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Efficient methods for enol phosphate synthesis using carbon-centred magnesium bases†

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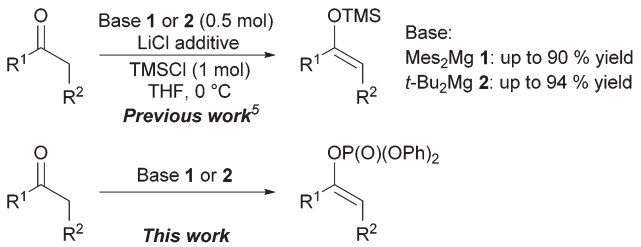
Efficient conversion of ketones into kinetic enol phosphates under mild and accessible conditions has been realised using the developed methods with di-*tert*-butylmagnesium and bismesitylmagnesium. Optimisation of the quench protocol resulted in high yields of enol phosphates from a range of cyclohexanones and aryl methyl ketones, with tolerance of a range of additional functional units.

Introduction

Versatile functional handles – groups which may be transformed into a range of different products – are highly prized, both in complex molecule synthesis in particular and synthetic organic chemistry in general. To this end, enol phosphates have often played a key role in the synthesis of natural products and biologically active compounds.[1] The high stability of enol phosphates, in conjunction with their wide-ranging portfolio of derivatisations,[2] such as within cross coupling processes,[3] are key aspects of their preparative popularity. Although various synthetic methodologies have been developed to allow access to enol phosphates,[4] the most convenient strategy consists of the deprotonation of an enolisable ketone using a strong base, followed by reaction of the subsequent metal enolate with a phosphoryl chloride.[1a–d] Specifically, this procedure usually employs strong organolithium bases, such as lithium di-iso-propyl amide (LDA) at low temperature (−78 °C), with the obvious attendant drawbacks in terms of functional group compatibility, energy efficiency, and competing side-reactions.[5] Recently, however, we have reported the use of diaryl- and dialkylmagnesium bases **1** and **2**, respectively, for the efficient formation of silyl enol ethers under mild conditions (Scheme 1).[6] These diorganomagnesium species, readily prepared from their corresponding Grignard reagents, were found to function effectively as bases without presenting any nucleophilic reactivity towards the ketone substrates. Diaryl- and dialkylmagnesium bases **1** and **2** also displayed high levels of chemo- and regioselectivity in the deprotonation of a broad range of ketones, establishing an efficient process for the formation of silyl enol ethers under readily accessible conditions. In terms of reaction time, the use of Mes_2Mg **1** afforded high yields of the silyl enol ether products in 8 h,[6a,b] whereas the use of *t*-Bu_2Mg **2**, a more reactive base, resulted in the same levels of reactivity in only 1 h.[6c] Encouraged by the efficacy of these carbon-centred magnesium bases in the preparation of silyl enol ethers, we proposed to extended their application to the synthesis of the related, but more versatile, enol phosphates under similarly mild conditions. Herein we report our studies on the use of diorganomagnesium bases **1** and **2** in the formation of enol phosphates.[7]



Scheme 1 Synthesis of silyl enol ethers using carbon-centred magnesium bases and proposed extension to enol phosphates.

Results and discussion

The active magnesium bases were readily prepared from commercially available reagents. As shown in Scheme 2, dimesitylmagnesium **1** was prepared in a one-pot process involving the formation of the Grignard reagent from bromomesitylene, followed by disproportionation towards the diarylmagnesium

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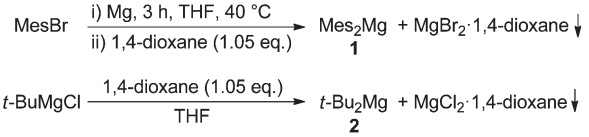
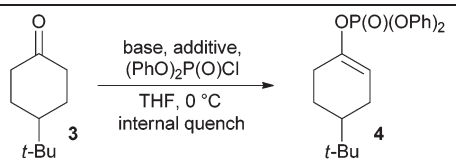


Scheme 2 Formation of carbon-centred bases.

species **1**, induced by addition of 1,4-dioxane. The dialkylmagnesium base, di-*tert*-butylmagnesium **2**, was readily prepared from the commercial Grignard reagent *tert*-butylmagnesium chloride in a similar manner. The two newly-formed bases were stored at room temperature under an argon atmosphere and were standardised[8] prior to use.

