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Zincate-Mediated Arylation Reactions of Acridine: Pre- and Post-arylation Structural Insights

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Supporting Information Placeholder

ABSTRACT: This study explores the synthetic utility of homo(aryl) lithium zincate reagents [LiZnPh₂] (2) and [Li₂ZnPh₃] (3), made by co-complexation of variable amounts of their monometallic components LiPh and ZnPh₂ (1), as chemoselective nucleophilic arylating reagents. Both lithium zinctes 2 and 3 were characterized by multinuclear (¹H, ¹³C and ⁷Li) NMR spectroscopy and in the case of 2, a classical reagent in heterobimetallic chemistry, the molecular structure of its O₆Bu₂ solvate [LiZnPh₂(O₆Bu₂)] 2·O₆Bu₂ has been established by X-ray crystallography. Using synthetically relevant N-heterocyclic molecule acridine (acr, NC₆H₄), a new zincate-mediated arylating approach is demonstrated which allows the chemoselective arylation of acridine at its C₉ position, affording 9,10-dihydro-9-phenylacridine 4 in a 95% yield using microwave irradiation (125°C, 20 minutes). These conditions contrast with previous transition-metal catalyzed methodologies using ZnPh₂ as an arylating reagent, which require significantly longer reaction times (130°C, 20 h). Oxidation of 4 with DDQ furnished 9-phenylacridine 5 in a 71% yield. New insights into the constitution of the intermediate organometallic species involved in these reactions prior to the hydrolysis step have been gained by trapping homometallic ([THF]₃Li(NC₆H₄Ph)₂) (6). Interestingly the reaction of acr with 3 equivalents of PhLi/TMEDA led to the isolation of a different product, namely novel paramagnetic ([THF]₃(TMEDA)Li(NC₆H₄Ph⁺⁻) (7) which contains a radical anion of 9-phenylacridine. The structure of donor-acceptor complex (7)ZnPh₂ (8) is also been included as a result of the reaction of 1 with acr.

INTRODUCTION

Nitrogen-containing heteroaromatic ring systems are found widely in natural products, biologically active molecules and pharmaceuticals.¹ Acridine (acr) scaffolds in particular (Figure 1) exhibit important biological activities including anticancer,² antibacterial¹⁴ and antifungal actions.³ Notably their capacity to function as an intercalating ligand with DNA and related systems has earned them a prominent place in the field of chemical biology.⁴ Surprisingly, despite their synthetic relevance, the methods available for the efficient functionalisation of non-substituted acridine motifs are limited.⁵ Thus, most of the approaches described in the literature rely heavily on the assembly of pre-functionalised ring systems.¹⁶,¹⁷,¹⁸ This method builds on the well-established reactivities of polar organolithium and Grignard reagents, which undergo 1,2-addition to pyridines, affording dihydropyridines which can subsequently be re aromatized via oxidation, to yield 2-substituted products.⁵ By using either nickel¹⁴ or rhodium¹⁵ catalysts, it is possible to activate milder organozinc reagents such as ZnPh₂ (1), which offer greater regioselectivities and functional group tolerance, towards the nucleophilic arylation of the electron-deficient N-heterocyclic substrate.¹⁶ Mechanistic studies suggest that in this approach ZnPh₂ plays an important role, by activating the aromatic substrate and transferring its aryl substituent to the transition metal catalyst⁶ as well as acting as an internal oxidant. Notwithstanding, it should be noted that these reactions still require the use of harsh reaction conditions, involving long reaction times (up to 20 hours) and high temperatures (60 – 130°C).¹⁶,¹⁷ Contrasting with this approach, we have recently disclosed a straightforward transition-metal free method which allows the efficient chemoselective C-H alkylation of pyrazine under mild reaction conditions (room temperature, 30 minutes) using the lithium homoalkylzincate [(PMDETA)LiZnBu₃] (PMDETA = N₅N⁺,N''⁺,N⁴⁺-pentamethyldiethylenetriamine) (Scheme 1).⁹ Structural characterization of the organometallic intermediate prior to the hydrolysis step, I (Scheme 1) showed that the addition of a tert-butyl group from the zincate anion.
had taken place at the C2 position of the heterocycle, bringing about its dearomatisation. Significantly, neutral ZnBu₂ to its own fails to promote the addition of a Bu₂ group to pyrazine, demonstrating that formation of 1 is a genuine example of cooperative bimetallic synthesis. The greater nucleophilic power of the lithium zincate species in comparison to that of neutral organozinc reagents has also been assessed using theoretical calculations by Uchiyama et al. within the context of 1,2 addition reactions to formaldehyde. Similarly, work carried out by Ishihara and our group has shown the successful chemoselective alkylation of ketones by magnesium tri(alkyl) zincates generated in situ via salt-metathesis of the relevant Grignard reagents and ZnCl₂. The enhanced reactivities exhibited by these mixed-metal systems can be rationalized in terms of metal-metal cooperative effects. Thus, by forming a zincate anion it is possible to overcome the large kinetic barrier of the lower polarity Zn-C bonds in neutral ZnR₂ reagents, but the more electropositive metal present in these reagents (either Li or Mg) also plays a major role in these transformations, acting as an internal Lewis acid, by anchoring the organic substrate (thus lowering entropic barriers) and facilitating its nucleophilic attack by the \{ZnR₃\}⁻ anion.

**Scheme 1** Zincate-mediated regioselective C-H alkylation of pyrazine.

Building on these initial studies, herein we extend this bimetallic approach using lithium ary1 zincates combinations to promote transition-metal-free, direct arylation of electron-deficient N-heterocycles, employing the biologically significant substrate acidine (acr) as a case study. By isolating key organometallic intermediates involved in these reactions prior to the hydrolysis/oxidation stages new insights have been gained into how these bimetallic arylating reagents operate.

