Direct lateral metallation using alkali-metal mediated zincation (AMMZn): SiC-H vs.Si-O bond cleavage[†]

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A new application of zincate $[(THF)Li(TMP)(^{t}Bu)Zn(^{t}Bu)]$ (1) in alkali-metal mediated zincation (AMMZn) is reported by isolating and structurally defining the first intermediates of direct lateral zincation (DlZn) of trimethyl(phenoxy)silane (2) both of which adopt novel six-element {ZnCSiOLiN} ring structures.

Pioneered 150 years ago by Wanklyn, alkali-metal zincates constitute the oldest known heterobimetallic ('ate') compounds.¹ Neglected for a long time by synthetic chemists, they have recently proved to be outstanding reagents for functionalisation of a broad range of organic molecules via different fundamental transformations such as metal-halogen exchange, deprotonative metallation or nucleophilic addition.² TMP-dialkyl zincates (TMP = 2,2,6,6-tetramethylpiperidine) have received special attention due to their highly chemo- and regioselectivities shown in deprotonative metallation reactions, allowing the direct (one-step) zincation of a wide range of aromatic substrates under mild conditions.³ Combining the high reactivity typically associated with alkali-metal amides with the exceptional functional group tolerance and the greater selectivity of neutral organozinc reagents (R₂Zn), lithium TMP-zincate [(THF)Li(TMP)('Bu)Zn('Bu)] (1),⁴ has directly zincated anisole, 4a,b,5 benzonitrile, 4a methyl benzoate 4a and N,N-diisopropyl benzamide.^{4a,6} These deprotonations where the departing hydrogen is replaced by zinc but require the presence of the alkali-metal to succeed are best regarded as alkali-metal mediated zincations (AMMZn).3 To date all reported examples of AMMZn using TMP-zincates involve the regioselective removal of a proton from an aromatic carbon. In this paper we reveal the first example of direct lateral zincation (DlZn) of an aromatic molecule, trimethyl-(phenoxy)silane (2), by 1 establishing a new synthetic route to α -zincated aryloxysilanes.

 α -Metallated silanes (α -carbanions) have attracted considerable attention due to their numerous applications in synthesis.⁷ They can participate in similar reactions to other heteroatom-substituted carbanions but, in addition, the presence of a silyl group in the α -position provides additional stabilisation of their negative charge.⁸ Although there are several indirect routes to prepare these important reaction intermediates, there are only a handful of examples that involve a direct metal–hydrogen

exchange reaction. This is due, to a great extent, to the poor acidity of silyl methyl protons. This problem can be overcome when more activated heteroatom-substituted silanes are employed such as alkoxysilanes.⁹ Thus, the latter can be easily lithiated by 'BuLi in pentane at low temperatures (-78 °C). However, when the same methodology is extended to phenyl-substituted alkoxysilanes, significant amounts of a silicon-substituted product, resulting from the cleavage of the Si–O bond, are formed.⁹

In our hands when trimethyl(phenoxy)silane (2) is treated with 'BuLi in THF at -78 °C, no net C-H metallation occurs and LiOPh and 'Bu-SiMe₃ are the sole products observed resulting from the competing nucleophilic substitution reaction at silicon (Scheme 1).¹⁰ This difference in comparison with alkoxysilane reactivity is probably due to the better leaving ability of the OPh group. When LiTMP is employed, the reaction gave a complicated mixture of products including the substitution products LiOPh and TMP-SiMe₃ and a marginal amount of the lithiated product. We next probed the reaction of 2 with the lithium zincate 1 at room temperature which afforded [(THF)Li(TMP){PhOSi(CH₃)₂CH₂}Zn(^tBu)] (3) as determined by NMR spectroscopy and X-ray crystallography, in an isolated yield of 52% (Scheme 1).11 Multinuclear (1H, 13C and ⁷Li) NMR studies carried out in C₆D₆ solutions established that α -deprotonation of 2 had occurred, which was indicated by an informative singlet at -0.52 ppm in the



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¹H NMR spectrum and a remarkable downfield resonance at -3.9 ppm in the ${}^{13}C{}^{1}H$ NMR spectrum for the SiCH₂ group. These chemical shifts contrast with those found for the remaining non-metallated CH₃ groups attached to silicon (0.29 and 0.14 ppm in the ¹H and ${}^{13}C{}^{1}H$ NMR spectrum, respectively) which are similar to those found in **2** for the SiMe₃ moiety (0.15 and 0.2 ppm in the ¹H and ${}^{13}C{}^{1}H$ NMR spectrum, respectively).

