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Suppressing the Anionic Fries Rearrangement of Aryl Dialkylcarbamates; the Isolation of a Crystalline *ortho*-Deprotonated Carbamate

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In the presence of organolithium bases phenyl dialkylcarbamates have previously been shown to undergo facile rearrangement to yield the corresponding salicylamides. However, heterometallic lithium diethyl(2,2,6,6-tetramethylpiperidido)zincate achieves the clean directed *ortho*-metallation (DoM) of phenyl dialkylcarbamates, with $[C_6H_4\{OC(O)NMe_2\}\{Zn(\mu\text{-TMP})Et\}Li]_2$ having been structurally characterized. DFT studies point to a stepwise deprotonative mechanism in which the zincate reagent exhibits kinetic amido basicity.

Strategies aimed at achieving directed *ortho*-metalation (DoM) have been developed over a number of years,[1] and now represent a core tool in the elaboration of complex aromatic compounds. While organolithium reagents have historically been used to achieve this chemistry, their nucleophilicity has brought with it the risk of competing reactions at the directing group. The need to circumvent this issue has led to the design of the heterometallic bases $R_2Zn(TMP)Li$ [R = Et, *t*Bu (**1**); TMP = 2,2,6,6-tetramethylpiperidide]. These have been successfully used to elaborate functionalised aromatic compounds incorporating directing groups normally susceptible to nucleophilic degradation.[2] Moreover, initial questions over whether these bases effect alkyl or amido basicity[3] appear to have now been resolved, with recent density functional theory (DFT) work establishing the view that they exhibit a kinetic preference for amido ligand exchange[4] according to a stepwise reaction mechanism.[4c] We have also used this idea to explain the experimentally observed *poly*basicity of **1** (R = Et, *t*Bu).[4c,5] Whilst our understanding of these systems has, therefore, increased, it is nonetheless apparent that structural studies on *ortho*-zincation have so far focused on systems in which *ortho* deprotonation is also achievable using organolithium reagents (e.g., tertiary amides, anisoles).[4,5] We therefore considered that we might harness the recorded stability of intermediary aromatic zincates (relative to their lithium analogues) and utilise their documented ability to form cleanly and without complications from subsequent rearrangement[6] or side-reactions[7] to achieve DoM in a system where the isolation of an *ortho*-lithiated intermediate was *not* viable.

DoM involving amide-type functional groups (e.g., secondary and tertiary amides, carbamates and oxazolines) has revolutionised the synthesis of aromatic compounds. Moreover, the amide-type directing groups mentioned are among the best directors of reaction; and carboxylic amide and oxazoline DoM has recently undergone structural study in the context of deprotonation by organolithium reagents.[8] However, spontaneous anionic Fries rearrangement of the *ortho*-lithiate (Scheme 1) means that the same cannot be said of carbamate DoM.[9] Hence, whilst aryl dialkylcarbamates are the most effective directors of lithiation, the *N*,*N*-dimethyl analogue undergoes facile rearrangement at –78 °C to yield the corresponding salicylamide.[10] While this may be controlled by employing diethylcarbamates at –78 °C, carbamoyl rearrangement still occurs on warming.[1a,10] Further manipulation of the rearrangement process can be effected by utilizing bulky NR_2 groups. However, this makes subsequent deprotection more demanding.[9] Overall, the carbamoyl translocation is so ubiquitous, that synthetic applications of aryl carbamates have focused on *tandem ortho*-lithiation/anionic Fries rearrange-

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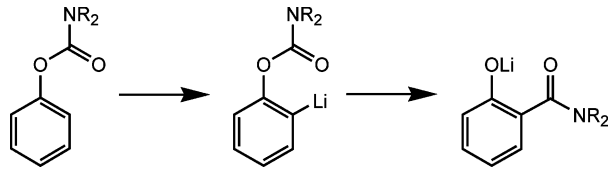
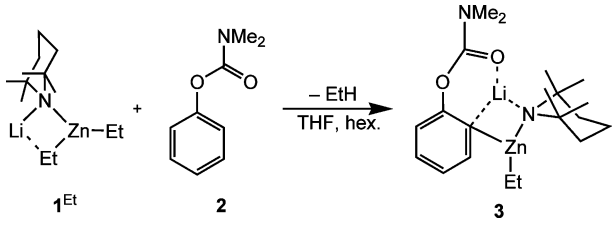
ment.[11] However, by utilizing a heterometallic base designed to target intermediary aromatic metalates resistant to subsequent rearrangement, we can now report the first structural investigation of *ortho*-metalated aryl dialkylcarbamates that resist anionic Fries rearrangement at room temperature.



