Zwitterionic Zincation

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Synergic Synthesis of Benzannulated Zincabicyclic Complexes, α-Zincated N Ylides, through Sodium-TMEDA-Mediated Zincation of a Haloarene**

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The zinc–hydrogen exchange reaction has undergone a remarkable transformation in recent times from obscurity to a novel alternative, and in many cases the preferred option, to long-established lithiation methods for generating aromatic organometallic intermediates suitable for subsequent functionalization. Simple zinc reagents (alkyls, amides), as kinetically sluggish bases, are generally useless for such applications. Installing high metalation power within a zinc reagent usually requires a more complex composition, in which reactivity is boosted through cooperative effects between its different components. Modified from their magnesiating "turbo-Grignard" reagents, Knochel's three-component systems $[(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl]$[1] and $[\{i\mathrm{Pr}(t\mathrm{Bu})N\}_2Zn{\cdot}2MgCl_2{\cdot}2LiCl]$[2] are excellent complex zincators for both aromatic and heteroaromatic substrates (TMP is 2,2,6,6-tetramethylpiperidide). Formally a two-component lithium amide–zinc alkyl mixed complex, "$[LiZn(TMP)(t\mathrm{Bu})_2]$" introduced by Kondo and Uchiyama, is also a potent chemo- and regioselective zincator for similar substrates.[3] Our own group has contributed the related sodium TMP-zincate $[(TMEDA){\cdot}Na(\mu\text{-}TMP)(\mu\text{-}t\mathrm{Bu})Zn(t\mathrm{Bu})]$[4] (**1**), which depending on the organic substrate can execute regioselective *ortho*-, *meta*-, or dizincation in reactions that have been structurally defined.[5]

Here we report the first investigation of the surprising reactivity of **1** towards an aryl halide, namely chlorobenzene. Fully characterized by X-ray crystallography and NMR spectroscopy, the unexpected final product isolated from this reaction is the remarkable zwitterionic benzannulated bicyclic zinc complex $[\{1\text{-}Zn(t\mathrm{Bu})\}^-\text{-}\{2\text{-}N(Me)(CH_2)CH_2CH_2NMe_2\}^+\text{-}C_6H_4]$ (**2**). Formation of **2** can be rationalized by a novel four-step *ortho*-zincation, zincate (or sodium chloride) elimination, azazincation–addition, amine α-zincation sequence. An intermediate along this path formed prior to the final step (amine α-zincation), $[\{1\text{-}Zn(t\mathrm{Bu})_2\}^-\text{-}\{2\text{-}N(Me)_2CH_2CH_2NMe_2\}^+\text{-}C_6H_4]$ (**Int**), has also been isolated from the reaction and crystallographically characterized.

In the few previous studies of reactions of aryl halides and TMP-zincates,[6] no experimental evidence has been collected on the chemistry taking place between the limits of the starting materials and the zinc-free quenched products. Therefore, to shed light on the critical metal (and bimetal) activity stage of these reactions, our primary objective was to get inside these limits by isolating and characterizing representative zinc-containing intermediates. This was realized through the synthesis of **2**, which were isolated as small colorless block crystals in 20.7% yield from the equimolar reaction of **1** and chlorobenzene in hexane solution.

Since it was reported earlier[6] that reaction of $[LiZn(TMP)(t\mathrm{Bu})_2]$ with haloarenes followed by electrophilic trapping produced polyfunctional haloarenes (i.e., with retention of the original halogen substituent), we expected **2** to be an *ortho*-zincated chlorobenzene derivative. Surprisingly, however, chloride is absent and while its aromatic ring appears to have been *ortho*-zincated,[7] **2** has several other unexpected new bonding features. Thus, a nitrogen from TMEDA that links to the zinc atom through a CH_2 bridge and a $CH_2CH_2N(Me)_2$ bridge, is now attached to the ring. Terminal methyl and *tert*-butyl groups on the aryl-attached nitrogen and zinc atoms, respectively, complete the formulation, which can be interpreted as a mesoionic zwitterion[8] with a $^+NR_3\text{-}CH_2\text{-}Zn^-$ β-dipole. Alternatively, **2** can be classified as an α-zincated N ylide.

