FULL PAPER

Contrasting synergistic heterobimetallic (Na-Mg) and homometallic (Na or Mg) bases in metalation reactions of dialkyl-phenylphosphines and dialkylanilines: lateral vs ring selectivities

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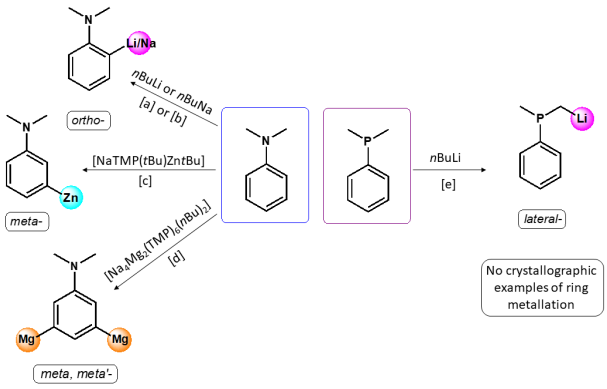
Abstract: A series of dialkyl phenylphosphines and their analogous aniline substrates have been metallated with the synergistic mixed-metal base [(TMEDA)Na(TMP)(CH_2SiMe_3)Mg(TMP)] **1**. Different metallation regioselectivities for the substrates were observed, with predominately lateral or *meta*-magnesiated products isolated from solution. Three novel heterobimetallic complexes [(TMEDA)Na(TMP)(CH_2PCH_3Ph)Mg(TMP)] **2**, [(TMEDA)Na(TMP)(*m*-$C_6H_4PiPr_2$)Mg(TMP)] **3** and [(TMEDA)Na(TMP)(*m*-$C_6H_4NEt_2$)Mg(TMP)] **4** and two homometallic complexes [{(TMEDA)Na($EtNC_6H_5$)}$_2$] **5** and [(TMEDA)Na_2(TMP)(C_6H_5PEt)]$_2$ **6** derived from homometallic metalation have been crystallographically characterised. Complex **6** is an unprecedented sodium-amide, sodium-phosphide hybrid with a rare $(NaNNaP)_2$ ladder motif. These products reveal contrasting heterobimetallic deprotonation with homometallic induced ethene elimination reactivity. Solution studies of metallation mixtures and electrophilic iodine quenching reactions confirmed the metallation sites. In an attempt to rationalise the regioselectivity of the magnesiation reactions the C-H acidities of the six substrates were determined in THF solution using DFT calculations employing the M06-2X functional and cc-pVTZ Dunning's basis set.

Introduction

A fundamental challenge within synthetic chemistry is to control the chemo- and regio-selectivity when functionalising organic molecules. Organometallic alkyl- and aryl-lithium compounds and the lithium secondary amides (the "utility amides"[1]) have a long-established role in the synthetic chemists repertoire.[1–3] Synthetic approaches including directed *ortho*-metallation (DoM) is without doubt the classical concept in organo-alkali chemistry, allowing the selective functionalisation of aromatic molecules. DoM is of particular importance in the synthesis of pharmaceutical products.[4] However, exceptions to *ortho*-metallation are relatively scarce.[2] The demand to develop new methods to selectively functionalise neighbouring *meta*- and *para*- positions led to several new classes of bi-metallic reagents emerging in the past two decades. Most prominent are 'turbo-Grignards' reagents pioneered by Knochel. Typified by the mixed lithium halide-magnesium amide complex (TMPMgCl.LiCl),[5,6] these salt-modulated organometallic reagents can regiospecifically functionalize an impressive variety of aromatic and heteroaromatic compounds and offer good compatibility with sensitive functional groups. Recently, a new halogen-magnesium exchange reagent *s*BuMgOR.xLiOR (X= 1 or 2; R= 2-ethylhexyl) has been developed allowing fast Br/Mg or Cl/Mg exchange reactions producing heteroaryl magnesium alkoxides in non-polar solvents.[7] Mongin and co-workers have developed a range of bimetallic ate complexes for the metallation of many functionalised aromatics, combining lithium with a variety of secondary metals including zinc,[8–12] copper[13] or magnesium.[14–15] These metallating agents usually consist of a mixed alkyl or amido lithium species with either a divalent metal salt or a di-alkyl/amido metallic species. Of particular relevance to this work are the bi-metallic bases formed by the co-complexation of an alkali metal amide (most commonly NaTMP) and a dialkyl subordinate metal partner, typically zinc,[12,16–18] magnesium[14,15,19,20] aluminium[21,22] or manganese.[23–25] Early examples of the effectiveness of these bases include the magnesiation (C-*H* to C-*Mg*) of benzene[26] and the selective *meta*-magnesiation of toluene,[27] both achieved utilising the sodium magnesiate base [(TMEDA)Na(*n*Bu)(TMP)Mg(TMP)].[26,27] There are presedents in the literature for these bimetallic systems metallating aniline based substrates. A notable example is with the sodium zincate, [(TMEDA)Na(*t*Bu)(TMP)Zn(*t*Bu)], where a novel *meta*-zincation of *N,N*-dimethylaniline[28] (Scheme 1) was achieved. However, subsequent *in situ* electrophilic quenching studies with iodine revealed a mixture of *ortho*-, *meta*- and *para*- iodoanilines.[29]



Scheme 1 Structurally characterised examples of the products of metallation of N, N-dimethylaniline and dimethylphenylphosphine. Note only metals shown for clarity. Reagents and conditions: [a] *n*BuLi, hexane, reflux, 16 hours[33] [b] *n*BuNa, hexane, 0°C,[29] [c] [NaTMP(*t*Bu)Zn(*t*Bu)], hexane, reflux, 2 hours,[28] [d] [$Na_4Mg_2(TMP)_6(nBu)_2$], methylcyclohexane, reflux, 4 hours,[31] [e] *n*BuLi.TMEDA, hexane.[34]

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More recently a sophisticated template approach[30] has been reported employing the sodium magnesiate base $[Na_4Mg_2(TMP)_6(nBu)_2]$. This powerful method relies on the azametallo ring scaffold, which can override acidity criteria and direct remarkable selective and regiospecific polymetallations. For example *ortho-meta'* or *meta-meta'* di-metallations of substituted arenes and anilines (Scheme 1)[31] has been accomplished, while reaction with the polyaryl substrate *para*-terphenyl results in di- or even tetra-metallated substrates.[32]

