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Concerning the Structures of Alkali-Metal-Mediated *ortho* Zincation of Benzamides and Phenyl *O*-Carbamate

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As a further contribution to alkali-metal-mediated metalation, a method for converting C−H bonds directly to C−Zn bonds without the need for an additional salt metathesis step, reactions of the sodium TMP-zincate [(TMEDA)Na(μ-TMP)(μ-^{t}Bu)Zn(^{t}Bu)] (**1**) with three different electron-rich aromatic substrates, have been investigated. Under ambient-temperature conditions, *N*,*N*-diethylbenzamide, *N*,*N*-diethyl-3-methoxybenzamide, and *N*,*N*-diethyl phenyl *O*-carbamate were zincated *ortho* to the substituent group (in between both substituents in the second case) in the crystalline products [(TMEDA)Na(μ-TMP){μ-2-[1-C(O)NEt$_2$]C$_6$H$_4$}Zn(^{t}Bu)] (**3**), [(TMEDA)Na(μ-TMP){μ-2-(1-C(O)NEt$_2$)(3-OMe)C$_6$H$_3$}Zn(^{t}Bu)] (**4**), and [(TMEDA)Na(μ-TMP){μ-2-(1-OC(O)NEt$_2$)C$_6$H$_4$}-Zn(^{t}Bu)] (**6**). X-ray crystallography established that, in each case, the deprotonated aromatic fragment is captured by the residue of the bimetallic base, giving rise to seven-membered (NaNZnCCCO) ring structures for **3** and **4** and an eight-membered (NaNZnCCOCO) ring structure for **6**. The new zincated aromatics were also characterized by solution-state ^{1}H and ^{13}C NMR spectroscopy. Reactivity studies of **3**, **4**, and **6** were also performed with iodine. In each case, three molar equivalents of iodine in THF solution gave the *ortho*-iodo products *N*,*N*-diethyl-2-iodobenzamide (**7**), *N*,*N*-diethyl-2-iodo-3-methoxybenzamide (**8**), and *N*,*N*-diethyl-2-iodophenyl-*O*-carbamate (**9**) in quantitative, 71% and 75% yields as determined by NMR analysis, respectively.

Introduction

Directed *ortho*-metalation (DoM) is widely regarded as a premier technique for regioselective construction of polysubstituted aromatics and heteroaromatics.[1,2] The DoM reaction is reliant on a heteroatom substituent with proficient directed metalating group (DMG) capability for blending the basic properties required for good metal coordination and the acidic properties required for C−H deprotonation. Foremost in their efficiency are tertiary amide and *O*-carbamate DMGs.[3,4] Although the mechanistic details of the DoM process are still controversial,[5] the qualitative DMG power derives from complementary acid−base properties comprising a highly basic heteroatom (primed for coordinating to a metal) and an electron-withdrawing acidifying effect (weakening the *ortho* C−H bond). However, a major complication with such DMGs is their electrophilicity, which leaves them open to hostile nucleophilic attacks from metalating agents, leading to undesired side reactions and complicating synthetic utility.

Traditionally, the reagents employed to realize DoM have been the highly polar organolithiums, typically alkyl lithium reagents or bulky lithium amides.[6,7] However, as a consequence of their elevated reactivity, attacks upon sensitive functional groups (e.g., C=O), and the instability of the developing *ortho*-lithiated intermediates, the use of cryogenic temperatures is often necessary to promote effective reactions.

Since its discovery, the original DoM process[6] via lithiation (i.e., C−H to C−Li exchange) has witnessed broad application[1,3,7] *per se* but also in transmetalation to Mg, Zn, Sn, and B to cross-coupling reactions, which provide significant synthetic advantage.[8] However, examples are considerably less for direct zincations (C−H to C−Zn exchange). Recently, both we and other research groups have pioneered new, related mixed-metal reagents as a fresh alternative to the long-established lithiation reaction. Although organozinc reagents are a central component in many organic transformations, their use in deprotonative metalation has been hampered by their poor kinetic reactivity.[9,10] In spite of

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this, when included as part of a novel multicomponent concoction, the reactivity of a zinc reagent can be significantly enhanced through cooperative effects between the diverse components. Knochel has successfully blended his “turbo-Grignard” reagents with $\mathrm{ZnCl_2}$ to fashion the composite bases $[(\mathrm{TMP})_2\mathrm{Zn}\cdot 2\mathrm{MgCl_2}\cdot 2\mathrm{LiCl}]$[11] and $[\{^i\mathrm{Pr}(^t\mathrm{Bu})\mathrm{N}\}_2\text{-}\mathrm{Zn}\cdot 2\mathrm{MgCl_2}\cdot 2\mathrm{LiCl}]$[12] (where TMP is 2,2,6,6-tetramethylpiperidide), both of which are capable of directly zincating a wide range of aromatic and heteroaromatic substrates. Alkali-metal zincates demonstrate greater selectivity and functional group tolerance than the more established reagents and, additionally, exhibit improved reactivity in comparison with kinetically retarded, charge-neutral dialkyl zinc compounds. Established by Kondo and Uchiyama, “$[\mathrm{LiZn(TMP)}(^t\mathrm{Bu})_2]$” has been shown to be an effective complex zincator towards various organic substrates,[13] and our group introduced the related sodium TMP-zincate $[(\mathrm{TMEDA})\mathrm{Na}(\mu\text{-}\mathrm{TMP})(\mu\text{-}^t\mathrm{Bu})\mathrm{Zn}(^t\mathrm{Bu})]$ (**1**) (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine). Subsequent to its initial report in 2005,[14] this complex has proven to be a powerful and efficient reagent for promoting direct zincation of several different aromatic molecules. This mixed-metal approach enables the use of much milder reaction conditions, generally at room temperature, and can present unique metalation regioselectivities previously thought be unobtainable with substrates such as toluene,[15] *N*,*N*-dimethylaniline,[16] and benzyl methyl ether.[17] In addition to monozincation, dizincation of unactivated arenes such as benzene[18] and naphthalene[19]—where no zincation at all would be anticipated using conventional zinc reagents—is smoothly accomplished to generate new dizinc aryl species. These remarkable reactions are the upshot of a synergic effect, in that neither of the homometallic reagents of which the mixed-metal base is composed can replicate this special reactivity. While the alkali-metal component is essential, it is the less electropositive zinc that effects the deprotonation, filling the position vacated by the proton; thus these reactions are best interpreted as alkali-metal-mediated zincations (AMM*Zn*). In this paper, we widen AMM*Zn* in the direction of the most powerful classes of directed *ortho*-metalation groups: tertiary amides and *O*-carbamates to generate *ortho*-zincated species whose structures have been elucidated by X-ray crystallographic analysis.

