
This version is available at https://strathprints.strath.ac.uk/62132/

Strathprints is designed to allow users to access the research output of the University of Strathclyde. Unless otherwise explicitly stated on the manuscript, Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Please check the manuscript for details of any other licences that may have been applied. You may not engage in further distribution of the material for any profitmaking activities or any commercial gain. You may freely distribute both the url (https://strathprints.strath.ac.uk/) and the content of this paper for research or private study, educational, or not-for-profit purposes without prior permission or charge.

Any correspondence concerning this service should be sent to the Strathprints administrator: strathprints@strath.ac.uk
Ligand-induced reactivity of β-diketiminate magnesium complexes for regioselective functionalization of fluoroarenes via C–H or C–F bond activations†

Laia Davin, Ross McLellan, Alan R. Kennedy‡ and Eva Hevia*‡

Using β-diketiminate Mg(ii) complexes containing either alkyl, aryl or amide groups, the regioselective functionalization of a wide range of fluoroarenes is accomplished but in uniquely different ways. Overcoming common limitations of traditional s-block bases, kinetically activated [[DippNacnac]Mg(TMP)] (1) deprotonates these molecules at room temperature, trapping sensitive fluoroaryl anions that can then engage in Negishi cross-coupling; whereas [[DippNacnac]Mg(R)THF] (R = 8Bu, Ph, benzofuryl) have proved to be effective reagents for C–F bond alkylation/arylation via pyridine directed C–F bond cleavage.

Fluoroarene molecules represent one of the most prevalent entities within biologically active and pharmaceutical compounds. The regioselective manipulation of such significant synthetic building blocks is therefore of paramount importance in the quest for efficient molecular design strategies, especially as naturally occurring fluoroarenes are exceptionally rare. Two powerful methods in this regard are metallation, that is, a C–H/C–M conversion, and C–F activation. The latter has predominantly been investigated employing carefully designed systems that favour C–F activation over competing C–H activation processes. Main group activity in C–F activation is much rarer, though it has been recently shown that Grignard reagents can undergo metatllation and C–F bond activation processes. While the β-diketiminate ligand acts as a spectator in the metallation step, it plays a major role facilitating the trapping and stabilization of the newly formed sensitive heterocyclic anions. The kinetic basicity of the TMP ligand is best illustrated when comparing the reactivities of 1 with those observed for the n-butyl analogue [[DippNacnac]Mg(8Bu)THF] (2), in which most cases only forms coordination adducts with these N-heterocyclic substrates. During these studies the substituted pyridine 2-(2,4-difluorophenyl)pyridine (ppf) was also regioselectively metallated ortho to both fluorine substituents, without observing decomposition of the metallated intermediate at room temperature, hinting at the potential of [[DippNacnac]Mg(TM)] (1) to promote Mg-H exchange processes for fluorinated aromatic molecules.

Opening wider the synthetic relevance of β-diketiminate stabilised magnesium complexes, here we present their applications for functionalisation of challenging fluoroaromatic substrates, uncovering their ability to promote regioselective metallation and C–F bond activation processes.

We started our investigations assessing the reactivity of 1 with a range of fluorinated aromatics at room temperature in d₈-THF in a J. Young NMR tube (Table 1). All reactions were probably as a consequence of their reduced metallating power, recent reports have shown that Grignard reagents can undergo coupling reactions via C–F bond activation.

