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# Directed *meta*-Metalation Using Alkali-Metal-Mediated Zincation**

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Transforming a carbon–hydrogen bond of an organic compound into a more useful, more reactive carbon–metal bond (so-called deprotonative metalation), which, in turn, can be treated with an electrophile to create a new carbon–carbon or carbon–heteroatom bond, is one of the most fundamental synthetic approaches that chemists employ to construct compounds.[1,2] Many of these reactions involve a special type of deprotonative metalation, in which an activating functional group is positioned adjacent to the hydrogen atom (strictly a proton) that is to be replaced by the metal cation.

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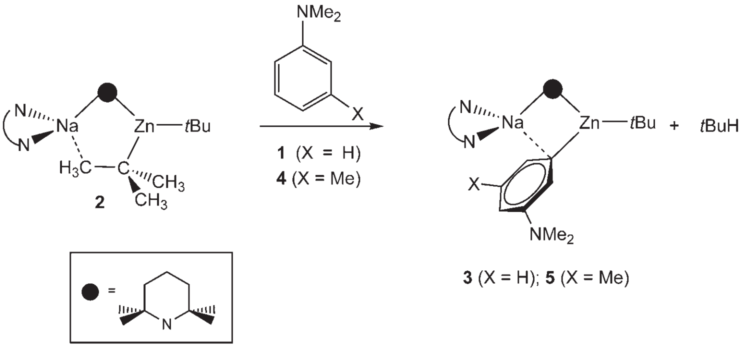
Directed *ortho*-metalation (DOM, in which the metal is usually lithium) represents the best-developed, most heavily utilized technique of this type.[3,4] Defined as a metalation (lithiation) of an aromatic ring directed towards a position adjacent (*ortho*) to an activating heteroatom-containing functional group, DOM now probably surpasses classical electrophilic aromatic substitution as the number one methodology for constructing regiospecifically substituted aromatic rings.[5] DOM is therefore practiced routinely in synthetic laboratories all across the world, both in academia, for general preparative purposes, and in industry, for the manufacture of fine chemicals, pharmaceuticals, and other biologically important aromatic compounds.

The tools most commonly employed for effecting DOM and the other types of metalation are single-metal (homometallic) reagents, typically alkyl lithium or lithium amide reagents. Recently, we and a few other research groups have begun to explore the behavior of related but mixed-metal (heterobimetallic) reagents with amide-based ligands in this important area of directed metalation.[6–10] These initial studies have established that in certain cases these mixed-metal alternatives can exhibit a remarkable chemical synergy that enables them to perform special metalation reactions that cannot be reproduced by either of the single-metal components that make up the mixed-metal reagent.[11] In these synergic metalation reactions, the departing hydrogen atom is replaced by magnesium or zinc, but the participation of an alkali metal is mandatory for the reaction to follow its special course. Metalation reactions of this type are therefore best regarded as an alkali-metal-mediated magnesiation (AMMM) or alkali-metal-mediated zincation (AMMZ).

In the context of the new work reported herein, the best example of synergic metalation to date has been achieved with the alkyl arene toluene. Conventional metalation reagents, such as the alkyl lithium BuLi·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), normally deprotonate toluene at the methyl (lateral) site to generate the resonance-stabilized benzyl "carbanion" ($PhCH_2^-$). In contrast, under AMMM conditions using the sodium–magnesium monoalkyl bisamido reagent [(tmeda)·Na(μ-Bu)(μ-tmp)Mg(tmp)] (TMP = 2,2,6,6-tetramethylpiperidide), the site of deprotonation is switched to the *meta* site on the ring and the methyl substituent remains intact.[12] Although the regiospecificity of this deprotonation is most unusual, it does not infringe any expected DOM effect, as toluene does not possess a heteroatom-containing functional group. To overcome any DOM effect and direct metalation to a normally inaccessible site would be exceptional news for chemists that could have major implications for synthetic chemistry. We report herein two case studies that prove that such a desirable situation can be engineered using the special chemistry inherent in AMMZ.

As *N*,*N*-dimethylaniline (**1**) possesses an activating dimethylamino substituent, it undergoes directed *ortho*-metalation with phenyllithium in poor yield or *n*-butyllithium in good yield.[13–15] Changing the metalation agent from these mainstream homometallic species to heterometallic [(tmeda)·Na(*t*Bu)(tmp)Zn(*t*Bu)] (**2**), a sodium TMP/zincate reagent recently introduced by our group, remarkably switches the orientation of the deprotonation to the *meta* site (Scheme 1).[16,17] The carbanion generated by this regiospecific *meta*-proton abstraction is stabilized through coordination to a bimetallic alkyl amido cation (the residue of the base following alkyl transfer), which advantageously permits the metalated product of the reaction [(tmeda)·Na(μ-Ar*)(μ-tmp)Zn(*t*Bu)] (**3**; Ar* = 3-$C_6H_4NMe_2$) to be obtained in a stable crystalline form, which is isolable at room temperature. Direct zincation of a tertiary anilide is not possible using mainstream alkyl zinc reagents, so the unprecedented carbon–hydrogen to carbon–zinc transformation accomplished can be attributed to the synergy inherent in AMMZ. Characterized in solution by $^1$H and $^{13}$C NMR spectroscopic studies, **3** was also subjected to an X-ray crystallographic study, which unambiguously established its molecular structure (Figure 1).[18] A four-element NaNZnC rhomboidal ring with a mixed TMP Ar* bridging ligand set forms the core, which is completed by terminal TMEDA (*N*,*N*-attached) and