The molecular structure of **3** established by X-ray crystallographic studies[‡] confirms that the metallation of **2** is actually a zincation (Fig. 1a). Retaining the backbone of 1 $\{(THF)Li(TMP)Zn(^{t}Bu)\}$, the structure of **3** is completed by the α -zincated trimethyl(phenoxy)silane that coordinates asymmetrically through a methyl C to Zn, forming a strong (short) sigma bond [Zn1-C14, 2.0769(15) Å] and through the oxygen to Li via a dative bond [Li1-O1, 1.974(3) Å]. This gives rise to a novel six-element {ZnCSiOLiN} ring which adopts a pseudo-boat conformation, where Si1, Zn1, N1 and O1 lie almost coplanar (torsion angle 4.84(2)°) whereas Li1 and C14 constitute the boat vertices (Fig. 1b). This boat conformation is presumably influenced by the secondary interaction between Li1 and C14; the C atom of the silane experiences the metallation and therefore bears a partial negative charge (shown with a dashed line in Fig. 1a and 1b). This contact is relatively long (weak) [Li1–C14, 2.568(3) Å] in comparison with other related compounds such as dimeric [{(TMEDA)Li(CH₂SiMe₃)}₂] (mean Li-C bond length. 2.264 Å).¹² Both metals exhibit a distorted trigonal planar geometry, with Zn coordination (sum of the angles around Zn, 360°) accomplished by a terminal ^tBu group whereas Li completes its coordination sphere with a terminal THF molecule. The structure of **3** in the solid state appears to be retained in C_6D_6 solution as shown by the inequivalence of the α -Me groups and β -H of the TMP ligand (at 1.38/1.18 ppm and at 1.68/1.45 ppm, respectively, in the ¹H NMR spectrum).

Thus, in 3, the original molecule of trimethyl(phenoxy)silane (2) has been regioselectively deprotonated at one of the methyl groups of the SiMe₃ group, leaving intact the Si–O bond. Zn occupies the position previously filled by a hydrogen atom, binding strongly to an sp³ carbon. Therefore, the dialkyl(amido) base 1 has behaved as an overall alkyl base, where the co-product of the reaction is ^{*t*}BuH. This reaction constitutes to the best of our knowledge the first example of direct lateral zincation (Dl*Zn*). Note that in stark contrast with 3, in all

previous examples of AMMZn of arenes the deprotonations always occur at the aromatic ring, leaving the lateral groups (methyl) untouched.¹³ In addition, it is noteworthy that ^tBu₂Zn on its own failed to metallate (even to react) with 2 which shows that this unprecedented zinc-hydrogen exchange accomplished by 1 is a genuine example of synergic bimetallic induced reaction.³ Furthermore, the synthesis of α -zincated trimethyl(aryloxy)silanes through an indirect route, which involves firstly deprotonation of the substrate by a more reactive group 1 organometallic reagent (such as 'BuLi or LiTMP) followed by a metathesis reaction with ZnCl₂, is not viable since as previously mentioned organolithium reagents fail to selectively deprotonate 2 at the methyl position, favouring Si-O bond cleavage or affording an undesirable complex mixture of products. This illustrates the great scope that AMMZn offers as a synthetic tool, achieving the regioselective metallation of 2 that is otherwise inaccessible when conventional monometallic reagents are employed.