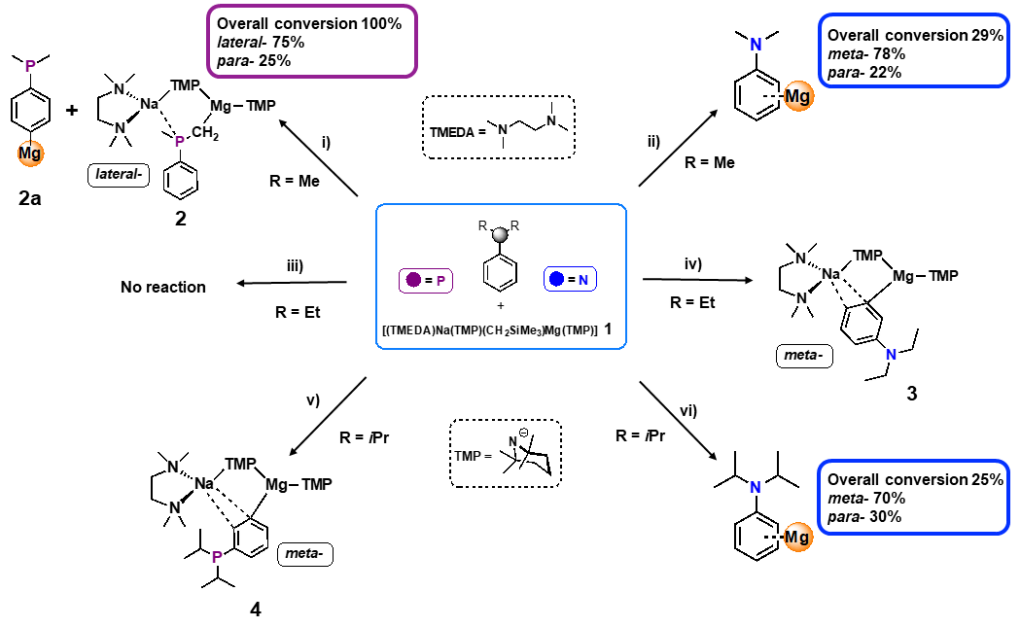
Surprisingly, compared to the established mono- and bi-metallic metallation chemistry of tertiary amines, analogous studies based on tertiary phosphines are relatively scarce. Given the synthetic utility of phosphorus based ligands in catalyst design,[35] material chemistry and the stabilisation of main group and transition metal complexes[36] investigation of their functionalisation and reactivity is of special importance. In context to synthetic medicinal chemistry, alkali metal amide complexes feature prominently,[37] while related phosphorus containing compounds have been generally overlooked. Recently, a phosphine-oxide containing compound Brigatinib (AP26113), developed by Huang and co-workers, was approved by the FDA for the treatment of lung cancer,[38] making the metallation of phosphorus containing compounds of high interest, providing new prospects in medicinal chemistry.

This study reports, the selective magnesiation of a range of dialkyl substituted phenylphosphines and their aniline counterparts employing the sodium magnesiate base $[(TMEDA)Na(TMP)(CH_2SiMe_3)Mg(TMP)]$ **1** (TMEDA = *N,N,N',N'*-tetramethylethylenediamine, TMP = 2,2,6,6-tetramethylpiperdide). To the best of our knowledge, no phosphorus containing substrates have been investigated to date, whereas, **1** has previously been used in metallation of furan,[20] thiophene[39] and most recently *N*-substituted indoles.[40] This work discloses the subtle electronic and steric influences of N *versus* P substitution, showcasing in some instances unexpected metallation sites. To provide a rational for the different selectivities observed, pK_a calculations have been performed.

Results and Discussion

Synthesis

Starting with the simplest benchmark methyl substituted analogues, reaction of **1** with *N,N*-dimethylaniline in hexane at room temperature resulted in a viscous oil identified (via ^{1}H NMR spectroscopy) as predominately starting material (<10% metallated species). When the reaction mixture was heated to reflux (2 hours), a mixture of *meta*- and *para*- magnesiated *N,N*-dimethylaniline was observed (overall conversion 29%; *meta*- 78 %, *para*- 22%). Heating beyond 2 hours leads to decomposition of the base and an oil which was consistent with starting amine confirmed via NMR spectroscopy (see ESI). In contrast, reaction of a hexane solution of **1** with *P,P*-dimethylphenylphosphine at room temperature resulted in the isolation of a white crystalline solid identified by X-ray crystallography as the laterally magnesiated phosphinomethanide complex $[(TMEDA)Na(TMP)(CH_2PCH_3Ph)Mg(TMP)]$ **2**, in a 58% crystalline yield. Moving on to the ethyl-analogues, *N,N*-diethylaniline could be successfully *meta*-magnesiated upon reaction with **1** in hexane solution to afford the crystalline



Scheme **2** Reagents and conditions: i) hexane, r.t., overnight ii) hexane, reflux, 2 hours iii) hexane, no reaction observed at r.t. for 1-7 days or reflux for 1, 2, 6 or 18 hours, iv) hexane, r.t., overnight, v) hexane, r.t., overnight, vi) hexane, reflux, 3 hours

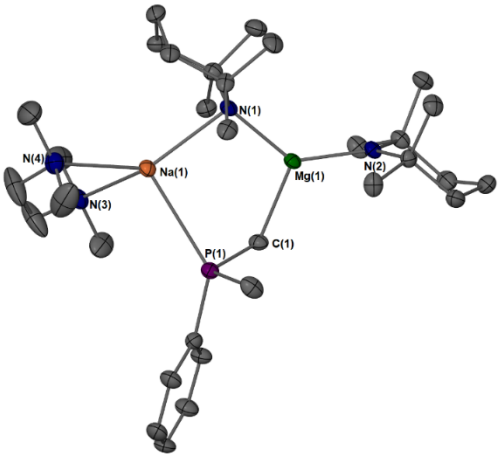


Figure **1** Molecular structure of [(TMEDA)Na(TMP)(CH_2PCH_3Ph)Mg(TMP)] **2** with thermal ellipsoids at 40 % probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Mg(1) – N(1), 2.069(5); Mg(1) – N(2), 2.001(5); Mg(1) – C(1), 2.182(6); Na(1) – N(1), 2.463(5); Na(1) – N(3), 2.528(6); Na(1) – N(4), 2.495(5); Na(1) – P(1), 2.919(2); P(1) – C(1), 1.777(6); P(1) – C(2), 1.823(8); N(1) – Na(1) – P(1), 95.24(12); Na(1) – N(1) – Mg(1), 103.5(2); N(1) – Mg(1) – C(1), 108.8(2); Mg(1) – C(1) – P(1), 118.4(3); C(1) – P(1) – Na(1), 88.40(19).