**RESULTS AND DISCUSSION**

**Synthesis and characterization of homolectic aryl lithium zincates.** To avoid possible side reactions, for this study we employed the homolectic aryl zincates, \[\text{Li}_{2}\text{ZnPh}_{3}\] (2) and \[\text{Li}_{2}\text{ZnPh}_{4}\] (3). Pioneered by Wittig in 1951, heterobimetallic 2 is a classical reagent in mixed-metal chemistry, as the study of its reactivity for the deprotonation of fluorene constitutes one of the first reported synthetic applications of alkali-metal zincate reagents. In this epochal report, 2 is prepared in situ by reacting equimolar amounts of PhLi and ZnPh₂ in diethyl ether. Using a similar interlocking co-complexation approach, we began our investigations by exploring the reactions of different stoichiometries of phenyllithium and ZnPh₂ (1). A 1:1 ratio of these monometallic aryl reagents in a THF/hexane solvent mixture, furnished Wittig’s lithium tris(aryl) zincate \[\text{Li}_{2}\text{ZnPh}_{3}\] (2) as a microcrystalline solid in a 68% yield. Its higher-order congener \[\text{Li}_{2}\text{ZnPh}_{4}\] (3) was isolated as a colorless oil using the same method but employing 2 molar equivalents of PhLi (Scheme 2). It should be noted that compounds 2 and 3 are obtained with were obtained with three and four THF solvating molecules respectively. Both lithium zincates 2 and 3 were characterized in de-THF solutions by multinuclear \(^1\text{H}, ^{13}\text{C}\) and \(^7\text{Li}\) NMR spectroscopy (Table 1). For classical zincate 2, crystals of its dibutyl ether solvate \[\text{Li}_{2}\text{ZnPh}_{3}(\text{OBu})_{2}\] (2·OBu₂) could be isolated by carrying the co-complexation reaction in neat hexane using a commercial solution of PhLi in dibutyl ether, and its solid-state structure was determined by X-ray crystallographic studies (Figure 2).

**Scheme 2** Interlocking co-complexation reactions to form lithium phenyl zincates 2 and 3.

In the crystal 2·OBu₂ forms a contacted ion-pair lithium zincate arrangement. Zinc is sigma bonded to three phenyl groups in a trigonal planar geometry (sum of the angles around Zn = 359.99°); whereas lithium α-engages with two of the three Ph rings, adopting an orthogonal disposition (dihedral angle between the plane defined by C13-C18 and C1-C6 phenyl rings and the plane defined by C13Li1C1, 77.9(1)°) and is further solvated by two molecules of di-n-butylether (Figure 2). It should be noted that a similar distinct σ/π bonding preference of Zn and the alkali-metal in aryl zincate intermediates has been previously described in the literature within the context of alkali-metal zinication (AMM/Zn) chemistry of aromatic substrates, where it seems to play an important role in tuning the overall regioselectivity of the metallation processes.

**Figure 2** Molecular structure of \[\text{Li}_{2}\text{ZnPh}_{3}(\text{OBu})_{2}\] (2·OBu₂), with ellipsoids drawn at 30% probability level and hydrogen atoms and minor disorder on the OBu₂ ligands omitted for clarity. Selected bond lengths (Å) and angles (°): Zn1-C1 2.034(3), Zn1-C7 1.99(1), Zn1-C13 2.032(3), Li1-C1 2.494(5), Li1-C6 2.786(5), Li1-C13 2.521(5), Li1-C18 2.832(5), C7-Zn1-C13 122.2(10), C7-Zn1-C1 120.77(11), C13-Zn1-C1 117.00(10), O1-Li1-C1 113.9(2), O1-Li1-C13 98.1(2), O1-Li1-O2 112.8(3).

This contacted structure of 2·OBu₂, with Li and Zn separated by 2.753(4) Å contrasts with that reported for the same zincate anion in \[\{\text{Mg}_{2}\text{Br}_{2}(\text{THF})_{6}\}\] (ZnPh₂), which exhibits a solvent-separated ion pair structure. Although the average Zn-C bond distances for each compound are similar (2.019 Å for 2·OBu₂ vs. 2.007 Å for the Mg-zincate), a close inspection of the individual values shows that the Zn-C bond distance involving the Ph groups which interact with the Li atoms in 2·OBu₂ are marginally elongated (2.034(3) and 2.032(3) Å) compared to that observed for the terminal Ph group (1.991(2) Å).
found in the homometallic precursor \([\text{ZnPh}_2]\) (1), which displays a simple dimeric motif \([\text{ZnC}]_2\) (average \(\text{Zn-C} \) bond distance, 2.207 Å).\(^{21}\) Although there is only a handful of tris(aryl) alkali-metal zincates structurally characterized,\(^{22}\) in most cases their aryl groups carry heteroatomic substituents, such as alkali-metal zincates structurally characterized,\(^{23}\) as an example, to the lithium atom via \(\eta^2\) π-contacts involving their \(\text{ipso}\) and one of their \textit{ortho} carbons, with Li-C distances ranging from 2.494(5) to 2.832(5) Å. These values are considerably longer than those previously found in structures of \(\text{PhLi}_{2}\) or \(\text{CONPr}_{2}\) which dative stabilize the alkali-metal. Contrastingly, in \(\text{2-OBu}_{2}\), two of the phenyl rings coordinate to the lithium atom via \(\eta^2\) π-contacts and/or \(\eta^1\) \(\text{C}'s\) in the spectra of \(\text{PhLi}_{2}\) 

