Zinc(II)-catalyzed Grignard additions to ketones with RMgBr and RMgI†

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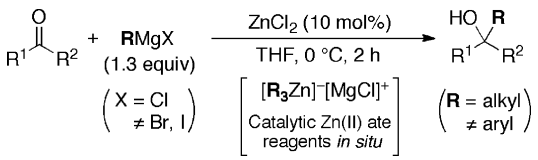
Received (in Cambridge, UK) 11th December 2009, Accepted 19th January 2010
First published as an Advance Article on the web 9th February 2010
DOI: 10.1039/b926243a

Highly efficient alkylations and arylations of ketones with Grignard reagents (RMgBr and RMgI) have been developed using catalytic $ZnCl_2$, Me_3SiCH_2MgCl, and LiCl. Tertiary alcohols were obtained in high yields with high chemoselectivities, while minimizing undesired side products produced by reduction and enolization.

The Grignard addition to ketones and aldehydes has provided a versatile method for synthesizing tertiary and secondary alcohols.[1,2] However, the reaction of carbonyl compounds with Grignard reagents often gives undesired by-products *via* β-H transfer and/or enolization. To avoid these problems, some improvements have been achieved through the use of stoichiometric or excess amounts of inorganic additives.[3] Imamoto *et al.*[4a] and Knochel *et al.*[4b,c] have developed highly useful stoichiometric organolanthanoid complexes, which are prepared prior to use from Grignard reagents (RMgX, X = Cl, Br, I) and lanthanoid(III) chlorides ($CeCl_3$, $LnCl_3$, and $NdCl_3$) by prolonged binary metal complexation (*ca.* 1–2 days). In sharp contrast to procedures involving these lanthanoid reagents, we have developed a $ZnCl_2$-catalyzed alkylation of ketones with RMgCl *via* trialkylzinc(II) ate complexes $[R_3Zn]^-[MgCl]^+$ (Scheme 1).[5,6] Unfortunately, however, the catalytic $ZnCl_2$ system could not be applied to many commercially available RMgBr as well as RMgCl, since RMgBr is readily prepared from RBr/Mg but generally less reactive than RMgCl.[1] To improve our preliminary catalytic system with RMgCl (R = alkyl) as limited Grignard reagents, we devised a highly efficient addition to ketones using RMgBr and RMgI (R = alkyl, aryl) with LiCl along with catalytic amounts of $ZnCl_2$ and trimethylsilylmethyl magnesium chloride ($TMSCH_2MgCl$), which effectively minimizes side reactions.



Scheme 1 $ZnCl_2$-catalyzed RMgCl addition to ketones.

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† Electronic supplementary information (ESI) available: Experimental details and product characterization. See DOI: 10.1039/b926243a

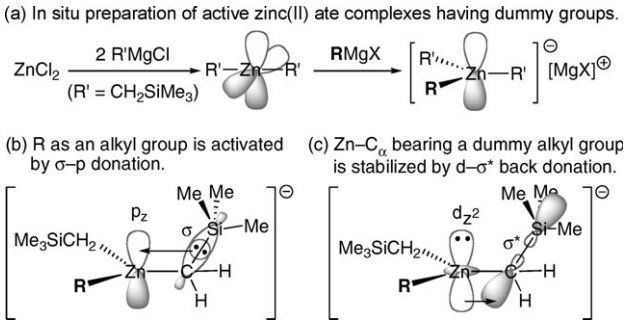
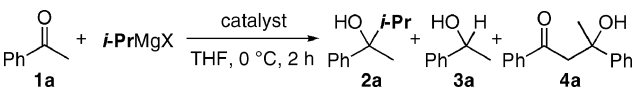


Fig. 1 Design of catalytic zinc(II) ate reagents *in situ*.

