

# Using Iron amides as Basic Reagents for Fluoroarene Metalation

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**Abstract:** Fluoroarenes are important motifs in modern synthesis, yet regioselective C–H functionalization while preserving strong C–F bonds remains a significant challenge. Building on recent studies from our group, here we describe the potential of iron(II) amides to selectively promote regioselective mono- and di-ferration of a diverse range of fluoroaromatic substrates under mild conditions *via* Fe(II)–H exchange. Two alternative strategies are presented which include the use of a sodium ferrate which switches on heterobimetallic cooperation; and the development of a super basic iron amide containing TMP (2,2,6,6-tetramethylpiperidide) groups which allow for the efficient ferration of fluoroarenes under mild reaction conditions.

**Keywords:** Bimetallic cooperativity · Deprotonative metalation · Iron amides · Sodium



**Jennifer Kuziola** received her MSc in Chemistry from the University of Rostock (Germany). During her studies, she conducted research in asymmetric catalysis in the group of Prof. Nicolai Cramer at EPFL and completed her Master's thesis on spirocyclic compounds under the supervision of Dr. Christopher Newton at the University of Adelaide (Australia). She then pursued her PhD at the Max-Planck-Institut für

Kohlenforschung with Dr. Josep Cornella, focusing on structural chemistry and catalysis. She is currently a postdoctoral researcher in the group of Prof. Eva Hevia at the University of Bern, where her research focuses on cooperative bimetallic systems based on earth-abundant transition metals.

## 1. Introduction

Deprotonative metalation constitutes one of the most fundamental chemical transformations in synthetic chemistry, facilitating the functionalization of organic compounds through a metal–hydrogen exchange. Traditionally, these reactions are dominated by organolithium reagents (*i.e.* *n*BuLi) or *s*-block metal amides (*i.e.* LiHMDS; HMDS = N(SiMe<sub>3</sub>)<sub>2</sub>), which are highly activated due to the large polarity of their Li–C or Li–N bonds.<sup>[1,2]</sup> Despite their widespread application, their high reactivity is often accompanied by limited regioselectivity, poor functional group tolerance, and the requirement of cryogenic conditions due to the lack of stability of the intermediates. In recent years, these limitations have led to increased interest in the development of alternative metalation strategies. In this context, heterobimetallic systems<sup>[2,3]</sup> have emerged as a powerful and conceptually novel class of synergic bases for the regioselective functionalization of aromatic compounds. By combining an alkali-metal with a less electropositive main group metal such as Mg, Al, or Zn to form an ate complex, these heterobimetallic reagents can display enhanced reactivities and unique regioselectivities that cannot be achieved with their monometallic counterparts. This is exemplified by the *meta* mag-

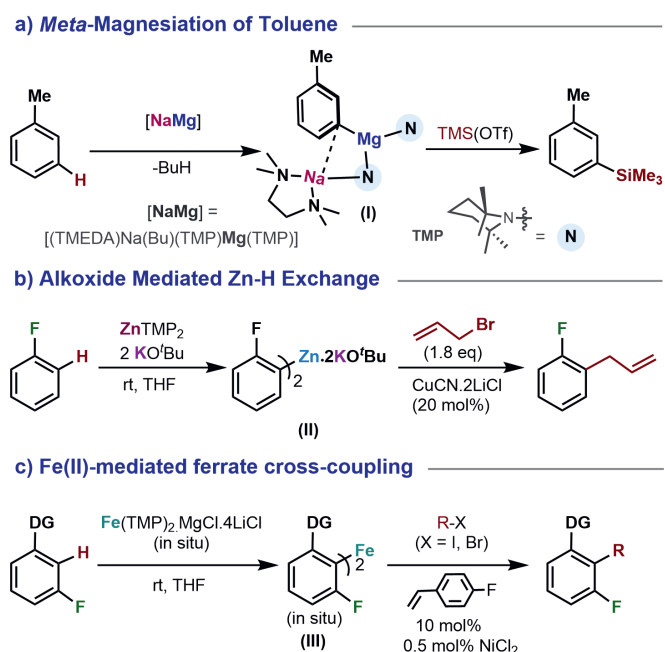
nesiation of toluene reported by Mulvey using sodium magnesiate [(TMEDA)Na(Bu)(TMP)Mg(TMP)] (TMEDA = N,N,N',N'-tetramethylethylenediamine, TMP = 2,2,6,6-tetramethylpiperidide) as a base (Scheme 1, a).<sup>[4]</sup> Recently, our group has also shown that the bimetallic combination of ZnTMP<sub>2</sub>/KO<sup>t</sup>Bu facilitates the zincation of sensitive fluoroarenes while operating at room temperature (Scheme 1, b).<sup>[5]</sup>

