Metalation

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Alkali-Metal-Mediated Zincation of Polycyclic Aromatic Hydrocarbons: Synthesis and Structures of Mono- and Dizincated Naphthalenes**

William Clegg, Sophie H. Dale, Eva Hevia,
Lorna M. Hogg, Gordon W. Honeyman,
Robert E. Mulvey, and Charles T. O'Hara*

Since the pioneering work of Schlenk nearly a century ago, alkali-metal–organic compounds (organolithium reagents, in particular) have served as frontline reagents in the battle to advance chemical synthesis. Metal–hydrogen exchange (metalation) in which a relatively inert carbon–hydrogen bond is transformed into a more labile carbon–alkali-metal bond, thus opening up a myriad of bond-forming possibilities at the carbon center, represents one of the oldest and still most important general uses of these centurial reagents.[1,2] Recently, however, new variations of these fundamental synthetic strategies have started to emerge in which the alkali metal, though still actively involved in the exchange reaction, takes on more of a secondary, supporting role, as the vanguard metals attacking the carbon centers are now either magnesium, zinc, or aluminum. On their own, these less electropositive metals generally form slow-reacting, ineffectual metalating agents, but combining them with an alkali-metal component appears to activate a special synergy that greatly enhances the power of the magnesiation, zincation, or alumination. Kondo et al. emphasized the importance of the "precomplexation of lithium TMP and $t\mathrm{Bu}_2\mathrm{Zn}$" (TMP = 2,2,6,6-tetramethylpiperidine) in the zincate reagent "$[\mathrm{Li}^+\{t\mathrm{Bu}_2\mathrm{Zn(tmp)}\}]^-$", which acts as a highly chemoselective base towards a series of functionalized aromatic and heteroaromatic compounds.[3] We recently extended this idea of alkali-metal-mediated zincation (AMMZ) to sodium through the *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediamine (TMEDA)-chelated zincate $[(\mathrm{tmeda})\mathrm{Na}(\mu\text{-tmp})(\mu\text{-}t\mathrm{Bu})\mathrm{Zn}(t\mathrm{Bu})]$ (**1**),[4] which can effect the directed *ortho*-zincation of *N*,*N*-diisopropylbenzamide,[5] directed *meta*-zincation of *N*,*N*-dimethylanilines,[6] and the selective delivery of a $t\mathrm{Bu}^-$ nucleophile to the 6-position of benzophenone.[7] Herein, we report the first study in which AMMZ with **1** has been applied to a fused-ring aromatic hydrocarbon, using the simplest and most important compound of this type, naphthalene, as a case study. This investigation breaks new ground in establishing that AMMZ can provide 1) access to new zincated naphthalene molecules not directly accessible by mainstream organozinc reagents; 2) an improved method for metalation of naphthalene; 3) a degree of stoichiometric control, which enables di- and monometalation applications; and 4) an unprecedented set of crystalline 2-monometalated and 2,6-dimetalated naphthalene products from which the first crystal structures of zincated (or any metalated in the 2,6-case) naphthalene compounds have been obtained.

Scheme 1 summarizes the reactions between **1** and naphthalene that yielded crystalline products. Carried out under mild conditions (room temperature, stirring for 2 h), the equimolar experiment (pathway a) produced yellow $[(\mathrm{tmeda})\mathrm{Na}(\mu\text{-tmp})(\mu\text{-}2\text{-}\mathrm{C}_{10}\mathrm{H}_7)\mathrm{Zn}(t\mathrm{Bu})]$ (**2**) in yields of typically 50% of the isolated product. ^{1}H and ^{13}C NMR spectra of a solution of an isolated sample **2** in $\mathrm{C}_6\mathrm{D}_6$ reveal a pattern of seven and ten distinct resonances, respectively, in the aromatic region consistent with monometalation/monodeprotonation of naphthalene at the 2-position (NMR spectra of the remaining filtrates showed only the starting material naphthalene and no other metalated isomers). This regioselectivity was confirmed by X-ray crystallography (see below). The reasonable yield of this pure 2-naphthalenide compares favorably with previous metalation studies that used, for example, BuLi[8] or superbasic LICKOR,[9] both of which are nonselective in affording mixtures of the isomers 1- and 2-naphthalene after quenching protocols (yields of the combined products, 20 and 28%, respectively). In contrast, when a solution of an isolated sample of **2** in THF was quenched with I_2, the yield of 2-iodonaphthalene was found to be (83 ± 5)% from quantitative NMR spectroscopic studies with ferrocene as the internal standard.

