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

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ABSTRACT: ABSTRACT: *This study explores the synthetic utility of homo(aryl) lithium zincate reagents [LiZnPh$_3$} (2) and [Li$_2$ZnPh$_4$] (3), made by co-complexation of variable amounts of their monometallic components LiPh and ZnPh$_2$ (1), as chemoselective nucleophilic arylating reagents. Both lithium zincates 2 and 3 were characterized by multinuclear (^{1}H, ^{13}C and ^{7}Li) NMR spectroscopy and in the case of 2, a classical reagent in heterobimetallic chemistry, the molecular structure of its O^{n}Bu$_2$ solvate [LiZnPh$_3$(O^{n}Bu$_2$)$_2$] 2·O^{n}Bu$_2$ has been established by X-ray crystallography. Using synthetically relevant N-heterocyclic molecule acridine (acr, NC$_{13}$H$_9$), a new zincate-mediated arylating approach is demonstrated which allows the chemoselective arylation of acr at its C9 position, affording 9,10-dihydro-9-phenylacridine 4 in a 95% yield using microwave irradiation (125ºC, 20 minutes). These conditions contrast with previous transition-metal catalyzed methodologies using ZnPh$_2$ as an arylating reagent, which require significantly longer reaction times (130ºC, 20h). 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)$_3$Li(NC$_{13}$H$_9$-Ph)] (6). Interestingly the reaction of acr with 3 equivalents of PhLi/TMEDA led to the isolation of a different product, namely novel paramagnetic [(THF)(TMEDA)Li{NC$_{13}$H$_8$-Ph}$^{-}$·] (7) which contains a radical anion of 9-phenylacridine. The structure of donor-acceptor complex [(acr)ZnPh$_2$] (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] antibacterial[1a] 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.[1a,1h,6]
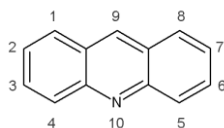

Figure 1 IUPAC numbering system of acridine (**acr**).

Recent studies by Chatani and Tobisu have shown that regioselective C-H arylation of a range of electron-deficient N-heterocyclic molecules, including acridine, can be readily accomplished by neutral arylzinc reagents but only under transition-metal catalysis.[1g,5c,7] 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 rearomatized via oxidation, to yield 2-substituted products.[8] By using either nickel[1g,7] or rhodium[5c] catalysts, it is possible to activate milder organozinc reagents such as ZnPh$_2$ (**1**), which offer greater regioselectivities and functional group tolerance, towards the nucleophilic arylation of the electron-deficient N-heterocyclic substrate.[1g] Mechanistic studies suggest that in this approach ZnPh$_2$ plays an important role, by activating the aromatic substrate and transferring its aryl substituent to the transition metal catalyst[1g] 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).[1g,7]

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)LiZntBu$_3$] (PMDETA = *N,N,N',N'',N''*-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 Zn*t*Bu$_2$ on its own fails to promote the addition of a *t*Bu group to pyrazine, demonstrating that formation of **I** is a genuine example of cooperative bimetallic synthesis.[10] 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.[11] Similarly, work carried out by Ishihara[12a,b] and our group[12c] 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 ZnCl$_2$.[12] The enhanced reactivities exhibited by these mixed-metal systems can be rationalized in terms of metal-metal cooperative effects.[10] Thus, by forming a zincate anion it is possible to overcome the large kinetic barrier of the lower polarity Zn-C bonds in neutral ZnR$_2$ 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 {ZnR$_3$}$^-$ anion.
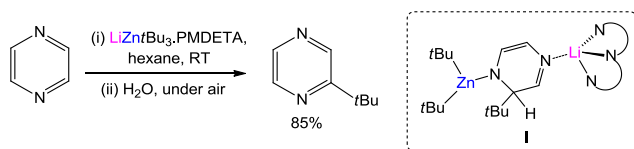

Scheme 1 Zincate-mediated regioselective C-H alkylation of pyrazine.

Building on these initial studies, herein we extend this bimetallic approach using lithium aryl zincate combinations to promote transition-metal-free, direct arylation of electron-deficient *N*-heterocycles, employing the biologically significant substrate acridine (**acr**) as a case study. By isolating key organometallic intermediates involved in this 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 homoleptic aryl lithium zincates. To avoid possible side reactions,[13] for this study we employed the homoleptic aryl zincates, [LiZnPh$_3$] (**2**) and [Li$_2$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.[14] In this epochal report, **2** is prepared *in situ* by reacting equimolar amounts of PhLi and ZnPh$_2$ in diethyl ether. Using a similar interlocking co-complexation approach,[15] we began our investigations by exploring the reactions of different stoichiometries of phenyllithium and ZnPh$_2$ (**1**).[16] A 1:1 ratio of these monometallic aryl reagents in a THF/hexane solvent mixture, furnished Wittig's lithium tris(aryl) zincate [LiZnPh$_3$] (**2**) as a microcrystalline solid in a 68% yield. Its higher-order[17] congener [Li$_2$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 repectively.[18] Both lithium zincates **2** and **3** were characterized in d$_8$-THF solu-