Results and Discussion

Having previously realized chemo- and regioselective zincation of a selection of aromatic and heteroaromatic substrates, the sodium TMP-zincate $[(\mathrm{TMEDA})\mathrm{Na}(\mu\text{-}\mathrm{TMP})(\mu\text{-}^t\mathrm{Bu})\mathrm{Zn}(^t\mathrm{Bu})]$ (**1**) was used as the AMM*Zn* reagent in all of the reactions reported herein. A hexane solution of **1**—prepared *in situ* from a cocomplexation reaction between its three distinct components NaTMP, $^t\mathrm{Bu_2Zn}$, and TMEDA—was treated with one molar equivalent of *N*,*N*-diethylbenzamide, *N*,*N*-diethyl-3-methoxybenzamide, or *N*,*N*-diethyl phenyl *O*-carbamate at room temperature. After 18 h stirring of the reaction mixtures and storing them in a refrigerator (at 5 °C) or freezer (at −28 °C), colorless crystalline products were deposited in each case and subsequently analyzed by X-ray crystallography. In each of the examples reported herein, the compounds obtained are the result of regioselective *ortho*-deprotonation adjacent to the strong DMG.

Metalation of *N*,*N*-diisopropylbenzamide has been extensively studied; moreover various *ortho*-metalated intermediates have been isolated and characterized by X-ray crystallography from the reaction with ^{t}BuLi[20] and an assortment of mixed-metal reagents [containing low-polarity metals ranging from Zn, Al, Mn(II)],[21] including the *ortho*-deprotonated complex $[(\mathrm{TMEDA})\mathrm{Na}(\mu\text{-}\mathrm{TMP})\{\mu\text{-}2\text{-}[1\text{-}\mathrm{C(O)N}^i\mathrm{Pr_2}]\text{-}\mathrm{C_6H_4}\}\mathrm{Zn}(^t\mathrm{Bu})]$[21b] (**2**) acquired from reaction with **1**. There is significantly less known about the structures derived from *N*,*N*-diethylbenzamide.

Over the years, the metalation chemistry of *N*,*N*-diethylbenzamide has been widely explored in search of the optimum procedure for *ortho*-deprotonation.[22] At the outset, Hauser reported that applying ^{n}BuLi led to attack at the carbonyl group of a dialkyl amide to give ketone products by reference to previous work and showed that, by charge deactivation, *N*-methylbenzamide undergoes the DoM reaction with excess ^{n}BuLi.[23] Subsequent studies by Beak revealed that *N*,*N*-diethylbenzamide may be metalated by employing the hindered, non-nucleophilic reagent LiTMP, but only incomplete deprotonation is achieved and, undesirably, the *ortho*-lithio intermediate instantly attacks another molecule of starting material to give a benzophenone product.[24] However, in salient experiments that triggered major synthetic application,[1,6,7] Beak discovered that by

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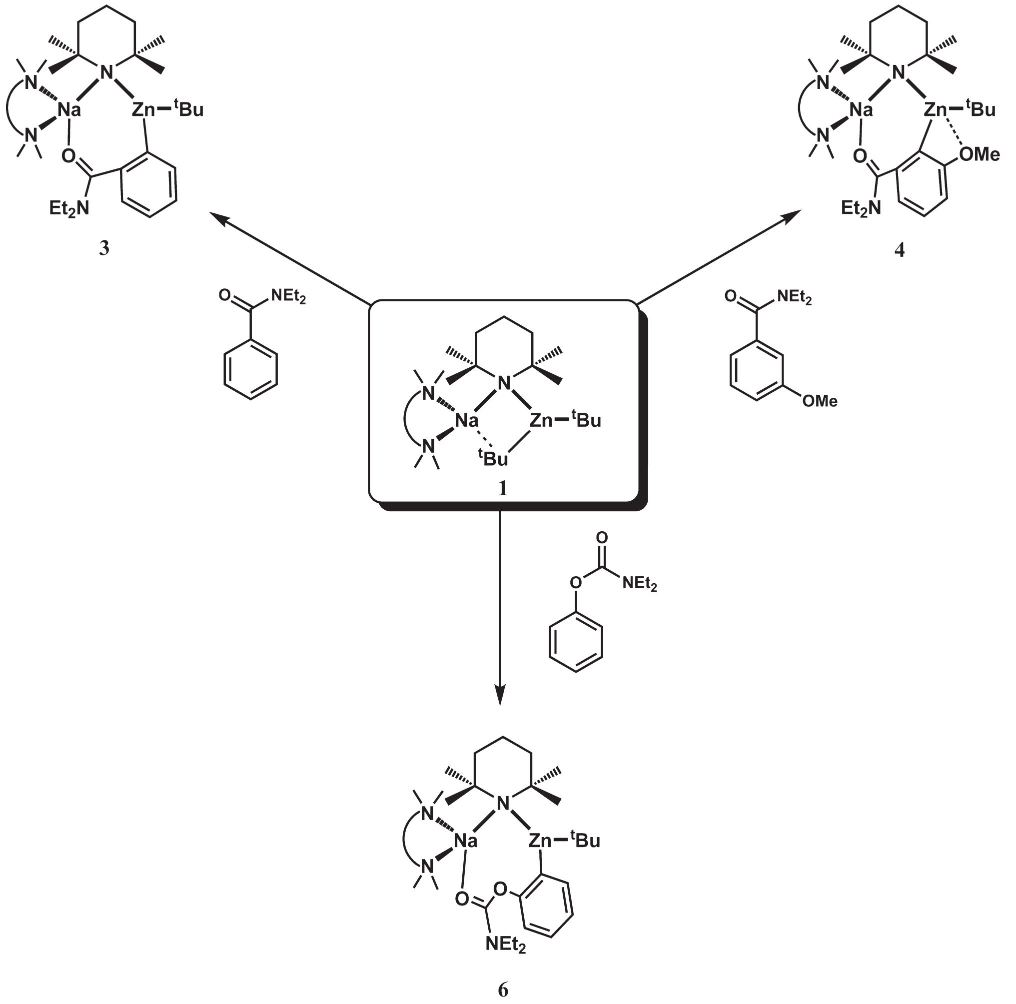
Scheme 1. Reactivity of Zincate Base 1 toward Tertiary Amide and *O*-Carbamate Aromatic Compounds



using the ^{s}BuLi/TMEDA combination, the diethylbenzamide can be efficiently *ortho*-metalated in THF.[25] Although this reaction requires subambient temperature conditions (−78 °C), it has found application in industrial practice on a very large scale.[1] In contrast and a harbinger of potential future application, our sodium TMP-zincates with special synergic chemistry may be harnessed to perform DoM of *N*,*N*-diethylbenzamide at room temperature to produce the heterotrianionic zincate [(TMEDA)Na(μ-TMP){μ-2-[1-C(O)NEt$_2$]C$_6$H$_4$}Zn(^{t}Bu)] (**3**) in a yield of 54% of isolated crystalline material.