With these bases in hand, we applied our previously optimised conditions for the formation of silyl enol ethers, using base **1** [6b] with model substrate **3**, and employing diphenylphosphoryl chloride as the phosphorus source. Lithium chloride was used as an additive, since this had previously been found to be beneficial in our studies on the formation of silyl enol ethers.[6a,c] Under these conditions (entry 1, Table 1), the deprotonation of 4-*tert*-butylcyclohexanone **3** with base **1** afforded a disappointingly low 29% yield of the enol phosphate product **4** after a reaction time of 16 h. Given the enhanced reactivity of the phosphoryl electrophile, shorter reaction times were also investigated. However, when the reactions were quenched after either 8 h (entry 2, Table 1) or 1 h (entry 3, Table 1), similar outcomes were observed. In continuing these optimisation studies, it was noted that, in the formation of silyl enol ethers, base **2** had exhibited a higher reactivity than base **1**, allowing the transformation to be completed in only 1 h.[6c] In turn, applying the conditions used in entry 3, Table 1 but with base **2** were rewarded with a much improved yield of 68% (entry 5, Table 1) of the enol phosphate product **4**. To further increase the reactivity of our diorganomagnesium bases, we investigated the use of *N*,*N*′-dimethylpropyleneurea (DMPU) as an inexpensive and non-toxic additive which, more importantly, is known to be an excellent disaggregating agent for several organometallic species.[9] Indeed, the use of this additive resulted in a higher level of conversion when combined with base **1** (entry 4, Table 1), and, when subsequently applied to our more reactive base **2**, afforded a 75% yield of enol phosphate **4** (entry 6, Table 1). Thus, this brief screening process allowed us to rapidly identify base **2** as being optimal for enol phosphate formation, and, more importantly, revealed that, as an additive, DMPU was more suitable than lithium chloride.

Table 1 Preliminary studies on enol phosphate formation using carbon-centred magnesium bases



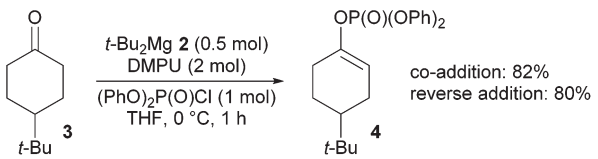
Entry	Base	Additive	Time	Yield[a]
1	Mes_2Mg **1**	LiCl	16 h	29%
2	Mes_2Mg **1**	LiCl	8 h	31%
3	Mes_2Mg **1**	LiCl	1 h	27%
4	Mes_2Mg **1**	DMPU	1 h	40%
5	*t*-Bu_2Mg **2**	LiCl	1 h	68%
6	*t*-Bu_2Mg **2**	DMPU	1 h	75%

Reaction conditions: 4-*tert*-butylcyclohexanone **3** (1 mmol), base **1** or **2** (0.5 mmol), additive (2 mmol), diphenylphosphoryl chloride (1 mmol), THF (11 mL), internal quench. [a] Average isolated yield over two runs.