tions by multinuclear (^{1}H, ^{13}C and ^{7}Li) NMR spectroscopy (Table 1). For classical zincate **2**, crystals of its dibutyl ether solvate [LiZnPh$_3$(OBu$_2$)$_2$] (**2·OBu$_2$**) could be isolated by carrying out 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).
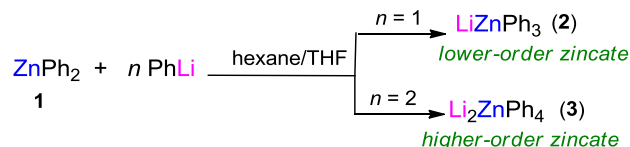
Scheme 2 Interlocking co-complexation reactions to form lithium phenyl zincates **2** and **3**.[17,18]

In the crystal **2·OBu$_2$** 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 π-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 zincation (AMMZ*n*) chemistry of aromatic substrates, where it seems to play an important role in tuning the overall regioselectivity of the metallation processes.[19]
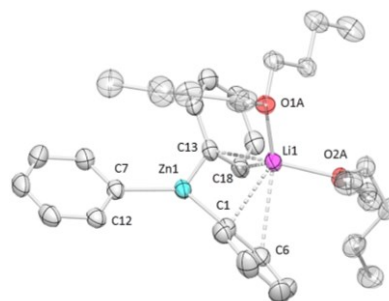

Figure 2 Molecular structure of [LiZnPh$_3$(OBu$_2$)$_2$] (**2·OBu$_2$**) with ellipsoids drawn at 30% probability level and hydrogen atoms and minor disorder on the OBu$_2$ ligands omitted for clarity. Selected bond lengths (Å) and angles (°); Zn1-C1 2.034(3), Zn1-C7 1.991(2), Zn1-C13 2.032(3), Li1-C1 2.494(5), Li1-C6 2.786(5), Li1-C13 2.521(5), Li1-C18 2.832(5); C7-Zn1-C13 122.22(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·OBu$_2$**, with Li and Zn separated by 2.753(4) Å contrasts with that reported for the same zincate anion in [{Mg$_2$Br$_3$(THF)$_6$}$^+${ZnPh$_3$}$^-$], which exhibits a solvent-separated ion pair structure.[19] Although the average Zn-C bond distances for each compound are similar (2.019 Å for **2·OBu$_2$** *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 atom in **2·OBu$_2$** are marginally elongated [2.034(3) and 2.032(3) Å] compared to that observed for the terminal Ph group [1.991(2)

Å]. Interestingly, reflecting its anionic constitution, these bridging Zn-C bond distances are noticeably shorter than those found in the homometallic precursor [ZnPh$_2$] (**1**), which displays a simple dimeric motif {ZnC}$_2$ (average Zn-C$_{bridge}$ 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 NMe$_2$ or CON^{i}Pr$_2$, which datively stabilize the alkali-metal. Contrastingly, in **2·OBu$_2$**, two of the phenyl rings coordinate to the lithium atom via η^2 π-contacts involving their *ipso* and one of their *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 PhLi solvates such as [(PhLi·OEt$_2$)$_4$] and [PhLi·(−)-sparteine]$_2$ which exhibit Li-C$_{ipso}$ sigma bridges at average values of 2.335 and 2.299 Å respectively.[23]

Multinuclear (^{1}H, ^{13}C and ^{7}Li) NMR spectroscopic studies of **2** confirmed its bimetallic constitution in deuterated THF solutions (Table 1). The ^{1}H NMR spectrum showed a single set of signals for the 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 *ipso* C of the Ph groups, at a chemical shift intermediate to those observed for the relevant *ipso* C's in the spectra of PhLi (187.5 ppm) and Ph$_2$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 **2**. The presence of lithium was confirmed by a sharp singlet at 1.09 ppm in the ^{7}Li NMR spectrum. Interestingly, ^{1}H-^{7}Li –HOESY experiments carried out on solutions of **3** in deuterated THF and C$_6$D$_6$ solutions, suggested that the structure of this zincate in solution changes depending on the donor ability of the deuterated solvent. Thus, in d$_8$-THF solutions, no HOESY cross-peaks were observed for the interaction of ^{7}Li with any of the aromatic protons of the phenyl groups, supporting the formation of solvent-separated ion-pair species. Contrastingly, using C$_6$D$_6$ solutions, a strong interaction between ^{7}Li and the *ortho*-H of the 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 **2.2OBu$_2$** (see Supporting Information for details).

