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Utilising Sodium-Mediated Ferration for Regioselective Functionalisation of Fluoroarenes via C-H and C-F Bond Activations


Abstract: Pairing iron bis(amide) Fe(HMDS)$_2$ with Na(HMDS) to form new sodium ferrate base [(dioxane)$_0.5$NaFe(HMDS)$_2$] (1) enables regioselective mono and di-ferration (via direct Fe-H exchange) of a wide range of fluoroaromatic substrates under mild reaction conditions. Trapping of several ferrated intermediates has provided key insight into how synchronised Na/Fe cooperation operates in these transformations. Furthermore using excess I$_2$ at 80°C on a remarkable cascade process inducing the collective 2-fold C-H/3-fold C-F bond activations, where each C-H bond is transformed to a C-Fe bond whereas each C-F bond is transformed into a C-N bond.

Attracted by low cost, high natural abundance and low toxicity of the metal, organoiron chemistry continues to expand as increasing focus is directed towards sustainable practices. Though iron complexes have demonstrated proficiency in a myriad of cornerstone organic bond forming transformations under both stoichiometric and catalytic regimes, an area that remains surprisingly scant is deprotonative metallation. Metal-hydrogen exchange (metallation) is one of the World’s most practiced reactions.[5] Alkylithium or lithium amide reagents dominated metallation for decades, but recently new bimetallic systems have gained prominence as more efficient, more chemoselective alternatives.[5] Only limited advances have been made in direct ferration of aromatic molecules. For example, Mongin used an in situ 1:3, FeBr$_2$/LiTMP stoichiometry for ferration of substituted pyridines, though Fe(II)/Fe(III) or Fe(II)/Fe(IV) couples were proposed to interfere, leading to homocoupling side reactions.[6] Knochel similarly prepared trimetalllic (TMP)Fe$_2$MgCl$_2$-4LiCl in situ to ferrate a range of functionalised arenes to form diaryl Fe(II) compounds.[7] Significantly, the identities of the iron intermediates involved in this challenging chemistry were not identified. A case where structural elucidation proved possible was Mulvey’s regioselective 2-fold ferration of benzene at the 1,4-positions by the sodium ferrate [(TMEDA)NaFe(TMP)$_2$-(CH$_3$SiMe$_3$)$_2$], which affords an iron-host inverse crown complex.[8] While iron bis-amide, Fe(HMDS)$_2$ [HMDS = N(SiMe$_3$)$_2$], has been reported as a useful precursor to access low-coordinate Fe complexes,[9] the low polarity of its Fe-N bonds makes it, a priori, unsuitable for C-H metallation applications. Breaking new ground in this field, by pairing this seemingly toothless base with its sodium congener, we disclose (i) a new methodology for regioselective functionalisation of fluoroarenes which occurs via direct ferration of these aromatic scaffolds, and (ii) an unprecedented ate-mediated C-F bond activation process for C-N bond conversion.

While naturally occurring fluoroarenes are rare, synthetic forms are extremely valuable building blocks. Thus developing methods allowing the incorporation of these units into more complex molecular scaffolds is highly important[9] Interestingly, deprotonation of these molecules via organolithium bases still remains a challenge, primarily due to the exceptionally fragile stability of generated intermediates, which even at cryogenic conditions can eliminate LiF, to form benzyne intermediates as well as engaging in complex cascade processes involving autocatalysis.[10] Also, even when low polarity metallators are used, fluoride elimination cannot be halted as shown recently by our group on alumination of fluoroarenes using trans-metal-trapping Li/Al combinations, where metallated products decompose at room temperature.[11] We started the study by preparing the sodium tris(amido)ferrate [(dioxane)$_0.5$NaFe(HMDS)$_2$] (1) in an isolated crystalline yield of 64% by co-complexing Na(HMDS), Fe(HMDS)$_2$ and dioxane from a 1:1:1 mixture in benzene.[11] X-ray crystallography confirmed the bimetallic constitution of 1, made up by two [NaFe(HMDS)$_2$]$_2$ fragments connected via a Na-dioxane-Na bridge (see SI for details). Reacting 1,3-difluorobenzene with equivmolar 1 at room temperature effected a colour change from green to brown solution. Cooling this solution afforded heteroleptic [(dioxane)$_0$NaFe(HMDS)$_2$(1,3-F$_2$-C$_6$H$_3$)] (2) in 67% yield. In 2 the aromatic substrate is metallated at its C$_2$ position between the F substituents. Electrophilic interception of 2 with iodine affords 1,3-difluoro-2-iodobenzene 3a in 84% yield (Scheme 1).

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Supporting information for this article is given via a link at the end of the document.
HMDS bridge. Fe completes its coordination sphere by bonding to a terminal HMDS, while Na is solvated by two dioxane molecules.

