Modifying Alkylzinc Reactivity with 2,2’-Dipyridylamide: Activation of tBu–Zn Bonds for para-Alkylation of Benzophenone**

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Many of the recent eye-catching advances in zincate executed metallation chemistry have centered on the secondary monoamide 2,2,6,6-tetramethylpipеридине (TMP). Developed by Kondo, Uchiyama, and co-workers, the original TMP zincate reagent [LiZn(TMP)Bu2] is an effective base for both aromatic and heteroaromatic substrates.[1] Knochel and co-workers have since compiled a library of new TMP-based metalating agents, including the zinc pivalate [(TMP)Zn(OPiv)LiCl] (OPiv = pivalate), which like [LiZn(TMP)Bu2], displays strong deprotonating power and exceptional functional-group tolerance but has the added advantage that its arylzincated derivatives boast prolonged air stability.[2] The area of zincate metallation chemistry that is best structurally defined is that involving the sodium TMP reagent [(TMEDA)Na(TMP)BuZn(tBu)] (1; TMEDA = N,N,N’,N’-tetramethylethlenediamine). This reagent, which exhibits enhanced reactivity over the aforementioned lithium zincates, and many of its arylzincated derivatives adopt similar structures, which are designed on an architectural template of a Na–anion–Zn–anion ring carrying terminal ligands, namely a neutral donor and an anion on Na and Zn, respectively (Figure 1). To break this template and develop new structural motifs that could stimulate new reactivity we have investigated replacing monofunctional TMP with multifunctional 2,2’-dipyridylamide [dpa, (2-NC5H4)2N]. Offering three potential ligating N sites, this N-bridged bis(N heteroleptic zincate) finds utility in a diverse range of applications including medicine,[3] catalysis,[4] photoluminescence,[5] and supramolecular chemistry.[6] Herein we report a remarkable set of novel arylzincated derivatives boasting prolonged air stability. The neutral, heteroleptic zinc complex [(dpa)Zn(tBu)] (2) was synthesized straightforwardly through the 1:1 stoichiometric combination of tBuZn and the amine dpa(H) in a hexane solution. NMR studies of the filtrate revealed the absolute yield was higher than the 70% yield of the isolated crystals. Possessing an attractive hour-glass-shaped core, the centrosymmetric molecular structure of 2 (Scheme 1) is dimeric with the distorted tetrahedral zinc atom[7] bonded to the deprotonated N of one amido unit, which occupies the dipyridyl pocket of the other and completes its coordination with a terminal tBu ligand. In the hour-glass description (see the Supporting Information), each bulb comprises a puckered, six-atom (NCNCNZn) ring with Zn situated 1.0991(3) Å from the nearest NCNCN plane and 1.7143(3) Å from the second NCNCN plane. This motif bears a strong resemblance to that of the isoelectronic neutral zinc dimer [MeZnC(H)-Py2]+[Py=2-pyridyl].[8] To our knowledge, 2 represents the first crystallographically characterized Zn/dpa complex showing a Zn(bridgehead)N bond, although it has been noted in alkylated dimeric derivatives wherein the mode of dimerization is distinct from that in 2.[9] The anti[anti] conformation[10] (i.e., both pyridyl N atoms directed away from the bridgehead N) within 2 also contrasts with the synanti conformations found in polymorphs of dpa(H)[11] and the aforementioned alkylated dpa derivatives.

A simple transamination reaction[12] between TMP/zincate 1 and dpa(H) in a hexane solution was anticipated, but instead the isolated crystalline product was the disodium monozinc species [(TMEDA)2Na(μ-dpa)2Zn(tBu)] [3; 70% yield based on the dpa(H) stoichiometry]. Formally transamination has occurred but the 2:1 Na2/Zn stoichiometry of 3 is inconsistent with the 1:1 stoichiometry of the reaction. Its molecular structure (Figure 2) can be viewed as a cocomplex between a TMEDA-complexed sodium amide dimer and
a bis(alkyl) zinc monomer with the connection being two dative Zn/C0N(pyr) bonds completing a distorted tetrahedral (C2N2) zinc environment. To bind to Zn, one dipyridylamide must adopt an anti/anti disposition with its pyridine N atoms oriented away from the [Na(amido)N]2 ring, while the second has a syn/syn conformation with each Na bonded to the amido N and one or other of the pyridine N atoms. Resonance delocalization within the dipyridylamide scaffold is usually associated with shorter C-N(amido)-C bridges (e.g., about 1.34 Å each), longer C-N(pyr) bonds (e.g., about 1.38 Å), and a dihedral angle between the two pyridine ring planes approaching 0° as ascertained by data from several neutral dpa(H) and anionic dpa complexes[11,13] (see the Supporting Information). The corresponding dimensions within 3 [e.g., C10–N1, 1.371(2) Å; C15–N1, 1.373(2) Å; C10–N2, 1.347(2) Å; C15–N3, 1.346(2) Å; dihedral angle of unit bonded to Zn, 22.9°] suggest the degree of delocalization is small. This prompts the thought that though formally a higher-order zincate (conforming to the empirical formula Na2ZnR2R'), 3 is best interpreted as a neutral donor-acceptor bis(alkyl)zinc complex with a metalloligand as a donor. Supporting this view, the structure of 3 is novel as it bears little resemblance to the common Weiss motif of dialkali-metal zincate and related ate structures[14] (Figure 3) but shows more in common with homonuclear zinc complexes such as [tBu2Zn-{(iPrN(H)CH2CH2N(H)iPr}] or [(tBu2Zn)3(C4H4N2)4].[16]

