

Fig. 1 Stepwise synthesis of $[(\text{Ph}_2\text{Si}(\text{NAr}^*)_2\text{Zn}(\text{TMP}))\text{K}(\text{THF})_6]^+$ (**1**). Molecular structure of the anion present in **1**. Thermal ellipsoids are rendered at 50% probability. Hydrogen atoms are omitted and Ph and Ar* fragments are drawn as wire frames for clarity.

be reduced significantly by heating to refluxing conditions affording $[(\text{Ph}_2\text{Si}(\text{NAr}^*)_2\text{Zn}(\text{C}_6\text{H}_2\text{F}_3))\text{K}(\text{THF})_6]^+$ (**3a**) in a 90% yield in three hours (Fig. 2). In contrast, evidencing the kinetic activation of **1**, 1,3,5-trifluorobenzene is inert towards zincation using single metal $\text{Zn}(\text{TMP})_2$. Notwithstanding, the TMP amide group seems to be key for the success of the reaction since potassium alkylzincate **2** failed to react with this fluoroarene after 24 h at 69 °C. It should also be noted that reaction conditions required to form **3** are significantly milder than those reported for the zincation of 1,3,5-trifluorobenzene using Pd-catalysis (up to 6 days at 50/80 °C).⁸

Trying to ascertain the role of the potassium in the reaction producing **3a**, metallation studies were repeated using the sodium zincate congener $[(\text{Ph}_2\text{Si}(\text{NAr}^*)_2\text{Zn}(\text{TMP}))\text{Na}(\text{THF})_6]^+$ and using **1** in the presence of macrocyclic Lewis donor

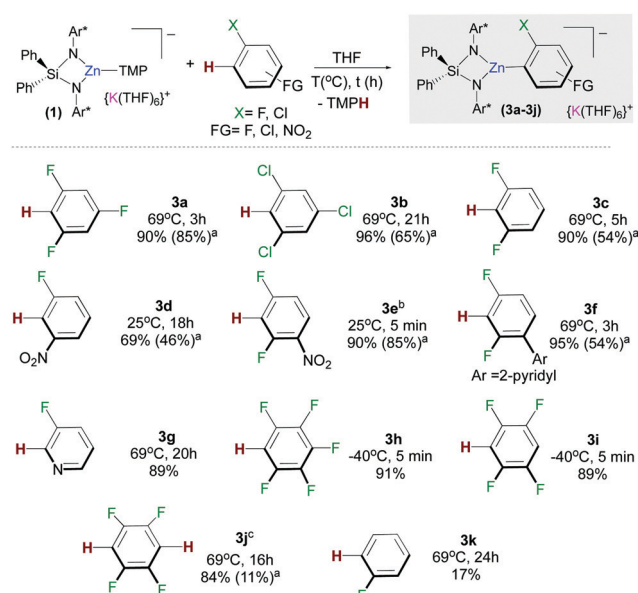


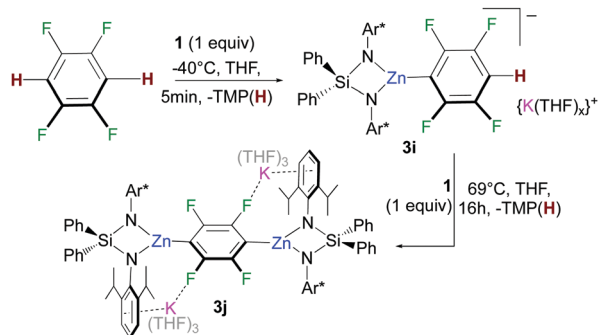
Fig. 2 Scope of the C–H zincation of fluoroarenes using potassium zincate **1**. NMR yields determined by ¹H NMR spectroscopic data using hexamethylbenzene as an internal standard. ^aIsolated crystalline yields. ^bCompound **2e** is light sensitive. ^cReaction carried out using 0.5 equivalents of 1,2,4,5-tetrafluorobenzene.