Emphasising the cooperativity between sodium and iron inherent in the reactivity of mixed-metal base 1, neither homometallic Na(HMDS) or Fe(HMDS)₂ on their own can deprotonate 1,3-difluorobenzene (Scheme 1). Thus 2 can be regarded as a product of sodium-mediated ferration, with Fe actioning the deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation, but sodium being essential for this reaction to occur. Interestingly, it should also be noted that ferrated deprotonation.

Encouraged by this initial reactivity, we extended this approach to a range of fluoroaromatic substrates. Reactions were carried out in benzene, allowing mixtures to stir overnight prior to 1₂ quenching (Table 1). Each metallation occurred at a position adjacent to at least one fluorine atom, affording iodo-fluoroarenes 3b-1 in good to excellent yields (40-91%). While Holland has reported that Fe(II) complexes can promote C-F bond activation processes when treated with perfluorinated arenes,[13] here, selective Fe-H exchanges occur at RT or 0°C (refluxed in C₂D₆ at 80°C for 24h).

Figure 1 Monomeric, dinuclear structure of ferrate 2 with H atoms omitted for clarity and displacement ellipsoids displayed at 50% probability level.

Table 1 Ferration of fluoroarenes using sodium ferrate 1.[16]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>1b</td>
<td>91%</td>
<td>RT, 91%</td>
</tr>
<tr>
<td>1c</td>
<td>80%</td>
<td>50°C, 80%</td>
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<tr>
<td>1d</td>
<td>68%</td>
<td>0°C, 68%</td>
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<tr>
<td>1g</td>
<td>88%</td>
<td>50°C, 45%</td>
</tr>
<tr>
<td>1h</td>
<td>78%</td>
<td>50°C, 78%</td>
</tr>
<tr>
<td>1i</td>
<td>74%</td>
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<td>1j</td>
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<td>50°C, 78%</td>
</tr>
<tr>
<td>1k</td>
<td>80%</td>
<td>50°C, 80%</td>
</tr>
</tbody>
</table>

To shed more light on these intriguing findings, we next investigated key metallated intermediates 4a and 4b (Fig. 2), resulting from dieration of 1,3,5-trifluorobenzene and 1,2,4,5-tetrafluorobenzene prior to electrophilic interception.

Both structures bear a strong resemblance to that of 2, with the Fe centres occupying positions previously filled by H atoms (mean Fe-C distance, 2.110 and 2.134 Å for 4a and 4b respectively), whereas each Na atom binds dative with one F at the ortho positions (mean Na-F distance, 2.335 and 2.297 Å for 4a and 4b respectively). The distinct bonding preferences of Fe and Na in these structures, lying up C and F lone pairs respectively, must contribute to the unusual room temperature stability of these potentially hypersensitive fluoroaryl dianions. Steric stabilization of the Fe-C bonds via the bulky HMDS...
groups is presumably another factor. As far as we can ascertain, 4a represents the first structurally defined example of dimethylation of 1,3,5-trifluorobenzene whereas for 1,2,4,5-tetrafluorobenzene only two examples have been reported, though neither were made via direct metal-H reactions.[20]

Previous studies of heterobimetallic amide bases such as alkali-metal zinctates have shown that metatation regioselectivities can be influenced by coordination of the substrate to the alkali-metal prior to the metatation step.[21] A similar scenario could be envisaged here, where initially the fluoroarene could coordinate to Na in 1 via a dative Na-F bond similar to those seen in 2, 4a and 4b, bringing its adjacent H into close proximity to the anionically-activated ferrate (Fe(HMDS))3 moity, primiting the intramolecular Fe-H exchange. Na···F interactions could therefore hold the key to the ortho-F selectivity/reactivity witnessed for all substrates studied (vide supra), whereas lack of such interactions could be a factor in the inertness of 1 with chloroarenes.

Exploring the ferrating limits of 1, we next pondered if the three H atoms in 1,3,5-trifluorobenzene are exchangeable by Fe centres. Thus reacting the fluoroarene with excess 1 at 80°C (Scheme 2) gave a solution colour change from green to dark yellow and the formation of a precipitate. Cooling this solution gave yellow crystals of unmetallic iron complex [1,3-(Fe(HMDS))2]2-2,4,6-(HMDS)-C6H (5a) in 87% yield, where the fluoroarene has undergone an extraordinary 2-fold C-H/3-fold C-F activation, five bond-breaking process (Scheme 2).[22] This approach could also be extended to 1,2,3,5-tetrafluorobenzene and 1-bromo-2,4,6-trifluorobenzene, furnishing bis(iron) compounds 5b and 5c (Scheme 2).

