Bismesitylmagnesium: a thermally stable and non-nucleophilic carbon-centred base reagent for the efficient preparation of silyl enol ethers†

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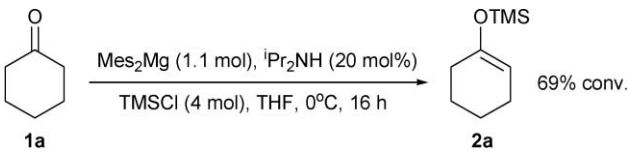
Bismesitylmagnesium has been established as an accessible, practical, convenient, and non-nucleophilic carbon-centred base reagent for efficient access to silyl enol ethers from a series of ketone substrates at readily utilisable temperatures.

Enolisation with lithium amide reagents is employed extensively throughout preparative chemistry.[1] In this regard, lithium di-*iso*-propylamide (LDA) is perhaps the reagent of this class which is most commonly used in organic synthesis.[2,3] Additionally, asymmetric variants have been widely developed and are now well-established, delivering good levels of reactivity and selectivity.[4] Furthermore, the use of magnesium-based amide reagents is now becoming more widespread due to a series of potential practical advantages over their lithium counterparts, as well as their increasing accessibility.[5] However, stoichiometric metal-amide systems can have several drawbacks: they require (i) (at least) a stoichiometric quantity of amine; (ii) a stoichiometric quantity of metal; and typically (iii) low temperatures to utilise. Moreover, problems of addition and reduction can exist, even with the normally more stoic LDA.[6]

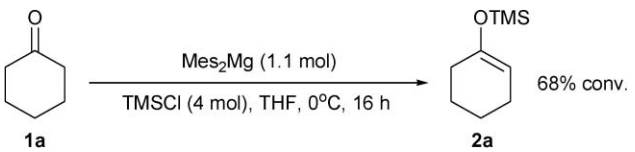
Following on from our extensive studies on asymmetric deprotonations using stoichiometric magnesium amide bases,[7] we sought to develop a recycling system, which would operate using sub-stoichiometric quantities of amine, with the requisite amide being (re-)generated by a suitable source of magnesium. Our preliminary investigations demonstrated that attempted ketone deprotonations using lowered quantities of amines coupled with primary and secondary bisalkylmagnesium reagents ($^{n}Bu_2Mg$ and $^{i}Pr_2Mg$) led to high proportions of alkylated (*i.e.* addition) and reduced products. Consequently, we realised that a more bulky, non-nucleophilic, source of R_2Mg, without β-hydrogens, would be required to (re-)generate the desired magnesium amide *in situ*. This led to the selection of Mes_2Mg[8] as a potentially viable stoichiometric source of magnesium. In due course and with work in the asymmetric arena underway, the possibility of establishing a more generally utilisable catalytic *achiral* base procedure was envisaged.

Preliminary deprotonation reactions utilised di-*iso*-propylamine (20 mol%) as the sub-stoichiometric amine source, with a slight excess of Mes_2Mg in an internal quench process (using four equivalents of TMSCl). A temperature study found the best conversion was obtained at a convenient 0 °C (although similar outcomes were observed at −40 °C and r.t.). Our initial system operated satisfactorily delivering a moderate 69% conversion (Scheme 1).



Scheme 1 Use of Mes_2Mg in a recycling amide base protocol.

Following these preliminary observations, necessary control experiments were performed. To our surprise, these subsequent investigations revealed that an amine was not required for the deprotonation process to proceed with efficiency and that Mes_2Mg was, itself, capable of mediating the formation of the desired silyl enol ether (Scheme 2). It is also worth noting that there was no evidence of ketone reduction or addition by-products. These initial studies, therefore, provided the basis for a system by which such deprotonations could be carried out with a magnesium-based carbon-centred base reagent without the requirement for any additional amine components. Indeed, this provides the first example of a carbon-based magnesium species reacting selectively in this fashion, as a base reagent, without any concomitant issues of addition or reduction. In terms of precedent, it should be noted that only a relatively small number of examples of carbon-centred bases have been described in the literature, presumably due to competing carbonyl addition. In particular, the enolisation of hindered ketones, such as trityl ketones, has been achieved with *n*-butyllithium[9] and also with trimethylaluminium[9,10] using, at least, stoichiometric quantities of the organometallic reagent. Additionally, the bulky triphenylmethyllithium[11] and triphenylmethylpotassium[11,12] reagents have been used to mediate the enolisation of certain ketones. More recently, gallium-based reagents, such as $GaEt_3$, have been used to deprotonate methylene protons with some selectivity, although elevated temperatures (125 °C) and 1.5 molar equivalents of the organometallic reagent are required.[13]



Scheme 2 A Mes_2Mg-mediated deprotonation protocol.

