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Highly Efficient Alkylation to Ketones and Aldimines with Grignard Reagents Catalyzed by Zinc(II) Chloride

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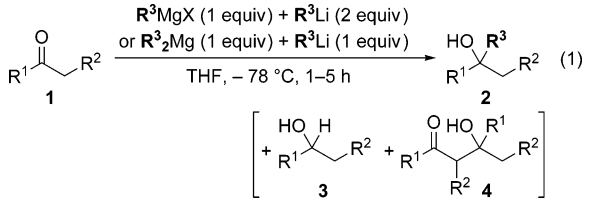
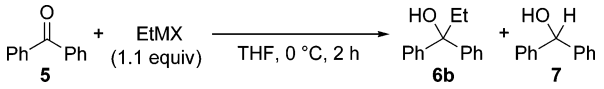
For carbon−carbon bond-forming reactions, the addition of organometal reagents to ketones is a versatile method for synthesizing tertiary alcohols.[1,2] However, Grignard and alkyllithium reagents for ketones (**1**) give the desired adducts (**2**) along with (1) competitive reduction products (**3**) due to the β-hydride transfer of alkyl groups and (2) aldol adducts (**4**) due to enolization by their strong basicity (eq 1).[3] Recently, the addition of stoichiometric or an excess amount of $CeCl_3$,[3] LiCl,[4] $LiClO_4$,[5] $FeCl_2$,[6] and $LnCl_3$·2LiCl[7] with Grignard reagents has shown good results with smooth alkylations and minimum side products. These additive effects were based on either a stoichiometric Lewis acid activation of carbonyl compounds or enhancement of the nucleophilicity of stoichiometric alkylation reagents (e.g., $RCeCl_2$, $RMgCl_2$·Li, etc.), which were prepared in situ from oligomeric Grignard reagents by binary metal complexations or transmetalations. While somewhat expensive $LnCl_3$ (Ln = La, Ce) salts have been the best alternatives to date, these stoichiometric compounds must be synthesized prior to use.[3,7] In our previous research, trialkylmagnesium(II) ate complexes, as good alkylation reagents with weak basicity, namely, R_3MgLi, which can be easily prepared from Grignard reagents (RMgX) and alkyllithiums (RLi) in situ,[8] have improved the efficiency of alkylation to ketones (eq 1).[9] However, in that case, more than equimolar amounts of expensive RLi (1−2 equiv) were indispensable. To overcome these problems, we report here the highly efficient alkylation to ketones and aldimines with Grignard reagents in the presence of *catalytic* trialkylzinc(II) ate complexes ($R_3ZnMgCl$) derived from $ZnCl_2$ in situ. The *catalytic* use of *simple and inexpensive* $ZnCl_2$ without further purification, instead of above stoichiometric additives, would offer significant advantage over the existing technologies.



First, ethylation to benzophenone (**5**) with organometal reagents (1.1 equiv) was examined in THF at 0 °C for 2 h. EtLi, EtMgCl, EtMgBr, and Et_2Zn were ineffective, and the Et adduct (**6b**) was obtained in 0−64% yield along with a large amount (up to 78%) of the undesired reduction product (**7**) (Table 1, entries 1−4). A salt effect of LiCl, $LiOBu^t$, or $LiClO_4$ with EtMgCl or Et_2Zn for **5** was not clearly observed (entries 5−8). However, the combined use of EtMgCl (1.1 equiv) and Et_2Zn (1.1 equiv), that is, in situ preparation of stoichiometric $Et_3ZnMgCl$, promoted the Et addition reaction, and **6b** was obtained in 85% yield as a major product (entry 9). Interestingly, a catalytic amount of Et_2Zn (10 mol %), which led to 10 mol % of $Et_3ZnMgCl$, was still effective and gave **6b** in 84% yield (entry 10). Preparation of $Et_3ZnMgCl$ from $ZnCl_2$ (10 or 5 mol %) and EtMgCl (1.3 or 1.2 equiv) also gave the desired tertiary alcohol **6b** in 84 or 70% yield, respectively (entries 11 and 12).[10,11] We thus can come to use convenient RMgX independent of the availability of dialkylzinc reagents (R_2Zn). Therefore, we

