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Evaluating *cis*-2,6-Dimethylpiperidide (*cis*-DMP) as a Base Component in Lithium-Mediated Zincation Chemistry

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Abstract: Most recent advances in metallation chemistry have centred on the bulky secondary amide 2,2,6,6-tetramethylpiperidide (TMP) within mixed metal, often ate, compositions. However, the precursor amine TMP(H) is rather expensive so a cheaper substitute would be welcome. Thus this study was aimed towards developing cheaper non-TMP based mixed-metal bases and, as *cis*-2,6-dimethylpiperidide (*cis*-DMP) was chosen as the alternative amide, developing *cis*-DMP zincate chemistry which has received meagre attention compared to that of its methyl-rich counterpart TMP. A new lithium diethylzincate, [(TMEDA)-LiZn(*cis*-DMP)Et_2] (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) has been synthesised by co-complexation of Li(*cis*-DMP), Et_2Zn and TMEDA, and characterised by NMR (including DOSY) spectroscopy and X-ray crystallography, which revealed a dinuclear contact ion pair arrangement. By using *N*,*N*-diisopropylbenzamide as a test aromatic substrate, the deprotonative reactivity of [(TMEDA)LiZn-(*cis*-DMP)Et_2] has been probed and contrasted with that of the known but previously uninvestigated di-*tert*-butylzincate, [(TMEDA)LiZn(*cis*-DMP)-*t*Bu_2]. The former was found to be the superior base (for example, producing the *ortho*-deuteriated product in respective yields of 78% and 48% following D_2O quenching of zincated benzamide intermediates). An 88% yield of 2-iodo-*N*,*N*-diisopropylbenzamide was obtained on reaction of two equivalents of the diethylzincate with the benzamide followed by iodination. Comparisons are also drawn using 1,1,1,3,3,3-hexamethyldisilazide (HMDS), diisopropylamide and TMP as the amide component in the lithium amide, Et_2Zn and TMEDA system. Under certain conditions, the *cis*-DMP base system was found to give improved results in comparison to HMDS and diisopropylamide (DA), and comparable results to a TMP system. Two novel complexes isolated from reactions of the di-*tert*-butylzincate and crystallographically characterised, namely the pre-metallation complex [{(*i*Pr)$_2$N(Ph)C=O}LiZn(*cis*-DMP)*t*Bu_2] and the post-metallation complex [(TMEDA)Li(*cis*-DMP){2-[1-C(=O)N-(*i*Pr)$_2$]C_6H_4}Zn(*t*Bu)], shed valuable light on the structures and mechanisms involved in these alkali-metal-mediated zincation reactions. Aspects of these reactions are also modelled by DFT calculations.

Keywords: amides · lithium · metallation · structural elucidation · zincates

Introduction

Metallation today: Metallation (transformation of a relatively inert, nonpolar C–H bond to a more reactive, more polar C–metal bond), the seminal reaction that defines polar organometallic chemistry,[1] has undergone a remarkable period of advancement during the past decade. Prior to this, certainly in the context of aromatic chemistry, metallation usually meant lithiation as the polarity of $C^{\delta-}$–$Li^{\delta+}$ bonds powered the basicity/nucleophilicity of their $C^{\delta-}$ moieties making them powerful deprotonating agents towards activated C–H bonds.[2] Today a metallation reaction could be, for example, a magnesiation,[3] zincation,[4] or alumination,[5] that is executed by a metal, which by being significantly less electropositive than lithium was considered by conventional wisdom to be insufficiently basic to deprotonate aromatic substrates.[6] Conventional organometallic compounds of these comparatively soft metals are indeed poor bases. However, building multicomponent systems combining these poor metal bases with other metal compounds (e.g., commonly lithium chloride or alkali metal amides)[3a] not only greatly boosts their deprotonating power but also transfers the point of reactivity from the alkali metal to the less electropositive metal.[6b] Though the reasons for this transfer of metallating power are not yet fully understood and may be

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different in different systems, a general contributory factor must be the migration of the anions to the more electrophilic non-alkali-metal, leading to a complexed moiety which must carry the most negative charge in the system. The most studied such multicomponent systems include the Knochel turbo-Grignard reagent,[7] [(TMP)MgCl.LiCl], the Kondo-Uchiyama lithium zincate,[8] [LiZn(TMP)tBu$_2$], the Mongin tris(amido) cadmate,[9] [LiCd(TMP)$_3$], and our own sodium zincate,[4a] [(TMEDA)NaZn(TMP)tBu$_2$]. Common to all of these examples is the TMP (2,2,6,6-tetramethylpiperidide) anion. It is the base engine of these multicomponent systems, driving C–H deprotonations of aromatic substrates kinetically generating aromatic anions and the parent amine TMP(H), though in some cases alkyl anions within the base residue can deprotonate TMP(H) in a second thermodynamic step to regenerate TMP concomitantly releasing alkane.[4a,10] A disadvantage of TMP that has prevented its large scale utilisation is its excessive cost,[11] accordingly, finding a cheaper alternative is a key goal in this fundamentally important area of synthetic chemistry.

Background on 2,6-*cis*-dimethylpiperidide (*cis*-DMP): Searching for alternatives to TMP an obvious contender is *cis*-DMP. Exhibiting the same structural framework but having two methyl branches less than TMP, *cis*-DMP has been likened more to another strong amide base, diisopropylamide (DA), being described as a "tied-back variant of DA"[12] (Figure 1).

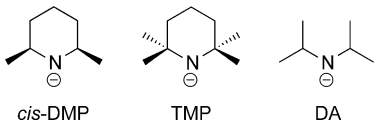


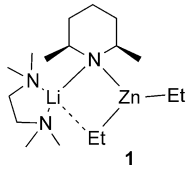
Figure 1. Structural comparison of *cis*-DMP with common amides.

Our interest in *cis*-DMP was lit by the relative cheapness of its parent amine *cis*-DMP(H) compared to TMP(H)[13] and heightened by a recent theoretical study by Streitwieser and co-workers that computed the pK(Li) of monomeric Li(*cis*-DMP) to be 34.75, only marginally less than the 35.53 found for LiTMP.[14] Compared to the wealth of synthetic studies employing LiTMP, those employing Li(*cis*-DMP) are extremely scarce. There are isolated reports of the use of Li(*cis*-DMP) as a base in the synthesis of cyano-substituted benzamidines,[15] N-substituted boron heterocycles,[16] annulated nicotine analogues,[17] and exocyclic allylic alcohols[18] and it has also been used to probe the mechanisms involved in dehalogenation reactions of aryl halides.[19] In addition, a TMEDA–hemisolvate of Li(*cis*-DMP) was shown to initiate anionic polymerisation of methyl methacrylate.[20] Surprisingly, however, though a handful of *cis*-DMP-based multicomponent systems are known,[12,21] there have been no previous reports of their use in synthesis in contrast to the revolution in metallation chemistry driven by TMP multicomponent systems. Introducing the new lithium *cis*-DMP zincate, [(TMEDA)LiZn(*cis*-DMP)Et$_2$], **1**, and drawing comparisons with its known di-*tert*-butyl analogue[12] [(TMEDA)LiZn(*cis*-DMP)tBu$_2$], **2**, this work details the first systematic study of *cis*-DMP multicomponent metallation of an aromatic substrate and subsequent electrophilic interception reactions.

Results and Discussion

Synthesis, characterisation and structural aspects of the new lithium zincate: A simple deprotonation–cocomplexation approach was used to synthesise **1** [Eq. (1)]. Cocomplexation is a self-assembling method of making multicomponent systems that relies on the latent Lewis acidity and/or Lewis basicity of the individual components. Here mixing together the three components in hexane solution affords **1** in which TMEDA acts as a Lewis base to the lithium amide, the lithium amide acts simultaneously as a Lewis acid to TMEDA and a Lewis base (through its N atom) to diethylzinc, and diethylzinc acts as a Lewis acid to the lithium amide.

$$\text{Li}(\textit{cis}\text{-DMP}) + \text{Et}_2\text{Zn} + \text{TMEDA} \xrightarrow{\text{hexane}} [(\text{TMEDA})\text{LiZn}(\textit{cis}\text{-DMP})\text{Et}_2]\ (\mathbf{1}) \qquad (1)$$



1

This new lithium bisalkyl-amidozincate was isolated as pale yellow needle crystals in a yield of 61 %. It was characterised in solution by a combination of ^{1}H, ^{7}Li and ^{13}C NMR spectroscopy as well as by diffusion-ordered NMR spectroscopy (DOSY). Full details are presented in the Experimental Section and in the Supporting Information. Table 1 compares ^{1}H NMR chemical shifts for [D$_6$]benzene solutions of free *cis*-DMP(H), diethylzinc, and the alkyl variant zincates **1** and **2**. Main points to note are the signals for **1** are consistent with the molecular formula elucidated by X-ray crystallography (vide infra) and their chemical shifts relative to those of *cis*-DMP(H) show an identical pattern to those reported previously for **2** (e.g., the amine α-CH signal experi-

Table 1. Comparison of ^{1}H NMR data (C$_6$D$_6$, 400.03 MHz, 300 K) for zincates [(TMEDA)LiZn(*cis*-DMP)Et$_2$] (**1**) and [(TMEDA)LiZn(*cis*-DMP)tBu$_2$] (**2**), Et$_2$Zn and *cis*-DMP(H).

