Transamination chemistry of sodium TMP-zincate: synthesis and crystal structure of a chiral amidozincate†

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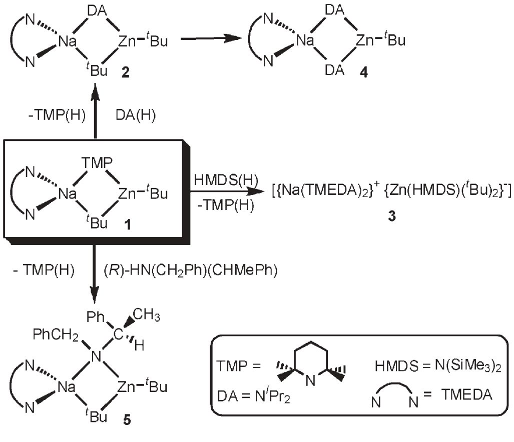
In a new type of reactivity for sodium TMP-zincate [(TMEDA)NaZn(^{t}Bu)$_2$(TMP)] (1), transamination reactions with the amines diisopropylamine, DA(H), hexamethyldisilazane, HMDS(H) and chiral (*R*)-*N*-benzyl-α-methylbenzylamine have produced new sodium amido-di-*tert*-butyl zincates (all structurally characterised) with concomitant loss of TMP(H).

Alkali metal zincates have been known since the synthesis of NaZnEt$_3$ by Wanklyn in 1858.[1] However, only recently have they been revealed as effective chemo- and regioselective reagents in synthesis, sometimes surpassing the performances of common commercial monometallic reagents such as alkyl lithiums or Grignard reagents.[2] TMP-zincates in particular have proved to be exceptionally good regioselective reagents in metal–hydrogen exchange reactions. It has been shown that lithium di-*tert*-butyl(TMP) zincate, LiZn(TMP)(^{t}Bu)$_2$ (TMP = 2,2,6,6,-tetramethylpiperidide)[3] is an excellent chemoselective amide base that successfully accomplishes the directed zincation of a wide range of functionalised aromatics. Recently our group have prepared and fully characterized the sodium TMP-zincate [(TMEDA)NaZn(^{t}Bu)$_2$(TMP)] (1)[4] (TMEDA 1,1,3,3-tetramethylethylenediamine), which has proved to be a highly selective alkyl base towards benzene,[4] tertiary amides,[5] dimethylanilines[6] and naphthalene.[7] Hitherto **1** has always displayed ultimately alkyl basicity towards these aromatic substrates, eliminating *t*BuH as the result of the relevant deprotonation–metallation process. This reactivity contrasts with previous results using the closely related zincate LiZn(TMP)(^{t}Bu)$_2$ in neat THF, which can also perform metallation of a broad range of substituted aromatic substrates, behaving as an amide base.[3]

We describe here the first examples of the reactivity of **1** towards several amines, where unusually this base acts as an amido base, releasing TMP(H) as a co-product. These reactions reveal themselves to be a general methodology for preparing new sodium amidozincates including [(TMEDA)NaZn(^{t}Bu)$_2$(N^{i}Pr$_2$)] (**2**) and [{(TMEDA)$_2$Na}$^+${Zn(^{t}Bu)$_2$(HMDS)}$^-$] (HMDS = 1,1,1,3,3,3-hexamethylsilazide) (**3**), as a novel alternative to the conventional co-complexation route of the alkali metal amide with the organozinc reagent. Moreover the transamination reaction of **1** with the chiral amine (*R*)-*N*-benzyl-α-methylbenzylamine affords the first chiral amido zincate (*R*,*R*)-[(TMEDA)NaZn(^{t}Bu)$_2${N(CH$_2$Ph)(CH(CH$_3$)Ph)}] (**5**).

Turning to the experimental details, to a solution of **1** in neat hexane, one molar equivalent of diisopropylamine, DA(H), was added. The resulting solution produced the new zincate **2** (Scheme 1) as colourless crystals which were characterized by ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallography.[8] It is noteworthy that the position previously occupied by the TMP group has now been replaced by DA in **2**, with the retention of the two *tert*-butyl groups on the zinc, concomitant with a switch from the well established overall alkyl basic mode of **1**[2,4–7] to an unprecedented amide one.

This surprising result prompted us to carry out a theoretical study (at the DFT level using B3LYP functionals and the 6-311G** basis set)† of the reaction of **1** with DA(H) (Scheme 2). We modelled this reaction through two different pathways: **A** which mimics the experimental result, with **1** acting as an amide base and **B**, where **1** behaves as an alkyl base. Both routes were found to be exothermic, however, in contrast with our experimental findings, the more thermodynamically favourable route, by a difference of 15.97 kcal mol^{-1}, is **B**. These results suggest that kinetic factors must dominate in these transamination reactions, and that route **B** must involve a much higher activation barrier than route **A**. On the other hand, every metallation reaction previously reported for **1** has included the formation of a new Zn–C bond and the loss of ^{t}BuH. However, in this reaction with DA(H), a new Zn–N bond has to be formed at the expense of an already existing Zn–C bond or Zn–N bond. Thus, the strong carbophilicity of Zn may contribute predominately to the



Scheme 1 Transamination reactions of sodium TMP-zincate **1**.

