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Zinc(II)-Catalyzed Addition of Grignard Reagents to Ketones

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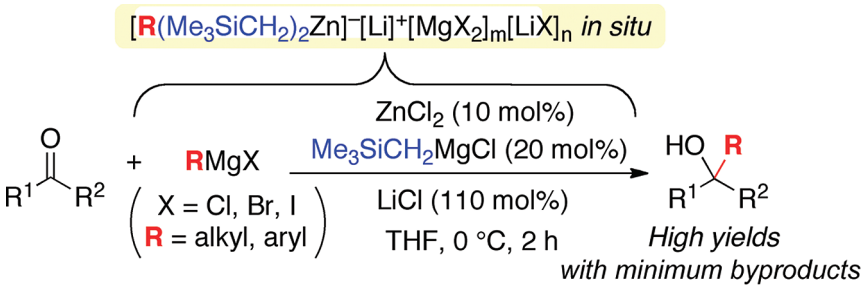
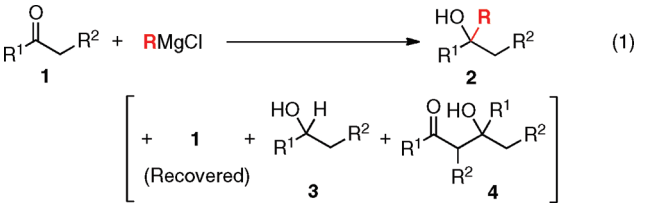


The addition of organometallic reagents to carbonyl compounds has become a versatile method for synthesizing tertiary and secondary alcohols via carbon−carbon bond formation. However, due to the lack of good nucleophilicity or the presence of strong basicity of organometallic reagents, the efficient synthesis of tertiary alcohols from ketones has been particularly difficult and, thus, limited. We recently developed highly efficient catalytic alkylation and arylation reactions to ketones with Grignard reagents (RMgX: R = alkyl, aryl; X = Cl, Br, I) using $ZnCl_2$, Me_3SiCH_2MgCl, and LiCl, which effectively minimize problematic side reactions. In principle, RMgBr and RMgI are less reactive than RMgCl for the addition to carbonyl compounds. Therefore, this novel method with homogeneous catalytic $ZnCl_2 \cdot Me_3SiCH_2MgCl \cdot LiCl$ is quite attractive, since RMgBr and RMgI, which are easily prepared and/or commercially available, like RMgCl, can be applied successfully. As well as ketones and aldehydes, aldimines were effectively applied to this catalysis, and the corresponding secondary amines were obtained in high yield. With regard to mechanistic details concerning β-silyl effect and salt effect, in situ-prepared $[R(Me_3SiCH_2)_2Zn]^-[Li]^+[MgX_2]_m[LiCl]_n$ (X = Cl/Br/I) is speculated to be a key catalytic reagent to promote the reaction effectively. The simplicity of this reliable $ZnCl_2 \cdot Me_3SiCH_2MgCl \cdot LiCl$ system in the addition of Grignard reagents to carbonyl compounds might be attractive for industrial as well as academic applications.

Introduction

Over the past century, the addition of Grignard reagents to ketones and aldehydes has been a versatile method for synthesizing tertiary and secondary alcohols via carbon−carbon bond formation.[1,2] However, the reaction of carbonyl compounds with Grignard reagents often gives undesired side products, such as reduction product **3** via β-H transfer and/or the self-aldol product **4** via enolization (eq 1). In particular, when Grignard reagents are strongly basic, ketones are often enolized with Grignard reagents and recovered by an acidic workup procedure.



(1)

To avoid these problems, some progress has been achieved through the use of stoichiometric or excess amounts of inorganic additives.[3] Imamoto et al.[4a] developed highly useful heterogeneous stoichiometric organocerium(III) complexes (eq 2), and later Knochel et al.[4b,c] developed homogeneous[5]

(1) Excellent textbooks and reviews for Grignard reagents: (a) Lai, Y.-H. *Synthesis* **1981**, 585. (b) Wakefield, B. J. *Organomagnesium Methods in Organic Chemistry*; Academic Press: San Diego, CA, 1995. (c) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996. (d) Richey, H. G., Jr. *Grignard Reagents: New Development*; Wiley: Chichester, UK, 2000. (e) 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. (f) Knochel, P. *Handbook of Functionalized Organometallics*; Wiley-VCH: Weinheim, Germany, 2005.