Although the higher-order zincate could only be isolated as a colorless oil and therefore its structure could not be determined crysta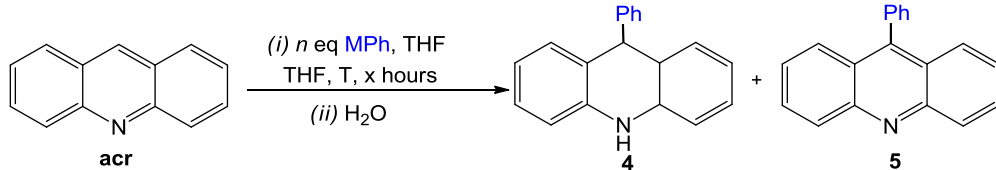llographically, it is pertinent that a few related lithium tetraorganozincates of general formula Li$_2$ZnR$_4$ (R= alkyl, aryl) have been structurally defined, forming contacted ion-pair aggregates, with two Li cations oppositely disposed to a central dianionic {ZnR$_4$}$^{2-}$ tetrahedron within a trinuclear Li...Zn...Li chain arrangement.[17b,22a,25] The same structural motif has been described previously by Weiss in the magnesium analog of **3**, tetra(aryl)magnesiate [(TMEDA)$_2$Li$_2$MgPh$_4$].[26] Compound **3** was characterized by a combination of ^{1}H, ^{13}C and ^{7}Li NMR spectroscopic studies (see Supporting Information and Table 1). A singlet (1.63 ppm) in the ^{7}Li NMR spectrum of **3** in deuterated THF solution established the presence of lithium. Its ^{1}H NMR spectrum revealed a single set of resonances for the Ph groups, at similar chemical shifts to those found for the tris(aryl) derivative **2**.[27] Reflecting the dianionic character of **3**, the *ipso* C of the Ph groups resonates at 173.1ppm, which is noticeably deshielded to that observed for monoanionic **2** (169.3 ppm) and neutral ZnPh$_2$ (156.8 ppm).[17a]

Reactivity studies: zincate-mediated arylation of acridine. As mentioned above, previous studies have shown that 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).[5c] 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 **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 aryl 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 KOtBu under microwave irradiation.[30] Control reactions show that even under these conditions ZnPh$_2$ itself is unable to perform the nucleophilic addition, (entry 4, Table 2). However, ^{1}H NMR analysis of the crude reaction mixtures containing **acr** and 1. 2 equivalents of the zincate **2** showed almost complete

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

	PhLi (δ^7Li = 3.4)		ZnPh$_2$ (**1**)		LiZnPh$_3$ (**2**) (δ^7Li = 1.1)		Li$_2$ZnPh$_4$ (**3**) (δ^7Li = -0.1)	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
ipso	-	187.5	-	156.8	-	168.3	-	173.1
***o*-Ph**	7.98	144.2	7.55	126.1	7.88	141.1	7.93	142.8
***m*-Ph**	6.93	125.0	7.09	127.2	7.05	126.1	7.01	125.8
***p*-Ph**	6.83	123.3	7.02	139.6	6.96	124.2	6.90	123.9

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

Entry	MPh	n	Time (h)	T(°C)	Yield (%)[a]	
					4	**5**
1	ZnPh$_2$ (**1**)	1.2	24	66	0	0
2	LiZnPh$_3$ (**2**)	1.2	24	66	56	8
3	Li$_2$ZnPh$_4$ (**3**)	1.2	24	66	68	10
4[b]	ZnPh$_2$ (**1**)	1.2	0.33	125	0	0
5[b]	LiZnPh$_3$ (**2**)	1.2	0.33	125	70	6
6[b,c]	LiZnPh$_3$ (**2**)	1.2	0.33	125	0	61
7[b]	Li$_2$ZnPh$_4$ (**3**)	1.2	0.33	125	95	0
8[b,c]	Li$_2$ZnPh$_4$ (**3**)	1.2	0.33	125	0	71
9[b,c]	PhLi	1.2	0.33	125	0	49

[a] 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. [b] Reaction was carried out under microwave irradiation. [c] 1.5 equivalent of DDQ was added to the hydrolysed sample. [c]

