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New insights into addition reactions of dialkylzinc reagents to trifluoromethyl ketones: Structural authentication of a β-hydride elimination product containing a tetranuclear zinc chain†

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A systematic study of the stoichiometric alkylation reactions of 2,2,2-trifluoroacetophenone **1** with $[ZnR_2(TMEDA)]$ (R= Me, Et, ^{t}Bu, CH_2SiMe_3; TMEDA= *N,N,N′,N′*-tetramethylethylenediamine) monitored by ^{1}H and ^{19}F NMR spectroscopy is presented. For R = Me, Et the alkylation products alkyl(alkoxides) $[(TMEDA)Zn(R)\{OC(CF_3)(R)Ph\}]$ (R = Me, **2**: Et, **3**) are obtained as the single products of the reaction. When the steric bulk of the dialkylzinc reagent is increased the alkylation reaction is inhibited. Thus, for R = ^{t}Bu, the reduction product $[(TMEDA)Zn(^tBu)\{OC(CF_3)(H)Ph\}]$ is obtained as a result of β-hydride elimination from one of the ^{t}Bu groups of the organometallic reagent. ^{1}H NMR spectroscopic monitoring of the reaction allowed the detection of isobutene as a side product of this reduction process. For the highly sterically demanding group R = CH_2SiMe_3 which lacks hydrogen atoms at the β position, no reaction is observed even under refluxing conditions. Two important intermediates from these reactions have been structurally elucidated: $[(TMEDA)Zn(Me)\{OC(CF_3)(Me)Ph\}]$ (**2**) which could be involved in the previously reported alkylation reaction of trifluoromethyl ketones by ZnR_2 catalysed by TMEDA and unprecedented tetranuclear $[(^tBu)_2Zn_4\{OC(CF_3)(H)Ph\}_6]$ (**5**) resulting from the reduction of **1** when reacted with $^tBu_2Zn$, which displays a rare Zn···Zn···Zn···Zn linear chain arrangement for a zinc alkyl(alkoxide).

Introduction

The development of new methodologies to prepare organofluorine compounds, in particular trifluoromethyl-substituted molecules has recently become a target for many synthetic chemists due to the unique properties, reactivities and assorted applications of these compounds in areas such as agrochemicals, materials, and pharmaceuticals.[1] This activity has included several studies on asymmetric alkylation reactions of trifluoromethyl ketones that yield chiral trifluoromethyl-substituted alcohols which are important subunits in several pharmaceuticals[2] including anticonvulsants, anaesthetics and the anti-HIV drug Efavirenz.[3]

Amongst the catalogue of main group organometallic reagents, organozinc compounds are usually the reagents of choice in asymmetric alkylations of ketones, due to their softer nucleophilic character and greater functional group tolerance compared to that of other organometallic reagents (such as orgonolithium, RLi, or Grignard reagents, RMgX).[4] However, in the context of trifluoromethyl ketones, their use has been relatively limited due to their tendency to undergo β-hydride elimination reactions that afford the unwanted reduction products. Overcoming this severe limitation, Wolf has successfully reported the addition of diethylzinc to a wide range of trifluoromethyl ketones using the popular chelating diamine TMEDA (TMEDA = *N,N,N′,N′*-tetramethylethylenediamine) as a catalyst which affords the relevant tertiary alcohols in good yields (84–99%).[5,6] An asymmetric variant to prepare enantiomerically enriched α-trifluoromethyl tertiary alcohols was also introduced by using the chiral N-donor ligand TBOX (TBOX = 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]) as a catalyst. Structural information of the metallated intermediates (existing prior to the hydrolysis step) has not yet been forthcoming.

Following our success in isolating and spectroscopically and crystallographically characterising organozinc intermediates for metallation (zincation) reactions,[7] we have endeavoured to probe similarly the intermediates from Wolf-type alkylation reactions. Accordingly, herein, we report specifically a ^{1}H and ^{19}F NMR spectroscopic investigation of the stoichiometric alkylation reactions of $[(TMEDA)ZnR_2]$ (R = Me, Et, ^{t}Bu, CH_2SiMe_3) with 2,2,2-trifluoroacetophenone (**1**). A putative intermediate in the catalytic process, the addition product $[(TMEDA)Zn(Me)\{OC(CF_3)(Me)Ph\}]$ (**2**) has been successfully isolated and structurally characterized by X-ray crystallography. In addition we report the synthesis and structural characterization of the unprecedented tetranuclear cage $[(^tBu)_2Zn_4\{OC(CF_3)(H)Ph\}_6]$ (**5**) which was obtained as the reduction product of the reaction of $^tBu_2Zn$ with ketone **1**.