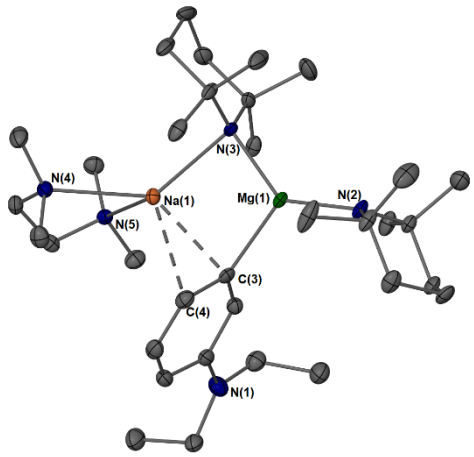


Figure **2** Molecular structure of [(TMEDA)Na(TMP)(*m*-$C_6H_4NEt_2$)Mg(TMP)] **3** with thermal ellipsoids at 40 % probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Mg(1) – C(3), 2.182(2); Mg(1) – N(3), 2.0794(16); Mg(1) – N(2), 1.9989(17); Na(1) – C(3), 3.036(2); Na(1) – C(4), 2.648(2); Na(1) – N(3), 2.4779(18); Na(1) – N(4), 2.5401(18); Na(1) – N(5), 2.5291(18); N(2) – Mg(1) – C(3), 120.48(8); N(2) – Mg(1) – N(3), 134.32(7); N(3) – Mg(1) – C(3), 105.16(7); Na(1) – N(3) – Mg(1), 89.35(6).

compound [(TMEDA)Na(TMP)(*m*-$C_6H_4NEt_2$)Mg(TMP)] **3** in a 65% crystalline yield. Contrastingly, when **1** was treated with a molar equivalent of *P,P*-diethylphenylphosphine, no reaction was observed, even under reflux conditions, resulting in quantitative recovery of the phosphine substrate. Lastly, reaction of **1** at room temperature with the more sterically encumbered *N,N*-diisopropylaniline at room temperature results in an oil identified as starting material. When the reaction mixture is heated to reflux, a mixture of *meta*- and *para*- magnesiated anilinophenyl species are obtained (overall conversion 25%; *meta*- 70 %, *para*- 30%), as well as significant unreacted starting amine (see ESI), whereas reaction of **1** with *P,P*-diisopropylphenylphosphine affords the crystalline *meta*-magnesiated phosphinophenyl complex [(TMEDA)Na(TMP)(*m*-$C_6H_4PiPr_2$)Mg(TMP)] **4** selectively in a 31% crystalline yield.

Solid-state structures

To the best of our knowledge complexes **2** and **4** represent the first structurally characterised magnesiated dialkylphenylphosphines,[41] while complex **3** is a rare structural example of a ring-magnesiated aniline[31] with the only other reported literature examples being of *in situ* magnesiations followed by electrophilic quenching studies.[5,6,42,43]

X-ray crystallographic analysis of compound **2** (Figure 1) reveals the first example of lateral magnesiation of *P,P*-dimethylphenylphosphine. The bimetallic monomer is composed of one sodium atom connected to magnesium via an amido TMP bridge, with the magnesium coordination completed by a further TMP (terminal) and a CH_2 unit of a metallated phosphine. The sodium atom occupies a distorted tetrahedral environment (bond angles range 73.88°-134.47°), comprising a TMP bridge, a bridging $[C_6H_5PCH_3CH_2]^-$ and a bidentate chelating TMEDA ligand. The sodium atom forms a strong bond with the phosphorus lone pair [Na(1) – P(1) 2.919(2) Å] to close a central 5-atom 5-element (NaNMgCP) ring. The coordination environment of the magnesium atom is essentially trigonal planar (Σ bond angles = 359.96°) in common with this structural motif, with a terminal and bridging TMP molecule and a methyl magnesiated P,P-dimethylphenylphosphine anionic unit, with a typical covalent Mg-C bond length of 2.182(6) Å. Overall, **1** has executed alkyl basicity, with the loss of $SiMe_4$. Previous studies on the lateral metallation of *P,P*-dimethylphenylphosphine with *n*BuLi in the presence of the activating bidentate ligand TMEDA have been reported[34,44] revealing the dimer $[(TMEDA)Li(CH_2PCH_3Ph)]_2$. Contrasting the reactivity of the analogous dimethyl P/N substrates with **1**, a distinction in metallation site is observed, namely, lateral *versus* ring (Scheme 1). These differences can be rationalised at least in part by considering the electronic nature of the different directing groups. The poor directing ability of the dimethyl amino group,[45] attributed to lone pair delocalisation into the aromatic ring, makes the aryl H atoms weakly acidic, resulting in *ortho*-metallation. In contrast, the lone pairs on the dimethyl phosphorus system are not delocalised, resulting in increased acidity of the methyl substituents and hence directing metallation to the methyl group.

The molecular structures of **3** (Figure 2) and **4** (Figure 3) display a similar structural backbone {(TMEDA)Na(TMP)Mg(TMP)} to that of **2**, completed by a selectively *meta*-magnesiated dialkyl N or P substrate. In both **3** and **4** the magnesium atom lies coplanar to the aromatic ring, indicative of a strong Mg-C σ-bond to the *meta*-carbon of the aromatic ring [2.182(2) and 2.181(4) Å in **3** and **4** respectively]. In contrast, the sodium atom lies almost perpendicular to the magnesiated ring, forming modest Na-π interactions with the π-system of the aromatic ring, primarily with the deprotonated *meta*-carbon [Na(1)-C(3) 2.648(2) and Na(1)-C(2) 3.036(2) Å in **3**; Na(1)-C(3) 2.684 and Na(1)-C(2) 3.038(4) Å in **4**].[46] A distinction here is that the Ph ring engages with the sodium through a η^2

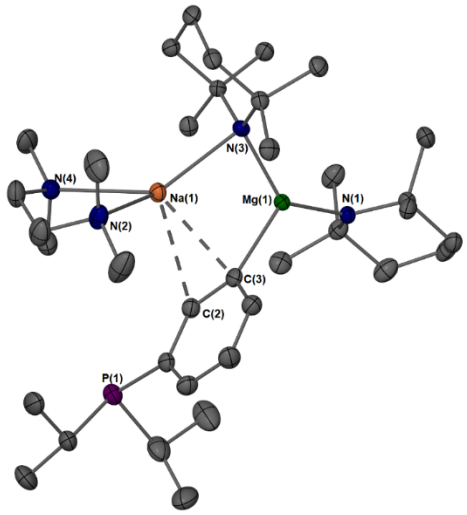


Figure **3** Molecular structure of [(TMEDA)Na(TMP)(*m*-C_6H_4P*i*Pr_2)Mg(TMP)] **4** with thermal ellipsoids at 40 % probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Mg(1)-C(3), 2.181(4); Mg(1)N(1), 1.994(3); Mg(1)-N(3), 2.071(3); Na(1)-N(3), 2.485(3); Na(1)-N(2), 2.457(3); Na(1)-N(4), 2.569(3); Na(1)-C(2), 3.038(4); Na(1)-C(3), 2.684(4); N(1)-Mg(1)-N(3), 133.51(13); N(1)-Mg(1)-C(3), 119.21(14); C(3)-Mg(1)-N(3), 107.11(13); Na(1)-N(3)Mg(1), 87.25(11).