The molecular structure of **2** (Figure 1)[10] reveals that the zinc center is located at the deprotonated 2-position (Zn–C(1): 2.076(4) Å) and lies in the naphthyl-ring plane (deviation from mean plane: 0.007 Å); whereas, the sodium center engages in a long η^2-interaction at the 1- and 2-positions (Na–C(2): 2.857(4) Å; Na–C(1): 2.828(4) Å) and lies 2.490 Å from this plane. These distinctions confirm that the metalation process that leads to **2** was AMMZ as opposed to sodiation. A comparison of the structure of **2** with that of its precursor **1**[4] reveals that, aside from substitution of a $t\mathrm{Bu}^-$ by a $\mathrm{C}_{10}\mathrm{H}_7^-$ ion, there is retention of connectivity within the remainder of the molecule. Thus, linked by a TMP N bridge (Zn–N(1): 2.020(3) Å; Na–N(1): 2.427(3) Å), the Zn and Na atoms also carry terminal *t*Bu (C-attached) and TMEDA (*N*,*N*′-attached) ligands, respectively. As **2** represents the first authenticated zinc–naphthalenide structure, there is no precedent available for comparison. Moreover, there is only one previous structure containing both a Na center and naphthalene ligands, although only remotely related to **2**: In the lutetium complex $[\{[(\mathrm{C}_5\mathrm{Me}_5\mathrm{Lu})_3(\mathrm{C}_{10}\mathrm{H}_8)(\mathrm{C}_{10}\mathrm{H}_7)(\mathrm{H})][\mathrm{Na}(\mathrm{thf})_3]\}_2\mathrm{C}_{10}\mathrm{H}_8]$,[11] Na interacts in a η^3-mode (Na–C: 2.686,

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[*] Dr. E. Hevia, L. M. Hogg, Dr. G. W. Honeyman, Prof. R. E. Mulvey, Dr. C. T. O'Hara
WestCHEM
Department of Pure and Applied Chemistry
University of Strathclyde, Glasgow, G1 1XL (UK)
Fax: (+44) 141-552-0876
E-mail: r.e.mulvey@strath.ac.uk
Prof. W. Clegg, Dr. S. H. Dale
School of Natural Sciences (Chemistry)
University of Newcastle
Newcastle upon Tyne, NE1 7RU (UK)

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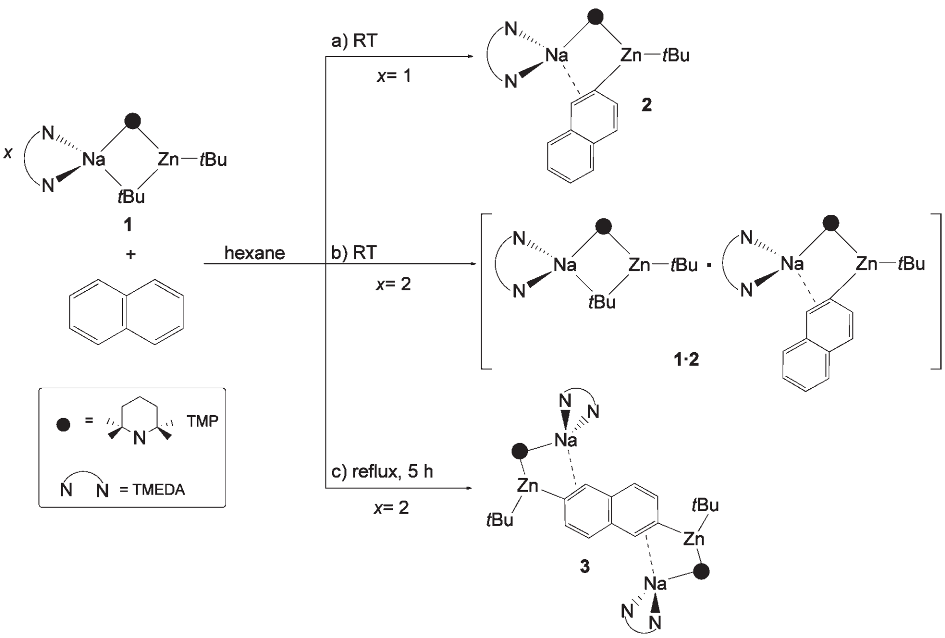

