Bis(amido)magnesium mediated aldol additions: first structural characterisation of an amidomagnesium aldolate intermediate

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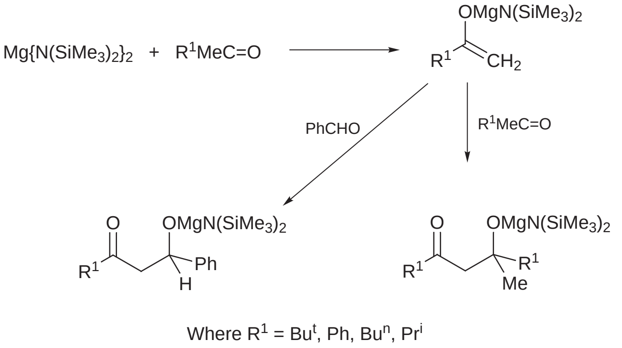
Bis(hexamethyldisilazido)magnesium has successfully been used to mediate aldol additions of selected ketones and aldehydes in hydrocarbon media, and the structure of an intermediate amido(aldolate), [{$(Me_3Si)_2NMg[\mu$-OC(Me)-$Bu^tCH_2C(Bu^t)=O]\}_2$] 17, produced by the self-coupled reaction of pinacolone has been characterised by X-ray crystallography.

Addition of the α carbon of an aldehyde or ketone to a second carbonyl unit is known as the aldol addition and has become one of the cornerstone reactions of modern synthetic chemistry.[1] Several methods have been developed to mediate this transformation, one of the most useful being the formation of a metal enolate by abstraction of a proton α to the carbonyl using a strong base. This is most commonly achieved through the use of lithium reagents and more specifically bulky lithium amides such as lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LHMDS).[2] We are interested in exploring the utility of amidomagnesium compounds as reagents to perform similar transformations since they are less reactive, more thermally stable and, in some instances, more selective than their lithium counterparts.[3] Magnesium has previously been used to mediate aldol additions *via* transmetallation of preformed lithium enolates with magnesium halides.[2] Reactions of this type have proved problematic due to 'salt-effects'.[4] In this respect, we have recently reported the presence of Schlenk-type equilibria for Hauser bases (R_2NMgX) and halomagnesium enolates, which complicates their use.[5] In comparison, bis(amido)magnesium compounds [$(R_2N)_2Mg$] have scarcely been studied as reagents.[6] In part this is due to complications with their synthesis, leading to troublesome side reactions of *in situ* prepared complexes.[7] These experimental problems have recently been overcome and we now report the use of bis(amido)magnesium compounds as reagents.[8] Herein we exploit an ether-free preparation of the bis(amide) [$Mg\{N(SiMe_3)_2\}_2$] **1**, and examine its utility in the aldol addition reaction.

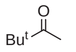
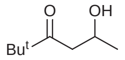
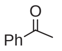
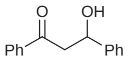
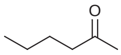
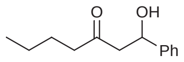
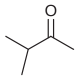
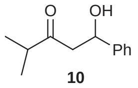
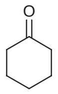
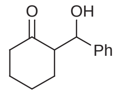
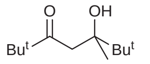
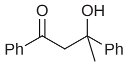
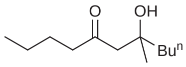
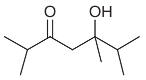
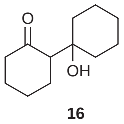
A mixture of commercially available Bu_2Mg and 2 equivalents of hexamethyldisilazane was heated to reflux in heptane solution for several hours, and slow cooling to room temperature resulted in the crystallisation of **1** in high yield.[9] Crystalline **1** was then isolated and used as a stock reagent. In turn, reactions with pinacolone **2**, acetophenone **3**, hexan-2-one **4**, 3-methylbutan-2-one **5** and cyclohexanone **6** were performed (Scheme 1), and Table 1 lists the results of the aldol addition reactions mediated by **1**.†

Isolated yields from the ketone/aldehyde reactions compare favourably with lithium-mediated additions (reactions 1–5).[2] In most instances the reaction of the ketone enolates with



Scheme 1

Table 1 Aldol addition reactions mediated by **1**

Entry	Ketone	Carbonyl added (mol. equiv.)	Major product	Yield (%)
1		PhCHO (1.5)	 **7**	86
2		PhCHO (2)	 **8**	86
3		PhCHO (2)	 **9**	94
4		PhCHO (2)	 **10**	82
5		PhCHO (2)	 **11**	90
6	**2**	**2** (1)	 **12**	56
7	**3**	**3** (1)	 **13**	38
8	**4**	**4** (1)	 **14**	80
9	**5**	**5** (1)	 **15**	63
10	**6**	**6** (1)	 **16**	62