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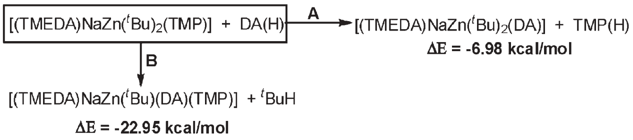


Scheme 2 Relative energetics of modelled DFT transamination reactions.

seemingly higher transition state hurdle associated with the more energetically favourable pathway **B**, in contrast with the Zn–N bond which is presumably easier to break in the reaction coordinate in pathway **A**. This lack of alkyl reactivity in **1** can be compared with the low kinetic basicity of neutral dialkyl zinc reagents.[9] In these cases, more often than not, the high covalency of the Zn–C bonds within ZnR_2 results in an incomplete amination at the Zn centre to form alkyl zinc amides instead of zinc bis(amides).

Compound **2**[8] undergoes a slow disproportionation after 48 h at room temperature to the bis(amido)alkyl zincate [(TMEDA)NaZn(^{t}Bu)(N^{i}Pr$_2$)$_2$] (**4**) and the homoleptic species [(TMEDA)NaZn(^{t}Bu)$_3$].[10] Surprisingly, compound **2** failed to react with an extra equivalent of diisopropylamine to generate **4** through direct deprotonation. In contrast, DFT calculations showed that this reaction should proceed as it is exothermic by 16.84 kcal mol^{-1}. Hence, the lack of reactivity of **2**, which still has two potentially basic ^{t}Bu groups, with an excess of DA(H) can be attributed to the kinetics of the reaction as well as to the low tendency of Zn to form new Zn–N bonds at the cost of existing Zn–C ones. What kind of process could then be involved in the formation of **4**? A plausible rationale could be the existence of an equilibrium in solution of the in-contact ion pair zincate **2** and the solvent-separated species (Scheme 3). The latter could dimerize[11] and subsequently undergo unsymmetrical cleavage to generate **4** and the tri-*tert*-butyl zincate [(TMEDA)NaZn(^{t}Bu)$_3$]. The parent TMP-zincate **1** does not appear to suffer from this kind of disproportionation in solution, which can be attributed to the greater basicity of the TMP ligand and resulting in a stronger interaction with the Na(TMEDA)$^+$ cation.

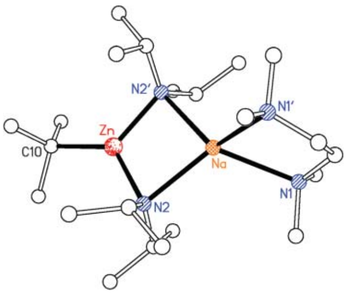
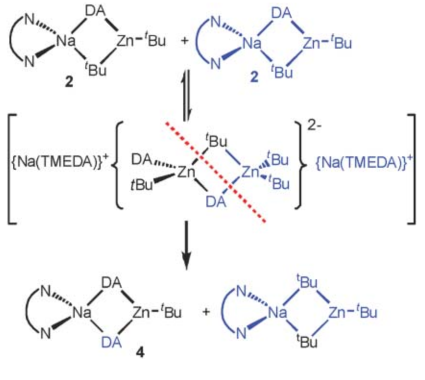


Fig. 1 Molecular structure of **4** with hydrogen atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Zn–N2: 2.020(4), Zn–C10: 2.044(7), Na–N2: 2.419(4), Na–N1: 2.489(4). N2–Zn–N2′: 105.4(2), N2–Zn–C10: 127.28(10), N2–Na–N2′: 83.26(18), Na–N2–Zn: 85.65(13); symmetry operator for N1′ and N2′: $1 - x, y, \; - z$. Atoms Na, Zn and C10 lie on a twofold rotation axis, such that the ^{t}Bu group is disordered; the two ^{i}Pr groups are also disordered.



Scheme 3 Proposed pathway for the dismutation of zincate **2**.

