Inverse Crown Compounds

Selective *Meta*-Deprotonation of Toluene by Using Alkali-Metal-Mediated Magnesiation**

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Deprotonative metalation, whereby a proton is substituted by a metal cation to transform a parent organic compound to a more reactive metallic intermediate, which, in turn, can be used to transfer the organic fragment to another molecule, is one of the fundamental synthetic tools that chemists employ to construct compounds.[1] Thus this indispensable tool is put to labor on a daily basis in laboratories across the world, both in academia, for general synthesis, and in industry, for the manufacture of fine chemicals and pharmaceuticals. With polyatomic organic compounds containing two or more hydrogen atoms, there is often a requirement to be selective in choosing the specific hydrogen atom to be removed to generate the desired organic fragment. Owing largely to their polar nature, alkali-metal alkyl ("RM") and amide ("R_2NM") compounds, especially those of lithium, are often the best reagents for effecting deprotonative metalation, but there are limits to their selectivity.[2,3]

A primary source of aromatic compounds, alkylbenzenes, typified by toluene, offer several sites for metalation: the alkyl side chain or the *ortho*, *meta*, or *para* ring sites.[4] However, in practice, toluene is almost exclusively metalated on the CH_3 substituent by common reagents such as BuLi-(tmeda) (tmeda is *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), BuNa, or BuK.[5–7] This situation follows conventional wisdom as the newly formed benzyl "carbanion" ($PhCH_2^-$) is resonance stabilized, and thus in these mainstream monometallic systems it is the most thermodynamically stable of the four isomers possible when a proton is abstracted from toluene. All of the relevant studies hitherto have achieved metalation at kinetic ring sites to only a very minor, synthetically useless, extent, and anyway this is usually followed by isomerization to the thermodynamic benzyl structure. For this reason, metalation reactions of toluene have had a limited scope of usefulness within organic synthesis. Given this background, chemists will be surprised to learn that it is now possible to reverse this order of thermodynamic stability in favor of ring as opposed to methyl deprotonation of toluene by using a special synergic (bimetallic)[8] approach. Moreover, this approach enables regioselective metalation at the *meta* position, to contrast with the normal *ortho*-, *para*-directing effect that the methyl group of toluene exerts in reactions such as electrophilic aromatic substitution. Thus we report the selective *meta* deprotonation of toluene in the mixed sodium–magnesium amido complex $[(\text{tmeda})\text{Na}(\mu\text{-C}_6\text{H}_4\text{CH}_3)(\mu\text{-tmp})\text{Mg}(\text{tmp})]$ (**1**; where tmp is 2,2,6,6-tetramethylpiperidide). We describe the synthesis and characterization of **1**, as well as reporting the results of theoretical calculations on model compounds, which can offer an explanation for this unexpected *meta* selectivity.

As part of a study working towards the development of new mixed-metal amide-based reagents which can display remarkable synergic reactivities, we recently introduced the bimetallic sodium-magnesium monoalkyl bisamido complex $[(\text{tmeda})\text{Na}(\mu\text{-Bu})(\mu\text{-tmp})\text{Mg}(\text{tmp})]$ (**2**).[9] This new reagent is best prepared by combining the individual monometallic alkyl compounds and treating the mixture with equimolar amounts of the parent cyclic amine tmp(H) and the chelating auxiliary tmeda (Scheme 1). In this way **2** is produced in near-quantitative yields in a pure, crystalline form ideal for synthetic utilization. We anticipated that **2** could have special Brønsted basic properties as it has a number of characteristics of different existing bases, but all combined within a single molecule: these include bulky amide ligands (as in Li(tmp)), a strongly nucleophilic alkyl ligand (as in BuLi or BuNa) but one within a unique sterically hindered environment, a mixed-metal mixed-anion set (as in the Lochmann–Schlosser, lithium carbon potassium alkoxide (LICKOR) superbases), and a diamine molecule known to activate alkali metal reagents in many reactions.[1] Furthermore, **2** is soluble in many common organic solvents (such as hydrocarbons). Its