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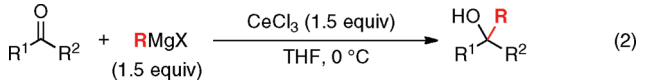
stoichiometric and semistoichiometric organolanthanum(III) complexes (eq 3). However, to prepare these reagents, lanthanoid chloride hydrates ($CeCl_3 \cdot 7H_2O$ and $LaCl_3 \cdot 6H_2O$) should be dried step-by-step to the corresponding anhydrides[6] at room temperature to 160 °C under reduced pressure for a prolonged time (ca. 1−2 days) (eq 4).[4b]



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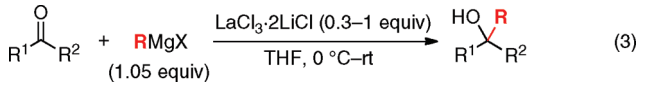

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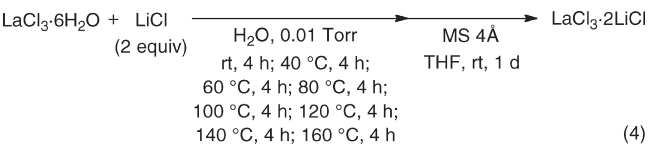
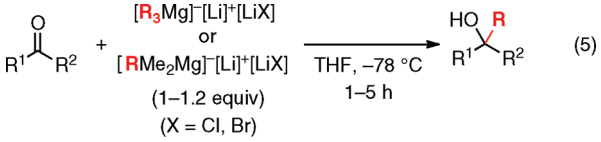


(4)

In sharp contrast to complicated procedures involving these lanthanoid(III) reagents, we have developed a homogeneous stoichiometric alkylation to ketones with trialkylmagnesium(II) ate complexes ($[R_3Mg]^-[Li]^+[LiX]$ or $[RMe_2Mg]^-[Li]^+[LiX]$), which were prepared from RMgX/RLi or RMgX/MeLi (X = Cl, Br) (eq 5).[7a] After that report, we also developed a homogeneous $ZnCl_2$-catalyzed alkylation to ketones with RMgCl via trialkylzinc(II) ate complexes $[R_3Zn]^-[MgCl]^+[MgCl_2]_2$ (eq 6).[7b,c,8] To the best of our knowledge, this is the first efficient catalytic system, and the routine reaction of ketones with Grignard reagents can be significantly promoted in the presence of a catalytic amount of $ZnCl_2$ in THF at 0 °C. Unfortunately, however, in the $ZnCl_2$-catalyst system, Grignard reagents have been limited to RMgCl (R = alkyl, but not aryl), and RMgBr and RMgI could not be used effectively.



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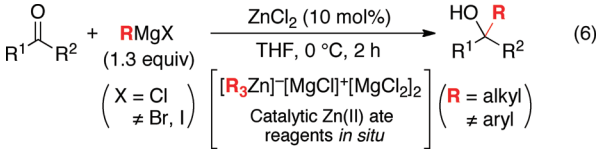
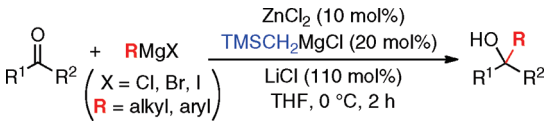


(6)

To improve our preliminary catalytic system with RMgCl (R = alkyl) as limited Grignard reagents, we recently devised a highly efficient addition of RMgX (R = alkyl, aryl; X = Cl, Br, I) to ketones with LiCl along with catalytic amounts of $ZnCl_2$ and trimethylsilylmethyl magnesium chloride ($TMSCH_2MgCl$) under homogeneous reaction conditions (Scheme 1).[9] The key to the design of further active catalytic zinc(II) ate reagents is nontransferable ligands, which themselves are not used as alkylating groups (Figure 1).[10,11] As a nontransferable ligand, a $TMSCH_2$ group should be highly attractive.[12,13] Indeed, 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 (Figure 1a). Moreover,

SCHEME 1. Addition of Grignard Reagents to Ketones with the Use of $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



(2) Recent reviews for secondary and tertiary alcohol synthesis: (a) García, C.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849. (b) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127. (c) Riant, O.; Hannedouche *J. Org. Biomol. Chem.* **2007**, *5*, 873. (d) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (e) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647.