consumption of the starting materials with the subsequent formation of the arylation products **4** and **5** (yields of 70 and 6% respectively, entry 5, Table 2). Under these reaction conditions, tetraorganozincate **3** furnished **4** in almost quantitative yield (95%, entry 7). The reaction of **acr** with substoichiometric amounts of higher-order zincate **3** (0.6 equivalents) was also investigated in order to assess if **3** could transfer more than one of its Ph groups. However, under these conditions **5** was obtained in a modest 56% yield (see Supporting Information for details).The enhanced nucleophilicity of bimetallic reagents **2** and **3** when compared to parent ZnPh$_2$ can be attributed to a combination of the anionic activation of the zinc reagent, by forming {ZnPh$_3$}$^-$ or {ZnPh$_4$}$^{2-}$ 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 arylating 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.[17a, 31] 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)[1g,5a] 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).[32] 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)$_3$Li(NC$_{13}$H$_9$-Ph)] (**6**) in a 31% yield (see Scheme 3 and Supporting Information).
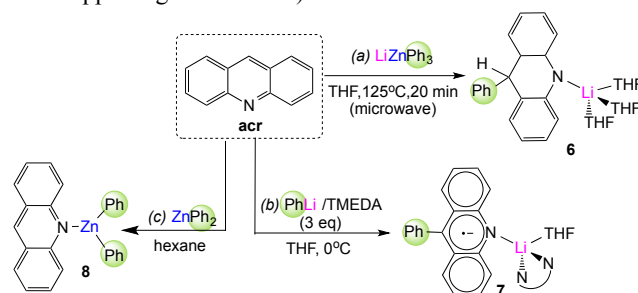
Scheme 3 Synthesis of the organometallic intermediates **6, 7** and **8** resulting from the reactions of **acr** with (a) Li$_2$ZnPh$_4$ in THF under microwave irradiation; (b) PhLi in THF at 0°C, and (c) ZnPh$_2$ in hexane at room temperature, respectively.

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,[33] but similar to that recently found in the 1,2-dihydropyridyllithium complex [2-*t*BuC$_5$H$_5$NLi(Me$_6$TREN)] [Me$_6$TREN= tris(*N,N*-dimethyl-2-aminoethyl)amine], resulting from the addition of *t*BuLi to pyridine [1.971(2) Å].[34] 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

heterocyclic ring is noticeably puckered, with C18 representing now a chiral sp^3-tetrahedral carbon which lies 0.316(3) Å outside the mean plane of the four sp^2 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].
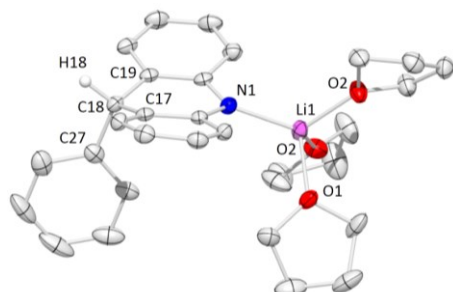

Figure 3 Molecular structure of [(THF)$_3$Li(NC$_{13}$H$_9$-Ph)] (**6**) with ellipsoids drawn at 30% probability level and hydrogen atoms (excluding H18) omitted for clarity. Selected bond lengths (Å) and angles (°); Li1-N1 1.989(4), Li1-O1 1.974(4), Li1-O2 1.930(4), Li1-O3 2.014(4); O1-Li1-O2 104.72(16), O1-Li1-O3 98.14(16), O1-Li1-N1 109.36(16), O2-Li1-O3 105.19(15), O2-Li1-N1 120.64(19), N1-Li1-O3 115.96(17), 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 **I** resulting from the reaction of pyrazine by [LiZn*t*Bu$_3$(PMEDTA)] (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 Zn*t*Bu$_2$ fragment.

Fitting its structure in the solid state, ^{1}H and ^{13}C NMR studies of d$_8$-THF solutions of **5** confirmed the dearomatization of the acridine central ring. Thus an informative singlet at 5.03 ppm is observed in the ^{1}H NMR spectrum, which can be assigned to the 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 ^{13}C 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 d$_8$-THF solvent. Despite the complexity of this ^{1}H 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 C*H*(Ph) appears at 5.03 ppm, *vide supra*). A comparison of the aromatic region of the ^{1}H NMR spectrum of this crude reaction mixture with those obtained for zincate **2**, ZnPh$_2$ **1** 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 ZnPh$_2$ 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(NC$_{13}$H$_9$-Ph)Ph$_2$] which, under the conditions required for crystallization, can then undergo redistribution to give a mixture of homometallic **6** and ZnPh$_2$.[36]

Considering the single-metal composition of **6**, we also examined the reaction of **acr** with PhLi. Ray *et al.*[5a] have reported the formation of 9-phenyl acridine (**5**) by treating **acr** with 3 equivalents of PhLi/TMEDA (*N,N,N',N'*-tetramethylethylenediamine) in THF at 0°C, followed by a hydrolysis/oxidation step. Interestingly, when we carried out this reaction under these conditions, we observed first the formation of a dark brown solution which over time developed a persistent intense violet color, strongly suggesting the formation of a radical species. Storage of this solution at room temperature allowed the isolation of the mixed donor complex [(THF)(TMEDA)Li{NC$_{13}$H$_8$-Ph$^{\bullet-}$}] (**7**) as dark purple crystals in a 42% yield. X-ray crystallographic studies established the molecular structure of **7** as a novel radical anion lithium complex, comprising one Li atom, solvated by a chelating TMEDA ligand and molecule of THF, which is bonded to the N atom of radical anion {NC$_{13}$H$_8$-Ph$^{\bullet-}$}, resulting from the replacement of the H atom attached at the C9 position of the original **acr** ring [i.e. C7] by a Ph group (Figure 4).[37]