C_{meta}-$C(H)_{para}$ interaction in **3**, but through a η^2C_{meta}-$C(H)_{ortho}$ interaction in **4.** Interestingly, in comparison to laterally metallated **2**, where the sodium atom binds to the phosphorus, here in **3** and **4** the heteroatom is orientated away from the metal centres, with the sodium atom opting to predominately π-engaging with the arene-ring opposed to typical dative bonding through the N/P atoms. As far as we can ascertain, the only reported, structurally characterised example of a ring metallated *N,N*-ethylaniline complex is the *para*-metallated dirhenium complex [$Re_2(CO)_8$(*μ*-H)(*p*-$C_6H_4NEt_2$)], [47] while hitherto no structurally characterised examples of ring-metallated dialkylphenylphosphine complexes exist.

Solution studies and Quenching

To build up a solution picture of complexes **2**-**4** NMR spectroscopic studies were performed in C_6D_6 followed by a series of I_2 and D_2O quenching studies. Interestingly this revealed some unexpected solution behaviour.

^{1}H and ^{31}P NMR spectra of complex **2** each revealed two sets of signals, suggesting a second species, other than the solid state structure, coexists in solution. In the $^{31}P\{^1H\}$ spectrum two resonances are present, a broad singlet at -29.7 ppm (belonging to **2**) and a smaller signal at -28.6 ppm attributed to **2a** (Scheme 2). Similarly, the ^{1}H and $^{13}C\{^1H\}$ NMR spectra indicate the presence of two species, the major species being assigned as **2** by three triplets 7.85, 7.27 and 7.12 ppm (corresponding to the *ortho*-, *meta*- and *para*-protons) and aliphatic signals at 1.40 ppm for the CH_3 and two non-equivalent signals for the Mg-CH_2 protons at 0.60 and -0.23 ppm (assigned by ^{1}H-^{13}C HSQC). While in the same spectra a second minor species can be identified as **2a** by a set of resonances at 7.83, 7.30 and 1.40 ppm. Note that this solution also contains resonances for TMEDA and TMP (see ESI). In an attempt to confirm the presence of the regioisomer **2a** and not another product within the sample C:H:N analysis was also carried out. Microanalysis and NMR spectroscopic studies are consistent with the minor species being the *para*-magnesiated *P,P*-dimethylphenylphosphine regioisomer complex **2a**. For further confirmation, attempts to isolate the observed *para*-isomer **2a** were made via electrophilic iodine and D_2O quenches. For ease of handling and purification, the quenched products were subject to aerial oxidation during workup to give the corresponding phosphorus(V) oxide compounds. Iodination of a crystalline sample of **2** lead to a mixture of multi-iodinated products (see ESI). However, quenching studies with D_2O afforded the expected corresponding single deuterated product, $CH_3(CH_2D)P{=}OPh$ with no other deutero-regioisomer isolated, suggesting **2a** to be a solution artefact.

^{1}H and ^{13}C NMR spectroscopic studies of complexes **3** and **4** returned no such complications and are consistent with the retention of their structures in solution. For **3**, the disappearance of the aromatic signals related to the parent aniline (7.24, 6.76 and 6.62 ppm) and appearance of four new aromatic signals, at 7.45 (doublet), 7.12 (singlet), 7.11 (doublet) and 6.48 ppm (doublet of doublet of triplets) are characteristic of a *meta*-deprotonated species. Similarly, the presence of four new aromatic resonances in the ^{1}H NMR spectrum of compound **4** at 8.15 (doublet of doublets), 7.83 (doublet), 7.23 (multiplet) and 7.17 ppm (triplet) indicate the formation of a *meta*-deprotonated species. The $^{31}P\{^1H\}$ NMR spectrum shows an upfield shift of the phosphorus signal from 10.42 ppm (parent phosphine) to 9.42 ppm in the metallated species **4**.

Iodolysis of **3** and **4** resulted in the expected *N,N*-diethyl-3-iodoaniline and (3-iodophenyl)diisopropylphosphine respectively. Interestingly, small quantities (<10%) of *N,N*-diethyl-4-iodoaniline were also present from **3**, likely resulting from the electrophilic aromatic substitution of iodine with free *N,N*-diethylaniline.[48]

Due to the lack of isolable magnesiated intermediates for *N,N*-dimethyl- and *N,N*-diisopropyl-aniline substrates, iodolysis of the reaction mixtures were conducted to gain insight into the metallation site selectivity observed in solution. A ^{1}H NMR study of the crude material obtained following iodolysis of the reaction mixture of **1** with *N,N*-dimethylaniline at room temperature was found to have an overall conversion of 26 %, with an iodo-*meta*:*para* ratio of 73:27, which is in agreement with the *in situ* monitoring (compared to 29 % for metallated species and *meta*:*para* ratio 78:22, Scheme 2, see ESI). Switching the reaction conditions to 4 hours reflux and then quenching with iodine, resulted in predominantly the *para*-product *N,N*-dimethyl-4-iodoaniline being isolated, as well as small amounts of residual starting material. In a similar fashion, iodolysis of the reaction of **1** with *N,N*-diisopropylaniline resulted in an overall conversion of 25% with an iodo-*meta*:*para* ratio of 7:3 (identical to the ^{1}H NMR identified metallated species prior to iodine quench, Scheme 2, see ESI). In both magnesiation reactions no *ortho*-iodonated products were isolated. In keeping with our findings that the *meta*-isomer monopolized the selectivity the reported metallation of *N,N*-dimethylaniline with the mixed metal zincate reagent [(TMEDA)Na(TMP)(*t*Bu)Zn(*t*Bu)] also results in the isolation of a

mixture of the regioisomers[29] upon iodolysis quenching studies, with the *meta*-isomer the major product.

Homo-metallic studies

Wanting to determine if the reactions of base 1 displayed any synergistic character we next sought to probe the reactivity of the homo-metallic components of **1,** NaTMP.TMEDA and $Mg(CH_2SiMe_3)_2$. Literature examples for the mono-metallation of the dimethyl N/P substrates (Scheme 1) have been reported,[29,33,34] prompting us to investigate the reactivity of the diethyl analogues *N,N*-diethylaniline and *P,P*-diethylphenylphosphine. Reaction of a molar equivalent of *N,N*-diethylaniline or *P,P*-diethylphenylphosphine with (NaTMP.TMEDA) at room temperature resulted in the isolation of the crystalline compounds $[\{(TMEDA)Na(EtNC_6H_5)\}_2]$ **5** and $[(TMEDA)Na_2(TMP)(C_6H_5PEt)]_2$ **6** in a 46 and 35%(max yield 50%) yield respectively. On the other hand, reaction with $Mg(CH_2SiMe_3)_2$, even under forcing reflux conditions, resulted in quantitative recovery of the starting materials (Scheme 3).