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$$2\,\mathrm{BuNa} + 2\mathrm{Bu_2Mg} + 2\mathrm{tmp(H)} + 2\mathrm{tmeda} \xrightarrow{-\mathrm{BuH}}$$

$$\underset{\mathbf{2}}{[\mathrm{(tmeda)Na(Bu)(tmp)Mg(tmp)}]} + \mathrm{NaMgBu_3(tmeda)}$$

$$[\mathrm{(tmeda)Na(Bu)(tmp)Mg(tmp)}] + \mathrm{C_6H_5CH_3} \xrightarrow{-\mathrm{BuH}}$$

$$\underset{\mathbf{1}}{[\mathrm{(tmeda)Na(C_6H_4CH_3)(tmp)Mg(tmp)}]}$$

Scheme 1. Synthesis of the bimetallic base **2** and its reaction with toluene to form **1**.

deprotonative ability was first demonstrated with benzene, which was readily converted into $C_6H_5^-$ within the product [(tmeda)Na(μ-C_6H_5)(μ-tmp)Mg(tmp)] (**3**).[9] Regioselectivity was not an issue in this case. Deprotonation of toluene (Scheme 1) also proved straightforward, by simply adding it to a hexane solution of **2** and heating the mixture to reflux. The solid product of the reaction was colorless, crystalline **1** (58% yield), the formation of which was accompanied by butane gas evolution. When the reaction was repeated using a stoichiometric amount of toluene instead of a tenfold excess, **1** was still obtained in a 30% yield. Characterized by both ^{1}H and ^{13}C NMR spectroscopic studies (recorded in [D$_6$]benzene solution), **1** displays a pattern in the aromatic region of the ^{1}H NMR spectrum (a singlet, two doublets, and a triplet) consistent with *meta*-deprotonated toluene (i.e., corresponding to the *ortho**-, *ortho*/*para*-, and *meta*-hydrogen atoms respectively). This assignment is confirmed by the presence of the CH_3 resonance of toluene and the absence of a benzylic CH_2 resonance. Furthermore, there is no sign of other possible regioisomers of metalated toluene, each of which, if present, would give rise to distinctive resonance patterns in the aromatic region. The spectra also reveal that at ambient temperature both types of tmp ligand are equivalent and that the tmeda coligand remains coordinated to the sodium center. It should be noted that in the absence of tmeda, a 1:1:3 mixture of BuNa, Bu_2Mg, and tmp(H), thought to generate "[{tmp(H)}Na(Bu)(tmp)$_2$Mg]" in situ,[9] reacts with toluene to give [(tmp)$_6$Na$_4$Mg$_2${C$_6$H$_3$(Me)}][10] in which toluene is dideprotonated in the 2,5-positions. The low yield of this product and the new discovery of **1**, suggests that this twofold deprotonation is a subsequent reaction effected by strong heating, which probably involves intramolecular deprotonation of a monodeprotonated toluene species and elimination of Mg(tmp)$_2$ as the Na:Mg ratio changes from 1:1 in **1** to 2:1 in the other product.

X-ray crystallographic studies established the molecular structure of **1** (Figure 1).[11] A four-element NaNMgC ring, with a mixed tmp/$C_6H_4CH_3$ bridging ligand set, forms the central feature of the structure, which is completed by a terminal tmp on magnesium and a bidentate attached tmeda on sodium. Thus its basic connectivity is the same as that in **2** and **3**, with only the identity of the carbon bridge changing ($C_6H_4CH_3$ in **1**, Bu in **2**, C_6H_5 in **3**). In **1** (as in **3**), the central NaNMgC ring is essentially planar (sum of endocyclic bond angles, 359.94°), whereas in **2** there is a deviation from planarity (corresponding sum, 356.33°). This distinction reflects the aromatic/aliphatic nature of the carbon bridge and its hybridization (sp^2/sp^3, on discounting the long contacts to Na). In forming a short, strong bond to the *meta*-C1 atom (2.197(5) Å), close to coplanarity with the tolyl ring plane (as shown by the Mg1C1C6C5 torsion angle, −168.9(4)°), the Mg1 atom in **1** in effect refills the position vacated by the abstracted proton. This result implies intriguingly that the metalation reaction is formally a magnesiation as opposed to a sodiation, which runs counter to the normal reactivity order of organomagnesium versus organosodium compounds (i.e., that organosodium compounds are orders of magnitude more reactive).[12] Contrary to the parallel orientation of Mg1, Na1 lies almost perpendicular to the tolyl ring plane (Na1-C1-Mg1 bond angle, 80.78(16)°). The shortest Na1-tolyl contact is to the *meta* C1 (2.681(5) Å), where most of the negative charge resides, but the proximate C atoms also lie close by (Na1-C6, 3.147(5)Å; Na1-C2, 3.333(5) Å). This bonding distinction between magnesium and sodium with respect to the deprotonated substrate, signifying more σ character for magnesium and more π character for sodium, is also found in inverse crown complexes.[13,14]