All the anticipated different types of hydrogen atom in **2** are accounted for and well resolved in its ^{1}H NMR spectrum recorded from C_6D_6 solution. Belonging to metalated TMEDA, the Me_2N and $Me'N$ resonances appear at $\delta = 1.96$ and 2.49 ppm, respectively, while all six H atoms of the three unique CH_2 groups are inequivalent having separate resonances at $\delta = 0.96/1.94$, 1.63/2.44, and 2.22/2.34 ppm, consistent with the rigid, bicyclic conformation of the structure. The pairing most upfield (0.96/1.94 ppm) can be attributed to the deprotonated NCH_2 unit of TMEDA. Four aromatic resonances at $\delta = 8.32$, 7.26, 7.07, and 6.67 ppm denote the H atoms at the 6 (*ortho* to Zn), 5, 4, and 3 (*ortho* to N) positions, and the *t*Bu resonance at $\delta = 1.76$ ppm completes the assignment.

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Similarly the ^{13}C NMR spectrum of **2** is easily fully assignable (see Supporting Information for details). The molecular structure of **2** (Figure 1)[9] is mononuclear, with both Zn and N(Me′) atoms chiral as each is attached to four different substituents, though overall the crystal structure is centrosymmetric and hence the material is racemic.[10] Three anionic C atoms (two aliphatic sp^3 atoms from the tBu and deprotonated CH$_2$N groups and one aryl sp^2 atom) bind to zinc [lengths 2.0245(15)/2.0611(16) and 2.0615(15) Å, respectively] with a dative interaction from the N(Me$_2$) atom [length, 2.3313(13) Å] completing its distorted tetrahedral coordination. Ring constraints severely distort this geometry with bond angles ranging from 84.54(6)° (C2-Zn1-C10) to 134.05(6)° (C10-Zn1-C13) and a mean value of 107.39°. The atoms Zn and N1 lie slightly to one side of the benzene ring plane (by 0.138 and 0.090 Å, respectively).

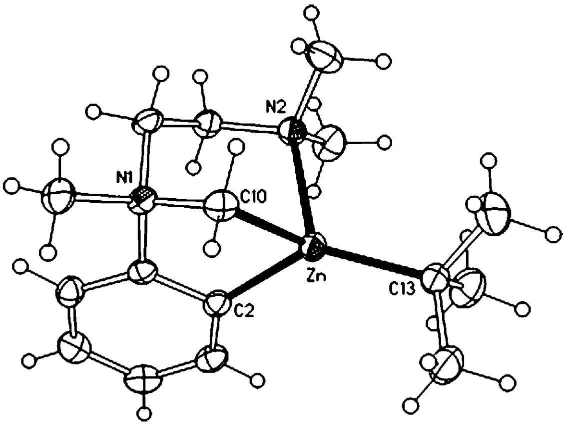
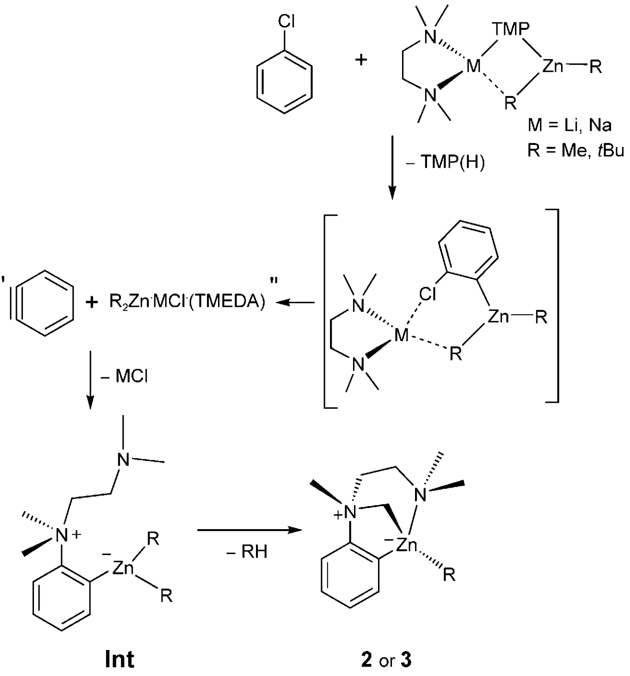


