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Structural and Synthetic Insights into Sodium-Mediated-Ferration of Fluoroarenes

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Dedicated to Prof. Peter Kündig on the occasion of his 75th birthday

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Exploiting chemical cooperation between Na and Fe(II) within the bimetallic base [dioxane \cdot NaFe(HMDS)₃] (I), $(dioxane = 1,4-dioxane, HMDS = N(SiMe_3)_2)$ the selective ferration of fluorobenzene, 1-fluoronaphthalene, 1,4difluorobenzene, 1,2,4-trifluorobenzene, 1,3,5-trifluorobenzene, 1-bromo-3,5-difluorobenzene, 3-fluoroanisole and 3,5-difluoroanisole has been realized, affording sodium ferrates [dioxane $Na(HMDS)(2-F-C_6H_4)Fe(HMDS)]_{\infty}$ (1), $[dioxane \cdot Na(HMDS)(2-F-C_{10}H_6)Fe(HMDS)]_{\infty}$ (2), $[\text{dioxane} \cdot \{\text{Na}(\text{HMDS})(2,5-F_2-C_6H_3)Fe(\text{HMDS})\}_2]_{\infty}$ (3), $[dioxane \cdot {Na(HMDS)(2,3,6-F_3-C_6H_2)Fe(HMDS)}_2]_{\infty}$ (4), $[(dioxane)_{1.5} \cdot Na(HMDS)(2,4,6-F_3-C_6H_2)Fe(HMDS)]_2$ (5), $(HMDS)_3^{-1}_{\infty}$ (7) and $[dioxane \cdot \{Na(HMDS)(4-methoxy-2,6-F_2-C_6H_2)Fe(HMDS)\}_2]_{\infty}$ (8), respectively. Reactions take place under mild reaction conditions, with excellent control of the selectivity and no competing C-F bond activation is observed. Showcasing complex polymeric arrangements in some cases, the structures of compounds 1-8 have been determined by X-ray crystallographic studies. In all cases, the Fe(II) centers occupy the position in the relevant fluoroarene that was previously filled by a proton, confirming that these metallations are actually ferration processes whereas the Na atoms prefer to form Na…F dative interactions. Compounds 1-8 are thermally stable and do not undergo benzyne formation (through NaF elimination) and their formation contrasts with the inertness of Fe(HMDS)₂ which fails to act as a base to metallate fluoroarenes.

Keywords: cooperative effects, ferrates, fluoroarenes, metallation, sodium.

Introduction

Fluoroarenes are highly valuable building groups present in many biologically active and pharmaceutical compounds.^[1,2] Despite their synthetic relevance, their deprotonation using organolithium bases is particularly challenging due to the fragility of the relevant metallated intermediates which can undergo numerous unwanted side reactions (benzyne formation, auto-metallation) even when cryogenic conditions are employed.^[3,4] To address some of these limitations several main-group metal-mediated alternatives have been developed using single metal bases and heterobimetallic reagents. Thus, regioselective magnesiation of fluoroarenes has been accomplished at room temperature by using a magnesium amide base supported by a bulky β -diketiminate ligand which can provide steric stabilization to the sensitive fluoroaryl fragments.^[5] Exploiting bimetallic cooperation, a variety of mixed-metal bases combining an alkali-metal with another main-group metal have been reported in the literature.^[6] Thus, the groups of *Uchiyama* and *Knochel* have shown that lithium zincates containing the basic amide TMP (2,2,6,6tetramethylpiperidide) are exceptionally mild and efficient bases for the zincation fluoroarenes and other

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sensitive aromatic substrates while operating at room temperature.^[7-9] Our group in collaboration with *Mulvey* has also demonstrated that LiTMP combined with a group 13 complex such as $AI(TMP)/Bu_2$ or $Ga(CH_2SiMe_3)_3$ promotes regioselective stepwise metallation of fluoroarenes, where first the substrate is deprotonated by the lithium amide followed by fast transmetallation to the Group 13 metal trap which permits for the stabilization of the fluoroaryl fragment.^[10] Related to these findings, *Crimmin* has recently found that Pd can catalyze the zincation of a wide range of fluoroarenes, operating through a heterobimetallic Pd–Zn reaction pathway.^[11,12]