This is particularly remarkable as lithiation of these synthetically relevant substrates typically requires the use of cryogenic conditions (–78 °C) in order to avoid unwanted side reactions due to the decomposition of the relevant metalated intermediates.<sup>[6]</sup> These special reactivity profiles have been rationalized in terms of bimetallic cooperativity.<sup>[3]</sup> Going beyond main group metal chemistry, seminal studies by Knochel have shown the latent potential of Fe by an *in situ* generated Fe(TMP)<sub>2</sub>MgCl<sub>4</sub>·LiCl system which can promote the ferration of a wide range of substituted aromatics, including fluoroarenes, to generate putative FeAr<sub>2</sub> intermediates which can subsequently engage in Ni-catalysed cross coupling reactions (Scheme 1, c).<sup>[7]</sup> Inspired by this work, our group has recently developed two complementary methods which enable the ferration of fluoroarenes *via* Fe(II)/H exchange, relying on the use of sodium ferrates and the superbasic amide Fe(TMP)<sub>2</sub> as metalating reagents.

## 2. Sodium-mediated Ferration

Aiming to exploit bimetallic cooperativity, we first investigated the ferration of fluoroarenes using sodium ferrate [NaFe(HMDS)<sub>3</sub>] (**1**) as a base and 1,3-difluorobenzene as a model substrate.<sup>[8]</sup> Initial studies revealed that both single metal components, Fe(HMDS)<sub>2</sub> and NaHMDS, are inert towards the metalation of this substrate (Fig. 1, a). Contrastingly, the combination of both homometallic reagents in an equimolar mixture with 1,4-dioxane furnished sodium ferrate [(dioxane)<sub>0.5</sub>·NaFe(HMDS)<sub>3</sub>] (**1-dioxane**), which in turn reacted with the fluoroarene to form [(dioxane)NaFe(HMDS)<sub>2</sub>(1,3-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)] (**2**) in 67% isolated yield. Single crystal X-ray diffraction analysis (SC-XRD) confirmed that this metalation is a genuine ferration with the replacement of

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Scheme 1. a) *Meta*-magnesium of toluene. b) Alkoxide mediated Zn-H exchange. c) Fe(II)-mediated ferrate cross-coupling of functionalized arenes.

the C2–H bond by an Fe(II)–C  $\sigma$ -bond. In contrast, the Na atom binds to one of the F atoms which is *ortho* disposed to the C that has been deprotonated (Fig. 1). This redox neutral reactivity contrasts with those reported in the literature using iron complexes towards fluoroarenes that typically involve a change in the oxidation state of the metal and where C–F bond activation can compete with the C–H bond activation process.<sup>[9]</sup> This approach could be extended to a wide range of fluoroarenes which can be selectively monoferrated under mild conditions, and further functionalized by electrophilic interception with I<sub>2</sub>.<sup>[8]</sup>

Remarkably, by increasing the amount of base **1-dioxane** to 2 equivalents it was possible to selectively di-ferrate 1,3,5-trifluorobenzene and 1,2,4,5-tetrafluorobenzene.<sup>[8]</sup> Furthermore, these studies also show that in the case of 1,3,5-trifluorobenzene, increasing the amount of **1-dioxane** to 3 equivalents and the reaction temperature to 80 °C unfolds a unique cascade process furnishing [1,3-{Fe(HMDS)<sub>2</sub>}<sub>2</sub>-2,4,6-(HMDS)<sub>2</sub>-C<sub>6</sub>H] (**3**), which is the result of an unprecedented two-fold C–H and three-fold C–F activation at higher temperature (Fig. 1, b). The reaction takes place with the concomitant formation of HMDS(H) and elimination of NaF. The solid-state structure of **3** confirmed the replacement of each fluorine atom in the substrate by one HMDS group and the formation of two new Fe–C bonds at the C2 and C6 positions of the aromatic ring (Fig. 1, b). Combining DFT studies with the trapping of key reaction intermediates using