Scheme 1.

The treatment of HTMP with *n*BuLi and Et_2Zn in THF at –78 °C under N_2 yielded $\mathbf{1}^{Et}$ (= **1**; R = Et) in situ. Injection of phenyl dimethylcarbamate (**2**) afforded a solution that was warmed to room temperature and stirred for 2 h to give a red emulsion. This was concentrated to give an oil that was taken up in toluene and stored at –30 °C to yield crystals (Scheme 2). Analysis of this material by X-ray diffraction revealed a dimer of $[C_6H_4\{OC(O)NMe_2\}\{Zn(\mu\text{-}TMP)Et\}\text{-}2]Li$ (**3**) (there resided one molecule of disordered lattice toluene per dimer).[12] We were pleased to observe that, in contrast to previous reports on the rearrangement of aryl dialkylcarbamates, employment of $\mathbf{1}^{Et}$ allowed retention of the directing group in spite of the use of an *N*,*N*-dimethylated system. The carbamate unit is twisted nearly perpendicular to the aryl moiety [C16–C15–O2–C14 83.13(46)°, Figure 1], the *ortho* position of which is zincated [2.055(4) Å] to give an dialkyl(aryl)zincate ion. The alkali metal ion is coordinated both by the carbamoyl O-center [2.003(8) Å] and the bridging TMP ligand [N1–Zn1 2.033(4) Å, N1–Li1 2.057(8) Å]. Unlike in sodium complex $[C_6H_4\{C(O)NMe_2\}\{Zn(TMP)(t\text{Bu})\}\text{-}2]Na\cdot TMEDA$, where a polydentate Lewis base precludes association,[5] further support of the Li^+ ion in **3** comes from dimerization [Li1–O1A 1.940(7) Å in $(\mathbf{3})_2$]. Moreover, the structure of **3** contrasts with those of previously noted *ortho*-lithiated aromatic amides[8a,8c] in that external solvent is excluded, presumably by virtue of the crowding effects of TMP and the NMe_2 groups. Instead, and consistent with previous observation,[2c] weak support of the alkali metal is provided by the zincated aromatic carbon atom [2.600(8) Å]. We are not aware of any structural data in the literature on *ortho*-deprotonated aryl carbamates, though oxidative addition has afforded the bis(PPh_3) solvate of *ortho*-metalated ArPdI {Ar = $C_6H_4[OC(O)N(Me)(CH_2CH{=}CH_2)]$}.[13]



$\mathbf{1}^{Et}$ **2** **3**

Scheme 2.

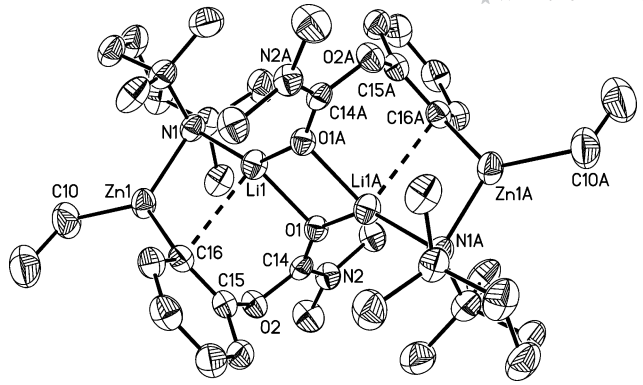
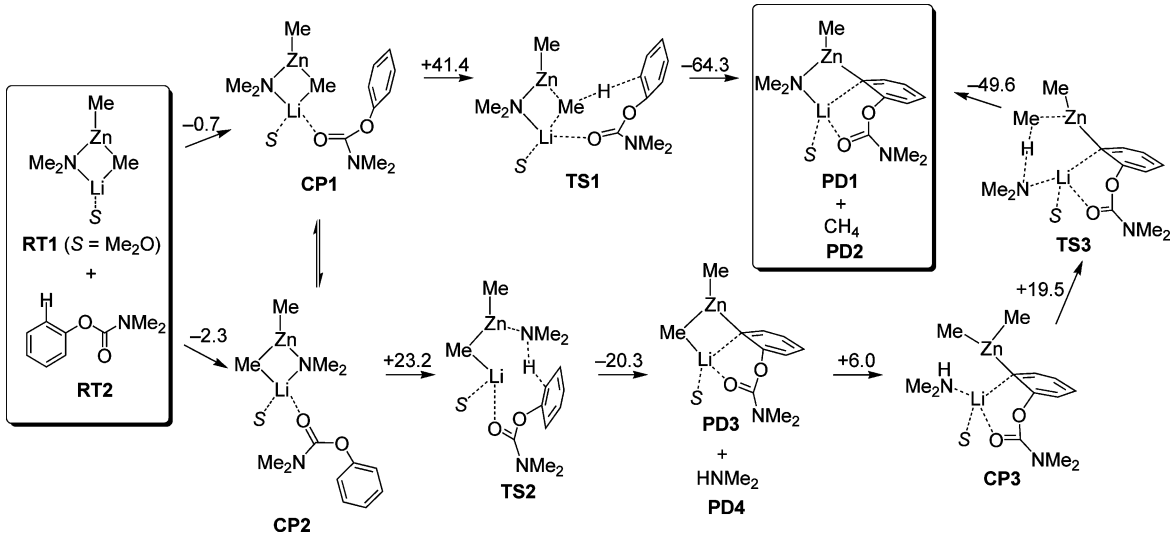