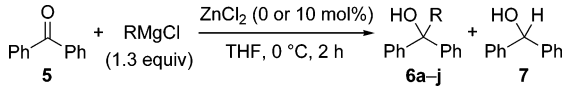
Table 1. Ethylation to Benzophenone with Organometal Reagents[a]



entry	EtMX	yield (%) of **6b** [**7**]	entry	EtMX	yield (%) of **6b** [**7**]
1	EtLi	64 [30]	7	EtMgCl + $LiClO_4$	18 [57]
2	EtMgCl	25 [71]	8	Et_2Zn + LiCl	0 [0]
3	EtMgBr	20 [78]	9	EtMgCl + Et_2Zn	85 [6]
4	Et_2Zn	5 [0]	10[b]	EtMgCl + cat. Et_2Zn	84 [15]
5	EtMgCl + LiCl	22 [70]	11[c]	EtMgCl + cat. $ZnCl_2$	84 [15]
6	EtMgCl + $LiOBu^t$	22 [70]	12[d]	EtMgCl + cat. $ZnCl_2$	70 [28]

[a] EtMX (1.1 equiv) was used unless otherwise noted. [b] EtMgCl (1.1 equiv) and Et_2Zn (10 mol %) were used. [c] EtMgCl (1.3 equiv) and $ZnCl_2$ (10 mol %) were used. [d] EtMgCl (1.2 equiv) and $ZnCl_2$ (5 mol %) were used.

Table 2. Alkylation to Benzophenone Catalyzed by $ZnCl_2$



entry	R		Yield (%) of **6** [**7**] with Zn	Yield (%) of **6** [**7**] without Zn	entry	R		Yield (%) of **6** [**7**] with Zn	Yield (%) of **6** [**7**] without Zn
1	Me	**6a**	94 [0]	91 [0]	6	*s*-Bu	**6f**	50 [23]	43 [26]
2	Et	**6b**	84 [15]	25 [72]	7[a]	*c*-Hex	**6g**	57 [9]	51 [14]
3[a]	*n*-Pr	**6c**	71 [29]	14 [86]	8	vinyl	**6h**	96 [0]	92 [0]
4	*i*-Pr	**6d**	75 [10]	62 [14]	9	allyl	**6i**	>99 [0]	>99 [0]
5[b]	*n*-Bu	**6e**	74 [24]	11 [81]	10	Bn	**6j**	>99 [0]	90 [0]

[a] Solvent was Et_2O. [b] $ZnCl_2$ (30 mol %) and *n*-BuMgCl (1.7 equiv) were used.

next examined other alkylations to **5** with various Grignard reagents (1.3 equiv) in the presence of 10 mol % of $ZnCl_2$ (Table 2). As expected, some alkylations with only Grignard reagents gave rise to reduction product **7** in considerable yield. In contrast, with the use of 10 mol % of $ZnCl_2$, not only Et adduct **6b** but also Me, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu, and *c*-Hex adducts (**6a,c**−**g**) were obtained with improvements in decreasing side product **7** (entries 1 and 3−7). Vinyl, allyl, and Bn addition, in which β-H transfer (i.e., reduction) is not probable, also proceeded with slight improvements in yield for **6h**−**j** when 10 mol % of $ZnCl_2$ was added (entries 8−10).