Determined by X-ray crystallography‡ the molecular structure of **4** (Fig. 1) can be described as an ion-contact zincate, containing a four-atom (NaNZnN) ring, where the two metals are connected by two DA bridges. Zn has a distorted trigonal planar environment, binding to a terminal ^{t}Bu group. The Zn–N distance [2.020(4) Å] is similar to that found in the closely related zincate **2** [2.050(2) Å][8] and considerably longer than the one found in the homometallic compound LZn(DA), L = CH–(CMeNC$_6$H$_3$-2,6-^{i}Pr$_2$)$_2$ [1.852(2) Å][12] where the DA group is terminal. Comparison of the Na–N distances [2.419(4) Å for DA, 2.489(4)Å for TMEDA] with the dimensions of the homodimeric structure of [{NaDA(TMEDA)}$_2$][13] (mean lengths, 2.447 Å for DA, 2.6195 Å for TMEDA) shows that TMEDA can approach more closely to the sodium in the heterobimetallic species **4** than in the sodium amide dimer. In other words, the sodium centre in **4** displays a stronger Lewis acid character which can be an important clue to rationalise the special synergic reactivity that these mixed metal compounds can often display.

In view of these results, **1** was reacted with another classical utility amine, hexamethyldisilazane, HMDS(H). Colourless crystals of the solvent-separated ion pair zincate [{(TMEDA)$_2$-Na}$^+${Zn(^{t}Bu)$_2$(HMDS)}$^-$] (**3**) were obtained in a yield of 39%, that improved to 58% when an extra equivalent of TMEDA was introduced to the reaction mixture. Here again **1** has reacted as a TMP-base, to afford **3** which constitutes to the best of our knowledge the first example of a solvent-separated ion pair amido-bis(alkyl) zincate to be structurally characterised. The unprecedented anion (Fig. 2) contains a zinc centre in a distorted trigonal planar geometry comprising two ^{t}Bu groups and the amido ligand HMDS. Both Zn–N and Zn–C bond distances are similar to the ones found in previously reported ion-contact zincates. The countercation, pseudotetrahedral [Na(TMEDA)$_2$]$^+$, is already known;[14] one TMEDA ligand is disordered in the structure of **3**.

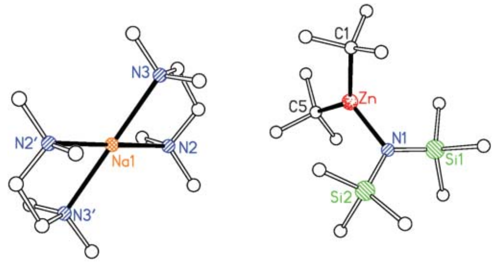


Fig. 2 One cation and the anion of **3** with hydrogen atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Zn–N1: 2.0284(17), Zn–C1: 2.052(2), Zn–C5: 2.048(2), C1–Zn–C5: 127.40(9), C5–Zn–N1: 116.91(8), C1–Na–N1: 115.65(8). Two independent cations both have inversion symmetry (operator $2 - x, 1 - y, -z$ for N2′ and N3′).

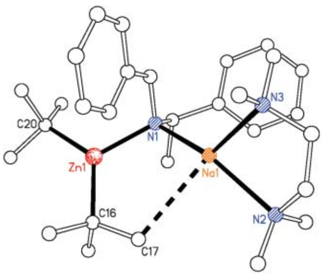


Fig. 3 Molecular structure of **5** with hydrogen atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Zn1–N1: 2.068(3), Zn1–C16: 2.038(4), Zn1–C20: 2.043(4), Na1–N1: 2.374(4), C16–Zn1–C20: 127.53(17), C16–Zn1–N1: 114.73(15), C20–Zn1–N1: 117.61(15), Zn1–N1–Na1: 113.34(14).

The formation of **3**, even in a deficiency of TMEDA, is surprising since all attempts to prepare a solvent-separated ion pair ’ate derived from the TMP and the DA zincates **1** and **2** failed, even when a vast excess of TMEDA was employed. This can be rationalised again in terms of the greater basicity of the latter amides in comparison with HMDS. Thus, the Na–N bonds must be stronger for the TMP and DA zincates than for HMDS [in the case that a possible ion-contacted zincate $NaZn(^tBu)_2(HMDS)$ could be formed] and therefore, being more robust, they are more resistant to cleavage to afford solvent-separated ion pairs even in the presence of extra equivalents of the chelating diamine TMEDA.[15]