	cis-DMP(H)	TMEDA	Et$_2$Zn	**1**	**2**[12]
α-CH	2.45	–	–	3.12	3.32
β-CH_2	1.43, 1.00	–	–	1.67, 0.64	1.67, 0.39
γ-CH_2	1.65, 1.24	–	–	1.91, 1.73	1.83, 1.72
CH_3	0.96	–	–	1.08	1.05
NH	0.75	–	–	–	–
TMEDA (CH_3)	–	2.12	–	1.76	1.66
TMEDA (CH_2)	–	2.36	–	1.63	1.48
Et (CH_2CH$_3$)	–	–	0.12	0.39	–
Et (CH$_2$CH_3)	–	–	1.11	1.92	–

ences a downfield shift from $\delta = 2.45$ to $\delta = 3.12$ ppm and $\delta = 3.32$ ppm on incorporation into the zincates **1** and **2**, respectively). Both ^{1}H and ^{13}C NMR spectra reveal only one set of signals for the two ethyl groups in **1**, implying they are identical in solution on the NMR timescale. As two distinct ethyl environments are present in the solid-state structure (vide infra), the implication is that the Li···CH_2(Me) contact breaks in solution enabling free rotation about the Zn–N bond axis. Analysis of **1** in [D_8]THF solution reveals a straightforward, clean ^{1}H NMR spectrum of the expected 1:1:2, *cis*-DMP:TMEDA:Et ratio. Comparing this spectrum with those of Li(*cis*-DMP) (see the Supporting Information) and $[(TMEDA)\{Li(cis\text{-}DMP)\}_2]_\infty$[20a] suggests neither of these monometallic amide species exist in the solution of **1**.

A more complete picture of solution behaviour (providing information on the number of species present; aggregation and solvation phenomena) can be pieced together by including DOSY NMR spectroscopic studies within the characterisation package. DOSY can be particularly informative in polar organometallic chemistry[22] as recently illustrated for example by Williard and Keresztes for THF solvates of *n*-butyllithium,[23] Stalke and co-workers for structural variations of lithium trimethylzincates,[24] and our own group for metal[25] and mixed-metal[26] TMP bases. Here, building on the identification of components from the routine ^{1}H NMR spectroscopic study, qualitative inspection of the DOSY spectrum of **1** in [D_6]benzene solution (Figure 2) show these components lie at similar diffusion coefficients implying they are assembled into a single multicomponent molecule (akin to the solid-state structure: vide infra). Calibrated against known standards (see the Supporting Information), the molecular weight of **1** was estimated to be 279.9 g mol^{-1}, 78% of that obtained from the X-ray crystallographic study (358.8 g mol^{-1}). Two possible explanations for this significant discrepancy are that compounds containing a large central atom surrounded by smaller atoms can sometimes give artificially low molecular weights compared to their true value[26b] or that a coordination/decoordination event involving TMEDA on lithium is occurring since the value calculated for **1** (279.9 g mol^{-1}) is intermediate between those of TMEDA-coordinated (358.8 g mol^{-1}) and -decoordinated (242.6 g mol^{-1}) species. Importantly, it suggests that cocomplexation of the lithium and zinc organometallics is taking place and that no oligomerisation is occurring. Assessment of the DOSY spectrum of **1** recorded in [D_8]THF solution (see the Supporting Information) shows TMEDA is fully displaced by [D_8]THF ligands, which are present in vast excess. This substitution, well known in other areas of polar organometallic chemistry[27] probably takes place within a similar multicomponent contacted ion-pair structure [e.g., [([D_8]THF)$_n$LiZn(*cis*-DMP)Et_2] (where $n = 1$ or 2)], though a solvent-separated (segregATE) variant ([Li([D_8]THF)$_n$]$^+$ [Zn(*cis*-DMP)Et_2]$^-$) (where $n = 4$) cannot be unequivocally ruled out.

Determined by an X-ray diffraction study, diethylzincate **1** crystallises in the monoclinic crystal system in space group $P2_1/n$ with two unique, but essentially identical molecules in the unit cell. Since one molecule has some disorder in one ethyl group, discussion is restricted to the other molecule. Figure 3 shows its contacted ion-pair arrangement, comprising a TMEDA-chelated Li(*cis*-DMP) monomer contacted through a *cis*-DMP N bridge to a diethylzinc monomer. Alternatively it could be viewed as having a four-atom, four-element LiNZnC ring, but the Li1···C3 bond "closing" the ring is very long [2.721(7) Å, cf. mean Li–C bond length in $(EtLi)_4$,[28] 2.36 Å] and the acuteness of the Li1-C3-Zn1 angle [68.8(2)°] suggests this elongated side of the ring is largely a steric artefact of the N bridge bringing one arm of the trigonal planar (NC_2) zinc centre into close proximity to the vacant lithium coordination site. However, a small electronic contribution to this Li···C contact is implicated from the lengthening of the associated Zn1–C3 bond [2.047(4) Å] compared to that of the other unequivocally terminal Zn1–C1 bond [1.994(3) Å]. Bonded strongly to both metal centres [Li1–N1 2.010(6) Å; Zn1–N1 2.059(3) Å], the *cis*-DMP bridge adopts a chair conformation with equatorial Me substituents. TMEDA chelates slightly asymmetrically to lithium which, discounting the long, weak Li1–C3 contact occupies a pseudo-trigonal-planar N_3 geometry (summed N-Li-N bond angles, 354.5°).

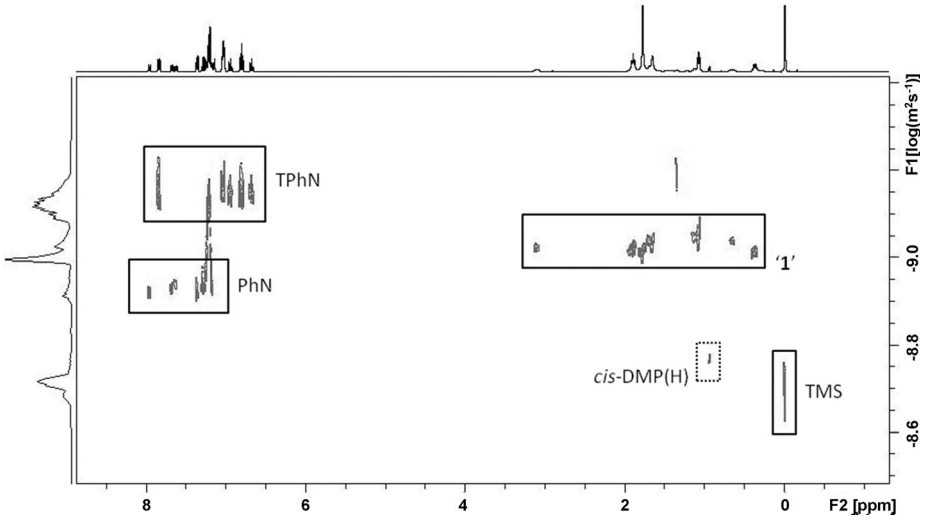


Figure 2. ^{1}H DOSY NMR spectrum of **1** in [D_6]benzene solution at 300 K in the presence of inert standards 1,2,3,4-tetraphenylnaphthalene (TPhN), 1-phenylnaphthalene (PhN) and tetramethylsilane (TMS). Contamination due to grease impurity and *cis*-DMP(H) are present.

The structure of **1** bears a close similarity to that of its di-*tert*-butyl variant **2**. In component connectivity they are identical. However, the steric impact of substituting the dieth-

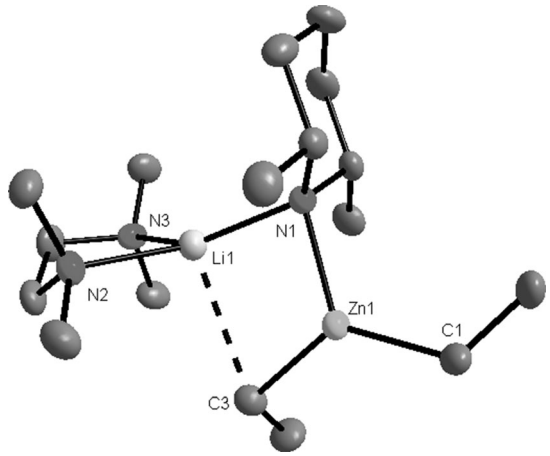


Figure 3. Molecular structure of new lithium zincate **1**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity. The dashed line represents a long-range interaction between Li1 and C3. Selected bond lengths [Å] and bond angles [°]: Li1–N2 2.133(6), Li1–N3 2.198(6), Li1–N1 2.010(6), Li1···C3 2.721(7), Zn1–C1 1.994(3), Zn1–C3 2.047(4), Zn1–N1 2.059(3); N2-Li1-N3 86.1(2), N1-Li1-N3 134.4(3), N2-Li1-C3 98.1(2), N1-Li1-N2 134.0(3), N3-Li1-C3 105.1(3), N1-Li1-C3 91.5(2), Li1-N1-Zn1 85.0(2), Zn1-C3-Li1 68.8(2), C1-Zn1-C3 127.8(1), C1-Zn1-N1 119.1(1), C3-Zn1-N1 113.0(1).

ylzinc component by the di-*tert*-butylzinc component is reflected most in the Li···alkyl contact. Branching about the quaternary C anion [$(Me)_3C^-$] shields it from Li [separation distance 3.545(3) Å] leaving the shortest Li···C contact with one of the coordinatively saturated Me groups [2.813(3) Å], though even this contact is longer than the Li1···(anionic)C3 contact in **1**. Note also that the shallow pyramidisation is more evident in **1** [summed N-Li-N bond angles, 354.5°, cf., 356.36° in **2**] reflecting the greater significance of its long-range Li···C contact. The closest lithium diethylzincate analogy to **1** is unsolvated [$LiZn(TMP)Et_2$] (Figure 4).[10a] Not affecting the trigonal planarity of the $Et_2Zn(NR_2)$ moiety, the absence of a solvating ligand dramatically alters the connectivity of the lithium amide which now bonds to two Et anions, one as part of a Li-N-Zn-C ring [Li–C 2.374(3) Å], the other the "terminal" Et on an adjacent zincate unit [Li–C 2.264(3) Å to CH_2 2.547(3) Å to CH_3] within a polymeric chain structure.