Exploiting ligand–ligand cooperation by combining a sterically operative β-diketiminate ligand with a kinetically-activated basic TMP amide group, we recently reported the regioselective magnesiumation of a range of N-heterocyclic molecules such as diazines and 1,3-benzoazoles using [[DippNacnac]Mg(TM)] (1) [[DippNacnac = Ar*N(Me)CHC(Me)NAr*; Ar* = 2,6-Pr₂-C₆H₃; TMP = 2,2,6,6-tetramethylpiperidide] (Fig. 1). While the β-diketiminate ligand acts as a spectator in the metallation step, it plays a major role facilitating the trapping and stabilization of the newly formed sensitive heterocyclic anions. The kinetic basicity of the TMP ligand is best illustrated when comparing the reactivities of 1 with those observed for the n-butyl analogue [[DippNacnac]Mg(8Bu)THF] (2), in which most cases only forms coordination adducts with these N-heterocyclic substrates. During these studies the substituted pyridine 2-(2,4-difluorophenyl)pyridine (ppf) was also regioselectively metallated ortho to both fluorine substituents, without observing decomposition of the metallated intermediate at room temperature, hinting at the potential of [[DippNacnac]Mg(TM)] (1) to promote Mg-H exchange processes for fluorinated aromatic molecules.

Opening wider the synthetic relevance of β-diketiminate stabilised magnesium complexes, here we present their applications for functionalisation of challenging fluoroaromatic substrates, uncovering their ability to promote regioselective metallation and C–F bond activation processes.

We started our investigations assessing the reactivity of 1 with a range of fluorinated aromatics at room temperature in d₈-THF in a J. Young NMR tube (Table 1). All reactions were probably as a consequence of their reduced metallating power, recent reports have shown that Grignard reagents can undergo coupling reactions via C–F bond activation.

Exploiting ligand–ligand cooperation by combining a sterically operative β-diketiminate ligand with a kinetically-activated basic TMP amide group, we recently reported the regioselective magnesiumation of a range of N-heterocyclic molecules such as diazines and 1,3-benzoazoles using [[DippNacnac]Mg(TM)] (1) [[DippNacnac = Ar*N(Me)CHC(Me)NAr*; Ar* = 2,6-Pr₂-C₆H₃; TMP = 2,2,6,6-tetramethylpiperidide] (Fig. 1). While the β-diketiminate ligand acts as a spectator in the metallation step, it plays a major role facilitating the trapping and stabilization of the newly formed sensitive heterocyclic anions. The kinetic basicity of the TMP ligand is best illustrated when comparing the reactivities of 1 with those observed for the n-butyl analogue [[DippNacnac]Mg(8Bu)THF] (2), in which most cases only forms coordination adducts with these N-heterocyclic substrates. During these studies the substituted pyridine 2-(2,4-difluorophenyl)pyridine (ppf) was also regioselectively metallated ortho to both fluorine substituents, without observing decomposition of the metallated intermediate at room temperature, hinting at the potential of [[DippNacnac]Mg(TM)] (1) to promote Mg-H exchange processes for fluorinated aromatic molecules.

Opening wider the synthetic relevance of β-diketiminate stabilised magnesium complexes, here we present their applications for functionalisation of challenging fluoroaromatic substrates, uncovering their ability to promote regioselective metallation and C–F bond activation processes.

We started our investigations assessing the reactivity of 1 with a range of fluorinated aromatics at room temperature in d₈-THF in a J. Young NMR tube (Table 1). All reactions were
Table 1 Metallation of fluorinated aromatics with 1, and subsequent Negishi cross-coupling with iodobenzene where applicable

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Metallated product</th>
<th>Cross-coupling product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorobenzene</td>
<td>(3a) 74% (66)</td>
<td>—</td>
</tr>
<tr>
<td>1,3-Difluorobenzene</td>
<td>(3b) 78% (43)</td>
<td>(4a) 64% (70)</td>
</tr>
<tr>
<td>1,3,5-Trifluorobenzene</td>
<td>(3c) ≥99% (66)</td>
<td>(4b) 63% (60)</td>
</tr>
<tr>
<td>1,2,4,5-Tetrafluorobenzene</td>
<td>(3d) ≥99% (56)</td>
<td>(4c) 65% (63)</td>
</tr>
<tr>
<td>Pentafluorobenzene</td>
<td>(3e) ≥99% (66)</td>
<td>(4e) 69% (69)</td>
</tr>
<tr>
<td>2-(2,4-Difluorophenyl)pyridine</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a Yields determined by $^1$H NMR using ferrocene as internal standard after 1 h at RT. b Isolated yields in parenthesis after 2 h at RT. c No reaction after 24 h, heating at 80 °C. d Full conversion after 2 h at RT. e General conditions: 5 mol% Pd(PPh$_3$)$_2$, 1.25 equivalents PhI. f Except 10 mol% Pd(PPh$_3$)$_2$ and 2 equivalents PhI. g 2 equivalents PhI. h Reacted as an isolated solid. i Prepared in situ and reacted.

