Structural Basis for Regioisomerization in the Alkali-Metal-Mediated Zincation (AMMMZn) of Trifluoromethyl Benzene by Isolation of Kinetic and Thermodynamic Intermediates

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Abstract: Performed with a desire to advance knowledge of the structures and mechanisms governing alkali-metal-mediated zincation, this study monitors the reaction between the TMP-dialkylzincate reagent [[(TMEDA)Na(TMP)](Bu)Zn(Bu)] 1 and trifluoromethyl benzene C6H4-CF3 2. A complicated mixture of products is observed at room temperature. X-ray crystallography has identified two of these products as ortho- and meta-regiosomers of heterotrianionic [(TMEDA)Na(TMP)(C6H4-CF3)Zn(Bu)], 3-ortho and 3-meta, respectively. Multinuclear NMR data of the bulk crystalline product confirm the presence of these two regioisomers as well as a third isomer, 3-para, in a respective ratio of 20:11:1, and an additional product 4, which also exhibits ortho-zincation of the aryl substrate. Repeating the reaction at 0 °C gave exclusively 4, which was crystallographically characterized as [(TMEDA)2Na][Zn(C6H4-CF3)(Bu)3]. Mimicking the original room-temperature reaction, this kinetic product was subsequently reacted with TMP(H) to afford a complicated mixture of products, including significantly the three regioisomers of 3. Surprisingly, 4 adopts a solvent-separated ion pair arrangement in contrast to the contacted ion variants of 3-ortho and 3-meta. Aided by DFT calculations on model systems, discussion focuses on the different basicities, amido or alkyl, and steps, exhibited in these reactions, and how the structures and bonding within these isolated key metallic intermediates (prior to any electrophile interception step), specifically the interactions involving the alkali metal, influence the regioselectivity of the Zn–H exchange process.

Introduction

Organic reagents play a pivotal role in many fundamental organic reactions, being among the most commonly utilized reagents in synthesis.1 Their main attractions are their marked “soft nucleophilicity” and exceptional functional group tolerance; however, their poor kinetic reactivity has limited their applications in deprotonative metalation (Zn–H exchange reactions).2 Notwithstanding, recent breakthroughs in the area have established that this drawback can be circumvented by pairing organozoic reagents with a group 1 organometallic compound to form alkali metal zincates.3 Among these mixed-metal reagents, TMP-dialkyl zincates [MZn(TMP)R2] (M = Li, Na, K; TMP = 2,2,6,6 tetramethylpiperidide) have risen to prominence as powerful deprotonating agents that allow the direct zincation of aromatic substrates that usually are inert toward conventional organozoic reagents, including benzene, anisole, toluene, naphthalene, pyridines, indoles, benzamides, benzonitriles, or anilines to name a few. These deprotonations where the departing hydrogen in the H exchange process.

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molecule is replaced by zinc but that require the presence of an alkali-metal to succeed have been branded as examples of alkali-metal-mediated zinication (AMMZn).\(^3\) The use of this mixed-metal approach has enabled the performing of special metatarsations exhibiting unique regioselectivities that cannot be reproduced by classical monometallic reagents such as alkyl lithiums or lithium amides. Furthermore, as recently highlighted in Science,\(^{15}\) the synergic entrapment of highly sensitive anions such as α-metalled THF can be accomplished without any ring-opening or cleavage when THF is reacted with the sodium zinicate \(\text{[TMEDA}Na(TMP)(\text{CH}_2\text{SiMe}_3)\text{Zn(CH}_2\text{SiMe}_3)]\).

First introduced in 2005, another sodium zinicate \(\text{[TMEDA}Na(TMP)'(\text{Bu})\text{Zn('Bu)]}\) (1) is an effective and versatile zinctoring agent for a wide range of aromatic molecules.\(^4\) Structurally mapping these reactions (by X-ray crystallography) confirmed that these deprotonations are genuine zincations, and also mapping these reactions (by X-ray crystallography) confirmed these structural studies only provide evidence on the starting agent for a wide range of aromatic molecules. \(^5\) Structurally the most acidic sites in the first time compelling experimental evidence of the possibility of a two-step mechanism for these TMP-zincates.

In a second step, the intermediate \(\text{[TMEDA}Na(aryl)'(\text{Bu})\text{Zn('Bu)]}\) reacts with concomitant TMP(H) giving \(\text{[TMEDA}Na(TMP)(aryl)Zn('Bu)]\) and isobutane, in agreement with the overall alkyl basicity observed experimentally.