The successful growth of crystalline material allowed valuable insight into the structural makeup of the metalated intermediates. The molecular structure of **3** (Figure 1) preserves the "{(TMEDA)Na(μ-TMP)Zn(^{t}Bu)}" spine of the reactant zincate **1**, which is completed by the *ortho*-metalated benzamide fragment. Bridging asymmetrically through its oxygen and *ortho*-carbon atoms, the zincated benzamide closes a seven-membered, five-element (NaNZnCCCO) ring. The availability of structure of **3** enables comparison with the analogous *ortho*-zincated *N*,*N*-diisopropylbenzamide **2**. As anticipated, varying the alkyl group from ethyl to isopropyl has a negligible effect on the bond distances and angles in the environs of the core ring system. Classifiable as contacted ion pairs, both structures exhibit a trigonal-planar Zn coordination (made up of C, C, N atoms) encompassing one terminal (^{t}Bu) and two bridging ligands (TMP and a monozincated benzamide). The Zn−C$_{aryl}$ bond lengths [2.0637(17) and 2.077(3) Å in **3** and **2**, respectively] are similar, while the aryl ligand bonds to Na through the *O*-heteroatom [Na−O 2.2855(12) Å] to secure the seven-membered ring. A bidentate TMEDA ligand completes the distorted tetrahedral (N, N, N, O) environment of Na. Thus defining the metalation as a zincation, the alkali-metal binds to the carbonyl oxygen atom but is distant from the *ortho*-carbon anion [Na1···C1 2.9250(16) Å], while zinc engages in shorter, stronger σ-bonds with the deprotonated carbon. While the Na1···C1 distance is longer than that found for PMDETA-solvated phenylsodium, [(PMDETA)NaPh]$_2$[26] (mean Na···C bond distance of 2.669 Å), it is within the typical range of π-arene−Na contacts. For example, it is similar to the Na···C contacts found in the sodium phosphanide [(TMEDA)Na[P(C$_6$H$_4$-2-NMe$_2$){CH(Me$_3$Si)$_2$}]] of 3.0072(14) and 2.8792(14) Å.[27]

Following the accomplishment of direct zincation of the benzamide, the metalation ability of the synergic base towards substituted benzamides was tested. In lithiation DoM chemistry, the electron-donating methoxy group can direct the metalation through a combined coordination-inductive effect of

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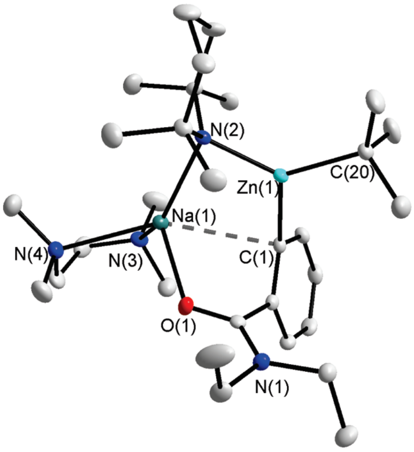

Figure 1. Molecular structure of **3** with selective atom labeling and 40% probability ellipsoids. Hydrogen atoms omitted for clarity. The long Na$\cdots$C$_{ortho}$ contact is highlighted by a dashed line. Selected bond lengths (Å) and angles (deg): Zn(1)–N(2) 2.0047(12), Zn(1)–C(1) 2.0637(17), Zn(1)–C(20) 2.0434(16), Na(1)$\cdots$C(1) 2.9250(16), Na(1)–O(1) 2.2855(12), Na(1)–N(2) 2.4445(14); N(2)–Zn(1)–C(20) 132.11(6), N(2)–Zn(1)–C(1) 116.07(6), C(20)–Zn(1)–C(1) 111.59(6), Na(1)–N(2)–Zn(1) 88.08(5), O(1)–Na(1)–N(2) 110.20(5).

the oxygen. With the synergic but bulkier base, it appears that the metalation regioselectivity is not overly sensitive to the other substituents, in that the metalation proceeds in between the methoxy and tertiary amide substitutents in *N*,*N*-diethyl-3-methoxybenzamide akin to when an organolithium reagent is employed.[25]

Applying the synthetic procedure, which successfully leads to the synthesis of **3**, the heterobimetallic base **1** was treated with one molar equivalent of the methoxybenzamide in hexane solution and led, after refrigeration, to the growth of colorless block crystals. X-ray crystallographic analysis revealed the crystals to be the new alkyl-aryl-amido zincate [(TMEDA)Na(μ-TMP){μ-2-(1-C(O)NEt$_2$)(3-OMe)C$_6$H$_3$}Zn-(^{t}Bu)] (**4**), with the position of zincation between the two aryl substituents.

The molecular structures of **3** and **4** have the mutual structural motif of a highly puckered central seven-membered ring. The Na–N$_{TMP}$ and Na–O bond lengths [2.4370(13) and 2.2722(11) Å, respectively] in the latter complex are in good agreement with the corresponding bonds in the diethylamide complex **3** [2.4445(14) and 2.2855(12) Å]. A key distinction between these two complexes arises from the introduction of the additional methoxy substituent and the extra albeit weak interaction it permits with Zn. The distorted trigonal-planar geometry adopted by Zn in **3** is also exhibited in **4**, but the position taken up by the methoxy group allows a long Zn$\cdots$O interaction in **4** [2.8625(10) Å]. This distance between the Zn and methoxy O center is noticeably longer than those found in a series of alkylzinc fencholates,[28] with bond distances ranging from 2.15 to 2.40 Å. Similarly, in calixarene complexes prepared by Raston[29] and Vigalok[30] the distance between the ether oxygen atoms and zinc [2.222(7); and 2.1944(16); 2.391(2); 2.406(2) Å] is shorter than the corresponding distance in **4**.

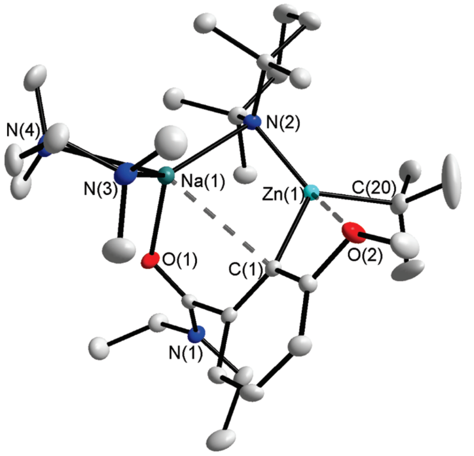

Figure 2. Molecular structure of **4** with selective atom labeling and 40% probability ellipsoids. Hydrogen atoms are omitted for clarity. The long Na$\cdots$C$_{ortho}$ contact and the Zn$\cdots$OMe contact are highlighted by dashed lines. Selected bond lengths (Å) and angles (deg): Zn(1)–N(2) 2.0170(11), Zn(1)–C(1) 2.0827(14), Zn(1)–C(20) 2.0531(15), Zn(1)$\cdots$O(2) 2.8625(10), Na(1)$\cdots$C(1) 2.9548(14), Na(1)–O(1) 2.2722(11), Na(1)–N(2) 2.4370(13); N(2)–Zn(1)–C(20) 129.86(6), N(2)–Zn(1)–C(1) 114.35(5), C(20)–Zn(1)–C(1) 115.80(6), Na(1)–N(2)–Zn(1) 90.68(5), O(2)–Na(1)–N(2) 105.72(4).