In order to gain more understanding of the metallation of 2 by 1, we next endeavoured to perform the reaction of 2 with an unco-complexed mixture of LiTMP and ^tBu₂Zn.¹⁴ Previous studies by Thomas and Bates¹⁵ on α-lithiation of methoxytrimethylsilane by 'BuLi have revealed that at low temperatures (-78 °C) a transient premetallation complex between the relevant alkoxysilane and 'BuLi (['BuLi 2S]₂; S = MeOSiMe₃) can be detected and spectroscopically characterised (¹³C and ⁷Li NMR) which is in dynamic equilibrium with the starting materials (tetrameric ^tBuLi and $S = MeOSiMe_3$). When 2 was reacted with an equimolar mixture of LiTMP and ^tBu₂Zn in hexane at room temperature colourless crystals of mixed-metal compound [(PhOSiMe₃)Li(TMP){PhOSi(CH₃)₂CH₂}Zn(^tBu)] (4) were obtained in an isolated 16% yield (Scheme 1). NMR spectroscopic analysis of 4 in C_6D_6 revealed the presence of α -deprotonated 2 as indicated by an informative resonance at -0.68 ppm in the ¹H NMR spectrum for the SiCH₂ moiety (similar to that found for 3, -0.59 ppm). Remarkably the ¹H NMR also showed the signals corresponding to nonmetallated 2 in a ratio of 1 : 1 with the α -metallated fragment, at slightly different chemical shifts (7.10, 6.84, 0.15 ppm) to those found for free 2 in the same deuterated solvent (7.10, 6.88, 0.15 ppm). X-Ray crystallographic studies established the molecular structure of 4[±] (Fig. 2) which is similar to that of 3. Li and Zn are connected through a mixed TMP-\alpha-deprotonated trimethyl(phenoxy)silane ligand



Fig. 1 (a) Molecular structure of **3**. (b) Inorganic core of **3** highlighting the pseudo-boat conformation of the {ZnCSiOLiN} ring.



Fig. 2 Molecular structure of 4.

set, forming a six-element {ZnCSiOLiN} ring which displays a pseudo-boat conformation. As found in **3**, both metals have distorted trigonal planar geometries; Zn binds to a terminal 'Bu ligand, whereas lithium is now coordinated to a non-metallated molecule of **2** which acts as Lewis donor through the oxygen atom (Li1–O4, 2.075(3) Å) mimicking the role previously played by THF in **3**. Remarkably in contrast with **3**, the lithium–carbon contact in **4** is significantly weaker (as indicated by the elongated value found for the Li1–C11 bond length, 2.776(3) Å). This is probably a consequence of the increase in steric hindrance about Li by coordinating a molecule of **2** which contains a highly sterically demanding SiMe₃ group instead of THF, which prevents it approaching closer to C11.

The yield of 4 can be improved (to 37%) when two equivalents of silane 2 are employed. The fact that 4 is obtained, even when only one molar equivalent of 2 is used, implies that the rate of metallation of 2 is faster than the rate of formation of the putative mixed-metal intermediate $[(PhOSiMe_3)Li(TMP)(^{t}Bu)Zn(^{t}Bu)]$ (I) (Scheme 2) which once formed must react with the remaining non-coordinated silane 2 to generate 4. In order to detect the formation of I, the reaction was carried out at -78 °C; however, this resulted in the precipitation of a white solid which was isolated and identified as LiTMP using NMR analysis. Thus, these results suggest that LiTMP, ^tBu₂Zn and 2 in hexane solution must be in equilibrium with the mixed-metal compound I (Scheme 2). The latter as soon as it is formed reacts with some non-coordinated 2, driving the equilibrium towards I and therefore towards the formation of the metallated product 4. At low temperatures, the solubility of LiTMP in hexane decreases, causing its precipitation, and therefore shifting the equilibrium towards the monometallic reagents (left) and inhibiting metallation of 2.

In summary this work has revealed a new application of **1** in AMMZ*n*, by isolating and structurally defining the first intermediates of direct lateral zincation (DlZ*n*) of the trimethyl(phenoxy)silane **2**. These compounds are not accessible by a conventional two-step metathesis reaction, using monometallic reagents, illustrating the large potential that mixed-metal chemistry can offer to synthetic chemists. In addition the reaction of the unco-complexed LiTMP and 'Bu₂Zn with **2** has also been explored, which shows that these



Scheme 2

two monometallic reagents must form mixed-metal reagent analogues of **1** but with a molecule of trimethyl(phenoxy)silane acting as a donor on the lithium reagent. Once formed in solution it must react rapidly with some non-coordinated (free) trimethyl(phenoxy)silane to afford the metallated intermediate **4**.

