (C3), 112.11 (C2), 109.74 (C6), 82.58 (C1), 42.25 (CH_2), 15.35 (CH_3) ppm. HRMS (ESI) ([M + H]$^+$) calcd. for $C_{10}H_{10}IN$: 271.9936, found 271.9925. IR: $\tilde{\nu}$ = (ax =) 3052 (w), 2939 (w), 1602 (w), 1512 (m), 1463 (s), 1420 (m), 1385 (m), 1316 (s), 1241 (s), 1205 (m) 1130 (m), 1075 (s), 1008 (s), 919 (m), 837 (m), 733 (s), 698 (s) cm^{-1}. ***N*-isopropyl-2-iodoindole**: 0.22 g, 78 %: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 7.50–7.45 (m, 2 H, H4/7), 7.05–7.00 (m, 2 H, H5/6), 6.67 (d, $^3J_{HH}$ = 0.9 Hz, 1 H, H2),4.78 (septet, $^3J_{HH}$ = 7.1 Hz, 1 H, CH), 1.56 (d, $^3J_{HH}$ = 7.1 Hz, 9 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ = 123.00 (C4/7), 120.91 (C5/6), 120.85 (C5/6), 119.68 (C4/7), 111.19 (C3), 57.96 (CH), 21.12 (CH_3) ppm. HRMS (ESI) ([M + H]$^+$) calcd. for $C_{11}H_{12}IN$: 286.0093, found 286.0082. IR: $\tilde{\nu}$ = (ax =) 2967 (m), 2931 (m), 2440 (w), 1701 (w), 1457 (s), 1438 (s), 1400 (s), 1383 (m), 1336 (m), 1303 (s), 1260 (m), 1220 (s), 1087 (s), 1011 (s), 906 (m), 800 (m), 738 (s) cm^{-1}.

Cross-Coupling Protocol: To a stirred solution of either **2**, **3** or **4**, was added iodobenzene (5 equiv. for **2** and **3**, 2 equiv. for **4**), followed by the addition of 4 mol-% of Pd(dbbf)Cl_2. The reaction was refluxed for 16 hours. After cooling to room temperature, the solution was quenched with saturated NH_4Cl, extracted with dichloromethane, dried with anhydrous $MgSO_4$ and the solvent was removed in vacuo. *N*-methyl-2-phenylindole and *N*-ethyl-2-phenylindole were isolated as crystalline solids, and *N*-isopropyl-2-phenylindole was isolated as a pale yellow oil following flash chromatography (silica gel, *n*-hexane). Compounds prepared were consistent with literature values. ***N*-methyl-2-phenylindole**:[13] 0.68 g, 82 %: ^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ = 7.65 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, H4), 7.52 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.3 Hz, 2 H, *ortho*-H), 7.48 (t, $^3J_{HH}$ = 7.6 Hz, 2 H, *meta*-H), 7.41 (t, $^3J_{HH}$ = 7.3 Hz, 1 H, *para*-H), 7.38 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, H7), 7.28–7.23 (m, 2 H, H6), 7.18–7.13 (m, 1 H, H5), 6.57 (s, 1 H, H3), 3.76 (s, 3 H, CH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 300 K): δ = 141.79, 138.55, 133.07, 129.60 (*meta*-C), 128.70 (*ortho*-C), 128.17, 128.07 (*para*-C), 121.87 (C6), 120.68 (C5), 120.07 (C4), 109.81 (C7), 101.86 (C3), 31.40 (CH_3) ppm. ***N*-ethyl-2-phenylindole**:[33] 0.60 g, 68 %: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 7.63 (dt, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.0 Hz, 1 H, H4), 7.53–7.36 (m, 6 H, Ph + H7), 7.26–7.19 (m, 1 H, H6), 7.13 (ddd, $^3J_{HH}$ = 8.0, 7.0, $^4J_{HH}$ = 1.0 Hz, 1 H, H5), 6.52 (d, $^4J_{HH}$ = 0.9 Hz, 1 H, H3), 4.18 (t, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2), 1.32 (d, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ = 141.30, 137.31, 133.44, 129.59 (*meta*-C), 128.69 (*ortho*-C), 128.53, 128.14 (*para*-C), 121.74 (C6), 120.80 (C4), 119.98 (C5), 110.08 (C7), 102.31 (C3), 38.96 (CH_2), 15.59 (CH_3) ppm. ***N*-isopropyl-2-phenylindole**:[34] 0.17 g, 71 %: 7.64–7.59 (m, 2 H, H4/7), 7.5–7.4 (m, 5 H, phenyl-H), 7.20–7.15 (m, 2 H, H5/6), 6.45 (d, 1 H, J = 0.8,

H3), 4.68 (septet, 1 H, J = 7.0, CH), 1.6 (d, 1 H, J = 7.0, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ = 141.41, 135.44, 133.81, 131.98, 129.64 (*meta*-C), 128.42 (*ortho*-C), 127.93 (*para*-C), 121.01 (C5/6), 120.85 (C5/6), 119.44 (C4/7), 112.40 (C4/7), 102.21 (C3), 47.90 (CH), 21.57 (CH_3) ppm.

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