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Unravelling Nucleophilic Aromatic Substitution Pathways with Bimetallic Nucleophiles

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The reaction of a metal complex containing a polar Fe–Mg bond with 2-(pentafluorophenyl)pyridine leads to selective C–F bond activation. A stepwise S_NAr mechanism involving attack of the bimetallic nucleophile on the electron-deficient aromatic ring has been identified by DFT calculations. Despite the long and rich history of metal anions in organic synthesis, this is the first time the S_NAr mechanism has been elucidated in detail for metal-based nucleophiles.

Nucleophilic aromatic substitution (S_NAr) typically proceeds by a non-aromatic intermediate referred to as a Meisenheimer complex.[1,2] The S_NAr mechanism is a cornerstone of physical organic chemistry and a closely related pathway, concerted nucleophilic aromatic substitution (cS_NAr), has been described.[3-5] This latter pathway does not involve a defined intermediate; rather a single transition state connects reactants and products.

The intricacies of the S_NAr mechanism have been investigated in depth for simple organic nucleophiles.[6-10] There is growing appreciation that many reactions previously believed to be stepwise processes may in fact be concerted.[11] Surprisingly little is known about systems that involve transition metal-based nucleophiles. Understanding S_NAr with metal anions should lead to deeper insight into this fundamental mechanism. Furthermore, if the counter-cation is closely associated with the nucleophilic metal anion then the mechanism is likely to include aspects of dual activation absent for more classical organic nucleophiles.[12-14]

The reactions of transition metal carbonyl anions, such as $[CpFe(CO)_2]^-Na^+$, with fluoroarenes were studied in the 1960s.[15-19] Transition metal hydride anions such as $[Cp^*Rh(H)(PMe_3)]^-$ have been proposed as intermediates in reactions of metal dihydride complexes with fluoroarenes.[20,21] Aromatic nucleophilic substitution is frequently invoked as a mechanism in these reactions,[22] and is often discussed alongside oxidative addition,[23] metal–halogen exchange,[24,25] and single-electron transfer processes.[26] The data that support the S_NAr mechanism are, however, severely limited. Furthermore, there has been little or no attempt to differentiate stepwise S_NAr and related concerted cS_NAr pathways.[27]

In this paper, we report an S_NAr mechanism and associated Meisenheimer intermediate in the reaction of a metal-based nucleophile with an aromatic substrate. We show that both the S_NAr and cS_NAr mechanism are potentially operating in the reaction of M–M bonds with fluoroarenes (M = Mg, Fe). A switch in the regioselectivity of aromatic substitution observed with different nucleophiles correlates with a switch in the mechanism. Complex **1** is related to $[CpFe(CO)_2]^-Na^+$ and may be prepared cleanly from the reduction of $[CpFe(CO)(\mu\text{-}CO)]_2$ with 1 equiv. of **2** (Figure 1).

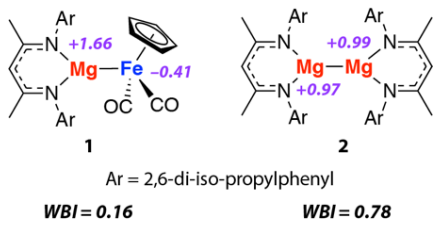

Figure 1. Structures and bonding analysis of **1** and **2**. Values on the structures are NPA charges, those listed below are Wiberg Bond Indices (WBI).

The key advantage of this procedure over existing methods is that the preparation can be conducted in hydrocarbons allowing exclusion of coordinating polar solvents, such as THF, from the reaction mixture and hence providing access to a previously unattained solvent free complex. There are a few reports of related heterobimetallic complexes and the

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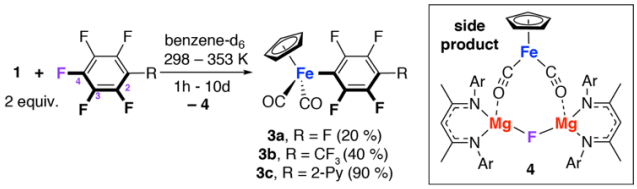
spectroscopic data on **1** (multinuclear NMR, DOSY, IR) are unremarkable in comparison to these known systems.[28-32] A single crystal X-ray diffraction study (Figure 3) revealed that the Fe–Mg distance (2.5190(7) Å) of **1** sits just outside the range established for its analogues (2.530(3)–2.6326(4) Å).[29-31] This bond length is considerably shorter than the Mg–Mg distance in **2** (2.8457(8) Å).[33]

Calculations on **1** and **2** provide insight in to the nature of the M–M bonds. The Fe–Mg bond of **1** may be unambiguously classified as highly polar and the Mg–Mg bond of **2** as apolar. NBO calculations show that the charge distribution in **2** is near perfectly balanced on both metals, while **1** shows localisation of negative and positive charge at Fe and Mg respectively. The large ionic contribution to the bonding is further reflected in the Wiberg Bond Index of **1**, which is appreciably smaller than that of **2** (Figure 1).