Comparative reactivity studies: From their formulae, **1** and **2** could be considered as TMEDA-solvated *cis*-DMP ana-

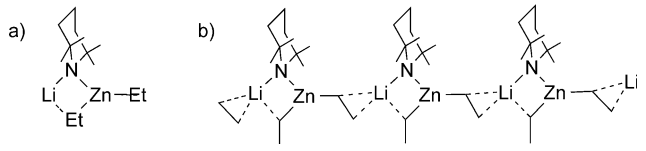
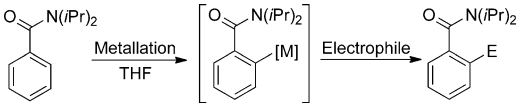


Figure 4. Graphical representations of a) the monomeric unit of the lithium zincate [$LiZn(TMP)Et_2$] and b) a section of the polymeric structure.[10a]

logues of Kondo and Uchiyama's "$LiZn(TMP)tBu_2$", which has been employed successfully for the metallation of a variety of aromatic and heteroaromatic substrates.[8] Thus we sought to determine whether these less bulky amido zincates could similarly be effective as reagents for the selective deprotonation of aromatic substrates. For the organic substrate we chose *N,N*-diisopropylbenzamide [$C_6H_5C(=O)NiPr_2$] (**3**). Tertiary amides rank amongst the strongest directors of *ortho*-metallation.[29] Good bases for tertiary amides require substantial steric bulk to avoid competitive nucleophilic addition at the carbonyl function.[29b] What is more, with alkyllithium or LiTMP (aided by TMEDA) bases subambient temperatures (commonly −78 °C in THF solution)[29b] are mandatory to avoid decomposition processes. Table 2 lists a selection of literature data on the *ortho*-deprotonation of *N,N*-diisopropylbenzamide using these conventional reagents or new heterobimetallic TMP ate species.

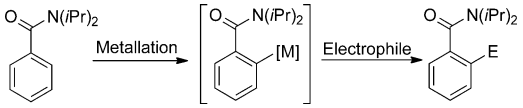
A comparison between **1** and **2** established that the former is the better base (Table 3). D_2O quenching of their reactions with the benzamide in hexane solution for three hours gave the *ortho*-deuteriated benzamide product in respective yields of 78% and 48%. Similarly, iodination after

Table 2. Selected literature data on the deprotonation of *N,N*-diisopropylbenzamide.



Metallation Conditions	Electrophile	E	Yield [%]
sec-BuLi/TMEDA (1.1 equiv), −78 °C	D_2O	-D	90[30]
	allyl bromide	-Br	60[30]
$LiZn(TMP)(tBu)_2$ (2 equiv), RT	I_2	-I	100[8a]
$LiAl(TMP)(iBu)_3$ (2 equiv), 0 °C	allyl bromide	$-CH_2CHCH_2$	100[31]
	D_2O	-D	100[31]
$LiAl(TMP)_2(iBu)_2$ (1 equiv), RT	I_2	-I	88[5c]
$Li_2Cu(TMP)(CN)(Me)$ (2 equiv), 0 °C	TMSCl	-TMS	99[32]
	benzoyl chloride	-C(O)Ph	84[32]
	allyl bromide	$-CH_2CHCH_2$	99[32]
	D_2O	-D	100[32]

Table 3. Comparative deprotonation results of bases **1** and **2** with *N,N*-diisopropylbenzamide.



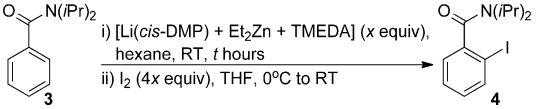
Entry	Metallation Conditions	Electrophile	E	Yield [%]
1	**1** (1.2 equiv), hexane, RT, 3 h	D_2O	-D	78[a]
2	**2** (1.2 equiv), hexane, RT, 3 h	D_2O	-D	48[a]
3	**1** (1.2 equiv), hexane, RT, 3 h	I_2	-I	68[b]
4	**2** (1.2 equiv), hexane, RT, 3 h	I_2	-I	35[b]

[a] Extent of deuteriation estimated by ^1H NMR spectroscopy. [b] Yield was determined by ^1H NMR spectroscopy using hexamethylbenzene as internal standard.

reaction of the benzamide with **1** or **2** afforded 2-iodo-*N,N*-diisopropylbenzamide (**4**) in yields of 68% and 35%, respectively. Note that these metallation reactions were run at room temperature in contrast to the subambient temperatures needed for the aforementioned conventional bases reflecting the milder, more functional group compatible nature of the zincate reagents. These test deprotonation results coupled with the advantage that the dialkylzinc component of **1** is commercially available (as indeed are all its components) unlike that in **2** which needs to be prepared in a separate reaction, made **1** become the focus of more in depth reactivity studies.

The effects of varying the reaction time (three hours or leaving overnight for 22 h) and increasing the number of equivalents of the base (from 1.2 to 2.0) was studied first. Base **1** was prepared in situ in hexane solution and stirred for 15 min prior to the addition of the benzamide. Reactions were quenched with a THF solution of excess iodine (four molar equivalents with respect to the base) at 0°C, then the mixtures were allowed to warm to room temperature and were stirred for at least four hours before work up and analysis of crude product mixtures. Using a slight excess of the base over 22 h produced 82% of the iodinated product **4** together with 11% of recovered benzamide starting materials (Table 4, entry 2). However, the starting material was completely consumed on increasing the base quantity to two equivalents with **4** isolated via alumina column chromatography in a yield of 88% (Table 4, entry 4).

Table 4. Effect of variation of reaction time and equivalents of base on metallation-iodination of *N,N*-diisopropylbenzamide using in situ *cis*-DMP zincate mixture.

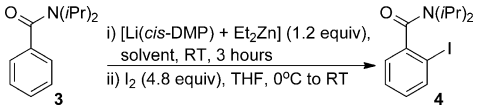


Entry	*x* (equiv)	*t* (hours)	Yield [%][a] **3**	**4**
1	1.2	3	20	68
2	1.2	22	11	82
3	2	3	15	77
4	2	22	0	88[b]

[a] Yield was determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard. [b] Yield of isolated product.

Next the effect of varying the solvent used in the metallation part of the metallation–iodination procedure was monitored. This included studying the influence of TMEDA on the in situ base mixtures. At room temperature, using a bulk hexane solution containing 1.2 molar equivalents of the components of lithium zincate **1** but omitting TMEDA completely shut down its reactivity, with recovered benzamide starting material and only minute traces of the 2-iodo-benzamide (almost 0%) observed by ^{1}H NMR spectroscopy (Table 5, entry 1). It is possible that in place of TMEDA chelation to lithium, substrate coordination via its carbonyl function takes place (an intermediate of this type, [{(*i*Pr)$_2$N(Ph)C=O}LiZn(*cis*-DMP)*t*Bu$_2$], (**5**), has been crystallographically characterised for the *tert*-butyl variant, vide infra) and that this ties up the substrate leaving it unavailable for deprotonation.[33] Recovery of benzamide starting material after iodination and work-up is consistent with this reasoning. Subsequent preparation of an equimolar mixture of Li(*cis*-DMP), Et$_2$Zn and *N,N*-diisopropylbenzamide afforded only a pale yellow oil as opposed to the crystalline sample of its *tert*-butyl variant, though ^{1}H NMR spectroscopic analysis of this oil in [D$_6$]benzene solution confirmed no resonances consistent with metallation. Free *N,N*-diisopropylbenzamide is also not observed, rather the aromatic region of the spectrum shows resonances of similar chemical shifts to those seen for the *tert*-butyl variant of the substrate complex (**5**). Most tellingly, in addition to the overlapping resonances at $\delta = 7.09$–7.03 ppm integrating for three hydrogen atoms, a resonance corresponding to the two remaining aromatic hydrogens is observed at $\delta = 7.01$–6.94 ppm, an upfield shift of approximately 0.3 ppm with respect to that in free *N,N*-diisopropylbenzamide. On changing the bulk solvent from non-coordinating hexane to lone-pair coordinating THF metallation proceeded without TMEDA support and the *ortho*-iodinated product was formed in reasonable yield (Table 5, entry 3). These conditions enable THF to solvate the lithium atom in place of TMEDA. Similar results were obtained when including TMEDA in the base mixture in bulk THF (Table 5, entry 4). Increasing to two equivalents of the base led to complete consumption of benzamide starting material and a 92% yield of the product within three hours, whereas the hexane/TMEDA solvent mixture failed to reach complete conversion on this time scale (Table 5, entries 5 and 2).

