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Alkali-Metal-Mediated Zincation of Anisole: Synthesis and Structures of Three Instructive Ortho-Zincated Complexes

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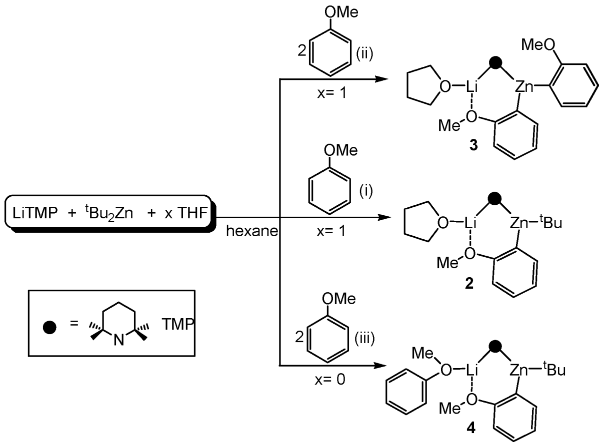
Anisole has been a key molecule in both the practical and theoretical development of directed ortho-metalation (DoM) chemistry.[1] Historically, it was pioneering lithiations of anisole by Gilman[2] and by Wittig[3] that sowed the seeds of this ever-blossoming synthetic methodology, which arguably has now outgrown classic aromatic electrophilic substitution as the most powerful method for regioselective functionalization of aromatic rings.[4] The lithiation of anisole has been studied using NMR spectroscopy,[5] semiempirical calculations,[5,6] kinetic isotope effects,[7] and X-ray crystallography.[8] Especially noteworthy are the rate studies by Collum[9] which show that methoxy-lithium dative interactions are negligible in the rate-limiting transition structure, thus suggesting that the acidifying inductive effect of the methoxy substituent is more important than the complex-induced proximity effect (CIPE)[10] in directing the metalation. We describe here the first study in which the new concept of alkali-metal-mediated zincation (AMMZ)[11] is applied to anisole. This study establishes that anisole can be ortho-zincated by AMMZ. Furthermore, due to stabilization of the ortho-deprotonated anisole anion by the mixed-metal cation, ortho-zincated "intermediates" can be isolated from solution, permitting their crystallographic and spectroscopic characterization. Three such intermediates, demonstrating explicitly the ligand transfer selectivity, stoichiometric dependence, and solvent dependence of the AMMZ process, are described, thus providing collectively a structural study of the metalation of anisole of unprecedented clarity.

First introduced by Kondo and Uchiyama in 1999,[12] lithium di-*tert*-butyltetramethylpiperidinozincate (**1**) was employed as the AMMZ reagent. We chose **1** because of its track record in effecting DoM (for example, of alkyl benzoates)[12] and because its crystal structure, formulated as [THF•Li(μ-TMP)(μ-^{t}Bu)Zn(^{t}Bu)], has recently been determined,[13] thus providing a structural foundation from which subsequent reactions can be monitored. Scheme 1 summarizes the reactions investigated. Adapting the original Kondo/Uchiyama preparation of **1** by replacing the bulk solvent THF with hexane to which was added sequentially a single stoichiometric amount of THF and one molar equivalent of anisole [pathway (i)] afforded crystals of [THF•Li(μ-TMP)(μ-o-C_6H_4OMe)Zn(^{t}Bu)] (**2**), with the coproduct being *tert*-butane gas. These crystals were characterized by $^1H/^{13}C/^7Li$ NMR spectroscopy[14] and X-ray crystallography (see below).[14]

Scheme 1. Lithium-Mediated Zincation Reactions of Anisole with [(i), (ii)] and without [(iii)] the Presence of THF



Noteworthy in the NMR data is the inequivalence of the α-Me groups of the TMP ligand (at 1.61/1.56 ppm in the ^1H spectrum; at 35.34/35.14 ppm in the ^{13}C spectrum), indicative of a fixed, stereochemically inflexible Li(μ-TMP)Zn bridge. In the previous DoM reactions with a variety of aromatic and heteroaromatic substrates, **1** functions as a TMP base,[12,15] so the retention of TMP within **2**, concomitant with **1** switching to an alkyl basic mode, is surprising. This switch appears to be activated by changing the bulk reaction solvent from THF to hexane. In **2** the ^{t}Bu bridge is replaced by an ortho-deprotonated anisole fragment, with two potentially basic ligands, a TMP and a terminal ^{t}Bu, remaining on zinc. This led us to ponder the question, "Could **1** also function as a *di*basic reagent?" Accordingly, the reaction was repeated but with two molar equivalents of anisole [pathway (ii)], and the reaction mixture was stirred for a longer time. Also characterized spectroscopically and crystallographically, the product was the bis(ortho-deprotonated anisole) complex [THF•Li(μ-TMP)(μ-o-C_6H_4OMe)-Zn(o-C_6H_4OMe)] (**3**).[14] In **3**, TMP is again retained in its rigid bridge disposition (corresponding Me resonances at 1.61/1.35 and 36.56/33.45 ppm), with two indistinguishable (on the NMR time scale at room temperature) ortho-deprotonated anisole fragments bound to Zn. Here, therefore, **1** functions as a stoichiometrically efficient dialkyl reagent, subjecting two molecules of anisole to ortho-metalation (t-BuH is also produced), whereas with the aforementioned other substrates it had functioned as a TMP base and was usually employed in excess. The most surprising result came when THF was omitted altogether [pathway (iii)]. As we have found here that LiTMP and ^{t}Bu$_2$Zn require a donor solvent (either in a stoichiometric amount or in bulk) to effect cocomplexation, we introduced two molar equivalents of anisole to a LiTMP/^{t}Bu$_2$Zn/hexane mixture, reasoning that the ether might act as both a Lewis base and a C−H acid. Remarkably, both features are exhibited in the crystalline product [Ph(Me)O•Li(μ-TMP)(μ-o-C_6H_4OMe)-Zn(^{t}Bu)] (**4**), which has also been fully characterized.[14] In this reaction, reagent **1** again functions as a ^{t}Bu base. As with **2** and **3**, the TMP Me groups in **4** are inequivalent (corresponding resonances at 1.39/1.21 and 35.59/34.99 ppm). Note that **4** is also produced, but in a smaller yield, when only one molar equivalent of anisole is used. This implies that the rate of anisole metalation is faster