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† Electronic supplementary information (ESI) available: Experimental procedures, IR and ^{1}H NMR for known compounds, full data for novel compounds. See DOI: 10.1039/b711407a

Table 1 Optimisation of the Mes_2Mg deprotonation conditions

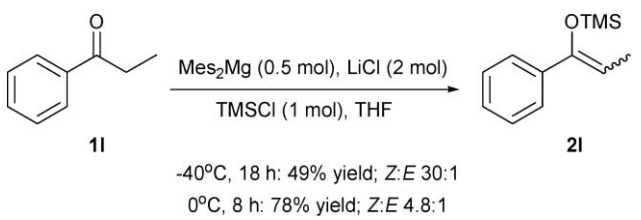
Entry	Mes_2Mg/mol	LiCl/mol	TMSCl/mol	T/°C	Time/h	Conv.[a] (%)
1	1.1	—	4	0	16	68
2	0.5	—	4	0	16	62
3	0.5	2	4	0	16	94
4	0.5	1	4	0	16	72
5	**0.5**	**2**	**1**	**0**	**16**	**98**
6	**0.5**	**2**	**1**	**0**	**8**	**98**
7	0.5	2	1	−40	8	86
8	0.5	2	1	−78	8	16
9	—	2	1	0	8	0

[a] Determined by G.C. analysis.[14]

Returning to our investigations with Mes_2Mg, a detailed programme of optimisation was undertaken in attempts to improve the overall efficiency of the emerging system (Table 1). While reasonable results were obtained using an excess (1.1 mol) of Mes_2Mg, a similar conversion was observed with only 0.5 mol of this reagent (entry 2, Table 1), exploiting the availability of the two anionic aryl units present. Moreover, addition of LiCl dramatically increased the efficiency of the system, with 2 mol of this additive appearing to be optimal (entries 3 and 4). Pleasingly, reducing the quantity of the TMSCl electrophile to only 1 mol equiv. led to a sustained high conversion (entry 5),[15] whilst entry 6 shows that the reaction approaches completion after only 8 h at 0 °C. Table 1 also shows that the Mes_2Mg deprotonation protocol can be performed effectively at −40 °C, again with only 0.5 mol of the organometallic reagent, whilst lowering the temperature further leads to only low conversion.

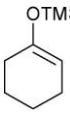
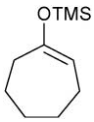
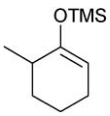
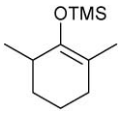
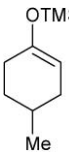
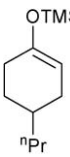
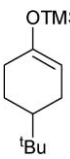
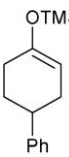
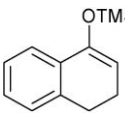
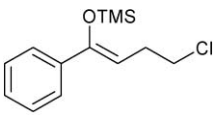
Having established the optimum system as described, the applicability of this protocol was assessed with a range of ketones. Gratifyingly, the developed conditions worked well for all substrates applied, with good isolated yields of enol ethers being obtained throughout (Table 2). In this regard, the result realised with 4-chlorobutyrophenone is particularly notable. In this case, the product enol ether **2k** was obtained in a good yield, again at the conveniently accessible temperature of 0 °C, further emphasising the non-nucleophilicity of the developed reagent system. Comparatively, treatment of the same chloroketone with LDA, under similar conditions, led only to elimination products. Moreover, treatment of cyclohexanone with the equivalent lithiated species, MesLi, using the same protocol at 0 °C, delivered only 13% conversion to the desired enol ether, with the major product being *C*-silylated mesitylene.[16]

In order to probe the stereoselectivity of enol ether formation with Mes_2Mg, propiophenone was employed as a suitable and well-known substrate.[17] As shown in Scheme 3, the favoured *Z*-isomer remained predominant throughout, with an optimum 30 : 1 ratio of stereoisomers being achieved at −40 °C, compared



Scheme 3 Deprotonation of propiophenone using Mes_2Mg.

Table 2 Application of the Mes_2Mg deprotonation process[a]

Entry	Product		Yield[b] (%)
1		**2b**	88
2		**2a**	88
3		**2c**	90
4		**2d**	89
5		**2e**	76
6		**2f**	82
7		**2g**	85
8		**2h**	89
9		**2i**	76
10		**2j**	83
11		**2k**	81

[a] For a typical procedure, see supporting data. [b] Isolated yield after purification.

to that (4.8 : 1) achieved at 0 °C. It should also be further noted here that reaction of the same ketone **1l** led to an 89% yield of enol ether **2l** at 40 °C, with no observed by-product formation. This

further illustrates the thermal stability and chemoselectivity of the Mes_2Mg reagent, even at such relatively elevated temperatures.

In summary, we have developed a new magnesium-based carbon-centred base reagent protocol, which offers a number of distinct advantages over existing and analogous systems. In particular, the key Mes_2Mg reagent is non-nucleophilic and non-reductive, even at temperatures above ambient. Additionally, only 0.5 mol of the metal-based reagent is required and no appreciable reaction cooling needs to be applied, with processes being routinely performed at 0 °C. Furthermore, the system operates effectively with lowered amounts of electrophile and, perhaps more importantly, without any amine reagent (*cf.* the widely employed LDA). As such, reaction by-products are limited to the innocuous mesitylene and inorganic salts, thus expediting work-up procedures. Consequently, we believe that the practical benefits offered by these processes could lead to their widespread adoption by the preparative community.

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