Figure 1. The crystallographic dimer $(\mathbf{3})_2$ shown at 40% probability and with lattice toluene and hydrogen atoms omitted. Selected parameters [Å, °]: C10–Zn1 2.008(5), C16–Zn1 2.055(4), N1–Zn1 2.033(4), N1–Li1 2.057(8), O1–Li1 2.003(8), O1A–Li1 1.940(7); Zn1–C16–C15 126.6(3), N1–Zn1–C16 110.33(15), Zn1–N1–Li1 85.6(2), N1–Li1–O1 128.5(4), N1–Li1–O1A 139.6(4), C16–C15–O2–C14 83.13(46).

As in recent examples of the employment of zincate bases[3,4c] DoM has occurred with overall alkane elimination. Based on theoretical work that points to a stepwise deprotonative mechanism whereby amine elimination is followed by re-coordination at the alkali metal atom with subsequent alkane loss,[4c] we considered that both electronic and steric effects must influence the composition of any isolated organometallic compound. This prompted us to extend our recent calculations on directed metallation[4c] to also consider the relative favourabilities of external solvation of the monomer (e.g. **3**·sol) versus dimerisation (viz. $\mathbf{3}_2$).[12]

The competition between ligand transfer preferences was investigated, the conversions of reagents (**RT**) into pre-reaction complexes (**CP**) and products (**PD**) being optimized at the B3LYP/631SVPs level (Scheme 3).[14] Modeling of direct bridging-alkyl transfer and the conversion of $MeZn(Me)(NMe_2)Li\cdot OMe_2$ (**RT1**) into $MeZn(Ar)(NMe_2)Li\cdot OMe_2$ [**PD1**; ArH = $PhOC(=O)NMe_2$] revealed an exothermic (ΔG = –23.6 kcal/mol) profile with a high activation barrier ($\Delta G^{\ddagger}$ = +41.4 kcal/mol). In contrast, *stepwise* amido ligand exchange (**CP2** → **TS2**) followed by coordination of generated $HNMe_2$ (**PD4**) at the Li^+ ion in $Me_2Zn(Ar)Li\cdot OMe_2$ (**PD3**), with subsequent alkane loss affording **PD1**, showed a low activation barrier for the initial deprotonation ($\Delta G^{\ddagger}$ = +23.2 kcal/mol). While this process was nominally endothermic (ΔG = +0.6 kcal/mol), it was clearly kinetically preferred to direct alkyl exchange. Moreover, and consistent with the observation of **3**, the recombination of **PD3** and **PD4** was significantly exothermic (ΔG = –24.1 kcal/mol, $\Delta G^{\ddagger}$ = +19.5 kcal/mol).

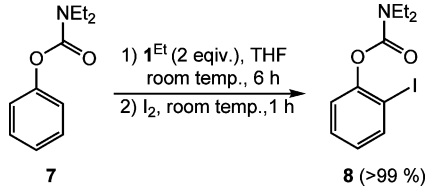
The formation of a dibasic structure type, synonymous with that recently noted for $RZn(\mu\text{-}Ar)_2Li\cdot 2L$ [R = *t*Bu, Ar = $C_6H_4C(O)N(i\text{Pr})_2$-2, L = 0.5(TMEDA) (**4a**); R = Et, Ar = $C_{10}H_6C(O)N(i\text{Pr})_2$-2, L = THF (**4b**)][4c,5] was computed by modeling the reaction of **PD1** with $PhOC(=O)NMe_2$. The data revealed a kinetically plausible ($\Delta G^{\ddagger}$ = +13.3 kcal/mol) but significantly endothermic process (ΔG = +9.5 kcal/mol).[12] In line with this, experimental observation tells us



Scheme 3. Calculated structures and Gibbs free energy changes [kcal/mol] (B3LYP/631SVPs level) for carbamate *ortho*-zincation.