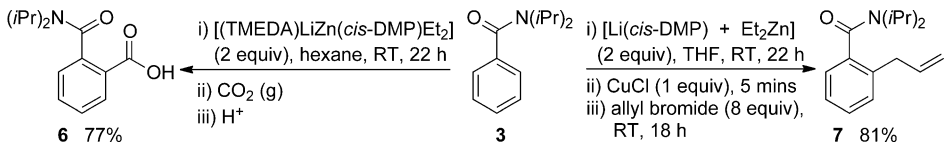
Table 5. Effect of variation of reaction solvent.



Entry	Solvent	Yield of **4** [%][a]
1	hexane	<1
2	hexane + TMEDA[b]	68
3	THF	79
4	THF + TMEDA[b]	77
5	THF + TMEDA[b]	92[c]

[a] Yield determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard. [b] 1 equivalent with respect to base mixture. [c] 2 equivalents of the base mixture were used.

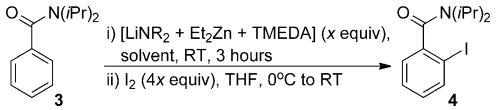
Since reaction of **1** with *N,N*-diisopropylbenzamide could be quenched with iodine and the iodinated product isolated in 88% yield, other electrophiles were considered (Scheme 1). After metallation using **1**, the system could also be quenched by carbon dioxide to isolate 2-(diisopropylcarbamoyl)benzoic acid (**6**) after acidic work up. Allyl bromide quenching in the presence of a copper catalyst gave the 2-allylated product **7** in a 81% isolated yield after column chromatography.



Scheme 1. Electrophilic quenching using alternative electrophiles.

A direct comparison was also made with different amido components. Therefore, in turn, the three most important utility amides in organolithium chemistry [1,1,1,3,3,3-hexamethyldisilazide, HMDS, $N(SiMe_3)_2$; diisopropylamide, DA, $N(iPr)_2$; and TMP] were used in the in situ base mixture in place of *cis*-DMP. The reaction with the benzamide was repeated employing 1.2 molar equivalents of the base mixture in hexane solution at ambient temperature and stirred for 3 h. The results obtained (Table 6) showed that HMDS completely shut down the deprotonating reactivity of the in situ mixture: both in hexane and THF solution no 2-iodobenzamide product was observed. DA was effective in this H–Zn/Zn–I double exchange process producing a yield (76%) intermediate to that of **1** and the TMP variant in hexane solution, but gave lower yields than the *cis*-DMP and TMP mixtures in THF solution. As expected from previous reports of the use of "[LiZn(TMP)Et_2]" for deprotozincations of *N,N*-diisopropylbenzamide, *N,N*-diisopropylnaphthamide[10a] and phenyl dimethylcarbamate[34] a TMP base mixture effectively metallated **3**, giving the best yield of the amides studied in hexane solution (82%, 15% higher than that achieved by **1**). Increasing the number of equivalents of base to two, in THF solution, the results achieved by **1** were comparable to those with the TMP mixture. On the basis of these initial results, in contrast to the HMDS system, there is clearly potential for making a *cis*-DMP-based multicomponent reagent that is competitive with both TMP and DA systems provided further refinements could be made to the existing in situ base mixture.

Table 6. Effect of variation of amide in base mixture.



Entry	NR_2	Solvent	*x*	Yield of **4** [%][a]
1	HMDS	hexane	1.2	0
2	DA	hexane	1.2	76
3	TMP	hexane	1.2	82
4	*cis*-DMP	hexane	1.2	68
5	HMDS	THF	2	0[b]
6	DA	THF	2	77
7	TMP	THF	2	90
8	*cis*-DMP	THF	2	92

[a] Yield determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard. [b] After 22 h.

Probing co-operative effects and structural aspects: Some control reactions were carried out to check whether the individual single-metallic components of **1** could also affect the deprotonation of *N,N*-diisopropylbenzamide. Thus omitting the zinc component and treating the benzamide with Li(*cis*-DMP) in either hexane or THF solvent at ambient temperature for 3 h, followed by iodination returned only the benzamide starting material, with no evidence of any 2-iodinated benzamide product as determined by ^{1}H NMR spectroscopic analysis. The same outcome was found when the hexane reaction was repeated in the presence of a molar equivalent of TMEDA. Alkylzinc reagents are notoriously poor bases so it was with scepticism but for completeness that we attempted to metallate the benzamide with diethylzinc on its own in hexane solution. Again no metallation was inferred as following the iodination work-up no 2-iodobenzamide was observed but only starting material.

The failure of these homometallic control reactions implies that the origin of the moderately strong deprotonative capability of **1** lies in co-operative effects between its different components that must be set in motion by the structure or structures of the multicomponent mixture. It is therefore important to collect structural information about the system. Knowing the solid-state structure of **1** and that non-polar hexane would provide little donating incentive for breaking it up, it seems certain that the starting point for reaction with the benzamide would be the contacted ion-pair structure with Li and Zn bridged via the *cis*-DMP N and, in view of the aforementioned shut down of the reaction in its absence, with TMEDA coordination of Li. What changes to the structure of **1** could ensue upon addition of the benzamide? As alluded to earlier no direct solid-state structural information could be gleaned from the reaction of **1** or its TMEDA-free mixture with benzamide as no crystalline products could be obtained. However excellent indirect evidence was forthcoming from success in crystallising products from the corresponding reactions with the *tert*-butyl analogue **2**. *ortho*-Zincation (zinc–hydrogen exchange) of the benzamide was confirmed by the molecular structure of the heterotrianionic complex [(TMEDA)Li(*cis*-DMP){2-[1-C(O)N(*i*Pr)$_2$]C_6H_4}Zn(*t*Bu)], **8** (Figure 5).

Isolated in 25% yield, these crystals grew from a hexane solution comprising a 2:1 mixture of the base **2** and the benzamide [Eq. (2)]. Full details of the spectroscopic characterisation of **8** are given in the Experimental Section. Its molecular structure most significantly reveals a Zn–*ortho*-(benzamide) bond [Zn1−C18 2.039(3) Å] replacing the *t*Bu "bridge" in **2**. The carbonyl (C=*O*) function of the deprotonated benzamide binds to lithium [Li1−O1 2.019(5) Å]. These two bonds aside, the structure retains the same (TMEDA)LiNZn(*t*Bu) backbone found in the starting base **2**, so there is a seven-atom, five-element (LiNZnCCCO)

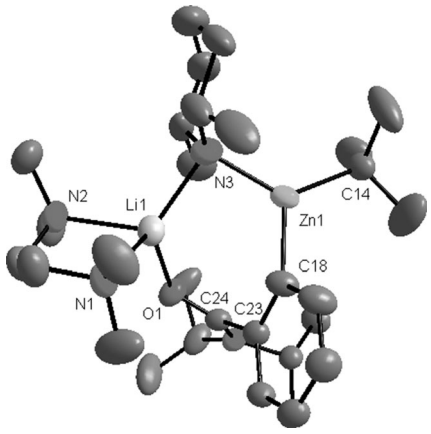
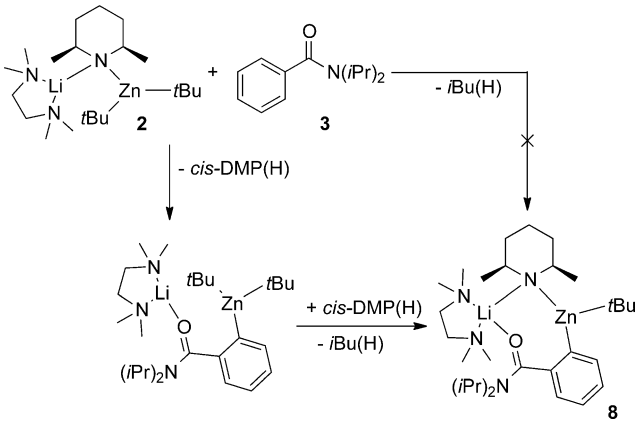


Figure 5. Molecular structure of [(TMEDA)Li(*cis*-DMP){2-[1-C(O)N-(*i*Pr)$_2$]C$_6$H$_4$}Zn*t*Bu] (**8**). Hydrogen atoms and disorder in the *cis*-DMP ring have been omitted for clarity. Ellipsoids are shown at the 50% probability level. Selected bond lengths [Å] and bond angles [°]: Li1–N1 2.316(6), Li1–N2 2.233(6), Li1–N3 2.138(6), Li1–O1 2.019(5), Zn1–N3 2.015(3), Zn1–C14 2.028(3), Zn1–C18 2.039(3), C18–C23 1.406(4), C23–C24 1.499(4), C24–O1 1.245(3); N3-Zn1-C14 127.5(1), N3-Zn1-C18 113.5(1), C14-Zn1-C18 118.9(1), O1-Li1-N3 114.2(2), O1-Li1-N2 99.8(2), N3-Li1-N2 114.8(3), O1-Li1-N1 109.0(3), N3-Li1-N1 129.0(2), N2-Li1-N1 82.0(2), C24-O1-Li1 126.5(2), C18-C23-C24 119.0(2), Zn1-N3-Li1 94.9(2), C23-C18-Zn1 126.7(2).