The zincation of the *N*,*N*-diethyl phenyl *O*-carbamate, bearing the most powerful DMG,[1] was undertaken. The corresponding *N*,*N*-dimethyl *O*-carbamates once *ortho*-lithiated are generally unstable and rearrange rapidly by a carbamoyl transfer mechanism known as the "anionic *ortho*-Fries rearrangement".[3,4] However, the more hindered *N*,*N*-diethyl *O*-carbamates are stable at −78 °C and rearrange slowly to salicylamides on warming to higher temperatures.[31] In 2008, Uchiyama and Wheatley reported the first structural evidence for the *ortho*-metalation of aryl dialkyl *O*-carbamates that resist anionic Fries rearrangement at room temperature.[32] Treatment of phenyl dimethylcarbamate with an *in situ* mixture of ^{n}BuLi, TMP(H), and Et$_2$Zn afforded dimeric, *ortho*-zincated [(C$_6$H$_4${OC(O)NMe$_2$}-{Zn(μ-TMP)Et}-2)Li]$_2$, **5**. Furthermore, the stability of the intermediate zincate was reflected in the near-quantitative conversion of the *N*,*N*-diethyl analogue, upon iodination, to the 2-iodophenyl derivative, although no metalated intermediates were isolated prior to the final electrophilic quench with iodine.

Changing the alkali-metal to Na in our work, *N*,*N*-diethyl phenyl *O*-carbamate was treated with synergic base **1** in hexane at ambient temperature. The resulting yellow solution was concentrated by the removal of solvent *in vacuo* and stored at 5 °C in a refrigerator to yield crystals. Analysis of these crystals revealed *ortho*-deprotonation of the aryl carbamate manifested in the formation of [(TMEDA)Na-(μ-TMP){μ-2-(1-OC(O)NEt$_2$)C$_6$H$_4$}Zn(^{t}Bu)] (**6**). As with structures **3** and **4**, zincate base **1** has performed DoM as an overall alkyl base, by means of the *ortho*-deprotonated carbamate unit substituting the bridging ^{t}Bu group.

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In an attempt to rationalize the observed alkyl basicity, Uchiyama and Nobuto have presented a comprehensive theoretical study that proposes that these deprotonations occur via a two-step mechanism.[33] Their calculations reveal that the sodium TMP-zincate serves kinetically as an amide base, with release of concomitant TMP(H) to produce a bisalkyl(aryl) zincate intermediate. It follows that this intermediate then undergoes reaction with the coexistent TMP-(H) in the second step to afford the experimentally observed [(TMEDA)Na(μ-TMP)(μ-aryl)Zn(^{t}Bu)] product. Recently, Hevia and co-workers successfully prepared and characterized the proposed reaction intermediates in closely related experimental studies, before exploring their reactivity toward TMP(H) mirroring the second step of the process.[34,35] Their findings provided the first examples of experimental evidence for a two-step mechanism in deprotonative metalation reactions with TMP zincates. On the basis of this study, it is highly likely that complexes **3**, **4**, and **6** are the thermodynamic products of their respective two-step reactions.

Structure **6** embodies a larger eight-membered (NaNZnCCOCO) interior ring system through the inclusion of an additional O atom (in comparison to **3** and **4**). In the monozincated benzene complex [(TMEDA)Na(μ-TMP)(μ-Ph)Zn(^{t}Bu)][14] and *meta*- and *para*-deprotonated toluene regiosiomers [(TMEDA)Na(μ-TMP)(μ-C_6H_4Me)Zn(^{t}Bu)],[15] the Zn atom is lying almost coplanar with the arene ring [deviation from the arene plane of 0.213(4), 0.19(3), and 0.18(2) Å, respectively], while the Na center adopts a more perpendicular disposition [deviation of 2.6604(14), 2.6830(14), and 2.7006(14) Å], interacting more with the π-system of the aromatic ring. In complexes **3**, **4**, and **6**, the increased functionality of the organic substrate causes the alkali-metal to seek out the oxygen heteroatom (as opposed to the more sterically shielded π-system) to satisfy its coordinative/electronic unsaturation. The consequence for complexes **3** and **4** is the formation of the highly strained seven-membered (NaNZnCCCO) ring and with it comes a minor divergence away from the plane of the aryl ring for the Zn atom [0.5165(2) and 0.3913(2) Å for **3** and **4**, respectively]. However, increasing the size of the internal ring, as in **6** with the introduction of the additional oxygen atom, reduces the strain involved and brings the Zn back closer to lying coplanar with the arene ring [deviation of only 0.2800(2) Å], while Na still bonds to the oxygen atom of the carbonyl group.

On the basis of a search of the Cambridge Structural Database,[36] it would appear that **6** represents the first example of a crystallographically characterized monomeric *ortho*-zincated (or indeed *ortho*-metalated) phenyl dialkyl *O*-carbamate to be prepared by direct metalation.[37] Consequently, the aforementioned dimer **5** denotes the best comparison for compound **6** and emphasizes the effect of increased sterics on the constitution of the resulting structure. In addition to the aggregation state change (due to no donor uptake in the Li reaction), the upshot of transferring from Li to the larger Na is an increased Na1−N2−Zn1 bond angle of 92.98(4)° (in contrast to a Li−N−Zn angle of 88.6° in **5**), and this theme is also reflected in the bond distance between the alkali-metal and the carbamoyl O-center [2.003(8) and 2.2728(10) Å in **5** and **6**, respectively]. Moreover, the bulkier ^{t}Bu group in **6** gives rise to a longer terminal Zn−alkyl bond [2.0426(13) Å] when matched to the Zn−Et bond in **5** [2.008(5) Å]. As anticipated, the transannular Na1···C1 distance in **6** [3.0438(14) Å] is longer than the corresponding interaction in complexes **3** and **4** [2.9250(16) and 2.9548(14) Å] as a consequence of the increased ring size.

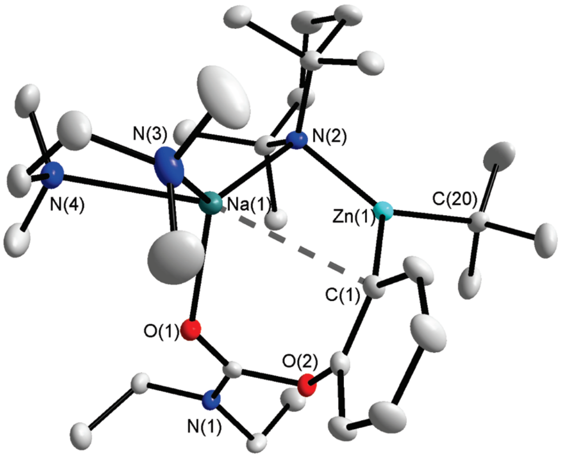

Figure 3. Molecular structure of **6** with selective atom labeling and 40% probability ellipsoids. Hydrogen atoms and minor disordered component of TMEDA are omitted for clarity. The long Na···C_{ortho} contact is highlighted by a dashed line. Selected bond lengths (Å) and angles (deg): Zn(1)−N(2) 2.0112(11), Zn(1)−C(1) 2.0581(13), Zn(1)−C(20) 2.0426(13), Na(1)···C(1) 3.0438(14), Na(1)−O(1) 2.2728(10), Na(1)−N(2) 2.4741(11); N(2)−Zn(1)−C(20) 132.26(5), N(2)−Zn(1)−C(1) 113.56(5), C(20)−Zn(1)−C(1) 113.99(5), Na(1)−N(2)−Zn(1) 92.98(4), O(1)−Na(1)−N(2) 111.69(4).