Multinuclear \(^{1}H, ^{13}C\) and \(^{7}Li\) NMR spectroscopic studies of \(\text{2}\) confirmed its bimetallic constitution in deuterated THF solutions (Table 1). The \(^1\text{H}\) NMR spectrum showed a single set of signals for the \(\text{Ph}\) groups (see Supporting Information and Table 1) consistent with the formation of solvent-separated ion-pair species in solution, where all the phenyl groups are equivalent. Its \(^{13}C\) NMR spectrum displayed an informative resonance at 168.3 ppm for the \textit{ipso} \(\text{C}\) of the \(\text{Ph}\) groups, at a chemical shift intermediate to those observed for the relevant \textit{ipso} \(\text{C}\)'s in the spectra of \(\text{PhLi}\) (187.5 ppm) and \(\text{Ph}_2\text{Zn}\) (156.8 ppm). Following a trend previously reported in NMR studies of alkali-metal zincates,\(^{21}\) this value is closer to that exhibited by the zinc species than the lithium precursor, indicative of a significant proportion of “zinc-character” being retained in the mixed-metal species \(\text{2}\). The presence of lithium was confirmed by a sharp singlet at 1.09 ppm in the \(^{7}\text{Li}\) NMR spectrum. Interestingly, \(^1\text{H}-^{7}\text{Li}\) -HMQC experiments carried out on solutions of \(\text{3}\) in deuterated THF and \(\text{C}_6\text{D}_6\) solutions, suggested that the structure of this zincate in solution changes depending on the donor ability of the deuterated solvent. Thus, in \(\text{C}_6\text{D}_6\)-THF solutions, no HMQC cross-peaks were observed for the interaction of \(^{7}\text{Li}\) with any of the aromatic protons of the phenyl groups, supporting the formation of solvent-separated ion-pair species. Contrastingly, using \(\text{C}_6\text{D}_6\) solutions, a strong interaction between \(^{7}\text{Li}\) and the \textit{ortho}-\(\text{H}\) of the \(\text{Ph}\) groups was observed which is consistent with a contacted-ion pair structure, similar to that found in the solid state for the dibutyl ether solvate \(\text{2.2OBU}_{2}\) (see Supporting Information for details).

Although the higher-order trend could only be isolated as a colorless oil and therefore its structure could not be determined crystallographically, it is pertinent that a few related lithium tetraorganozincates of general formula \(\text{Li}_2\text{ZnR}_4\) (R = alkyl, aryl) have been structurally defined, forming contacted ion-pair aggregates, with two Li cations oppositely disposed to a central dianionic \(\{\text{ZnR}_4\}^2\) tetrahedron within a trinuclear Li...Zn...Li chain arrangement.\(^{19,20,25}\) The same structural motif has been described previously by Weiss in the magnesium analog of \(\text{3}\), tetra(aryl)magnesium \([\text{TMEDA}]_2\text{Li}_2\text{MgPh}_3\).\(^{26}\) Compound \(\text{3}\) was characterized by a combination of \(^1\text{H}, ^{13}C\) and \(^{7}\text{Li}\) NMR spectroscopic studies (see Supporting Information and Table 1). A singlet (1.63 ppm) in the \(^{7}\text{Li}\) NMR spectrum of \(\text{3}\) in deuterated THF solution established the presence of lithium. Its \(^1\text{H}\) NMR spectrum revealed a single set of resonances for the \(\text{Ph}\) groups, at similar chemical shifts to those found for the tris(aryl) derivative \(\text{2.2}\). Reflecting the dianionic character of \(\text{3}\), the \textit{ipso} \(\text{C}\) of the \(\text{Ph}\) groups resonates at 173.1ppm, which is noticeably deshielded to that observed for monoanionic \(\text{2}\) (169.3 ppm) and neutral \(\text{ZnPh}_2\) (156.8 ppm).\(^{17a}\)

**Reactivity studies: zincate-mediated arylation of acridine.** As mentioned above, previous studies have shown that \(\text{ZnPh}_2\) (1) is unable to transfer one of its phenyl groups to acridine (acr) in the absence of a transition metal catalyst and harsh reaction conditions (130°C, 20h).\(^{26}\) We initially examined the reaction of acr with zincates 2 and 3 at room temperature in THF,\(^{28}\) however after 48 hours, no arylation products were observed. On increasing the temperature to 66°C over a 24 hour period, it was possible to detect the formation in both cases of the dihydroacridine \(4\) as the major reaction product (in yields of 56 for \(2\) and 68% for \(3\); Table 2, entries 2-3), resulting from the successful arylation of \(\text{acr}\), along with small amounts of the fully aromatized product 9-phenyl acridine \(5\) (8 and 10% yield respectively, entries 2 and 3, Table 2). Since extended reaction times were required to promote the arylation transfer processes, alternative conditions utilizing microwave irradiation were investigated (125°C, 20 minutes, entries 4-8, Table 2), as previous studies in organozincate chemistry have shown that the use of microwave irradiation can boost the reactivity of these bimetallic systems.\(^{29}\) Furthermore, biaryl coupling of electron-deficient \(N\)-heterocyclic molecules such as pyrazine and haloarenes has been accomplished by using KORBu under microwave irradiation.\(^{30}\) Control reactions show that even under these conditions \(\text{ZnPh}_2\) itself is unable to perform the nucleophilic addition, (entry 4, Table 2). However, \(^1\text{H}\) NMR analysis of the crude reaction mixtures containing acr and 1.2 equivalents of the zinate 2 showed almost complete...