Results and discussion

The TMEDA-complexed dialkylzinc starting materials $[ZnR_2(TMEDA)]$ (R = Me, Et) were prepared in situ by reaction of the relevant dialkylzinc reagent with an equimolar amount of TMEDA in a mixture of toluene/*n*-hexane solvent affording in each case colourless solutions. 2,2,2-Trifluoroacetophenone

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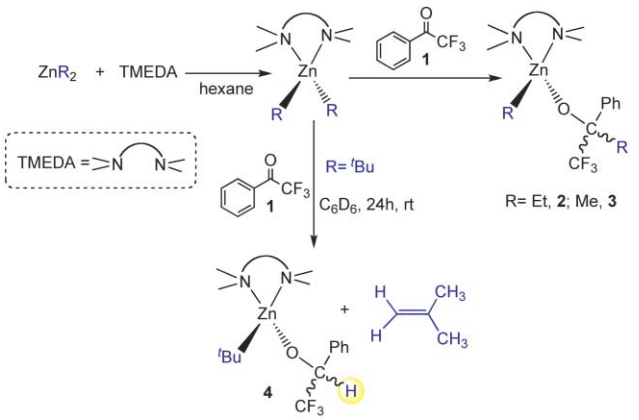
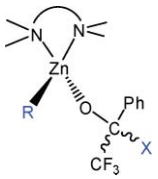
(**1**) was added at −10 °C giving pale yellow solutions which were allowed to stir for 24 hours at room temperature. The resulting solutions deposited colourless crystals of the nucleophilic addition products [(TMEDA)Zn(R){OC(CF$_3$)(R)Ph}] (R = Me, **2**; Et, **3**) as determined by NMR spectroscopy and X-ray crystallography (for **2**)‡ in isolated yields of 54% and 61% respectively (Scheme 1).



Scheme 1 Synthesis of alkyl(alkoxide) compounds **2–4**.

Multinuclear (^{1}H, ^{13}C and ^{19}F) NMR spectroscopic studies recorded in deuterated benzene solution established that the alkylation reactions of ketone **1** by the relevant [ZnR$_2$(TMEDA)] (R = Me, Et) have taken place (Table 1 and Table 2). Thus, the ^{1}H NMR spectrum of **2** (see Table 1 and Experimental Section) showed two distinct resonances for the (non-TMEDA) methyl groups present in the molecule; a singlet at 1.93 ppm corresponding to the methyl group that has added across the C=O bond of the ketone **1** and a further upfield singlet for the one directly bonded to zinc at a chemical shift (–0.61 ppm) similar to that found in the starting material [ZnMe$_2$(TMEDA)] in the same deuterated solvent (–0.52 ppm).[8] For the TMEDA ligand a single broad resonance at 1.77 ppm is observed for the CH_3 and CH_2 groups which contrasts with the usual pattern found for this ligand in deuterated benzene solution. Previously in the literature it has been described that the relative positioning of the distinct signals in the ^{1}H NMR spectrum of TMEDA denotes if the diamine is coordinated to the metal in solution or alternatively if it is not coordinated.[9] The fact that only a broad signal is observed for the TMEDA ligand in **2** suggests that at room temperature in solution, a dynamic process must be taking place in the molecule. This was confirmed by a variable temperature NMR study using deuterated toluene as a solvent,[10] which shows that at low temperature (–35 °C) the broad signal observed at room temperature (Fig. 1b) splits into 4 singlets (at 2.30, 2.03, 1.82 and 1.70 ppm, each of which integrates as three hydrogens) and four multiplets (at 2.15, 1.89, 1.62 and 1.53 ppm, each of which integrates as one hydrogen) (Fig. 1c). This spectrum indicates that at low temperature, TMEDA remains coordinated to zinc and also that there is no symmetry in the molecule, which makes each methyl group and each hydrogen of the CH_2 groups appear inequivalent. Thus, as a result, eight distinct resonances are observed for the protons of the TMEDA ligand. This lack of symmetry must be caused by the hindered rotation at low temperature around the O-C bond in the chiral alkoxide ligand {OC(Me)(CF$_3$)(Ph)}. On the other hand, a ^{1}H NMR spectrum of **2** at high temperature (T = 80 °C) shows a completely different splitting pattern than those observed at low temperature or ambient temperature. Instead, two singlets at 2.14 ppm (NCH_3) and 2.06 ppm (NCH_2) (Fig. 1a) are observed. The relative positioning of these signals suggests that even at high temperature TMEDA remains coordinated,[9] however, now the splitting pattern is consistent with a symmetric TMEDA, which must be due to the fact that as the temperature is increased, the

Table 1 Selected chemical shifts in the ^{1}H NMR spectra of **1-4** in C_6D_6 solution



Compound	$\delta(^1H)_X$	$\delta(^1H)_{Zn\text{-}R}$	$\delta(^1H)_{Ph}$
PhC(=O)CF$_3$ (**1**)			7.80, 7.07, 6.92
2 (R = X = Me)	1.93	-0.61	7.98, 7.34, 7.19
3 (R = X = Et)	2.22, 2.51 (q, CHH′), 0.83 (t, CH_3)	0.38 (q, CH_2), 1.57 (t, CH_3)	7.94, 7.36, 7.20
4 (R = ^{t}Bu; X = H)	5.47 (q, $J^3_{H\text{-}F}$= 7.4 Hz)	1.19	7.67, 7.24, 7.14

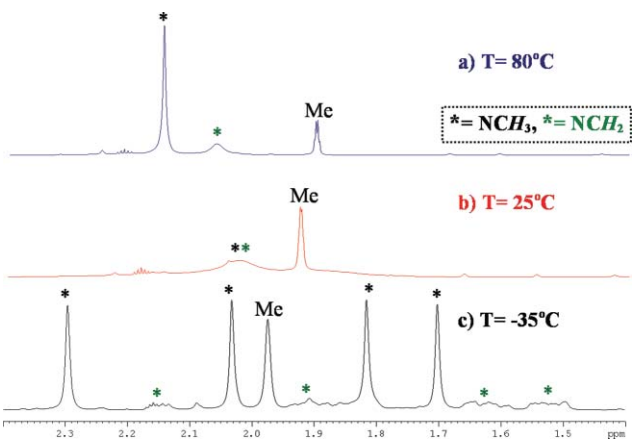


Fig. 1 Selected aliphatic region showing the TMEDA resonances and Me resonances from the alkoxide ligand {OC(CF$_3$)(Me)Ph} in the ^{1}H NMR spectrum of **2** in deuterated toluene solution at variable temperatures.