Scheme 2. Possible two-step mechanism in reaction of **2** with *N,N*-diisopropylbenzamide to form **8**.

puckered ring [torsion angle: C24-O1-Li1-N3 65.0(2)°] at its core. Similar to the description of **1**, the structure of **8** could be interpreted as a contact ion pair between a TMEDA-chelated Li(*cis*-DMP) monomer and an aryl-ethylzinc monomer with the contact made through an amido N bridge and an O appendage of the aryl group. This Li–O dative bond provides extra electronic stabilisation compared to the weak agostic Li···Me interaction in **2** and thus the Li–N(amido) bond in **8** is weaker [Li1–N3 2.138(6) Å] than its counterpart in **2** [Li–N 2.027(3) Å]. From the molecular formula of **8** it appears that it has been produced via **2** behaving as an alkyl base (the co-product being isobutane). However, mimicking the reactivity found in many TMP-driven alkali-metal-mediated metallations established both theoretically[10a] and experimentally,[10b] it is likely that the *cis*-DMP ligand performs the *ortho* deprotonation (reflecting the greater kinetic liability of Zn–N versus Zn–C bonds), with the resulting *cis*-DMP(H) then deprotonated in turn by a *tert*-butyl ligand, in a two-step mechanism (Scheme 2).

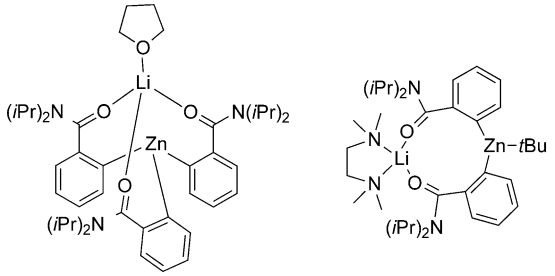
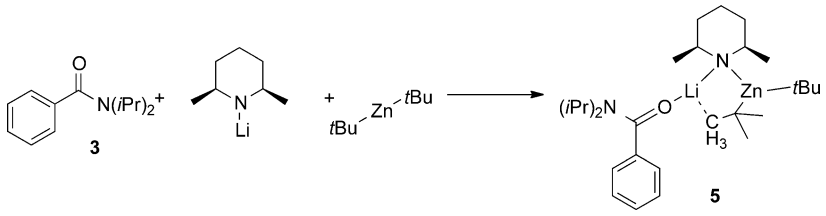


Figure 6. Known lithium zincates containing deprotonated *N,N*-diisopropylbenzamide components.[10a,39]

A search of the Cambridge Crystallographic Database (CCDB)[35] for structures containing *ortho*-deprotonated *N,N*-diisopropylbenzamide bound to any metal uncovered only eight hits. Of these, one is a monometallic *ortho*-lithiated dimer[36] and the remainder are heterobimetallic species. In each of these seven species, the aromatic ring is *ortho*-metallated (aluminated,[37] manganated[38] or zincated[10a,39]), whilst the carbonyl oxygen atom of the amide moiety datively coordinates to an alkali metal (lithium or sodium). There are only two lithium zincates containing deprotonated *N,N*-diisopropylbenzamide on the CCDB,[35] having the structures shown in Figure 6. The key difference between these and post-metallation zincate **4** is that they each contain multiple monodeprotonated benzamide units. Each of these was made from a TMP–zincate. Tripodal homoleptic lithium zincate [(THF)LiZn{2-[1-C(=O)N(*i*Pr)$_2$]C$_6$H$_4$}$_3$], in which zinc is surrounded by three *ortho*-deprotonated benzamide units, was obtained by reaction of [LiZn(TMP)Et$_2$] with *N,N*-diisopropylbenzamide in a 1:1 ratio in THF solution;[10a] whilst bis-arenide zincate [(TMEDA)Li{2-[1-C(=O)N(*i*Pr)$_2$]C$_6$H$_4$}$_2$Zn*t*Bu] arose from reaction of "LiZn(TMP)*t*Bu$_2$" with the benzamide in hexane solution containing TMEDA.[39]

$$2\ [(\text{TMEDA})\text{LiZn}(\textit{cis}\text{-DMP})t\text{Bu}_2]\ (\mathbf{2}) + \text{C(=O)N}(i\text{Pr})_2\text{C}_6\text{H}_5\ (\mathbf{3}) \longrightarrow [(\text{TMEDA})\text{Li}(\textit{cis}\text{-DMP})\{2\text{-}[1\text{-C(O)N}(i\text{Pr})_2]\text{C}_6\text{H}_4\}\text{Zn}(t\text{Bu})]\ (\mathbf{8}) \quad (2)$$

Further investigation of the reaction between **2** and the benzamide revealed a second isolable product in the aforementioned donor-acceptor complex **5** where the donor is the non-deprotonated benzamide substrate and the acceptor is the TMEDA-free variant of base **2**. Initially complex **5** was detected as the minor product along with major product **8** in a 1:1 base:benzamide mixture in hexane solution. Subsequently complex **5** was synthesised rationally in a good isolated yield of 81% by mixing together its three components



Scheme 3. Rational synthesis of pre-metallation complex **5** by a cocomplexation reaction.

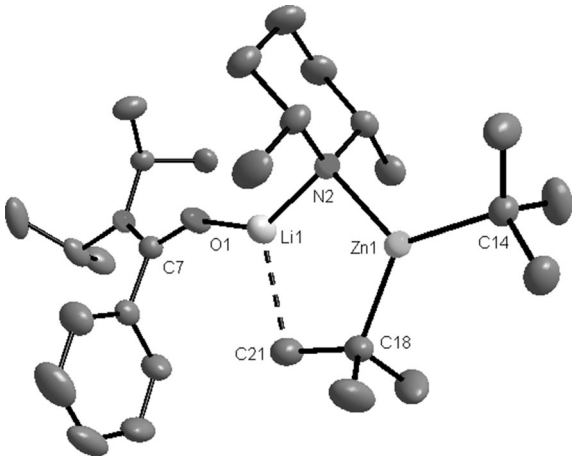


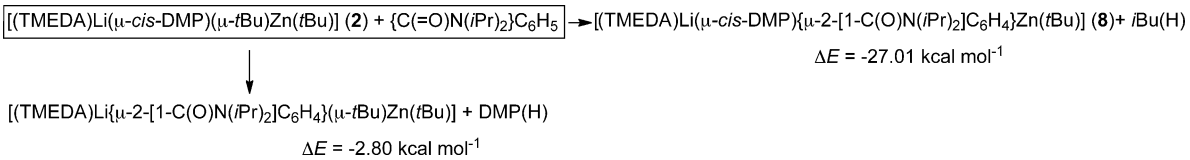
Figure 7. Molecular structure of [{(*i*Pr)$_2$NC(Ph)(=O)}LiZn(*cis*-DMP)*t*Bu$_2$] **5**. Hydrogen atoms are omitted for clarity. Ellipsoids are shown at the 50% probability level. The dashed line represents an agostic interaction between Li1 and C21. Selected bond lengths [Å] and bond angles [°] Li1–N2 1.933(4), N2–Zn1 2.062(2), Zn1–C18 2.049(2), C18–C21 1.525(3), C21···Li1 2.45(4), Li1–O1 1.814(3), O1–C7 1.247(2); O1-Li1-N2 136.5(2), Li1-N2-Zn1 97.7(1), N2-Zn1-C18 113.67(7), N2-Zn1-C14 118.53(7), C14-Zn1-C18 127.80(8).

N,N-diisopropylbenzamide, Li(*cis*-DMP), and di-*tert*-butylzinc in a co-complexation reaction (Scheme 3).

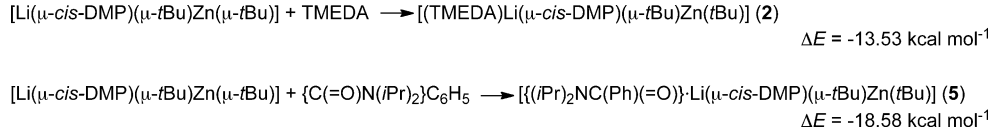
X-ray crystallographic studies established the molecular structure of **5** (Figure 7), its salient features being the carbonyl (C=O) dative bond to lithium and the retention of the benzamide *ortho*-hydrogen atoms. Moreover the business end of the base, the zincate anion [(*cis*-DMP)Zn(*t*Bu)$_2$]$^-$, remains intact. Direct comparison of the dimensions of **5** and **2** reveal the effect of substituting the neutral benzamide donor for TMEDA. Most significantly the Li-N(*cis*-DMP)-Zn bridge shortens (and presumably strengthens) [Li–N 1.933(4) Å; Zn–N 2.062(2) Å; Li···Zn 3.009(3) Å] as the monodentate O donor replaces the bidentate N donor [Li–N 2.027(3) Å; Zn–N 2.062(1) Å; Li···Zn 3.269(3) Å]. This contraction is in line with the change in coordination number (from 2 in **5** to 3 in **2** discounting the weak agostic contacts) at the lithium centre. The implication of this contraction is that the kinetic base component, the *cis*-DMP anion, is held more tightly in **5** than in **2**. Hence the formation of **5** in the 1:1 reaction mixture of the benzamide and base **2** could have two detrimental effects that could explain the poor/incomplete conversion to the electrophilic quench products (see Table 3): first, it reduces the amount of free benzamide in solution available to undergo deprotonation, and second, its deactivates the *cis*-DMP anion which is more tightly held within its framework than that in the TMEDA base complex **2**.