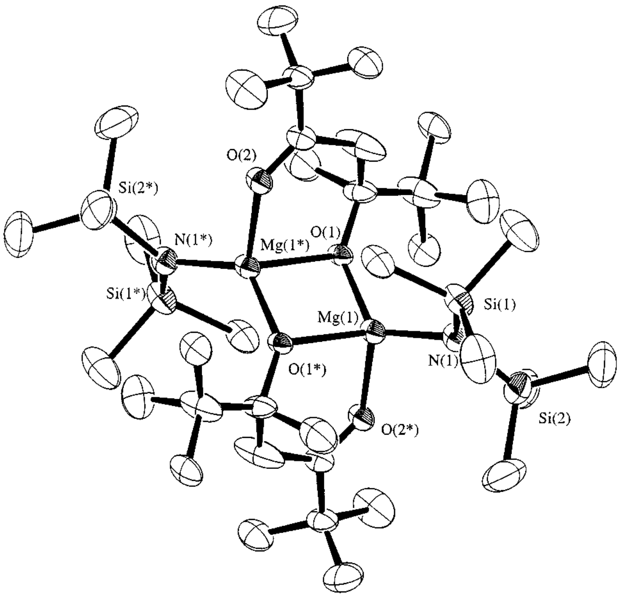


Fig. 1 Molecular structure of the major isomer of **17** with hydrogen atoms omitted for clarity. Key bond lengths (Å) and angles (°): Mg(1)–O(1) 1.9540(15), Mg(1)–O(1*) 1.9881(15), Mg(1)–N(1) 1.9920(19), Mg(1)–O(2*) 2.0619(15), O(1)–Mg(1)–O(1*) 85.90(6), O(1)–Mg(1)–N(1) 126.96(7), O(1*)–Mg(1)–N(1) 129.57(7), O(1)–Mg(1)–O(2*) 111.60(7), O(1*)–Mg(1)–O(2*) 87.18(6), N(1)–Mg(1)–O(2*) 108.51(7), C(7)–O(1)–Mg(1) 144.29(16), C(7)–O(1)–Mg(1*) 116.06(13), Mg(1)-O(1)–Mg(1*) 94.10(6), C(14)–O(2)-Mg(1*) 130.27(12).

benzaldehyde resulted in a small quantity (4–16%) of self-addition products. Significantly, this problem was overcome by adding 2 equivalents of the aldehyde to a solution of **1** before addition of the ketone. Also, no aldimine formation was detected.[10] Analogies with Corey's internal quench method for formation of silyl enol ethers are clear.[11]

It is known that ketone–ketone aldol coupling is usually less favourable than ketone–aldehyde additions. Using high temperature conditions (25–70 °C) the self-aldol reactions were found to proceed in reasonable yields (reactions 6–10).[12] The ability to perform these reactions at higher temperatures contrasts appreciably with the lithium analogues, where the aldolates commonly undergo retro-aldol reactions above −30 °C or eliminate LiOH to give enones.[2] With the systems reported here, the enone only becomes the major product after extended reflux. Furthermore, reactivity of both amide functions bonded to magnesium is suggested by reaction of 4 equivalents of **2** with **1** which yielded 55% of aldol product **12** (calculated with respect to ketone).

It should be noted that when polar donor solvents such as THF or HMPA were present, the yield of aldolate was significantly reduced ($<10\%$ for entry 6). This is consistent with the observation that, in lithium-mediated reactions, increasing the solvent polarity increases yields of enolisation but disfavours addition. However, this effect appears to be more dramatic for magnesium, since the lithium reactions are commonly performed in THF solution. This may be a consequence of the magnesium centres being more sterically crowded than those of lithium, resulting in blocking of the incoming carbonyl.

The intermediate from the pinacolone self-coupled reaction, $[\{(Me_3Si)_2NMg[\mu\text{-}OC(Me)Bu^tCH_2C(Bu^t)=O]\}_2]$ **17**, was characterised by X-ray crystallography (Fig. 1).‡ The centrosymmetric structure is based on a *trans*-6,4,6-fused ring system in which each aldolate acts as both bridge and chelate.

Two superimposed isomers are present within the crystal lattice of **17**. The isomers differ in the conformation of the six-membered aldolate chelate rings where half-chair and twist-boat conformation are found in a ratio of 80.5(3):19.5(3). Chelate isomers are also found in aldolate derivatives of lithium,[13] zinc,[14] titanium[15] and aluminium.[16] These isomers adopt half-boat, chair, half-chair and twist boat structures, illustrating the shallow energy surface separating these conformations.

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Notes and references

† Base **1** (2 mmol) was suspended in 10 ml of hexane and cooled to −78 °C. Aldehyde (4 mmol) or alternatively ketone (2 mmol) was then added, followed by dropwise addition of the ketone (2 mmol). The aldehyde reactions were stirred at −78 °C for 30 min then quenched with 1 M HCl. The self-coupled reactions were warmed to room temperature and stirred for 48–72 h before quenching in 1 M HCl. Improved yields of **12** and **13** were obtained on heating the mixtures to reflux for several hours. Further improvements in yields are expected on optimising the reaction conditions.

‡ *Crystal data* for **17**: $C_{36}H_{82}Mg_2N_2O_4Si_4$, $M = 768.02$, $T = 123(2)$ K, triclinic space group, $P\bar{1}$, $a = 9.610(3)$, $b = 11.381(2)$, $c = 12.024(4)$ Å, $\alpha = 98.90(2)$, $\beta = 104.00(2)$, $\gamma = 105.996(19)°$, $U = 1191.5(5)$ Å^3, $Z = 1$, μ(Mo-Kα) = 0.185 mm^{-1}, $D_c = 1.070$ Mg m^{-3}, $2\theta_{max} = 56°$, 6084 reflections collected, 5746 unique, ($R_{int} = 0.0173$) all were used in the calculations. The minor disorder component was treated isotropically with no hydrogen atoms attached. All other non-hydrogen atoms were treated anisotropically and all other hydrogens included in a riding model. The final $wR(F^2)$ was 0.1417 and conventional R was 0.0488. Programs were standard diffractometer control software and members of the SHELX family (G. M. Sheldrick, University of Göttingen, Germany). The structure was solved using direct methods and refined by full-matrix least-squares refinement on F^2. A single crystal of **17** was mounted in inert oil and transferred to the cold N_2 gas stream of the diffractometer.

CCDC 18/1286. See http://www.rsc.org/suppdata/cc/1999/1325/ for crystallographic files in .cif format.

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