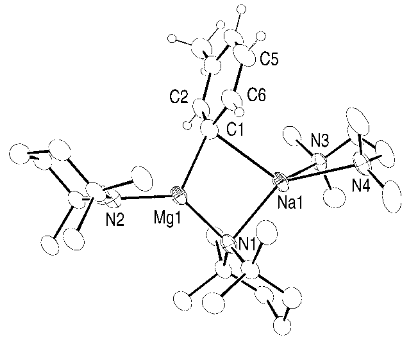

Figure 1. Molecular structure of **1**. Hydrogen atoms, apart from those of the tolyl group, are omitted for clarity.

The origin of this unexpected *meta* selectivity was probed by theoretical calculations. Preliminary geometry optimizations on all molecules were performed at the Hartree–Fock level, using the 6-13G* basis set, then the optimized structure so obtained was re-refined at the density functional theory (DFT) level, employing the B3LYP method and the 6-311G** basis set.[13] The reaction between **2** and toluene to give **1** (Scheme 1) was calculated to be exothermic by 8.21 kcal mol^{-1}. Four regioisomers of the model compound [Na(μ-tolyl)(μ-tmp)Mg(tmp)] (**1A**–**1D**; Figure 2), where tolyl represents a toluene molecule singly deprotonated in the *ortho* (**1A**), *meta* (**1B**), *para* (**1C**), or *methyl* (**1D**) positions, were examined. Consistent with the experimental structure of **1**, the most stable theoretical structure is calculated to be the *meta* isomer **1B** (relative energy, 0.00 kcal mol^{-1}). The next lowest energy structure is the *para* isomer **1C** (at +2.35 kcal mol^{-1}) followed by the *ortho* isomer **1A** (at 5.12 kcal mol^{-1}). Somewhat surprisingly, the least stable structure of all is the benzyl isomer **1D**, which is 7.77 kcal mol^{-1} less stable than **1B**. Comparing the dimensions of **1B** and **1D**, it is clear that the major contribution to the energetic preference for **1B** lies not in Mg−C σ bonding but in

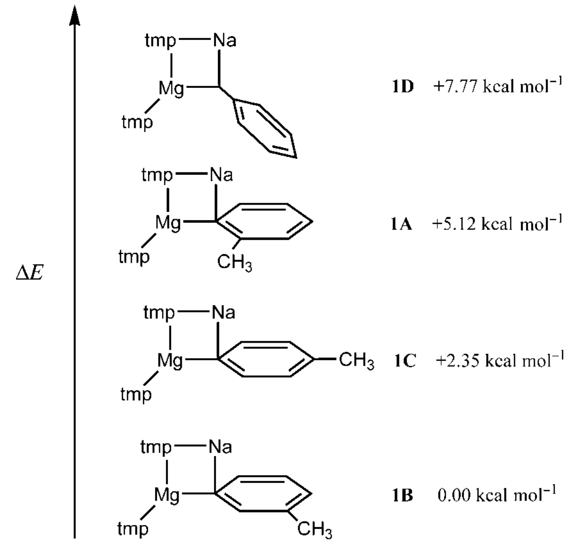

Figure 2. The theoretical structures **1A**–**1D**, in order of decreasing stability.