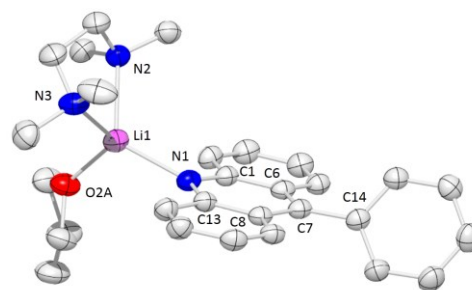**Figure 4** Molecular structure of [(THF)(TMEDA)Li{NC$_{13}$H$_8$-Ph$^{\bullet-}$}] (**7**) with ellipsoids drawn at 30% probability level, hydrogen atoms disorder within THF/TMEDA[38] are omitted for clarity. Selected bond lengths (Å) and angles (°); N1-Li1 2.070 (6), N1-C13 1.367(3), N1-C1 1.370(4), 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 {NC$_{13}$H$_8$-Ph$^{\bullet}$} 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 sp^2

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,[38] a close inspection of the C-C bond distances within the fused tricyclic 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.
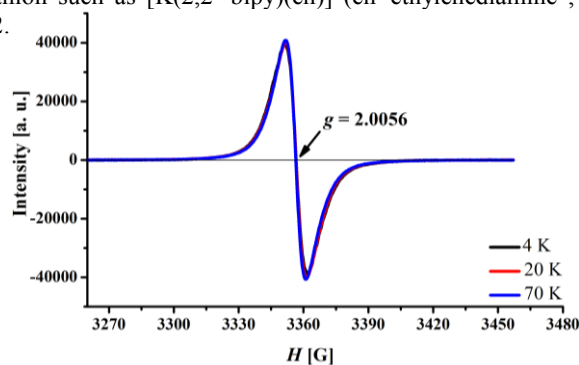

Figure 5 Variable temperature (4 to 70 K) X-Band (9.421 GHz) EPR spectra of a solid sample of **7**

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 a 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 ZnPh$_2$(**1**) with **acr** in hexane which furnished coordination adduct [(**acr**)ZnPh$_2$] (**8**) in a 29% crystalline yield. ^{1}H and ^{13}C 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*),[21] **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 [Ph$_2$Zn(NC$_5$H$_5$)$_2$] (average 2.1505 Å).[45] Multinuclear (^{1}H and ^{13}C) NMR spectroscopic analysis of **8** in C$_6$D$_6$, 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 ^{1}H NMR spectrum, C$_9$-*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. [1g]
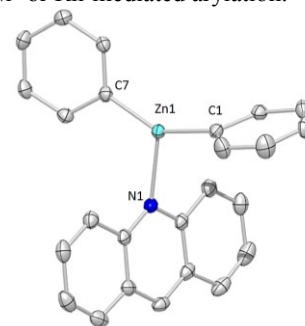

Figure 6 Molecular structure of [(**acr**)ZnPh$_2$] (**8**) with ellipsoids drawn at 30% probability level and hydrogen atoms omitted for clarity. Selected bond lengths (Å) and angles (°); Zn1-C1 1.942(11), Zn1-C7 1.9647(13), Zn1-N1 2.1598(11); C7-Zn1-N1 146.9(5), C7-Zn1-N1 108.97(5), C1-Zn1-N1 104.1(5).

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 arylating reagents, LiZnPh$_3$ (**2**) and Li$_2$ZnPh$_4$ (**3**) have been prepared straightforwardly using co-complexation by mixing appropriate amounts of PhLi with ZnPh$_2$ (**1**). X-ray crystallographic studies established the molecular structure of the dibutyl ether solvate of **2**, [LiZnPh$_3$(OBu$_2$)$_2$] (**2·OBu$_2$**). Significantly, though the parent triorganozincate **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 enhaced arylating power, furnishingthe 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)$_3$Li(NC$_{13}$H$_9$-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$_{13}$H$_8$-Ph$^{\bullet-}$}] (**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 argon atmosphere using standard Schlenk techniques. Hexane, tetrahydrofuran (THF), and toluene were dried by heating to reflux over sodium benzophenone 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.[16] Ph$_2$Zn was prepared according to literature method. Solvent-free PhLi was prepared as a solid and stored in the glove box, following the reported procedure.[16] NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, operating at 400.13 MHz for ^{1}H, 150.32 MHz for [7]Li and 100.62 MHz for [13]C. 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.OBu$_2$** (too air sensitive) and **7** (co-crystalline mixture of two donor variants)[48] 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.[47] 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.[48] Structure **7** is a cocrystal of [Li(phenylacridine)(THF)$_3$] and [Li(phenylacridine)(THF)(TMDA)] 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 restrained 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$_2$** and the disordered phenyl ring of **8**. Selected crystallographic details are presented in Table S1 and full information in cif format has been deposited with the CCDC 1035850-1035853.

