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Highly Alkyl-Selective Addition to Ketones with Magnesium Ate Complexes Derived from Grignard Reagents

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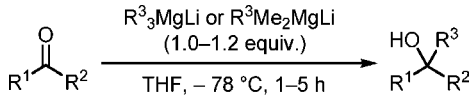
ABSTRACT



Highly alkyl-selective addition

A highly efficient alkyl-selective addition to ketones with magnesium ate complexes derived from Grignard reagents and alkyllithiums is described. The nucleophilicity of R in R_3MgLi is remarkably increased compared to that of the original RLi or RMgX, while the basicity of R_3MgLi is decreased. Furthermore, a highly *R*-selective addition to ketones is demonstrated using RMe_2MgLi in place of R_3MgLi.

While Grignard and organolithium reagents continue to remain popular choices for C−C bond formation in organic chemistry,[1−3] their reactions with ketones can, on occasion, give rise to reduction products or aldol addition adducts/starting ketone due to competing enolization problems.[4] In light of this, we decided to examine the reactions of a range of "typical" ketones with various metal "ate" complexes, formed from Grignard reagents and organolithiums[5−7] to see if this rise to improved results; we report here our findings.

First, *n*-Bu-addition to acetophenone **1** was examined with various common lithium and/or magnesium reagents (1.0 equiv in *n*-hexane or *n*-heptane solution) in THF at −78 °C for 5 h (Table 1). *n*-BuLi gave the corresponding alcohol **2** in 62% yield along with 7% of an undesired aldol product **3**, since it is sufficiently basic to generate enolate from **1** (entry 1). Grignard reagent *n*-BuMgCl was similarly ineffective and gave **2** in 50% yield, **3** in 9% yield, and the reduced product **4** in 8% yield (entry 2). *n*-Bu_2Mg gave rise to a better conversion than traditional *n*-BuLi and *n*-BuMgCl, although the selectivity of **2** decreased, along with an increase

(1) (a) Wakefield, B. J. *Organomagnesium Methods in Organic Chemistry*; Academic Press: San Diego, 1995. (b) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996. (c) Richey, H. G., Jr. *Grignard Reagents: New Development*; Wiley: Chichester, 2000.

(2) Reviews: (a) Lai, Y.-H. *Synthesis* **1981**, 585−604. (b) Eisch, J. J. *Organometallics* **2002**, *21*, 5439−5463. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320.

(3) Inoue, A.; Shinokubo, H.; Oshima, K. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 25−36.

(4) Grignard reagent with $CeCl_3$: (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *38*, 4233−4236. (b) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *39*, 4763−4766. (c) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(5) (a) Uchiyama, M.; Kondo, Y.; Sakamoto, T. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 29−41. (b) Uchiyama, M. *J. Pharm. Soc. Jpn.* **2002**, *122*, 29−46. (c) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081−2091.

(6) (a) Schulze, V.; Hoffmann, R. W. *Chem. Eur. J.* **1999**, *5*, 337−344. (b) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481−2483. (c) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841−4844. (d) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oxhima, K. *J. Org. Chem.* **2001**, *66*, 4333−4339. (e) Inoue, A.; Kondo, J.; Shinokubo, H.; Oshima, K. *Chem. Eur. J.* **2002**, *8*, 1730−1740. (f) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **2003**, *44*, 2033−2035.

(7) (a) Ashby, E. C.; Chao, L.-C.; Laemmle, J. *J. Org. Chem.* **1974**, *39*, 3258−3263. (b) Richery, H. G., Jr.; DeStephano, J. P. *J. Org. Chem.* **1990**, *55*, 3281−3286.