Expanding beyond main-group metal chemistry, Knochel has reported trimetallic $(TMP)_{2}Fe \cdot 2MqCl_{2} \cdot 4LiCl$ as a regioselective base which enables the functionalization of fluoroarenes through deprotonative metallation followed by a Ni-catalyzed cross-coupling with alkyl halides.^[13] This study demonstrated for the first time the ability of Fe(II) amides to acts as bases for arene metallation when combined with an alkali-metal, although its constitution and the mechanisms involved in these transformation still remain unknown. Inspired by this work we have recently demonstrated that sodium ferrates made up by a combination of a Fe(II) bis(amides) with a sodium amide, are powerful bases for arene deprotonation.^[14–17] For example, [NaFe(HMDS)₃] deprotonates pentafluorobenzene at room temperature almost instantaneously (Scheme 1). By the isolation and characterization of the organometallic intermediates involved in this process we can confirm that it is actually a ferration.^[14,16] Combining reactivity and DFT

SiMe Me₃S SiMe arene coordination SiMe Me₂Si SiMe SiMe Meas Na-H exchange Me₃S Me₃S - HMDS(H) SiMea intramolecular transmetallation to Fe SiMe Me₂Si SiMe

studies a new type of bimetallic cooperation was revealed. Thus, although the isolated product is formally the result of a Fe–H exchange, pentafluorobenzene undergoes first sodiation (Na–H exchange). This step is favored by the coordination of the substrate to Na through one of its F-atoms. Fast intramolecular transmetallation to Fe follows the sodiation, where the fragile C_6F_5 fragment is trapped and stabilized by the formation of a more covalent Fe–C bond (*Scheme 1*). This type of reaction where both Na and Fe are required for the success of the metallation.^[14]

Building on this work, here we extend this ferration approach to a range of fluoroarenes exhibiting different degrees of activation (in terms of the pK_a of their H-atoms) and substitution patterns. Using sodium ferrate [dioxane·NaFe(HMDS)₃] (I)^[14] as a bimetallic base, we report our findings on the isolation and structural authentication of the intermediates involved in these transformations.

Results and Discussion

We started our studies assessing the reactivity of $[dioxane \cdot NaFe(HMDS)_3]$ (I) with the less activated mono-fluorinated substrates fluorobenzene and 1-fluoronaphthalene (*Scheme 2*). While no reaction was observed at room temperature, these fluoroarenes undergo ferration when used as neat solvents and stirred at 50 °C overnight. In both cases deprotonation at the *ortho* position of the F-atom and concomitant release of HMDS(H) is observed affording [dioxane \cdot Na-



Scheme 1. Sodium-mediated ferration of pentafluorobenzene by $[NaFe(HMDS)_3]$. The substrate is formally deprotonated by Na before rapid transmetallation to Fe.

Scheme 2. Ferration of mono-fluoroarenes to access complexes 1 and 2.

 $(HMDS)(2-F-C_6H_4)Fe(HMDS)]_{\infty}$ (1) and $[dioxane \cdot Na-(HMDS)(2-F-C_{10}H_6)Fe(HMDS)]_{\infty}$ (2) in yields of 92% and 38% after crystallization, respectively (*Scheme 2*, see *Supporting Information* for experimental details).

Neither of the monometallic components of I were able to demonstrate controlled metallation of fluorobenzene. $Fe(HMDS)_2$ showed no reactivity in C_6H_5F , even at reflux, whilst NaHMDS appeared to sluggishly metallate C_6H_5F with concomitant NaF salt elimination and benzyne formation resulting in a complex mixture of products. Contrary to this, products 1 and 2 are selectively formed and isolated as stable solids, exhibiting remarkable thermal stability in solution when heated to reflux, showing no evidence of salt elimination/benzyne formation. These results are particularly striking considering fluorobenzene is a common solvent used in organometallic chemistry for highly polar species^[18-20] and typically considered as relatively inert (e.g. the pK_a of ortho-H in fluorobenzene is 36.8).^[21] Furthermore, HMDS is a relatively mild basic amide when compared to other commodity amides typically used in deprotonative metallation such as diisopropylamide (DA) or tetramethvlpiperidide (TMP).^[22] It should also be noted that attempts to generate complex 1 employing a single equivalent of C₆H₅F in benzene were unsuccessful; with only traces of product be detected by ¹H-NMR spectroscopy. These findings contrast with our previous work assessing the deprotonation of pentafluorobenzene by I which occurs almost instantaneously at room temperature using stoichiometric amounts of the substrate.^[16]