Optimisation of enol phosphate formation using *t*-Bu_2Mg 2

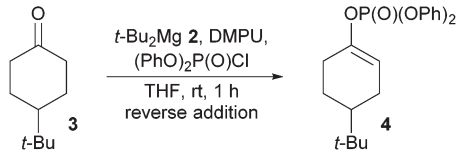
With both additive and base optimised to deliver a good isolated yield of enol phosphate **4**, our attention turned to the other tuneable aspects of the reaction, and, in particular, the quench protocol, which is an extremely important parameter in reactions involving organometallic bases. So far we had employed an internal quench protocol (*i.e.* the ketone is slowly added to a solution of base and electrophile), as this was the optimised process in our previous studies on the formation of silyl enol ethers.[6] However, this internal quench procedure requires the presence of the electrophile and the base together in the reaction vessel, and can increase the potential for by-product formation when used with reactive electrophiles. We thus opted to interrogate alternative quench procedures, starting with an exploration of a co-addition protocol (*i.e.* a solution of the ketone and electrophile is added to a solution of the base). In contrast to the internal quench, the co-addition protocol supplies an equimolar amount of ketone and electrophile to the reaction mixture, thus potentially reducing side reactions involving base and electrophile. As depicted in Scheme 3, use of this co-addition protocol afforded an improved 82% yield of enol phosphate **4**. Encouraged by this improvement, we extended these studies to the more practically-convenient reverse addition protocol, whereby base **2** was added dropwise into the reaction mixture already containing the electrophile, ketone, and additive. Pleasingly, under these revised conditions, we were able to isolate the enol phosphate product **4** in a high yield of 80%. Although compared to the co-addition protocol the isolated yield was slightly lower, in terms of overall process time and ease of application, the reverse addition proved to be the most effective approach, and was utilised in subsequent optimisations.

Next, our attention turned towards exploring more accessible, room temperature conditions. While higher reactivity of



Scheme 3 Studies on the quench protocol using dialkylmagnesium base **2**.

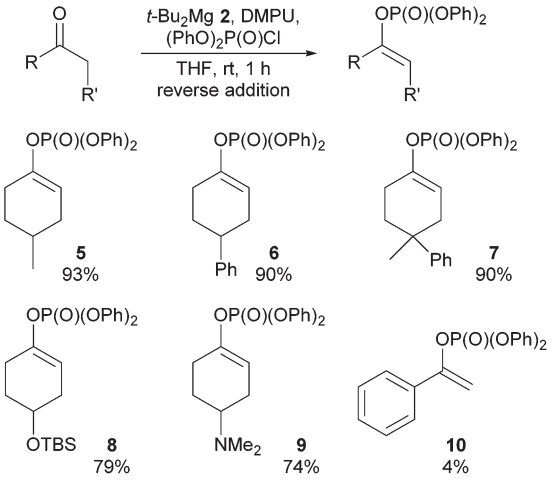
Table 2 DMPU loading study at room temperature using base **2**



Entry	DMPU eq.	Yield[a]
1	0	84%
2	0.5	86%
3	1	88%
4	1.5	90%
5	2	91%
6	3	94%
7	4	95%
8	5	93%

Reaction conditions: 4-*tert*-butylcyclohexanone **3** (1 mmol), base **2** (0.5 mmol), diphenylphosphoryl chloride (1 mmol), THF (11 mL), reverse addition. [a] Average isolated yield over two runs.

Table 3 Substrate scope under optimised conditions using base **2**



Reaction conditions: ketone (1 mmol), base **2** (0.5 mmol), DMPU (4 mmol), diphenylphosphoryl chloride (1 mmol), THF (11 mL), reverse addition. Average isolated yield over two runs.

the base was expected at room temperature, the importance of the DMPU additive was also investigated at various loadings. Firstly, however, the deprotonation reaction was carried out at room temperature without any DMPU additive, and as observed in entry 1, Table 2, the reaction afforded a good 84% yield of enol phosphate **4**. Addition of DMPU to the reaction mixture resulted in an increase in reactivity, as observed in entries 2–7, Table 2, where, starting from 86% yield with 0.5 eq. of DMPU (entry 2, Table 2), an excellent 95% isolated yield of enol phosphate **4** was obtained when 4 eq. of the additive was employed (entry 7, Table 2). In contrast to these accessible, room temperature conditions, use of more conventional lithium amide bases in the formation of **4** generally involves the use of a slight excess (1.1–1.3 eq.) of base at −78 °C.[10] Increasing the amount of DMPU additive beyond 4 eq. did not result in further improvements (entry 8, Table 2). Thus, with an optimal set of reaction conditions in hand, the efficacy of our developed carbon-centred magnesium base protocol was explored across a range of substrates.