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Notes and references

‡ Crystal data for 3: C₂₆H₄₈LiNO₂SiZn, $M_r = 507.05$, triclinic, space group $P\bar{1}$, a = 11.2813(5), b = 11.3700(6), c = 13.0987(6) Å, $\alpha = 79.264(4)^\circ$, $\beta = 79.106(4)^\circ$, $\gamma = 61.575(5)^\circ$, V = 1441.91(12) Å³, Z = 2, $\lambda = 0.71073$ Å, $\mu = 0.913$ mm⁻¹, T = 123 K; 20418 reflections, 7908 unique, $R_{int} 0.0326$; final refinement to convergence on F^2 gave R = 0.0314 (F, 6081 obs. data only) and $R_w = 0.0725$ (F^2 , all data), GOF = 0.967. Crystal data for 4: C₃₁H₅₄LiNO₂Si₂Zn, $M_r = 601.23$, monoclinic, space group $P2_1/c$, a = 12.4930(3), b = 12.8910(3), c = 20.8841(5) Å, $\beta = 92.494(2)^\circ$, V = 3360.14(14) Å³, Z = 4, $\lambda = 0.71073$ Å, $\mu = 0.828$ mm⁻¹, T = 123 K; 55721 reflections, 9627 unique, $R_{int} 0.0426$; final refinement to convergence on F^2 gave R = 0.0352 (F, 7223 obs. data only) and $R_w = 0.0742$ (F^2 , all data), GOF = 0.997.

- 1 For a historical essay on organozinc compounds see: D. Seyferth, *Organometallics*, 2001, **20**, 2940.
- 2 P. Knochel and P. Jones, in *Organozinc Reagents: A Practical Approach*, ed. L. H. Harwood and C. J. Moody, Oxford University Press, Oxford, 1999.
- 3 (a) R. E. Mulvey, Organometallics, 2006, 25, 1060;
 (b) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, Angew. Chem., Int. Ed., 2007, 46, 3802.
- 4 (a) Y. Kondo, M. Shilai, M. Uchiyama and T. Sakamoto, J. Am. Chem. Soc., 1999, 121, 3539; (b) W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman and R. E. Mulvey, Angew. Chem., Int. Ed., 2006, 45, 2370; (c) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi and K. Morokuma, J. Am. Chem. Soc., 2006, 128, 8748.
- 5 W. Clegg, S. H. Dale, A. M. Drummond, E. Hevia, G. W. Honeyman and R. E. Mulvey, J. Am. Chem. Soc., 2006, 128, 7434.
- 6 W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. W. Honeyman and R. E. Mulvey, *Angew. Chem., Int. Ed.*, 2006, 45, 2374.
- 7 T. H. Chan and D. Wang, Chem. Rev., 1995, 95, 1279.
- 8 (a) P. W. Weber, Silicon Reagents for Organic Synthesis, Springer Verlag, New York, 1983; (b) D. Ager, Organic Reactions, ed. L. Paquette, Wiley, New York, 1990, vol. 38.
- 9 T. F. Bates, S. A. Dandekar, J. L. Longlet, K. A. Wood and R. D. Thomas, J. Organomet. Chem., 2000, 595, 87.
- 10 When this reaction was carried out in hexane a white solid was obtained that could only dissolve in neat d_8 -THF and which NMR analysis showed was a complex mixture of products, with no resonances at negative chemical shifts, which are usually indicative that α -metallation has occurred.
- 11 The formation of **3** proved to be quantitative when equimolar amounts of **1** and **2** were reacted in C_6D_6 as was monitored by ¹H and ⁷Li NMR spectroscopy.
- 12 T. Tatic, H. Ott and D. Stalke, Eur. J. Inorg. Chem., 2008, 3765.
- 13 D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman and R. E. Mulvey, *Angew. Chem.*, *Int. Ed.*, 2006, 45, 3775.
- I4 In non-polar solvents the presence of a Lewis donor is usually required to yield a mixed-metal compound: M. Westerhausen, B. Rademacher and W. Schwarz, Z. Anorg. Allg. Chem., 1993, 619, 675.
- 15 T. F. Bates and R. D. Thomas, J. Organomet. Chem., 1989, 359, 285.