(3) $LiClO_4$: (a) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. (b) Ipaktschi, J.; Eckert, T. *Chem. Ber.* **1995**, *128*, 1171. Alkaline metal complexes: (c) Richery, H. G., Jr.; DeStephano, J. P. *J. Org. Chem.* **1990**, *55*, 3281. $YbCl_3$: (d) Matsubara, S.; Ikeda, T.; Oshima, K.; Uchimoto, K. *Chem. Lett.* **2001**, *30*, 1226. LiCl: (e) Fujii, N.; Nakai, K.; Habashita, H.; Yoshizawa, H.; Ibuka, T.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *26*, 4227. (f) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. $FeCl_3$: (g) Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440. $FeCl_2$: (h) Sada, M.; Matsubara, S. *Chem. Lett.* **2008**, *37*, 800.

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

(5) Addition of LiCl can help solubilize insoluble or less-soluble organometallic reagents. See refs 3e,3f and 4b,4c.

(6) At this time, anhydrous cerium(III) chloride and anhydrous lanthanum(III) chloride are commercially available. However, stoichiometric or substoichiometric use of these expensive reagents is another issue.

(7) (a) Hatano, M.; Matsumura, T.; Ishihara, K. *Org. Lett.* **2005**, *7*, 573. (b) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998. (c) Hatano, M.; Suzuki, S.; Ishihara, K. *Synlett* **2010**, 321.

(8) Recently, a $ZnCl_2 \cdot$TMEDA-catalyzed nucleophilic substitution reaction of chlorosilanes with RMgX was reported by Oshima and co-workers: Murakami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2009**, *74*, 1415.

(9) Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* **2010**, *46*, 2674.

(10) Recent design of ate chemistry: (a) Uchiyama, M.; Furumoto, S.; Saito, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11425. (b) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (c) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481. (d) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841. (e) Uchiyama, M.; Nakamura, S.; Ohwada, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 10897. (f) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (g) Nobuto, D.; Uchiyama, M. *J. Org. Chem.* **2008**, *73*, 1117.

(11) Intramolecular reactions of triorganozincates: (a) Harada, T.; Osada, A.; Oku, A. *Tetrahedron Lett.* **1995**, *36*, 723. (b) Harada, T.; Wada, H.; Oku, A. *J. Org. Chem.* **1995**, *60*, 5370. (c) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377.

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

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

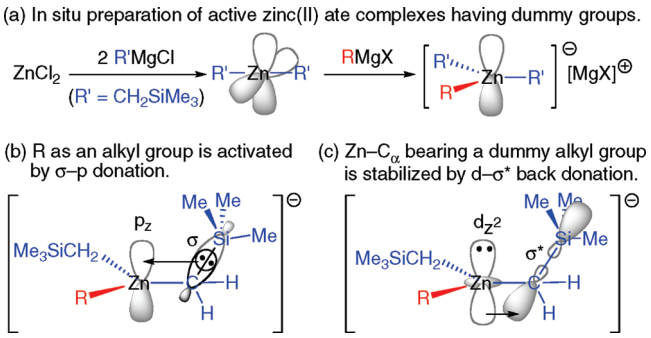


FIGURE 1. Design of catalytic zinc(II) ate reagents in situ.

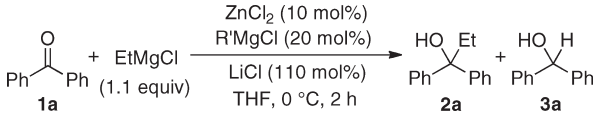
the activity of $TMSCH_2$−mixed alkylzinc(II) ate complexes as alkylating reagents should increase with regard to β-silyl effect.[14,15] On one hand, the nucleophilicity of an alkylating group (R) would be increased by electron transfer through double σ(C−Si)−Zn(p_Z) overlaps (Figure 1b).[14] On the other hand, two nontransferable groups ($TMSCH_2$) would be stabilized by back-donation through double d_Z2(Zn)−σ*(C−Si) overlaps (Figure 1c).[15]