The key to the design of further active catalytic zinc(II) ate reagents is the use of dummy alkyl groups, which themselves do not transfer to substrates on alkylation (Fig. 1).[7,8] As a dummy alkyl group, a $TMSCH_2$ (R′) group should be highly attractive,[9,10] since (1) the corresponding mixed zinc(II) ate complexes $[R(TMSCH_2)_2Zn]^-[MgX]^+$ can be quickly prepared *in situ* from commercially available materials such as $ZnCl_2$, $TMSCH_2MgCl$, and RMgX (Fig. 1a), (2) an alkylating R group would be activated by electron transfer through double σ(C–Si)–Zn(p_z) overlaps (Fig. 1b),[11] and (3) two dummy groups ($TMSCH_2$) would be stabilized by back donation through double d_{z^2}(Zn)–σ*(C–Si) overlaps (Fig. 1c).[12] Therefore, the activity of R and $TMSCH_2$ mixed zinc(II) ate complexes should increase with regard to these β-silyl effects.[11]

First we examined the isopropylation of acetophenone (**1a**) with *i*-PrMgX, which is very simple but one of the most difficult Grignard addition reactions (Table 1). The reactions

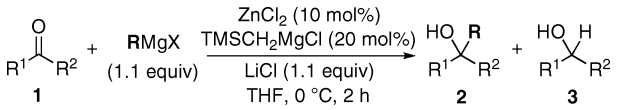
Table 1 Isopropylation of acetophenone (**1a**) catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl

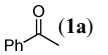
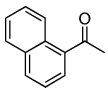
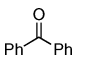
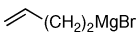
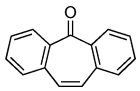
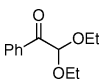
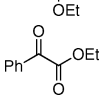


Entry	*i*-PrMgX [equiv.]	$ZnCl_2$ (equiv.)	R′MgCl[a] (equiv.)	LiCl (equiv.)	Yield (%) of 2a	3a	4a
1	*i*-PrMgCl [1.1]	—	—	—	31	11	6
2	*i*-PrMgBr [1.1]	—	—	—	29	24	12
3	*i*-PrMgBr [1.1]	—	—	1.1	42	16	17
4	*i*-PrMgCl [1.3]	0.1	—	—	85	0	7
5	*i*-PrMgBr [1.3]	0.1	—	—	48	9	19
6	*i*-PrMgBr [1.1]	0.1	0.2	—	80	8	6
7	*i*-PrMgBr [1.3]	0.1	—	1.1	84	5	8
8	*i*-PrMgBr [1.1]	0.1	0.2	1.1	96	0	2
9	*i*-PrMgCl [1.1]	0.1	0.2	1.1	99	1	0
10[b]	*i*-PrMgI [1.1]	0.1	0.2	1.1	>99	0	0

[a] R′ = $TMSCH_2$. [b] Et_2O was used as a solvent.

Table 2 Grignard addition to ketones catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



Entry	1	RMgX	Yield (%) of **2** (**3**)[a] With $ZnCl_2$·R′MgCl·LiCl	With $ZnCl_2$	Without $ZnCl_2$·R′MgCl·LiCl
1	 (**1a**)	MeMgI	93 (0)	58 (0)	40 (0)
2		4-FC_6H_4MgBr	92 (0)	88 (0)	86 (0)
3		*i*-PrMgBr	94 (0)	75 (11)	36 (17)
4		*i*-PrMgBr	95 (4)	78 (14)	25 (50)
5		*i*-PrMgBr	81 (0)	56 (0)	51 (0)
6		MeMgI	90 (0)	59 (0)	42 (0)
7		*i*-PrMgBr	85 (5)	55 (19)	16 (36)
8		MeMgI	91 (0)	62 (0)	48 (0)
9		*i*-PrMgBr	83 (0)	55 (0)	30 (2)
10		*n*-OctylMgBr	>99 (0)	90 (5)	91 (7)
11		*i*-PrMgBr	92 (0)	73 (0)	76 (0)
12		*i*-PrMgBr	51	25	27
13		EtMgBr	80 (16)	28 (65)	18 (80)
14		1-NaphMgBr	82 (0)	39 (0)	49 (0)
15		*i*-PrMgBr	82 (0)	49 (0)	41 (0)
16			64 (32)	15 (42)	11 (89)
17		*i*-PrMgBr	94 (6)	37 (41)	11 (89)
18		*c*-HexMgBr	68 (24)	38 (59)	37 (58)
19		*i*-PrMgBr	90 (10)[b]	17 (82)[c]	15 (85)
20		*i*-PrMgBr	72 (25)	39 (58)	30 (65)
21		EtMgBr	71	69	45