For brevity, only the higher quality structure of 2 (with no disorder present) is discussed since both 1 and 2 are structurally analogous. Confirming that the metallation of 1-fluoronaphthalene is actually a ferration, in **2**, Fe forms a σ bond at the 2-position of the aromatic ring [Fe–C14, 2.0029(16) Å] occupying the position previously filled by a H center, whereas Na interacts with the F [Na–F1, 2.2277(14) Å; Figure 1] closing a six-membered {NaNFeCCF} ring. Both metals are also connected by an HMDS bridge. Fe completes its distorted trigonal planar coordination sphere (sum of internal angles around $Fe = 359.88^{\circ}$) by bonding to a terminal HMDS group, while Na is solvated by two dioxane molecules. Possessing two O-atoms at positions 1 and 4, each dioxane connects the {NaFe(2-F- $C_{10}H_6$)(HMDS)₂} unit with a neighboring unit through Na–O(CH₂)₂O–Na bridges, giving rise to a one-dimensional 'zig-zag' polymeric chain structure (see Supporting Information, Figure S13).



Figure 1. Molecular structure of complex **2** showing an extra equivalent of 1,4-dioxane present in its asymmetric unit. H-Atoms omitted for clarity. Thermal ellipsoids displayed at 50% probability level. Symmetry operator O1(1): 1-x, -y, 1-z; O2(2): -x, -y, 1-z.

Compounds 1 and 2 both exhibit good solubility in C₆D₆, suggesting that their polymeric structures observed in the solid state are not retained in solution. The solution-phase effective magnetic moments of 1 and 2 were determined using the Evans method affording values of 4.95 $\mu_{\rm B}$ for both, which is in the range of the spin-only magnetic moment value (4.90 $\mu_{\rm B}$) for a high-spin (S=2) Fe(II) center. The paramagnetic character of these heterobimetallic compounds is also manifested in the broad paramagnetically shifted resonances observed in their ¹H-NMR spectra.^[23] Protons for the HMDS groups appear as one very broad resonance centered at -2.88 and -3.14 ppm for **1** and **2**, respectively. This suggests that in solution both bridging and terminal HMDS groups can interconvert at room temperature through a fluctional process. A singlet for the dioxane molecules is observed at 3.35 and 4.19 ppm for 1 and 2, respectively. Remarkably, the relevant signals for all the aromatic protons of the metallated fluoroarenes can be visualized. For 1, three highly downfield shifted signals are observed at 188.84, 134.22 and 70.60 ppm, with the fourth upfield shifted at -56.11. Similarly, for 2, seven aromatic signals were observed spread between 176.90 and -20.43 ppm (see Supporting *Information* for details). Neither **1** or **2** shows ¹⁹F{¹H} resonances between 500 and -500 ppm, nor did any of the subsequently reported complexes. This has



been previously found by Holland for Fe(II) complexes and attributed to the very rapid relaxation of the $^{19}\mathrm{F}$ nuclei. $^{[24]}$

Formation of **1** and **2** can be rationalized as shown in *Scheme 1*, through initial sodiation of the substrate followed by fast intramolecular trapping of the fragile fluoroaryl by the Fe(II) center, rendering the formal products of ferration of fluorobenzene and 2-fluoronaphthalene respectively. In this regard dioxane also plays an important role as its monodentate nature favors the formation of contacted-ion pair species, where both metals Na and Fe can communicate with each other. This contrast with recent studies reported by our group using chelating crown ether 15-crown-5 which furnishes solvent-separated sodium ferrate [{Na-(15-crown-5)₂}⁺{Fe(HMDS)₃}⁻] which is completely inert towards metallation of even the activated substrate C_6F_5H .^[16]

