Journal Name

COMMUNICATION

Magnesium-Mediated Arylation of Amines via C-F Bond Activation of Fluoroarenes

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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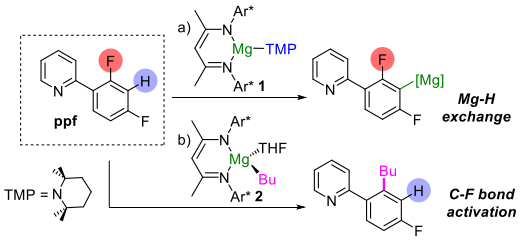
A series of new Mg(II) amides featuring a bulky β-diketiminate backstop ligand, has been synthesised. These complexes are demonstrated to be excellent sources of nucleophilic amides that can participate in rapid C-F activation of several fluoroarenes at room temperature or using microwave assistance, leading to the installment of synthetically important C-N bonds via nucleophilic substitution.

Fluorinated aromatic molecules are essential building blocks in medicinal chemistry, where it has been estimated that 20% of new drugs contain at least one C-F bond in their structure.[1] Given the rarity of naturally occurring fluorinated organic molecules, the regioselective functionalisation of fluorinated building blocks is of importance synthetically to expand the pool of fluoro organic molecules.[2] Metallation is a powerful and productive tool used in this regard,[3] but despite the advantages and renowned activity of the ubiquitous organolithium reagents, such metallations are often impaired by poor selectivity and unwanted side reactions.[3a] C-F bond activation is a much rarer route to fluorinated organic molecules and is dominated by precious transition metal complexes, wherein careful complex construction is usually required to favour C-F over competing C-H activation.[4] The use of main group complexes in C-F activation is starting to motor, accelerated in part by the aspiration to turn towards more sustainable chemical transformations. It has recently been reported that low valent Mg(I), Al(I) and Si(II) complexes can regioselectively promote oxidative addition of fluoroarene C–F bonds.[5] Moreover, Grignard reagents, traditionally poor metallating reagents can participate in C-C coupling reactions via nucleophilic substitution although in most cases the presence of a directing group is required.[6] Nucleophilic aromatic substitution has also shown promise in accessing arylated amines via C-F bond cleavage. Thus, Diness has recently reported arylation of several amines by reaction with fluoroarenes in the presence of LiHMDS as an early main group alternative to transition metal catalysed Ullman and Buchwald-Hartwig couplings, although high temperatures (100°C) are required.[7] Other Group one examples using such as BuLi, LiH or KO^{t}Bu have also been described[8] although selectivity control has proved challenging due to the high basicity of the group 1 metal reagent. Notably, harsh reaction conditions are employed (high T, long reaction times, excess of metal reagent) and very limited tangible information is available regarding the nature of the organometallic intermediates involved. In parallel to these studies, it has been shown that other main group metals such as Al, Pb and Sn can facilitate the transformation of C-F bonds into C-NR_2 (R= Me, Et). [9]



Scheme 1. Contrasting reactivity of β-diketiminate stabilised magnesium complexes towards ppf: (a) deprotonative metallation vs C-F bond activation.

Recently we reported the synthesis and applications of specially designed β-diketiminate stabilized mononuclear Mg systems [(^{Dipp}Nacnac)Mg(TMP)] (**1**) (TMP=2,2,6,6-tetramethylpiperidide; ^{Dipp}Nacnac = Ar*NC(Me)CHC(Me)NAr*; Ar* = 2,6-iPr_2-C_6H_3) and [(^{Dipp}Nacnac)Mg(^{n}Bu)·THF] (**2**).[10] Combining a sterically controlling β-diketiminate ligand with a kinetically-activated basic TMP amide, **1** has emerged as a regioselective base capable of promoting the room temperature direct Mg–H exchange of a range of challenging N-heterocyclic substrates and fluoroarenes such as **ppf** [= 2-(2,4-difluorophenyl)pyridine] (Scheme 1a).[10a] Contrastingly, replacing TMP by a butyl group switches on an alternative reaction pathway, affording the relevant C-F bond activation