In spite of these insightful theoretical studies, to date the proposed reaction intermediates \(\text{[TMEDA}Na(aryl)'(\text{Bu})\text{Zn('Bu)]}\) have not been detected even when the deprotonations are performed at subambient temperatures. In a closely related study for the AMMzinc of anisole by the analogous lithium TMP-zinicate \(\text{[THF}Li(TMP)'(\text{Bu})\text{Zn('Bu)]}\),\(^{17}\) we have prepared the putative intermediate \(\text{[THF}LiZn(C}_6\text{H}_4-O\text{Me('Bu)]}\) suggested by the theoretical studies via an indirect route (cocomplexation of ortho-lithiated anisole with 'Bu2Zn, combined with a lithium—zinc transfer, Scheme 2) and explored its reactivity toward TMP(H), mirroring the second step of the theoretically studied process. The outcomes of this study have provided for the first time compelling experimental evidence of the possibility of a two-step mechanism for these TMP-zincates.

Herein we extend our mechanistic and structural studies to the metatation of the aromatic substrate trifluoromethyl benzene (2) by the bimetallic base 1. From a merely electronic point of view, the most acidic sites in 2 should be the ortho-protons due to the activating inductive effect of the CF3 group.\(^{18}\) However, on the other hand, ortho-deprotonation can be disfavored by the steric hindrance exerted by this functional group which is a rather large sterically demanding substituent (intermediate between an α and a β group).\(^{19}\) Thus, it can be anticipated that the regioselectivity of these deprotonation reactions will be largely dominated by the counterbalance of these two fundamental effects. Previous studies by Roberts and Curtin have shown that when 2 is treated with 'BuLi in refluxing hexane, followed by quenching with carbon dioxide, a 100:4:1 mixture of the ortho-, meta- and para- isomers of the relevant carboxylic acid in a 33–48% yield is obtained.\(^{20}\)

More recently Schlosser has reported the regioselective deprotonation of 2 when reacted with superbasic LICKOR reagent at −75 °C which suggest that these deprotonations occur via a two-step mechanism where kinetically the sodium zinicate acts first as an amide deprotonating the aromatic molecule (Scheme 1) to form a bisalkyl(aryl) intermediate and releasing concomitantly TMP(H).

Scheme 1

\begin{align*}
\text{Na(TMP)} & \quad \text{Bu} \\
\text{H}_2\text{C} & \quad \text{Zn} \\
\text{H}_2\text{C} & \quad \text{Bu} \\
\text{H}_2\text{C} & \quad \text{Zn} \\
\text{H}_2\text{C} & \quad \text{Bu} \\
\text{H}_2\text{C} & \quad \text{Zn} \\
\end{align*}

Scheme 2

\begin{align*}
\text{Li} & \quad \text{Zn} \\
\text{H}_2\text{C} & \quad \text{Zn} \\
\text{H}_2\text{C} & \quad \text{Zn} \\
\text{H}_2\text{C} & \quad \text{Zn} \\
\end{align*}

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allows the preparation of 2-(trifluoromethyl)benzoic acid in a 94\% yield.\textsuperscript{21} However, information regarding the characterization or isolation of the relevant metalated intermediates, prior to an electrophilic quenching protocol, has not yet been forthcoming. Starting to fill this important gap of knowledge, in this work we report the first intermediates of AMM$^+Zn$ of trifluoromethyl benzene 2 using sodium zinicate 1 which affords a mixture of ortho, meta and para regioisomers of [(TMEDA)$^-$Na(TMP)](C$_6$H$_4$CF$_3$)Zn(Bu)] (3) in a 4.3:2.6:1.0 ratio.\textsuperscript{22} Furthermore, this report includes, to the best of our knowledge, the first successful isolation and spectroscopic/crystallographic characterization of a key reaction intermediate, obtained via the actual experimental conditions used to perform direct zinication of trifluoromethyl benzene demonstrating that these direct zinication reactions indeed proceed via a two-step mechanism. The kinetic product surprisingly has the solvent-separated formulation [(TMEDA)$_2$Na]$^-$[Zn(C$_6$H$_4$CF$_3$)(Bu)]$^+$ (4). Furthermore, mimicking the second proposed step predicted by the theoretical calculations, we also report the reaction of 4 with TMP(H), in which $^1$H NMR monitoring reveals key implications for the final outcome of the reaction, affecting the yield and the regioselectivity of the AMM$^+Zn$ of 2. In addition, to quantify and provide an explanation for these different regioselectivities encountered, a theoretical study using DFT calculations has been carried out.

Results and Discussion

Sodium TMP-zinicate 1 was prepared in situ in hexane solution and reacted with one molar equivalent of trifluoromethyl benzene 2 at room temperature, affording a yellow solution that on cooling deposited colorless crystals. Multinuclear ($^1$H, $^{13}$C, and $^{19}$F) NMR spectroscopic analysis of these crystals evidenced that 2 has been deprotonated, affording a complex mixture of products (Scheme 3). $^1$H and 2D-$[^1$H,$^1$H] COSY NMR spectra from deuterated benzene solution revealed the presence of the three possible regioisomers for the monometalation of 2 (Figure 1a and Table 1). Thus, four multiplets at 7.85, 7.54, 7.19, and 6.98 ppm are observed for the major ortho-metalated product (3-ortho), three multiplets at 7.74, 7.34, and 7.06 ppm and a singlet at 8.14 ppm for the next most abundant meta-product (3-meta), and two doublets at 7.71 and 7.42 ppm for the minor para-product (3-para) (Figure 1a and Table 1) in a 20:11:1 ratio. In addition, another para-metalated product, different from 3-ortho, 4 is evident (from four multiplets at 8.06, 7.51, 7.20, and 6.96 ppm) (Figure 1a and Table 1). A $^{19}$F NMR spectrum displayed four different signals at $-$59.9, $-$61.5, $-$61.7, and $-$61.8 ppm (see Experimental Section) in agreement with the presence in solution of four distinct organometallic species.