Synthesis of LiZnPh$_3$ (2). To a solution of ZnPh$_2$ (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 allow to stir at room temperature for 10 minutes. Hexane was then introduced (5 mL). Refrigeration of this solution at – 68 ºC afforded a crop of microcrystalline solid (yield 0.18 g, 68 %) NMR analysis of this solid in C$_6$D$_6$ showed the presence of three solvating molecules of THF. This has been taken into account when calculating the yield of **2** and its elemental analysis. Anal. Calcd for C$_{30}$H$_{39}$LiO$_3$Zn: C, 69.30; H, 7.56. Found: 70.05; H, 7.31. ^{1}H NMR (400.13 MHz, 298 K d$_8$-THF) δ ppm: 7.88 (d, 6H, H$_{ortho}$), 7.05 (t, 6H, H$_{meta}$), 6.96 (t, 3H, H$_{para}$), 3.58 (m, 12H, H$_\alpha$-THF), 1.74 (m, 12H, H$_\beta$-THF).^{13}C {^{1}H} NMR (100.62 MHz, 298 K, d$_8$-THF) δ ppm: 169.3 (C$_{ipso}$), 141.3 (C$_{ortho}$), 125.9 (C$_{meta}$), 124.0 (C$_{para}$) 68.4 (C$_\alpha$-THF), 26.2 (C$_\beta$-THF). ^{7}Li NMR (298 K, d$_8$-THF, reference LiCl in D$_2$O at 0.00 ppm) δ ppm: 1.09.

Synthesis of [LiZnPh$_3$(OBu)$_2$] (2.2OBu$_2$). To a suspension of ZnPh$_2$ (0.11 g, 0.5 mmol) in hexane (5 mL) was added PhLi (0.28 mL of a 1.8 M solution in dibutyl ether, 0.5 mmol). Toluene (15 mL) was then introduced and the resulting suspension was glently heated with a heat gun affording a pale yellow solution from which colourless crystals of **2.2OBu$_2$** were deposited upon cooling this solution to -28ºC (yield 0.14 g, 57 %). ^{1}H NMR (400.13 MHz, 298 K d$_8$-THF) δ ppm: 7.90 (d, 6H, H$_{ortho}$), 7.05 (t, 6H, H$_{meta}$), 6.90 (t, 3H, H$_{para}$), 3.41 (m, 8H, OCH$_2$, OBu$_2$), 1.55 (m, 8H, CH$_2$, OBu$_2$), 1.44 (m, 8H, CH$_2$, OBu$_2$), .0.99 (m, 12H, CH$_3$, OBu$_2$). ^{13}C {^{1}H} NMR (100.62 MHz, 298 K, d$_8$-THF) δ ppm: 169.4 (C$_{ipso}$), 141.1 (C$_{ortho}$), 125.8 (C$_{meta}$), 123.8 (C$_{para}$), 70.9 (OCH$_2$, OBu$_2$), 32.6 (CH$_2$, OBu$_2$), 20.1 (CH$_2$, OBu$_2$), 14.1 (CH$_3$, OBu$_2$). ^{7}Li NMR (298 K, d$_8$-THF, reference LiCl in D$_2$O at 0.00 ppm) δ ppm: 1.15.

Synthesis of Li$_2$ZnPh$_4$ (3). To a solution of Ph$_2$Zn (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. Depite several attempts, storing of this solution at different temperatures (3ºC, -28ºC and -68ºC), no crystalline solid could be obtained. Removal of all volatiles under vacuum led to the isolation of **3** as a colourless oil. ^{1}H NMR analysis of this oil in deuterated THF showed the presence of four solvating molecules of THF. ^{1}H NMR (400.13 MHz, 298 K d$_8$-THF) δ ppm: 7.93 (d, 8H, H$_{ortho}$), 7.01 (t, 8H, H$_{meta}$), 6.96 (t, 4H, H$_{para}$), 3.56 (m, 16H, H$_\alpha$-THF), 1.74 (m, 16H, H$_\beta$-THF). ^{13}C {^{1}H} NMR (100.62 MHz, 298 K, d$_8$-THF) δ ppm: 173.1 (broad, C$_{ipso}$) 142.8 (C$_{ortho}$), 125.8 (C$_{meta}$), 123.9 (C$_{para}$), 68.3 (C$_\alpha$-THF), 26.3 (C$_\beta$-THF). ^{7}Li NMR (298 K, d$_8$-THF, reference LiCl in D$_2$O at 0.00 ppm) δ ppm: -0.13.