‡ Crystal data for **2**: $C_{16}H_{27}F_3N_2OZn$, M_r = 385.77, monoclinic, space group $P2_1$, a = 8.2967(4), b = 12.6431(4), c = 9.5096(4) Å, β = 109.426(5) °, V = 940.73(2) Å^3, Z = 2, ρ_{calc} = 1.362 g cm^{-3}, $Cu_{K\alpha}$ radiation, λ = 1.5418 Å, μ = 2.103 mm^{-1}, T = 123 K, R(int) = 0.0369; Final refinement to convergence on F^2 gave R = 0.0454 (F, 3892 obs. data only) and R_w = 0.1172 (F^2, 4909 unique data), GOF = 0.981, 212 refined parameters. Samples were twinned by a 180° rotation about 1 0 0, ratio of twin components refined to 0.689:0.311. Residual electron density max. and min. 0.727 and –0.654 e Å^{-3}. Estimated Flack parameter 0.09(4). Crystal data for **5**: $C_{56}H_{54}F_{18}O_6Zn_4$, M_r = 1426.47, triclinic, space group $P\bar{1}$, a = 10.7331(4), b = 12.0496(4), c = 12.6837(3) Å, α = 96.141(2), β = 113.380(3), γ = 98.272(3) °, V = 1465.52(8) Å^3, Z = 1, ρ_{calc} = 1.616 g cm^{-3}, $Mo_{K\alpha}$ radiation, λ = 0.71073 Å, μ = 1.722 mm^{-1}, T = 123 K, R(int) = 0.0249; Final refinement to convergence on F^2 gave R = 0.0602 (F, 5873 obs. data only) and R_w = 0.2032 (F^2, 8333 unique data), GOF = 1.125, 391 refined parameters. Residual electron density max. and min. 2.741 and –1.352 e Å^{-3}. It is believed that the higher than expected residuals are due to some R/S substitution. Attempting to model this disorder failed.

Table 2 Selected chemical shifts in the $^{13}C\{^1H\}$ NMR spectra in C_6D_6 solution

Compound	$\delta(^{13}C)_{Zn\text{-}R}$	$\delta(^{13}C)_X$	$\delta(^{13}C)_{C\text{-}O}$	$\delta(^{13}C)_{CF3}$	$\delta(^{19}F)$
$PhC(=O)CF_3$ (**1**)			180.3 (q, $J^2_{C\text{-}F} = 34.8$ Hz)	117.3 (q, $J^1_{C\text{-}F} = 291.7$ Hz)	-71.48
2 (R = X = Me)	−16.7	28.7	76.4 (q, $J^2_{C\text{-}F} = 25.1$ Hz)	129.2 (q, $J^1_{C\text{-}F} = 290.5$ Hz)	-79.63
3 (R = X = Et)	1.3 (CH_2), 14.9 (CH_3)	30.9 (CH_2), 8.9 (CH_3)	81.9(q, $J^2_{C\text{-}F} = 25.3$ Hz)	131.8(q, $J^1_{C\text{-}F} = 291.7$ Hz)	-79.05
4 (R = ^{t}Bu; X= H)	20.6 ($C(CH_3)_3$), 34.5 (CH_3)	—	78.8 (q, $J^2_{C\text{-}F} = 27.8$ Hz)	128.0(q, $J^1_{C\text{-}F} = 287.5$ Hz)	-77.85

rotation around O-C bond in the alkoxide ligand becomes fast relative to the NMR timescale.

The ^{13}C NMR spectrum of **2** revealed a set of four aromatic signals for the phenyl group and two singlets at 28.7 and −16.7 ppm corresponding to the methyl group that has been added across the C=O bond of **1** and that coordinated to zinc respectively (Table 2). In addition two quartets with remarkably different coupling constants are observed at 129.2 and 76.4 ppm. The former with a coupling constant of 290.5 Hz corresponds to the CF_3 group and appears significantly downfield to that of the ketone **1** (117.3 ppm, $J^1_{C\text{-}F} = 291.7$ Hz). The remaining quartet at 76.4 ppm ($J^2_{C\text{-}F} = 25.1$ Hz) can be assigned to the electrophilic carbon that has experienced the alkylation reaction, which appears considerably more deshielded than the carbonyl group of ketone **1** ($\delta = 180.3$ ppm, $J^2_{C\text{-}F} = 34.8$ Hz).

The transformation of ketone **1** into the zinc alkyl(alkoxide) **2** has little effect on the ^{19}F NMR spectra, as both compounds display a singlet at similar chemical shifts (at −71.48 and −79.63 ppm respectively).