***Scheme 1.*** Synergic metalation of *N*,*N*-dimethylaniline and its 3-methyl derivative using a sodium TMP/zincate base.

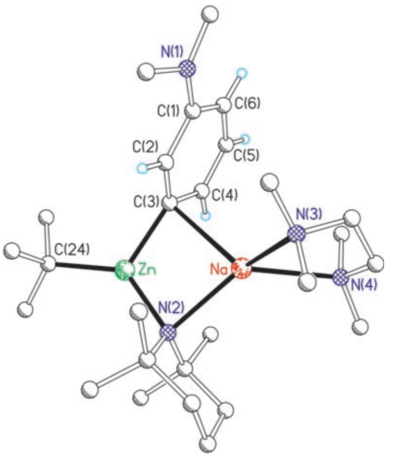


***Figure 1.*** Molecular structure of **3** with selective atom labeling. Hydrogen atoms, apart from those of the anilide ring, and minor disorder components are omitted for clarity.

*t*Bu (*C*-attached) ligands on the Na and Zn centers, respectively. In general terms, the structure can be categorized as an ion-contacted heterotrianionic zincate. Its key geometrical feature concerns how the deprotonated anilide engages differently with the two metal atoms: Zn forms a short bond to the *meta* C(3) atom (bond length: 2.035(4) Å), which is close to coplanarity with the aryl ring plane (the bond is inclined at 4.5° to the plane), whereas the Na–C(3) bond is significantly longer (2.691(4) Å) and inclined at an angle of 76.1° to the same plane. This parallel/perpendicular distinction to the deprotonated substrate–metal interactions, which implies more $\sigma$ character for the former and more $\pi$ character for the latter, has become a signature feature of these mixed-metal compounds,[10] which may provide a vital clue to the origin of the synergy (see below).

The second case study focused on 3-methyl-*N*,*N*-dimethylaniline (**4**), chosen as it has both a methyl (cf toluene) and a dimethylamino substituent on its aromatic ring. To our knowledge, **4** has never been previously metalated, though its 2- and 4-methyl isomers undergo preferential lithiation *ortho* to the activating dimethylamino substituent (methyl deprotonation in the case of the 2-methyl isomer).[19] However, applying AMMZ to **4** using the same reagent **2**, also achieves a *meta*-orientated deprotonation (Scheme 1), manifested in the crystalline product [(tmeda)·Na(μ-Ar**)(μ-tmp)Zn(*t*Bu)] (**5**; Ar** = 5-(3-Me)$C_6H_3NMe_2$). Characterized by NMR spectroscopic and X-ray crystallographic studies,[16] **5** adopts a molecular structure (Figure 2) remarkably similar to that of **3**, which includes the parallel ($\sigma$)/perpendicular ($\pi$) distinction in the aryl–metal bonding (corresponding angles: 4.5 and 67.8°, respectively).

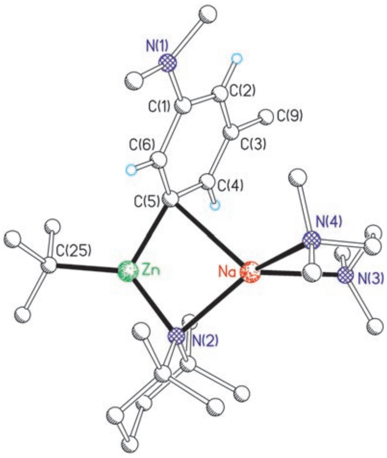


***Figure 2.*** Molecular structure of **5** with selective atom labeling. Hydrogen atoms, apart from those of the anilide ring, and minor disorder components are omitted for clarity.