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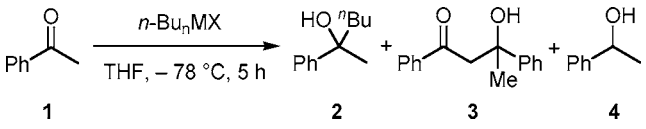
Table 1. Addition to Acetophenone **1** with Li- or Mg-alkyl Reagents



1 2 3 4

		yield (%)		
entry	n-Bu$_n$MX[a]	**2**	**3**	**4**
1	n-BuLi	62	7	0
2	n-BuMgCl	50	9	8
3	n-Bu$_2$Mg	48	27	20
4[b]	***n*-Bu$_3$MgLi**	**82**	**0**	**0**

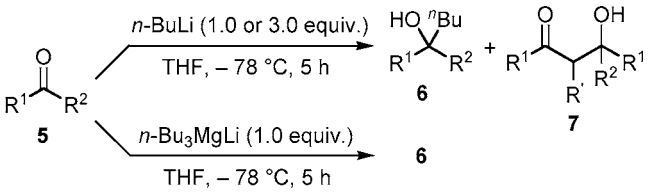
[a] n-Bu$_n$MgX (1.0 equiv) was used. [b] n-Bu$_3$MgLi was prepared in situ from 1 equiv each of n-BuLi and n-Bu$_2$Mg.

in byproducts **3** and **4**. These results indicate that the careful control of alkyl reagents between the minimum basicity and maximum nucleophilicity is necessary to achieve the desired addition to a ketone.[8] When we examined the ate complex n-Bu$_3$MgLi, which is easily generated in situ from a 1:1 mixture of n-BuLi and n-Bu$_2$Mg, we found that it exhibited high reactivity and gave **2** in 82% yield, with no side reactions.

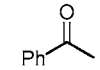
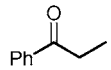
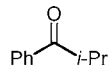
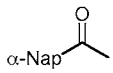
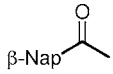
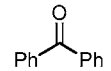
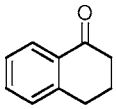
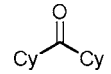
Encouraged by these results with n-Bu$_3$MgLi, we next examined the scope of its reaction with ketones of general structure **5** with n-Bu$_3$MgLi in comparison with n-BuLi (Table 2). However, even 3.0 equiv of n-BuLi could not bring about a full conversion to product **6** in several cases (see data in parentheses in entries 1, 4, and 7). Interestingly, we found that the addition of equimolar 2,2′-bipyridyl (Bpy) to n-Bu$_3$MgLi was quite effective at accelerating the butylation of acetophenone; this giving the corresponding alcohol in 96% yield as the sole product without a self-aldol reaction (entry 1).[9] The other alkylphenyl ketones reacted readily with n-Bu$_3$MgLi/Bpy, as evidenced by the reaction of propiophenone which proceeded readily to give the alcohol product **6** in 97% yield (entry 2); isobutyrophenone also showed an enhancement in yield with n-Bu$_3$MgLi as did acetophenone (entry 3 vs entry 1). n-Bu$_3$MgLi/Bpy was suitable for other aromatic ketones such as α- and β-acetonaphthone which gave the corresponding alcohols in improved respective yields of 71%[10] and 93% compared to n-BuLi (entries 4 and 5). For the cyclic ketone, α-tetralone, the corresponding alcohol was again formed in higher (77%) yield with n-Bu$_3$MgLi/Bpy (entry 7). When n-Bu$_3$MgLi/Bpy was reacted with dicyclohexyl ketone, no significant advantages were noted and the products were obtained in almost the same yield (95%) as with n-BuLi (entry 8). Significantly, a troublesome aldol and/or reduction reaction did not occur under any of the conditions tested in n-Bu$_3$MgLi systems. Thus, the n-Bu$_3$MgLi reagent rather than n-BuLi or n-BuMgCl has an ideal nucleophilicity and a negligible basicity that makes it ideal for addition to ketones.

With regard to the effect of Bpy, n-Bu$_3$MgLi prepared with n-BuLi (2.0 equiv) and n-BuMgCl (1.0 equiv) was found to be useful for this butylation *without* additives and gave **6** in 99% yield (data in brackets in entry 1, Table 2).[11] A magnesium ate complex with a *homo* component [e.g., R$_3$MgLi, prepared from RLi (2.0 equiv) and RMgX (1.0 equiv)] was examined in its reaction with benzophenone **8**

Table 2. Addition to Ketones **5** with n-Bu$_3$MgLi[a,b]