Similar trends in the NMR spectroscopic data are observed for the ethyl derivative **3** (Tables 1 and 2 and Experimental Section). The main difference appears in the ^1H NMR spectrum, since the CH_2 protons of the ethyl group which has added to ketone **1** are diastereotopic, two distinct multiplets at 2.22 and 2.51 ppm, each of them integrating as one hydrogen, are observed.

The molecular structure of **2** (Fig. 2) established by X-ray crystallographic studies confirms that the addition of a methyl group from the dialkylzinc [$ZnMe_2$(TMEDA)] to the trifluoromethyl ketone **1** has occurred. Methyl(alkoxide) **2** adopts a monomeric

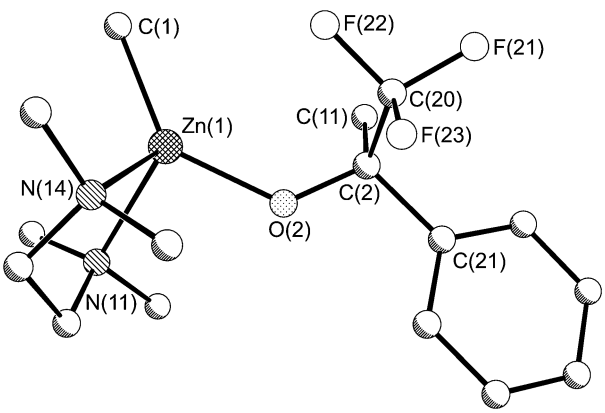
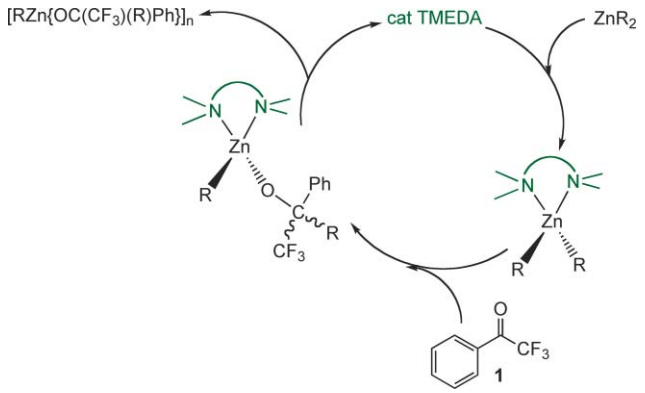


Fig. 2 Molecular structure of **2**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and bond angles (deg): Zn1-O2 1.912(3), Zn1-C1 1.972(5), Zn1-N14 2.184(6), Zn1-N11 2.199(6), C2-O2, 1.362(6), C2-C11 1.538(7), O2-Zn1-C1 137.0(2), O2-Zn1-N11 97.1(2), C1-Zn1-N11 117.2(2), O2-Zn1-N14 100.9(2), C1-Zn1-N14 108.1(3), N14-Zn1-N11 82.7(3), C2-O2-Zn1 128.9(3).

structure where zinc occupies a distorted tetrahedral geometry bonded to two nitrogens from the chelating ligand TMEDA, a carbon from the methyl group and an oxygen from the chiral tertiary alkoxide ligand {$OC(CF_3)(Me)Ph$} resulting from the nucleophilic addition of a methyl group to ketone **1**.[11] Surprisingly, and despite several alkyl(alkoxide) zinc compounds $[Zn(OR)(R')]_n$ being previously structurally defined, compound **2** represents the first such example solvated by a molecule of TMEDA. A closely related species to **2** is the pyridine-solvated ethylzinc-fluoroalkoxide $[(py)_2Et_2Zn_2\{OCH(CF_3)_2\}_2]$ prepared by reaction of Et_2Zn with the relevant fluorinated alcohol as a possible precursor to fluorine-doped ZnO films.[12] The latter exhibits a dimeric arrangement where each zinc binds to two bridging alkoxide ligands, a terminal ethyl group and a molecule of pyridine. As expected, from coordination number considerations, the Zn-O bond distance in **2** [1.912(3) Å] is shorter than those found in the aforementioned dimer [average Zn-O bond length, 2.032 Å], whereas the values of the Zn-C bond distances are within the same range [1.972(5) Å for **2**, 1.980 Å (average) for dimeric compound].

In order to gain a greater understanding about the formation of compounds **2** and **3**, the reactions of the dialkylzinc precursors [ZnR_2(TMEDA)] (previously prepared and isolated as crystalline solids) with the ketone **1** in C_6D_6 solutions were investigated and monitored by ^1H and ^{19}F NMR spectroscopy. The ^1H NMR spectrum revealed that in both cases, the alkylation reactions are quantitative, which means that with [$ZnEt_2$(TMEDA)] no formation of the reduction product resulting from the competitive β-hydride elimination reaction is observed. Note that in the absence of TMEDA, the reduction product is the main species obtained in the reaction of **1** and $ZnEt_2$.[5] Remarkably, the rate of these alkylation reactions seems to be strongly dependent on the nature of the alkyl group of the organozinc reagent. Thus, the formation of **3** is almost quantitative after 10 minutes, whereas the reaction of [$ZnMe_2$(TMEDA)] with **1** requires 24 hours to reach completion, and after 10 minutes it shows only a 5% conversion.