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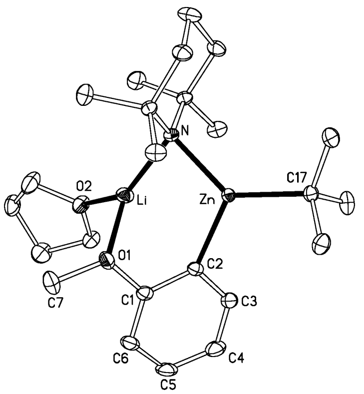

Figure 1. Molecular structure of **2** with 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

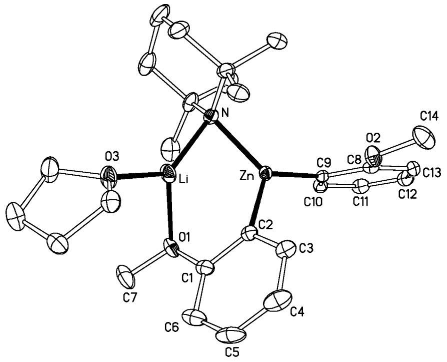

Figure 2. Molecular structure of **3** with 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

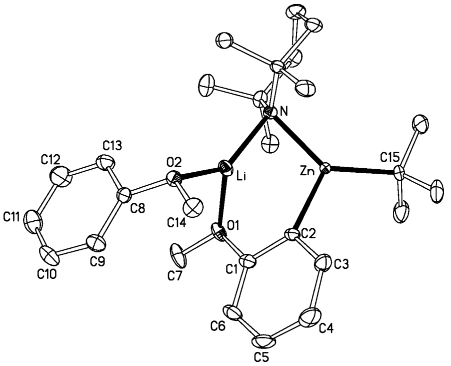

Figure 3. Molecular structure of **4** with 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

than the rate of formation of the mixed-metal reagent, presumably [anisole·Li(μ-TMP)(μ-^{t}Bu)Zn(^{t}Bu)], and that this intermediate, once formed, reacts with non-coordinated anisole to generate **4**.

Linking Li to Zn through a mixed TMP-ortho-deprotonated anisole ligand set, a six-membered (LiNZnCCO) ring is common to the molecular structures of **2**−**4** (Figures 1−3, respectively).[14] The trigonal planar Zn coordination is completed in **2** and **4** by a terminal ^{t}Bu ligand, and in **3** by a terminal ortho-deprotonated anisole ligand. The Li coordination is also trigonal planar, with the terminal sites filled by THF in **2** and **3** and by a neutral anisole ligand in **4**. Formally, complex **4**, with one non-deprotonated anisole O-ligated to Li and one deprotonated anisole, can be considered a pre-metalation complex (in a CIPE sense),[10] or at least a key intermediate in the reaction pathway to complex **3** with its two deprotonated anisole ligands. In conventional organolithium chemistry, reactive intermediates of this type would normally be expected to decompose long before ambient temperature was reached, but the dual metal coordination, combined with the steric protection of TMP and coligands, appears to enhance stabilization in these heterometallic cases. Diluting this possibility of a CIPE, we note that adding THF to **4** (isolated and then redissolved in hexane solution) converts it to **2**, which in turn leads to **3** on further stirring. Hence, in agreement with Collum's findings on the lithiation reaction, it appears not to be necessary to invoke a CIPE to explain this zincation of anisole, though a donor ligand is required to generate the mixed-metal base.

To conclude, this study adds a new dimension to the use of **1** as a reagent for deprotonative zincation. In establishing that it can effect directed ortho-zincation of anisole, the ability to tune the reactivity of the reagent from a TMP base to a monoalkyl base or a dialkyl base has been demonstrated. This exceptional versatility for a single zincate reagent broadens significantly the potential scope of utility of AMMZ in synthetic chemistry, especially considering that both "R" alkyl groups, the R$_2$N amide group and the alkali metal cation, can also be interchanged and that auxiliary ligands such as TMEDA (not used here, but proving effective in sodium zincate reactions)[16] can be introduced.

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Supporting Information Available: Full experimental details and crystallographic data for **2**−**4** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org

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