that, for $\mathbf{1}^{Et}$ + **2**, *mono*basicity dominates with **3** dimerising instead. Dimerisation was computed to be nominally exothermic (ΔG = –0.4 kcal/mol for the aggregation of **PD1** with the concomitant loss of two Me_2O molecules).[12] The ramifications of aggregation appear pronounced; the dual action of TMP and the NMe_2 groups remove both the electrostatic need and space for ether solvation (vide supra), and it also prevents the coordination (at Li^+) of unreacted carbamate. This prevents initial complex formation (viz. **CP1/2**) and suggests that, like the presence of strong Lewis base additives,[4c] aggregation acts to limit intermediary zincate reactivity.

A ^{1}H NMR spectroscopic analysis of **3** in [D_8]THF reveals three species in solution at room temperature (labeled #1–#3, see Exp. Sect.).[12] The first of these (#1) is consistent with limited reformation of carbamate **2** on dissolution. This phenomenon, which we have observed before in the study of *ortho*-deprotonated aromatic systems,[8c] could not be eradicated in spite of repeated spectroscopic examinations. The remaining species (#2, #3) analyze as **3** and are tentatively attributable to different aggregation states. Heating of the sample to 50 °C followed by reacquisition of the spectrum at room temperature reveals that these species are replaced by a fourth species (#4). These data point to the Fries rearrangement of *ortho*-zincate **3** and, consistent with this notion, ^{1}H NMR spectroscopy on aliquots obtained from the hydrolytic workup of solutions of **3** in THF reveal signals attributable only to **2** and rearranged 2-hydroxy-*N*,*N*-dimethylbenzamide (**5**) irrespective of whether the solution was exposed to only room temperature or elevated temperatures. We observed consistent behaviour during an examination of the reactivity of **3** with iodine.[12] Combination of $\mathbf{1}^{Et}$ with equimolar amounts of carbamate **2** in THF at –78 °C gave a mixture that was stirred at room temperature for 1 h before being returned to –78 °C and quenched with I_2. Washing and concentration gave an oil. ^{1}H NMR spectroscopy showed that this material comprised 18% rearranged **5** and 28.5% starting material, but that its major component was non-rearranged 2-iodophenyl dimethylcarbamate (**6**) (53.5%). The data improved dramatically when **2** was replaced by its analogue, phenyl diethylcarbamate (**7**). While the *ortho*-lithiate of **7** is known to convert cleanly to 2-iodophenyl diethylcarbamate (**8**) at –78 °C, it undergoes Fries rearrangement to give 2-hydroxy-*N*,*N*-diethylbenzamide (**9**) if allowed to exceed this temperature.[1a] In contrast, reaction of **7** with $\mathbf{1}^{Et}$ (1 equiv.) at room temperature revealed the complete suppression of rearrangement and gave only non-rearranged **8** (53%) and starting material **7** (47%). The use of excess zincate reagent has been shown to encourage higher yields in the past,[2] and in an attempt to encourage reaction we now employed 2 equiv. of $\mathbf{1}^{Et}$, while stirring the reaction mixture at room temperature for 6 h. Analysis of the product revealed complete elimination of Fries rearrangement and essentially quantitative conversion of **7** into **8** (> 99% by NMR spectroscopy, Scheme 4).[12]



Scheme 4.

In conclusion, we have presented the first structural evidence for an *ortho*-deprotonated aryl dialkylcarbamate obtained by DoM. This has been achieved through the targeted use of a heterometallic substrate based on our recognition that zincates such as $\mathbf{1}^{Et}$ react selectively with aromatic species to give stable intermediates *that resist rearrangement*.[6] The structure reveals *ortho*-zincation and the retention of TMP, the presence of which is consistent with a recently described stepwise deprotonative mechanism.[4c] Data suggest the significant resistance of **3** to anionic Fries rearrangement, even after extended periods at

room temperature, with complete stability of the intermediate zincate recorded in the essentially quantitative conversion of *N*,*N*-diethyl analogue **7** into 2-iodophenyl compound **8**. An improved understanding of the mechanism operative here, yielded by the tandem employment of X-ray and DFT analysis, and the discovery that rearrangement can be excluded even at room temperature, are highly relevant from the point of view of reagent design.

Supporting Information (see footnote on the first page of this article): Experimental procedures including spectroscopic data and X-ray crystallographic data for **3**. Full DFT methods and coordinates.

Note Added in Proof (December 11, 2007): The characterization of an *ortho*-zincated aromatic nitrile has recently been reported.[15]

Acknowledgments

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