As previously mentioned, Wolf has reported the alkylation of several trifluoromethyl ketones, including **1**, *via* $ZnEt_2$ catalysed by TMEDA.[5] Compounds **2** and **3** could be important intermediates in this catalytic reaction. This catalytic process could take place by the initial coordination of the chelating diamine to ZnR_2 (Scheme 2), which would enhance the nucleophilicity of the organometallic reagent, favouring the alkylation reaction over β-hydride elimination, followed by the reaction with trifluoromethyl ketone **1** to afford a zinc alkyl(alkoxide) intermediate (as **2** and **3**). To allow the catalytic cycle to continue, the release of TMEDA would be required. Thus, in the catalytic reaction, TMEDA should depart from the alkyl(alkoxide) zinc compound, to coordinate to more unreacted ZnR_2 and regenerate the alkylating reagent [ZnR_2(TMEDA)]. The loss of TMEDA would be highly disfavoured on the grounds of the chelate effect, however, only a



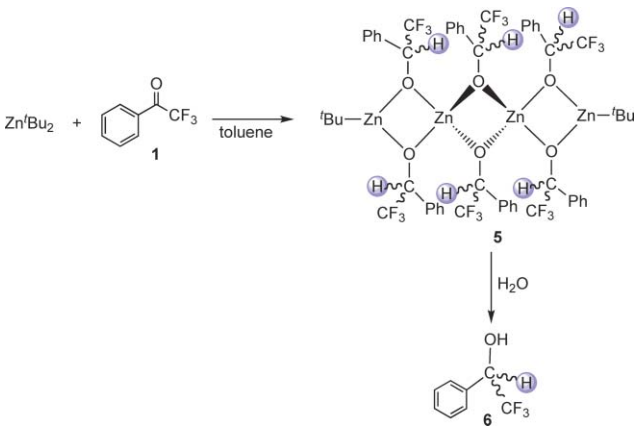
Scheme 2 Proposed catalytic cycle for alkylation of **1** by ZnR_2 using TMEDA as a catalyst.

small extent of ligand dissociation is required within the proposed catalytic cycle. The unsolvated zinc alkyl(alkoxide) compound would probably oligomerise to a higher aggregate, affording, after the hydrolysis step, the relevant trifluoromethyl-substituted tertiary alcohol. This proposed mechanism was strongly supported by the fact that the reaction of $ZnMe_2$ with one equivalent of **1** in the presence of substoichiometric amounts of isolated crystals of **2** (10 mol%), followed by hydrolysis afforded alcohol $PhC(Me)(CF_3)(OH)$ in almost quantitative yields, which shows the preference of the TMEDA ligand to coordinate to $ZnMe_2$ over the alkyl(alkoxide) zinc compound **2**.

Since the rate of the alkylation reaction seemed to be dependent on the nature of the dialkylzinc reagent employed we also investigated and monitored by ^1H and ^{19}F NMR spectroscopy the reaction of **1** with the much more sterically hindered reagent $[Zn^tBu_2(TMEDA)]$.[13] After 30 minutes, no evidence of reaction was observed, however, after 24 hours, the ^1H and ^{19}F NMR spectra revealed the formation of the reduction product $[(TMEDA)Zn(^tBu)\{OC(CF_3)(H)Ph\}]$ (**4**) in an almost quantitative yield (Scheme 1). Thus, the ^{19}F NMR spectrum of the reaction mixture showed a doublet at −77.85 ppm resulting from the coupling of the fluorines of the CF_3 group with the hydrogen atom that has added across the C=O bond in **1** ($J^3_{H\text{-}F} = 7.4$ Hz). Furthermore, the ^1H NMR spectrum showed a new set of aromatic resonances at 7.67, 7.24 and 7.14 ppm, which are modestly more shielded than those found for **1** (Table 1), a singlet at 1.19 ppm for the *tert*-butyl group which is still coordinated to zinc (slightly more upfield than that found for $[Zn^tBu_2(TMEDA)]$, 1.34 ppm) and a distinct quartet at 5.47 ppm for the hydrogen that has added to the carbonyl group of **1**, due to its coupling with fluorine. Moreover, the formation of isobutene, the co-product of this β-hydride elimination reaction can also be detected as indicated by two additional singlets at 4.73 and 1.60 ppm which can be assigned to its olefinic hydrogens and Me groups respectively (Scheme 1).

We next endeavoured to perform the reaction of **1** with $[Zn(CH_2SiMe_3)_2(TMEDA)]$[14] which contains a β-hydrogen free, highly sterically demanding trimethylsilylmethyl ligand. After four days at room temperature or even when the reaction mixture was refluxed for 2 hours in toluene no reaction was observed. These results show that when the steric bulk of the alkyl group of the organometallic reagent $[ZnR_2(TMEDA)]$ is increased, the alkylation reaction is inhibited, favouring the reduction reaction instead (when the alkyl group has β-hydrogens). This can be rationalised in terms of the size of the CF_3 group in ketone **1**, which in sharp contrast with the small size of fluorine (van der Waals radius of fluorine is the next smallest after hydrogen), it is a rather large sterically demanding substituent (intermediate between an ^{i}Pr and a ^{t}Bu group).[15]

Attempts to grow crystals of the β-hydride elimination product **4** were unsuccessful due to the excellent solubility of this compound in *n*-hexane. However when the reaction of $^tBu_2Zn$ with one molar equivalent of ketone **1** was carried out in the absence of TMEDA, colourless crystals of the reduction product $[(^tBu)_2Zn_4\{OC(CF_3)(H)Ph\}_6]$ (**5**) were obtained in an 13% isolated yield (Scheme 3). The identity of **5** was confirmed by ^1H and ^{19}F NMR spectroscopy and its molecular structure was determined by X-ray crystallography (Fig. 3).