In the present study, both β-silyl effect and salt effect were investigated through the catalytic and stoichiometric $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ reaction system, and a possible reaction pathway with an extremely reactive catalytic zinc(II) ate reagent in situ was proposed. We explored zinc(II)-catalyzed addition of Grignard reagents to ketones, aldehydes, and aldimines, which covers not only RMgCl but also RMgBr and RMgI (R = alkyl, aryl), and highly effective catalytic syntheses of tertiary and secondary alcohols and secondary amines were demonstrated with the combined use of $ZnCl_2$, $TMSCH_2MgCl$, and LiCl. This catalysis is extremely practical since the traditional noncatalyzed Grignard addition and the previous $ZnCl_2$-catalyzed Grignard addition, which were compared to this $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ catalysis in all cases, were sometimes ineffective, particularly with RMgBr and RMgI.

Results and Discussion

***β*-Silyl Effect in Zinc(II) Ate Complexes.** To clarify the mechanistic details, we first examined the effect of nontransferable alkyl groups (R′) on the zinc(II) ate catalysts in the reaction of benzophenone (**1a**) with EtMgCl (Table 1). The use of R′MgCl decreased the reduction compound (**3a**) (entry 2 vs entries 3−5). In place of the simple and commercially available $TMSCH_2MgCl$ (entry 3), other nontransferable R_3SiCH_2 groups derived from $Me_2PhSiCH_2MgCl$ (entry 4) and (*i*-PrO)Me_2SiCH_2MgCl (entry 5) could be used effectively. However, doubly β-Si-substituted $(TMS)_2CHMgCl$ did not show improved results, probably since the bulkiness of four TMS groups of $((TMS)_2CH)_2Zn$ would prevent $((TMS)_2CH)_2Zn$ from transforming into the corresponding zinc(II) ate complex (entry 6). Me_3CCH_2MgCl, which could make nontransferable neopentyl groups on a zinc(II) center, was not effective (entry 7 vs entries 2 and 3−5). These results suggest that β-Si is critical for promoting the alkyl-selective Grignard addition reaction, and the expected β-silyl effect is generally observed with $[Et(SiCH_2)_2Zn]^-$ species (see Figure 1).

TABLE 1. Effect of Nontransferable *β*-Silylalkyl Groups



entry	R′MgCl	yield (%) 2a	3a
1[a]		20	78
2		88	12
3	Me_3SiCH_2MgCl	94	4
4	$Me_2PhSiCH_2MgCl$	93	7
5	(*i*-PrO)Me_2SiCH_2MgCl	90	6
6	$(Me_3Si)_2CHMgCl$	76	11
7	Me_3CCH_2MgCl	83	11

[a]In the absence of $ZnCl_2$, LiCl, and R′MgCl.

Next, the optimal amount of $TMSCH_2MgCl$ was investigated (Table 2).[16] To prepare the expected $(TMSCH_2)_2Zn$ precursor in situ, less than 20 mol % of $TMSCH_2MgCl$ in proportion to 10 mol % of $ZnCl_2$ might be inefficient (see Figure 1). In fact, when the amount of $TMSCH_2MgCl$ was decreased from 20 to 10 mol % in the reaction of acetophenone (**1b**) with *i*-PrMgBr, the yield of the product (**2b**) was slightly decreased from 80% to 74% (entry 1 vs entry 2). However, when 30 mol % of $TMSCH_2MgCl$ was used, a compatible yield (81%) was still observed without the generation of $TMSCH_2$ adduct (**5b**) (entry 3). This interesting result prompted us to investigate the trimethylsilylmethylation of **1b** in the absence of *i*-PrMgBr. The reaction with $TMSCH_2MgCl$ (110 mol %) or the combined use of $TMSCH_2MgCl$ (130 mol %) and $ZnCl_2$ (10 mol %) gave almost the same results to afford **5b** (entries 4 and 5). Therefore, $TMSCH_2$-saturated zinc(II) ate complex $[(TMSCH_2)_3Zn]^-[MgCl]^+[MgCl_2]$ was unlikely to participate in or was much less reactive in this reaction. Moreover, a competitive reaction of **1b** with the use of *i*-PrMgBr (1.1 equiv) and $TMSCH_2MgCl$ (130 mol %) in the presence of $ZnCl_2$ catalyst was also examined, and *i*-Pr adduct (**2b**) was exclusively obtained in 97% yield (entry 6). This result strongly supported the high activity of the $ZnCl_2/TMSCH_2MgCl$ catalyst for alkylation, which would lead to active $[R(TMSCH_2)_2Zn]^-[MgX]^+[MgX_2]$ in situ, but not for trimethylsilylmethylation.