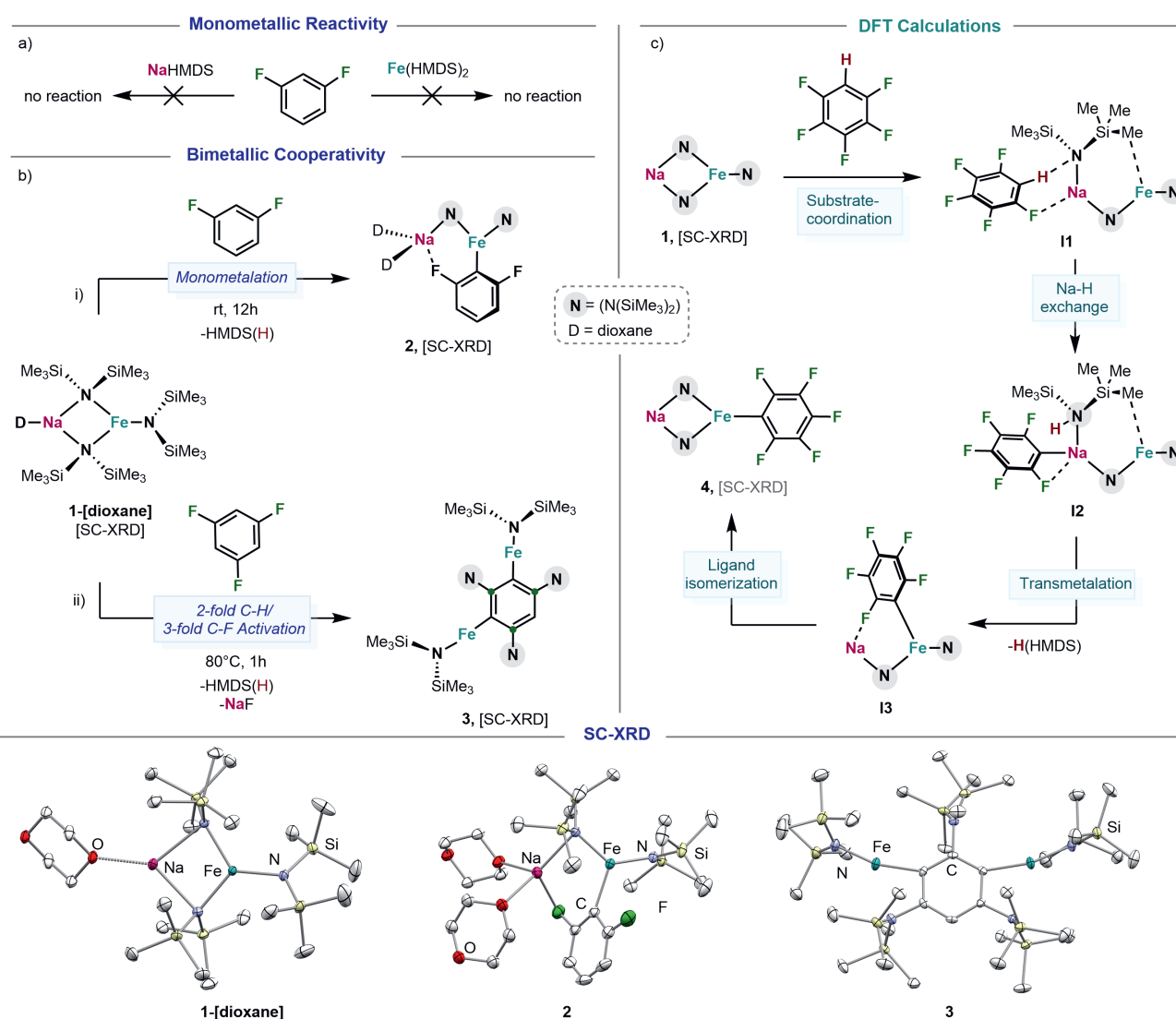


Fig. 1. a) Attempts towards the metalation of fluoroarenes with monometallic bases. b) Metalation of fluoroarenes using bimetallic cooperativity. c) Proposed mechanism of the sodium-mediated ferration of fluoroarenes.

[NaFe(HMDS)<sub>3</sub>] (**1**) as a base and pentafluorobenzene as a model substrate, mechanistic insights on how these ferration processes take place have been gained (Fig. 1, c). Initially, coordination of the fluoroarene to the sodium centre occurs *via* Na...F interactions. This induces a rearrangement within the ferrate fragment, positioning one of the amide ligands in a terminal orientation relative to sodium, bringing it into close proximity to the C–H of the fluoroarene, facilitating the Na–H exchange to generate intermediate **11**. Subsequently, **11** undergoes a rapid intramolecular transmetalation to the Fe(II) centre, affording intermediate **12**, in which the sensitive C<sub>6</sub>F<sub>5</sub> fragment has been stabilized by the formation of a more covalent Fe–C bond. Isomerization of the aryl from a bridging to terminal position furnishes the final isolable and stable product [Na(HMDS)<sub>2</sub>Fe(C<sub>6</sub>F<sub>5</sub>)] (**4**).<sup>[10]</sup> These studies reveal that these metalations are truly synergic in origin, with both Na and Fe playing an essential role, operating in a stepwise manner.