X-ray crystallographic studies established the molecular structures of 3-ortho and 3-meta. Thus, in a single crystal a mixture of the ortho and meta regioisomers of 3 in a respective ratio of 91:9$\%$ was found, with the asymmetric unit consisting of one molecule of 3-ortho and one site occupied by a disordered mixture of 3-ortho and 3-meta (Figures 2a and 2b).\textsuperscript{23} Exhibiting contacted ion pair structures, both molecules contain a Na-TMP-Zn backbone where TMEDA chelates to sodium and a tert-butyl group binds terminally to zinc. This backbone is also present in the bimetallic base 1. As previously observed for other products of AMMZn, zinc fills the position previously occupied by a hydrogen atom, adopting a distorted trigonal planar geometry, lying almost coplanar with the aromatic ring and forming a strong Zn$-$C $\sigma$-bond. However, the structures of 3-ortho and 3-meta differ strikingly in the manner in which the metalated arene engages with the alkali-metal. For 3-ortho one fluorine atom of the CF$_3$ group binds with the sodium center, closing a seven-membered [NaN$\equiv$ZnCCF$_3$] ring (Figure 2a) and no interaction exists between the aromatic ring and the alkali metal. In contrast, for 3-meta, sodium $\pi$-engages with the aromatic ring, interacting primarily with the meta-carbon (that has experienced the metalation and therefore carries most of the developed negative charge), which gives rise to a four-membered [NaN$\equiv$ZnC] ring with the CF$_3$ group situated too far from the alkali metal to form any type of contact. This distinct $\alpha/\pi$ bonding mode for Zn and Na respectively has become a general feature observed for AMMZn products derived from nonheteroatom-substituted arenes,\textsuperscript{3} as for example in [(TMEDA)$^-$Na(TMP)(meta-C$_6$H$_4$CH$_3$)Zn(Bu)] obtained by reaction of 1 with toluene,\textsuperscript{8} which exhibits a structure identical in its key features to that displayed by 3-meta. Unfortunately the disorder and high displacement parameters affect the precision of this structure and thus prevent discussion of the bond lengths or bond angles though the connectivity is definite. That notwith-
standing, 3-ortho and 3-meta represent to the best of our knowledge the first examples of metalated intermediates of trifluoromethyl benzene to be structurally elucidated. In order to determine the molecular structures of the compounds 3-para and 4 (which are also formed in the reaction of 1 with 2 at room temperature) X-ray crystallographic studies of several crystals were attempted. However the only crystals suitable for these analyses proved to be the same mixture of 3-ortho/3-meta regioisomers (vide supra).24

In an attempt to modulate the regioselectivity of the zincation of 2 and to trap other reaction intermediates that could shed light on the identity of the other metalated species observed (labeled as 4 in Figure 1), trifluoromethyl benzene 2 was reacted with 1 in hexane at the lower temperature of 0 °C (cf. -the earlier preparation at room temperature) for 30 min. The resulting pale yellow solution was placed in the freezer (−30 °C) affording colorless crystals. The comparatively simple 1H NMR spectrum of these crystals in deuterated benzene solution revealed that under these reaction conditions, compound 4 is the only product obtained whereby substrate 3 has been selectively ortho-metalated (four multiplets at 8.06, 7.51, 7.20, and 6.96 ppm) (Figure 1b). Furthermore, the analysis of the aliphatic region of both 1H and 13C[1H] NMR spectra showed relevant resonances for tert-buty1 and TMEDA ligands (see Experimental Section for details); however, no signals attributable to a TMP group were observed. A 19F[1H] NMR spectrum displayed a single resonance at −61.2 ppm.

