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VIP Hauser Bases

Unmasking Representative Structures of TMP-Active Hauser and Turbo-Hauser Bases**

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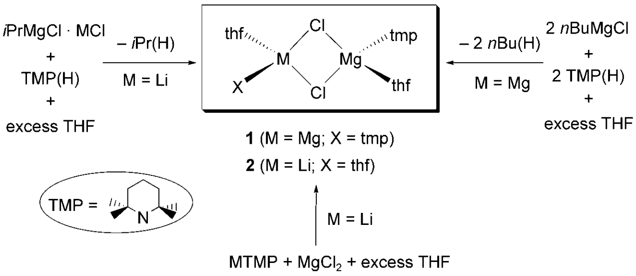
Dedicated to Professor Gernot Boche on the occasion of his 70th birthday

Halomagnesium amides of empirical formula R_2NMgX are among the earliest known organomagnesium compounds, being first introduced by Meunier in 1903.[1] Later in the middle of the 20th century, Hauser and co-workers developed their use as special Brønsted bases, a contribution acknowledged today by their generic description as Hauser bases.[2] In 1989 Eaton et al. extended this class of compounds to sterically demanding amido ligands, most notably 2,2,6,6-tetramethylpiperidide (TMP) within (tmp)MgBr, utilizing them in *ortho*-magnesiation reactions of carboxamides.[3] The chloride congener (tmp)MgCl was reported in 1995 by Mulzer and co-workers[4] who found it more effective than the bromide in *ortho*-magnesiation reactions of pyridinecarboxamides and carbamates. Very recently there has been an explosion of interest in TMP Hauser bases and related "turbo-Grignard" chemistry,[5] fueled by a blitz of new, improved synthetic methods for regioselective functionalization of aryl, heteroaryl, and metallocenyl compounds in groundbreaking research by Knochel. The reactions involved fall into two categories, namely metal–halogen exchange[6] and metal–hydrogen exchange.[7] One of the key reagents used to execute the latter lithium-powered metalation reactions is formulated as (tmp)MgCl·LiCl,[8] which by analogy with turbo-Grignard reagents (RMgCl·LiCl; R = alkyl) could be labeled a "turbo-Hauser base". Invariably it is employed as a reagent in solution form in THF, in which it possesses excellent solubility, but until now no solid composition of it has been isolated from solution or characterized. Similarly, to date, conventional TMP Hauser bases including (tmp)MgCl have been generated in situ in solution and not investigated in solid form. Herein, we shine light on these special "black-box" reagents by reporting the first isolation, crystallographic, and spectroscopic characterization of both a TMP Hauser base and its upgraded turbo model. We also reveal an alternative simplified procedure for preparing the turbo-Hauser base.



Scheme 1. Synthesis of Hauser base **1** and its lithium chloride supported turbo model **2**.

Following Mulzer's original preparation,[4] we synthesized the TMP Hauser base (tmp)MgCl by reaction of equimolar amounts of *n*BuMgCl and TMP(H) in THF, but refluxed the solution for longer (5 h instead of 1.5 h; Scheme 1). The white solid obtained was recrystallized from toluene to afford colorless crystals (yield of isolated product 50 %) identified as the THF solvate [tmp(thf)Mg(μ-Cl)$_2$Mg(thf)tmp] (**1**).[9] Shorter reaction times, lower reaction temperatures, or the use of weaker Lewis basic solvent Et_2O (instead of THF) resulted in residual butyl groups in the isolated product mixture as determined by NMR spectroscopic studies. The role of the bulk THF solution is therefore vital for not only does it ensure the amination of the alkyl Grignard reagent is complete, it also stops, or at least greatly reduces, any possible Schlenk equilibrium that would produce disproportionation of **1** leading to magnesium bis(amide) and bis(halide) complexes.

To prepare the turbo (lithium chloride stabilized) model of **1**, we initially followed Knochel's procedure for generating a solution of (tmp)MgCl·LiCl in THF via *i*PrMgCl·LiCl and the amine TMP(H) (Scheme 1).[8] To adapt the procedure to obtain crystalline material, we removed the solvent in vacuo to obtain an oily, off-white solid, which was recrystallized from 3:2 hexane/THF at −27 °C. The crystalline product obtained in 26 % yield was characterized as the tris(thf) solvate [(thf)$_2$Li(μ-Cl)$_2$Mg(thf)tmp] (**2**).[9] In an alternative reaction avoiding the alkyl Grignard reagent (see the Supporting Information for full details) we simply added one molar equivalent of LiTMP to a suspension of $MgCl_2$ in THF (Scheme 1) and stirred the mixture for 1 day. Removing the THF in vacuo and adding hexane afforded a white solid,