Scheme 3 Formation of **5** and hydrolysis reaction to yield **6**.

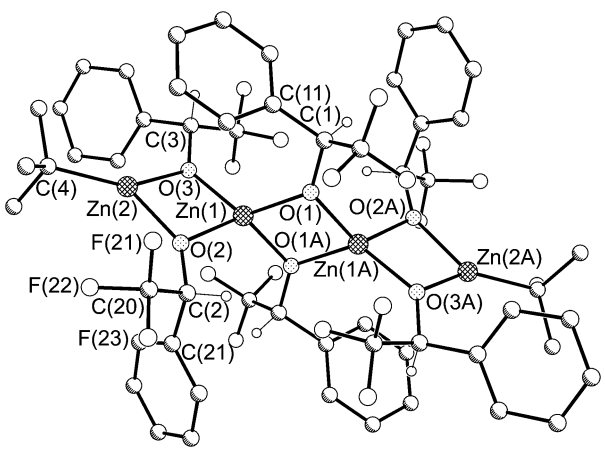


Fig. 3 Molecular structure of **5**. Hydrogen atoms, except for the alkoxide C-H, are omitted for clarity.

Formally dimeric, new alkyl(alkoxide) **5** exhibits a tetranuclear Zn···Zn···Zn···Zn arrangement in which the metals are connected through the secondary chiral alkoxide ligand $\{OC(H)(CF_3)Ph\}$ (Fig. 3). The molecule in **5** is centrosymmetric, containing three orthogonal fused {ZnOZnO} four membered-rings (Fig. 4). These three rings are planar as evidenced by the sum of their internal angles (358.58, 360 and 358.58° respectively) and the arrangement of the four metals is almost linear [Zn2···Zn1···Zn1A 167.78(6)°]. Two distinct zinc environments

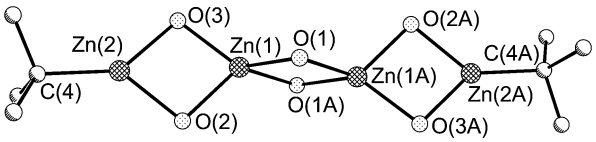


Fig. 4 Inorganic chain motif of **5**.

are observed, thus the outer zinc atoms (Zn2, Zn2A) display a distorted trigonal planar geometry bonded to two alkoxide ligands and a terminal *tert*-butyl group whereas the remaining two zinc atoms in the interior of the tetranuclear chain (Zn1, Zn1A), are tetracoordinated in a distorted tetrahedral geometry, bonded to four alkoxide oxygens. Unfortunately a large amount of motion appears to be present within the alkoxide ligands in **5**, perhaps associated with R/S substitution disorder. This adversely affects the accuracy of this structure and thus prevents discussion of its bond lengths or bond angles. That notwithstanding, **5** represents to the best of our knowledge the first example of a tetranuclear zinc alkyl(alkoxide) with a linear chain arrangement.[16] As previously mentioned, zinc alkyl(alkoxide) compounds have attracted a considerable amount of interest due to their applications in materials science as precursors for ZnO nanoparticles.[17] Depending on the steric bulk and functionalisation of the ligands, unsolvated $[RZn(OR^*)]_n$ can display a wide range of structural motifs and aggregation states (n = 1–6).[18] For n = 4 these compounds display a cubane structure[19] which contrasts markedly with the linear arrangement exhibited by **5**. The closest structural precedent to **5** is trimetallic arylzinc alkoxide $[Ar_2Zn_3(OCH^iPr_2)_4]$ (Ar = *p*-$CF_3C_6H_4$, C_6F_5),[20] where the three metals also adopt a linear disposition connected by bridging alkoxide ligands, with a central pseudotetrahedral zinc atom (exclusively bonded to alkoxide ligands) and two outer zincs, each of them bonded to two alkoxides and a terminal aryl group. Compound **5** can be envisaged as an intermediate in the reduction of ketone **1** to the secondary alcohol $PhC(H)(CF_3)OH$ (**6**) prior to the hydrolysis stage. To the best of our knowledge this is the first example of a structurally defined zinc alkyl(alkoxide) compound, resulting from a β-hydride elimination process.