Determined by X-ray crystallography, the solvent-separated ion pair [(TMEDA)2Na]1+[Zn(C6H3−CF3)(Bu)2]− (4) adopts a significantly different structural motif from that observed for 3-ortho or 3-meta (Figure 3). Thus its anion comprises a molecule of trifluoromethyl benzene selectively ortho-deprotonated and two tert-buty1 groups bonded to zinc, whereas the cation comprises a sodium center tetrahedrally coordinated by two TMEDA molecules. There is disorder in the positions of the tBu groups in the structure of 4 which precludes a detailed discussion of the bond distances and angles. Nevertheless, this bis(alkyl)-aryl sodium zincate represents the first truly kinetic intermediate of an AMMZn reaction of an aromatic molecule to be isolated and structurally defined, which proves unequivocally that these deprotonations must proceed via a two-step mechanism; as previously proposed by theoretical studies (Scheme 1),16 where TMP-zincate 1 deprotonates arene 2 by sequential combination of amido/alkyl basic behavior. As mentioned in the introduction and within the context of lithium zinicates and the deprotonation of anisole, we have recently reported an experimental study which strongly supported this two-step mechanism; however, the putative TMP-free kinetic intermediates have to be prepared using an indirect route (cocomplexation approach) since their formation could not be detected in the actual AMMZn reaction.17 Compound 4 is isolated in a 22% yield, however, when the reaction is carried out in the presence of a molar equivalent of TMEDA (additional to that in precursor 1), this yield can be improved to 49%. Note that the isolated crystals of 4 are pure and so is the only ortho-zincated product deposited from the solution. Furthermore, NMR monitoring of the reaction filtrates confirms it is also the major product in the remaining solution with only small amounts of 3-ortho, 3-meta, and 3-para (as a consequence of the second step of the reaction starting to take place).

These results prompted us to pursue the reaction of 4 with the amine TMP(H), in order to replicate the anticipated second

### Table 1. Aromatic Chemical Shifts in the 1H NMR Spectra of 3–4 in C6D6 Solution

| compound | δ(Ha) | δ(Hb) | δ(Hc) | δ(Hd) |
|----------|-------|-------|-------|-------|
| [Na(TMP)(o-C6H4−CF3)Zn(tBu)] (3-ortho) | 7.54 (d) | 7.19 (t) | 6.98 (t) | 7.85 (d) |
| [Na(TMP)(m-C6H4−CF3)Zn(tBu)] (3-meta) | 7.34 (d) | 7.06 (t) | 7.74 (d) | 8.14 (s) |
| [Na(TMP)(p-C6H4−CF3)Zn(tBu)] (3-para) | – | – | – | – |
| [(Na(TMEDA)2)[Zn(tBu)(o-C6H4−CF3)]] (4) | 7.51 (d) | 7.20 (t) | 6.96 (t) | 8.06 (d) |

**Figure 2.** Molecular structures of (a) 3-ortho and (b) 3-meta. Hydrogen atoms and other disorder components are omitted for clarity.
The process, far from being a simple substitution of a deprotonation, revealed that the second step of the AMM was introduced. 

\[ \text{1H NMR monitoring of the reaction provided in deuterated benzene and a stoichiometric amount of TMP(H) were reacted with iodine (preventing the second step from taking place), which greatly affects the final outcome of the metalation, not only by diminishing the yield but also by altering the regioselectivity of the aromatic deprotonation reaction. It should be stressed that much of this information on how amido(dialkyl)zincates operate would be hidden if the reactions were performed in situ then followed by electrophilic quenching. To explain, when trifluoromethyl benzene 2 is reacted with one molar equivalent of the bimetallic base 1 at room temperature followed by treatment with iodine, a 6:2.3:1 mixture of ortho, meta, and para isomers of iodo(trifluoromethyl)benzene is obtained in a modest 45% yield. This low yield, which now can be explained in terms of the competitive reaction of TMP(H) (generated in the first step of the reaction) with the metlated arene group of the kinetic intermediate 4, can be improved to 92% when two equivalents of zincate 1 are employed. In addition, the amount of ortho-iodo(trifluoromethyl)benzene observed arises from the combined electrophilic quenching of the two different organometallic compounds 3-ortho and 4. Furthermore, a comparison of this ratio of products with that observed for the metalated intermediates in the reaction of 4 with one equivalent of TMP(H) (a 6.3:2.6:1 ratio of the metalated products at the ortho (combined ratio of 3-ortho and 4), meta (3-meta) and para (3-para) positions) demonstrates that by reacting 4 with TMP(H), we are genuinely mimicking the second step involved in the AMMZn of 2. In contrast, if isolated crystals of the kinetic product 4 are reacted with iodine (preventing the second step of the AMMZn to from taking place), ortho-iodo(trifluoromethyl)benzene is formed exclusively in almost quantitative yields.

To shed some light upon the unconventional control on the regioselectivity of this reaction, where the second step of the AMMZn seems to play a key role, theoretical calculations at the DFT level using the B3LYP method and the 6-311G** basis set were employed to compute the relative stabilities of the three possible regioisomers of 3, in which trifluoromethyl benzene 2...
is deprotonated at the ortho (3A), meta (3B), or para (3C) positions. In support of the experimental findings we find that the ortho isomer (3A) is energetically the most preferred (relative energy: 0.00 kcal mol\(^{-1}\)), closely followed by 3B (+2.31 kcal mol\(^{-1}\)) and then 3C (+2.75 kcal mol\(^{-1}\)). Our theoretical studies also show that the reaction of sodium zinicate 1 with 2 to yield 3 is exothermic by −27.16 kcal mol\(^{-1}\). The modest difference in the relative energies obtained for the three possible regioisomers of 3 could explain the experimentally observed isomerization of some of 3-ortho to 3-meta and 3-meta (vide supra), which is in sharp contrast with the larger difference in the relative energies when the deprotonation of 2 was modeled using the conventional monometallic reagent BuLi/TMEDA,29 where the ortho-metalated product is the minimum-energy structure (by 7.48 and 10.58 kcal mol\(^{-1}\) from the meta and para isomers respectively).