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† This is a peer reviewed, accepted author manuscript of the following research article: Bole, L. J., Davin, L., Kennedy, A. R., McLellan, R., & Hevia, E. (2019). Magnesium-mediated arylation of amines via C-F bond activation of fluoroarenes. Chemical Communications, 55(30), 4339-4342. https://doi.org/10.1039/C9CC01670H

product (Scheme 1b).[10b] While the β-diketiminate ligand acts as a spectator in these reactions, it plays a mandatory role facilitating stabilization of the newly formed sensitive anion in the metallation reactions as well as generating a unique coordination environment for Mg, enabling substrate coordination which favours nucleophilic addition/substitution besides controlling the regioselectivity of the Mg for hydrogen exchange reactions.[10]

Expanding the synthetic potential of β-diketiminate stabilised magnesium complexes, here we present their first applications towards promoting regioselective amination of fluoroarenes to access a range of N-aryl tertiary amines.

To begin we elected to prepare a series of new complexes containing a nucleophilic (and less basic than benchmark **1**) magnesium amide functionality by the amine exchange reaction of **1** with aliphatic amines, nBu$_2$NH, piperidine or morpholine in THF at room temperature, which resulted in rapid deprotonation of the respective amine. In all cases we were able to structurally characterise the new magnesium amides [(^{Dipp}Nacnac)Mg(N^{n}Bu$_2$).THF] (**3**), [(^{Dipp}Nacnac)Mg(NC$_5$H$_{10}$)]$_2$ (**4**) and [(^{Dipp}Nacnac)Mg(NC$_4$H$_8$O).THF] (**5**), albeit the data quality of **5** is poor and only suitable for general connectivity (see SI). The molecular structures of **3** and **5** are monomeric with Mg surrounded by 3 N atoms and an O atom of THF. In contrast, **4** surprisingly displays a dimeric rearrangement (Fig. 1), despite piperidine having a nearly identical steric profile to morpholine, which is reminiscent to that described by Hill for the pyrrolidide adduct [(^{Dipp}Nacnac)Mg(NC$_4$H$_8$)]$_2$ (**6**).[11]

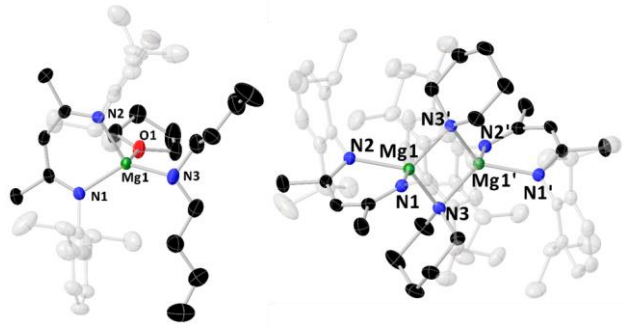


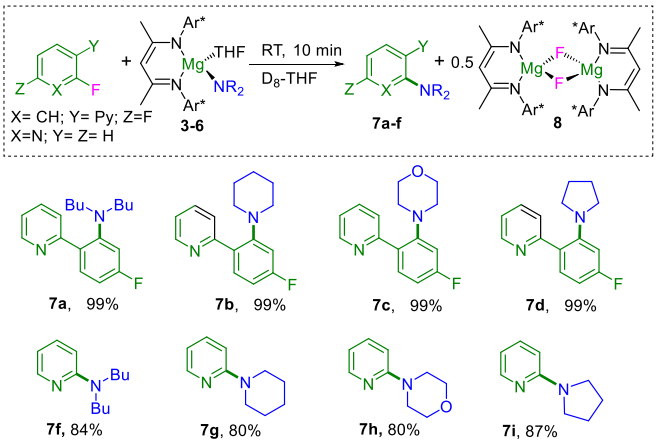
Figure 1 Molecular structures of **3** (left) and **4** (right). Hydrogen atoms are omitted for clarity and thermal ellipsoids are rendered at 30% probability. Dipp substituents drawn as transparent for clarity.

Interestingly, ^{1}H DOSY NMR studies of **4** and **6** revealed that in d_8-thf solution, both species also exhibit monomeric arrangements as those seen in crystalline **3** and **5**. With these potentially nucleophilic sources of amides in hand, we next assessed their suitability for C-F activation using **ppf** and 2-fluoropyridine as model substrates.