In order to start determining the potential utility of *ortho*-zincated compounds **3**, **4**, and **6** some preliminary reactivity studies were performed with iodine. Following a standard electrophilic quenching procedure, *in situ* mixtures of **3**, **4**, or **6** were treated with three molar equivalents of iodine in THF solution, giving the expected *ortho*-iodo products. The products were analyzed via NMR spectroscopy. For *N*,*N*-diethylbenzamide, the yield was essentially quantitative, while good yields were also obtained for the iodination of *N*,*N*-diethyl-3-methoxybenzamide and *N*,*N*-diethyl phenyl *O*-carbamate (yields of 71% and 75%, respectively).

Solution-State Studies

Complexes **3**, **4**, and **6** are soluble in deuterated benzene (C_6D_6) solution, which allowed a detailed solution-state analysis by NMR spectroscopy. Tables 1 and 2 compare the most diagnostic chemical shifts in the ^{1}H and ^{13}C NMR spectra, respectively, of these three zincate compounds. Accentuating the hindered, rigid nature of molecules **3** and **4**, the ^{1}H NMR spectra revealed all four TMP CH_3 groups to be chemically distinct; thus these resonances are observed at different chemical shifts in acquiescence with the solid-state structures obtained from the X-ray data. The steric strain

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(33) Nobuto, D.; Uchiyama, M. *J. Org. Chem.* **2008**, *73*, 1117.

(34) Clegg, W.; Conway, B.; Hevia, E.; McCall, M. D.; Russo, L.; Mulvey, R. E. *J. Am. Chem. Soc.* **2009**, *131*, 2375.

(35) Armstrong, D. R.; Blair, V. L.; Clegg, W.; Dale, S. H.; García-Álvarez, J.; Honeyman, G. W.; Hevia, E.; Mulvey, R. E.; Russo, L. *J. Am. Chem. Soc.* **2010**, *132*, 9480.

(36) CSD version 5.31 see: Allen, F. H. *Acta Crystallogr., Sect. B* **2002**, *58*, 380.

(37) *ortho*-Metalated ArPdI where Ar is [C_6H_4{OC(O)N(Me)-($CH_2CH{=}CH_2$)}] has been prepared as the bis(PPh_3) solvate via oxidative addition; see: Bocelli, G.; Catellani, M.; Chiusoli, G. P.; Cugini, F.; Lasagni, B.; Mari, M. N. *Inorg. Chim. Acta* **1998**, *270*, 123.

involved in all three complexes is further emphasized by the nature of the resonances depicting the ethyl arms of the amide. In the free, uncomplexed substrate both the CH_2 and CH_3 units appear as sole signals in C_6D_6 solution, covering the region 3.08−3.13 and 0.89−0.94 ppm, respectively. Upon *ortho* zincation and incorporation as part of a bulky, heterotrianionic zincate, these resonances split and appear inequivalent. The discrete CH_3 resonances are highlighted in Table 1. The CH_2 groups decoalesce into a series of multiplets to underline the inflexible conformation of the aromatic ring in these compounds. The ^{13}C NMR spectra, which were assigned utilizing 2D $^1H-^{13}C$ HSQC experiments, also support these data, while the chemical shift of the *ortho*-carbon atom reaffirms the position of metalation. As a result of zincation, the *ortho*-carbon resonances in complexes **3**, **4**, and **6** are observed at 168.9, 167.9, and 159.4 ppm, a significant move downfield from those of the free, nonmetalated substrates (126.8, 112.4, and 122.1 ppm, respectively).[38]

Table 1. Selected ^1H NMR (400.13 MHz) Chemical Shifts (δ in ppm) for Zincates 3, 4, and 6 in C_6D_6 Solution

compound	$\delta(CH_3\text{-TMP})$	$\delta(\beta\text{-TMP})$	$\delta(\gamma\text{-TMP})$	$\delta(CH_3\text{-Ethyl})$
3	1.52, 1.50, 1.32, 1.21	1.88, 1.57	1.96	1.02, 0.79
4	1.62, 1.59, 1.34, 1.31	1.82[a], 1.34	2.04, 1.84	1.02, 0.81
6	1.38−1.26 (br)	1.60	1.96	1.00, 0.89

[a] See Experimental Section for full analysis.

Table 2. Selected ^{13}C NMR (100.62 MHz) Chemical Shifts (δ in ppm) for Zincates 3, 4, and 6 in C_6D_6 Solution

compound	$\delta(CH_3\text{-TMP})$	$\delta(\beta\text{-TMP})$	$\delta(\gamma\text{-TMP})$	$\delta(\alpha\text{-TMP})$	$\delta(CH_3\text{-Ethyl})$
3	37.4, 35.2, 34.6, 34.4	40.7, 39.7	20.4	52.8,	13.9, 12.9
4	36.6, 35.6, 35.5, 33.0	41.8, 41.2	20.4	53.2	13.9, 12.9
6	35.0	40.1	20.4	52.6	14.0, 13.3

The ^1H NMR spectrum of complex **6** in C_6D_6 solution resembles that of **3** and **4** with the exception of resonances denoting the TMP ligand. The fact that a broad signal (spanning 1.26−1.38 ppm) is observed for the TMP CH_3 groups intimates that a dynamic process must be occurring in solution at room temperature. Variable-temperature NMR spectroscopic studies of a d_8-toluene solution of **6** validate this scenario. At low temperature (250 K), the broad signal observed at room temperature splits into three separate signals (at 1.18, 1.21, and 1.36 ppm, each with an integration of three hydrogen atoms) and, upon further cooling to 230 K, the fourth and final CH_3 resonance emerges at 1.55 ppm from beneath the ^{t}Bu group to complete the full complement of CH_3 signals. Additionally, in Figure 4 it can be seen that the two β-TMP CH_2 groups are chemically distinct in d_8-toluene solution at room temperature. However, on warming, the signal furthest downfield broadens, and by 340 K the two signals have coalesced to one resonance (see Supporting Information).