followed by $^1$H and $^{19}$F NMR spectroscopy (see ESI† for details). While 1 fails to deprotonate fluorobenzene (entry 1), even under forcing conditions (80 °C, 24 h), the reaction with 1,3-difluorobenzene afforded [2-(DippNacnac)Mg-1,3-F$_2$-C$_6$F$_4$H$_2$] (3a) in 74% yield after just one hour at room temperature (entry 2). Further monitoring of this reaction showed that after 2 h the conversion of 1 into 3a is nearly quantitative. Similarly, 1,3,5-trifluorobenzene (2 hours), 1,2,4,5-tetrafluorobenzene and pentafluorobenzene (both 1 hour) all undergo facile Mg–H exchange processes quantitatively at room temperature giving [2-(DippNacnac)Mg-1,3,5-F$_3$-C$_6$F$_4$H$_2$] (3b), [3-(DippNacnac)Mg-1,2,4,5-F$_4$-C$_6$F$_4$H] (3c) and [(DippNacnac)Mg-C$_6$F$_3$] (3d) (entries 3–5). This reactivity pattern is consistent with the increase in the C–H acidity of fluoroaranes as the number of F atoms in the aromatic ring increases.$^{11}$ Metallation products 3a–3d were isolated as pure crystalline solids in yields ranging from 43–66% (see ESI† for experimental details and full spectroscopic characterization).

Insight into the solution constitutions of these compounds in THF was gained by Diffusion Ordered Spectroscopy (DOSY) experiments,$^{12}$ which suggest these new complexes adopt monomeric structures in this coordinating solvent. Consistent with this solution picture, X-ray crystallographic studies revealed the monomeric structure of 3c, confirming magnesiation of 1,2,4,5-tetrafluorobenzene had occurred (Fig. 2) with a {(DippNacnac)Mg} fragment occupying the position previously filled by a H atom, binding to the C3 atom of the fluoroarene [i.e., C30 in Fig. 1, Mg1–C30, 2.1705(19) Å]. Although the Mg–F distances are too long to suggest some significant interaction, F4 forms a shorter contact than F1 [3.2773 vs. 3.3214 Å]. While from a synthetic viewpoint the isolation and characterization of 3a–d as the result of a direct Mg–H exchange process is unique, it should be noted that the structure of 3c is similar to those reported by Crimmin for the products of C–F bond addition of perfluorinated arenes to Mg–Mg bonds of Mg(i) complex [(DippNacnac)Mg]$_2$.b

These findings establish 1 as an effective and regioselective base for the metallation of hypersensitive fluorinated organic building blocks. A significant advantage of 1 over conventional s-block metallating reagents is its ability to trap and stabilise the emergent fluoroaryl anions. Metallated intermediates 3a–e display a remarkable stability in solution. Taking 3b as an exemplar, $^1$H and $^{19}$F NMR reaction monitoring experiments in the presence of benzyne trapping agents such as durene or 1,3-diphenylisobenzofuran show no evidence of decomposition, even in the face of harsh reaction conditions (80 °C, 5 h). Considering the relative polarity of the Mg–C bonds and the proximity of F atoms to Mg (vide supra), the robustness of these complexes may seem rather unexpected. However, this can be rationalised in terms of the steric protection provided by the bulky β-diketiminate ligand, providing shelter to the newly formed Mg–C bond, which confers a greater degree of stability to these sensitive carbonanionic species. This behaviour contrasts with our recent work on the aluminamation of fluoroarenes by using Li/Al basic combinations, where the metallated products decompose at room temperature to eliminate lithium fluoride aluminate [LiAl(F)(TMP)Bu$_2$].$^{13}$ Chen recently reported
a similarly negative result for a novel scandium-mediated dehydro-
fluorination of fluoroarenes, proposed to occur by initial metal-
lation of the substrate which in turn undergoes rapid fluoride
elimination with subsequent benzyne formation.14