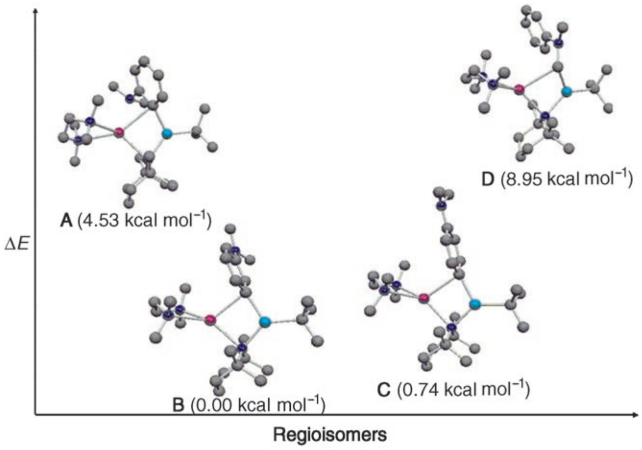


***Figure 3.*** Relative energy sequence of the four theoretical regioisomers (**3 A–D**) of the experimentally observed product **3**.

Theoretical calculations at the DFT level employing the B3LYP method and the 6-311G** basis set were used to compute the relative stabilities of the four regioisomers of **3**, in which the anilide ring is deprotonated at the *ortho* (**3A**), *meta* (**3B**), *para* (**3C**), or methyl (**3D**) positions (Figure 3).[17] In support of the experimental findings, the *meta* isomer **3B** is the energy minimum structure (relative energy: 0.00 kcal mol$^{-1}$); the *ortho* isomer is destabilized further (at 4.53 kcal mol$^{-1}$); and the least stable of all is the methyl isomer (at 8.95 kcal mol$^{-1}$). Through modeling studies, the overall reaction (**2**→**3B** + *t*BuH) is found to be exothermic by −22.21 kcal mol$^{-1}$. Comparison of the dimensions of **3B** and **3C** show that it is noticeable that the Na contacts to the aryl C atoms are invariably shorter in **3B** (bond lengths: 2.594, 3.070, 3.212, 3.959, 4.097, 4.403 Å) than in **3C** (bond lengths: 2.596, 3.178, 3.239, 4.135, 4.185, 4.596 Å). By contrast the Zn–C(aryl) bonds are within 0.001 Å of each other (2.084 and 2.083 Å, respectively). In the *ortho* isomer **3 A**, the product expected from conventional metalation, the Na–C(*ortho*) bond is much longer (2.747 Å) and thus weaker than the Na–C(*meta*) bond in **3B** (2.594 Å) as a result of increased steric constraints. Therefore, the important distinction lies in maximizing the strength of the Na···C$\pi$ contacts, and although they may be weak individually, collectively they must contribute significantly to the stability of **3B**. This favorable enthalpic effect, coupled with the minimal structural reorganization required by reagent **2** to form product **3** (in effect there is retention of structure except for the deprotonated anilide that refills the position vacated by the *t*Bu$^-$ base), appears to be a major factor in the unexpected *meta* selectivity observed.

To establish whether these *meta*-zincated dimethyl aniline complexes could be intercepted by electrophiles, we have carried out a preliminary iodolysis reaction of isolated crystals of **3** in a solution of THF with $I_2$. On the basis of $^1$H NMR experiments with ferrocene as an internal standard, iodination at the *meta* position was quantitative within experimental error (±5%), thus producing *N*,*N*-dimethyl-3-iodoaniline.[20] This augurs well for opening up a gateway for *meta*-substituted derivatives previously closed to synthetic aromatic chemistry.

## *Experimental Section*

Synthesis of **3** and **5**: A solution of *t*Bu$_2$Zn (0.358 g, 2 mmol) in hexane (10 mL) was transferred by cannula to a suspension of NaTMP in hexane (prepared in situ by reaction of BuNa (0.16 g, 2 mmol) with TMP(H) (0.34 mL, 2 mmol)). This was followed by the addition of a molar equivalent of TMEDA (0.30 mL, 2 mmol). The resultant suspension was heated gently to form a yellow solution. At this stage, one molar equivalent (2 mmol) of the relevant dimethylaniline was introduced, and the reaction mixture was refluxed at 65 °C for 2 h. The resulting yellow solution was transferred to the freezer to aid crystallization. A crop of transparent crystals formed in solution which were suitable for X-ray crystallographic analysis in yields of 39 % for **3** (0.38 g) and 43 % for **5** (0.46 g) for the first batch of isolated crystals. See Supporting Information for the labeling scheme.