Figure 3. Graphical representation of a Weiss motif structure.

Surprisingly when the same metal components in 3 were mixed together in the presence of THF and in the absence of TMEDA, the structural outcome was remarkably different (Scheme 1). Substituting TMEDA by THF can be trivial in organoalkali-metal chemistry with one bidentate TMEDA being replaced by two monodentate THF molecules without altering the basic structure of the complex, but the reactivity may be changed.[17] However, here the structural effect is more profound. Unlike the contact ion-pair 3 with its 2:1 Na/ Zn stoichiometry, the isolated product is the solvent-separated monosodium dizinc complex {Na(THF)6}+[Zn(tBu)2(dpa)Zn(tBu)2]− (4). The octahedrally coordinated cation of 4 is known[18] but its anionic moiety (Figure 4) is unprecedented. Two tBu2Zn monomers connect through one dpa anion which, lying flat in an anti/anti conformation, presents a chelating pyridyl pocket to one Zn atom, thus making it four coordinate, and the bridgehead amido N to the other Zn, thus
Table 1: Reaction of zinc reagents with benzophenone in a hexane solution for 18 h.

| Entry | Reagent | T [°C] | para addition (1,6) | Carboxyl addition (1,2) | ortho addition (1,4) | benzhydrol (H⁺ addition) | total |
|-------|---------|--------|---------------------|------------------------|---------------------|------------------------|-------|
| Stoichiometric | | | | | | | |
| 1 | tBu₂Zn (1 equiv) | RT | 1 | 0 | 0 | 0 | 1 |
| 2 | tBu₂Zn-2pyridine (1 equiv) | RT | 1 | 0 | 0 | 0 | 1 |
| 3 | tBu₂Zn-TMEDA (1 equiv) | RT | 1 | 1 | 0 | 0 | 2 |
| 4 | [(TMEDA)Na(TMP)](tBu₂Zn[tBu₂]) (1:1 equiv) | RT | 58 | 14 | 3 | 0 | 75 |
| 5 | [(TMEDA)₂Na₂(μ-dpa)₂Zn[tBu₂]] (3:1 equiv) | RT | 40 | 6 | 0 | 11 | 57 |
| 6 | [(Na(THF)₆)⁺{Zn(tBu₂)(dpa)Zn(tBu₂)}] (4:1 equiv) | RT | 42 | 13 | 0 | 3 | 58 |
| Substoichiometric | | | | | | | |
| 7 | tBu₂Zn (1 equiv) | 75 | 11 | 1 | 0 | 8 | 20 |
| 8 | tBu₂Zn (1 equiv) + [(TMEDA)Na(TMP)] (0.1 equiv) | 75 | 33 | 8 | 0 | 6 | 47 |
| 9 | tBu₂Zn (1 equiv) + [(TMEDA)Na(dpa)] (0.1 equiv) | 75 | 52 | 12 | 0 | 7 | 71 |
| 10 | tBu₂Zn (1 equiv) + [(Na(THF)₆)⁺{Zn(tBu₂)(dpa)Zn(tBu₂)}] (0.1 equiv) | 75 | 33 | 7 | 0 | 9 | 49 |

[a] Yields were determined by ¹H NMR spectroscopy using hexamethylbenzene (10 mol%) as an internal standard.

making it three coordinate. Unfortunately, the anion lies on a crystallographic center of symmetry, and as this symmetry can only be approximately satisfied by the dpa ligand, the structure is disordered over two sites. This prevents any discussion of dimensions, though the atomic connectivity is definite. We therefore turned to a DFT study using the B3LYP[29] method and the 6-311G(d,p)[30] basis set in which the anionic moiety of 4 was modeled. Its dimensions (see the Supporting Information for full details) revealed slightly more delocalization than that implied in 3. Key indicators are the C–Namide bond lengths [1.363 Å; 1.372 Å (mean) in 3] and the dihedral angle between the N(amide)–C bonds [C–N–N–C is 3.9° in 4; 26.0° in 3]. Also within the pyridyl rings there are long C–N and two relatively short C–C bonds akin to a N=C–C=C–C(N) pattern (bond lengths 1.345/1.345, 1.380/1.380, 1.401/1.401, 1.374/1.374, 1.429/1.428, and 1.360/1.359 Å) similar to that found in a series of [M(2MPy)₃N] complexes, where M is Al, Ga, In, or Tl.[31] Formally 4 could be regarded as a sodium zincinate[21] by combining a neutral tBu₂Zn unit with a [Zn(dpa)₂]⁻, though, the true electronic distribution, as reflected by the theoretical calculations, lies between these two extremes. We also successfully prepared the potassium congener [K(THF)₄]⁺[Zn(tBu₂)(dpa)Zn(tBu₂)]⁻ (5; see the Supporting Information for details).