Compound **5** was also characterised in deuterated benzene solution using multinuclear (^1H and ^{19}F) NMR spectroscopy. The ^1H NMR spectrum was extremely complicated; showing a large number of overlapping resonances, grouped in three discernible main areas of the spectrum: 7.77 to 6.82 ppm, 5.60 to 4.29 ppm and 1.36 to 0.57 ppm which can be assigned to the phenyl ring, CH group of the alkoxide ligand and the ^{t}Bu ligand on the zinc respectively. The $^{19}F\{H\}$ NMR spectrum is also very complex, displaying a myriad of overlapping signals (from –76.13 to –78.47 ppm), which is consistent with the existence of a mixture of species in solution. This could be rationalised assuming that the structure of **5** in the solid state is retained in the deuterated benzene solution. Since **5** possesses six chiral alkoxide ligands, each of them with a stereocentre, 64 stereoisomers (36 diastereomeric relationships) of **5** can be formed.[21] This possibility was supported when compound **5** was quenched with water, which afforded secondary alcohol $PhC(H)(CF_3)OH$ (**6**) in an almost quantitative yield (Scheme 3). Alcohol **6** displays a considerably simpler ^1H NMR spectrum than organometallic precursor **5**, with a single set of well resolved multiplets for the aromatic protons (at 7.32 and 7.03 ppm), a quartet at 4.59 for the CH group (due to its coupling with the CF_3 group, $J^3_{H\text{-}F} = 7.4$ Hz) and a broad signal at 2.66 ppm for the OH group. In addition, the $^{19}F\{H\}$ NMR spectrum showed a single resonance at –77.87 ppm.

Conclusions

A systematic study of the alkylation reactions of trifluoromethyl ketone **1** with $[ZnR_2(TMEDA)]$ (R = Me, Et, ^{t}Bu, CH_2SiMe_3) has been carried out which revealed for R = Me and Et, the alkylation reaction takes place in quantitative yields, being considerably faster for R = Et than for R = Me. Increasing the steric bulk on the alkylating reagent has a dramatic effect on the final outcome of the reaction. Thus, for R = ^{t}Bu, the alkylation reaction is inhibited and instead, the reduction reaction (β-hydride elimination) is favoured, affording the alkyl(alkoxide) compound $[(TMEDA)Zn(^tBu)\{OC(CF_3)(H)Ph\}]$ (**4**) and isobutene (the formation of which can be detected by monitoring the reaction by ^1H NMR spectroscopy). When the highly sterically demanding, but also β-hydrogen free dialkylzinc $[Zn(CH_2SiMe_3)_2(TMEDA)]$ is employed, no alkylation of **1** is observed, indicating that these reactions are strongly dependent on the steric bulk of the organometallic reagent. In addition, two important intermediates of the reaction of **1** with dialkylzinc reagents have been structurally elucidated. Monomeric $[(TMEDA)Zn(Me)\{OC(CF_3)(Me)Ph\}]$, resulting from the stoichiometric reaction of **1** with $[ZnMe_2(TMEDA)]$, which could be an important intermediate for the reaction of Et_2Zn with **1** catalysed by TMEDA previously reported in the literature and novel tetranuclear $[(^tBu)_2Zn_4\{OC(CF_3)(H)Ph\}_6]$ (**5**), an intermediate for the β-hydride elimination reaction, which represents to the best of our knowledge the first zinc (alkyl) alkoxide compound structurally defined, resulting from the reduction of a ketone. The latter displays an unusual tetranuclear Zn···Zn···Zn···Zn linear chain arrangement.

Experimental section

General

All reactions were performed under a protective argon atmosphere using standard Schlenk techniques. *n*-Hexane, THF and toluene were dried by heating to reflux over sodium benzophenone ketyl and distilled under nitrogen prior to use. $ZnMe_2$ and $ZnEt_2$ were purchased from Aldrich Chemicals as a 1M solution in heptane and 1 M solution in hexane respectively. Zn^tBu_2[22] and $[Zn(CH_2SiMe_3)_2(TMEDA)]$[14] were 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 $^{19}F\{^1H\}$ and 100.62 MHz for $^{13}C\{^1H\}$. Satisfactory elemental analysis of compounds **2–5** could not be obtained due to its highly air and moisture sensitive nature.

Synthesis of [(TMEDA)Zn(R){OC(CF$_3$)(R)Ph}] (R = Me, 2; Et, 3)

The relevant dialkylzinc reagent (4 mL of a 1M solution in heptane for $ZnMe_2$ or 4 mL of a 1 M solution in hexane for $ZnEt_2$) was added to a solution of TMEDA (0.6 mL, 4 mmol) in toluene (10 mL) at –10 °C and the resulting colourless solution was allowed to stir for 10 min. Trifluoroacetophenone (**1**) (0.56 mL,