The centrosymmetric molecular structure of **5** indicates that instead of a deprotonative ring metallation as seen in **3**, the β-elimination of one ethyl group on the *N,N*-diethylaniline substrate has occurred (Figure 4). The complex is dimeric with a planar (NaNNaN) ring core (∑Na-N bond angles = 360°) with each sodium atom in a tetrahedral N_4 environment. The phenyl groups of the *N*-ethylaniline units are disposed *trans* to each other maximising Na···C electrostatic interactions to both *ipso*- and *ortho*-*Ph* sites (Na – C bond lengths of 2.8782(12) and 2.8805(13) Å respectively). TMEDA completes the Na coordination sphere in its common bidentate fashion.

Akin to complex **5**, **6** adopts a dimeric composition in the crystal, but with an overall ladder-type arrangement. The mixed sodium-amide/sodium-phosphidep ladder molecule is composed of a central (Na_2P_2) strictly planar core (∑Na-P bond angles = 360°) and two outer planar (NaNNaP) rings lying out of the central plane by 26.87(4)°. Displaced from the central core ±1.230(1) Å, the outer Na atoms [Na(2) and Na(2)'] are capped by a chelating TMEDA molecule, while the inner two engage in two Na···C electrostatic interactions, one short [Na(1)-C(1) 2.7474(19) Å] to the *ipso*-carbon and one long [Na(1)-C(2) 2.983(2) Å] to the *ortho*-carbon of the phenyl ring.[49] Comparable to **5**, the *P,P*-diethylphenylphosphine substrate has lost one of its ethyl limbs, most likely occurring from a β-elimination reaction and concurrent formation of ethene. Interestingly, unlike in **5**, where all the basic TMP arms have been consumed, two NaTMP units remain unreacted in **6**. Thus **6** can be regarded as an example of a hybrid co-complex between a sodium amide and a sodium phosphide, with the closest structurally characterised example being the monomeric amino-functionalised sodium phosphanide complex $[[\{(Me_3Si)_2CH\}(C_6H_4\text{-}2\text{-}NMe_2)P]Na(TMEDA)]$[50] and the pyridyl-functionalised phosphanide $[\{(Me_3Si)_2CH\}(2\text{-}C_5H_4N)P]Na\}_2\cdot(Et_2O)]_2$[50] which adopts a similar dimer of dimers motif to **6**. The composition of complex **6** fits the laddering principle established in lithium amide chemistry[51] with **6** representing a product of 'secondary laddering' assembly.

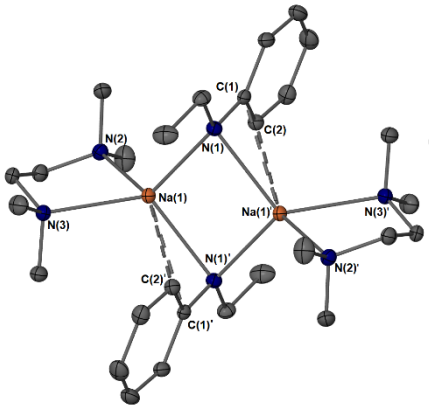
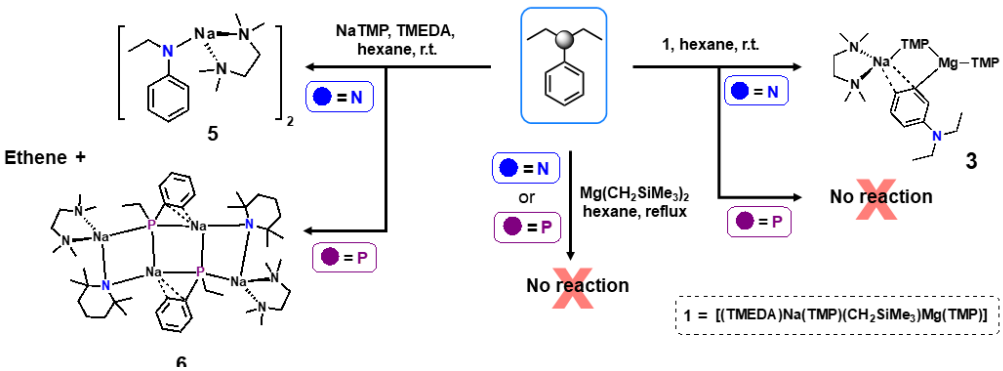


Figure **4** Molecular structure of $[\{(TMEDA)Na(EtNC_6H_5)\}_2]$ **5** with thermal ellipsoids at 40 % probability. Hydrogen atoms have been omitted for clarity. Symmetry operator ' = 1-x, 1-y, 1-z. Hydrogen atoms omitted for clarity. Selected bond lengths (Å) and angles (°): Na(1) – N(1), 2.4116(10); Na(1) – C(1)', 2.8782(12); Na(1) – C(2)', 2.8805(13); Na(1) – N(2), 2.4744(11); Na(1) – N(3), 2.4825(10); Na(1) – N(1) – Na(1)', 79.85(3); C(1) – N(1) – Na(1)', 92.04(7), N(1) – Na(1)' – N(1)', 100.15(3).

^1H and ^{13}C NMR spectroscopy of compounds **5** and **6** confirmed the retention of their crystal structure in solution. A downfield shift of the remaining ethyl protons to 3.32 and 1.48



Scheme **3** Contrasting homometallic metallations of N,N-diethylaniline and P,P-diethylphenylphosphine with sodium TMP and bis(trimethylsilylmethyl)magnesium.

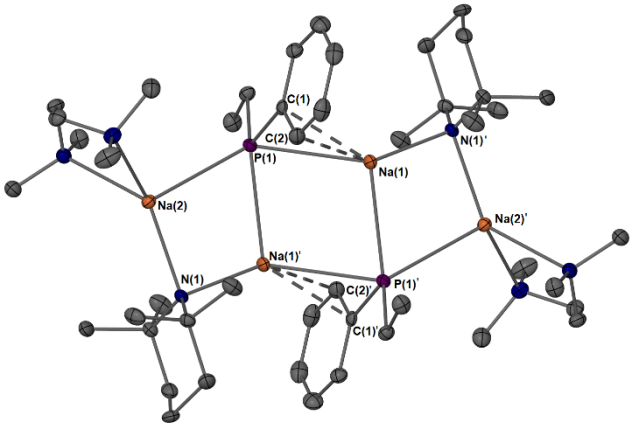


Figure **5** Molecular structure of $[(TMEDA)Na_2(TMP)(C_6H_5PEt)]_2$ **6** with thermal ellipsoids shown at 40 % probability. Hydrogen atoms are omitted for clarity. Symmetry operator ' = 1-x, 1-y, 1-z. Selected bond lengths (Å) and angles (°): Na(1) – P(1), 2.9256(8); Na(1) – N(1)', 2.318 (4); Na(2) – P(1), 2.9891(9); Na(2)-N(1), 2.408 (4) Na(1)' – P(1), 2.8848(8); Na(1) – C(1), 2.7474(19); Na(1) – C(2), 2.983(2); Na(2) – P(1) – Na(1), 68.41(2); P(1) – Na(1) – N(1)', 75.96(4); Na(1) – N(1)' – Na(2)', 88.64(5), P(1) – Na(1)' – N(1), 104.04(4); P(1) – Na(1)' – P(1)', 104.29(2); P(1)' – Na(2)' – N(1)', 98.80(4).