### 3. TMP-based Basic Reagents

s-Block metal amides such as LiTMP and TMPMgCl·LiCl bearing sterically demanding TMP ligands are well-established basic reagents for deprotonative metalation. The steric hindrance imparted by the TMP ligand enhances basicity while decreasing nucleophilicity, minimizing possible side reactions. Remarkably, the synthesis and applications of TMP-amides containing earth abundant transition metals like Fe or Co has remained virtually unexplored. This section showcases our findings on the synthesis, and reactivity studies of Fe(TMP)<sub>2</sub>.<sup>[11]</sup>

#### 3.1 Synthesis of FeTMP<sub>2</sub>

Adopting a methodology similar to that reported for other Fe(II) metal amides, FeTMP<sub>2</sub> (**5**) was synthesized *via* salt metathesis between FeBr<sub>2</sub> and 2 equivalents of LiTMP. An alternative transamidation approach employing Fe(HMDS)<sub>2</sub> and NaTMP also proved to be successful (Fig. 2, a).<sup>[11]</sup> Single-crystal X-ray diffraction of **5** revealed a rare example of a monomeric, near-linearly coordinated Fe(II) bisamide complex bearing an N1–Fe1–N2 angle of 172.09(14)°. Both sterically demanding TMP ligands

bind to the Fe(II) metal centre in a twisted position to minimize steric repulsion (Fig. 2, a).

Compound **5** was further characterized by superconducting quantum interference device (SQUID) magnetometry and Mössbauer spectroscopy, which supports the presence of a high-spin Fe(II) electronic configuration.

#### 3.2 Assessing Metalating Capabilities of FeTMP<sub>2</sub> Towards Fluoroarenes

With Fe(TMP)<sub>2</sub> (**5**) in hand, we investigated its reactivity towards deprotonative C–H metalation using pentafluorobenzene and 1,2,4,5-tetrafluorobenzene. It should be noted that these systems fail to react with the related Fe(II) amide Fe(HMDS)<sub>2</sub> even under elevated temperatures. While these fluoroarenes are relatively activated in terms of the pK<sub>a</sub> values of their C–H units (pK<sub>a</sub>'s: C<sub>6</sub>F<sub>5</sub>H = 29; C<sub>6</sub>F<sub>4</sub>H<sub>2</sub> = 23.1) their high degree of fluorination also makes them more prone to undergo competing C–F bond activation. Remarkably, **5** reacts at room temperature with 1 equivalent of these substrates in pentane, leading to their selective C–H ferration with the concomitant formation of TMP(H). Metalation products [{Fe(TMP)(ArF)}<sub>2</sub>] (**6a**, Ar<sup>F</sup> = C<sub>6</sub>F<sub>5</sub>; **6b**, Ar<sup>F</sup> = C<sub>6</sub>F<sub>4</sub>H) could be isolated in excellent yields and <sup>1</sup>H NMR reaction monitoring studies indicated that their formation is quantitative (Fig. 2, b). The structures of **6a** and **6b** were established by X-ray crystallography analysis displaying a dimeric constitution with the Fe(II) centres connected by two bridging TMP groups (Fig. 2). <sup>1</sup>H NMR analysis in C<sub>6</sub>D<sub>6</sub> is consistent with the retention of their dimeric structure in solution. It should be stressed that these reactions also take place *via* a redox neutral pathway, which contrast with previous studies in the literature using low valent Fe complexes.<sup>[6,9]</sup> Interestingly, while **6a** failed to react with another equivalent of pentafluorobenzene in pentane (even under harsh conditions, 80 °C, 16 h) swapping the solvent to the strong Lewis donor THF allows the isolation of bis(aryl) complex [(THF)<sub>2</sub>Fe(ArF)<sub>2</sub>] (**7**) (Fig. 2, b). These findings highlight the pivotal role of coordination effects in promoting these transformations, which in turn allow **5** to exhibit polybasic reactivity. Further mechanistic insights were gained with the aid of density functional theory (DFT) calculations, which revealed the