Table 2. Selected Bond Distances (Å) Calculated for the Three Theoretical Regioisomers 3A–C

|           | 3A (ortho) | 3B (meta) | 3C (para) |
|-----------|------------|-----------|-----------|
| Zn···Cmetalated | 2.132      | 2.101     | 2.094     |
| Na···Cmetalated | 2.860      | 2.703     | 2.652     |
| Na···FCF\(_3\) | 2.435      | 4.986     | 5.464     |
| Na···Caryl | 3.349, 3.741, | 3.200, 3.565, | 3.120, 3.231, 4.468, 4.765, 5.083 | 3.969, 4.445, 3.950, 4.040, 4.621 | 4.439 |

This view of the importance of the alkali metal is supported by previous structural elucidations of key metalated intermediates from the reactions of 1 with other substituted aromatic molecules which show that, when their substituents possess strong Lewis donor groups, as for example in N,N-diisopropylbenzamide,12a sodium interacts with the basic heteroatom of the functional group and the deprotonation occurs exclusively at the ortho position. On the other hand, when the aromatic substrate lacks a heteroatomic functional group that can coordinate strongly to the alkali metal (as in N,N-dimethylaniline\(^{14}\) where the lone pair on the nitrogen is not available for coordination since it is involved in conjugation with the aromatic ring), then the interaction of sodium takes place through metal−π arene interactions directing the deprotonation to the position in the molecule where these π contacts\(^{31}\) are maximized (in this case the meta position). Furthermore, it is only when the latter scenario occurs that unusual regioselectivities are observed for AMMZn reactions, at positions not available for conventional monometallic reagents, where these favorable π-interactions between the metalated substrate and sodium are not feasible.\(^8\),\(^9\),\(^14\)

In general for substrate 2, the CF\(_3\) substituent can be considered as a weak ortho-directing group (in comparison with other more powerful directing groups such as sulfones, tertiary amides or carbamates, to name a few),\(^32\) where the metalation is directed almost entirely by the inductive acidifying effect of the CF\(_3\) group. Notwithstanding, the large steric hindrance exerted by this group and the poor donor ability of highly electronegative fluoride atoms to coordinate to the organometallic base can hinder ortho-metalation of 2. Using alkali-metal zinicate 1 as a base, we can propose that for formation of kinetic product 4, which exhibits a solvent-separated ion pair structure, and therefore contains no interactions between sodium and the metalated substrate, the coordination and steric effects of the CF\(_3\) group do not greatly influence the regioselectivity of the reaction, which occurs exclusively at the ortho position, removing the most acidic proton in 2. However, for the thermodynamic products, (3-ortho, 3-meta, and 3-para) which involve the formation of contacted ion pair species, although the acidifying effect of the CF\(_3\) group is still dictating the regioselectivity of the reaction with formation of ortho-metalated 3-ortho as the major product, the isomerization of some of this compound to the meta and para isomers (3-meta and 3-para), which appear relatively close in stability, must also take place. This could probably be a consequence of the competing Na···C π stabilizing interactions of the metalated aryl with the relatively weak Na···F dative bond, which experimentally translates into the formation of a 6:2:3:1 ratio mixture of 3-ortho, 3-meta, and 3-para.

Collectively, these results show for the first time that AMMZn reactions can exhibit distinct kinetic/thermodynamic regioselectivities. In the first step of the reaction, which involves the formation of solvent-separated ion pair compounds,\(^33\) steric effects will be of less importance, as the cation species is not covalently bound to the anionic component, and no communication between sodium and zinc is possible. Therefore deprotonation/zincation will occur at the most acidic position (following the same principles as conventional monometallic reagents).\(^34\) However, in the second step, by regenerating the synergic bridge TMP, the regioselectivity of the reaction can change, where the cooperative effect of both metals can induce an isomerization on the metalated aryl product where the interaction between sodium and the metalated arene will be more favored, allowing
Conclusions

The AMM[Zn] of trifluoromethyl benzene (2) by sodium
zincate [(TMEDA)Na(TMP)(tBu)Zn(tBu)] (1) has been structur-
ally mapped by isolation of the kinetic [(TMEDA)Na]2
−
[(Zn(C6H4−CF3)Li(TMEDA)] (4) and thermodynamic [(TMEDA)Na(TMP)(C6H4−CF3)Zn(tBu)] (3) products providing the first ex-
perimental proof that these bimetallic bases operate by a
combination of kinetic amide/thermodynamic alkyl basicity.