[2.2.2]-cryptand. The latter has the ability to coordinatively trap and sequester the K cation (see ESI† for details).¹⁰ In each case no significant differences between the yields, reaction times and selectivity were observed from those reported for **3a** when using **1**. This is somewhat surprising since many studies on alkali-metal ates have unearthed a marked alkali-metal effect in the reactivity of such heterobimetallic complexes.¹¹ Furthermore, mechanistic studies on the ferration of fluoroarenes by sodium trisamidoferrate $[\text{NaFe}(\text{HMDS})_3]$ (HMDS = $\text{N}(\text{SiMe}_3)_2$) have revealed that initial coordination of the substrate to the alkali-metal *via* $\text{Na} \cdots \text{F}$ interactions is key for the reaction to take place, which involves a two-step mechanism with initial Na–H exchange followed by fast intramolecular transmetalation to iron.^{6c} Interestingly, here, for the zincation of 1,3,5 trifluorobenzene potassium appears to play a secondary role, stabilizing the zincate anion intermediates. These findings suggest that the enhanced basicity of **1** may mainly be due to the kinetic activation of the zincate anion when compared to more conventional neutral zinc amide bases.

The scope of this approach was then further investigated (Fig. 2). 1,3,5-Trichlorobenzene and 1,3-difluorobenzene can also be zincated by **1** furnishing **3b** and **3c** in 96 and 90% yields respectively, although longer reaction times are required. Reflecting the stabilizing effect of the bulky $\{\text{Ph}_2\text{Si}(\text{NAr}^*)_2\}^{2-}$, the formation of **3b** under these conditions (21 h, 69 °C) contrasts with previous studies by Mulvey on the zincation of chlorobenzene by $[(\text{TMEDA})\text{NaZn}(\text{TMP})\text{tBu}_2]$, where the relevant metallated intermediate undergoes rapid NaCl elimination forming a benzyne species that can be trapped by *t*Bu₂Zn-TMEDA.¹² Encouraged by these findings we next pondered if this approach could also tolerate nitro groups. Previous work by Knochel^{4c,13} has shown promise on the compatibility of these bimetallic reagents with this highly sensitive functional group. Pleasingly it was found **1** reacts at room temperature with 3-fluoronitrobenzene and 2,4-difluoronitrobenzene forming **3d** and **3e** in respective 69% and 90% yields. This approach is also compatible with pyridine-substituted substrates as shown for zincation of 2-(2,4-difluorophenyl)pyridine which takes place regioselectively *ortho* to both fluorine substituents (**3f**, 95%). C2-Zincation is also observed for 3-fluoropyridine (**3g**, 89%) contrasting with previous studies using organolithium reagents or the Lochmann–Schlosser super base reagent where C4-metallation is preferred.¹⁴ Reactions of **1** with the more activated substrates¹⁵ 1,2,4,5-tetrafluorobenzene and pentafluorobenzene furnished zincated products **3h** and **3i** in 91% and 89% yields respectively; whereas for fluorobenzene low conversions were observed after 24 h at 69 °C (**3k** in Fig. 2). While **3h** and **3i** are stable at room temperature, low temperatures (–40 °C) were employed for their synthesis in order to control the TMP-reactivity of **1** (*vide infra*).

Remarkably in the case of 1,2,4,5-tetrafluorobenzene dizincation can be achieved by using 2 equivalents of **1** (**3j**, 84%, Fig. 2 and Scheme 1). ¹H NMR monitoring of this reaction established its stepwise nature. Formation of mono-zincated product **3i** occurs almost instantaneously, which in turn, can be twofold metallated by the second equivalent of **1** (Scheme 1).





Scheme 1 Stepwise 1,4-di-zincation of 1,2,4,5-tetrafluorobenzene by **1**.

While this second step requires forcing conditions to achieve good conversions (16 h, 69 °C), these findings show the potential of **1** to promote polyzincation reactions which to the best of our knowledge is unprecedented for fluoroarenes.

Compounds **3a–e**, **3h** and **3j** were isolated as crystalline solids and their structures were authenticated by X-ray crystallography (Fig. 3, 4 and ESI[†]), demonstrating that these compounds are indeed genuine products of Zn–H exchange reactions. Solvent-separated ion pair motifs were found for **3a–d** and **3h**, comprising, in each case, a potassium cation solvated by six molecules of THF. Their anionic moiety comprises a trigonal planar zinc centre which binds to the bidentate silylbis(amido) ligand and a terminal aryl group. Contrastingly **3e** exhibits a contacted ion pair structure, where potassium is now solvated by three THF molecules and interacts with the zincate anion by π -engaging with one of its Ar* rings in a η^4 -fashion and by forming two further bonds with a F and one nitro O atom (F1 and O1 in Fig. 3c).