The reaction of **1** with 2-(pentafluorophenyl)pyridine, perfluorobenzene and perfluorotoluene in benzene-d_6 were monitored by ^{1}H and ^{19}F NMR spectroscopy. The aromatic substitution of a series of electron-deficient fluorinated aromatics was achieved at 298–353 K (Scheme 1).



Scheme 1. Reaction of **1** with a series of fluoroarenes.

Reactions proceed with a 2:1 stoichiometry of **1** to the aromatic substrate. The efficiency of these reactions was dependent on the nature of the fluorocarbon. While perfluorobenzene and perfluorotoluene gave only small amounts of **3a** and **3b**,[19,34] 2-(pentafluorophenyl)pyridine reacts cleanly to form **3c**. This latter complex was isolated and characterized by single crystal X-ray diffraction (Figure 2).

The unusual 2:1 reaction stoichiometry can be understood by considering the structure of the reaction by-product **4** (Scheme 1). The trimetallic **4** forms from the reaction of the initial by-product, a molecular magnesium fluoride, with a further equivalent of starting material. **4** is a rare example of a coordination complex of a transition metal and a main group fluoride for which there is only limited precedent (Figure 3).[35] The $\{CpFe(CO)_2\}^-$ fragment adopts a two-legged piano stool geometry and is bound to two magnesium centres by isocarbonyl ligands. **4** appears to be a poor metal-based nucleophile that does not react with a further equiv. of the substrates described herein.

The regioselectivities of aromatic substitution are noteworthy. While perfluorotoluene is well known to react at the 4-position, typically 2-(pentafluorophenyl)pyridine undergoes reactions at the site adjacent to the pyridyl directing group. For example, the C–F borylation of this substrate with B_2pin_2 (*bis*(pinacolato)diborane) can be catalysed by $[Rh(COD)_2]^+BF_4^-$ and occurs exclusively at the 2-position.[36] Similarly, in a previous report we showed that **2** and related Mg–Mg and Mg–Zn species react only at the 2-position of this substrate.[37,38]

As the switches in regioselectivity could be indicative of a switch in mechanism, the plausible pathways for aromatic substitution with **1** were explored using DFT calculations.[39] Two mechanisms for nucleophilic aromatic substitution were found; the expected cS_NAr pathway, and a genuine S_NAr pathway with a low energy Meisenheimer intermediate (Figure 3).

The cS_NAr pathway proceeds by initial formation of an encounter complex which leads via a concerted transition state **TS-1** (+35.2 kcal mol^{-1}) directly to the product of nucleophilic substitution, **Int-1**. Regardless of the site of nucleophilic attack on the electron-deficient ring, this cS_NAr pathway is high in energy and likely disfavoured under the conditions of the experiment (*vide infra*). In contrast, the stepwise S_NAr pathway is a low energy process. This mechanism could only be identified for attack of **1** on the 4-position of the electron-deficient ring of the substrate. Initial formation of **Int-2** is followed by rate-limiting formation of the Meisenheimer intermediate, **Int-3**, via **TS-2** (+16.5 kcal mol^{-1}). **Int-3** involves complete charge separation of the two metal fragments. This species is relatively stable, it is only 11.7 kcal mol^{-1} above the separated reactants and leads to product formation by F^- elimination followed by recombination with the cationic Mg centre.