5 6 7

		yield (%) of **6** and **7**			
		n-BuLi		n-Bu$_3$MgLi/Bpy	
entry	ketone (**5**)	**6**	**7**	**6**	**7**
1		62 (77)[c]	7 (0)[c]	**96** [**99**][d]	**0** [**0**][d]
2		90	0	**97**	**0**
3		53	0	**80**	**0**
4		45 (63)[c]	0 (0)[c]	**71**	**0**
5		61	4	**93**	**0**
6		58	–	**80**	–
7		39 (52)[c]	0 (0)[c]	**77**	**0**
8		96	0	**95**	**0**

[a] Reactions were carried out in THF at −78 °C for 5 h with ketone and n-BuLi (1.0 equiv) or n-Bu$_3$MgLi (1.0 equiv)/Bpy (1.1 equiv). n-Bu$_3$MgLi was prepared in situ from 1 equiv each of n-BuLi and n-Bu$_2$Mg, except for d in entry 1. [b] No reduced products were obtained in any of the runs. [c] Isolated yield when 3.0 equiv of n-BuLi were used. [d] n-Bu$_3$MgLi prepared with n-BuLi (2.0 equiv) and n-BuMgCl (1.0 equiv) was used without Bpy.

(8) (a) Sassian, M.; Panov, D.; Tuulmets, A. *Appl. Organomet. Chem.* **2002**, *16*, 525−529. (b) Tuulmets, A.; Panov, D.; Sassian, M. *Tetrahedron Lett.* **2003**, 3943−3945. (c) Sussian, M.; Tuulmets, A. *Helv. Chim. Acta* **2003**, *86*, 82−90.

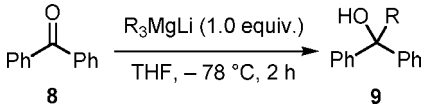
(9) 12-Crown-4 instead of Bpy was also an effective activator, and **2** was obtained in 99% yield under the same reaction conditions.

(10) Interestingly, with α-acetonaphthone, 2-(α-naphthyl)-2-butanol (Et-adduct) was obtained in 16% yield in entry 4. The ethyl-moiety in the butyl-unit may migrate to the carbonyl, with carbon−carbon bond cleavage and the release of ethylene. Detailed mechanistic studies are now underway.

(11) These additives, such as Bpy and 12-crown-4, generally did not have any effects with other R$_3$MgLi prepared from RLi and RMgX, and such effects were only observed with n-Bu$_2$Mg. These additives may affect the effective ate complexation of n-Bu$_3$MgLi from n-Bu$_2$Mg as a magnesium source, although the details are still unclear.

and gave the desired product in high yield without reduction products (Table 3).

Table 3. Addition to Benzophenone **5** with R_3MgLi



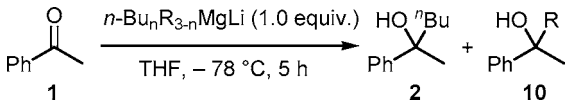
entry	R_3MgLi	yield (%) of **9**
1[a]	*n*-Bu_3MgLi	95
2[b]	Ph_3MgLi	87
3[c]	Me_3MgLi	>99
4[d]	Et_3MgLi	64

[a] *n*-Bu_3MgLi: 2 equiv of *n*-BuLi and 1 equiv of *n*-BuMgCl. [b] Ph_3MgLi: 2 equiv of PhLi and 1 equiv of PhMgBr. [c] Me_3MgLi: 2 equiv of MeLi and 1 equiv of MeMgBr. [d] Et_3MgLi: 2 equiv of EtLi and 1 equiv of EtMgBr.

n-Bu_3MgLi, Ph_3MgLi, and Me_3MgLi gave **9** in respective yields of 95%, 87%, and >99% (entries 1, 2, and 3). A dramatic enhancement in reactivity was observed with Et_3MgLi to afford **9** in 64% yield, since ethylation with 1.2 equiv of EtLi showed 37% yield[12] while that with 1.2 equiv of EtMgBr showed 14% yield (entry 4).

