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Structure and Reaction Pathway of TMP-Zincate: Amido Base or Alkyl Base?

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Improved access to functionalized organometallic compounds has considerably increased the scope of these nucleophilic reagents in organic synthesis. The deprotonative metalation (also termed “directed *ortho* metalation (DoM)”)[1] of functionalized aromatic rings allows aromatic C−H bonds to serve as direct feedstocks for functionalized aromatic compounds. Strong bases, such as organolithiums, have traditionally been used for this transformation, as one naturally expects that deprotonation of an aromatic C−H bond would require a high basicity.[2] Therefore, their application to the elaboration of complex organic structures has generally been limited by low functional group tolerance, the strict requirements for reaction conditions, and the extremely low temperature typically required in such reactions. Recently, one of our groups has developed TMP-Zn-ates[3] ($R_2Zn(TMP)Li$; R = Me (**1**) or ^{t}Bu (**2**)) and TMP-Al-ate[4] (^{i}Bu$_3$Al(TMP)Li), which promote highly chemoselective DoM reactions of multi-functionalized aromatic compounds *under mild conditions*. However, the real structures and reaction pathways of these ate bases remain poorly understood, despite the fact that knowledge of the structural features and the deprotonation mechanisms would be helpful in improving the reactivity and selectivity of the DoM reactions, as well as in designing more efficient metal reagents.

Very recently, Mulvey and co-workers reported a crystallographic and density functional (DFT) study on the structure of [^{t}Bu$_2$Zn(TMP)Na·TMEDA] (**3**), an analogue of $R_2Zn(TMP)Li$, and on the reaction pathway in the reaction of benzene with **3**, proposing that the deprotonation reaction involves an alkyl (^{t}Bu) ligand, not the TMP ligand on **3**.[5] However, their compound, **3**, differs from that used in our original work, ^{t}Bu$_2$Zn(TMP)Li (**2**), in several respects, that is, the countercation, an additional bidentate ligand (TMEDA), and the substrate. In our initial screening investigation of effective zincates for the chemoselective DoM reaction of functionalized benzenes,[3a] we found that changing the countercation of **2** from Li^+ to Na^+ drastically decelerated the deprotonative zincation. In the absence of any directed metalation group (ester, cyano, alkoxy, etc.) on the benzene ring, no deprotonation reaction occurred even with the most effective TMP-Zn-ate, **2**. On the basis of these observations, one would naturally expect a different chemistry for activation of the zincate than in the case of coordination of a TMEDA ligand to the Na cation, which enables deprotonation of an inert unfunctionalized benzene proton by an alkyl ligand. Herein, we report the first comprehensive structural and mechanistic investigation, by means of X-ray, NMR, and DFT studies, of the DoM reaction employing our original TMP-Zn-ate base.

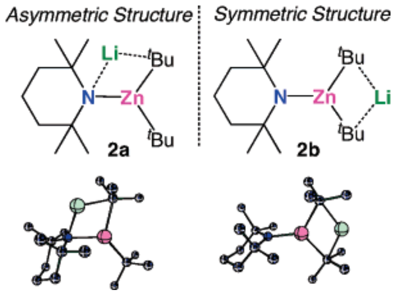

Figure 1. Possible structures of ^{t}Bu$_2$Zn(TMP)Li.

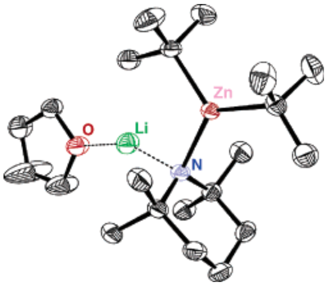

Figure 2. Crystal structure of ^{t}Bu$_2$Zn(TMP)Li·THF (**2a-*S***). Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

^{t}Bu$_2$Zn(TMP)Li (**2**) was selected for the initial investigation using DFT calculation (gas phase), single-crystal X-ray diffraction (solid phase), and NMR (solution phase) methods because it presents the most effective basicity among TMP-Zn-ates and is well-known to undergo chemoselective DoM reaction under mild conditions. As shown in Figure 1, two structures are a priori possible for **2**, the asymmetrical one (**2a**) and the symmetrical one (**2b**). The gas phase calculations indicated that **2a** is 17.3 kcal/mol lower in energy than the symmetrical isomer (**2b**). After several attempts, we were pleased to obtain X-ray-grade crystals from a THF solution of the complex generated from ^{t}Bu$_2$Zn and LTMP in a ratio of 1:1. The crystal structure of ^{t}Bu$_2$Zn(TMP)Li is in good agreement with the DFT results: a trigonal planar and asymmetric geometry with a molecule of THF coordinated to the lithium atom (**2a-*S***) (Figure 2).[6,7]