Scheme 1. Stoichiometry- and temperature-dependent reactions of naphthalene with the synergic zincate base **1**.

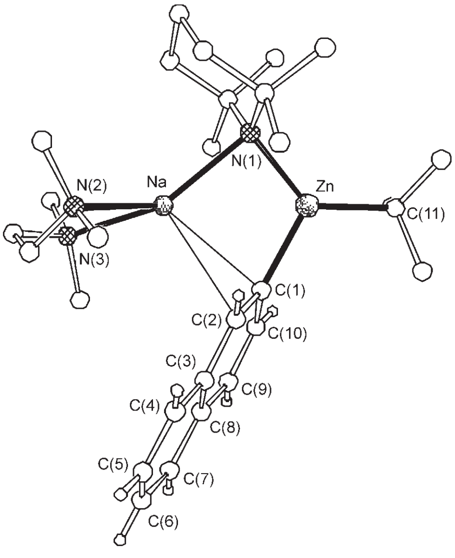

Figure 1. Molecular structure of **2** with selective atom labels indicated and Na–π(arene) interactions shown as thin lines. Hydrogen atoms, except for those of the naphthalenide ring and minor disorder components, are omitted for clarity.

2.852, and 2.912 Å), with a nonplanar (but planar in **2**) $C_{10}H_7$ ligand.

Hitherto, applications of **1** have been confined to monozincation reactions. It was therefore of interest to investigate the effect of subjecting naphthalene to an excess of **1**. Polymetalation of naphthalene by superbasic LICKOR is an unsatisfactory, messy operation: with a threefold excess of the base in hexane, a mixture of mono- and disubstituted naphthalenes is obtained in yields of 28 and 25%, respectively, with the latter containing all 10 disubstituted isomers, although some only at trace level.[9] Intriguingly, the first attempt to use **1**, carried out at room temperature with two equivalents of base (pathway b), produced crystals of [{(tmeda)Na(μ-tmp)(μ-*t*Bu)Zn(*t*Bu)}·{(tmeda)Na(μ-tmp)(μ-2-$C_{10}H_7$)Zn(*t*Bu)}] (**1·2**), in which molecules of "unreacted" base **1** and monozincated naphthalene **2** sit side by side in 1:1 ratio in the crystal structure.[12] This stand-off can be largely overcome by applying more forceful reaction conditions. Following a reflux for 5 h, the same reaction solution yielded a mixture of the dizincated 2,6-naphthalenediide [$(tmeda)_2Na_2(\mu\text{-tmp})_2(\mu\text{-}2,6\text{-}C_{10}H_6)Zn_2(t\text{Bu})_2$] (**3**; pathway c), the monozincated product **1** and starting material naphthalene in 7:1:1 ratio, as confirmed by NMR spectroscopic analysis of the isolated solid (NMR spectra of the remaining filtrate revealed only the starting material naphthalene). Longer reflux times did not appear to improve this ratio further. Complex **3** was characterized by ^1H and ^{13}C NMR spectroscopic analysis; the aromatic region of the former was especially diagnostic and showed the expected singlet and two distinct doublets of a symmetrical 2,6-dideprotonated naphthalene.