To test the scope of our bimetallic approach we next investigated the reactivity of **I** towards more activated polyfluorinated arenes 1,4-difluorobenzene, 1,2,4-trifluorobenzene, 1,3,5-trifluorobenzene and 1-bromo-3,5-difluorobenzene (*Scheme 3*). Reactions were carried out in benzene using stoichiometric amounts of the fluoroarene with the exception of 1,4-difluorobenzene which was used as the solvent of the reaction. It should be noted that 1,4-difluorobenzene has a higher calculated pK_a than fluorobenzene (40.1).^[21] These reactions afforded the new products

Complexes 3 and 4 (Figure 2) are almost structurally identical, both hemi-solvate dimers (connected through 1,4-dioxane) where the fluoroaryl unit bridges between Na and Fe in the same manner as for 1 and 2. They possess similar metrics for the key bonding interactions; Fe1-C16 2.094(3) and 2.114(2) Å, Na1--F1 2.256(2) and 2.2173(18) Å for **3** and **4**, respectively. Beyond the intramolecular Na-F contacts, these compounds also display longer intermolecular Na-F interactions. The outcome of such ancillary bonding results in higher-order structures manifested in 2D networks of fused rings (i.e. a honeycomb-type lattice, see Supporting Information Figures S15 and S18), where each ring is comprised of six Na atoms, four fluoroaryl units and two 1,4-dioxane molecules. In 3, Na1 establishes contact to F2 (para position with respect to F1) of an adjacent monomeric unit (2.3559(2) Å). Whilst in 4 (which contains three monomeric units in the asymmetric unit) both Na1 and Na3 intermolecularly bond with para positioned fluorines of adjacent units



Scheme 3. Reactions of I with polyfluorinated benzenes to form complexes 3-6.



Figure 2. Monomeric unit of complex **4** with an extra half equivalent of 1,4-dioxane shown. H-Atoms omitted for clarity. Thermal ellipsoids displayed at 50% probability level.

(at distances of 2.4615(18) and 2.4407(18) Å, resp.), as well as an F-atom each from different equivalents of co-crystallized fluorobenzene (Na1…F11(1) 2.749(2) Å, Na3…F10 2.903(4) Å). Na2 differs marginally as it holds no interaction with any co-crystallized solvent and thus resides closer to an adjacent unit allowing for contact with *meta* F2 as well as *para* F3 (2.8764(17) and 2.3556(17) Å, resp.).

The ¹H-NMR spectra of **3** and **4** were recorded in C_6D_6 and (D_8) toluene, respectively and both feature very highly shifted resonances for the remaining aryl protons ranging from 218.75 to -60.52 ppm. Broad *singlet* resonances for 1,4,-dioxane appear at 3.49 and 5.27 ppm, respectively and very broad resonances for HMDS protons are centered at -2.67 and -1.50 ppm, respectively. Solution magnetic moments (D_8 toluene) were measured using the *Evans* method^[25-27] to give μ_{eff} values of 5.19 and 5.53 μ_B , for **3** and **4**, respectively; both higher than the spin-only value (4.90 μ_B for an S=2, high spin Fe(II) center) but within an appreciable range.^[28]

Previously, we have described the reactivity of multiple equivalents **I** and 1,3,5-trifluorobenzene (*Scheme 4*) which affords di-ferrated product [{dioxane·NaFe(HMDS)₂}₂(2,4,6-C₆HF₃)]₂ (**II**), which can react onwards through novel C–F to C–N bond conversion to furnish [1,3-bis(FeHMDS)-2,4,6-*tris*(HMDS)-C₆H] (**III**).^[14] However by controlling the temperature of the reaction, on a strictly 1:1 stoichiometric basis at 0 °C, the mono-metallated product **5** can be selectively prepared and successfully isolated. Similarly, 1-bromo-3,5-difluorobenzene can also be mono-ferrated in the same manner to afford **6** (*Fiqure 3*); this substrate will



Scheme 4. Summary of reactions of 1,3,5-trifluorobenzene with different stoichiometric quantities of I to afford complexes **5**, **II** and **III**.^[14]



Figure 3. Monomeric unit of complex **6** with an extra half equivalent of 1,4-dioxane shown. H-Atoms and positional disorder in one TMS and one 1,4-dioxane group omitted for clarity. Thermal ellipsoids displayed at 50% probability level. Symmetry operator O3(1): 1-x, -y, 1-z.

also afford **III** with the application of high temperature and a three molar excess of sodium ferrate **I** are employed.