A series of reactions between **3**-**6** with 2-(2,4-difluorophenyl)pyridine or 2-fluoropyridine were conducted in J. Young's NMR tubes at room temperature in d_8-THF (Table 1). Monitoring these reactions by ^{1}H and ^{19}F NMR revealed in each case, quantitative conversion (for **ppf**) or (*ca.* 80% for 2-fluoropyridine) to the desired tertiary amine, resulting from a regioselective C-N bond forming/C-F bond cleavage process (Table 1). In all cases the reaction occurs with formation of a large amount of white precipitate, which has been identified as C-F activation coproduct [{(^{Dipp}Nacnac)MgF}$_2$.2THF] (**8**)[12] which can also be seen in small amounts in the ^{19}F NMR spectrum of the reaction crudes at -189 ppm.

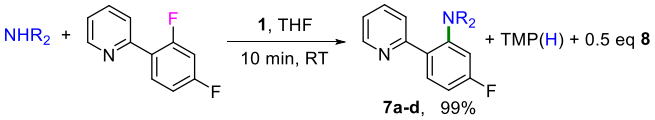
Illustrating the potent nucleophilic power of these magnesium systems, the mild reaction conditions (rt, 10 min) sit in sharp contrast with those recently reported for the lithium-mediated amination of 2(2-fluorophenyl)pyridine with secondary amines, that not only require high temperatures and long reaction times (110^{o}C, 12h), but also a large excess of amine and lithium hydride.[8c] Remarkably, in all cases selective C-F bond activation is observed suppressing completely the competitive deprotonative metallation of the substrate, a selectivity problem which has previously noted when using polar group 1 organometallics.[7,8b] Additionally, while amination of 2-halopyridines has been extensively studied using transition metal catalysis (e.g., using Pd, Ni, Cu or Cr),[13] or by substitution reactions using highly basic lithium amides, investigations of magnesium systems have been scarce. A notable exception is the work of Knochel on amination of pyridine-2-sulfonyl chloride with mixed-metal amides NR$_2$MgCl.LiCl.[14]

Table 1 Reactions of β-diketiminate magnesium amides **3-6** with **ppf** and 2-fluoropyridine.[a][b]



[a] Reactions carried out using 0.25 mml of **ppf** or 2-F-pyridine, 0.25 mmol of relevant Mg amide complex in 0.5 mL of D$_8$-THF. See ESI for experimental details. [b] Yields determined by ^{1}H NMR using 15 or 20 mol% FeCp$_2$ as an internal standard.

Furthermore, *in situ* studies have revealed that arylamides **7a-d** can be formed in similar yields using a one pot approach by reacting the relevant amine with **ppf** in the presence of equimolar amounts of TMP-base **1** (Scheme 2). Despite the fact that **1** has proved to readily deprotonate this substrate at its C3 position on the fluorinated ring (Scheme 1a),[10b] formation of the relevant amide complex **3-6** is preferred, switching on the C-F bond activation reaction pathway.



Scheme 2. One-pot arylation of amides with **ppf** using TMP-amido magnesium complex **1**.

At this point it is evident that sufficiently nucleophilic β-diketiminate magnesium amides, that are monomeric in solution are excellent in promoting C-F activation, thus we decided to test the generality of the reaction using the less nucleophilic amines diphenylamine and aromatic N-heterocycle benzotriazole. Reaction of **1** with both amines resulted in isolation as off-white crystalline solids in each case, corresponding to [(^{Dipp}Nacnac)Mg(NPh_2)] (**9**) and [(^{Dipp}Nacnac)Mg($N_3C_6H_4$)]$_2$ (**10**), in 61 and 55% isolated yields (see ESI for details). X-ray crystallographic studies revealed a monomeric structure for **9**; whereas **10** is a dimer, where the benzotriazolyl anions connect the Mg centres through their N=N junction, giving rise to a six-membered {MgNCMgNC} ring, with each Mg clamped by a β-diketiminate ligand (Fig. 2). Reflecting the lower basicity and higher degree of electronic delocalization on the amido N groups, in both complexes the geometry around this N atom in both complexes is trigonal planar (sum of the angles around N_{amide} is 359.77 and 360.1° for **9** and **10** respectively).