ppm and 2.31 and 1.52 ppm for **5** and **6** respectively (parent *N,N*-diethylaniline 2.99 and 0.89 ppm and *P,P*-diethylphenylphosphine 1.51 and 0.94 ppm respectively) and integration analysis confirm the loss of an ethyl group. The $^{31}P\{^1H\}$ spectrum of **6** shows a substantial upfield shift from a sharp singlet at -16.59 ppm to a broad, less resolved signal at -55.85 ppm, which lies in the same range as previously reported alkali-metal bis(*o*-anisyl)phosphides.[36,52]

Highlighting the power of the bi-metallic alliance of **1** in the effective deprotonation of these substrates, no ring metallation is observed in **5** or **6**, with an alternative ethene elimination pathway predominating. This elimination reaction, resulting from a P-C and N-C cleavage fits nicely with the theme of 'cleave and capture chemistry' – a new concept recently introduced in the literature.[24,53,54]

Computational aspects

In an attempt to rationalize the different metallation regioselectivities afforded by the homo- and heterobi-metallic bases, DFT calculations[55] of the C-H acidities in THF (Figure 6) of the different dialkyl substituted phenylphosphine and aniline substrates where conducted (see ESI for full information). All geometry optimizations were performed with the M06-2Z functional,[56] cc-pVTZ Dunnings basis set[57] and a universal solvation model based on density(SMD)[58] with THF as a solvent. Frequency calculations were carried out to ensure the location of the energy minima[56] which calculated the six substrates to have typical weak CH acidities covering a broad 35.5 – 53.6 pK_a span in this polar solvent.

Overall the acidity of the phenyl ring H atoms across all six substrates shows little to no variation comparing the *ortho*-, *meta*- and *para*-protons of the analogous P versus N substrates. These minor differences in pK_a values rationalise the non-selective metallation seen for the reaction of **1** with dimethyl- and diisopropyl-aniline where a mixture of regioisomers are observed (albeit predominately the *meta*-species). Interestingly, the experimentally observed regioselectivities of the isolated *meta*-isomers (**3** and **4**) of the diethylaniline and diisopropylphenylphosphine substrates conflict with the most acidic H atoms belonging to the methylene (pK_a 35.5, **3**) and ^{iPr}C-H (pK_a 36.8, **4**) groups (Figure 6). This would suggest metallation of these substrates is controlled by other contributing factors such as sterical orientation and electrostatic interactions.

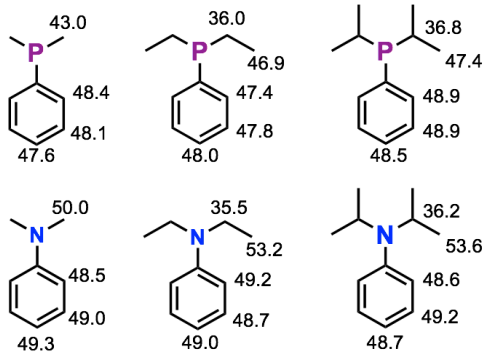


Figure 6 Calculated values of pK_a(THF) of the dialkyl substituted phenylphosphine and aniline substrates

The largest differences in calculated relative C-H acidity are seen upon changing the alkyl substituent on the P and N centres. In the dimethyl case, the P-CH_3 hydrogen atoms are significantly more acidic (pK_a 43.0) than the analogous N-CH_3 atoms (pK_a 50.0), consistent with the observed lateral metallation seen with phosphine complex **2**. In contrast, ring metallation is favoured for the nitrogen system, where pK_a change is not so significant but still goes the other way and favours ring metalation (pK_a ring average 48.9; methyl 50.0).

The experimental findings from the homometallic reaction of NaTMP with the diethyl phenylphosphine and aniline substrates fit the predicted acidity values well. Here the elimination of one of the ethyl groups *via* initial alpha-deprotonation and ethene evolution, is supported by the most acidic methylene protons in both the N (pK_a 35.5) and P (pK_a 36.0) systems and reactivity similar to the alkali-metal decomposition and cleavage pathways of ethers and similar substrates.[59]

Conclusions

In this systematic metalation study, we have shown for the first time the successful alkali-metal mediated magnesiation of a series of dialky phenylphosphines and their aniline counterparts. Contradicting lateral versus *meta*-magnesiation products were

seen for the dimethyl substituted phenylphosphine and aniline substrates respectively, while predominately *meta*-magnesiation was observed for the other diethyl and diisopropyl substrates. These findings were in agreement with the theoretically calculated pK_as indicating little to no variation in the relative aciditys of the *ortho*- *meta*- and *para*-ring protons across all substrates. Highlighting the cooperative effect of bimetallic base **1**, mono-metallic studies (NaTMP) on the diethlyphenylphosphine and aniline substrates lead to no ring metallation and a competitive ethene elimination pathway. In summary, this reactivity study has shown exchanging the nitrogen for a softer phosphorus centre results in more selective metallation outcomes, eliminating competitive regioisomer mixtures seen predominately for their nitrogen analogues.

Experimental Section

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 diethylether using a MBRAUN SPS-800 solvent purification system and were stored over 4 Å molecular sieves under a dinitrogen atmosphere. TMEDA and TMP(H) were dried by reflux over CaH_2 and stored over 4 Å molecular sieves. ^{1}H 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*BuNa,[60] $Mg(CH_2SiMe_3)_2$[20] and *N,N*-diisopropylaniline[61] were prepared according to literature procedures. See ESI for full details of X-ray crystallographic information and electrophilic quenching studies. X-ray crystallographic information files (CIFS) for compounds **2**, **3, 4, 5, 6** and **7** has been deposited with the Cambridge Crystallographic Database with CCDC number 1831594, 1831592, 1831590, 1831593, 1850750 and 1831591 respectively.

Synthesis of *P,P*-diethylphenylphosphine: Ethylmagnesium bromide (25 mL, [3 M in diethyl ether], 75 mmol) was added dropwise to a stirred solution of phenylphosphorus dichloride (5 mL, 37 mmol) in 60 mL of diethyl ether at 0 °C over 60 minutes. After filtration, the reaction was quenched with 5 mL of deoxygenated water. The aqueous layer was removed via a gas-tight syringe, and the ethereal layer dried with anhydrous magnesium sulphate. The solution was filtered, the solvent removed under vacuum and the phosphine purified by vacuum distillation (0.15 torr, 30 °C) to afford the product as a colourless air-sensitive liquid. Typical yield 4.3 mL, 65 %. ^{1}H NMR (400 MHz, C_6D_6, 300K): δ 7.56 (m, 2 H, *ortho*-H), 7.1 – 7.3 (m, 3 H, *meta/para*-H), 1.61 (m, 4 H, CH_2), 1.05 (dt, 6 H, *J* = 7.6, 7.2 Hz, CH_3). ^{13}C NMR (100 MHz, C_6D_6, 300K): δ 139.1 (d, quaternary-C), 132.4 (d, *ortho-C*), 128.4 (s, *para*-C), 128.2 (d, *meta*-C), 20.3 (d, CH_2), 9.7 (d, CH_3). ^{31}P{^{1}H} NMR (162 MHz, C_6D_6, 300K): δ -16.59 (s).