[a] R′ = $TMSCH_2$. [b] 0.3 equiv. of $ZnCl_2$, 0.6 equiv. of $TMSCH_2MgCl$, 1.1 equiv. of LiCl, and 1.1 equiv. of *i*-PrMgBr were used. [c] 0.3 equiv. of $ZnCl_2$ and 1.7 equiv. of *i*-PrMgBr were used.

with *i*-PrMgCl, *i*-PrMgBr, and *i*-PrMgBr·LiCl in the absence of catalysts gave mixtures of the desired product (**2a**) and by-products (**3a** and **4a**) (entries 1–3). Our previous method using 10 mol% of $ZnCl_2$ with *i*-PrMgCl improved the yield of **2a** (entry 4), but the combined use of $ZnCl_2$ and *i*-PrMgBr was not effective (entry 5), since this method has been limited to RMgCl.[5b] In sharp contrast, the yield of **2a** was dramatically improved to 80% with the use of 10 mol% of $ZnCl_2$ and 20 mol% of $TMSCH_2MgCl$, even with *i*-PrMgBr (entry 6 *vs.* entries 3 and 5). Moreover, the addition of $ZnCl_2$ and LiCl (1.1 equiv.) to *i*-PrMgBr was found to be effective (entry 7),[3e] and ultimately **2a** was obtained in 96% yield through the use of $ZnCl_2$, $TMSCH_2MgCl$, and LiCl (entry 8). Under the optimized conditions, *i*-PrMgCl and *i*-PrMgI in place of

i-PrMgBr also showed excellent reactivity (entries 9 and 10). Remarkably, the $TMSCH_2$ adduct of **1a** was not obtained in any of the reactions, which strongly indicated that $TMSCH_2$ was effectively a dummy group.

Using the optimized $ZnCl_2$·$TMSCH_2MgCl$·LiCl system, we next examined the catalytic addition of Grignard reagents (RMgBr and MeMgI) to various ketones (Table 2). Without $ZnCl_2$·$TMSCH_2MgCl$·LiCl (*i.e.* traditional Grignard addition conditions) or with only $ZnCl_2$ catalyst, the yields of the desired tertiary alcohols were generally low to medium, due to side reactions. In almost all cases, in addition to undesired reduction, the starting material was recovered *via* enolization/protonation, although a self-aldol product was scarcely obtained due to the steric hindrance of the ketone. However, in the presence of $ZnCl_2$·$TMSCH_2MgCl$·LiCl, not only aromatic ketones, but also heteroaromatic ketones, aliphatic ketones, and biaryl ketones gave the corresponding tertiary alcohols in high yields. Moreover, MeMgI, which is a popular methylation reagent, could be successfully used in this method with minimum recovery of the starting material (entries 1, 6, 8). To our delight, arylation such as 4-fluorophenylation and 1-naphthylation proceeded smoothly under $ZnCl_2$·$TMSCH_2MgCl$·LiCl conditions, while our previous system with $ZnCl_2$ catalyst did not show the conspicuous improvements (entries 2 and 14). Cyclohexylation as 2°-alkylation other than isopropylation (entry 18), and long chain alkylation such as *n*-octylation (entry 10) also proceeded smoothly in the presence of $ZnCl_2$·$TMSCH_2MgCl$·LiCl. Other α-functionalized ketones such as α,α,α-trifluoroacetophenone, an α,α-acetal ketone, and an α-ketoester were explored, and the corresponding α-functionalized tertiary alcohols were obtained in high yields without the decomposition of α-groups (entries 19–21). Overall, this $ZnCl_2$·$TMSCH_2MgCl$·LiCl system may offer a great advantage over traditional Grignard addition or our previous $ZnCl_2$-catalysis, since highly useful but less reactive RMgBr and RMgI rather than RMgCl could be used successfully.