Conclusions

The applicability of AMM*Zn* has been expanded to include some of the aromatic templates frequently encountered in DoM-mediated aromatic synthesis. Treatment of *N*,*N*-diethylbenzamide, *N*,*N*-diethyl-3-methoxybenzamide, and *N*,*N*-diethyl phenyl *O*-carbamate with the sodium TMP-zincate

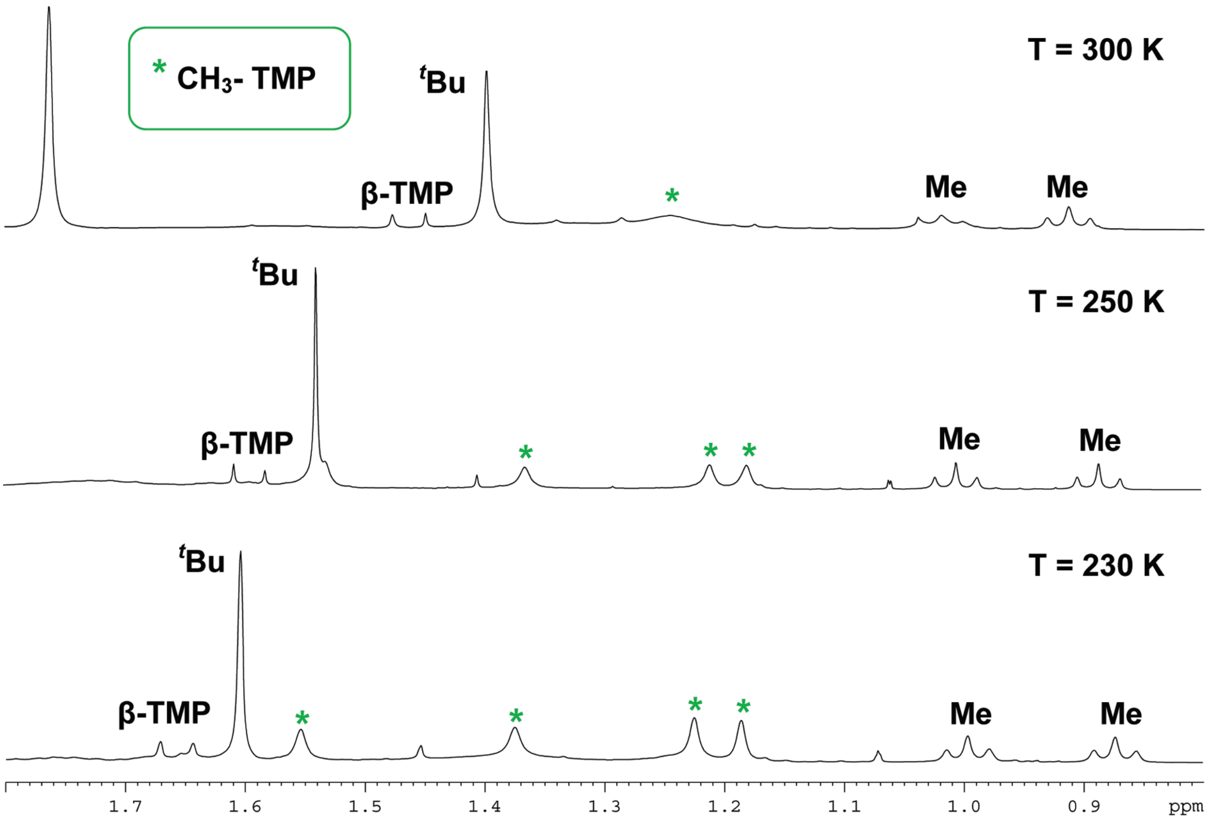

Figure 4. Selected aliphatic region showing the methyl resonances from the TMP ligand in the ^1H NMR spectrum of **6** in deuterated toluene solution at various temperatures.

base [(TMEDA)Na(μ-TMP)(μ-^{t}Bu)Zn(^{t}Bu)] (**1**) produced the three new selectively *ortho*-zincated crystalline complexes [(TMEDA)Na(μ-TMP){μ-2-[1-C(O)NEt$_2$]C$_6$H$_4$}Zn(^{t}Bu)] (**3**), [(TMEDA)Na(μ-TMP){μ-2-(1-C(O)NEt$_2$)(3-OMe)C$_6$H$_3$}Zn(^{t}Bu)] (**4**), and [(TMEDA)Na(μ-TMP){μ-2-(1-OC(O)NEt$_2$)-C$_6$H$_4$}Zn(^{t}Bu)] (**6**). Although the metalation regioselectivities observed in these reactions are not new, it is worth stressing that these highly chemo- and regioselective reactions are being performed at ambient temperatures with no suggestion of complications in the form of side reactions. This increased sensitivity can be exploited to trap and isolate the metalated intermediates (prior to electrophilic quenching) in clean, pure crystalline forms, which allows valuable insight to be drawn on the structure of the intermediates both in the solid state by X-ray crystallography and in solution by NMR spectroscopy. Collectively, these results highlight the efficiency of the synergic bimetallic bases, which is leading to the emergence of AMM*Zn* as a novel alternative to the established DoM reaction via lithiation.

Experimental Section

Hexane and THF, purchased from Sigma Aldrich, were distilled from sodium-benzophenone. All synthetic work was carried out under a protective inert argon atmosphere using standard Schlenk techniques. The ^{1}H NMR spectroscopic experiments were performed on a Bruker DPX400 spectrometer with an operating frequency of 400.13 MHz. The ^{13}C NMR spectra were recorded on the same instrument at an operating frequency of 100.62 MHz. All chemical shifts are quoted relative to TMS standard at 0.00 ppm. The IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer, and elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. Due to the extreme air and moisture sensitivity of **3**, **4**, and **6**, ideal analyses could not be obtained. Melting/decomposition points were measured on a Büchi melting point B-545 apparatus. The syntheses of ^{t}Bu$_2$Zn[14] and ^{n}BuNa[39] were as previously published.

X-ray Crystallography. All data were collected at 123(2) K on an Oxford Diffraction Gemini S diffractometer with Mo Kα radiation (λ = 0.71073 Å). Structures were solved using SHELXS-97,[40] while refinements were carried out on F^2 against all independent reflections by the full-matrix least-squares method using the SHELXL-97 program.[40] With the exception of the atoms of the minor disorder component present in **6** all non-hydrogen atoms were refined using anisotropic thermal parameters. CCDC 793876 (**3**), 793877 (**4**), and 793878 (**6**) contain the full 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.

Crystal data for **3**: C$_{30}$H$_{57}$N$_4$NaOZn, M = 578.16, monoclinic, $P2_1/n$, a = 10.4215(3) Å, b = 16.4560(3) Å, c = 19.5649(4) Å, β = 94.868(2)°, V = 3343.20(13) Å^3, Z = 4; 28 026 reflections collected, 9698 were unique, R_{int} = 0.0450, R = 0.0348, R_{w} = 0.0637, GOF = 0.841, 347 refined parameters, max. and min. residual electron density = 0.512 and $-$0.412 e·Å^{-3}.

Crystal data for **4**: C$_{31}$H$_{59}$N$_4$NaO$_2$Zn, M = 608.18, monoclinic, $P2_1/c$, a = 16.3094(2) Å, b = 10.3360(2) Å, c = 20.8204(4) Å, β = 98.105(2)°, V = 3474.72(10) Å^3, Z = 4. 34 313 reflections collected, 10 077 were unique, R_{int} = 0.0345, R = 0.0326, R_{w} = 0.0723, GOF = 0.923, 366 refined parameters, max. and min. residual electron density = 0.505 and $-$0.392 e·Å^{-3}.