Synthesis of *P,P*-diisopropylphenylphosphine: Isopropylmagnesium chloride (25 mL, [1 M in tetrahydrofuran], 25 mmol) was added dropwise to a stirred solution of phenylphosphorus dichloride (1.65 mL, 12.34 mmol) in 50 mL of anhydrous tetrahydrofuran at 0 °C over 60 minutes. After stirring overnight, the reaction was quenched with 5 mL of deoxygenated water. The aqueous layer was removed via a gas-tight syringe, and the tetrahydrofuran was removed under vacuum and replaced with diethylether. This solution was filtered, solvent removed and the phosphine purified by vacuum distillation (0.15 torr, 46 °C) to afford the product as a colourless air-sensitive liquid. Typical yield: 2 g, 81 %. ^{1}H NMR (400 MHz, C_6D_6, 300K): δ 7.53 – 7.62 (m, 2 H, *ortho*-H), 7.21 – 7.3 (m, 3 H, *meta/para*-H), 2.06 (ds, 2 H, *J* = 7.2, 1.6 Hz, CH), 1.16 (dd, 6 H, *J* = 14.8, 7.2 Hz, CH_3), 1.00 (dd, 6 H, *J* = 14.8, 7.2 Hz, CH_3). ^{13}C NMR (100 MHz, C_6D_6, 300K): δ 135.3 (d, quaternary-C), 134.6 (d, *ortho-C*), 128.6 (s, *para*-C), 127.8 (d, *meta*-C), 22.8 (d, CH), 19.7 (d, CH_3), 18.6 (d, CH_3). ^{31}P{^{1}H} NMR (162 MHz, C_6D_6, 300K): δ 10.35 (s).

General Procedure (GP): *n*BuNa (0.16 g, 2 mmol) was suspended in 10 mL of dry hexane. To this suspension TMP(H) (0.68 mL, 4 mmol) was added dropwise and the reaction allowed to stir at room temperature for at least 30 minutes**.** Next $Mg(CH_2SiMe_3)_2$ (0.4 g, 2 mmol) was introduced with subsequent addition of TMEDA (0.3 mL, 2 mmol) affording a pale yellow**,** transparent solution which was used in situ. If clumps of solid remain in solution following addition of TMEDA, the solution was sonicated until complete dissolution occurred.

Synthesis of [(TMEDA)Na(TMP)(CH_2PCH_3Ph)Mg(TMP)] 2: To a stirred solution of **GP**, 0.28 mL of *P,P*-dimethylphenylphosphine was added dropwise at room temperature. The resulting solution was stirred overnight, resulting in the formation of a large amount of white precipitate. This was isolated by filtration and transferred to an argon glovebox for storage. X-ray quality crystals were obtained upon recrystallisation from *n*-hexane. Crystalline yield = 0.67 g, 58 %. ^{1}H NMR (400 MHz, C_6D_6, 300K): 7.65 (t, 2 H, *J* = 6.84 Hz *ortho*-H), 7.27 (t, 2 H, *J* = 7.36 Hz, *meta*-H), 7.12 (t, 1 H, *J* = 7.24 Hz, *para*-H), 1.95 (m (br), 4 H, *γ*-CH_2, TMP), 1.74 (s (br), 12 H, CH_3 TMEDA), 1.68 (s (br), 4 H, CH_2 TMEDA), 1.55 - 1.65 (m (br), 24 H, CH_3 TMP), 1.45 – 1.41 (m (br), 4 H, *β*-CH_2 TMP) 1.40 (s, 3 H, CH_3), 1.36 - 1.30 (m (br), 4 H, *β*-CH_2 TMP), 0.60 (t, 1 H, *J* = 9.6 Hz, CH_2Mg), -0.23 (d, 1 H, *J* = 10 Hz, CH_2Mg). ^{13}C NMR (100 MHz, C_6D_6, 300K): *δ* 150.25 (d, *ipso*-C), 130.4 (*ortho*-C), 127.1 (*para*-C), 57.4 (CH_2-TMEDA), 46.4 (CH_3-TMEDA), 42.8 (*β*-C TMP), 36.21 (CH_3 TMP), 20.66 (*γ*-C TMP), 18.78 (CH_3), 8.0 (CH_2-Mg) Note: *meta*-C signal appears under the C_6D_6 residual peak (as determined by HSQC experiment). ^{31}P{^{1}H} NMR (162 MHz, C_6D_6, 300K): *δ* -28.58 (s (br)), *δ* -29.68 (s (br)). Microanalysis: Calculated for $C_{32}H_{62}N_4MgNaP$: C, 66.14; H, 10.75; N, 9.64. Found: C, 65.88; H, 10.53; N, 9.45. **[(TMEDA)Na(TMP)(*p*-PMe_2Ph)Mg(TMP)] 2a:** ^{1}H NMR (400 MHz, C_6D_6, 300K): *δ* 8.83 (s (br), 0.5 H), 7.30 (m, 0.3 H), 1.40 (s, 1.3 H, CH_3).

Synthesis of [(TMEDA)Na(TMP)(*m*-$C_6H_4NEt_2$)Mg(TMP)] 3: To a stirred solution of **GP**, *N,N*-diethylaniline (0.32 mL, 2 mmol) was added dropwise at room temperature. The resulting solution was stirred overnight, resulting in the formation of a large amount of white precipitate. This was isolated by filtration and transferred to an argon glovebox for storage. X-ray quality crystals were obtained upon recrystallisation from *n*-hexane and slow cooling in a hot oil bath. Yield = 0.77 g, 65 %. ^{1}H NMR (600 MHz, C_6D_6, 300K): *δ* 7.45 (d, 1 H, *J* = 2.9 Hz), 7.12 (s, 1 H, C2), 7.11 (d, 1 H, *J* = 1.8 Hz), 6.48 (m, 1 H, *meta'*-H), 3.17 (q, 4 H, *J* = 7 Hz, Ethyl-CH_2), 1.98 – 1.87 (m, 4 H, *γ*-CH_2 TMP), 1.66 (s (br), 24 H, CH_3 TMP), 1.63 (s (br), 12 H, CH_3-TMEDA), 1.55 (s, 6 H, CH_2 TMEDA), 1.44 – 1.31 (m, 8 H, *β*-CH_2-TMP), 1.04 (t, 6 H, *J* = 7 Hz, Ethyl-CH_3). ^{13}C NMR (151 MHz, C_6D_6, 300K): 173.41 (s, Mg-C), 147.22, 127.51, 126.03, 110.33 (*meta'*-C), 57.30 (CH_2 TMEDA), 46.34 (CH_3 TMEDA), 45.06 (CH_3), 42.76 (*β*-CH_2-TMP), 36.26 (CH_3 TMP), 20.76 (*γ*-CH_2 TMP), 13.48 (CH_3). Despite multiple attempts, satisfactory elemental analysis has not proved possible.