Reactivity studies subjecting **5** to different donor solvents found metallation of the benzamide occurred but never to completion. Adding one molar equivalent of TMEDA to a [D$_6$]benzene solution of **5** in an NMR tube produced some metallation as detected by the emergence of a doublet downfield (at $\delta = 8.03$ ppm) in the ^{1}H NMR spectrum. However, even after three days at room temperature metallation remained incomplete as the integration ratio of metallated:non-metallated benzamide was approximately 2.5:1.0. THF and PMDETA [*N,N,N′,N″,N″*-pentamethyldiethylenetriamine, (Me$_2$NCH$_2$CH$_2$)$_2$NMe] also promoted metallation of benzamide but again not to completion. It has been reported that addition of TMEDA to [{(*i*Pr)$_2$N(Ph)C=O}LiZn(TMP)*t*Bu$_2$], the TMP analogue of **5**,[40] promoted *ortho*-metallation though the reaction was not straightforward as the bis-benzamide zincate [(TMEDA)Li{2-[1-C(=O)N-(*i*Pr)$_2$]C$_6$H$_4$}$_2$Zn*t*Bu] was isolated from the reaction solution.[39] This behaviour could be regarded as evidence of the zincate starting material's dual basicity. In contrast no evidence of such dual basicity has been found in the reactions of **1** or **5**.

DFT calculations: To study the reaction of the *tert*-butyl version of the *cis*-DMP zincate base **2** with *N,N*-diisopropylbenzamide in more detail, DFT calculations were carried out using the Gaussian computational package G03[41] and the B3LYP[42] density functionals and the 6-311G(d, p)[43] basis set. After each geometry optimisation, frequency analysis was performed and the energy values quoted include the zero point energy contribution. In the modelled reaction (Scheme 4) overall loss of isobutane was found to be more thermodynamically favourable than loss of *cis*-DMP(H) by



Scheme 4. Energetics of modelled reaction pathways for the reaction of lithium zincate **1** with *N,N*-diisopropylbenzamide.



Scheme 5. Energetics of coordination of TMEDA or benzamide donor to a model of unsolvated **2**.

-24.21 kcal mol^{-1}. This is consistent with the experimental observations, as the metallated benzamide *cis*-DMP containing intermediate **4** was isolated from the reaction and crystallographically characterised.

It was also found that coordination of the neutral benzamide to the lithium site of an unsolvated model of **2** [Li(μ-*cis*-DMP)(μ-*t*Bu)Zn(*t*Bu)] was more energetically preferred to TMEDA coordination (Scheme 5) by a difference of -5.05 kcal mol^{-1}.

This observation points to the benzamide oxygen atom being favoured over TMEDA as a donor to lithium though the relatively small energy difference between the two Lewis acid–Lewis base complexes could make an equilibrium between the two species feasible. Again this agrees with the experimental findings as the benzamide donor complex **5** was formed in the reaction mixture of the base **2** and the benzamide along with the deprotonated benzamide complex **8**.

Conclusion

This study establishes that *cis*-DMP based lithium zincate reagents show promise as Brønsted bases for the selective deprotonation of substituted aromatic substrates. The new reagent synthesised in this work, [(TMEDA)LiZn(*cis*-DMP)Et$_2$], is particularly attractive as all its components are commercially available and it is easy to prepare simply by mixing them together (a cocomplexation reaction). Test reactions with *N*,*N*-diisopropylbenzamide show the diethylzincate base can outperform its di-*tert*-butyl congener and a related HMDS system, is competitive with a related diisopropylamide system, and is only marginally less efficient than a related TMP system. It is an open question whether the marginally greater yields of metallated/quenched products obtained in some cases via the TMP system over the *cis*-DMP system is worth the substantial extra expense of using TMP(H) versus *cis*-DMP(H). Small refinements to the composition and structure of multicomponent bases can have a profound effect on their reactivity so it may be feasible to design a *cis*-DMP based reagent that is equally efficient or indeed superior to TMP based reagents even though the bulkier TMP (in its naked anionic form) is intrinsically the superior base. Studies towards this challenging objective are ongoing.

Experimental Section

General methods: Reactions and manipulations were performed by using standard Schlenk techniques under argon gas. Products were isolated in an argon-filled glovebox. Hexane and THF were obtained from Aldrich and freshly distilled from sodium/benzophenone prior to use. *cis*-DMP(H) and TMP(H) were obtained from Aldrich and dried over 4 Å molecular sieves prior to use. TMEDA, DA(H) and HMDS(H) were obtained from Aldrich and were distilled from CaH_2 and stored over 4 Å molecular sieves. Other chemicals were obtained from Aldrich or Alfa Aesar and were used as supplied. *t*Bu$_2$Zn was prepared according to the literature method.[4a] The lithium zincate [(TMEDA)LiZn(*cis*-DMP)*t*Bu$_2$] (**2**) was prepared according to the literature method.[12] NMR spectra were recorded on a Bruker AV3 or AV400 MHz spectrometer. Correlations between protons and carbon atoms were obtained by using COSY and HSQC NMR spectroscopic methods.

Crystal structure determinations: Single-crystal data were recorded at 123(2) K on Oxford Diffraction Xcalibur and Gemini instruments. The structures were refined to convergence on F^2 and against all independent reflections by full-matrix least-squares using the SHELXL-97 program.[44] One of the ethyl groups of **1** was modelled as disordered over two sites, as was the DMP ligand in **8**. The geometries of the disordered groups were restrained to approximate typical values. Selected parameters are given in Table 7 and full details are given in the deposited cif files. CCDC-926494 (**1**), CCDC-926495 (**5**) and CCDC-926496 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of [(TMEDA)LiZn(*cis*-DMP)Et$_2$] (1): A solution of *n*BuLi (1.6 M in hexane, 1.25 mL, 2 mmol) and *cis*-DMP(H) (0.27 mL, 2 mmol) were added to dry hexane (5 mL). The resulting yellow solution was stir-

Table 7. Crystallographic data and refinement details for compounds **1**, **5**, **8**.

	1	**5**	**8**
empirical formula	$C_{17}H_{40}LiN_3Zn$	$C_{28}H_{51}LiN_2OZn$	$C_{30}H_{57}LiN_4OZn$
M_r [g mol^{-1}]	358.83	504.02	562.11
crystal system	monoclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/n$	$P2_1/n$
a [Å]	16.4746(12)	12.9964(3)	10.4518(2)
b [Å]	14.6396(7)	12.5693(3)	17.7709(4)
c [Å]	19.1568(14)	18.7851(4)	18.3392(4)
β [°]	114.419(9)	100.475(2)	103.575(2)
V [Å^{-3}]	4207.0(5)	3017.51(12)	3311.12(12)
Z	8	4	4
$2\theta_{max}$ [°]	54	146.04	146.82
λ [Å]	0.71073	1.5418	1.5418
measured reflections	15914	14872	13617
unique reflections	7740	5680	6477
R_{int}	0.0376	0.0205	0.0186
observed rflns [$I > 2\sigma(I)$]	5185	4912	5533
μ [mm^{-1}]	1.168	1.259	1.211
no. of parameters	421	310	367
R [on F, obs rflns only]	0.0507	0.0334	0.0579
wR [on F^2, all data]	0.1313	0.1013	0.1621
GoF	1.021	1.117	1.043
largest diff. peak/hole [e Å^{-3}]	1.373/−0.582	0.541/−0.243	0.890/−0.416

red for 15 min. Then a solution of Et_2Zn (1 M in hexane, 2 mL, 2 mmol) was added by using a syringe, followed by TMEDA (0.30 mL, 2 mmol). The yellow solution was stirred for 30 min and then placed in a freezer (−28 °C) overnight. This gave a crop of pale yellow crystals (0.44 g, 61 % yield); ^{1}H NMR (400.03 MHz, C_6D_6, 300 K): $\delta = 3.12$ (m, 2H, α-C*H* *cis*-DMP), 1.92 (t, $^3J(H,H) = 7.8$ Hz, 7H; including 6H; $ZnCH_2CH_3$ and 1H; γ-CH_2 *cis*-DMP), 1.76 (br s, 12H; CH_3 TMEDA), 1.73 (m, partially overlapped, 1H; γ-CH_2 *cis*-DMP), 1.67 (m, partially overlapped, 2H; β-CH_2 *cis*-DMP), 1.63 (br s, 4H; CH_2 TMEDA), 1.08 (d, $^3J(H,H) = 6.5$ Hz, 6H; CH_3 *cis*-DMP), 0.64 (m, 2H; β-CH_2 *cis*-DMP), 0.39 ppm (q, $^3J(H,H) = 7.8$ Hz, 4H; $ZnCH_2CH_3$); ^{13}C{^{1}H} NMR (100.60 MHz, C_6D_6 300 K): $\delta =$ 58.3 (C_α *cis*-DMP), 57.0 (*C*H$_2$ TMEDA), 46.2 (*C*H$_3$ TMEDA), 38.2 (C_β *cis*-DMP), 27.4 (C_γ *cis*-DMP), 25.3 (*C*H$_3$ *cis*-DMP), 14.5 ($ZnCH_2CH_3$), 2.6 ppm ($ZnCH_2$); ^{7}Li NMR (155.50 MHz, C_6D_6, 300 K): $\delta = 0.84$ ppm (minor shoulder). Further details of the NMR spectroscopic studies of **1** (DOSY NMR data and [D$_8$]THF data) are available in the Supporting Information. Due to the acute air sensitivity of this compound, satisfactory C,H,N analyses could not be obtained despite several attempts.

