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Magnesium Bis(diisopropylamide), a Useful Reagent for Regio- and Stereoselective Synthesis of Kinetic Silyl Enol Ethers

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Abstract: Less highly substituted silyl enol ethers are regiospecifically prepared in high yield, around room temperature under kinetic conditions, from unsymmetrical cyclic ketones and magnesium bis(diisopropylamide) [$(DA)_2Mg$] in THF/heptane. This high regioselectivity is markedly higher than these reported for bromomagnesium diisopropylamide (DAMgBr); it is also similar to this of LDA/DME at -78°C, but $(DA)_2Mg$ can be used at room temperature. In addition, a high E-enolization stereoselectivity is observed for benzylic ketones, reverse of this obtained with LDA.

Hauser bases[1] (R_2NMgX) and bis(amido)magnesium reagents[2] [$(R_2N)_2Mg$] are becoming more and more of interest and new data concerning their solid state structures, solvent-dependent aggregation and coordination have recently been reported.[2i - k] However, these reagents are often confused.[1e, f] Much less studied than their lithio-analogs, magnesium diamides are more thermally stable[2e, j] and less reactive leading to different selectivities. For example, they are compatible with ester and amide groups in direct "ortho magnesiation reactions" of substituted aromatics whereas lithio-analogs and even Hauser bases, more nucleophilic, are not.[2e]

As part of our ongoing research dealing with the study of chiral magnesium diamides as reagents for enantioselective deprotonation, needing kinetic conditions, we report our first results on the use of magnesium bis(diisopropylamide), $(DA)_2Mg$, as a model for kinetic deprotonation of symmetrical, unsymmetrical cyclic and benzylic ketones. This will lead us to compare with the reactivities of the corresponding Hauser base and of lithium diisopropyl amide (LDA). In the present work, reactions were carried out in tetrahydrofurane (THF)/heptane (2/1, vol) from 0°C to room temperature (r.t.) under kinetic trimethylsilyl chloride (TMSCl) internal quench.[3] Results obtained are listed in Table 1 and conclusions are the following.

First of all, symmetrical cyclic ketones **1** - **3** reacted efficiently or even quantitatively with $(DA)_2Mg$ just prepared from DAH and Bu_2Mg as previously described,[2e] providing the corresponding silyl enol ethers, in three hours, which is an improvement compared with Hauser bases. Actually, the use of DAMgBr/TMSCl/Et_3N/HMPA did not allow to prepare silyl enol ethers from unsubstituted cyclic ketones, but predominantly gave rise to aldol condensation products, limiting the methodology to relatively hindered

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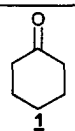
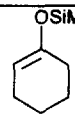
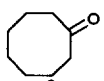
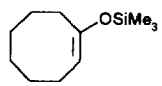
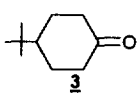
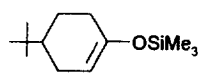
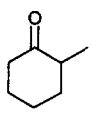
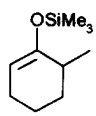
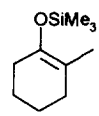
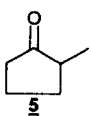
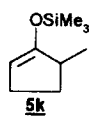
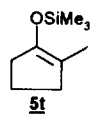
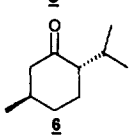
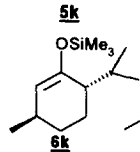
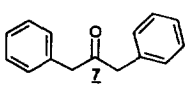
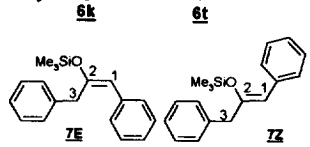
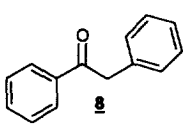
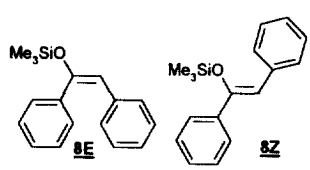
ketones.[1b] Apparently, the amine substituent moderates the reactivity of the intermediate aminomagnesium enolate compared with this of the bromomagnesium enolate by decreasing nucleophilicity and/or complexing ability with another ketone molecule. Electronic, steric factors and different aggregations can be invoked.