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**Table 1** Selected chemical shifts (ppm) in the \(^1\text{H}, ^{13}C\) and \(^{7}\text{Li}\) NMR chemical shifts (ppm) of \(\text{PhLi}, \text{ZnPh}_2\) and compounds 2 and 3 in deuterated THF solutions at 298 K.\(^{18}\)

<table>
<thead>
<tr>
<th></th>
<th>(\text{PhLi}) ((\delta^{\text{Li}} = 3.4))</th>
<th>(\text{ZnPh}_2) (1) ((\delta^{\text{Li}} = 1.1))</th>
<th>(\text{LiZnPh}_2) (2) ((\delta^{\text{Li}} = -1.1))</th>
<th>(\text{Li}_2\text{ZnPh}_4) (3) ((\delta^{\text{Li}} = -0.1))</th>
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<tr>
<td>(\text{ipso})</td>
<td>(^1\text{H}) 187.5</td>
<td>(^{13}C) 156.8</td>
<td>(^1\text{H}) 168.3</td>
<td>(^1\text{H}) 173.1</td>
</tr>
<tr>
<td>(\text{o-Ph})</td>
<td>7.98 144.2</td>
<td>7.55 126.1</td>
<td>7.88 141.1</td>
<td>7.93 142.8</td>
</tr>
<tr>
<td>(\text{m-Ph})</td>
<td>6.93 125.0</td>
<td>7.09 127.2</td>
<td>7.05 126.1</td>
<td>7.01 125.8</td>
</tr>
<tr>
<td>(\text{p-Ph})</td>
<td>6.83 123.3</td>
<td>7.02 139.6</td>
<td>6.96 124.2</td>
<td>6.90 123.9</td>
</tr>
</tbody>
</table>
The enhanced nucleophilicity of bimetallic reagents under these conditions to parent ZnPh centers. A comparison of the yields obtained for the or {ZnPh}(6% respectively, entry 5, Table 2). Under these reaction conditions, the congener furnished respective Table 2). Equivalents) was also investigated in order to assess if substoichiometric amounts of higher-order zincates over their triorgano analogs has been previously when compared to 2 when used zincate 5 when using zincate 0.5 mmol of acridine (acr) was employed. Yields were determined through addition of an internal standard (10 mol % ferrocene or hexamethylbenzene) after the hydrolysis step. Reaction was carried out under microwave irradiation. 1.5 equivalent of DDQ was added to the hydrolysed sample.

To isolate and characterise the organometallic species along the reaction coordinate to 4 and 5 prior to the hydrolysis step, the reaction of equimolar equivalents of acr with 2 was carried out at 125°C using microwave irradiation for 20 minutes. This afforded a dark brown solution which, after storage at -70°C, deposited light brown crystals of [(THF)3Li(NC6H5-Pb)] (6) in a 31% yield (see Scheme 3 and Supporting Information).

The enhanced nucleophilicity of bimetallic reagents 2 and 3 when compared to parent ZnPh2 can be attributed to a combination of the anionic activation of the zinc reagent, by forming [ZnPh2]⁻ or [ZnPh3]⁻ species, and the Lewis acid activation of the N-heterocyclic substrate acr by its dative coordination to the Li centers. A comparison of the yields obtained for the dihydroacridine product 4, showed a superior arylationing power for zincate 3 when compared to 2 (95% vs 70%), a pattern following the degree of negative charge in the zinc local coordination (i.e., 2 vs 1 vs 0 within 3, 2 and 1, respectively). The enhanced nucleophilicity of higher-order zincates over their triorgano analogs has been previously noted by Kondo and Uchiyama in several organic transformations, including Michael addition, carbozincation and epoxide ring-opening reactions. Since in both cases even under aerobic conditions the oxidation of dihydroacridine 4 to give 5 does not go to completion, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was employed as an external oxidant affording the aromatized product 5 in 71% yield when using zincate 3 whereas its lower-order congener furnished 5 in a 61% yield (entries 8 and 6 respectively, Table 2). Interestingly, illustrating the cooperative effect of Li and Zn in these bimetallic reagents, when acr was reacted with polar PhLi under the same reaction conditions, 5 was obtained in a diminished 49% yield (entry 9, Table 2).

In order to isolate and characterise the organometallic species along the reaction coordinate to 4 and 5 prior to the hydrolysis step, the reaction of equimolar equivalents of acr with 2 was carried out at 125°C using microwave irradiation for 20 minutes. This afforded a dark brown solution which, after storage at -70°C, deposited light brown crystals of [(THF)3Li(NC6H5-Pb)] (6) in a 31% yield (see Scheme 3 and Supporting Information).

X-ray crystallographic studies revealed the monometallic composition of 6 (Figure 3), confirming the successful addition of 3 across one C=C bond of acr, selectively introducing a Ph group to the C9 position [i.e., C18], giving rise to a new fused tricyclic amide fragment which binds to Li. As expected, the Li-N bond distance [1.989(4) Å] is shorter than those reported in the literature where related N-heterocyclic molecules such as pyridine or quinoline act as neutral two-electron donors to Li atoms, but similar to that recently found in the 1,2-dihydroydridiyldilithium complex [2-tBuC6H4NLi(Me6TREN)] [Me6TREN= tris(N,N-dimethyl-2-aminoethyl)amine], resulting from the addition of BuLi to pyridine [1.971(2) Å]. Lithium completes its distorted tetrahedral geometry [angles ranging from 105.19(15) to 125.65(16)] in 6 by coordinating to three solvating molecules of THF. Demonstrating its loss of aromaticity, the new

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**Table 2. Transition-metal free C9 arylation of acr using Zn arylation reagents 1, 2, 3 and PhLi.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>MPh</th>
<th>n</th>
<th>Time (h)</th>
<th>T(°C)</th>
<th>Yield (%)°</th>
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<tbody>
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<td>1</td>
<td>ZnPh2 (1)</td>
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<td>24</td>
<td>66</td>
<td>0</td>
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<tr>
<td>2</td>
<td>LiZnPh2 (2)</td>
<td>1.2</td>
<td>24</td>
<td>66</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Li2ZnPh2 (3)</td>
<td>1.2</td>
<td>24</td>
<td>66</td>
<td>68</td>
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<tr>
<td>4°</td>
<td>ZnPh2 (1)</td>
<td>1.2</td>
<td>0.33</td>
<td>125</td>
<td>0</td>
</tr>
<tr>
<td>5°</td>
<td>LiZnPh2 (2)</td>
<td>1.2</td>
<td>0.33</td>
<td>125</td>
<td>70</td>
</tr>
<tr>
<td>6°</td>
<td>LiZnPh2 (3)</td>
<td>1.2</td>
<td>0.33</td>
<td>125</td>
<td>0</td>
</tr>
<tr>
<td>7°</td>
<td>Li2ZnPh2 (3)</td>
<td>1.2</td>
<td>0.33</td>
<td>125</td>
<td>95</td>
</tr>
<tr>
<td>8°</td>
<td>Li2ZnPh2 (3)</td>
<td>1.2</td>
<td>0.33</td>
<td>125</td>
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<tr>
<td>9°</td>
<td>PhLi</td>
<td>1.2</td>
<td>0.33</td>
<td>125</td>
<td>0</td>
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</tbody>
</table>