General Procedure A for in situ formation of 1 in hexane solution: For each 1 mmol of **1** prepared, to dry hexane (2.5 mL) was added a solution of *n*BuLi (1.6 M in hexane, 0.625 mL, 1 mmol) followed by *cis*-DMP(H) (0.14 mL, 1 mmol) and the resulting pale yellow solution stirred for 15 min. Then a solution of Et_2Zn (1 M in hexane, 1 mL, 1 mmol) was added by using a syringe, followed by TMEDA (0.15 mL, 1 mmol). The resulting pale yellow solution was stirred for 15 min before addition of *N,N*-diisopropylbenzamide. A similar procedure was followed for the preparation of each 1 mmol of base mixtures in the study of the effect of variation of amides but in place of *cis*-DMP(H) was added TMP(H) (0.17 mL, 1 mmol) or DA(H) (0.14 mL, 1 mmol) or HMDS(H) (0.21 mL, 1 mmol).

General Procedure B for in situ formation of 1 in THF solution: For each 1 mmol of **1** prepared, *cis*-DMP(H) (0.14 mL, 1 mmol) was added to a solution of *n*BuLi (1.6 M in hexane, 0.625 mL, 1 mmol). The resulting pale yellow mixture was stirred for 15 min then dry THF (2.5 mL) was added, followed by a solution of Et_2Zn (1 M, 1.0 mL, 1 mmol). TMEDA (0.15 mL, 1 mmol) was then added and the resulting pale yellow solution was stirred for 15 min before the addition of *N,N*-diisopropylbenzamide.

General Procedure C for metallation–iodination of *N,N*-diisopropylbenzamide: *N,N*-Diisopropylbenzamide (0.205 g, 1 mmol) was added to **1** [1.2 (or 2) mmol] formed in hexane or THF according to General Procedure A or B. After stirring for 3 h or 22 h at ambient temperature, the reaction was quenched by addition of iodine [1 M solution in THF, 4.8 (or 8) mL, 4.8 (or 8) mmol] and stirred for at least 4 h. Then saturated aqueous NH_4Cl solution (10 mL) was added, followed by saturated aqueous sodium thiosulfate solution until bleaching occurred (ca. 10 mL). The mixture was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The yield of 2-iodo-*N,N*-diisopropylbenzamide (**4**) was determined by addition of hexamethylbenzene (0.0162 g, 0.1 mmol) as an internal standard to the crude product mixture. The crude product and internal standard were dissolved in $CDCl_3$ to give a homogeneous solution, an aliquot of which was further diluted with $CDCl_3$ and analysed by ^{1}H NMR spectroscopy. The solution yields of components in the mixture were determined by integration of signals corresponding to the iodinated products relative to the singlet for hexamethylbenzene (integrated to 1.8H) in the spectrum obtained.

Synthesis of 2-iodo-*N,N*-diisopropylbenzamide (4): General Procedure A was followed to form 2 mmol of the base **1** in situ in hexane solution. *N,N*-Diisopropylbenzamide (0.205 g, 1 mmol) was added to the base solution by using a solid addition tube, upon which the reaction mixture became bright yellow. An oil was formed in the reaction mixture, which dissolved into solution over approximately 15 min. After stirring for 22 h, the mixture was quenched at 0 °C by addition of iodine (1 M in THF, 8 mL, 8 mmol). The mixture was allowed to warm to room temperature and stirred overnight. After work up according to General Procedure C the crude material was dissolved in a minimum volume of dichloromethane, loaded onto a manually packed alumina column and purified by alumina column chromatography (0–20 % ethyl acetate in hexane). The relevant fractions were combined and the solvents were removed under reduced pressure to afford a white solid (0.290 g, 88 % yield). ^{1}H NMR (400.13 MHz, 300 K, $CDCl_3$): $\delta = 7.81$ (dd, $^3J(H,H) = 7.9$ Hz, $^4J(H,H) =$ 0.9 Hz, 1H; Ar-H) 7.35 (td, $^3J(H,H) = 7.5$ Hz, $^4J(H,H) = 1.0$ Hz,1H; Ar-H), 7.14 (dd, $^3J(H,H) = 7.6$ Hz, $^4J(H,H) = 1.6$ Hz, 1H; Ar-H), 7.03 (td, ^3J-(H,H) = 7.8 Hz, $^4J(H,H) = 1.6$ Hz, 1H; Ar-H), 3.58 (septet, $^3J(H,H) =$ 6.7 Hz, 1H; C*H* *i*Pr), 3.52 (septet, $^3J(H,H) = 6.8$ Hz, 1H; C*H* *i*Pr), 1.60 (d, $^3J(H,H) = 6.8$ Hz, 3H; CH_3 *i*Pr), 1.56 (d, $^3J(H,H) = 6.8$ Hz, 3H; CH_3 *i*Pr), 1.27 (d, $^3J(H,H) = 6.7$ Hz, 3H; CH_3 *i*Pr), 1.07 ppm (d, $^3J(H,H) =$ 6.7 Hz, 3H; CH_3 *i*Pr); ^{13}C{^{1}H} NMR (100.62 MHz, 300 K, $CDCl_3$): $\delta =$ 169.7 (*C*=O), 144.2 (C_{Ar}-C(O)), 139.3 (C_{Ar}-H), 129.4 (C_{Ar}-H), 128.1 (C_{Ar}-H), 125.8 (C_{Ar}-H), 92.2 (C_{Ar}-I), 51.15 (-*C*HMe$_2$ *i*Pr), 45.93 (-*C*HMe$_2$ *i*Pr), 20.7 (*C*H$_3$ *i*Pr), 20.0 ppm (*C*H$_3$ *i*Pr). NMR data is consistent with the literature values.[31]

Synthesis of [{(*i*Pr)$_2$NC(Ph)(=O)}LiZn(*cis*-DMP)*t*Bu$_2$] (5): A solution of *n*BuLi (1.6 M in hexane, 1.25 mL, 2 mmol) and *cis*-DMP(H) (0.27 mL, 2 mmol) were added to dry hexane (5 mL) in a Schlenk flask under argon and the resulting yellow solution was stirred for 15 min. Then freshly prepared *t*Bu$_2$Zn (0.36 g, 2 mmol) as a solution in dry hexane (5 mL) was added by using a syringe. To this solution was added *N,N*-diisopropylbenzamide (0.205 g, 1 mmol) by using a solid addition tube and the mixture was stirred for 30 min. Cooling to −28 °C overnight led to formation of a crop of colourless crystals (0.41 g, 81 % yield). Recrystallisation from dry hexane at room temperature gave crystals suitable for X-ray crystallographic analysis. ^{1}H NMR (400.03 MHz, C_6D_6, 300 K): $\delta =$ 7.02–6.97 (m, 3H; H_{meta} and H_{para} Ph), 6.89–6.82 (m, 2H; H_{ortho} Ph), 3.37 (s(br), 1H; C*H*, *i*Pr), 3.26 (m, 2H; α-C*H* *cis*-DMP), 2.88 (br s, 1H; C*H*, *i*Pr), 1.82–1.55 (m, 13H; 2H of γ-CH_2 *cis*-DMP, 2H of β-CH_2 *cis*-DMP, 9H of CH_3, *t*Bu), 1.44–1.21 (2 br s [partially overlapped] 15H; 9H CH_3, *t*Bu and 6H CH_3, *i*Pr), 1.10 (d, $^3J(H,H) = 6.4$ Hz, 6H; CH_3, *cis*-DMP), 0.54–0.41 ppm (m, 8H; 6H CH_3, *i*Pr and 2H β-CH_2 *cis*-DMP); ^{13}C{^{1}H} NMR (100.60 MHz, C_6D_6, 300 K): $\delta = 172.8$ (*C*=O), 137.3 (C_{ipso} Ph), 129.9 (C_{para} Ph), 129.2 (C_{meta} Ph), 124.9 (C_{ortho} Ph), 56.3 (C_α *cis*-DMP), 52.0 (*C*H(CH$_3$)$_2$ *i*Pr) 46.6 (*C*H(CH$_3$)$_2$ *i*Pr), 37.6 (C_β *cis*-DMP), 35.8 (*C*H$_3$ *t*Bu), 34.8 (*C*H$_3$ *t*Bu), 26.8 (C_γ *cis*-DMP), 26.2 (*C*H$_3$ *cis*-DMP), 20.2 (*C*H$_3$ *i*Pr), 19.7 ppm (*C*H$_3$ *i*Pr) (quaternary *t*Bu signals not observed); ^{7}Li NMR (155.50 MHz, C_6D_6, 300 K): $\delta = 1.74$ ppm. Due to the acute air sensitivity of this compound, satisfactory C,H,N analyses could not be obtained despite several attempts.