Crystal data for **6**: C$_{30}$H$_{57}$N$_4$NaO$_2$Zn, M = 594.16, monoclinic, $P2_1/c$, a = 18.2070(4) Å, b = 10.3460(2) Å, c = 19.9460(4) Å, β = 116.629(3)°, V = 3358.68(12) Å^3, Z = 4; 27 340 reflections collected, 8907 were unique, R_{int} = 0.0304, R = 0.0287, R_{w} = 0.0602, GOF = 0.894, 393 refined parameters, max. and min. residual electron density = 0.389 and $-$0.271 e·Å^{-3}.

Synthesis of [(TMEDA)Na(μ-TMP)(μ-^{t}Bu)Zn(^{t}Bu)], 1. ^{n}BuNa (2 mmol, 0.16 g) was suspended in hexane (10 mL) and sonicated for 10 min to form a fine dispersion. TMP(H) (2 mmol, 0.34 mL) was added, and the subsequent yellow suspension was allowed to stir for 1 h. In a separate Schlenk tube, freshly prepared ^{t}Bu$_2$Zn (2 mmol, 0.36 g) was dissolved in hexane (10 mL) and transferred to the already prepared NaTMP via cannula. TMEDA was then introduced (2 mmol, 0.3 mL), and the resulting suspension was gently heated to produce a homogeneous yellow solution to yield an *in situ* mixture of **1**, which was checked against an authentic sample of **1** via NMR spectroscopy but then repeated several times without further checking.

Synthesis of [(TMEDA)Na(μ-TMP){μ-2-[1-C(O)NEt$_2$]C$_6$H$_4$}-Zn(^{t}Bu)], 3. X-ray quality crystalline material was prepared by treating the aforementioned hexane solution of **1** with *N*,*N*-diethylbenzamide (2 mmol, 0.354 g), and the reaction mixture was allowed to stir at ambient temperature for 18 h. Following gentle heating, the orange solution was concentrated *in vacuo* and transferred to a freezer for storage ($-$28 °C), where colorless crystals of **3** were deposited overnight (0.63 g, 54%). Mp: 124 °C. ^{1}H NMR (400.1 MHz, C$_6$D$_6$, 300 K): δ 7.94 (1H, d, ^3J(H,H) = 7.23 Hz, *meta*), 7.21 (1H, t, ^3J(H,H) = 7.06 Hz, *para*), 6.99 (2H, m, *meta* and *ortho*), 3.46$-$3.20 (3H, m, CH_2-Ethyl), 2.93 (1H, m, CH_2-Ethyl), 1.99$-$1.88 (4H, m, γ- and β-TMP), 1.78 (4H, s, CH_2-TMEDA), 1.71 (12H, s, CH_3-TMEDA), 1.57 (2H, m, β-TMP), 1.52 (3H, s, CH_3-TMP), 1.50 (12H, s, CH_3-^{t}Bu and CH_3-TMP), 1.32 (3H, s, CH_3-TMP), 1.21 (3H, s, CH_3-TMP), 1.02 (3H, t, ^3J(H,H) = 7.14 Hz, CH_3-Ethyl), 0.79 (3H, t, ^3J(H,H) = 7.13 Hz, CH_3-Ethyl). ^{13}C NMR (100.6 MHz, C$_6$D$_6$, 300 K): δ177.9 (C=O), 168.9 (C_{ortho}-Zn), 145.8 (C_{ipso}), 141.3 (C_{meta}), 126.8 (C_{para}), 123.3 and 123.1 (C_{meta} and C_{ortho}), 57.3 (CH$_2$-TMEDA), 52.8 (2 × α-TMP), 45.6 (CH$_3$-TMEDA), 43.6 (CH$_2$-Ethyl), 40.7 (β-TMP), 39.7 (β-TMP), 38.3 (CH$_2$-Ethyl), 37.4 (CH$_3$-TMP), 35.8 (CH$_3$-^{t}Bu), 35.2 (CH$_3$-TMP), 34.6 (CH$_3$-TMP), 34.4 (CH$_3$-TMP), 20.4 (γ-TMP), 20.2 (Cq-^{t}Bu), 13.9 (CH$_3$-Ethyl), 12.9 (CH$_3$-Ethyl).

Synthesis of [(TMEDA)Na(μ-TMP){μ-2-(1-C(O)NEt$_2$)(3-OMe)C$_6$H$_3$}Zn(^{t}Bu)], 4. *N*,*N*-Diethyl-3-methoxybenzamide (2 mmol, 0.415 g) was introduced to the aforementioned hexane solution of **1**. To obtain a homogeneous solution, THF (2 mL) was added, and the resulting reaction mixture was allowed to stir at room temperature overnight. The dark orange solution was concentrated *in vacuo* and stored in a refrigerator (5 °C) preceding the growth of small, colorless block crystals of **4** (0.54 g, 44%). Mp: 121 °C. ^{1}H NMR (400.1 MHz, C$_6$D$_6$, 300 K): δ δ7.04 (1H, t, ^3J(H,H) = 7.72 Hz, *meta*), 6.68 (1H, d, ^3J(H,H) = 7.21 Hz, *ortho*), 6.51 (1H, d, ^3J(H,H) = 7.98 Hz, *para*), 3.51 (3H, s, OCH_3), 3.41$-$3.18 (3H, m, CH_2-Ethyl), 3.01 (1H, m, CH_2-Ethyl), 2.04 (1H, m, γ-TMP), 1.84 (5H, s, γ-TMP and CH_2-TMEDA), 1.77 (12H, s, CH_3-TMEDA), 1.62 (3H, s, CH_3-TMP), 1.59 (3H, s, CH_3-TMP), 1.46 (9H, s, CH_3-^{t}Bu), 1.34 (2H, m, β-TMP) 1.31 (3H, s, CH_3-TMP), 1.28 (3H, s, CH_3-TMP), 1.02 (3H, t, ^3J(H,H) = 7.13 Hz, CH_3-Ethyl), 0.81 (3H, t, ^3J(H,H) = 7.13 Hz, CH_3-Ethyl). *From 2D HSQC and COSY experiments, the second β-TMP resonance appears to be masked by the TMEDA signals around 1.82 ppm. ^{13}C NMR (100.6 MHz, C$_6$D$_6$, 300 K): δ δ177.4 (C=O), 167.9 (C_{ortho}-Zn), 155.3 and 146.3 (C_{ipso} and C_{meta}), 125.6 (C_{meta}), 117.1 (C_{ortho}), 107.1 (C_{para}), 57.4 (CH$_2$-TMEDA), 53.9 (OCH$_3$), 53.2 (2 × α-TMP), 45.7 (CH$_3$-TMEDA), 43.6 (CH$_2$-Ethyl), 41.8 (β-TMP), 41.2 (β-TMP), 38.3 (CH$_2$-Ethyl), 36.6 (CH$_3$-TMP), 35.8 (CH$_3$-^{t}Bu), 35.6

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(38) As found when recording NMR spectra of *N*,*N*-diethylbenzamide, *N*,*N*-diethyl-3-methoxybenzamide, and *N*,*N*-diethyl phenyl *O*-carbamate in C$_6$D$_6$ solution during this work.