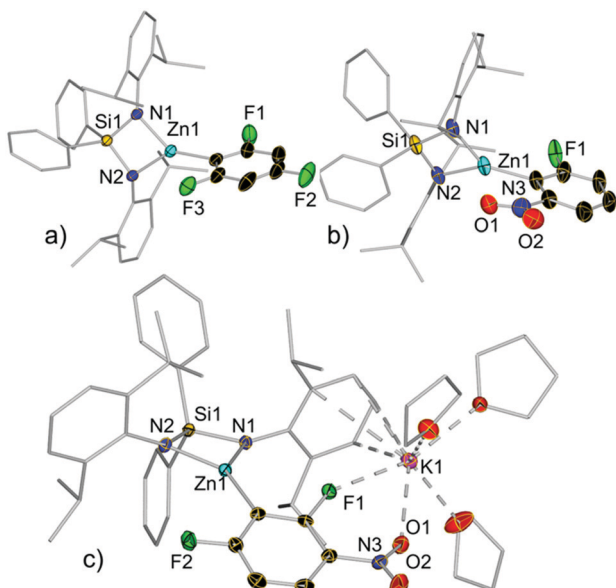


Fig. 3 Crystal structures of: (a) anion of **3a**; (b) anion of **3d**; and (c) **3e**. Thermal ellipsoids are rendered at 50% probability. Hydrogen atoms and minor disorder components are omitted and Ph and Ar* fragments and THF molecules are drawn as wire frames for clarity.

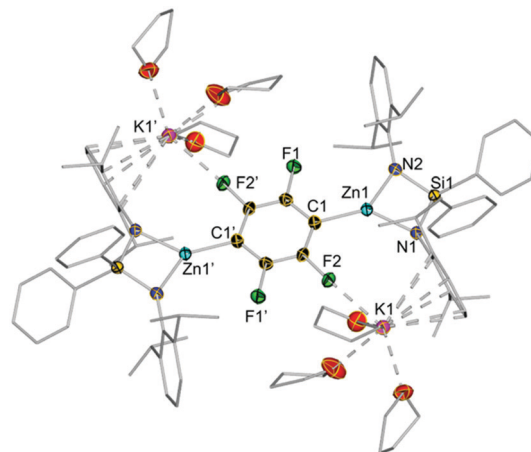


Fig. 4 Molecular crystal structures of **3j**. Thermal ellipsoids are rendered at 50% probability. Hydrogen atoms and minor disorder components are omitted and Ph and Ar* fragments and THF molecules are drawn as wire frames for clarity.

As far as we can ascertain **3d** and **3e** constitute the first examples of direct metallation of nitroarenes to be structurally characterized. We attribute their unexpected stability to the chelating bulky bis(amide) ligand which can offer steric protection for the fragile aryl fragments, allowing their isolation and characterization. This was further supported by the fact that attempts to isolate the product of the reaction of 2,4-difluoronitrobenzene with the related potassium zincate [(PMDETA)KZn(TMP)Et₂]¹⁶ (PMDETA = *N,N,N',N'',N'''*-penta-methylethylenediamine) led to the formation of a complex mixture of decomposition products.

The centrosymmetric molecular structure of **3j** confirmed a two-fold deprotonated 1,2,4,5-tetrafluoroaryl ring with two Zn centres occupying the positions previously filled by H atoms (Fig. 4). Solvated by three molecules of THF, each potassium interacts with one F atom of the ring as well as π -engaging with one Ar* group in a η^6 -fashion, lying essentially in the same plane defined by the fluoroaryl ring. As mentioned before for **3d–e**, the chelating silyl(bis)amide ligand may also play an important role by facilitating the formation of this structure providing a protective steric shelter for these newly formed Zn–C bonds.