Next, isopropylation to ketone **8** with *i*-PrMgCl (1.3 equiv) in the presence of 10 mol % of $ZnCl_2$ was examined because *sec*-RMgX often prefers reduction to the desired alkylation (Table 3). For aryl or heteroaryl ketones, the reactions proceeded smoothly to give the desired *i*-Pr adducts (**9**) in >75% yield (entries 1−3 and 5−11). Double isopropylation to an ester gave **9c** in 80% yield (entry 4). Aliphatic ketones, such as cyclohexanone and 2-adamantanone, were also suitable for this alkylation system using catalytic $ZnCl_2$, and isopropylation was improved to 51−52% yield (entries 12 and 13). Particularly, 2-alkyl-2-adamantanol is a useful photoresistant material,[12] but the reduction occurs in preference to the desired alkylation when only Grignard reagents are used.[13] In our method, a 100 mmol

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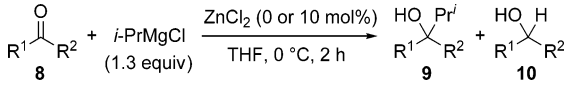
Table 3. Isopropylation to Ketones Catalyzed by $ZnCl_2$

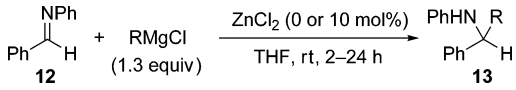


8 9 10

			Yield (%) of **9** [**10**]	
entry	ketone (**8**)		with $ZnCl_2$	without $ZnCl_2$
1	PhC(═O)Me (**8a**)	**9a**	85 [0]	31 [11]
2	PhC(═O)Et (**8b**)	**9b**	95 [0]	56 [38]
3	PhC(═O)Pr^i (**8c**)	**9c**	87 [12]	38 [59]
4[a]	PhC(═O)OEt	**9c**	80 [12]	61 [29]
5	PhC(═O)CF_3 (**8d**)	**9d**	78[b] [20]	23[c] [73]
6	α-NaphC(═O)Me (**8e**)	**9e**	76 [0]	33 [12]
7	β-NaphC(═O)Me (**8f**)	**9f**	76 [0]	35 [12]
8	α-tetralone (**8g**)	**9g**	80 [6]	20 [36]
9	2-thienylC(═O)Me (**8h**)	**9h**	91 [0]	40 [0]
10	3-thienylC(═O)Me (**8i**)	**9i**	86 [0]	29 [8]
11	4-pyridylC(═O)Me (**8j**)	**9j**	80 [7]	73 [11]
12	cyclohexanone (**8k**)	**9k**	60 [−]	43 [−]
13	2-adamantanone (**8l**)	**9l**	52[b] [27]	16[c] [78]

[a] *i*-PrMgCl (2.5 equiv) was used. [b] $ZnCl_2$ (30 mol %), LiCl (1.1 equiv), and *i*-PrMgCl (1.7 equiv) were used. [c] LiCl (1.1 equiv) was added.

Table 4. Alkylation to Aldimine Catalyzed by $ZnCl_2$[a]

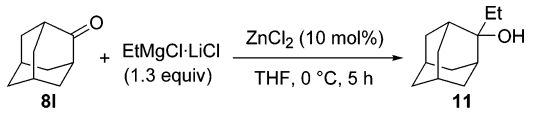


12 13

			Yield (%) of **13**					Yield (%) of **13**	
entry	R		with Zn	without Zn	entry	R		with Zn	without Zn
1[b]	Et	**13a**	81	41	7	*n*-Oct	**13g**	73	54
2[b,c]	*n*-Pr	**13b**	89	65	8	vinyl	**13h**	86	51
3	*i*-Pr	**13c**	82	28	9	allyl	**13i**	>99	>99
4	*n*-Bu	**13d**	81	47	10	Bn	**13j**	>99	>99
5	*s*-Bu	**13e**	88[d]	44	11[b,e]	Et	**14**	90 [10]	80 [20]
6[c]	*c*-Hex	**13f**	73	64	12[b,e]	*i*-Pr	**15**	77 [20]	33 [67]

[a] Reaction time was 24 h unless otherwise noted. [b] Reaction time was 2 h. [c] Solvent was Et_2O. [d] Diastereomeric mixture (ca. 3:2). [e] PhCH═NTs was used instead of **12**. Yields (%) in brackets were $PhCH_2NHTs$.

scale amount of 2-ethyl-2-adamantanol (**11**) was obtained from **8l** in 81% yield (14.6 g) by using EtMgCl/LiCl/$ZnCl_2$ (eq 2).