Figure 1. Molecular structure of **2** with selected atom labels. Displacement ellipsoids are drawn at the 50% probability level. Key bond lengths [Å]: Zn–C2 2.0615(15), Zn–C10 2.0611(16), Zn–C13 2.0245(15), Zn–N2 2.3313(13), N1–C10 1.5374(19).

Scheme 1 proposes a pathway for the formation of zincacyclic **2**. *ortho*-Zincation of chlorobenzene would be the first step, almost certainly through heteroleptic **1** functioning kinetically as a TMP base with concomitant release of TMP(H).[11] This would generate a sodium monoaryl-bisalkylzincate intermediate for which there are close analogies in lithium-TMP chemistry,[11] but the lack of TMP in the later intermediate **Int** is perhaps the strongest evidence. Next, the Zn and Cl σ-attachments to the benzene ring could both cleave to generate an *o*-benzyne intermediate and "(tBu)$_2$Zn·NaCl·TMEDA". Militating against this mechanism are Uchiyama's aforementioned studies of "LiZn(TMP)(tBu)$_2$",[6] which reveal no evidence for benzyne formation towards haloarenes, but that reaction must follow a different pathway to ours as the halogen substituent is retained on the aryl ring, whereas it is cleaved in our case.

Note that at this stage in our reaction the benzyne molecule may not be "naked" but could be involved in a benzyne–zincate intermediate in which one of the metals interacts with the π-system of the benzyne triple bond. Evidence for this type of cation–π intermediate comes from DFT calculations on model zincates in the aforementioned Uchiyama paper.[6] Subsequent addition of TMEDA and tBu$_2$Zn across the benzyne triple bond leads to **Int** with elimination of NaCl. The unexpected attachment of TMEDA might be interpreted as a type of complex-induced proximity effect (CIPE)[12] due to the Na(TMEDA) unit lying close to the C atom originally carrying the Cl substituent. By repeating the reaction with 4-chlorotoluene in place of chlorobenzene to get a fix on the position of zincation, we observed zinc adding to both the 3 and 4 positions, which supports the existence, at least in part, of such a benzyne mechanism (see Supporting Information for details).



Scheme 1.

Intermediate **Int** provides definitive proof of this stage of the reaction sequence. Made by reducing the experimental conditions (no refluxing of the solution), **Int** has a molecular structure (Figure 2)[9] akin to that of **2** but with two tBu ligands attached to zinc and with an intact TMEDA molecule occupying an *ortho*-position next to, but not attached to the Zn(tBu)$_2$ unit. In the final step, one tBu ligand deprotonates one NMe$_2$ arm of TMEDA to build an N-CH$_2$-Zn bridge, while concomitantly reduced steric constraints around the Zn center allow the free Me$_2$N terminal of the benzene-tethered TMEDA to datively bind to Zn to close a seven-atom (ZnCCNCCN) ring. Usually α-metalations of amines[13] have high kinetic barriers and would conventionally be considered impossible for only mildly electropositive zinc, but here the barrier must be reduced substantially by the close proximity of the tethered tBu$_2$Zn and TMEDA units which sets up a favorable intramolecular Zn–H exchange reaction with loss of BuH.[14]

As aforementioned, loss of the halogen substituent distinguishes this new alkali metal mediated zincation (AMM*Zn*) reaction from those of "LiZn(TMP)(tBu)$_2$", which, when intercepted by electrophiles, give polysubstitut-