Next, we turned our attention to *hetero* magnesium ate complexes, i.e., $R^1R^2_2MgLi$ ($R^1 \neq R^2$), instead of *homo* magnesium ate complexes such as R_3MgLi. Considering the atom economy of alkylation, the alkyl source (R) in magnesium ate complexes of R_3MgLi is not consumed completely during the reaction and the remaining R source would be sacrificed. This prompted us to examine $R^1R^2_2MgLi$ in the alkylation to ketones. The key to success here is likely the choice of a second alkyl source (R^2) in $R^1R^2_2MgLi$ complexes, which can be replaced as an unreactive "dummy". Me and Ph were found to be good inactive components in *n*-Bu_2RMgLi-type complexes and gave the Me-adduct (8%) and Ph-adduct (8%) as minor products **10** in the alkylation of acetophenone **1** (entries 1 and 2, Table 4). In both cases, the *n*-Bu-adducts **2** were the major products (77−78% yield)

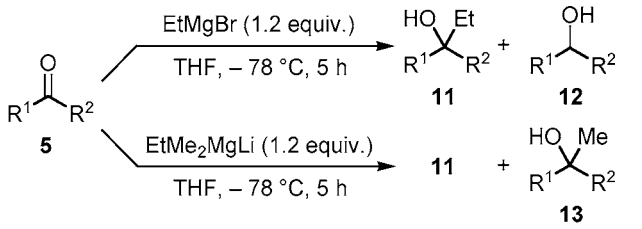
Table 4. Addition to Acetophenone **1** with *n*-$Bu_nR_{3-n}MgLi$[a,b]

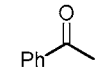
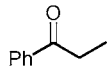
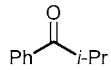
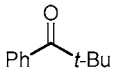
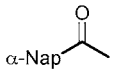
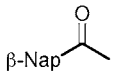
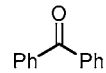
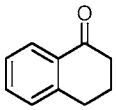
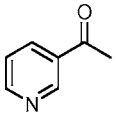
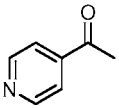


		yield (%)	
entry	*n*-$Bu_nR_{3-n}MgLi$	**2**	**10**
1	*n*-$Bu_2MeMgLi$	78	8
2	*n*-$Bu_2PhMgLi$	77	8
3	***n*-$BuMe_2MgLi$**	**72**	**26**
4	*n*-$BuPh_2MgLi$	57	41
5	*n*-Bu(*t*-Bu)$_2MgLi$	61	23

[a] Reactions of **1** with *n*-$Bu_nR_{3-n}MgLi$ (1.0 equiv) were carried out in THF at − 78 °C for 5 h. [b] No aldol and/or reduced products were obtained in any of the runs.

Table 5. Ethylation to Ketones **5** with $EtMe_2MgLi$ Reagents[a,b]



		yield (%) with EtMgBr		yield (%) with $EtMe_2MgLi$	
entry	ketone (**5**)	**11**	**12**	**11**	**13**
1		71	0	**93**	6
2		77	0	**93**	7
3		36	11	**92**	8
4		0	50	**89**	11
5		35	9	**94**	4
6		66	9	**95**	5
7		14	68	**>99**	<1
8		36	9	**89**	7
9[c]		56	39	**96**	4
10[c]		41	48	**97**	3

[a] Reactions of **5** with EtMgBr (1.2 equiv) or $EtMe_2MgLi$ (1.2 equiv) were carried out in THF at −78 °C for 5 h. [b] No reduced products **12** were obtained in any of the runs under $EtMe_2MgLi$ conditions. [c] Reaction time was 1 h.

(cf. entry 4, Table 1). In sharp contrast to the results with *n*-Bu_2RMgLi, a clear difference was observed between Me and Ph components in the *n*-BuR_2MgLi-type complexes, although it is not clear why a Me-moiety is more favorable than other "dummies". Despite the decrease in Bu groups present, the *n*-Bu-adduct **2** could be obtained in 72% yield as the major product (entry 3), while *n*-$BuPh_2MgLi$ did not lead to good alkyl selectivity (entry 4). While the yield of the *n*-Bu-adduct **2** with *n*-$BuMe_2MgLi$ was the same as that with *n*-$Bu_2MeMgLi$, the efficiency of *n*-Bu addition with

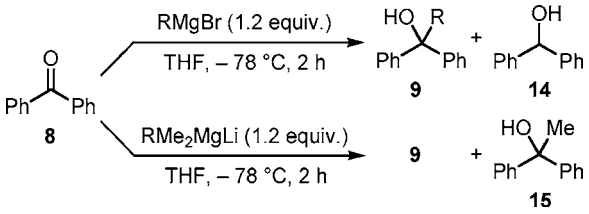
n-BuMe$_2$MgLi (72%) was superior to that with *n*-Bu$_2$MeMgLi (39% based on total *n*-Bu). Furthermore, the sterically more demanding *t*-Bu was inferior to Me as an inactive moiety (entry 5 vs entry 3).