(23) The asymmetric unit of this molecule has two inde-
pendent complexes, one of them is 3-ortho and
the other one contains an approxi-
mately 5:1 [0.828:0.172(s)] disordered mixture of 3-ortho and 3-meta, giving
overall a ratio of almost 11:1 for these two isomers in the crys-
tal structure.

(24) For 3-para a structural motif similar to that observed for 3-meta can be proposed, in which sodium atom will form a π-contact with the
para-carbon as observed previously for the related product of toluene
zincation, [(TMEDA)Na(TMP)(para-C6H4−CH3)Zn(tBu)], ref 8.

(25) It must be noted that 1H NMR spectroscopic monitoring of a solution of
isolated crystals of 4 in deuterated benzene over a 4 day period
showed no isomerisation of 4 to related meta or para products.

(26) The presence of free 2 could also be attributed to the partial hydrolysis
of the organometallic species 3 or 4 in deuterated benzene solution.
However we can rule out this possibility since formation of
2 could not be observed in solutions of compounds 3 and 4 monitored by
1H NMR spectroscopy over 3 days.

(27) Compound 1 reacts with the deuterated solvent CD6 (ref 5); therefore,
although it must be formed in the competing reaction of 4 with
TMP(H) that yields to the formation of 2 (reaction pathway i, Scheme 4), it could not be detected.

(28) This ratio has been determined using the integration values of the
1H NMR spectrum of the reaction of 4 with one equivalent of TMP(H)
(Figure 1c).

(29) These theoretical calculations have been carried out modeling the
monomeric base and the metated products as dimeric [{BuLi
(TMEDA)}2] and [{(C6H4−CF3)Li(TMEDA)}2]; see Supporting
Information for full details.

(30) For selected examples of structurally characterised compounds which
contain Na···F dative interactions, see: (a) Dias, H. V. R.; Jin, W.;
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Diodone, R. J. Am. Chem. Soc. 1996, 118, 356. (c) Jolas, J. L.; Hoppe,
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Forsyth, C. M.; Junk, P. C.; Wang, J. Chem.— Eur. J. 2009, 15, 3082.

(31) For key references to electrostatic π interactions between alkali metals
and aromatic molecules, see: (a) Ma, J. C.; Dougherty, D. A. Chem.
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A. R.; Mulfrey, R. E.; Roberts, B. A.; Rowlings, R. B. Organometallics
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(32) For key reviews of DoS see: (a) Ancill, E.; Snieckus, V. The Directed
ortho Metallation-Cross Coupling Nexus. Synthetic Methodology for
Aryl–Aryl and Heteroaromatic–Aryl Bonds. In Metal-Catalyzed
Cross-Coupling Reaction; 2nd ed.; Diederich, F., de Meijere, A., Eds.;
Wiley-VCH: New York, 2002; Vol. 330, p 367.

(33) Compound 4 contains two molecules of TMEDA which facilitates the
formation of the solvent-separated ion pair structure. In the absence
of the additional equivalent of TMEDA (which aids its crystallisation),
4 could exhibit a pseudo solvent-separated ion pair structure, similar
to that reported for kinetic intermediate [(PMDETA)Li(C3H6
−OME)Zn(tBu)]; (prepared by indirect route, Scheme 2, ref 17) where
the metals are separated by a large distance (>5 Å).

(34) For selected examples of direct Zn–H exchange reactions using other
alkali-metal zincates, see: (a) Wunderlich, S. H.; Knochel, P. Angew.
Chem., Int. Ed. 2007, 46, 7685. (b) Wunderlich, S. H.; Knochel, P. Org.
Lett. 2008, 10, 4705. (c) L’Helgoual’ch, J. M.; Seggio, A.;
Chevallier, F. I.; Yonehara, M.; Jeannet, E.; Uchida, M.; Mongin,
J.Org. Chem. 2008, 73, 177. (d) Wunderlich, S. H.; Knochel, P. Chem.
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lich, S. H.; Unnisa, A.; Li, J.; Knochel, P. Chem.— Eur. J. 2009, 15,
457. (f) Wunderlich, S. H.; Rohrbogner, C. J.; Unnisa, A.; Knochel,
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Thus, in the first step of the reaction arenè 1 is selectively ortho-
 deprotonated to give solvent-separated ion pair 4 with concomitant
release of TMP(H), which in turn reacts to produce contacted ion
pair 3 (affording a mixture of the ortho, meta, and para regiois-
omers) and isobutane. Simulating the second, multipart-step of the
AMM[Zn] process by reacting isolated crystals of 4 with TMP(H)
in deuterated benzene and monitoring the reaction by 1H NMR
spectroscopy, shows that, far from playing a minor role, this second
step, strongly influences the final outcome of the AMM[Zn] process,
afflicting not only the yield of the reaction but also the final regio-
selectivity of the metatalation. To elaborate, a complex mixture
of products is observed in solution that includes unreacted 4, a
mixture of the three possible regioisomers of 3, ortho, meta, or
para (in a 4.3:2:6:1 ratio, resulting from the amination reaction of
TMP(H) with one ‘Bu group of 4), and trifluoromethyl benzene
2 (obtained by the competing reaction of the amine with the meta-
tated alkyl ligand of 4).