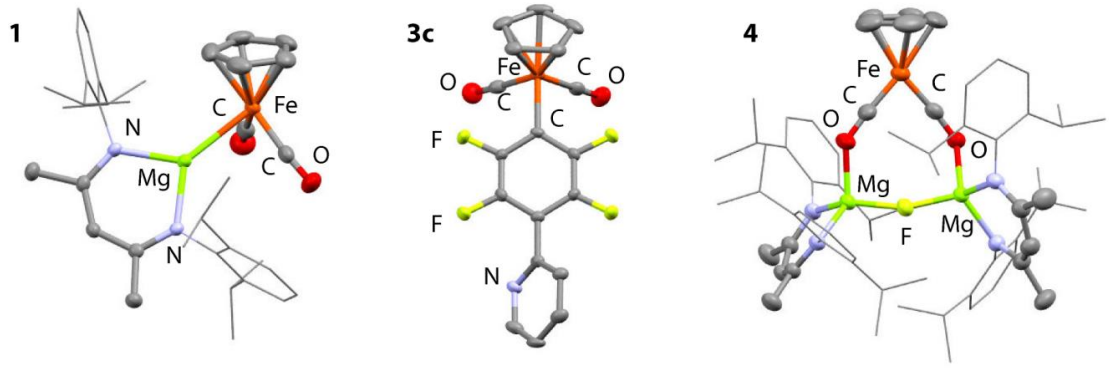


Figure 2. Solid-state structures of **1**, **3c** and **4**. Selected bond lengths (Å) **1**: 2.5190(7), Fe–CO 1.727 (3), 1.744(3), **3c**: Fe–CO 1.771(4), 1.772(4), C–O 1.136(4), 1.138(5), Fe–CAr 2.001(3). **4**: Fe–CO 1.679(2), 1.692(2), Mg–O 2.0160(15), 1.9885(17), Mg–F 1.8719(13), 1.8710(13), C–O 1.206(3), 1.200(3).

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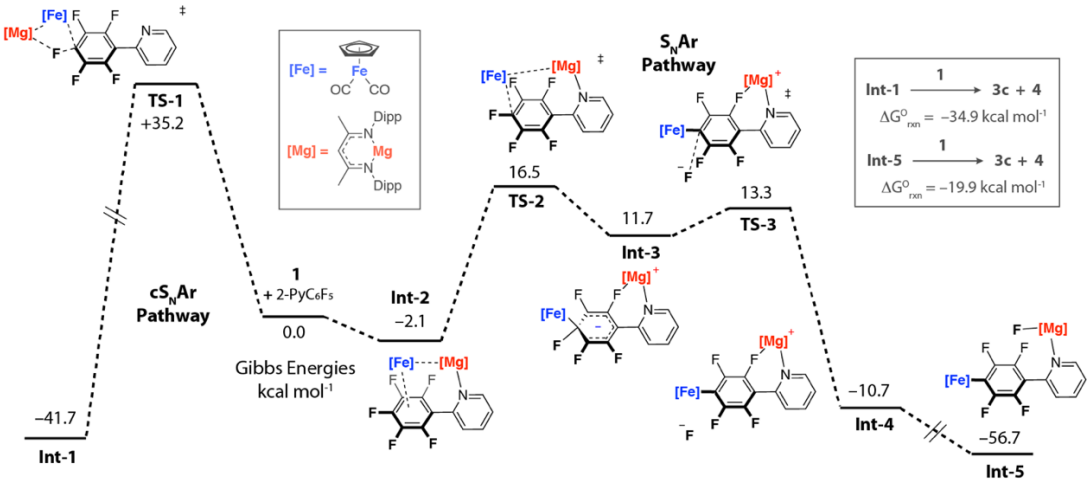


Figure 3. Calculated S_NAr and cS_NAr reaction pathways for the reaction of **1** with the 4-position of 2-(pentafluorophenyl). Insets: Key for abbreviation of the **[Fe]** and **[Mg]** fragments and thermodynamics of product generation.

The calculated products from both the S_NAr (**Int-5**) and the cS_NAr (**Int-1**) pathway can be considered as an adduct between **3c** and a single equiv. of a molecular β-diketiminate stabilised magnesium fluoride. Neither are observed experimentally. Further reaction of **Int-1** or **Int-5** with **1** leading to **3c** and **4** is, however, calculated to be thermodynamically favoured (Figure 3 - inset).

Identification of a true Meisenheimer complex through either theory or experiment from reaction of a transition metal-based nucleophile with an aromatic substrate is unprecedented.[40,41] Bond lengths and angles in **Int-3** may be compared with those determined for *(i)* a related Meisenheimer intermediate derived from nucleophilic attack of NH_3 on C_6F_6 that has been characterised by a combination of mass spectrometry, IR spectroscopy and DFT calculations[42] and *(ii)* a π-complex from addition of $[Ni(PEt_3)_2]$ to $C_{10}F_8$ that has been isolated and crystallographically characterised (Figure 4).[43]