Complexes **5** and **6** are structurally very similar, crystallizing as discrete dimers whereby the Na centers bridge through a 1,4-dioxane unit (Na1–O3 2.3354(16),



2.3407(18) Å, for **5** and **6**) and each Na bonds to a second terminally bound equivalent of 1,4-dioxane (Na1–O1 2.3192(17), 2.3010(19) Å, for **5** and **6**), likely preventing any *inter*molecular Na···F/Br interactions. Once more the *anchoring* bonds of the ligands to the Fe center are very similar for both complexes and to the previously discussed complexes (*e.g.* for **6** Fe1–C13 2.093(2) Å, Fe1–N1 1.9902(17) Å, Fe1–N2 1.9429(17) Å).

¹H-NMR Spectra of **5** and **6** (recorded in C_6D_6) are highly similar, displaying a single downfield resonance for the remaining equivalent aryl ring protons (101. 64 and 104.74 ppm, resp.) and broad *singlet* resonances for dioxane (4.85 and 5.20 ppm, resp.) and HMDS protons (-2.26 and -2.13 ppm, resp.). Their solution state magnetic moments were calculated to be 4.40 and 5.05 μ_B for **5** and **6**, respectively.

Within Directed ortho-Metallation (DoM) chemistry, a strong ortho-directing group is OMe,^[29] with anisole being a typically employed as a benchmark substrate in these reactions.^[30] Our recent studies have shown that when I is treated with anisole, coordination $[(PhOMe)_3Na(diox)_{0.5}]^+ \{Fe(HMDS)_3\}^-]_2$ adduct formed, where anisole acts as a neutral Lewis donor coordinating to the Na center but no ferration is observed even under forcing reaction conditions.^[16] Thus we next pondered if I could induce the deprotonation of fluoroarenes containing OMe substituents. Pleasingly, selective ferration of 3-fluoroanisole and 3,5-difluoroanisole was observed when I was reacted in benzene furnishing [{(dioxane)₂·Na₂Fe- $(HMDS)_2(2-methoxy-6-F-C_6H_3)\}^+{Fe(HMDS)}^-]_{\infty}$ (7) and $[dioxane \cdot \{Na(HMDS)(4-methoxy-2, 6-F_2-C_6H_2)]$ $Fe(HMDS)_{2}$, (8), respectively (*Scheme 5*).

In the case of 3-fluoroanisole, it is necessary to employ harsher reaction conditions (18 h, 50°C) with ferration occurring at the doubly-activated C2-position between the F and OMe substituents. Interestingly, compound 7 is formally the result of reaction of this substrate with two equivalents of I (Figure 4, top). Thus, X-ray crystallographic analysis revealed that 7 exhibits an unusual pseudo-solvent-separated ion-pair structure. Its cation comprises an Fe^{II} center bound to two HMDS ligands and the C2-ferrated fluoroaryl fragment through its C-atom, occupying the position vacated by a H atom. Each HMDS acts as a bridge between the Fe and Na centers, with Na2 coordinating also to the OMe group (Na2–O1, 2.365(2) Å) as well as one molecule of dioxane. In contrast, Na1 engages with the F substituent (Na1–F1, 2.309(2) Å) and forms an electrostatic anagostic interaction with one Me group of a different HMDS ligand belonging to the



Scheme 5. Syntheses of complexes 7 and 8.



Figure 4. Monomeric unit of complex **7** (top) and dimeric unit of complex **8** (bottom) with an extra equivalent of 1,4-dioxane shown. H-atoms omitted for clarity. Thermal ellipsoids displayed at 50% probability level. Symmetry operator O2(1): 1-x, -y, 1-z; O2(2): -x, -y, 1-z; O2(3): 1+x, y, z.