Synthesis of [(THF)$_3$Li(NC$_{13}$H$_9$-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 microwaved (125 ºC) for 20 minutes, affording a dark brown solution. The solution was filtered and stored at -70ºC overnight, resulting in the formation of pale brown crystals of **6** (0.24 g, 31% yield). Anal. Calcd for C$_{31}$H$_{40}$LiNO$_3$: C, 77,31; H, 8.37; N, 2.91. Found: C 77.46, H 8.06, N 3.11. ^{1}H NMR (400.13 MHz, 298 K d$_8$-THF) δ ppm: 7.11 (d, 2 H, H$_{ortho}$, Ph), 7.07 (t, 2 H, H$_{meta}$, Ph), 6.97 (t, 1H, H$_{para}$, Ph), 6.76 (d, , 2H, NC$_{13}$C$_9$), 6.69 (t, 2H, NC$_{13}$C$_9$), 6.49 (d, 2H, NC$_{13}$C$_9$), 6.23 (t, 2H, NC$_{13}$C$_9$), 5.03 (s, 1 H, C*H*Ph, NC$_{13}$C$_9$), 3.61 (m, 12 H, H$_\alpha$-THF), 1.76 (m, 12H, H$_\beta$-THF). ^{13}C{^{1}H} NMR (100.62 MHz, 298 K, d$_8$-THF) δ ppm: 153.9, 151.7 (C$_{quaternary}$, NC$_{13}$C$_9$), 141.2 (C$_{ipso}$, Ph), 129.3 (C1, NC$_{13}$C$_9$), 128.3 (C$_{ortho}$, Ph), 128.0 (C$_{meta}$, Ph), 126.3 (C3, NC$_{13}$C$_9$), 125.3 (C$_{para}$, Ph), 118.8 (C4, NC$_{13}$C$_9$), 114.1 (C2, NC$_{13}$C$_9$), 68.2 (C$_\alpha$-THF), 50.8 (CHPh, NC$_{13}$C$_9$), 26.3 (C$_\beta$-THF). ^{7}Li NMR (298 K, d$_8$-THF, reference LiCl in D$_2$O at 0.00 ppm) δ ppm: 0.74 ppm.

Synthesis of [(THF)(TMEDA)Li{NC$_{13}$H$_8$-Ph}$^{-\cdot}$] (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 ºC 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 2.006.

Synthesis of [(acr)ZnPh$_2$] (8) To a suspension of Ph$_2$Zn (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$_{25}$H$_{19}$NZn: C, 75.29; H, 4.80; N, 3.51 Found: C 75.24, H 4.79, N 4.03. ^{1}H NMR (400.13 MHz, 298 K, C$_6$D$_6$) δ ppm: 8.26 (m, 2H, H$_1$-acr), 7.97 (s, 1 H, H$_9$-acr), 7.82 -7.86 (m, 4H, H$_{ortho}$), 7.37 (m, 2H, H$_{para}$), 7.32-7.26 (m, 6 H, H$_{meta}$ and H4-acr overlapping), 7.03 (m, 2H, H$_2$-acr), 6.90 - 6.96 (m, 2 H, H$_3$-acr). ^{13}C {^{1}H} NMR (101.69 MHz, 298 K, C$_6$D$_6$) δ ppm: 154.9 (C$_{ipso}$, Ph), 147.7 (C$_{quaternary}$), 139.6 (C9, acr), 139.5 (C$_{ortho}$, Ph), 132.7 (C2,

acr), 128.8 (C_{para}, Ph), 127.7 (C_{meta}, Ph), 127.4 (C4, acr), 126.7 ($C_{quaternary}$, acr), 126.2 (C3, acr), 125.9 (C1, acr).

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 ZnPh$_2$, was added to acridine (0.09 g, 0.5 mmol). This mixture was then microwaved (125 ºC) for 20 minutes or refluxed over 14h at 66ºC, before being quenched with a saturated aqueous brine solution (5 mL). The product was extracted with diethyl ether (3 x 5 mL) and the combined organic phases dried (MgSO$_4$), filtered and concentrated under reduced pressure. Yields were determined by integration of the products resonances using ferrocene (10%) as internal standard in the ^{1}H NMR spectrum. Results of these studies are shown in Table 2. The reactions with ZnPh$_2$ (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 ZnPh$_2$. Examples of the ^{1}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.

ACKNOWLEDGMENT

DEDICATION

In the memory of Mike Lappert whose vision and discoveries have greatly helped shape modern organometallic chemistry.