Despite the unexpected stability of zincated products **3a–j**, preliminary reactivity studies have shown that their Zn–C bonds are still reactive enough to participate in C–C bond forming reactions, demonstrating their potential for onward reactivity applications. Thus, **3a** undergoes Pd catalysed cross-coupling with 4-bromo-benzonitrile, affording the anticipated bis(aryl) product in a 63% yield. **3a** also reacts with benzoyl chloride furnishing PhC(O)Ar^F (Ar^F = C₆H₂F₃) in a 70% yield (see ESI[†]).

In addition, ¹H/¹⁹F NMR reaction monitoring studies of the reaction of **1** with pentafluorobenzene revealed that at room temperature along with the formation of **3h** and TMP(H), variable amounts of Ph₂Si(NHAr*)₂ and a new organometallic species which also contained {C₆F₅}[–] groups could be detected



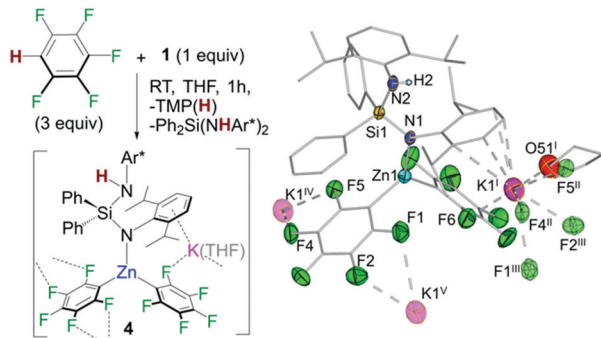


Fig. 5 Reaction of **1** with a three-molar excess of pentafluorobenzene. Molecular structure of **4** thermal ellipsoids are rendered at 50% probability. Hydrogen atoms are omitted and Ph and Ar* fragments and THF molecules are drawn as wire frames for clarity.

in solution. A similar observation was seen for 1,2,4,5-tetrafluorobenzene. These findings are consistent with potassium zincate **1** exhibiting poly-basicity using its silyl(bis)amide ligand. This was confirmed by repeating the reaction of **1** with a three molar excess of C₆F₅H which led to the formation and isolation of potassium zincate [Ph₂Si(NHAr*)(NAr*)KZn(C₆F₅)₂]_∞ (**4**) as a crystalline solid (Fig. 5). Exhibiting a contacted-ion pair structure, **4** is the result of the metallation of two equivalents of C₆F₅H by **1** using its TMP base and one amide base unit of its chelating {Ph₂Si(NHAr*)₂}²⁻ ligand. These findings show that while the latter acts as a spectator in most of these reactions (Fig. 3), it can also be basic enough to promote the metallation of particularly activated substrates with strong electron withdrawing substituents such as C₆F₅H or C₆F₄H₂. The newly generated silyl(amide)amine ligand coordinates to Zn via its amido N in a monodentate fashion {Ph₂Si(NHAr*)(NAr*)} whereas K π-bonds with four aromatic carbons of the Ar* ring located on the amido N (Fig. 5). Zn displays a distorted trigonal planar geometry binding to two C₆F₅ aryls, forming two strong sigma bonds with the metallated carbons. K completes its coordination by binding to one THF molecule and forming five additional K...F contacts. One F belongs to a C₆F₅ ring attached to Zn1 (F6 in Fig. 5) whereas the other four belong to two different C₆F₅ fragments from a neighbouring unit (F4'' and F5''; F1''' and F2''' in Fig. 5), giving rise to an intricate 3D polymeric structure (see ESI†).¹⁷ Compound **4** co-crystallizes with variable amounts of Ph₂Si(NHAr*)₂ resulting from the remaining amido group in **3** acting as a base towards C₆F₅H. Consistent with this interpretation the ¹⁹F NMR spectra of the reaction crudes show an additional species that we tentatively assign as the tris(fluoroaryl) zincate [(THF)_xKZn(C₆F₅)₃] (see ESI† for details).