(39) Schade, C.; Bauer, W.; Schleyer, P. v. R. *J. Organomet. Chem.* **1985**, *295*, c25.

(40) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.

(*C*H$_3$-TMP), 35.5 (*C*H$_3$-TMP), 33.0 (*C*H$_3$-TMP), 20.4 (γ-TMP), 19.6 (*C*q-^{t}Bu), 13.9 (*C*H$_3$-Ethyl), 12.9 (*C*H$_3$-Ethyl).

Synthesis of [(TMEDA)Na(μ-TMP){μ-2-(1-OC(O)NEt$_2$)C$_6$H$_4$}-Zn(^{t}Bu)], 6. To a hexane solution of **1** was introduced *N*,*N*-diethyl phenyl *O*-carbamate (2 mmol, 0.386 g), and the reaction mixture was allowed to stir at ambient temperature for 18 h. The yellow solution was concentrated by the removal of solvent *in vacuo* and then subsequently transferred to a refrigerator (5 °C), where colorless crystals were deposited (0.45 g, 38%). Mp: 127 °C. ^{1}H NMR (400.1 MHz, C$_6$D$_6$, 300 K): δ δ7.73 (1H, d, ^3J(H,H) = 6.85 Hz, *meta*), 7.13 (1H, t, ^3J(H,H) = 7.03 Hz, *para*), 7.05 (1H, t, ^3J(H,H) = 7.35 Hz, *meta*), 6.78 (1H, d, ^3J(H,H) = 7.68 Hz, *ortho*), 3.29−2.98 (3H, m, C*H*$_2$-Ethyl), 2.89 (1H, m, C*H*$_2$-Ethyl), 1.96 (2H, m, γ-TMP), 1.85 (4H, s, C*H*$_2$-TMEDA), 1.78 (12H, s, C*H*$_3$-TMEDA), 1.60 (4H, br, β-TMP), 1.53 (9H, s, C*H*$_3$-^{t}Bu), 1.38−1.26 (10H, br, C*H*$_3$-TMP), 1.00 (3H, t, ^3J(H,H) = 7.13 Hz, C*H*$_3$-Ethyl), 0.89 (3H, t, ^3J(H,H) = 7.13 Hz, C*H*$_3$-Ethyl). ^{13}C NMR (100.6 MHz, C$_6$D$_6$, 300 K): δ δ159.9 (*C*=O), 159.4 (*C*$_{\text{ortho}}$-Zn), 158.5 (*C*$_{\text{ipso}}$), 140.4 (*C*$_{\text{meta}}$), 126.3 (*C*$_{\text{meta}}$), 125.1 (*C*$_{\text{para}}$), 119.6 (C$_{\textit{ortho}}$), 57.5 (*C*H$_2$-TMEDA), 52.6 (α-TMP), 45.6 (*C*H$_3$-TMEDA), 41.9 (2 × *C*H$_2$-Ethyl), 40.1 (β-TMP), 35.1 (*C*H$_3$-^{t}Bu), 35.0 (*C*H$_3$-TMP), 20.4 (γ-TMP), 20.0 (*C*q-^{t}Bu), 14.0 (*C*H$_3$-Ethyl), 13.3 (*C*H$_3$-Ethyl).

Electrophilic Quenching Reactions. An *in situ* hexane solution of the previously reported[11] zincate **1** (2 mmol) was prepared as described above. The organic substrate (2 mmol) was then added to the base, and the reaction mixtures were allowed to stir at ambient temperature for 18 h. The resultant solutions were treated with a freshly prepared solution of 1 M iodine in THF (6 mmol, 6 mL) and allowed to stir for 2 h. A 5 mL amount of NH$_4$Cl was added along with the addition of saturated Na$_2$S$_2$O$_3$ until bleaching occurred (5 mL). The organic layer was separated from the aqueous layer and dried over magnesium sulfate for 1 h. After filtration, the solvent was removed under vacuum to give a light yellow oil. The NMR spectrum of the crude material was obtained to determine the yield of the iodo product relative to unreacted starting material.

***N*,*N*-Diethyl-2-iodobenzamide, 7.** Yield: >99%. NMR (400.1 MHz, C$_6$D$_6$, 300 K): δ 7.52 (1H, d, ^3J(H,H) = 8.01 Hz, *meta*), 6.90 (2H, m, *para* and *ortho*), 6.54 (1H, t, ^3J(H,H) = 7.62 Hz, *meta*), 3.70 (1H, br, C*H*$_2$-Ethyl), 3.04 (1H, br, C*H*$_2$-Ethyl), 2.75 (2H, m, C*H*$_2$-Ethyl), 1.14 (3H, t, ^3J(H,H) = 7.13 Hz, C*H*$_3$-Ethyl), 0.65 (3H, t, ^3J(H,H) = 7.13 Hz, C*H*$_3$-Ethyl).

***N*,*N*-Diethyl-2-iodo-3-methoxybenzamide, 8.** Yield: 70.8%. NMR (400.1 MHz, C$_6$D$_6$, 300 K): δ 6.89 (1H, t, ^3J(H,H) = 7.94 Hz, *meta*), 6.69 (1H, d, ^3J(H,H) = 7.55 Hz, *ortho*), 6.15 (1H, d, ^3J(H,H) = 8.30 Hz, *para*), 3.77 (1H, m, C*H*$_2$-Ethyl), 3.18 (3H, s, OC*H*$_3$), 3.03 (1H, m, C*H*$_2$-Ethyl), 2.86 (1H, m, C*H*$_2$-Ethyl), 2.75 (1H, C*H*$_2$-Ethyl), 1.17 (3H, t, ^3J(H,H) = 7.14 Hz, C*H*$_3$-Ethyl), 0.68 (3H, t, ^3J(H,H) = 7.14 Hz, C*H*$_3$-Ethyl).

***N*,*N*-Diethyl-2-iodophenyl-*O*-carbamate, 9.** Yield: 74.9%. NMR (400.1 MHz, C$_6$D$_6$, 300 K): δ 7.54 (1H, d, ^3J(H,H) = 8.01 Hz, *meta*), 7.06 (1H, d, ^3J(H,H) = 8.18 Hz, *ortho*), 6.92 (1H, t, ^3J(H,H) = 7.74 Hz, *para*), 6.45 (1H, t, ^3J(H,H) = 7.72 Hz, *meta*), 3.17 (4H, m, C*H*$_2$-Ethyl), 1.07 (3H, t, ^3J(H,H) = 7.13 Hz, C*H*$_3$-Ethyl), 0.97 (3H, t, ^3J(H,H) = 7.13 Hz, C*H*$_3$-Ethyl).

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Supporting Information Available: NMR and IR spectra of **3**, **4**, and **6**; CIF files for **3**, **4**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.