Alkylselective addition to ketones by Grignard reagents has been much studied with benzophenone, which is often used as a benchmark as its reactions can have several outcomes. Excellent progress has been made in carbonyl (1,2) additions most recently by Ishihara and co-workers who showed that catalytic amounts of ZnCl₂ (thus generating R₂ZnMgCl intermediates) can greatly enhance such reactions.[22] Hévia and co-workers also reported that adding just 10 mol% of the magnesium-zinc hybrid [(THF)₄MgCl]⁻[Zn₂Et₂]⁺ to the reaction of EtMgCl and benzophenone gave the 1,2-addition product in 90% yield.[23] These bimetallic zinc-mediated successes inspired us to test the tert-butylation performance of 3 and 4 in a hexane solution, noting that 1 had previously delivered a tBu nucleophile to the para (1,6) position of benzophenone albeit on the sole evidence of an isolated crystalline enolato intermediate.[24] Table 1 reveals that the three sodium zinicates 3, 4, and 1 give competitive yields of the challenging para-addition product 4-tert-butylobenzophenone in contrast to the near 0% yields witnessed for the homonuclear zinc species. A striking comparison is that the metalloligand solvated tBu₂Zn produces 40 times as much para product as unsolvated tBu₂Zn or its pyridine and TMEDA solvates. Olah and co-workers reported that reacting tBuLi with benzophenone in THF solvent gave a 52% yield of ring alklylation products (1:9, ortho/para ratio), but only at −100°C using toxic thionyl chloride as oxidant as an aqueous work-up dropped the combined yield to 28°C and running the reaction in hexane at ambient temperature switched the major product to that of 1,2 addition.[25] Clearly the zincate systems are advantageous since they give comparable yields at ambient temperature using a mild aqueous work-up. The most intriguing result came when a 1:1 mixture of tBu₂Zn and benzophenone was treated with only 10 mol% of the sodium amide [(TMEDA)Na(dpa)]⁻, presumably generating 10 mol% of 3 in situ in a hexane solution. At ambient temperature, 4-tert-butylbenzophenone was obtained in a low yield of 11% but this remarkably rose to 52% under reflux conditions, thus implying that the substoichiometric sodium amide is recycling in some way.

To conclude, this study has uncovered a set of alkylzinc-based compounds with unprecedented structures by utilizing a secondary amide equipped with two pyridyl appendages as a structural template-changing co-ligand. Unlike conventional alkylzinc reagents these heteroleptic compounds can directly alkylate (tert-butylate) benzophenone in the challenging para position. Most intriguingly, substoichiometric amounts of sodium amide [(TMEDA)Na(dpa)]⁻ can activate tBu₂Zn towards this tert-butylation through the inter-
mediacy of the zincate, the structure of which masquerades as a neutral donor-acceptor complex.

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Supporting Information and full details are given in 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. 

Crystal data for 2: C22H44N10Na2Zn; an orange colorless block gave monoclinic space group P21/c, a = 9.4833(8), b = 10.4377(4), c = 14.0888(5) Å, β = 105.844(4)°, V = 1341.58(8) Å3, Z = 2, R_all = 0.149 Mgm–1, R1 = 0.0413 [for 2840 reflections with I > 2σ(I)], wR2 = 0.1039 and S = 1.065 for 166 parameters and 3451 independent reflections. Crystal data for 3: C8H30N4Na2Zn; an orange block gave monoclinic space group P21/m, a = 11.5137(3) b = 21.6403(4), c = 18.3837(3) Å, β = 93.636(2)°, V = 4571.26(16) Å3, Z = 4, R_all = 1.160 Mgm–1, R1 = 0.0388 [for 8121 reflections with I > 2σ(I)], wR2 = 0.0864 and S = 1.032 for 492 parameters and 10516 independent reflections. 

Crystal data for 4: C0H12N6O2NaZn; an orange block gave triclinic space group P–1, a = 10.0075(11), b = 11.1283(9), c = 13.3084(15) Å, α = 69.353(9), β = 85.495(11)°, γ = 84.723(8)°, V = 1379.3(2) Å3, Z = 1, R_all = 1.166 Mgm–1, R1 = 0.0606 [for 5614 reflections with I > 2σ(I)], wR2 = 0.1679 and S = 1.057 for 321 parameters and 6820 independent reflections.
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