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28. The choice of solvent seems crucial for the success of the arylation process. When poorly-coordinating toluene is employed no reaction is observed after 24h under refluxing conditions. Considering our spectroscopic spectroscopic studies of **2** and **3** in THF solutions, these findings suggest that the arylation reactions are promoted by solvent-separated ion pair zincates.

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32. Small amounts of biphenyl were detected in all the NMR spectra, which are attributed to minor decomposition of the relevant organometallic reagent under these reaction conditions.

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34. Robertson, S. D.; Kennedy, A. R.; Liggat, J. J.; Mulvey, R. E., *Chem. Commun.* **2015**, *Advance Article*, DOI: 10.1039/C4CC06421F.

35. For a related interesting structure resulting from the reductive dimerization of acridine mediated by samarium see: Labouille, S.; Nief, F.; Le Goff, X.-F. Maron, L.; Kindra, D. R.; Houghton, H. L.; Ziller, J. W.; Evans, W. J., *Organometallics*, **2012**, *31*, 5196.

36. 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 ^{1}H NMR signals match those observed in the reaction crude of **acr** with zincate **2** (see Figure S8, Supporting Information).

37. The crystal structure of **7** is a co-crystalline mixture of the donor variants [(THF)₃Li{NC₁₃H₈-Ph[•−]}] and [(THF)(TMEDA)Li{NC₁₃H₈-Ph[•−]}]. Both molecules are disordered such that the [Li{NC₁₃H₈-Ph[•−]}] fragments of each lie on the same crystallographic sites and appear well ordered with the THF and TMEDA groups appearing disordered. Refinement of site occupancy factors gives a 0.735(3):0.265(3) ratio in favor of the [(THF)₃Li{NC₁₃H₈-Ph[•−]}] species

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39. Lomax, A.; Marcoux, L. S.; Bard, A. J., *J. Phys. Chem.* **1972,** *76*, 3958-3560.

40. For other examples of acridine radical derivatives, including both cationic and anionic species see: (a) Tamamushi, B.; Akiyama, H., *Trans. Faraday Soc.* **1939,** *35*, 491-494; (b) Noyori, R.; Katô, M.; Kawanisi, M.; Nozaki, H., *Tetrahedron* **1969,** *25*, 1125-1136. (c) Handoo, K. L.; Cheng, J.-P.; Parker, V. D., *J. Chem. Soc., Perkin Trans. 2* **2001**, 1476-1480; (d) Mackiewicz, N.; Delaire, J. A.; Rutherford, A. W.; Doris, E.; Mioskowski, C., *Chem. Eur. J.* **2009**, *15*, 3882-3888. (e) Chaudhuri, J.; Kume, S.; Jagur-Grodzinski, J.; Szwarc, M., *J. Am. Chem. Soc.* **1968**, *90*, 6421-6425; (f) Ishikawa, M.; Fukuzumi, S., *J. Am. Chem. Soc.* **1990,** *112*, 8864-8870; (g) Jaworski, J. S.; Cembor, M., *Tetrahedron Lett.* **2000,** *41*, 7267-7270; (h) Taguchi, M.; Moriyama, M.; Namba, H.; Hiratsuka, H., *Radiat. Phys. Chem.* **2002,** *64*, 115-122; (i) Fukuzumi, S.; Yuasa, J.; Satoh, N.; Suenobu, T., *J. Am. Chem. Soc.* **2004,** *126*, 7585-7594.

41. Gore-Randall, E.; Irwin, Denning, M. S.; M.; Goicoechea, J. M. *Inorg. Chem.* **2009**, *48*, 8304-8316.

42. 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.

43. (a) Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.;Hanafusa, T. *J. Org. Chem.* **1989**, *54*, 4706-8. (b) Yamataka, H.; Nagareda, K.; Takatsuka, T.; Ando, K.; Hanafusa, T.; Nagase, S. *J. Am. Chem. Soc.* **1993**, *115*, 8570-6. (c) Yamataka, H.; Nagareda, K.; Ando, K.; Hanafusa, T. *J. Org. Chem,* **1992**, *57*, 2865-9.

44. 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 0ºC followed

by treatment with DDQ and hydrolysis, **5** was obtained in 51% yield.

45. Lennartson, A.; Håkansson, M., Acta Crystallogr., Sect. C: Cryst. Struct. Commun. **2009**, m205-m207.
46. Contrastingly, using the deuterated solvent d_8-THF, with a greater coordinating ability, the NMR spectra of **8** only showed signals corresponding to free **acr** and ZnPh$_2$, consistent with the cleavage of the donor-complex.
47. Sheldrick, G. M. *Acta Crystallog.* **2008**, *A64*, 112-122.
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acr

(i) LiZnPh$_3$, THF, MW
125°C, 20 min
(ii) DDQ

Ph

pre-arylation

Li

Zn

post-arylation

N   Li