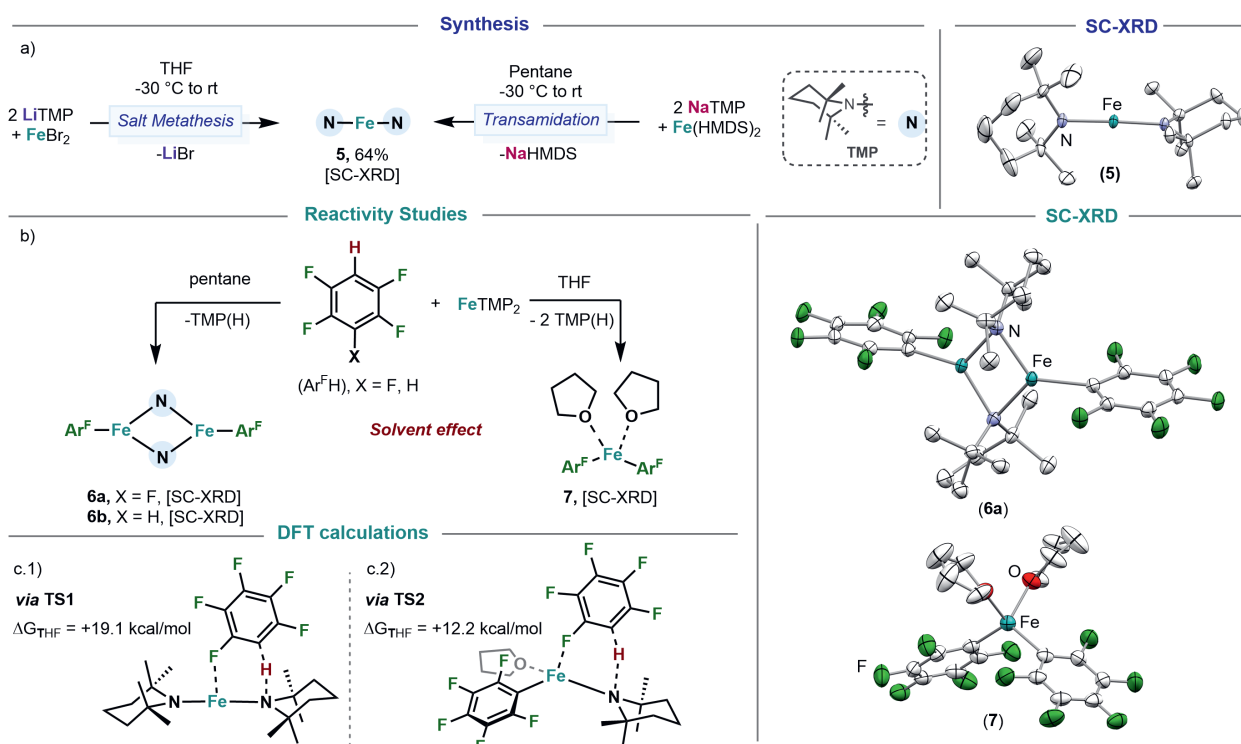


Fig. 2. a) Synthesis of FeTMP<sub>2</sub>. b) Deprotonative Metalation of Fluoroarenes with FeTMP<sub>2</sub>. c) DFT calculations.

critical role of the formation of non-covalent interactions (NCI) between the Fe(II) centre in **5** and one of the *ortho*-F atoms of the substrate. These interactions greatly contribute to the overall stabilization of the transition state involved in the formation of **6a** (see **TS1** in Fig. 2, c.1). In the reaction of **6a** with an additional equivalent of substrate, the computational investigations provided a mechanistic rationale for the experimental observations. Specifically, coordination of THF promoted cleavage of the dimeric motif of **6a**, thereby generating the monomeric species [(THF)Fe(TMP)(ArF)] in solution. Subsequent coordination of a second equivalent of C<sub>6</sub>F<sub>5</sub>H to this monomeric intermediate leads to the formation of **7** *via* the transition state **TS2** (Fig. 2, c.2).

#### 4. Conclusion

In conclusion, we have demonstrated the sodium-mediated metalation of fluorobenzene substrates using the heterobimetallic base NaFe(HMDS)<sub>3</sub>. Mechanistic studies demonstrated that these reactions rely on both metals operating in a cooperative stepwise manner. An alternative approach using a super basic Fe(II) amide, namely FeTMP<sub>2</sub>, has been uncovered for the direct ferration of perfluorinated substrates. This reactivity is highly dependent on coordination effects. Collectively, these results provide new mechanistic insights and open new avenues for the development of further applications of iron-mediated C–H functionalization of aromatic compounds.

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