Synthesis of [(TMEDA)Na(TMP)(*m*-C_6H_4P*i*Pr_2)Mg(TMP)] 4: To a stirred solution of **GP**, *P,P*-diisopropylphenylphosphine (0.4 g, 2 mmol) was added dropwise at room temperature. Upon addition, an immediate formation of a bright yellow solution was observed. After stirring overnight, the solution was filtered and its volume reduced *in vacuo*, where storage at -30°C resulted in the deposition of a large crop of yellow, block crystals Crystalline yield = 0.4 g, 31 %. ^{1}H NMR (600 MHz, C_6D_6, 300K): *δ* 8.15 (dd, 1 H, *J* = 8.4, 1.2 Hz, H), 7.83 (d, 1 H, *J* = 4.4 Hz, H^4), 7.23 (m, 1 H, H^5), 7.17 (t, 1 H, *J* = 6.6 Hz, H^2), 2.10 (septet, 2 H, *J* = 6.6 Hz, CH), 1.90 (t

(br), 4 H, J = 6 Hz, γ-CH_2 TMP), 1.61 (s (br), 36 H, CH_3 TMP/TMEDA), 1.36 (s (br), 6 H, CH_2 TMEDA), 1.19 (dd, 6 H, J = 14.7, 6.9 Hz, *i*Pr) 1.07 (d, J = 1.2 Hz, TMP), 1.02 (dd, 6 H, J = 10.5, 6.9 Hz, *i*Pr). $^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6, 300K): δ 9.42 (s). Satisfactory ^{13}C NMR has not been possible due to solubility issues. Despite multiple attempts, satisfactory elemental analysis has not proved possible.

Synthesis of [{(TMEDA)Na(EtNC$_6$H$_5$)}$_2$] 5: *N,N*-diethylaniline (0.32 mL, 2 mmol) was added dropwise at room temperature to a stirred suspension of *n*BuNa (0.16 g, 2 mmol), TMP(H) (0.36 mL, 2 mmol) and TMEDA (0.3 mL, 2 mmol). The resulting solution was stirred overnight at room temperature, and then filtered and its volume reduced *in vacuo*. Storage at room temperature deposited crystals of the title compound over a one week period. Crystalline yield: 0.12 g, 46 %. ^1H NMR (400 MHz, C_6D_6, 300K): δ 7.26 (br, 2 H, *meta*-H), 6.61 (d, 2 H, J = 7.6 Hz, *ortho*-H), 6.42 (t, 1 H, J = 7.2 Hz, *para*-H), 3.33 (q, 2 H, J = 7.2 Hz, CH_2), 1.77 (s (br), 12 H, CH_3-TMEDA), 1.66 (s (br), 4 H, CH_2-TMEDA), 1.49 (t, 3 H, J = 7.2 Hz). ^{13}C NMR (100 MHz, C_6D_6, 300K): δ 129.4 (*meta*-C, determined by HMBC), 107.6 (*ortho*-C, determined by HMBC), 101.27 (s, *para*-C), 57.27 (s, CH_3-TMEDA), 45.41 (CH_2-TMEDA), 45.06 (s, CH_2), 19.32 (s, CH_3). Elemental analysis: Calculated for $C_{14}H_{26}N_3Na$: C, 64.83; H, 10.10; N, 16.20. Found: C, 64.68; H, 9.88; N, 15.91.

Synthesis of [(TMEDA)Na$_2$(TMP)(C$_6$H$_5$PEt)]$_2$ 6: *P,P*-diethylphenylphosphine (0.18 mL, 1 mmol) was added dropwise at room temperature to a stirred suspension of *n*BuNa (0.08 g, 1 mmol), TMP(H) (0.18 mL, 1 mmol) and TMEDA (0.15 mL, 1 mmol). The resulting solution was stirred overnight at room temperature, and then filtered and its volume reduced *in vacuo*. Storage at room temperature deposited crystals of the title compound over a one week period. Crystalline yield: 0.15 g, 35 % (Maximum yield = 50% based on consumption of TMP(H)). ^1H NMR (400 MHz, C_6D_6, 300K) δ 7.37 (2 H, t, J 7.0, *ortho*-H), 7.12 (2 H, t, J 7.5, *meta*-H), 6.72 (1 H, tt, J 7.2, 1.2, *para*-H), 2.31 (2 H, qd, J 7.5, 1.8, CH_2), 2.10 – 2.00 (2 H, m, γ-CH_2 TMP), 1.85 (12 H, s, CH_3-TMEDA), 1.76 (4 H, s, CH_2-TMEDA), 1.52 (3 H, dt, J 14.9, 7.4, CH_3), 1.49 – 1.43 (4 H, m, β-CH_2 TMP), 1.27 (12 H, s, CH_3-TMP). $^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6, 300K): δ -55.87 (bs). ^{13}C NMR (100 MHz, C_6D_6, 300K): 128.27 (d, *ortho*-C), 125.67 (d, *meta*-C), 117.98 (d, *para*-C), 56.89 (CH_2-TMEDA), 52.31, 45.58 (CH_3-TMEDA), 42.08 (s, β-CH_2 TMP), 37.22 (s, CH_3-TMP), 21.03 (s, γ-CH_2 TMP), 16.07 (d, CH_2), 13.98 (d, CH_3). Despite multiple attempts, satisfactory elemental analysis has not proved possible.

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Keywords: anilines • dialkylphenyphosphines • magnesiation • metallation • regioselectivity • synergistic effect

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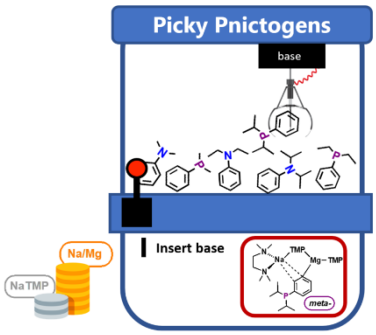
FULL PAPER

Picky Pnictogen: the first synergistic bimetallic metalation of dialkylphenylphosphines show marked regioselectivity differences from those of analogous anilines, while the separated homometallic components of the bimetallic bases induce ethene elimination in metallating the diethylphenylphosphine and aniline species.



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Contrasting synergistic heterobimetallic (Na-Mg) and homometallic (Na or Mg) bases in metalation reactions of dialkylphenylphosphines and dialkylanilines: lateral vs ring selectivities