°0.5 mmol of acridine (acr) was employed. Yields were determined through addition of an internal standard (10 mol % ferrocene or hexamethylbenzene) after the hydrolysis step. Reaction was carried out under microwave irradiation. 1.5 equivalent of DDQ was added to the hydrolysed sample.
heterocyclic ring is noticeably puckered, with C18 representing now a chiral sp³-tetrahedral carbon which lies 0.316(3) Å outside the mean plane of the four sp² hybridized carbons (C17, C19, C24 and C26). Furthermore, the bonding on the formerly aromatic central ring shows a clearly more localized double/single bond pattern [C-C distances ranging from 1.516(3) to 1.416(2) Å] in comparison with those previously involving the C atoms of the outer rings [C-C distances ranging from 1.415(2) to 1.369(3) Å].

Figure 3 Molecular structure of [(THF)₂Li(NC₅H₄-Ph)] (6) with ellipsoids drawn at 30% probability level and hydrogen atoms (excluding H18) omitted for clarity. Selected bond lengths (Å) and angles (˚); Li1-N1 1.989(4), Li1-O1 1.047(2), O1-Li1-O2 104.72(16), O1-Li1-O3 98.14(16), O1-Li1-N1 109.36(16), O2-Li1-N1 115.47(15), C24-N1-C26 115.47(15), C24-N1-Li1 118.42(16), C26-N1-Li1 125.65(16).

Interestingly, a search of the Cambridge Structural Database found no precedents for an alkylated/arylated acridine structure of zinc or lithium or indeed of any metal,³⁵ comparable to 6. Surprisingly, the “lithium-only” constitution of 6 contrasts with the heterobimetallic constitution of the arylating reagent 3, although paradoxically, it represents, to the best of our knowledge, the first example of a structurally defined reaction intermediate of the nucleophilic arylation of a zincate to an N-heterocyclic molecule. These findings contrast somehow with the bimetallic structure reported for the alkylation product 1 resulting from the reaction of pyrazine by [LiZnBu₃(TMEDA)] (Scheme 1),¹⁰ although this could perhaps be attributed to the presence of two N atoms in the heterocycle, where each of them coordinates to a different metal, allowing the trapping of the neutral ZnBu₃ fragment.

Fitting its structure in the solid state, ¹H and ¹³C NMR studies of d₅-THF solutions of 5 confirmed the deamination of the acridine central ring. Thus an informative singlet at 5.03 ppm is observed in the ¹H NMR spectrum, which can be assigned to the H originally attached to the C9 atom of acr, and, as it could be expected, appears significantly upfield when compared to that observed for acr (at 8.88 ppm). Reflecting its change in hybridization, C9 in 6 resonates at 50.8 ppm in the ¹³C NMR spectrum whereas in free acr, it appears at 136.3 ppm (see Supporting Information for experimental details). In order to gain a better understanding of the fate of zinc and how these mixed-metal reagents operate in the arylation process, NMR analysis of the reaction crude of acr and 2 was carried out in d₅-THF solvent. Despite the complexity of this ¹H NMR spectrum in the aromatic region (Figure S5 in Supporting Information), a diagnostic singlet at 5.34 ppm was observed, which would suggest the presence of a similar anionic 9-phenyl-9-hydroacridine group as the one present in 6 (δ CH(Ph) appears at 5.03 ppm, vide supra). A comparison of the aromatic region of the ¹H NMR spectrum of this crude reaction mixture with those obtained for zincate 2, ZnPh₂ and the lithium addition product 6 (Figure S7 in Supporting Information), suggests that these three species are present in the reaction mixture, although the chemical shifts observed for the resonances attributed to ZnPh₂ and 6 appear at slightly different (but noticeable) chemical shifts. A plausible explanation would be that in solution, these two species are interacting with each other forming heteroleptic zincate [LiZn(NC₅H₄-Ph)Ph₂] which, under the conditions required for crystallization, can then undergo redistribution to give a mixture of homometallic 6 and ZnPh₂.³⁶

Figure 4 Molecular structure of [(THF)(TMEDA)Li{NC₅H₄-Ph⁺}][2.070(6), N1-Li1 2.070 (6), N1-C13 1.367(3), N1-C1 1.370(4), C7-C8 1.425(4), C7-C14 1.489(4), C7-C6 1.422(4), C1-C6 1.440(4), C13-C8 1.444(4); Li1-N1-C1 118.7(2), Li1-N1-C13 122.1(2), C1-N1-C13 117.8(2), C6-C7-C8 118.5(3), C6-C7-C14 120.6(3), C8-C7-C14 120.8(2).