In addition DFT studies probing the reaction of 1 with 2 to
generate 3, showed that of the three possible regioisomers for
this reaction, although the ortho structure is energetically the
most preferred, the meta and para isomers are very close in
energy (both of them almost equally favored) to it, which could
explain the experimentally observed isomerization of some of
3-ortho into 3-para and 3-meta. Analysis of the dimensions of
the modeled structures,— suggest that this isomerization could
be partly due to the competing Na···C π stabilizing interactions
of the metatalated aryl present in the meta and para structures
with the Na—F dative bonding displayed in the ortho-isomer.
These results show that depending on the type of preferred
interaction between the alkali-metal and the metatalated mole-
cule in the contacted ion pair structures, the kinetic and ther-
modinic regioselectivities of the AMM[Zn] can be adjusted.

These findings not only highlight the complexity of these
metatalation reactions but also draw attention to the significance
of structurally identifying the metatalated intermedia-
tes which otherwise, if these reactions were carried out in situ
followed by subsequent electrophilic interception, would have
remained hidden.

Finally, we believe this study provides a greater understanding of the
mechanisms involved in direct zincation of aromatic molecules by
TMP-dialkyl zincate bases and may contribute to
further advances in the area of alkali-metal-mediated zincation
generally, in particular to rationalize the unusual regioselectivities
observed when bimetallic base 1 is employed which can be
explained in part by the different structures of the kinetic
and thermodynamic intermediates. In the former there is no metal—
metal communication, whereas in the latter Na and Zn are connected by
a TMP bridge that facilitates the interaction of sodium with the
deprotonated arenè, which seems to play a defining role in the
regioselectivity observed in the final AMM[Zn] product.

Experimental Section

General. All reactions were performed under a protective argon
atmosphere using standard Schlenk techniques. Hexane, THF and
toluene were dried by heating to reflux over sodium benzophenone
ketyl and distilled under nitrogen prior to use. [(TMEDA)Na(TMP)-
(Bu)Zn(Bu)] (1)1 was prepared according to literature methods. NMR
spectra were recorded on a Bruker DPX 400 MHz spectrometer,
operating at 400.13 MHz for 1H, 376.36 MHz for 19F{1H} and 100.62
MHz for 13C{1H}.

Reaction of [(TMEDA)Na(TMP)‘(Bu)Zn‘(Bu)] (1) with Trifuoro-
 methylene Benzene (2) at Room Temperature. A Schlenk tube was
charged with 2 mmol (0.358 g) of Zn(Bu)2, which was dissolved in
10 mL of hexane. In a separate Schlenk tube, 2 mmol of BuNa
(0.16 g) was suspended in 10 mL of hexane and one molar equivalent of TMP(H) (2 mmol, 0.34 mL) was added via syringe. The resultant creamy white suspension was allowed to stir for an hour, after which the hexane solution containing Zn/Bu₂ was added via syringe. The suspension changed from creamy white to a yellow hue (seemed to be less solid, but required TMEDA for it all to dissolve into solution). This was followed by the addition of a molar equivalent of TMEDA (2 mmol, 0.30 mL). The resultant suspension was heated gently to form a yellow solution which was allowed to cool to ambient temperature. Then, 2 mmol (0.25 mL) of trifluoromethyl benzene was added to the solution and it was allowed to stir at room temperature for 2 h before being moved to the freezer to aid crystallization. A large crop (0.52 g) of colorless crystals formed in solution which were suitable for analysis. Multinuclear (1H, 13C, and 19F) NMR spectroscopy confirmed the presence of a mixture of 3-ortho, 3-meta, and 3-para and 4 in 20: 11:1:8 ratio. 1H NMR (400.13 MHz, 298 K, CD₆D₆) δ 8.14 (1H, s, H₃, 3-meta), 8.06 (0.71H, d, H₄, 4), 7.84 (1.79H, d, H₆, 3-ortho), 7.74 (1.02H, d, H₅, 3-meta), 7.71 (0.19H, d, H₆, 3-para), 7.54 (1.78H, d, H₄, 3-ortho), 7.51 (0.72H, d, H₃, 4), 7.42 (0.19H, d, H₅, 3-para), 7.34 (1.03H, d, H₄, 3-meta), 7.22–7.17 (2.09H, m, H₃, 3-ortho and H₄, 4), 7.06 (1.03H, t, H₂, 3-meta), 7.00—6.96 (2.59H, m, H₃, 3-ortho and H₄, 4), 2.12—1.75 (m,broad, H₃ and H₅, TMP), 1.58—1.42 (m, broad, overlapping), CH₃, TMP, CH₃ and CH₂, TMEDA, and CH₃Bu group, 1.21, 1.14, 1.09 (s, broad, CH₃, TMP). (See Table 1 for labeling scheme of aromatic protons.) 13C{1H} NMR (100.62 MHz, 298 K, C₆D₆): δ 141.7, 140.2, 139.3, 138.5, 137.6, 137.7, 137.1, 134.3, 130.1, 129.5, 127.0, 129.5, 125.6, 124.7, 124.03, 123.6, 122.0 (C₆), 56.7 (CH₂, TMEDA), 52.4, 52.5 (C₆, TMP), (CH₃, TMEDA), 40.9, 40.2, 39.2 (C₆, TMP), 36.5, 36.0, 35.6, 35.4, 35.3 (CH₃, TMP), 35.1, 35.0, 34.9 (CH₃, Bu), 20.4, 20.1 (C₆, TMP) (the relevant resonances for the CF₃, Cipso, Zn—Caryl could not be detected). 19F{1H} NMR (298 K, CD₆D₆): δ −59.9, −61.5, −61.7, −61.8. 