In order to check the generality of this methodology, zincate **1** was reacted under the same conditions as previously described for DA(H) and HMDS(H) with the chiral amine (*R*)-*N*-benzyl-α-methylbenzylamine. This commercially available amine has been previously employed to synthesise new chiral magnesium[16] and lithium amides[17] which have established themselves as powerful reagents for enantioselective deprotonations. The new amido-di-*tert*-butyl zincate **5** was obtained as a crystalline solid, which was characterised by ^1H and ^{13}C NMR spectroscopy in C_6D_6 solution. At this point it is worth stressing that its TMP precursor **1** had to be characterised in solution in inert d_{12}-cyclohexane as it metallates benzene at room temperature. The stability of **5** in arene solvents, also displayed by zincates **2**,[8] **3** and **4**, can be considered an advantageous feature of DA-zincates over TMP-zincates in performing deprotonations in arene solutions. The structure of the ion-contact zincate **5** was successfully determined by X-ray diffraction (Fig. 3).‡ It contains two crystallographically independent molecules; the more ordered one of which is described here. This molecular structure of **5** can be envisaged as a five-atom NaNZnCC ring (counting an agostic Na···C17, 3.087(6) Å) where the two metals are connected predominately by an amide bridge, which binds strongly to both (Na1–N1 = 2.374(4) Å; Zn1–N1 2.068(3) Å). Due to this heterobimetallic bridge and the asymmetric nature of the amide ligand, N1 is a stereogenic centre, with an *R* absolute configuration. Overall, the chiral zincate **5** possesses two stereocentres, N1 and C2, and moreover, it can be selectively obtained by crystallisation in its diastereomerically pure (*R*,*R*) form in a 38% yield. An additional secondary (agostic) interaction between the Na centre and one of the methyl groups of the briding ^{t}Bu ligand completes the five-membered ring. The strong M–N bond is retained in solution in non-polar solvents whereas the agostic Na···C contact is not present in C_6D_6 solutions at room temperature as ^1H and ^{13}C NMR spectra of these species showed only one set of signals for the alkyl group.[4] It appears that unlike **2**, **5** does not undergo a dismutation process.

To conclude, herein we have presented a new synthetic methodology to prepare sodium amido-di-*tert*-butyl zincates by reaction of the mixed metal base **1** with the relevant amine. The synthesis of the first chiral zincate **5** opens up a new avenue of research for future investigation focused on its possible applications in enantioselective deprotonation or nucleophilic addition reactions.

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Notes and references

‡ Crystal data for **2–5** are given in the ESI.† CCDC 660688, 660908–660910. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b713987j

1 J. A. Wanklyn, *Ann. Chem. Pharm.*, 1858, **107**, 125.
2 R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802.
3 (*a*) Y. Kondo, M. Shilai, M. Uchiyama and T. Sakamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3539; (*b*) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi and K. Morokuma, *J. Am. Chem. Soc.*, 2006, **128**, 8748.
4 P. C. Andrikopoulos, D. R. Armstrong, H. R. L. Barley, W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, A. R. Kennedy and R. E. Mulvey, *J. Am. Chem. Soc.*, 2005, **127**, 6184.
5 W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. W. Honeyman and R. E. Mulvey, *Angew. Chem., Int. Ed.*, 2006, **45**, 2374.
6 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.
7 W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey and C. T. O’Hara, *Angew. Chem., Int. Ed.*, 2006, **45**, 6548.
8 For full synthetic and NMR and X-ray characterisation details, and an alternative synthetic route, see the ESI.
9 G. C. Forbes, A. R. Kennedy, R. E. Mulvey, R. B. Rowlings, W. Clegg, S. T. Liddle and C. C. Wilson, *Chem. Commun.*, 2000, 1759.
10 ^1H and ^{13}C NMR spectra of the filtrate of this reaction showed signals attributable to ^{t}Bu and TMEDA groups consistent with the formula $[(TMEDA)NaZn^tBu_3]$.
11 Similar dimeric structures for magnesiates and zincates containing two alkyl groups and an alkoxide ligand have been previously reported: R. M. Fabicon, M. Parvez and H. G. Richey, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 1412.
12 M. H. Chisholm, J. Gallucci and K. Phomphrai, *Inorg. Chem.*, 2002, **41**, 2785.
13 P. C. Andrews, N. D. R. Barnett, R. E. Mulvey, W. Clegg, P. A. O’Neil, D. Barr, L. Cowton, A. J. Dawson and B. J. Wakefield, *J. Organomet. Chem.*, 1996, **518**, 85.
14 See for example: (*a*) P. J. Bonasia and J. Arnold, *J. Chem. Soc., Chem. Commun.*, 1990, 1299; (*b*) N. S. Hosmane, K.-J. Lu, H. Zhang and J. A. Maguire, *Organometallics*, 1997, **16**, 5163.
15 D. V. Graham, E. Hevia, A. R. Kennedy and R. E. Mulvey, *Organometallics*, 2006, **25**, 3297.
16 (*a*) K. W. Henderson, W. J. Kerr and J. H. Moir, *Chem. Commun.*, 2000, 479; (*b*) K. W. Henderson and W. J. Kerr, *Chem.–Eur. J.*, 2001, **7**, 3430.
17 D. R. Armstrong, K. W. Henderson, A. R. Kennedy, W. J. Kerr, F. S. Mair, J. H. Moir, P. H. Moran and R. Snaith, *J. Chem. Soc., Dalton Trans.*, 1999, 4063.