Na–C π interactions: thus the Mg–C bond in **1B** (2.232 Å) is only modestly shorter than that in **1D** (2.279 Å); but whereas **1B** displays several short-to-medium length Na–C π interactions (2.453 Å, 2.915 Å, and 2.960 Å to *meta*, *para*, and *ortho* C atoms, respectively), the orientation of the benzyl ring in **1D** is such that there are no Na–C π contacts below 4.8 Å (the Na–C benzylic bond length is 2.475 Å). While each individual Na–C π interaction in **1B** may be weak, collectively they must contribute significantly to its overall stability. Hence the normal order of thermodynamic stability of toluene metalation products (side-chain isomer > ring-site isomer) has been reversed by using this special bimetallic approach. When tmeda is included in the calculations, the benzyl isomer is still less stable than the *meta* isomer, but by a reduced margin (+1.99 kcal mol⁻¹); also the *para* isomer is fractionally more stable than the *meta* isomer (relative energies, 0.00 and +0.05 kcal mol⁻¹, respectively). However, *meta*-deprotonation has also been observed in tmeda-free solutions in the synthesis of the dideprotonated complex $[Na_4Mg_2(C_6H_3CH_3)(tmp)_6]$, so the tmeda-free models **1A**–**1D** probably provide a reasonable guide to the experimental reaction. Noting that conventional magnesium bases are generally too weak to metalate toluene, this new synergic mixed-metal methodology that opens a direct route to *meta*-substituted toluenes,[15,16] is perhaps best regarded as alkali-metal-mediated magnesiation, a new form of magnesiation with greatly enhanced basic powers.[17]

To test its ability to be intercepted by electrophiles, **1** was treated with three molar equivalents of trimethylsilyl triflate in [D$_6$]benzene solution. A white precipitate formed instantaneously, and was removed by filtration. A ^{1}H NMR spectrum of the filtrate showed that **1** had converted essentially quantitatively into trimethyl *meta*-tolylsilane, as established by comparison with an authentic sample of trimethyl *meta*-tolylsilane.[16] This promising result confirms that **1** should be an excellent precursor to *meta*-substituted tolyl compounds.

Experimental Section

All reactions were carried out under a protective argon atmosphere.

1: Freshly prepared [(tmeda)Na(μ-Bu)(μ-tmp)Mg(tmp)] (**2**) (1.0 g, 2 mmol) was dissolved in hexane (10 mL). Next toluene (2 mL; 20 mmol) was added and the pale yellow solution obtained was heated to reflux for 90 min. The flask containing the resulting light orange solution was placed in a Dewar flask of hot water and allowed to cool slowly to room temperature affording colorless crystals of **1** (yield, 0.62 g, 58 %). ^{1}H NMR (400 MHz, 25 °C, [D$_6$]benzene): $\delta = 7.75$ ($H_{\text{ortho*}}$, C_6H_4-CH_3), 7.62 (H_{para}, C_6H_4-CH_3), 7.10 (H_{meta}, C_6H_4-CH_3), 6.92 (H_{ortho}, C_6H_4-CH_3), 2.19 (CH_3, C_6H_4-CH_3), 1.90 (m, 4H, tmp), 1.64 (s, 24H, CH_3, tmp), 1.56 (s, 12H, CH_3, tmeda), 1.48 (m, 4H, CH_2, tmeda), 1.35 ppm (m, 8H, tmp); ^{13}C{^{1}H} NMR (100.63 MHz, 25 °C, [D$_6$]benzene): $\delta = 172.83$ (Mg-$C_{\text{meta*}}$), 142.29 ($C_{\text{ortho*}}$), 137.48 (C_{para}), 135.76 (C_{ipso}), 127.04 (C_{meta}), 126.13 (C_{ortho}), 57.23 (CH_2, tmeda), 52.60 (N-*C*, tmp), 46.26 (CH_3, tmeda), 42.71 (tmp), 36.24 (CH_3, tmp), 22.45 (CH_3, C_6H_4-CH_3), 20.70 ppm (tmp).

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[11] Crystal data for **1**: $C_{31}H_{59}MgN_4Na$, $M_r = 535.12$. All measurements were made at 123 K on a Nonius Kappa CCD diffractometer. These gave, triclinic, space group $P\bar{1}$, $a = 9.8562(4)$, $b = 11.3668(4)$, $c = 16.0733(7)$ Å, $\alpha = 69.568(2)$, $\beta = 83.965(2)$, $\gamma = 83.558(2)°$, $V = 1672.59(12)$ Å^3, $Z = 2$, $\lambda = 0.71073$ Å, $\mu = 0.090$ mm^{-1}; 16555 reflections, 4467 unique, R_{int} 0.087; final refinement to convergence on F^2 gave $R = 0.0870$ (F, 3274 obs. data only) and $R_w = 0.2343$ (F^2, all data), GOF = 1.099. Diffraction intensity fell sharply beyond $2\theta = 45.5°$ and this had an adverse impact on the quality of the data collection and refinement. Atomic coordinates, bond lengths, and angles.

CCDC-257597 (**1**) contains 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.

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