The centrosymmetric molecular structure of **3** (Figure 2)[10] closely resembles that of **2** but with an additional {(tmeda)Na(μ-tmp)Zn(*t*Bu)} cationic unit grafted onto the 6-position, thus replacing the second cleaved proton. As a

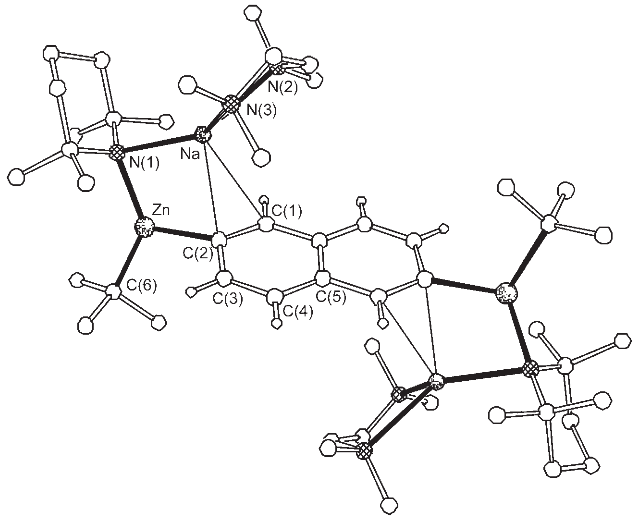

Figure 2. Molecular structure of **3** with selective atom labels indicated and Na–π(arene) interactions shown as thin lines. Hydrogen atoms, except for those of the naphthalenide ring, are omitted for clarity.

consequence of the centrosymmetry, the cationic-base residues occupy sterically minimizing transoid positions either side of the naphthalene-ring plane. The zinc center is located at the deprotonated 2- and 6-positions (Zn–C(2): 2.062(6) Å), only slightly out of the naphthyl-ring plane (deviation: 0.299 Å), whereas the sodium center engages in a long η^2-interaction at the 1- and 2-positions more asymmetrically than that in **2** (that is, Na–C(1): 2.957(6) Å; Na–C(2): 2.706(6) Å) and lies 2.443 Å out of this plane.

In summary, this case study of naphthalene establishes that AMMZ can effect dimetalation as well as monometalation of polycyclic aromatic hydrocarbons, thus resulting in access to new zincated naphthalenes inaccessible directly through mainstream organozinc reagents.

Experimental Section

Synthesis of **2**: A solution of $t\mathrm{Bu_2Zn}$ (0.358 g, 2 mmol) in hexane (10 mL) was transferred through a cannula to a suspension of NaTMP in hexane (prepared in situ by reaction of BuNa[13] (0.16 g, 2 mmol) with TMP(H) (0.34 mL, 2 mmol)), followed by the addition of a molar equivalent of TMEDA (0.30 mL, 2 mmol). The resultant suspension was heated gently to form a yellow solution. At this stage, one molar equivalent of naphthalene (0.26 g, 2 mmol) was added through a solids addition tube, and the reaction mixture was allowed to stir at room temperature for 2 h. The resulting yellow solution was transferred to the freezer to aid crystallization. A crop of transparent yellow crystals (0.52 g, 50 %) formed in solution which were suitable for X-ray crystallographic analysis.

Synthesis of **3**: Following a similar procedure as described above, [(tmeda)Na(μ-tmp)(μ-*t*Bu)Zn(*t*Bu)] was prepared in situ by reaction of $t\mathrm{Bu_2Zn}$ (0.358 g, 2 mmol), NaTMP (2 mmol), and TMEDA (0.30 mL, 2 mmol). Naphthalene (0.13 g, 1 mmol) was then introduced to the reaction mixture, which was heated to reflux for 5 h before being cooled to ambient temperature and moved to the freezer to aid crystallization. A crop of pale-yellow crystals (0.60 g) was formed in solution. Though this sample was contaminated with small amounts of **2** and free naphthalene, on the basis of NMR integrals the product equates to an absolute yield of **3** of (50 ± 5) %.