**3**: $^1$H NMR (400 MHz, 25 °C, $C_6D_6$): $\delta = 7.34$ (d, 1 H, $H_{ortho}$ (Ar*)), 7.17 (t, 1 H, $H_{meta'}$ (Ar*)), 7.10 (d, 1 H, $H_{ortho}$ (Ar*)), 6.54 (m, 1 H, $H_{para}$ (Ar*)), 2.63 (s, 6 H, $N(CH_3)_2$ (Ar*)),1.65 (s, 9 H, *t*Bu), 1.58 (s, broad, 14 H, $CH_3$ (TMEDA) and $H_\gamma$ (TMP)), 1.52 (s, broad, 14 H, $CH_3$ (TMP), $H_\beta$ (TMP), and $CH_2$ (TMEDA)), 1.16 ppm (s, broad, 6 H, $CH_3$ (TMP)); $^{13}C\{^1H\}$ NMR (100.63 MHz, 25 °C, $C_6D_6$): $\delta = 170.79$ (Zn−$C_{meta}$ (Ar*)), 150.87 ($C_{ipso}$ (Ar*)), 128.87 ($C_{meta'}$ (Ar*)), 127.18 ($C_{para}$ (Ar*)), 124.48 ($C_{ortho}$ (Ar*)), 111.18 ($C_{ortho'}$ (Ar*)), 57.58 ($CH_2$ (TMEDA)), 53.22 ($C_\alpha$ (TMP)), 46.46 ($CH_3$ (TMEDA)), 40.41 ($C_\beta$ (TMP)), 41.03 ($N(CH_3)_2$ (Ar*)), 36.75 ($CH_3$ (TMP)), 36.01 ($CH_3$ (*t*Bu)), 35.47 ($CH_3$ (TMP)), 21.10 ($C_\gamma$ (TMP)), 21.01 ppm (C (*t*Bu)).

**5**: $^1$H NMR (400 MHz, 25 °C, $C_6D_6$): $\delta = 7.08$ (d, 1 H, $H_{ortho}$ (Ar**)), 6.96 (s, broad, 1 H, $H_{para}$ (Ar**)), 6.37 (s, broad, 1 H, $H_{ortho'}$ (Ar**)), 2.68 (s, 6 H, $N(CH_3)_2$ (Ar**)), 2.25 (s, 3 H, $CH_3$ (Ar**)), 1.68 (s, broad, 14 H, $CH_3$ (TMEDA) and $H_\gamma$ (TMP)), 1.66 (s, 9 H, *t*Bu), 1.58 (s, 4 H, $CH_2$ (TMEDA)), 1.53 (s, broad, 6 H, $CH_3$ (TMP)), 1.31 (m, 4 H, $H_\beta$ (TMP)), 1.21 ppm (s, broad, 6 H, $CH_3$ (TMP)); $^{13}C\{^1H\}$ NMR (100.63 MHz, 25 °C, $C_6D_6$): $\delta = 170.01$ (Zn−$C_{meta}$ (Ar**)), 150.77 ($C_{ipso}$ (Ar**)), 136.54 ($C_{meta'}$ (Ar**)), 128.52 ($C_{para}$ (Ar**)), 121.55 ($C_{ortho}$ (Ar**)), 111.86 ($C_{ortho'}$ (Ar**)), 57.37 ($CH_2$ (TMEDA)), 52.96 ($C_\alpha$ (TMP)), 46.23 ($CH_3$ (TMEDA)), 41.22 ($N(CH_3)_2$ (Ar**)), 40.76 ($C_\beta$ (TMP)), 36.50 ($CH_3$ (TMP)), 35.77 ($CH_3$ (*t*Bu)), 35.32 ($CH_3$ (TMP)), 22.80 ($CH_3$ (Ar**)), 21.05 (C (*t*Bu)), 20.78 ppm ($C_\gamma$ (TMP)).

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[18] Crystal data for **3**: $C_{27}H_{53}N_4NaZn$, $M_r = 522.1$, monoclinic, space group $P2_1/c$, $a = 16.170(3)$, $b = 11.0651(19)$, $c = 18.683(3)$ Å, $\beta = 112.614(3)°$, $V = 3085.8(9)$ Å$^3$, $Z = 4$, $T = 150$ K. 23451 measured reflections (CCD diffractometer, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å), 6048 unique ($R_{int} = 0.042$), 362 refined parameters with constrained H atoms and disorder for TMEDA, $R = 0.061$ for $F$ values of 4622 reflections with $F^2 > 2\sigma(F^2)$, $R_w = 0.152$ for all $F^2$ values, GOF = 1.14, final difference map extremes = +0.94 and −0.47 e Å$^{-3}$. Crystal data for **5**: $C_{28}H_{55}N_4NaZn$, $M_r = 536.1$, monoclinic, space group $P2_1/c$, $a = 15.291(7)$, $b = 11.391(5)$, $c = 18.729(8)$ Å, $\beta = 99.992(7)°$, $V = 3213(2)$ Å$^3$, $Z = 4$, $T = 150$ K. 24659 measured reflections, 6299 unique ($R_{int} = 0.032$), 475 refined parameters with constrained H atoms and disorder for all ligands except anilide, $R = 0.034$ for $F$ values of 4948 reflections with $F^2 > 2\sigma(F^2)$, $R_w = 0.094$ for all $F^2$ values, t = 1.08, final difference map extremes = +0.43 and −0.32 e Å$^{-3}$. CCDC-297778 and -297779 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. See http://www.ccdc.cam.ac.uk/products/csd/request/ for details.

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