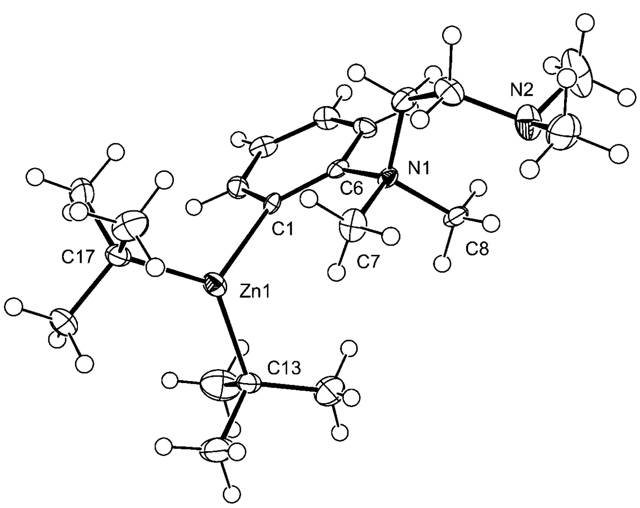


Figure 2. Molecular structure of pre-bicyclic, pre-ylidic intermediate **Int** with selected atom labels. Displacement ellipsoids are drawn at the 50% probability level. Key bond lengths and distances [Å]: Zn1-C1 2.079(4), Zn1–C13 2.041(5), Zn1–C17 2.036(5), N1–C6 1.542(5), N1–C7 1.494(5), N1–C8 1.508(5), C7···C13 4.007(7), C7···C17 4.220(6), C8···C13 4.939(7), C8···C17 6.235(7).

ed haloarenes. Emphasizing the strong solvent dependency of AMM*Zn* reactions, significantly the former was performed in hexane solution containing TMEDA, whereas the latter were performed in THF solution with no TMEDA. Zincate reactions are also sensitive to the alkyl group on Zn. Interestingly, Uchiyama reports that "LiZn(TMP)(Me)$_2$" behaves differently from "LiZn(TMP)(*t*Bu)$_2$" towards haloarenes, generating benzyne intermediates which can be trapped by dienes to produce polysubstituted halogen-free aromatic compounds.[6] The reaction leading to **2** thus represents a new, third variation on this theme.

Probing alkyl effects in our system, significantly we isolated the methyl analog of **2**, $[\{1\text{-Zn(Me)}\}^-\text{-}\{2\text{-N(Me)(CH}_2\text{)CH}_2\text{CH}_2\text{NMe}_2\}^+\text{-C}_6\text{H}_4]$ (**3**), from the reaction of chlorobenzene and the lithium methylzincate "(TMEDA)·LiZn(TMP)(Me)$_2$"[15] (**4**) (its crystalline yield was only 13% reflecting its high solubility; see Supporting Information for full details). Here the construction of the N-CH$_2$-Zn bridge must involve a methyl deprotonation (through a "Me-Zn" unit) of an N-Me group, a reaction normally even more difficult than a *tert*-butyl deprotonation (through a "*t*Bu-Zn" unit). Determined by X-ray crystallography, the molecular structure of **3** is essentially identical to that of **2** with Me instead of *t*Bu (see Supporting Information).

It is worth commenting that the primary role of TMEDA in organometallic chemistry[16] is as a didentate N donor ligand, but here in the formation of **2** and **3** it has an unusual three-fold function. It acts first as a neutral N nucleophile towards an electron-deficient aromatic C atom; second as an anionic C nucleophile towards Zn (through an unprecedented direct zincation of TMEDA); and third as a neutral N ligand towards Zn. Tertiary amines are known to attack benzynes nucleophilically.[17]

Yoshida et al. have recently demonstrated[18] elegant three-component couplings of benzynes, unsaturated nucleophiles, and electrophiles to generate (metal-free) benzannulated cyclic products. Formally **2**, **3**, and **Int** could be considered the products of three-component couplings of PhCl, R$_2$Zn (R = *t*Bu or Me), and TMEDA (with concomitant elimination of RCl and H$_2$), but such reaction mixtures do not lead to zincacyclic products (there was no trace of a zinc-aryl product even when harsh reflux conditions were applied). In practice, NaTMP or LiTMP must be present, so it is the cooperativity between the different components within **1** and **4** that is behind the construction of **2** and **3**, hence these reactions can be interpreted as new examples of "synergic synthesis". The intriguing question now is: Can this reaction be extended to a wide range of metals and neutral nucleophiles to provide access to new families of metalacyclic, ylidic, and zwitterionic compounds?