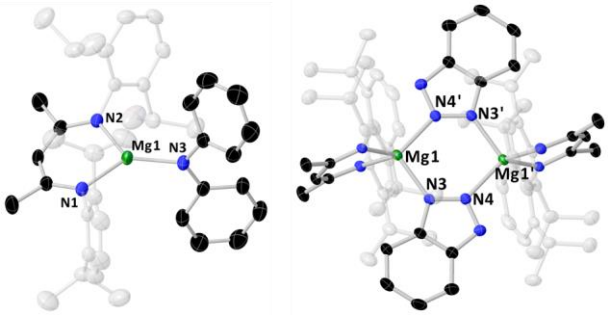
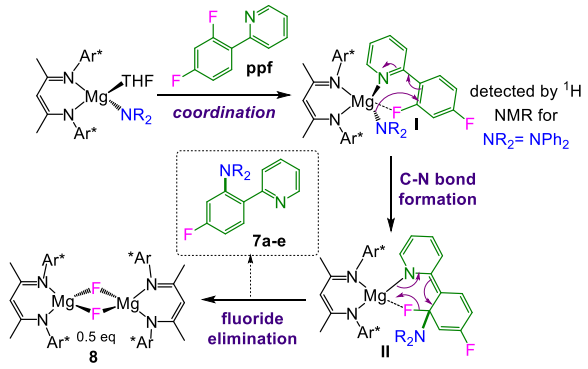


Figure 2 Molecular structures of **9** (left) and **10** (right). Hydrogen atoms are omitted for clarity and thermal ellipsoids are rendered at 30% probability. Dipp substituents drawn as transparent for clarity.

Reactivity studies of **9** and **10** with equimolar amounts of **ppf** show that at room temperature neither of these amido complexes can promote the C-F bond activation reaction. For **9**, by increasing the temperature of the reaction to 70°C for 11h tertiary amine **7e** was formed in a 75% yield (see ESI) whereas in the case of **10** even after 14h at this 110°C no reaction was observed. Revealing a close structure/reactivity interplay, these magnesium-mediated amine arylation processes seem to be limited to aliphatic amines, whereas aromatic ones formed more resonance stabilized magnesium intermediates which react sluggishly with the fluoroarene.

A proposed rationale for how these transition-metal free C-F bond cleavage/C-N bond forming processes may occur is depicted in Scheme 3. First the substrate (as illustrated with **ppf** in Scheme 3) may coordinate to Mg via the pyridyl N, placing the *ortho*-C-F bond of the aryl group, pre-activated by the pyridyl substituent, in close proximity to the reactive magnesium amide bond (intermediate **I** in Scheme 3). While **I** cannot be detected when **ppf** is reacted with Mg amides **3-6** as the reaction occurs almost instantaneously, using less nucleophilic diphenylamide **9** it can be detected spectroscopically. DOSY NMR studies of this proposed intermediate showed that resonances corresponding to **ppf**, and the amide diffuse together with those of the ^{Dipp}Nacnac ligand, confirming that a coordination adduct exists in solution (see ESI). A related pyridine coordination adduct has also structurally characterised by Hill.[15] This scenario, predisposes **ppf** for addition of the amide group to the aryl group generating a new C-N bond (see **II** in Scheme 3) which is followed by the elimination of the highly insoluble fluoride complex **8**, furnishing amination products **7a-d**. A similar pyridyl-directed amination can be envisaged in forming **7e-h**.



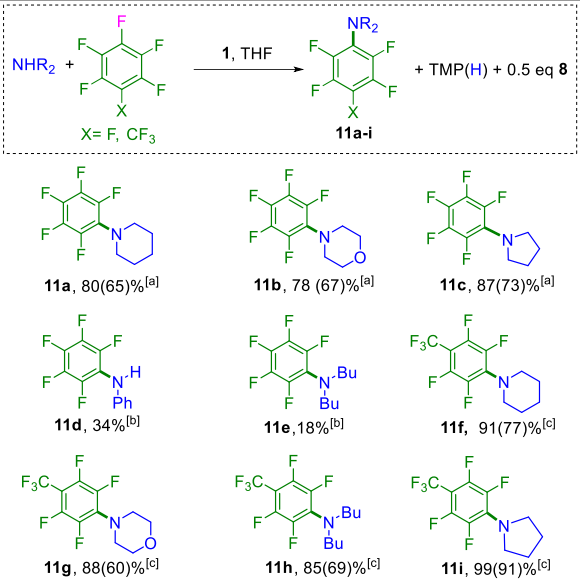
Scheme 3. Proposed reaction sequence for magnesium-mediated C-F bond amination of **ppf**. by **3-6**.