The monomeric arrangement of 7 is somewhat reminiscent to that described for 6, although in the latter the anionic N-heterocyclic ring is no longer aromatic (vide supra). Reflecting the radical anionic constitution of the {NC₅H₄-Ph⁺} fragment, the Li1-N1 distance in 7 [2.070(6) Å] is elongated by 0.081 Å to that observed in 6. Furthermore, the carbon atom now carries the phenyl substituent, C7, exhibits sp³
hybridization [sum of angles around C7, 359.9°], lying nearly coplanar to the mean plane defined by C1,C6,C8 and C13 (located just at 0.023(3) Å outside of this plane). Consistent with a high degree of electronic delocalization within this heterocyclic system, a close inspection of the C-C bond distances within the fused tricylic aromatic unit, shows that they cover the narrow range from 1.369(4) to 1.440(4) Å, with the incoming Ph group adopting a staggered orthogonal disposition [dihedral angle between the Ph and the acridine rings, 63.38(8)°]. As far as we can ascertain, 7 represents the first structural elucidation of a radical anion derived from 9-phenylacridine. Interestingly, in an earlier report, 39 Bard et al assessed the geometry of this radical anion with the aid of EPR and theoretical studies, estimating the twist angle between the Ph and the acridine ring to be 65° which is in close agreement to that determined for 7. 40 Demonstrating its paramagnetic nature, solid-state EPR measurements of a powdered sample of 7 at various temperatures (4, 20 and 70 K) showed a strong resonance centered at a g value of 2.0056 arising from the unpaired electron of the radical anion (Figure 5, and Supporting Information). The lack of resolution caused by g and A strains, as well as expected short spin-spin relaxation times preclude the observation of hyperfine splittings. The obtained g value is similar to those reported for other organic radical anions as for example in the alkali-metal salts of 2,2'-bipyridyl radical anion such as [K(2,2'-bipy)(en)] (en=ethylenediamine; g=2.

**Figure 5** Variable temperature (4 to 70 K) X-Band (9.421 GHz) EPR spectra of a solid sample of 7

The different nature of the anionic ligands present in the intermediates 6 and 7, indicates different reaction pathways must be in operation for the arylation of acr, depending on the organometallic reagent and the conditions employed. Thus, while the zincate-mediated process appears to formally be a polar addition reaction, though radicals may well be involved, when 3 equivalents of PhLi·TMEDA are employed, a radical (single electron transfer) mechanism appears to be definitively operative. 42 In this regard, it should be noted that related studies on the addition of PhLi to C=O bonds of ketones and aldehydes, have established that these reactions can take place via an electron-transfer/radical coupling sequence. 43 These findings not only highlight the complexity of these arylation processes but also draw attention to the significance of identifying the organometallic intermediates involved, which otherwise, if these reactions were carried out *in situ*, followed by subsequent hydrolysis and oxidation states, would have remained hidden, affording in both cases the same organic product, 9-phenylacridine (5). 44

For comparison, we also carried out the reaction of ZnPh₃ (1) with acr in hexane which furnished coordination adduct [(acr)ZnPh₃] (8) in a 29% crystalline yield. ¹H and ¹³C NMR analysis of the filtrate solution showed that 8 is the only species present in solution, suggesting that its modest isolated crystalline yield is due to its solubility in hexane under the crystallization conditions. The molecular structure of 8 was established by X-ray crystallography (Figure 6). Contrasting with the dimeric structure of 1 (vide supra), 13 8 displays a monomeric arrangement, where the trigonal planar Zn atom coordinates to two terminal Ph groups and the N of the neutral acr ligand. The Zn-N distance at 2.1598(11) Å is comparable to that previously reported for the related pyridine adduct [Ph₂Zn(NC₅H₄)₂] (average 2.1505 Å). 45 Multinuclear (¹H and ¹³C) NMR spectroscopic analysis of 8 in CD₈ shows that its structural integrity is retained in solution. 46 Thus the relevant resonances of acr in 8 in both NMR spectra, appear at distinctive downfield shifts compared to those observed for free acr [for example, in the ¹H NMR spectrum, C₃-H in 8 resonates at 8.10 ppm vs 7.97 ppm for acr]. It is noteworthy that similar coordination adducts to 8, where the relevant bis(aryl)zinc reagent is coordinated to the N-heterocyclic substrate, have been proposed to be involved in the first stages of the transition-metal catalyzed processes, providing the activation of the organic molecule towards nucleophilic Ni- or Rh-mediated arylation. 18

**Figure 6** Molecular structure of [(acr)ZnPh₃] (8) with ellipsoids drawn at 30% probability level and hydrogen atoms omitted for clarity. Selected bond lengths (Å) and angles (°): Zn1-C1 1.942(11), Zn1-C7 1.9647(13), Zn1-N1 2.1598(11), C7-Zn1-N1 146.9(5), C7-Zn1-N1 108.97(5), C1-Zn1-N1 104.1(5).

**CONCLUSIONS**

This study has examined the potential applications of lithium homo(aryl) zincates for chemoselective C-H arylation reactions of electron deficient N-heterocyclic molecules, using acridine as a case study. The arylation reagents, Li₂ZPh₃ (2) and Li₂ZnPh₃ (3) have been prepared straightforwardly using co-complexation by mixing appropriate amounts of PhLi with ZnPh₂ (1). X-ray crystallographic studies established the molecular structure of the dibutyl ether solvate of 2, [Li₂ZnPh₃(OBu₂)] (2·OBu₂). Significantly, though the parent triruganozincate 2 was first introduced by Wittig over 60 years ago, its structure still remains elusive.

Using microwave irradiation, both zincates can regioselectively transfer a Ph group to the C9 position of acr, affording mixtures of the arylation products 9,10-dihydro-9-phenylacridine 4 and 9-phenylacridine 5, without the need of transition metal catalysis. Reflecting its higher degree of activation, higher-order zincate 3 showed an enhanced arylation power, furnishing the reduced product 4 in a
95% yield (vs 70% using lower-order 2), which can be oxidized to 5 with DDQ. Under these conditions, Structural evidence for the success of the reaction has been gained by isolating addition product [(THF)_2Li(NC_3H_5-Ph)] (6). Interestingly, attempts to prepare 6 using PhLi/TMEDA (3 equivalents) and acr, led to the formation of a different type of arylation product, affording crystals of novel paramagnetic [(THF)(TMEDA)Li(NC_3H_5-Ph~^+)] (7), where now Li is bonded to a radical anion of 9-phenyl-acridine. Collectively these structural studies point towards different reaction pathways must be in operation for the arylation of acr, depending on the organometallic reagent and the reaction conditions employed. Thus, while the zincate-mediated process appears to be a polar addition reaction, at least formally, using an excess of PhLi, the arylation process occurs, at least in part, via a radical mechanism.