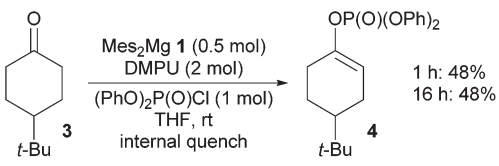
Substrate scope with *t*-Bu$_2$Mg 2

We first investigated the reactivity of **2** with various 4-substituted cyclohexanones, as presented in Table 3. The steric impact of the substituent at the 4-position of the cyclohexanone was explored initially with the relatively small methyl unit and the planar phenyl group, with the corresponding enol phosphates **5** and **6** being isolated in excellent 93% and 90% yields, respectively. When a substrate bearing a more hindered, all-carbon quaternary centre at the 4-position was employed, the corresponding enol phosphate **7** was still delivered in an excellent 90% yield. In relation to the presence of heteroatoms in the substrate, the bulky 4-(*tert*-butyldimethyl)silyloxy substituent was compatible with our developed conditions, with enol phosphate **8** delivered in a good 79% yield. The presence of the potentially coordinating dimethylamino unit also proved to be applicable, allowing isolation of the corresponding enol phosphate **9** in 74% yield. Having observed excellent reactivity across a range of 4-substituted cyclohexanones, we then extended the scope to include acyclic aryl methyl ketones, starting with the parent acetophenone. Surprisingly, in this case only a trace amount (4%) of product **10** was isolated. Instead, a large number of side reactions were observed. Among the various by-products, the product resulting from addition reaction of the base with the electrophile, and the aldol product were detected.

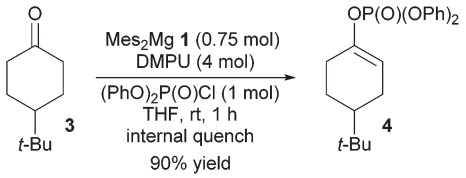
Further attempts to optimise the yield of product **10** using base **2** were unsuccessful. The high reactivity of this base was proposed to be responsible for the various side reactions; therefore, we turned our attention to dimesitylmagnesium **1**, which we had already established as being less reactive than **2**, and, in turn, a potentially more selective bases species.

Optimisation of enol phosphate formation using Mes$_2$Mg 1

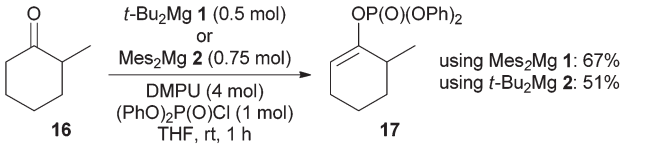
As with our initial studies with di-*tert*-butylmagnesium **2**, upon switching to dimesitylmagnesium **1**, we first focused on optimising the enol phosphate formation with benchmark ketone **3**. Bearing in mind the improvements observed when base **2** was employed at room temperature, we first examined this variable. As depicted in Scheme 4, the deprotonation reac-



Scheme 4 Room temperature enol phosphate formation using base **1**.



Scheme 5 Enol phosphate formation with a modest excess of base.



Scheme 6 Kinetic selectivity of the carbon-centred magnesium base system.

tion afforded an improved yield of 48% when base **1** was employed at room temperature, and, as before, quenching the reaction after 16 h instead of 1 h afforded the same yield of product.

Although various quench protocols were again explored (see ESI†), the more classical internal quench protocol delivered the best results in this case with dimesitylmagnesium **1**. We continued the optimisation by exploring the additive loading, and, as with base **2**, a loading of 4 eq. of DMPU delivered the most favourable outcome (see ESI†), improving the yield to a moderate 57%. We next examined the quantity of base used in the reaction. As shown in Scheme 5, employing only a relatively modest excess of base afforded an excellent 90% yield of enol phosphate product **4**. The electrophile stoichiometry was also explored (using 0.5 mol base), but no appreciable overall improvement was observed (see ESI†).

Pleased by this overall enhancement, we then returned to the aryl methyl ketones, to explore the reactivity of base **1** with a range of these more challenging substrates.