We next pondered if this approach could be extended to other fluoroarenes without a pyridyl directing group. ^{1}H and ^{19}F NMR monitoring of the reaction of piperidide complex **4** with perfluoroarene C_6F_6 showed no C-F bond activation at room temperature. By heating at 70°C over 40h, the ^{19}F spectrum of the reaction mixture showed formation of a new product which exhibiting three resonances in a 2:2:1 ratio -151.2, -164.7 and -165.2 ppm consistent with the activation of one C-F bond in C_6F_6 to form 2,3,4,5,6-pentafluoro-Npiperidide (**10a**), along with a resonance at -189 ppm which can be assigned to fluoride complex **8**. Disappointingly, despite the harsh reaction conditions the conversion observed for **11a** was 26%.

In an attempt to optimise the reaction conditions, we decided to probe microwave radiation which is known to accelerate reaction rates using milder conditions, affording in some cases higher yields with a greater control of the selectivity than that produced by conventional heating.[16] Pleasingly, reaction of **1**, piperidine and hexafluorobenzene in THF in a microwave vial (125 °C, 20 minutes) afforded **11a** in a yield of 80% (Table 2). This approach can also be extended to morpholine and pyrrolidine affording **11b** and **11c** in 78 and 87% yield respectively. On the other hand using primary amine aniline or dibutylamine the yields noticeably dropped (34 and 18% respectively, **11d-e** in Table 2); whereas diphenylamine and benzotriazole fail to react with C_6F_6. Extending this reactivity to octafluorotoluene revealed that efficient and selective C-F activation in just one hour at room temperature in THF affording arylation products **11f-11i** in excellent yields ranging from 99-85% (Table 2). When the reaction of **4** was attempted with less activated fluorobenzene (MW, 125°C, 60 min) only modest conversions to the activation product **11j** were obtained (20%), however it is important to note that no other reactions were observed (i.e. deprotonative metalation) (see SI for details). These results demonstrate the ability of β-

diketiminate stabilised magnesium amides to promote C-F activation of perfluoroarenes via the installation of synthetically relevant C-N bonds. For these reactions where the substrate lacks of a pyridyl directing group, approximation of the fluoroarene to the magnesium amide complex can be envisaged to occur by the formation of Mg..F-C interactions which could then facilitate the nucleophilic attack. The key role of these interactions has been elegantly demonstrated by Crimmin for the addition of fluoroarenes and fluoroalkanes to low valent Mg-Mg complexes.[17]

Table 2 C-F activation of non-directed fluoroarenes



[a] Reactions were carried out in a microwave reactor on a 1 mmol (0.5 M) scale in THF solvent at 125 °C for 20 min. Yields calculated against 10 mol% $FeCp_2$ as an internal standard. **11a-11c** purified and isolated by column chromatography. Isolated yields shown in brackets [b] Reaction time was extended to 1h. [c] Yields correspond to reactions carried out in a Schlenk flask for 1 h at room temperature in THF solvent. NMR yields determined against 10 mol% $FeCp_2$ as an internal standard. Isolated yields shown in brackets.

In summary, pushing forward the synthetic utility of β-diketiminate stabilised magnesium complexes, by synthesizing and structurally defining a range of nucleophilic amide complex, a new method for arylating amines via C-F bond activation of fluoroarenes is presented. Nucleophilic substitution is facile at room temperature when assisted by a pyridyl directing group or using perfluorinated octafluorotoluene; whereas for hexafluorobenzene, microwave assistance is required. Structural insights on how the reactivity profiles of these magnesium species can be finely tuned have also been unveiled.

We thank the European Research Council (ERC StG, MixMetApps) and the EPSRC (EP/N011384/1) for their generous sponsorship of this research. We also thank Prof. Robert E. Mulvey and Dr. Charles T. O'Hara for insightful discussions. Data supporting this research are openly available from www.datasettbc.com.

Conflicts of interest

There are no conflicts to declare.

Notes and references

Keywords: magnesium • amides • fluoroarenes • C-F bond activation •C-N bond formation • C-F bond activation •β-diketiminate

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