Table 1. Silyl Enol Ethers obtained from $(DA)_2Mg$/THF, heptane/TMSCl/0°C to r.t./3h.

Ketone	Conversion[a] (%)	Enoxysilanes	Ratio[a]	Literature kinetic conditions LDA	DAMgBr
 1	> 99		---		
 2	80		---		
 3	> 99		---		
 4	> 99	 4k  4t	k/t 100:0	k/t 99:1[b, 4]	k/t 3:97[c, 1b] 77:23[d, 1b] 87:13[e, 1b]
 5	> 99	 5k  5t	k/t 95:5	k/t 99:1[b, 4]	
 6	90[f]	 6k 6t	k/t 98:2[g]		k/t 3:97[c, 1b]
 7	> 99	 7E 7Z	E/Z 91:9	E/Z 17:83[b, 5]	
 8	> 99 (-20°C) 80	 8E 8Z	E/Z 73:27 80:20	E/Z 17:83[h, 6]	

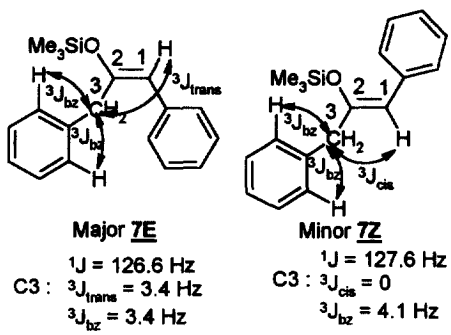
[a] Conversions and ratios were determined by ^1H NMR and GC (silicones SE 30); [b] LDA/DME/TMSCl/-78°C; [c] DAMgBr/TMSCl/Et_3N/Et_2O/HMPA; [d] id., THF solvent; [e] id., DME solvent; [f] 10 h reaction time was necessary; [g] The pure major **6k** isomer was isolated by silica-gel column chromatography (petroleum ether as eluent) in 81 % yield and was assigned the less substituted enolate by using ^1H, ^{13}C and 2D NMR spectroscopies; [h] LDA/THF/TMSCl/-78°C.

Secondly, unsymmetrical cyclic ketones afforded the less substituted "kinetic" trimethylsilyl enol ethers with a high regiospecificity: "kinetic"/"thermodynamic" enol ether ratios (k/t) are between 95:5 and 100:0 for ketones **4** - **6**. This high kinetic regioselectivity is markedly higher than these reported by Krafft and Holton when using DAMgBr/TMSCl/Et_3N/HMPA under kinetic conditions in THF (77:23 for **4**) or in dimethoxyethane (DME) (87:13 for **4**) and even is reversed in ether (3:97 for **4** and **6**).[1b] The interesting side of our results is that this regiospecificity can be achieved at r.t. with $(DA)_2Mg$ in a relative short time period. Even with the most substituted ketone **6**, consequently less reactive, needing a 10-hour-reaction time, no loss of regioselectivity was observed. It can be concluded that $(DA)_2Mg$ is a relatively bulky reagent that is in agreement with Henderson structural studies.[2i] Thus, this reagent can be an alternative at r.t. to the use of LDA in DME, which needs a low temperature of -78°C (k/t = 99:1 for **4** and **5**).[4]