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which on the basis of NMR and IR spectra was identified also as **2**.[9] Comparison of the unit cell of a crystal obtained from 3:2 hexane/THF at −27 °C also confirmed that it is the same compound as that obtained by reaction of *i*PrMgCl·LiCl with TMP(H). Both **1** and **2** are poorly soluble in arene solvents, but dissolve well in THF. Reflecting the strong resemblance of their TMP ligand environments, **1** and **2** exhibit similar ^{1}H and essentially identical ^{13}C NMR spectra in [D$_8$]THF: in the former spectra, the Me, β-H, and γ-H TMP resonances in **1**/**2** appear at $\delta = 1.12/1.16$, 1.19/1.17, and 1.60/1.57 ppm, respectively; in the latter the γ-C, CH$_3$, β-C, and α-C TMP resonances appear at $\delta = 20.9/21.0$, 36.1/36.2, 42.6/43.0, and 52.1/52.3 ppm, respectively. The presence of lithium in **2** was confirmed by a singlet (at $\delta = 0.29$ ppm) in the ^{7}Li NMR spectrum. One significant distinction discernible from the NMR experiments is that bis(solvate) **1** appears to be able to hold onto its ligating THF molecules better than tris(solvate) **2** as the TMP:THF integration ratio for the latter (1:2) conflicts with that (1:3) observed in the crystal structure of **2**. Presumably this loss of THF is a consequence of the isolation/drying procedure.

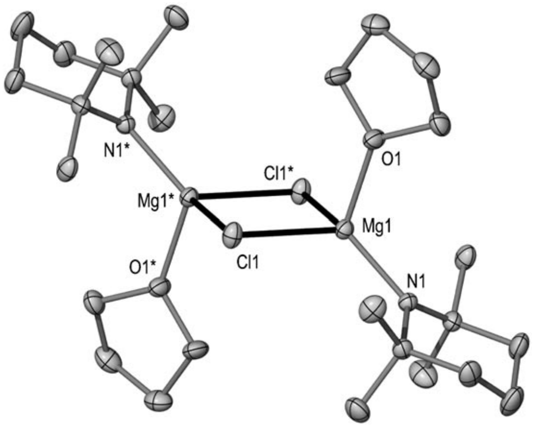


Figure 1. Molecular structure of **1** with hydrogen atoms and disordered toluene of crystallization omitted for clarity.

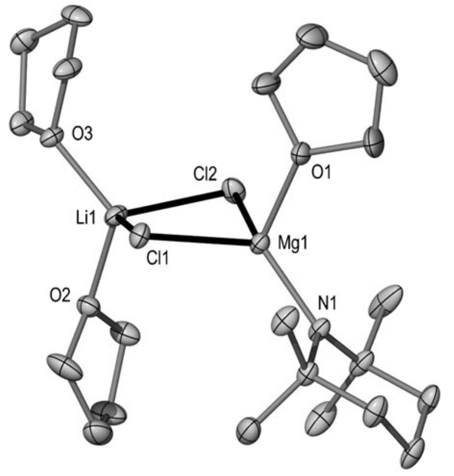
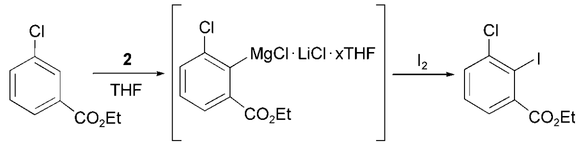


Figure 2. Molecular structure of **2** with hydrogen atoms omitted for clarity.

The molecular structures of **1** (Figure 1)[9] and **2** (Figure 2)[9] are closely related but not identical. Centrosymmetric dimer **1** exhibits a strictly planar (MgCl)$_2$ ring with terminal, transoid-disposed TMP and THF ligands giving overall a four-coordinate, distorted tetrahedral Mg center. There is also one disordered molecule of toluene per dimer in the crystal lattice. C_1-symmetric dinuclear compound **2** exhibits a nonplanar (LiClMgCl) ring [fold angle 21.9(2)°] with the same Mg coordination as in **1** but with a (thf)$_2$Li unit replacing the second Mg(thf)tmp unit of **1**. Significantly, the Mg–tmp interaction, the critical one with respect to magnesiating ability, is longer and presumably weaker in the case of **2** [Mg1−N1, 1.981(2) Å; compare with 1.9558(14) Å in **1**]. Interestingly, these distances are comparatively short for a four-coordinate Mg center, as there are several cases of longer Mg−N(tmp) terminal bonds involving three-coordinate Mg [e.g., mean length across the series tmeda·Na(μ-R)(μ-tmp)Mg(tmp) is 2.001 Å (R = *n*Bu, Ph,[10] or C$_6$H$_6$CrC$_6$H$_5$[11]; tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine)]. Power and co-workers highlight a similar shortening of the Mg−N bond in their account of the HMDS Hauser base [hmds(Et$_2$O)Mg-(μ-Cl)$_2$Mg(Et$_2$O)hmds] (hmds = 1,1,1,3,3,3-hexamethyldisilazide),[12] which is essentially isostructural to **1**, attributing it to the strongly electronegative Cl and O atoms contracting the effective radius of the Mg ion. Searching the Cambridge Crystallographic database[13] emphasized the general novelty of this first turbo-Hauser base structure **2** as no hits were found for a Li/Mg/TMP halogen combination or, more surprisingly, for any Li(μ-Cl)$_2$Mg ring. However, there is a strong structural similarity to bromomagnesium alkyl compounds such as [(thf)$_2$Li(μ-Br)$_2$Mg(thf){C(SiMe$_3$)$_3$}],[14] in which in comparison to **2** Br has replaced Cl and the alkyl ligand has replaced TMP essentially with retention of the basic structure.