Substrate scope with Mes_2Mg 1

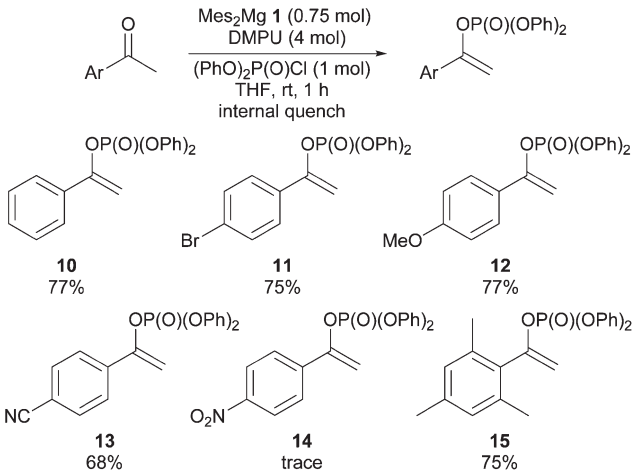
As shown in Table 4, and under the optimised conditions defined using base **1** in Scheme 5, the enol phosphate product **10**, derived from acetophenone, was isolated in 77% yield; this constitutes a dramatic improvement from the trace amounts obtained using base **2**. We then explored various acetophenone derivatives to further expand the scope of this process (Table 4). The 4-bromo derivative of acetophenone afforded a good 75% yield of product **11**. Notably, the halogen group remained intact, as observed previously with the use of carbon-centred magnesium bases,[6a,b] and no products derived from Br–Mg exchange were observed. Electron-rich enol phosphate **12**, bearing a 4-methoxy group, was obtained in a good 77% yield. Interestingly, with the 4-cyano-substituted analogue, a 68% yield of product **13** was obtained, and, notably, no addition of the mesitylene group onto the cyano unit was observed under the room temperature reaction conditions.

Disappointingly, however, the presence of a nitro group in the substrate resulted in only trace quantities of product **14** (3%) being obtained. We attribute this result to reaction of the nitro unit with the magnesium base.

Having investigated functional group compatibility, our attention then turned to a more sterically demanding substrate. The bulky mesityl methyl ketone afforded the corresponding enol phosphate product **15** in 75% yield. Overall and by way of contrasting with the accessible room temperature conditions developed here for the ready application of these more sensitive acyclic ketone substrates, the lithium amide base-mediated formation of enol phosphates **10**,[10a,b,11] **12** and **13** [12] all employ the considerably lower temperature of −78 °C.

Finally, having explored the reactivity and substrate scope of our bases, we turned our attention to the regioselectivity exhibited under our developed reaction conditions. Previous studies have shown that carbon-centred bases **1** and **2** allowed access to kinetic enolate products,[6b] but this selectivity was only studied at low temperatures. We therefore applied our optimised room temperature conditions to unsymmetrical ketone **16** (Scheme 6), and, pleasingly, both bases afforded the kinetic enol phosphate **17** in good yields (51–67%) with no thermodynamic enol phosphate isomer detected. However, the increased bulk in the vicinity of the ketone would have appeared to have influenced the reactivity, as the overall efficiency of the transformation is slightly lower when compared to the yields for enol phosphates **4–9**.

Table 4 Aryl methyl ketone substrate scope using base **1**



Average isolated yields over two runs are presented.

Conclusions

We have successfully developed an efficient and practically straightforward protocol for the synthesis of enol phosphates using carbon-centred magnesium bases. The process is charac-

terised by short reaction times, ambient temperature conditions, and high reaction selectivities. The use of *t*-Bu_2Mg, **2**, under a reverse addition protocol, delivered high reactivity in the case of 4-substituted cyclohexanone substrates. In contrast, Mes_2Mg, **1**, a less reactive base, allowed the formation of enol phosphates from more sensitive ketones, bearing a variety of functional units. The stability of the products, and the facile process developed herein using carbon-centred bases **1** and **2**, enables the enol phosphate products to be utilised as more readily accessible substrates for future synthetic challenges, which we will report on in due course.

Acknowledgements

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