**EXPERIMENTAL SECTION**

**General conditions.** All reactions were performed under a protective atmosphere using standard Schlenk techniques. Hexane, tetrahydrofuran (THF), and toluene were dried by heating to reflux over sodium benzenophene and distilled under nitrogen prior to use. PhLi (1.8 M solution in dibutyl ether) and acridine were purchased from Aldrich Chemicals and used as received. PhZn was prepared according to literature method. Solvent-free PhLi was prepared as a solid and stored in the glove box, following the reported procedure. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, operating at 400.13 MHz for 1H, 150.32 MHz for 13C. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser. X-Band (9.42 GHz) EPR spectra were determined with powdered samples on a Bruker ESP300E spectrometer, with a liquid helium cryostat. Satisfactory elemental analyses of the air sensitive products 2.0BuH (too air sensitive) and 7 (co-crystalline mixture of two donor variants) could not be obtained.

**Crystallographic data** All crystallographic measurements were made with Oxford Diffraction Instruments. Structures were refined against F^2 and against all independent reflections to convergence using SHELXL. Structure 6 contains disordered THF solvent of crystallisation that could not be satisfactorily modelled. Thus this structure was refined against a reflection dataset which was output by the SQUEEZE routine implemented in PLATON. Structure 7 is a cocrystal of [Li(phenylacridine)(THF)] and [Li[phenylacridine](THF)(TMEDA)] with both species occupying the same crystallographic sites. Site occupancy factors were refined to 0.735(3)/0.265(3) in favour of the first named species. Bond lengths of the resulting disordered fragments were retrained and both restraints and constraints required to be applied to the displacement parameters of the same groups. Similar treatments were used for the disordered ether ligands of 2.2OBu and the disordered phenyl ring of 8. Selected crystallographic details are presented in Table S1 and full information in the format has been deposited with the CCDC 1035850-1035853.

**Synthesis of LiZnPh (2).** To a solution of ZnPh (0.11 g, 0.5 mmol) in THF (2 mL) was added PhLi (0.04 g, 0.5 mmol), affording a pale yellow solution that was able to stir at room temperature for 10 minutes. Hexane was then introduced and the resulting solution was gently heated with a heat gun affording a pale yellow solution from which colourless crystals of 2.0BuH were deposited upon cooling this solution to 9°C (yield 0.14 g, 57%). 1H NMR (400.13 MHz, 298 K, d_8-THF) δ ppm: 7.90 (d, 6H, Hsthrough, 7.05 (t, 6H, Hsthrough), 6.90 (t, 3H, Hsthrough), 3.41 (m, 8H, OCH_2Bu), 1.55 (m, 8H, CH_2Bu), 1.44 (m, 8H, C_6H_5Bu). 13C (THF) NMR (100.62 MHz, 298 K, d_8-THF) δ ppm: 169.4 (C_6H_5), 141.1 (Csthrough), 125.8 (Cthrough), 123.8 (Cthrough), 70.9 (OCH_2Bu), 32.6 (CH_2Bu), 20.1 (CH_3Bu), 14.1 (CH_3Bu). 11Li NMR (298 K, d_8-THF, reference LiCl in D_2O at 0.00 ppm) δ ppm: 1.15.

**Synthesis of LiZnPPh (3).** To a solution of PhZn (0.11 g, 0.5 mmol) in THF (0.5 mL) was added PhLi (0.08 g, 1 mmol). The resulting pale yellow solution was stirred at room temperature for 10 minutes. Volatiles were removed under vacuum and the resulting colourless oil was dissolved in neat hexane (2 mL) affording a pale yellow solution. Despite several attempts, storing of this solution at different temperatures (3°C, -28°C and -68°C), no crystalline solid could be obtained. Removal of all volatiles under vacuum led to the isolation of 3 as a colourless oil. 1H NMR analysis of this oil in deuterated THF showed the presence of four solvating molecules of THF. 1H NMR (400.13 MHz, 298 K, d_8-THF) δ ppm: 7.93 (d, 8H, Hthrough), 7.01 (t, 8H, Hthrough), 6.96 (t, 4H, Hthrough), 3.56 (m, 16H, HZnH), 1.74 (m, 16H, HZnH). 13C (THF) NMR (100.62 MHz, 298 K, d_8-THF) δ ppm: 173.1 (broad, C_6H_5Ph, 125.8 (C_6H_5), 123.9 (C_6H_5), 68.3 (C_6H_2Ph), 26.3 (C_6H_2Ph). 1Li NMR (298 K, d_8-THF, reference LiCl in D_2O at 0.00 ppm) δ ppm: -0.13.