Although further investigation is necessary to fully understand the reaction mechanism,[13] the key in this catalysis is a postulated catalytic alkylating ate complex, $[R(TMSCH_2)_2Zn]^-[Li]^+$. The complex $[R(TMSCH_2)_2Zn]^-[Li]^+$ would be readily generated *in situ* from catalytic $(TMSCH_2)_2Zn$ and RMgX–LiCl reagents. In sharp contrast, $[R_3Zn]^-[MgCl]^+$ has been estimated in the absence of $TMSCH_2MgCl$ and LiCl in our previous $ZnCl_2$ catalysis with RMgCl (Scheme 1).[5b] Along with the β-silyl effect of $TMSCH_2$, which would dramatically activate the anion part of the zinc(II) ate complex (Fig. 1 and Table 1), the postulated active zinc(II) ate complex with $[Li]^+$ as the cation part can rationalize why not only RMgCl but also RMgBr and RMgI can be used in this catalytic system.

In summary, we have developed highly efficient alkylations and arylations of ketones with Grignard reagents (RMgBr and RMgI) using catalytic $ZnCl_2$, $TMSCH_2MgCl$, and LiCl. Desired tertiary alcohols were obtained in high yields with high chemoselectivities, while minimizing undesired side products by reduction and/or enolization. This method is highly attractive for academic as well as industrial research, since less reactive RMgBr, which is readily prepared and commercially available, as well as reactive RMgCl, can be used successfully.

Notes and references

1 Excellent textbooks and reviews on Grignard reagents: (*a*) Y.-H. Lai, *Synthesis*, 1981, 585; (*b*) B. J. Wakefield, *Organomagnesium Methods in Organic Chemistry*, Academic Press, San Diego, CA, 1995; (*c*) G. S. Silverman and P. E. Rakita, *Handbook of Grignard Reagents*, Marcel Dekker, New York, 1996; (*d*) H. G. Richey, Jr., *Grignard Reagents: New Developments*, Wiley, Chichester, UK, 2000; (*e*) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302; (*f*) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, Germany, 2005.

2 Recent reviews on secondary and tertiary alcohol synthesis: (*a*) M. Hatano, T. Miyamoto and K. Ishihara, *Curr. Org. Chem.*, 2007, **11**, 127; (*b*) M. Hatano and K. Ishihara, *Synthesis*, 2008, 1647.

3 $LiClO_4$: (*a*) E. C. Ashby and S. A. Noding, *J. Org. Chem.*, 1979, **44**, 4371; (*b*) J. Ipaktschi and T. Eckert, *Chem. Ber.*, 1995, **128**, 1171. Alkaline metal complexes: (*c*) H. G. Richery, Jr. and J. P. DeStephano, *J. Org. Chem.*, 1990, **55**, 3281. $YbCl_3$: (*d*) S. Matsubara, T. Ikeda, K. Oshima and K. Uchimoto, *Chem. Lett.*, 2001, 1226. LiCl: (*e*) A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2004, **43**, 3333. $FeCl_3$: (*f*) A. Fürstner, H. Krause and C. W. Lehmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 440. $FeCl_2$: (*g*) M. Sada and S. Matsubara, *Chem. Lett.*, 2008, **37**, 800.

4 (*a*) T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392; (*b*) A. Krasovskiy, F. Kopp and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 497; (*c*) A. Metzger, A. Gavryushin and P. Knochel, *Synlett*, 2009, 1433.