(2)

8l 15.0 g, 100 mmol — **11** 14.6 g (81%)

[*cf.* without both $ZnCl_2$ and LiCl: 29%, without LiCl: 58% in 30 mmol-scale]

Encouraged by the efficient alkylation to ketones, we next examined aldimine **12** with Grignard reagents in the presence of 10 mol % of $ZnCl_2$ (Table 4). In principle, aldimines are less reactive than ketones due to their weak electrophilic nature, and alkylation with Grignard reagents has not been easy.[2,14] As expected, the alkylation of **12** with only Grignard reagent at room temperature was slow as it progressed to full conversion. In contrast, $ZnCl_2$ promoted the alkylation, and the desired amines **13a**−**j** were obtained in high yield (73−99%) for 2−24 h. Alkylation to *N*-Ts imines also proceeded selectively (entries 11 and 12).[15]

Finally, a plausible catalytic cycle including transition-state assembly in this $ZnCl_2$-catalyzed alkylation to ketones and aldimine with Grignard reagents is shown in Figure 1. Interestingly, $Zn(OTf)_2$ (≥10 mol %) as a strong Lewis acid was not effective. Thus, this unique catalytic system should be based on trialkylzinc(II) ate complexes, $R_3ZnMgCl$. First, $R_3ZnMgCl$ is generated via R_2Zn from $ZnCl_2$ and RMgCl. $R_3ZnMgCl$ reagent coordinates to ketone (or aldimine) at the $[MgCl]^+$ moiety by a six-membered ring chair conformation,[16,17] and then $[R_2Zn-R]^-$ would attack the activated substrate followed by release of the corresponding adduct and the regeneration of $R_3ZnMgCl$. The key to promoting this catalytic system was the careful control of $R_3ZnMgCl$ reagent between the decreased basicity and the increased nucleophilicity from the original Grignard reagent.

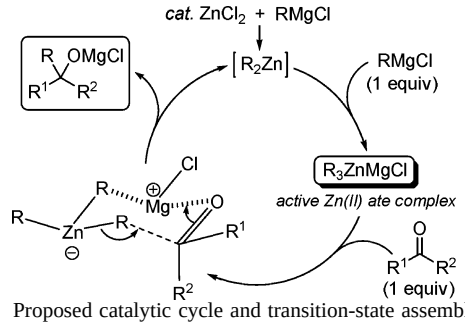


Figure 1. Proposed catalytic cycle and transition-state assembly.

In summary, we have developed a highly efficient alkylation to ketones and aldimines with Grignard reagents using *catalytic* $ZnCl_2$. This simple Zn(II)-catalyzed alkylation via trialkylzinc(II) ate reagents could relieve the serious problems of reduction and aldol reactions and give the desired alkylation products in high yield. Further applications to other reactions mediated by trialkylzinc(II) ate compounds are now under investigation.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The effect of released $MgCl_2$ in entry 11 in Table 1 can be denied because another method without $MgCl_2$ (entry 10) gave the same result.
(11) Other catalysts, such as CuCl, $CuCl_2$, CuCN, $AlCl_3$, $InCl_3$, $MnCl_2$, $FeCl_2$, $MgCl_2$, etc., were not effective in the alkylation to **5** with EtMgCl.
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(15) Et addition to less reactive PhCH═NBn proceeded in 27% yield with catalyst $ZnCl_2$ and in 12% yield without $ZnCl_2$.
(16) When LiCl is used as a co-additive, the $[MgCl]^+$ moiety may change to $[Li]^+$. Further investigations for the mechanistic aspects are underway.
(17) Six-membered ring assembly was proposed as in $(CH_3)_nMLi$ ate complexes (M = Mg, Al, and Zn): Ashby, E. C.; Chao, L.-C.; Laemmle, J. *J. Org. Chem.* **1974**, *39*, 3677. Also see ref 8f.

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