 ${Fe(HMDS)_3}^-$ moiety of **7** (Na1...C42, 2.9272(1) Å). Na1 is also solvated by another molecule of dioxane (*Figure 4*). The latter acts a bridge between Na1 and the Na2 of an adjacent unit, affording a linear 1D polymeric chain higher-order structure for **7** (see *Supporting Information, Figure S25*). Compound **7** can alternatively be envisaged as a co-complex of [dioxane·Na(HMDS)₃] (**I**) and metallation intermediate [dioxane·Na(HMDS)(2-methoxy-6-F-C₆H₃)Fe(HMDS)]. A related co-complex has recently been reported by us for the metallation of anisole by heteroleptic sodium ferrate [NaFe(TMP)(HMDS)₂].^[16]

Using 3,5-difluoroanisole as a substrate allowed us to assess optional site selectivity of the sodium ferrate base, where metallation could take place at the position either between the F-atoms of between an F and the methoxy substituent. With the isolation of complex 8, clear preference is established for ferration at the 4-position between the two F-atoms with the formation of a new Fe–C bond (2.1078(17) Å; Figure 4, bottom). Revealing a new structural motif to those described above, 8 displays a dimeric structure where each Na coordinates to one bridging HMDS group, a, molecule of dioxane, one of the F-atoms of the metallated aryl and the O from the OMe group of a monomeric neighboring fragment (Na1–O1(1), 2.3745(14) Å), which closes a 12-membered {NaFCC-CO₂ ring (Figure 4, bottom). Adding further complexity, the expanded structure of 8 is a linear 1D network of dimers where propagation is facilitated by the 1,4dioxane donors which act as bridges between sodium atoms of different dimeric units (Figure S27).

The regioselectivity observed for the ferration of 3,5-difluoroanisole is consistent with previous findings when 4-fluoroanisole is reacted with I followed by iodine quenching.^[14] In this case, iodination occurred exclusively *ortho* to the F substituent rather than the OMe group; suggesting that for this mixed Na/Fe base the regioselectivity of the metallation is controlled by the strong acidifying effect of the F substituents rather than the coordinating ability of the OMe group.

¹H-NMR Spectra of complexes **7** and **8** were recorded in (D₈)toluene. The OMe groups resonate at -14.84 and 9.51 ppm, respectively, with the degree of paramagnetic shifting roughly proportional to their through-bond and through-space distances from the paramagnetic Fe(II) center.^[31–35] Much more highly shifted are the aryl protons for **7** (106.38, 100.73 and -70.53 ppm) and **8** (101.46 ppm). Interestingly in the case of **7** two distinct overlapping signals are observed for the HMDS groups; at -2.77 and -4.86 ppm which can be assigned to the bridging HMDS and {Fe-(HMDS)₃} fragment, respectively.

Conclusions

Exploiting chemical cooperation between Na and Fe, the regioselective ferration of a range of fluorinated arenes by sodium ferrate I has been demonstrated. In all cases, metallation is observed at the *ortho* position of a F-atom. Isolation and structural elucidation of the metallated intermediates have revealed the structural variations of these heterobimetallic species which in most cases exhibit intricate polymeric arrangements. Despite their structural diversity they all share the same trigonal planar {Fe(HMDS)₂Ar}⁻ anchor, whereas the Na atoms affix to these fragments through Na–O, Na–F and Na-Me ancillary bonds.

Experimental Section

Synthetic protocols and full characterization of the new compounds are reported in the electronic supporting information. CCDC deposition numbers 1: 2107737, 2: 2107738, 3: 2107739, 4: 2107740, 5: 2107741, 6: 2107742, 7: 2107743 and 8: 2107744 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contribution Statement

L. C. H. M. carried out the experiments and characterizations of all materials. A. R. K. and L. C. H. M. performed the X-ray diffraction studies. L. C. H. M. and E. H. devised the project and supervised the work. All authors contributed to the production of the manuscript.



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