5 (*a*) M. Hatano, T. Matsumura and K. Ishihara, *Org. Lett.*, 2005, **7**, 573; (*b*) M. Hatano, S. Suzuki and K. Ishihara, *J. Am. Chem. Soc.*, 2006, **128**, 9998.

6 Very recently, a $ZnCl_2$·TMEDA-catalyzed nucleophilic substitution reaction of chlorosilanes with RMgX was reported by Oshima, *et al.*: K. Murakami, H. Yorimitsu and K. Oshima, *J. Org. Chem.*, 2009, **74**, 1415.

7 Recent design of ate chemistry: (*a*) K. Kitagawa, A. Inoue, H. Shinokubo and K. Oshima, *Angew. Chem., Int. Ed.*, 2000, **39**, 2481; (*b*) T. Iida, T. Wada, K. Tomimoto and T. Mase, *Tetrahedron Lett.*, 2001, **42**, 4841; (*c*) M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura and E. Nakamura, *J. Am. Chem. Soc.*, 2004, **126**, 10897.

8 Intramolecular reactions of triorganozincates: T. Harada, T. Katsuhira, A. Osada, K. Iwazaki, K. Maejima and A. Oku, *J. Am. Chem. Soc.*, 1996, **118**, 11377.

9 Pioneering works using $(TMSCH_2)_2Zn$: (*a*) S. Moorhouse and G. Wilkinson, *J. Organomet. Chem.*, 1973, **52**, C5; (*b*) S. Moorhouse and G. Wilkinson, *J. Chem. Soc., Dalton Trans.*, 1974, 2187. Synthesis of $[(TMSCH_2)_3Zn]^-[K]^+$: (*c*) A. P. Purdy and C. F. George, *Organometallics*, 1992, **11**, 1955. Synthesis of $[(TMSCH_2)_3Zn]^-[Li]^+$: (*d*) E. Rijnberg, J. T. B. H. Jastrzebski, J. Boersma, H. Kooijman, N. Veldman, A. L. Spek and G. van Koten, *Organometallics*, 1997, **16**, 2239.

10 $R(TMSCH_2)Zn$ have been used as stoichiometric reagents. Addition to aldehydes: (*a*) C. Lutz and P. Knochel, *J. Org. Chem.*, 1997, **62**, 7895. Michael addition: (*b*) S. Berger, F. Langer, C. Lutz, P. Knochel, T. A. Mobley and C. K. Reddy, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1496. Addition to aldimines: (*c*) J. F. Traverse, A. H. Hoveyda and M. L. Snapper, *Org. Lett.*, 2003, **5**, 3273. Ring-opening reaction: (*d*) J. B. Johnson, R. T. Yu, P. Fink, E. A. Bercot and T. Rovis, *Org. Lett.*, 2006, **8**, 4307. Recently, stoichiometric alkylations with $FeCl_2$–$TMSCH_2Li$–*n*-Bu_2Mg have been reported. See ref. 3*g*.

11 β-Silyl effect to metal centers: S. B. Bertz, M. Eriksson, G. Miao and J. P. Snyder, *J. Am. Chem. Soc.*, 1996, **118**, 10906.

12 The strength of the Zn–C_α bond is in the order $(TMSCH_2)_2Zn$ > Et_2Zn, *n*-Pr_2Zn, $(t\text{-}BuCH_2)_2Zn$ > *i*-Pr_2Zn ≫ *t*-Bu_2Zn. (*a*) I. E. Gümrükçüoglü, J. Jeffery, M. F. Lappert, J. B. Pedley and A. K. Rai, *J. Organomet. Chem.*, 1988, **341**, 53; (*b*) A. Haaland, J. C. Green, G. S. McGrady, A. J. Downs, E. Gullo, M. J. Lyall, J. Timberlake, A. V. Tutukin, H. V. Volden and K.-A. Østby, *Dalton Trans.*, 2003, 4356.

13 Comprehensive investigation of the salt effect on mechanistic aspects is now underway.