The ^{13}C, ^{7}Li, and ^{15}N NMR spectra of ca. 1.0 M ^{t}Bu$_2$Zn(TMP)Li (**2**) in THF at −50 °C each show only a set of singlets (Table 1 and Supporting Information), indicative of a single species. In all the NMR spectra, no signals corresponding to free ^{t}BuLi, LTMP, or ^{t}Bu$_2$Zn were detected. ^{t}Bu$_2$Zn(TMP)Li in THF gave a ^{13}C NMR spectrum containing two signals at 20.4 and 24.3 ppm, and they can reasonably be assigned to the two different α-carbons of the

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Table 1. ^{1}H, ^{13}C, ^{7}Li, and ^{15}N NMR Data of TMP, LTMP,[8] $^{t}BuLi$,[9] $^{t}Bu_2Zn$, and $^{t}Bu_2Zn(TMP)Li$[a]

reagent	^{1}H	^{13}C	^{7}Li	^{15}N
TMP	0.89 (s, NH), 1.01 (s, 12H) 1.24 (m, 4H), 1.59 (m, 2H)	19.3 (γ), 32.2 (Me) 39.0 (β), 50.0 (α)		75.4
LTMP[b]	1.06 (s, 12H), 1.15 (4H) 1.56 (m, 2H)	20.9 (γ), 36.2 (Me) 43.3 (β), 53.1 (α)	0.61 (monomer) 1.26 (dimer)	79.9
$^{t}BuLi$[b]	0.74	17.0 (α), 40.6 (β)	0.82	
$^{t}Bu_2Zn$[b]	0.85	22.7 (α), 34.4 (β)		
$^{t}Bu_2Zn(TMP)Li$ (**2**)	0.94 (s, 12H), 1.12 (4H) 1.57 (m, 2H), 0.83 (18H)	22.0 (TMP^{γ}), 34.8 (TMP^{Me}) 41.3 (TMP^{β}), 53.0 (TMP^{α}) 20.4 ($^{t}Bu^{\alpha}$), 24.3 ($^{t}Bu^{\alpha}$) 36.5−36.7 ($^{t}Bu^{\beta}$)	−2.67	63.7

[a] Unless otherwise noted, spectra were recorded for ca. 1.0 M THF solutions at −50 °C. Chemical shifts are reported in parts per million. ^{1}H and ^{13}C NMR spectra were referenced to a solvent THF signal. ^{7}Li NMR spectra were referenced to external 1.0 M LiBr in THF-d_8. ^{15}N NMR spectra were referenced to external 0.15 M [^{15}N]aniline in THF-d_8. [b] Recorded in THF at −100 °C.

two ^{t}Bu groups, supporting the presence of the unsymmetrical structure (**2a**) in solution (Figure 1).

Having obtained the structure of TMP-Zn-ate that is likely to be experimentally relevant, DFT calculations (B3LYP/631SVP) were performed to investigate the reaction pathway of the TMP-Zn-ate-mediated DoM reaction.[10] We employed $Me_2Zn(NMe_2)Li$ as a chemical model for TMP-Zn-ates with a molecule of Me_2O (a model of THF) coordinated to the Li atom. Although we must keep in mind the possibility that the simplification of the amide moiety of this model may lead to underestimation of the steric interactions, this structure provides a valuable starting point for our consideration of the reactivity of the TMP-Zn-ate bases. The reaction pathway of the DoM of anisole using $Me_2Zn(Me_2N)Li{\cdot}OMe_2$ (**4**) is shown in Figure 3. Initial electrostatic coordination of Li to anisole oxygen resulted in the formation of a complex (**CP1**) with a stabilization energy of 4.7 kcal/mol. From **CP1**, the DoM reaction using the Me_2N ligand of the zincate **4** can take two pathways through **TS1** ("closed form" TS) and **TS2** ("open form" TS).[11] The activation energies are reasonably low because the DoM reaction is facilitated by the push−pull synergy of the Lewis acidic Li atom and the negatively charged $Me_2Zn(NMe_2)$ moiety. Importantly, the two pathways have very similar magnitudes of activation energy, which means that the TMP-Zn-ate bases may be able to change their TS structures flexibly to adjust to various substrates without any special treatment.[11] This also implies high substrate compatibility of the TMP-zincate bases.