The complicated THF solution chemistry of organomagnesium compounds epitomized by Grignard reagents[15] necessitates caution when correlating crystal structures with solution structures. Therefore, although crystalline **2** may be the active magnesiating species in THF it cannot be concluded so unequivocally, especially as **2** was obtained from a THF/hexane mixture. However, it is definite that **2** is a bona fide magnesiating reagent under the conditions employed by Knochel, that is in neat THF. This fact was established by studying a mixture of redissolved crystalline **2**, ethyl 3-chlorobenzoate (a representative functionalized aromatic substrate), and iodine in a 1.2/1.0/1.5 ratio (Scheme 2). Measuring NMR spectra of the solution mixture before and after the iodine quench enabled us to observe directly the major intermediate of the reaction, the 2-magnesiated



Scheme 2. Regioselective magnesiation of ethyl 3-chlorobenzoate with redissolved crystalline **2** and subsequent electrophilic interception with iodine.

aromatic, and the final product, ethyl 3-chloro-2-iodobenzoate. Analogous results were obtained by using the aforementioned LiTMP/$MgCl_2$ mixture in THF. Full details are given in the Supporting Information.

What can we deduce about the source of the powerful regioselective magnesiating ability of **2** by surveying its structure? 1) It is a molecular halide, rather than saltlike; 2) its active basic ligand TMP binds to magnesium, not lithium; 3) the Mg–N(tmp) interaction is terminal, and thus only one bond needs to be broken to release the active base; 4) the four-coordinate Mg center is coordinatively saturated, but has a (potentially) labile THF ligand geminal to TMP, which on loss of THF could facilitate the precoordination of the functionalized aromatic substrate prior to magnesiation (note the ease of THF loss during the isolation procedure); and 5) the bimetallic, ate ("$Li^+MgR_3^-$") constitution, augmented by the presence of strongly electronegative ligands could be a key factor in its enhanced magnesiating ability. Points 1–4 and to some extent 5 apply also to the structure of **1**, so there now appears to be a structural justification for the special magnesiating powers exhibited by both conventional Hauser bases and turbo-Hauser bases (and, by implication, the whole turbo-Grignard family).

Experimental Section

1: TMP(H) (5 mmol, 0.85 mL) was added to a solution of *n*BuMgCl (5 mmol, 2.5 mL of a 2.0 M solution in THF) in bulk THF (10 mL). The resultant mixture was heated to reflux for 5 h and then stirred at room temperature overnight. Removal of the solvent yielded an off-white solid, which was recrystallized from hot toluene to give colorless crystals of **1** (0.68 g, 50%). ^{1}H NMR (400 MHz, [D$_8$]THF, 293 K): $\delta = 3.61$ (m, 8H, CH_2-O, THF), 1.76 (m, 8H, CH_2, THF), 1.60 (m, 4H, γ-CH_2, TMP), 1.19 (m, 8H, β-CH_2, TMP), 1.12 ppm (s, 24H, CH_3, TMP). ^{13}C{^{1}H} NMR (100 MHz, [D$_8$]THF, 293 K): $\delta = 68.5$ (CH_2-O, THF), 52.1 (α-C, TMP), 42.6 (β-CH_2, TMP), 36.1 (CH_3, TMP), 26.6 (CH_2, THF), 20.9 ppm (γ-CH_2, TMP). A small amount of TMP(H) was also detected in the spectrum, presumably as a result of hydrolysis during the measurement.

2: TMP(H) (30.24 mmol, 5.14 mL, 1.05 equivalents) was added dropwise at room temperature to a solution of *i*PrMgCl·LiCl in THF (28.8 mmol, 30.0 mL of a 0.96 M solution in THF), and the resultant pale gray yellowish solution was allowed to stir for 24 h (slightly modified procedure to the one described by Knochel[8]). The solvents were removed under vacuum to yield an off-white oily solid. This solid was recrystallized from 3:2 hexane/THF at −27 °C to afford colorless crystals of **2** (2.90 g, 26%, considering the loss of one molecule of THF of **2**) suitable for X-ray crystallographic analysis. ^{1}H NMR (400 MHz, [D$_8$]THF, 293 K): $\delta = 3.61$ (m, 8H, CH_2-O, THF), 1.76 (m, 8H, CH_2, THF), 1.57 (m, 2H, γ-CH_2, TMP), 1.17 (4H, m, β-CH_2, TMP), 1.16 ppm (12H, s, CH_3, TMP). ^{13}C{^{1}H} NMR (100.59 MHz, [D$_8$]THF, 293 K): $\delta = 68.5$ (CH_2-O, THF), 52.3 (α-C, TMP), 43.0 (β-CH_2, TMP), 36.2 (CH_3, TMP), 26.6 (CH_2, THF), 21.0 ppm (γ-CH_2, TMP). ^{7}Li NMR (155 MHz, [D$_8$]THF, 293 K, reference LiCl in D_2O at $\delta = 0.00$ ppm): 0.29.

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