**Synthesis of [[TFH][LiN(C_6H_5-Ph)] (6).** Acridine (0.5 mL of a 1 M solution in THF, 0.5 mmol) was added to a THF solution (2 mL) of zincate (3 0.5 mmol) prepared in situ as above. This mixture was then microwave (125 °C) for 20 minutes, affording a dark brown solution. The solution was filtered and stirred at 0-4°C overnight, resulting in the formation of pale brown crystals of 6 (0.24 g, 31% yield). Anal. Calcd for C_66H_48LiNO: C, 77.31; H, 8.37; N, 2.91. Found: C 77.46, H 8.06, N 3.11. 1H NMR (400.13 MHz, 298 K, d_8-THF) δ ppm: 7.11 (d, 2H, Hthrough, Ph), 7.07 (t, 2H, Hthrough, Ph), 6.97 (t, 1H, Hacac, Ph), 6.76 (d, 2H, NC_6H_5Ph), 6.69 (t, 2H, NC_6H_5Ph), 6.49 (d, 2H, NC_6H_5Ph), 6.23 (t, 2H, NC_6H_5Ph), 5.03 (s, 1H, CHPh, NC_6H_5Ph), 3.41 (m, 12H, HzPh), 1.76 (m, 12H, HzPh). 13C (THF) NMR (100.62 MHz, 298 K, d_8-THF) δ ppm: 153.9, 151.7 (Cacuracy, NC_6H_5), 141.2 (Cph), 129.3 (CNC_6H_5Ph), 128.3 (Cph), 128.0 (CNC_6H_5Ph), 126.3 (CNC_6H_5Ph, 118.8 (CNC_6H_5Ph), 114.1 (CNC_6H_5Ph, 68.5 (CPh). 50.8 (CPh), 26.3 (CPh) Li NMR (298 K, d_8-THF, reference LiCl in D_2O at 0.00 ppm) δ ppm: 0.74 ppm.

**Synthesis of [(THF)(TMEDA)Li[N(C_6H_5-Ph)] - 7.** To a solution of acr (0.18 g, 1 mmol) in THF (5 mL) was added TMEDA (0.45 mL, 3 mmol). The solution was cooled to 0°C and PhLi (1.12 mL of a 0.8 M solution in dibutyl ether, 3 mmol) was added dropwise, and the reaction stirred for 2 hours before being slowly warmed to room temperature. The solution deposited a deep purple microcrystalline solid in a 42% yield (0.19 g) on standing at room temperature for over 3 days. The X-band (9.42 GHz) EPR spectra of a solid sample of 7 recorded at 4, 20 and 70K revealed a strong resonance with a g value of 2.066.

**Synthesis of [acrZnPh] (8).** To a suspension of PhZn (0.22 g, 1 mmol) in hexane (10 mL) was added acridine (0.18 g, 1 mmol). 30 mL of hot toluene was added giving a yellow solution which was allowed to slowly cool to room temperature using a hot water bath, resulting in the deposition of colourless crystals of 8 in a 29% yield (0.12 g). Anal. Calcd for C_66H_48ZnPh: C, 75.29; H, 4.80; N, 3.51. Found: C 75.24, H 4.79, N 4.03. 1H NMR (400.13 MHz, 298 K, d_8-MeOH) δ ppm: 8.26 (m, 2H, Hzacr), 7.97 (s, 1H, Hzacr), 7.82-7.86 (m, 4H, Hthrough), 7.32-7.26 (m, 6H, Hacac and Hzacr overlapping), 7.03 (m, 2H, Hzacr), 6.90-6.96 (m, 2H, Hzacr). 13C (THF) NMR (100.62 MHz, 298 K, d_8-THF) δ ppm: 154.9 (Cacacy, Ph), 147.7 (Cacacy), 139.6 (Cacr, acr), 139.5 (Cph), 132.7 (C_6H_5Ph).
General procedure for the arylation studies of acr. A THF solution (2 mL) of zincate 2 or 3 (0.5 mmol) prepared in situ, via co-complexation of PhLi and ZnPh₂, was added to acridine (0.09 g, 0.5 mmol). This mixture was then microwaved (125 °C) for 20 minutes or refluxed over 14h at 66 °C, before being quenched with a saturated aqueous brine solution (5 mL). The product was extracted with diethyl ether (3 × 5 mL) and the combined organic phases dried (MgSO₄), filtered and concentrated under reduced pressure. Yields were determined by integration of the products resonances using ferrocene (10%) as internal standard in the ‘H NMR spectrum. Results of these studies are shown in Table 2. The reactions with ZnPh₂ (entries 1 and 4 of Table 2) were carried out under identical conditions as described above, using a solution of 0.5 mol (0.11 g) of ZnPh₂. Examples of the ‘H NMR obtained from these studies are shown in Figure S1 and S2.

Supporting Information available: CIF files giving crystallographic results and spectroscopic details are available free of charge via the internet [http://pubs.acs.org].
18. The 1H NMR spectra and elemental analysis of [LiZnPh2] revealed that it contains three solvating THF molecules. Thus, although its empirical formula should be (THF)3LiZnPh2, it does not appear to be solvated by THF molecules. However, the NMR spectra of Li2ZnPh2 has been employed instead of (THF)3LiZnPh2, see Experimental Section in Supporting Information for details.


23. Supporting this interpretation, addition of isolated crystals of 6 to a solution of ZnPh2 in deuterated THF led to the formation of a complicated mixture of products. Significantly some of the 1H NMR signals match those observed in the reaction crude of acr with zinicate 2 (see Figure S8, Supporting Information).

24. For a recent example of a structurally characterized lithium naphthalene radical anion see: Melero, C.; Gujararo, A.; Yus, M., Dalton Trans. 2009, 1259-1265.


28. Following the reported method (see reference 5a), the reaction of acr with PhLi/TMEDA has been carried out using excess organolithium reagent, which could also influence in the formation of 7. Supporting this interpretation, attempts to prepare 7 using equimolar amounts of acr, PhLi and TMEDA were unsuccessful.


30. Treatment of isolated crystals of radical species 7 with one equivalent of DDQ afforded 5 quantitatively. Contrastingly, when acr was treated by one equivalent of PhLi at 0°C followed
by treatment with DDQ and hydrolysis, 5 was obtained in 51% yield.

46. Contrastingly, using the deuterated solvent d-THF, with a greater coordinating ability, the NMR spectra of 8 only showed signals corresponding to free acr and ZnPh2, consistent with the cleavage of the donor-complex.