Of several possible TSs for the deprotonation of anisole using the Me ligand on the model zincate **4**, we could identify one, **TS3**. **TS3** in Figure 3 is an open form TS and is much less stable than **TS1** or **TS2**.[12] Orbital analysis lends some support to this ligand selectivity. The localized Kohn−Sham orbitals[13] of **TS1**, **TS2**, and **TS3** involved in the bond alteration associated with the H-abstraction are shown in Figure 4. It is well-known as an asset of nitrogen transfer[10] that a directional p-orbital corresponding to the lone pair orbital of the nitrogen atom can interact with the breaking aromatic C−H bond. The orientation of this orbital appears to be ideal in **TS1** or **TS2**. On the other hand, in the case of the Me ligand on the zincate, the contracted and ill-directed sp^{3}-like orbital of the carbon atom needs to be used in the C−H bond scission. This is consistent with the sharp ArH−C(Me)-Zn angle (45.9°) and also with the higher activation energy. Although Mulvey et al. concluded that there is a preference for alkyl over TMP transfer based on their computed thermodynamic energetics, the present

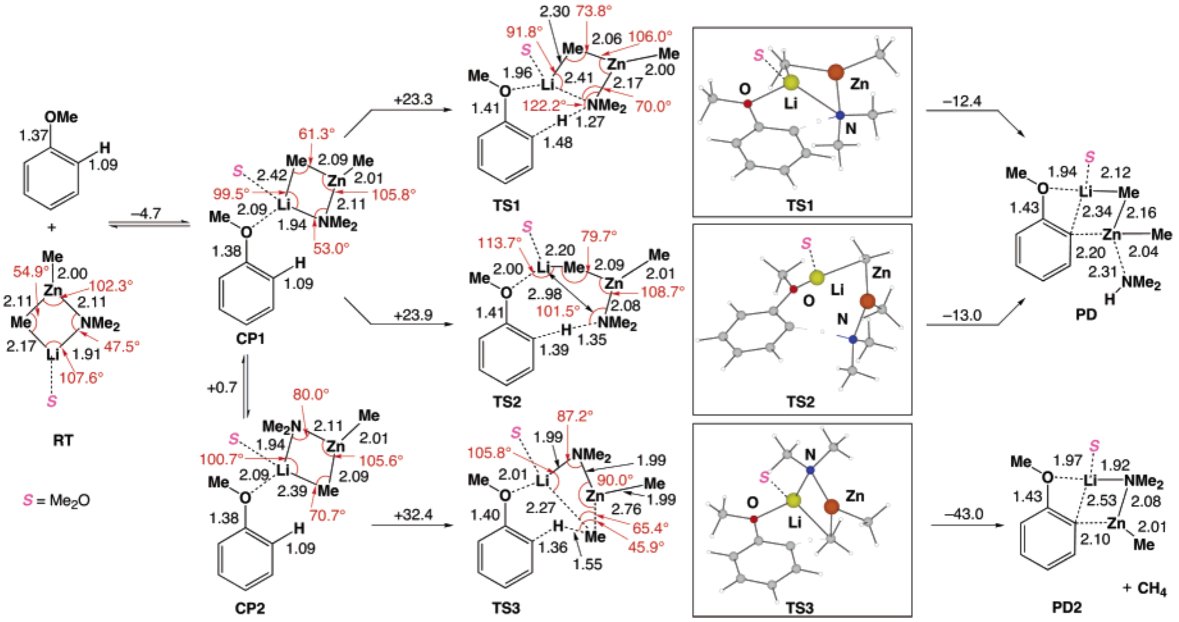


Figure 3. Reactants, complex, and TS in the DoM reaction of $Me_2Zn(Me_2N)Li$ with anisole. Bond lengths, angles, and energy changes at the B3LYP/631SVP level are shown in Å, deg, and kcal/mol, respectively.

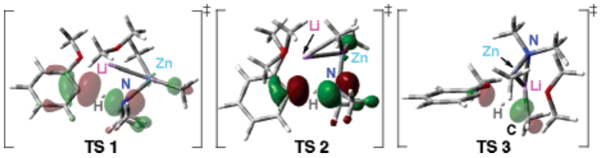
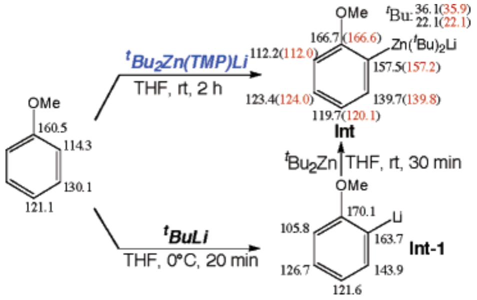


Figure 4. Localized Kohn−Sham MOs of **TS1**, **TS2**, and **TS3**.