4 mmol) was then introduced which instantaneously afforded a yellow solution which turned colourless after 20 minutes stirring at room temperature. This reaction mixture was allowed to stirr overnight and then placed in the freezer at (–20 °C) and left for 24 hours. Colourless crystals were obtained (0.83 g, 54% for **2**, 1.0 g, 61% for **3**). NMR data for compound **2**: ^{1}H NMR (298 K, C_6D_6) δ 7.98 (2H, d, H_{ortho}), 7.34 (2H, t, H_{meta}), 7.19 (1H, t, H_{para}), 1.93 (3H, s CH_3), 1.77 (16H, s, broad, CH_2 and CH_3, TMEDA), -0.61 (3H, s, Zn-CH_3). ^{13}C{^{1}H} NMR (298 K, C_6D_6) δ 147.8, 128.7, 127.5, 126.8 (Ph), 129.2 (q, $J^1_{C\text{-}F}$ = 290.5 Hz, CF_3), 76.4 (q, $J^2_{C\text{-}F}$ = 25.1 Hz, C-O), 56.3, 46.6, 46.2 (CH_3 and CH_2, TMEDA), 28.7 (CH_3), –16.7 (Zn-CH_3). ^{19}F{^{1}H} NMR (298K, C_6D_6): δ -79.63. NMR data for compound **3**:^{1}H NMR (298K, C_6D_6) δ 7.94 (2H, d, H_{ortho}), 7.36 (2H, t, H_{meta}), 7.20 (1H, t, H_{para}), 2.51, 2.22 (1H each, m, CHH′, Et), 2.01-1.77 (16H, m, broad, CH_2 and CH_3, TMEDA), 1.57 (3H, t, CH_3, Zn-Et), 0.83 (3H, t, CH_3, Et), 0.38 (2H, q, CH_2, Zn-Et). ^{13}C{^{1}H} NMR (298K, C_6D_6) δ 147.1, 129.2, 127.1, 126.4 (Ph), 129.8 (q, $J^1_{C\text{-}F}$ = 291.7 Hz, CF_3), 80.9 (q, $J^2_{C\text{-}F}$ = 25.3 Hz, C-O), 57.8, 47.8, 47.1 (CH_3 and CH_2, TMEDA), 30.9 (CH_2, Et), 14.9 (CH_3, Zn-Et), 8.9 (CH_3, Et), 1.3 (CH_2, Zn-Et). ^{19}F{^{1}H} NMR (298 K, C_6D_6): δ –79.05.

Synthesis of [(TMEDA)Zn(^{t}Bu){OC(CF_3)(H)Ph}] (4)

Zn^{t}Bu$_2$ (0.36 g, 2 mmol) was added to a solution of TMEDA (0.3 mL, 2 mmol) in toluene (10 mL) affording a colourless solution. Trifluoroacetophenone (**1**) (0.28 mL, 2 mmol) was then introduced affording a bright orange solution which was allowed to stir at room temperature overnight. Volatiles were removed under vacuum affording an orange oil which was analysed by multinuclear NMR spectroscopy. Attempts to grow crystals of **4** using different solvent systems such as neat hexane were unsuccessful which indicates that this compound is highly soluble in organic solvents. ^{1}H NMR (298 K, C_6D_6) δ 7.67 (2H, d, H_{ortho}), 7.24 (2H, t, H_{meta}), 7.14 (1H, t, H_{para}), 5.47 (1H, q ($J^3_{H\text{-}F}$ = 7.4 Hz), O-CH), 1.95 (16H, s, broad, CH_2 and CH_3, TMEDA), 1.19 (9H, s, ^{t}Bu). ^{13}C{^{1}H} NMR (298 K, C_6D_6) δ 144.2, 128.4, 127.5, 126.6 (Ph), 128.0 (q, ($J^1_{C\text{-}F}$ = 287.7 Hz), CF_3), 78.8 (q ($J^2_{C\text{-}F}$ = 27.8), CH), 56.8, 47.2, 46.9 (CH_3 and CH_2, TMEDA), 34.5 (CH_3, ^{t}Bu), 20.6 (C, ^{t}Bu). ^{19}F NMR (298 K, C_6D_6): δ –77.85 (d).

Synthesis of [(^{t}Bu)$_2$Zn$_4${OC(CF_3)(H)Ph}$_6$] (5)

Zn^{t}Bu$_2$ (0.72 g, 4 mmol) was dissolved in 10 mL of *n*-hexane and ketone **1** (0.56 mL, 4 mmol) was added affording a bright orange solution. The solution was left stirring at room temperature for 2 hours, concentrated by removing some of the solvent under vacuum. The Schlenk tube was placed in the freezer (–20 °C) and left for several days. A batch of colourless crystals was isolated (0.18 g, 13%, note maximum possible yield 16%). ^{1}H NMR (298 K, C_6D_6) δ 7.77–6.82 (30H m, broad overlapping, Ph) 5.60–4.29 (6H, m, broad overlapping, C*H*), 1.36–0.57 (18H, m, broad overlapping, ^{t}Bu). ^{19}F{^{1}H} NMR (298 K, C_6D_6): δ –76.13 to –78.47 (broad overlapping).

Synthesis of PhC(H)(CF_3)OH (6)

Isolated crystals of **5** (0.71 g, 0.5 mmol) were dissolved in toluene (20 mL) and quenched with a saturated NH_4Cl solution, extracted with CH_2Cl_2 and dried with $MgSO_4$. The solvents were removed under vacuum which afford **6** as a colourless oil. ^{1}H NMR (298 K, C_6D_6) δ 7.32 (2H, d, H_{ortho}), 7.03 (3H, m, H_{meta} and H_{para}), 4.59 (1H, q ($J^3_{H\text{-}F}$ = 7.4 Hz), C*H*), 2.66 (1H, s, broad, OH). ^{13}C{^{1}H} NMR (298 K, C_6D_6) δ 134.8, 129.3, 128.5, 127.7(Ph), 125.4 (q, ($J^1_{C\text{-}F}$ = 292.3 Hz), CF_3), 72.6 (q ($J^2_{C\text{-}F}$ = 32.8 Hz), CH). ^{19}F{^{1}H} NMR (298 K, C_6D_6): δ –77.87.

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