To conclude, a new mixed K/Zn base has been developed for the regioselective zincation of a range of fluoroarenes, including challenging substrates containing sensitive NO₂ groups. Reactions give good yields with excellent control of regioselectivity. Key for the success of this approach seems to be the combination of a sterically demanding bis(amide) supporting ligand, which provides stability to the fragile fluoroaryl

fragments in the metallated intermediates; and a terminal, one-coordinate, kinetically activated TMP basic site on **1**, which enables direct zincation of the substrates. Combining X-ray crystallographic studies with NMR monitoring of the reactions, the first structural and mechanistic insights into these Zn–H exchanges processes have been gained. Preliminary reactivity studies also show that these organometallic compounds can engage in onward C–C bond forming processes.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) J. Wang, M. Sánchez-Roselló, J. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- T. Ahrens, J. Kohlmann, M. Ahrens and T. Braun, *Chem. Rev.*, 2015, **115**, 931.
- (a) L. Gupta, A. C. Hoepker, K. J. Singh and D. B. Collum, *J. Org. Chem.*, 2009, **74**, 2231; (b) M. Schlosser, L. Guio and F. Leroux, *J. Am. Chem. Soc.*, 2001, **123**, 3822; (c) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, 2002.
- (a) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada and Y. Kondo, *J. Am. Chem. Soc.*, 2002, **124**, 8514; (b) S. Wunderlich and P. Knochel, *Angew. Chem., Int. Ed.*, 2007, **46**, 7685; (c) M. Mosrin and P. Knochel, *Org. Lett.*, 2009, **11**, 1837.
- (a) S. Wunderlich and P. Knochel, *Angew. Chem., Int. Ed.*, 2009, **48**, 1501; (b) R. McLellan, M. Uzelac, A. R. Kennedy, E. Hevia and R. E. Mulvey, *Angew. Chem., Int. Ed.*, 2017, **56**, 9566.
- (a) S. H. Wunderlich and P. Knochel, *Angew. Chem., Int. Ed.*, 2009, **48**, 9717; (b) L. C. H. Maddock, T. Nixon, A. R. Kennedy, M. R. Probert, W. Clegg and E. Hevia, *Angew. Chem., Int. Ed.*, 2018, **57**, 187; (c) L. C. H. Maddock, M. Mu, A. R. Kennedy, M. García-Melchor and E. Hevia, *Angew. Chem., Int. Ed.*, 2021, **60**, 15296–15301.
- Y. Okamoto, K. Yoshioka, T. Yamana and H. Mori, *J. Organomet. Chem.*, 1989, **369**, 285.
- M. Garçon, N. W. Mun, A. J. P. White and M. R. Crimmin, *Angew. Chem., Int. Ed.*, 2021, **60**, 614.
- (a) P. Mastropiero, Z. Livingstone, S. D. Robertson, A. R. Kennedy and E. Hevia, *Organometallics*, 2020, **39**, 4273; (b) P. Mastropiero, A. R. Kennedy and E. Hevia, *Eur. J. Inorg. Chem.*, 2021, 1016.
- J. Hicks, P. Vasko, J. M. Goicoechea and S. Aldridge, *J. Am. Chem. Soc.*, 2019, **141**, 11000.
- (a) T. X. Gentner and R. E. Mulvey, *Angew. Chem., Int. Ed.*, 2021, **60**, 9247; (b) T. X. Gentner, M. J. Evans, A. R. Kennedy, S. E. Neale, C. L. McMullin, M. P. Coles and R. E. Mulvey, *Chem. Commun.*, 2022, **58**, 1390.
- D. R. Armstrong, L. Balloch, W. Clegg, S. H. Dale, P. Garcia-Alvarez, E. Hevia, L. M. Hogg, A. R. Kennedy, R. E. Mulvey and C. T. O'Hara, *Angew. Chem., Int. Ed.*, 2009, **48**, 8675.
- M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 12898.
- (a) F. Marsais and G. Queginer, *Tetrahedron*, 1983, **39**, 2009; (b) G. Shi, S. Takagishi and M. Schlosser, *Tetrahedron*, 1994, **50**, 1129.
- H. H. Bölker, N. M. M. Nibbering, D. Espinosa, F. Mongin and M. Schlosser, *Tetrahedron Lett.*, 1997, **38**, 8519.
- B. Conway, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett and R. E. Mulvey, *Chem. Commun.*, 2008, 2638.
- For a review on the coordination chemistry of the CF unit in fluorocarbons, see: H. Plenio, *Chem. Rev.*, 1997, **97**, 3363.