Exemplifying the further functionalisation of these sterically
shielded magnesiated carbanions, complexes 3a–d as well as
complex 3e (resulting from the metellation of ppf in the position
of the C3 atom of the fluoroaryl ring),10† proved to be valuable
precursors in Negishi type cross-coupling reactions, using iodo-
benzene as the electrophilic coupling partner (Table 1). Reactions
were carried out using stoichiometric amounts of ZnCl₂, two
equivalents of PhI and 10 mol% of Pd(PPh₃)₄ (see ESI† for details).
After an organic work-up, and flash column chromatography the
relevant non-symmetric bis(aryls)

elimination with subsequent benzyne formation.

Interestingly, reaction of

with

ppf

involving activation of their C–F bonds. Interestingly, reaction of

1,3,5-trifluorobenzene no reaction was observed at room tem-
perature and formation of metallation product 3b only occurs at

elevated temperatures (60 °C for 138 hours). Notably, reactions
between 2 and the present fluoroarenes resulted, in some
cases, in formation of small amounts of highly insoluble crystals
discovered to be [[[[DippNacnac]Mg(C₆H₄F₃)]−THF]₃ (5).15,16

As described above, since 3a–e are remarkably stable towards
fluoride elimination even at high temperatures, this suggested an
alternative reaction pathway for 2 with these fluoroarene substrates
involving activation of their C–F bonds. Interestingly, reaction of 2
with pff over 24 hours at room temperature in toluene resulted in
almost quantitative formation of fluoride complex 5, indicating that
C–F bond activation of the substrate has readily occurred.
Investigating this reactivity more thoroughly, the reaction filtrate
was subjected to aqueous work-up and revealed that a new
compound, (2-(2-butyl-4-fluorophenyl)pyridine), 7a, formed in
92% yield (Scheme 1).

7a can be envisaged as a cross-coupling product between 2
and pff via cleavage of the C–F bond ortho to the pyridyl ring,
without the need of transition metal catalysis. A proposed rationale
for the formation of 7a is depicted in Scheme 1. Firstly, the substrate can coordinate to 2 via a dative bond from
the pyridyl nitrogen atom (I in Scheme 1). While this complex
cannot be intercepted, related coordination adducts of 2 have been
structurally defined for pyrazine and N-methyl benzimidazole.10
This scenario can be considered to doubly activate the ortho C–F
bond by both the pyridyl directing group (which is also electron-
withdrawing) and the proximity of the fluorine to the metal atom.
This step seems to be key as other fluoroarenes where pre-
coordination is not possible such as C₆F₆ or C₆HF₆ fail to react with 2. Secondly, pff is now predisposed for the addition of
the alkyl group to the benzene ring forming a new C–C bond (II in
Scheme 1), followed by elimination of fluoride complex 5, via the
cleavage of the C–F bond, affording alkylation product 7a. A related
pyridyl coordination assisted ortho-selective C–F bond activation
process has been reported by Zhang for Pd-catalysed hydro-
defluorination of polyfluoroarenes with Et₃SiH.17 Within Mg chem-
istry, Cao has noted a similar coordination effect for the reactions
of Grignard reagents with polyfluorouracenes, although no insights
on the constitution of the metallated intermediates are provided
and conditions required are significantly harsher than those
observed for 7a (2.5 molar excess of RMgX, 6–24 h at 65 °C).9d
Interestingly our approach is not limited to 2 and it also works well
for aryl complex [[[[DippNacnac]Mg(C₆H₄)THF] (13) affording C–F
arylation product 7b in an 82% yield (Scheme 1).