Synthesis of 2-(diisopropylcarbamoyl)benzoic acid (6): To a Schlenk flask containing [(TMEDA)LiZn(*cis*-DMP)Et$_2$] (0.86 g, 2 mmol) in anhydrous hexane (5 mL), was added, by using a solid addition tube, *N,N*-diisopropylbenzamide (0.205 g, 1 mmol) upon which a yellow oil was formed in the mixture. Over approximately 15 min this dissolved to give a yellow solution. The mixture was stirred for 22 h. The solvents were removed under reduced pressure and the oily residue was dissolved in anhydrous THF (5 mL). To a second Schlenk flask under argon was added CO_2(s). This flask was fitted with a cannula and CO_2 gas was bubbled through the reaction mixture for 30 min, during which the mixture became cloudy. The solvents were removed under reduced pressure and a 10 % aqueous NaOH solution (20 mL) was added. The mixture was washed with diethyl ether (3 × 15 mL) and the organic phase discarded. The aqueous phase was then acidified by slow addition of 2 M aqueous HCl solution to approximately pH 2 (determined by pH paper). The resulting solution was extracted with diethyl ether (3 × 15 mL) and the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white crystalline solid (0.192 g, 77 % yield). ^{1}H NMR (400.13 MHz, [D$_6$]DMSO, 300 K): $\delta = 13.10$ (br s, 1H; C(O)O*H*), 7.89 (dd, $^3J(H,H) = 7.8$ Hz, $^4J(H,H) = 1.0$ Hz, 1H; Ar-*H*), 7.59 (td, $^3J(H,H) =$ 7.5 Hz, $^4J(H,H) = 1.2$ Hz, 1H; Ar-*H*), 7.45 (td, $^3J(H,H) = 7.6$ Hz, ^4J-(H,H) = 1.2 Hz, 1H; Ar-*H*), 7.21 (dd, $^3J(H,H) = 7.5$ Hz, $^4J(H,H) = 0.7$ Hz, 1H; Ar-*H*), 3.55 (septet, $^3J(H,H) = 6.8$ Hz, 1H; C*H* *i*Pr), 3.46 (septet, ^3J-(H,H) = 6.8 Hz, 1H; C*H* *i*Pr), 1.43 (d, $^3J(H,H) = 6.8$ Hz, 6H; CH_3 *i*Pr), 1.04 ppm (m, 6H; CH_3 *i*Pr); ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO, 300 K): $\delta = 168.8$ (*C*=O amido), 167.0 (*C*=O acid), 140.4 (C_{Ar}), 132.4 (C_{Ar}), 130.0 (C_{Ar}), 128.0 (C_{Ar}), 127.6 (C_{Ar}), 125.8 (C_{Ar}), 50.5 (*i*Pr *C*H), 44.4 (*i*Pr *C*H), 20.6 (*i*Pr *C*H$_3$), 20.0 (*i*Pr *C*H$_3$), 19.6 (*i*Pr *C*H$_3$), 19.3 ppm (*i*Pr *C*H$_3$). This data is consistent with the literature values.[45]

Synthesis of 2-allyl-*N,N*-diisopropylbenzamide (7): General Procedure B was followed to form 2 mmol of **1** (in this case, TMEDA was omitted) in THF solution. To the base solution, *N,N*-diisopropylbenzamide (0.205 g, 1 mmol) was added via solid addition tube, upon which the reaction mixture became bright yellow. An oil was formed in the reaction mixture, which dissolved into solution over ~15 min. After stirring for 22 h, the mixture was cooled to 0 °C. Copper(I) chloride (1 mmol, 0.16 g) was added by using a solid addition tube and the mixture stirred for 5 min before the slow addition of allyl bromide by using a syringe (0.69 mL, 8 mmol). The mixture was allowed to warm to room temperature and stirred for 22 h. Saturated aqueous NH_4Cl solution (10 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (3×15 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Analysis by ^{1}H NMR spectroscopy using hexamethylbenzene as an internal standard showed **7** was present in 83% yield. The crude material was dissolved in a minimum volume (ca. 1 mL) of dichloromethane and loaded onto a manually packed alumina column. Purification by alumina column chromatography (eluent 0–25% ethyl acetate in hexane) afforded a colourless oil which solidified to an off-white solid (0.199 g, 81% yield). ^{1}H NMR (400.13 MHz, $CDCl_3$, 300 K): δ = 7.30–7.22 (m, 2H; 2 × Ar-*H*), 7.20 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.0 Hz, 1H, Ar-*H*), 7.10 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.0 Hz, 1H; Ar-*H*), 5.95 (ddt, ^3J(H,H) = 17.0 (d, *trans*), 10 (d, *cis*), 6.8 (t) Hz, 1H; CH_2CH=CH_2), 5.13–5.04 (m, 2H; CH_2CH=CH_2), 3.68 (septet, ^3J(H,H) = 6.8 Hz, 1H; C*H* *i*Pr), 3.49 (septet, ^3J(H,H) = 6.8 Hz, 1H; C*H* *i*Pr), 3.41 (d, ^3J(H,H) = 6.5 Hz, 2H; PhCH_2), 1.56 (d, ^3J(H,H) = 6.8 Hz; 6H, CH_3 *i*Pr), 1.11 ppm (2 d, overlapped, ^3J(H,H) = 6.8 Hz, 6H; CH_3 *i*Pr). ^{1}H NMR data is consistent with the literature values;[5a] ^{13}C{^{1}H} NMR (100.62 MHz, $CDCl_3$, 300 K): δ = 170.5 (*C*=O), 138.3 (C_{Ar} quaternary), 136.9 (CH_2CH=CH_2), 136.2 (C_{Ar} quaternary), 129.8 (C_{Ar}-H), 128.3 (C_{Ar}-H), 126.2 (C_{Ar}-H), 125.1 (C_{Ar}-H), 116.4 (CH_2CH=CH_2), 50.8 (*C*H *i*Pr), 45.9 (*C*H *i*Pr), 37.0 (CH_2CH=CH_2), 20.9 (CH_3 *i*Pr), 20.8 (CH_3 *i*Pr), 20.7 ppm (2 × CH_3 *i*Pr).

Synthesis of [(TMEDA)LiZn(*cis*-DMP){2-[1-C(O)N(*i*Pr)$_2$]C$_6$H$_4$}*t*Bu] (8): [(TMEDA)LiZn(*cis*-DMP)*t*Bu$_2$] (0.410 g, 1 mmol) was suspended in dry hexane (5 mL) in a Schlenk flask under argon. *N,N-D*iisopropylbenzamide (0.103 g, 0.5 mmol) was added by using a solid addition tube. A yellow oil was formed in the reaction mixture. The mixture was stirred at room temperature for four days. After this time the mixture contained a fine grey solid. After filtration, the filtrate was placed in a freezer (−28 °C) overnight, affording a crop of small pale yellow block crystals (0.07 g, 25% yield with respect to *N,N*-diisopropylbenzamide); ^{1}H NMR (400.03 MHz, [D$_8$]THF, 300 K): δ = 7.63 (d, ^3J(H,H) = 6.9 Hz, 1H; H_{meta} Ar′), 7.14–7.01(m, 2H; H_{ortho*} and H_{para} Ar′), 6.96 (t, ^3J(H,H) = 7.6 Hz, 1H; H_{meta*} Ar′), 4.21 (septet, ^3J(H,H) = 6.7 Hz, 1H; C*H* *i*Pr), 3.60 (septet, overlaps with solvent signal, ^3J(H,H) = 6.7 Hz, 1H; C*H* *i*Pr), 3.05–2.79 (m, 2H; α-C*H* *cis*-DMP), 2.31 (s, 4H; CH_2 TMEDA), 2.15 (s, 12H; CH_3 TMEDA), 1.73 (m, overlap with solvent signal, 1H, γ-CH_2 *cis*-DMP), 1.60–1.37 (m, 9H including 2H; β-CH_2 *cis*-DMP and 1H; γ-CH_2 *cis*-DMP and 6H; CH_3 *i*Pr, Ar′), 1.26 (d, ^3J(H,H) = 6.6 Hz, 3H; CH_3 *i*Pr, Ar′), 1.22–1.04 (m, 9H including 3H; CH_3 *i*Pr, Ar′ and 6H; CH_3 *cis*-DMP), 1.00 (br s, 9H; CH_3 *t*Bu), 0.82–0.68 ppm (m, 2H; β-CH_2 *cis*-DMP); ^{13}C{^{1}H} NMR (100.60 MHz, [D$_8$]THF, 300 K): δ = 179.7 (*C*=O), 167.7 (weak, C_{ortho} Ar′), 145.9 (weak, C_{ipso} Ar′), 141.2 (C_{meta} Ar′), 127.7 (C_{para} Ar′), 123.9 (C_{ortho*} Ar′), 123.3 (C_{meta*}H Ar′), 59.7, 59.3 (C_α *cis*-DMP), 58.8 (CH_2 TMEDA), 52.4 (*C*H *i*Pr, Ar′), 46.4 (*C*H *i*Pr, Ar′), 46.0 (CH_3 TMEDA), 38.0 (C_β *cis*-DMP), 34.7 (CH_3 *t*Bu), 27.5 (C_γ *cis*-DMP), 27.7, 26.5 (CH_3 *cis*-DMP), 23 3 (C(CH$_3$)$_3$ *t*Bu), 22.7 (CH_3 *i*Pr, Ar′), 21.2 (CH_3 *i*Pr, Ar′), 20.3 ppm (CH_3 *i*Pr); ^{7}Li NMR (155.50 MHz, [D$_8$]THF, 300 K): δ = 0.94 ppm. The labelling used in the assignment of signals for Ar' is shown in Figure 8.

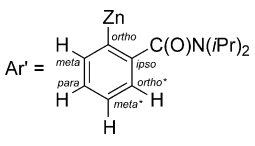


Figure 8. Labelling used in NMR data for Ar' in compound **8**.

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