DFT transition state calculation strongly suggests the kinetic preference of N-ligand over C-ligand transfer.[5a,14]

We confirmed that the TMP transfer from ${}^{t}Bu_2Zn(TMP)Li$ (**2**) occurs preferentially over ${}^{t}Bu$ transfer by monitoring the ^{13}C NMR spectrum of the reaction medium. The ^{13}C NMR chemical shifts (in black on **Int**, in Scheme 1) of the intermediary species (**Int**)[15] generated by the reaction using **2** were reasonably consistent with those (in red in parentheses on **Int**) of the species prepared by the stepwise treatment of anisole with ${}^{t}BuLi$, followed by complexation with ${}^{t}Bu_2Zn$. More importantly, ^{1}H NMR spectra indicated no significant loss of the ${}^{t}Bu$ moiety on the zincate during deprotonation, which clearly suggests no generation of any butane gas. Moreover, a set of peaks whose chemical shifts were consistent with those of TMPH was observed in the ^{13}C NMR spectra. These NMR observations strongly support the view that deprotonation involved the TMP ligand on **2** to form **Int** (Scheme 1).

Scheme 1. ^{13}C NMR Study of DoM Reaction Using ${}^{t}Bu_2Zn(TMP)Li$



In summary, the structures of TMP-Zn-ates both in solution and in the solid state have been determined. Furthermore, we have computationally studied and compared the possible reaction pathways of the DoM reaction of anisole with TMP-Zn-ate. The computational results for transition states strongly indicate that the deprotonation involving the TMP ligand on the TMP-Zn-ate is kinetically more favorable than that involving the alkyl ligand; this is a completely different result from that of Mulvey's analysis of the analogue **3**, probably due to the difference of the countercation and also the absence of TMEDA in our complex.[16] This view was also supported by monitoring of the ^{13}C NMR spectrum of the reaction mixture. These findings suggest that further DoM reagents can be developed through modification of the alkyl ligands of TMP-Zn-ates ($R_2Zn(TMP)Li$), in accordance with experimental observations of the resultant arylzincates in the TMP-Zn-ate-mediated benzyne formation reaction.[3b] In addition, the difference between our findings and Mulvey's has interesting implications for further modification of the TMP-Zn-ates by changing the nature of the countercation to improve reactivity and selectivity or to develop new reactions. Further studies on the effect of the electronic and steric properties of alkyl ligands and countercations are in progress.

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Supporting Information Available: Preparative procedures, spectral data, ORTEP diagrams, and crystallographic data for **2a-*S*** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The Gibbs and SCRF (solvent = THF) energies of activation (298.15 K) are as follows: TS1, 24.0 kcal/mol, 28.1 kcal/mol; TS2, 25.0 kcal/mol, 27.7 kcal/mol; TS3, 33.5 kcal/mol, 36.3 kcal/mol, respectively. Rather similar tendencies were seen, and the solvent effect does not change the conclusion of the above analysis.

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(14) The deprotonation of anisole using the TMP ligand on the TMP-Zn-ate is endothermic, which suggests that the DoM reaction of anisole could be reversible. Actually, ${}^{t}Bu_2Zn(TMP)Li$ was formed in the significant yield when TMPH was added to **Int** (Scheme 1) prepared by successive additions of ${}^{t}BuLi$ and ${}^{t}Bu_2Zn$ to anisole, judging from the ^{13}C NMR spectrum of the reaction mixture.

(15) Another similar intermediate species (**Int′**) was also present in the reaction mixture. The ^{13}C NMR chemical shifts for **Int′** are very similar to those for **Int**, and hence **Int′** should have a similar structure to **Int**, for example, with TMPH linked to **Int**, as in **PD** in Figure 3. Upon electrophilic treatment with I_2, both species were converted smoothly to a single *o*-iodinated product.

(16) During the review process of this manuscript, Mulvey et al. reported that a lithium TMP-Zn-ate, $[{}^{t}Bu_2Zn(TMP)Li{\cdot}TMEDA]$ reacts with aromatic amide via its amido and alkyl ligand. It seems likely that many factors, including the countercation, TMEDA, and the solvent, contribute to the ligand transfer selectivity. See ref 7.

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