**Reaction of [TMEDA Na(TMP)(Bu)Zn(Bu)] (1) with Trifluoromethyl Benzene (2) at 0 °C**. The above-mentioned procedure was repeated to prepare a solution of the base (1) (2 mmol) in situ in hexane. The resulting light yellow solution was cooled to 0 °C via an ice bath before trifluoromethyl benzene (0.25 mL, 2 mmol) was added. The yellow solution was immediately transferred to the refrigerator (at 5 °C) to aid crystallization. A crop of colorless prismatic crystals of 4 were deposited from the solution (0.26 g 22%). This yield can be increased to 49% (0.58 g) if an additional molar equivalent of TMEDA is introduced (2 mmol, 0.30 mL). 1H NMR (400.13 MHz, 298 K, CD₆D₆) δ 88.06 (1H, d, H₄, 4), 7.51 (0.1H, d, H₅, 4), 7.20 (1H, t, H₆, 4), 6.96 (1H, t, H₇, 4), 1.85—1.71 (32H, m, broad overlap), CH₃, and CH₂, TMEDA), 1.45 (18H, s, CH₃, Bu). 13C{1H} NMR (100.62 MHz, 298 K, CD₆D₆) δ 140.0, 130.1, 125.5, and 124.01 (C₆, C₅, C₄, and C₃), 57.3 (CH₂, TMEDA), 45.5 (CH₃, TMEDA), 30.9 (CH₃, Bu), 21.4 (Zn—C, Bu) (the relevant resonances for the remaining quaternary carbons in 4, CF₃, Cipso, Zn—Caryl could not be detected). 19F{1H} NMR (298 K, CD₆D₆): δ −61.2.

### Table 3. Crystallographic Data

|   | 3     | 4     |
|---|-------|-------|
| Chem form | C₂₅H₄₆F₄N₄NaZn | C₂₅H₄₆F₄N₄Na⁺·C₁₂H₂₂F₄Zn⁻ |
| Form wt | 547.0 | 580.1 |
| Cryst syst | monoclinic | triclinic |
| Space group | P2₁/c | P1 |
| a, Å | 18.935(4) | 10.4379(4) |
| b, Å | 10.6094(9) | 10.5920(4) |
| c, Å | 30.382(6) | 17.3032(7) |
| a, deg | 88.910(3) |
| β, deg | 103.88(2) | 89.721(3) |
| γ, deg | 60.559(2) |
| V, Å³ | 5970.4(18) | 1665.65(11) |
| Z | 8 | 2 |
| Reflns measd | 36191 | 14089 |
| Unique reflns | 7682 | 5341 |
| Rint | 0.076 | 0.060 |
| Refined params | 831 | 633 |
| Restraints | 1171 | 1982 |
| R(F, F² > 2σ) | 0.102 | 0.071 |
| R(B, all data) | 0.205 | 0.202 |
| GoF (F², all data) | 1.186 | 1.118 |
| Max, min el dens, e Å⁻³ | 0.60, −0.84 | 1.12, −0.58 |

### X-Ray Crystallography. Data were collected on Nonius KappaCCD (3) and Oxford Diffraction Gemini A Ultra (4) diffractometers, with MoKα radiation (λ = 0.71073 Å) at 150 K. Key crystallographic data are given in Table 3. Absorption corrections and frame scaling corrections were applied based on repeated and symmetry-equivalent data. The structures were solved by direct methods and refined on all unique F² values, with anisotropic non-H atoms and with constrained riding-model H atoms. Both structures display extensive disorder, which was modeled satisfactorily with the aid of restraints on geometry (similarity of equivalent groups) and displacement parameters. 3 has two independent molecules in the asymmetric unit, one of which shows minor disorder of the single 3-ortho isomer while the other consists of a disorder of the 3-ortho and 3-meta isomers on a common site. The noncentrosymmetric structure of 4 was found to be partially twinned by inversion and has two ion pairs in the asymmetric unit (which is the entire unit cell).

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### Supporting Information Available. NMR spectra, computational details and CIF files giving crystallographic data for compounds 3 and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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