The possibility that formation of 7a–b occurring via an
alternative radical pathway was investigated by carrying out the
reaction of 2 and pff in the presence of radical trapping
agent TEMPO (2,2,6,6-tetramethyl-1-piperidinomylx). In these
studies TEMPO, which is known to exhibit extensive coordina-
tion chemistry with Mg,18 acts as a mere spectator, affording 7a
in comparable yields to those observed when TEMPO is not present (vide supra).

Considering the divergent reactivities of 1 and 2 towards
ppf, which enable the regioselective activation of a C–H or C–F
bond of this substrate, to afford 3e or 7a respectively, a
competition experiment was performed between stoichiometric
1, 2 and pff in a 1 : 1 : 1 ratio (Scheme 2, left).19 H and 19F NMR
monitoring of the reaction revealed that under these conditions
C–H metallation product 3e is regioselectively obtained, whereas
Bu complex 2 remains intact. This demonstrates the
kinetic superiority of 1. Contrastingly when 2 is reacted with one
equivalent of the amine TMP(H) and pff at 80 °C, only
formation of C–F activation product 7a and fluoride complex 5
is observed (Scheme 2, right). This is somehow surprising
as under these more forcing conditions it could have been
anticipated that some of the amine TMP(H) could react with 2
to afford amide 1 in situ, which reacts faster than 2 with pff
to form metallation product 3e. Even if 1 and TMP(H) are allowed
to stir for 3 h before introducing pff, only formation of 5 and 7a
is observed.19

These studies illustrate how the chemical profiles of these
Mg(α) β-diketiminate complexes can be finely tuned for C–H/
C–F activation by modifying the nature of the remaining ligand
(Bu vs. TMP). This can be exploited for tandem functionalization
of organic molecules as shown in Scheme 3 for benzofuran. Reaction
with 1 accomplishes direct magnesiation of its α-C–H bond,
affording 8 (78% isolated yield) which structure was established by X-ray crystallography (Scheme 3, see ESI† for details). Addition of ppf enables the activation of the ortho C–F bond, to give coupled product 7c (71% yield) resulting from the cross coupling of benzoifuran and ppf, with the concomitant elimination of fluoride complex 5.

In conclusion, two new Mg-mediated strategies for the functionalization of challenging fluoroarenes via C–H or C–F bond activation processes are presented. Exploiting ligand-ligand cooperation, through a β-diketiminato-sheltered Mg centers, the reactivity of these systems can be finely tuned allowing excellent control of the regio- and chemoselectivity under mild reaction conditions. Tandem protocols, combining these two new reactivity profiles in sequence have uncovered a new method for transition metal-free cross couplings of heterocycles with ppf.

We thank the European Research Council (ERC StG, MixMetApps) and the EPSRC (EP/N011384/1) for their generous sponsorship of this research. Data supporting this research are openly available from http://dx.doi.org/10.15129/6b3146f2-fdd6-41b8-a546-ba79e8254174.

Scheme 2 Tuning C–H and C–F activation of ppf with magnesium complexes 1 and 2.

Scheme 3 One pot coupling of benzoifuran and ppf via tandem Mg-mediated C–H/C–F bond activation processes.

Conflicts of interest
There are no conflicts to declare.

Notes and references
16 Fluoride complex [[[[Nacnac]MgF(THF)]2]5] [5] has also been identified as a byproduct for reaction of perfluoroarenes with Mg(i) complex [[[Nacnac]Mg]2]see ref. 7b.
19 The lack of reactivity of 2 with TMP[H] contrasts with that reported by Gibson for the reactions of 2 with NHPr2 or NH(SiMe3)2 which form the relevant Mg amide complexes, see: A. P. Dove, V. C. Gibson, P. Horrín, E. L. Marshall, J. A. Segal, A. J. P. White and D. J. Williams, Dalton Trans., 2003, 3088.