Using RMe$_2$MgLi systems, we examined the ethylation to ketones. Due to the instability and difficulty of preparing and handling EtLi,[12] there are still limitations with traditional methods, such as with the use of a common Grignard reagent (EtMgX). In fact, ethylations to ketones **5** with Grignard reagent (EtMgBr) either failed or gave only a moderate yield (Table 5). In particular, the reaction of 2,2-dimethylpropiophenone with EtMgBr failed to give any of the desired product **11**; instead the reduced product **12** was obtained in 50% yield. By way of contrast, the corresponding reaction proceeded quite smoothly with the EtMe$_2$MgLi ate complex and gave the desired Et-adduct **11** in 89% yield (entry 4). For other low-yield examples (14∼36%) with EtMgBr such as isobutyrophenone, α-acetonaphthone, benzophenone and α-tetralone, EtMe$_2$MgLi showed high selectivities for the Et-adduct **11** as opposed to the Me-adduct **13**, giving the desired product in extremely high yield (89∼>99%) (entries 3, 5, 7, and 8). Although EtMgBr gave fair results with acetophenone, propiophenone and *β*-acetonaphthone (66∼77%), further improvements were observed with EtMe$_2$MgLi; with Et-adducts **11** were obtained in 93−95% yield (entries 1, 2 and 6). With a heterocyclic compound such as pyridine, EtMe$_2$MgLi gave the corresponding products in 96−97% yield (entries 9 and 10). Undesired Me-adducts **13** could be easily separated by SiO_2 flash column chromatography, although the selectivities between **11** and **13** were in fact high or perfect.

Finally, alkylations with other RMe$_2$MgLi systems were performed with benzophenone **8** at −78 °C for 2 h (Table 6). As expected, alkylations with *i*-PrMe$_2$MgLi, *n*-PrMe$_2$-MgLi, and *n*-BuMe$_2$MgLi with high selectivities for the corresponding R-adducts **9** in high yields of the products were also apparent. Comparable Grignard reagents were totally ineffective and gave significant amounts of the reduced byproducts **14**. In particular, dramatic results were seen with *n*-BuMe$_2$MgLi where the yield was improved from 0% to 92% (entry 4).

(12) EtLi is now commercially available from Aldrich. Direct ethylation to ketones with EtLi is not suitable at all. As another example, EtLi with **1** gave 34% of **2** along with 7% of **3**.

Table 6. Addition to Benzophenone **8** with RMe$_2$MgLi Reagents[a,b]



		yield (%) with RMgBr		yield (%) with RMe$_2$MgLi	
entry	R	**9**	**14**	**9**	**15**
1	Et	14	68	>**99**	<1
2	*i*-Pr	48	36	**87**	0
3	*n*-Pr	15	56	**88**	12
4[c]	*n*-Bu	0	56	**92**	8

[a] Reactions of **8** with RMgBr (1.2 equiv) or RMe$_2$MgLi (1.2 equiv) were carried out in THF at −78 °C for 2 h. [b] No reduced products **14** were obtained in any of the runs under RMe$_2$MgLi conditions. [c] *n*-BuMgCl was used.

In summary, we have developed a highly efficient alkyl-selective additions to ketones using magnesium ate complexes derived from Grignard reagents and alkyllithiums. Remarkable improvements were observed with the R$_3$MgLi ate complex systems. Furthermore, we have demonstrated that RMe$_2$MgLi as a R^{1}R$^2_2$MgLi ate complex system can be used for highly selective alkylmetal addition to ketones. These reactions are currently still under investigation in an effort to further expand the scope of this process, in particular, to aldehydes, esters, amides, imines, and α,*β*-unsaturated carbonyl compounds.

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Supporting Information Available: Experimental procedures for addition to ketones with R$_3$MgLi or RMe$_2$MgLi reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

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