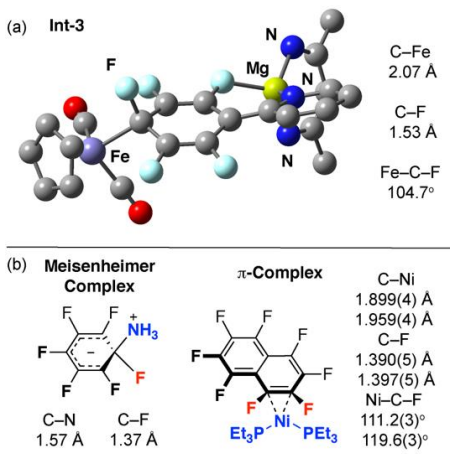
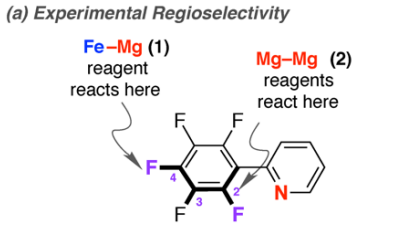


Figure 4. Structures and selected data on (a) I**nt-3** – aryl groups of magnesium fragment omitted for clarity, and (b) Meisenheimer complex $\{C_6F_6NH_3\}$ and π-complex $[Ni(PEt_3)_2(\eta^2\text{-}C_8F_{10})]$.

Int-3 possess a short Fe–C bond length of 2.07 Å along with a long C---F distance of 1.53 Å. The latter is extremely stretched when compared to the C–F distance for the remaining positions including that coordinated to Mg (C–F, 1.36 Å; C–F---Mg, 1.40 Å). The Fe–C–F bond angle of 105° is consistent with that found in $\{C_6F_6NH_3\}$ and suggests a rehybridisation of the carbon atom toward sp^3. For comparison the π-complex $[Ni(PEt_3)_2(\eta^2\text{-}C_8F_{10})]$ contains bonds between Ni and two carbon atoms resulting in a perturbation of both carbon centres.

The competition between the S_NAr and cS_NAr pathways explains the switch in the experimentally observed regioselectivity (Figure 5).



(b) Calculated Regioselectivity

Bimetallic Nucleophile	cS_NAr Pathway	S_NAr Pathway
δ^- δ^+ [Fe]—[Mg] (1)	25.2 (2-position) 34.0 (3-position) 35.2 (4-position)	***18.6*** (4-position)
δ^+ δ^+ [Mg]—[Mg] (2)	***11.8*** (2-position) 27.7 (3-position) 28.7 (4-position)	–[a]

Figure 5. (a) Experimental regioselectivity. (b) Calculated barriers (Gibbs energies in kcal mol^{-1}) for reactions of (2-pentafluorophenyl)pyridine with **1** and **2** by cS_NAr and S_NAr mechanisms. [a]pathway could not be identified.

While the cS_NAr mechanism is predicted to lead to substitution at the 2-position of 2-(pentafluorophenyl)pyridine, this pathway is energetically inaccessible for **1**. Instead, the polar ionic nature of Fe–Mg bond favours charge separation and the

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S_NAr pathway. Nucleophilic attack of the {Fp}⁻ anion occurs on the 4-position of (2-pentafluorophenyl)pyridine and the resulting Meisenheimer complex is greatly stabilised by coordination of the pyridine to the cationic Mg centre. The S_NAr pathway appears limited to this specific substrate. For alternate substrates that cannot stabilise the Meisenheimer intermediate to the same extent, such as C_6F_6 and perfluorotoluene the S_NAr is disfavoured and the reactions become sluggish (see supporting information). The situation is reversed for **2**, since charge separation to form a Meisenheimer intermediate is highly unfavourable for the apolar Mg–Mg reagent, the cS_NAr pathway now operates leading to substitution at the 2-position. The cS_NAr mechanism has a broader reaction scope and lower energy barriers for **2** compared with **1**.

In summary, we have reported the reaction of an iron-based nucleophile containing a polar Fe–Mg with 2-(pentafluorophenyl)pyridine. Mechanistic analysis suggests that a stepwise S_NAr mechanism is likely in operation and may be competitive with a concerted process previously identified for bimetallic nucleophiles containing apolar Mg–Mg bonds.[37,38] Switches in the predicted mechanism systematically correlate with switches in the experimentally determined regioselectivity. We rationalize the findings based on the polarization of the M–M bond and the ease of charge separation of the two metal fragments. We conclude that more polar metal-based nucleophiles are more likely to adopt a stepwise S_NAr pathway and less polar ones the cS_NAr pathway.

Conflicts of interest

There are no conflicts to declare.

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