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[1] M. Schlosser, *Organometallics in Synthesis*, Wiley, Chichester, 2nd ed., **2002**, chap. 1.

[2] The classical "LICKOR" (Li–C + KOR) superbases are heterobimetallic examples, see: a) M. Schlosser, *Mod. Synth. Methods* **1992**, *6*, 227; b) L. Lochmann, *Eur. J. Inorg. Chem.* **2000**, 115.

[3] a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) T. Imahori, M. Uchiyama, T. Sakamoto, Y. Kondo, *Chem. Commun.* **2001**, 2450; c) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y, Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514.

[4] P. C. Andrikopoulos, D. R. Armstrong, H. R. L. Barley, W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, A. R. Kennedy, R. E. Mulvey, *J. Am. Chem. Soc.* **2005**, *127*, 6184.

[5] a) W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 2430; *Angew. Chem. Int. Ed.* **2006**, *45*, 2370; b) W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 2434; *Angew. Chem. Int. Ed.* **2006**, *45*, 2374.

[6] D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 3859; *Angew. Chem. Int. Ed.* **2006**, *45*, 3775.

[7] E. Hevia, G. W. Honeyman, A. R. Kennedy, R. E. Mulvey, *J. Am. Chem. Soc.* **2005**, *127*, 13106.

[8] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109.

[9] M. Schlosser, J. H. Choi, S. Takagishi, *Tetrahedron* **1990**, *46*, 5633.

[10] Crystal data for **2**: $\mathrm{C_{29}H_{50}N_3NaZn}$, $M_r = 529.1$, orthorhombic, space group $Pca2_1$, $a = 18.169(4)$, $b = 10.9855(19)$, $c = 15.500(3)$ Å, $V = 3093.7(10)$ Å^3, $Z = 4$, $\rho_{\mathrm{calcd}} = 1.136\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{Mo_{K\alpha}}) = 0.83\ \mathrm{mm^{-1}}$, $T = 150$ K, $R = 0.058$ ($F^2 > 2\sigma$), $R_w = 0.100$ (for all F^2 values) for 7046 data and 344 refined parameters; final difference synthesis within $\pm 0.41\ \mathrm{e\,Å^{-3}}$. The *t*Bu group is disordered over two orientations with a common central C atom. All H atoms were constrained with a riding model. Crystal data for **3**: $\mathrm{C_{48}H_{92}N_6Na_2Zn_2}$, $M_r = 930.0$, monoclinic, space group $P2_1/c$, $a = 9.9246(16)$, $b = 18.848(8)$, $c = 15.716(3)$ Å, $\beta = 108.364(11)°$, $V = 2790.1(14)$ Å^3, $Z = 2$, $\rho_{\mathrm{calcd}} = 1.107\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{Mo_{K\alpha}}) = 0.91\ \mathrm{mm^{-1}}$, $T = 150$ K, $R = 0.062$ ($F^2 > 2\sigma$), $R_w = 0.138$ (for all F^2 values) for 3398 data and 273 refined parameters; final difference synthesis within $\pm 0.52\ \mathrm{e\,Å^{-3}}$. The molecule is ordered on a crystallographic inversion center. CCDC-609230 (**2**) and 609228 (**3**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] A. V. Protchenko, O. G. Almazova, L. N. Zakharov, G. K. Fukin, Y. T. Struchkov, M. N. Bochkarev, *J. Organomet. Chem.* **1997**, *536–537*, 457.

[12] As there are only minor geometrical differences between this composite structure and its separate components, **1·2** is not discussed further herein; see Supporting Information for the experimental details and crystal data.

[13] C. Schade, W. Bauer, P. v. R. Schleyer, *J. Organomet. Chem.* **1985**, *295*, C25.