Experimental Section

All reactions were carried out under a protective argon atmosphere. Full details can be found in the Supporting Information.

Synthesis of **2**: A hexane solution of **1** (2 mmol) was prepared as described previously.[4] Chlorobenzene (2 mmol, 0.2 mL) was added, and the mixture was heated to reflux for 1 h to produce a slightly cloudy yellow solution. The Schlenk tube was surrounded with a Dewar flask of hot water to allow the solution to cool slowly. This yielded small, colorless, X-ray quality crystals (0.13 g, 21%). To obtain a higher yield, a mixture of **1** (2 mmol) and chlorobenzene (1 mmol) was stirred for 48 h, which produced a powder of **2** (0.16 g, 51% based on consumption of chlorobenzene).

Synthesis of **3**: A solution of TMPH (2 mmol, 0.34 mL) in 10 mL of dry hexane was treated with 1.25 mL of *n*BuLi (1.6 M solution in hexane, 2 mmol). The solution was stirred at room temperature for 30 min. Me$_2$Zn (1.0 M solution in heptane, 2 mmol, 2 mL) was then added, before the addition of TMEDA (2 mmol, 0.3 mL). The mixture was stirred for 1 h to give a pale yellow solution. Chlorobenzene (2 mmol, 0.2 mL) was added, and the solution was heated at reflux for 1 h resulting in a slightly cloudy yellow solution. The solution was filtered through Celite to remove a small amount of precipitate in an effort to aid crystallization. The yellow solution was concentrated with the removal of solvent in vacuum and was transferred to a refrigerator operating at 0 °C. A small amount of highly hydrocarbon-soluble colorless, cubic crystals were deposited (0.07 g, 13%).

Synthesis of **Int**: A hexane solution of **1** (2 mmol) was prepared as described previously.[4] Chlorobenzene (2 mmol, 0.2 mL) was added, and the slightly cloudy yellow solution was transferred to a freezer operating at −28 °C. Overnight, this yielded a mixture of small, yellow, X-ray quality crystals of **Int** and colorless crystals of **2** (crude yield, 0.15 g, which equates to 12% of each as determined from an NMR analysis).

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[9] Crystal data for **2**: $C_{16}H_{28}N_2Zn$, $M_r = 313.8$, monoclinic, space group $P2_1/c$, $a = 9.7870(11)$, $b = 9.4959(10)$, $c = 18.276(2)$ Å, $\beta = 97.588(2)°$, $V = 1683.6(3)$ Å^3, $Z = 4$; $R(F) = 0.026$ for 3466 reflections with $F^2 > 2\sigma$, $R_w(F^2) = 0.066$ for all 3862 unique data ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $T = 150$ K, Nonius KappaCCD diffractometer) and 178 refined parameters, difference map between $+0.40$ and -0.27 e Å^{-3}. Crystal data for **Int**: $C_{20}H_{38}N_2Zn$, $M_r = 371.9$, orthorhombic, space group $Pbca$, $a = 9.6006(8)$, $b = 19.4973(13)$, $c = 22.8263(16)$ Å, $V = 4272.8(5)$ Å^3, $Z = 8$; $R(F) = 0.067$ for 2255 reflections with $F^2 > 2\sigma$, $R_w(F^2) = 0.123$ for all 4168 unique data ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $T = 123(2)$ K, Oxford Xcalibur S diffractometer) and 218 refined parameters, difference map between $+0.720$ and -0.411 e Å^{-3}. CCDC 741894 (**2**), 741895 (**3**) and 743469 (**Int**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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