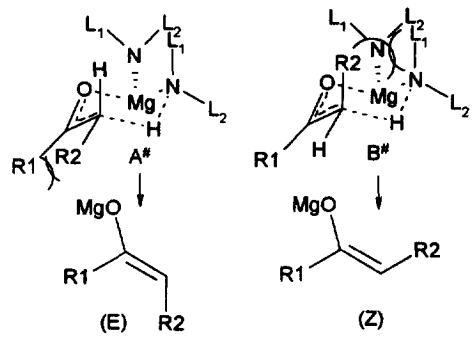
Thirdly, benzylic ketones **7** and **8** were chosen to check the stereoselectivity of $(DA)_2Mg$. But, if **8E**/**8Z** stereostructures were previously assigned by Davies,[6] those of **7E**/**7Z** were not. Tanaka[5] only reported that he obtained a silyl enol ethers major/minor ratio of 5:1 (or 83:17) from **7** without assignment of the Z/E geometries. Thus, we could assign the major **7** isomer obtained in this work the E structure, on the following data: i) According to the method of Heathcock,[7] the E structure corresponds to the more strongly shielded allylic ^{13}C NMR signal which is this of our major isomer (δ: 44.4 ppm, $CDCl_3$ solvent) compared with this of the minor one (δ: 49.0 ppm); ii) Moreover, in the undecoupled ^{13}C NMR spectrum of the major isomer an allylic C3-H1 coupling constant ($^3J_{trans}$ = 4.6 Hz) was observed (corroborating the E structure) whereas no allylic coupling was observed for the minor one ($^3J_{cis}$ = 0) (Scheme 1). In addition, our ^1H NMR spectra matching these of Tanaka; it can be concluded that his major isomer was Z.

Thus, Table 1 shows the high E-stereoselectivity obtained around r.t. from benzylic ketones **7** and **8** (**7E**/**7Z** = 91:9 and **8E**/**8Z** = 73:27 (or 80:20 at -20°C)), compared with the reverse stereo-selectivity observed with LDA at -78°C (17:83 for both).[5, 6] Similar E selectivities were observed with bromomagnesium isopropylcyclohexylamide, an Hauser base, upon reaction with the very particular hindered α-alkoxy ketones as reported by Heathcock.[1c] Our results can be rationalized considering steric interactions in Ireland's transition state model[8] which has been recently supported by Xie[9, 10] (Scheme 2). For LDA, the large repulsion of R_1 = $PhCH_2$-, Ph- and R_2 = Ph- in the cyclic chairlike transition state $A^{\neq}$ dominates and causes this route to be disfavored relative to transition state $B^{\neq}$ which leads to the Z-enolate. For $(DA)_2Mg$, it can be concluded that this magnesium base, bearing two diisopropyl amido substituents is much more bulkier than LDA affording a more severe $R_2 \leftrightarrow L_1$ steric interaction which destabilises the TS $B^{\neq}$ and leads to a net E-preference. This has been previously supported for other highly hindered lithium amide bases such as lithium t-butyl-t-octylamide[3] and lithium t-butyltrimethylsilylamide.[9] The lower E-selectivity observed for R_1 = Ph- than for R_1 = $PhCH_2$- is consistent with a higher steric hindrance for Ph- increasing the competing interaction $R_1 \leftrightarrow R_2$ in $A^{\neq}$.

Scheme 1. Undecoupled ^{13}C NMR spectrum of 7.



Scheme 2. Ireland's Transition State Model



It must be pointed out that THF must be added before reflux, otherwise a Z-selectivity is obtained (**8E/8Z** = 12:88) meaning that different aggregation states are formed; its amount was optimized to 33 equiv relatively to Bu_2Mg.

General procedure:

After 1h reflux under N_2 of 20 mL anhydrous THF (33 equiv), 15 mmoL DAH (2 equiv) and 7.5 mmoL Bu_2Mg (Aldrich, 1.0 M in heptane, 1 equiv), then cooling to 0°C, 9.5 mL (75 mmoL) of TMSCl were added followed by dropwise addition of 7.5 mmoL (1 equiv) of pure ketone (or dissolved in 2 mL of dry THF if solid). After stirring at room temperature for 3 h, the resulting mixture was concentrated, extracted with chilled petroleum ether, washed with chilled aqueous 5% HCl, saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. After evaporation of solvent, conversion and isomeric ratios were obtained by GC and ^1H NMR.

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