The molecular structures of 5a-c were established by X-ray crystallographic studies (see SI for full details and Fig. 3 for 5a). Since 5a-c are isostructural, only 5a is discussed. Containing a 1-diferrated-penta substituted aryl ring, where each Fe atom of 1,3,5-trifluorobenzene has been replaced by HMDS. 5a displays two low-coordinate Fe centres, each bonded to one C of the aromatic ring (mean Fe-C distance, 2.024 Å) and a terminal HMDS, adopting an unusual near-linear coordination (with C-Fe-N bond angles of 159.43(1) and 161.06(12)° for Fe1 and Fe2 respectively). Each Fe also forms a long-range contact with a neighboring HMDS attached to the aryl ring (mean Fe···N(HMDS)3, 2.389 Å). While these contacts are notably more elongated than those observed for HMDS groups directly attached to Fe (mean Fe-N distance, 1.919 Å), they are significant enough to induce the distortion from linearity observed in the Fe geometries. It should be noted that two-coordinate iron (II) complexes are scarce in coordination chemistry, although they have already demonstrated unique magnetic properties.[23] As far as we can ascertain 5a-5c are the first dinuclear systems containing two pseudo-linear Fe centres to be structurally defined.

While C-F bond activation of fluoroarenes by transition metals has been much investigated, to date, iron has shown limited promise in this area.[8,12,14] It should also be noted that methods for C-F/C-N conversion are scarce, confined mainly to nucleophilic aromatic substitution of activated fluoro- aromatics.[24] Here, the synergic power of this Na/Fe bimetallic partnership allows conversion of three C-F fluoroarene bonds into three new C-N bonds as well as two direct Fe-H exchanges (Scheme 2). Filtrate analysis from the reaction of 1,3,5-trifluorobenzene and 3 equivalents of 2 showed the presence of Fe(HMDS)2-(dioxane) complex and HMDS(H), while formation of precipitated NaF was confirmed by 19F NMR in D2O. Furthermore, it was found that 5a can also be prepared in excellent yield (90-95%) by treating diferrated product 4a with one equivalent of sodium ferrate 1 or just one equivalent of NaHMDS) at 80°C. Even more revealing, heating 4a on its own in benzene for over an hour at 80°C also furnished 5a albeit in a significantly lower yield (58%).

While this type of reactivity is unprecedented in transition-metal chemistry, Schlosser reported the conversion of 1,3,5-trifluorobenzene into 1,3,5-tris(tert-butyl)benzene using excess 'BuLi via dilithiated aryl intermediates.[9] Reflecting on that and our experimental findings, we propose that C-F bond activation products 5 form as a consequence of a cascade process, which takes place at 80°C. In a first step, differation of the fluoroaroyl (e.g. 1,3,5-trifluorobenzene in Scheme 3) by 2 equivalents of 1 will occur to form sodium ferrate 4a. While this compound is stable at room temperature (vide supra), at 80°C it reacts to give 5a, via an unstoppable domino of alternating NaF and Fe(HMDS)2 eliminations and subsequent Fe(HMDS)2 additions to benzene intermediates. The existing Na...F contacts in 4a may contribute to facilitate the activation of the relevant C-F bonds under these reaction conditions.[25] Each diferrated intermediate should be less stable than its precursor (III-IV->4a in Scheme 3), as this fast sequence of reactions does not stop until the three F atoms are replaced by HMDS groups, affording 5a, where now the low-coordinate Fe centres are protected by bulky HMDS groups on the aryl ring.[26] It should be noted that to facilitate the last NaF/ Fe(HMDS)2 elimination step (III—5a, Scheme 3), requires co-complexation of II with one Na(HMDS) equivalent. The sodium amide can be provided by a third equivalent of 1 (which explains the detection of


For a review on the coordination chemistry of the CF unit in fluorocarbons see: H. Plenio, Chem. Rev. 1997, 97, 3363.


4a and 4b form complex 2D-network structures with propagation occurring via their dioxane molecules which connect to neighbouring [NaFe(HMDS)2(diarene)] units, see S1.


Hydrolysis of 5a afforded tri-substituted benzene [1,3,5-(HMDS)2-C6H3] (6) in a 71% yield which was fully characterized by 1H, 13C NMR and elemental analysis. Its solid structure was established by X-ray crystallographic studies (see S1 for details).


Li⋯F interactions have been proposed to play a major role in the C-F bond activation of CFH by Li enolates, see: T. Iida, R. Hashimoto, K. Akawa, S. Ito, K. Mikami, Angew. Chem. 2012, 124, 5673; Angew. Chem. Int. Ed. 2012, 51, 9535.

Attempts to trap any of the proposed intermediates by hydrolysis resulted in the isolation of variable amounts of [1,3,5-(HMDS)2-C6H3] (see S1) and 1,3,5-trifluorobenzene.

Acknowledgements

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Keywords: metallation, iron, mixed-metal chemistry; C-F bond activation, alkali-metals
High Five! Exploiting bimetallic cooperation, sodium tris(amido) ferrate 1 induces the collective cleavage of five (three C-F and two C-H) bonds of trifluoroarene substrates via a cascade activation process.


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