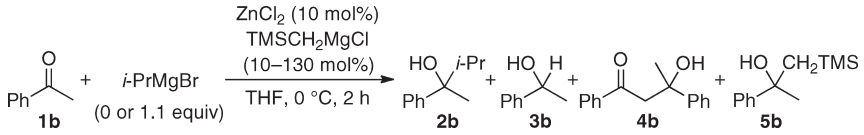
Effect of the Cation Moiety of Zinc(II) Ate Complexes in Stoichiometric Reactions. Before we investigated the salt effect in the catalytic reaction, we examined stoichiometric reactions of **1a** with EtMgX or EtLi (1.1 equiv) and Et_2Zn (1.1 equiv) (Table 3). In these stoichiometric reactions with Et_2Zn, we can exclude an external salt effect and thus specifically observe an internal salt effect, since internal spontaneous salts such as MgX_2 and/or LiX are never generated. The combination of EtMgBr and Et_2Zn provided a significant amount (39% yield) of reduction product (**3a**), and **2a** was obtained in only 54% yield (entry 1). In sharp contrast,

(14) The β-silyl effect toward metal centers: Bertz, S. B.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

(15) 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) Gümrükçüoglü, I. E.; Jeffery, J.; Lappert, M. F.; Pedley, J. B.; Rai, A. K. *J. Organomet. Chem.* **1988**, *341*, 53. (b) Haaland, A.; Green, J. C.; McGrady, G. S.; Downs, A. J.; Gullo, E.; Lyall, M. J.; Timberlake, J.; Tutukin, A. V.; Volden, H. V.; Østby, K.-A. *Dalton Trans.* **2003**, 4356.

(16) To avoid the strong effect of LiCl, the reaction was examined in the absence of LiCl.

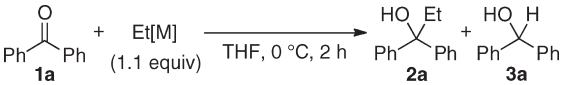
TABLE 2. Amount of $TMSCH_2MgCl$



			yield (%)			
entry	*i*-PrMgBr (equiv)	$TMSCH_2MgCl$ (mol %)	**2b**	**3b**	**4b**	**5b**
1	1.1	10	74	9	14	0
2	1.1	20	80	8	6	0
3	1.1	30	81	9	5	0
4[a]	0	110			9	78
5	0	130			8	73
6	1.1	130	97	0	1	0

[a]In the absence of $ZnCl_2$.

TABLE 3. Effect of the Cation Moiety of Zinc(II) Ate Complexes in Stoichiometric Reactions



		yield (%)		
entry	reagent Et[M] (equiv)	**2a**	**3a**	**1a**
1	EtMgBr (1.1) + Et_2Zn (1.1)	54	39	7
2	EtMgCl (1.1) + Et_2Zn (1.1)	81	14	5
3	EtLi (1.1) + Et_2Zn (1.1)	94	1	5

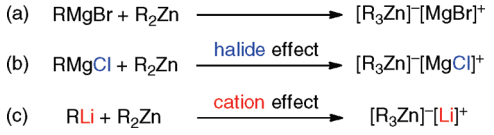
the combination of EtMgCl and Et_2Zn improved the yield of **2a** (81%) with a decrease in **3a** (14%) (entry 2). Moreover, the combination of EtLi and Et_2Zn greatly improved the yield of **2a** (94%) while significantly minimizing **3a** (1%) (entry 3). Therefore, the preferred cation moiety of zinc(II) ate complexes is in the order $Li^+ > [MgCl]^+ > [MgBr]^+$ (Scheme 2), and this order may be applied in catalytic reactions.

Salt Effect in Catalytic Reactions. We next investigated the effect of inorganic additives[3a−d,g,h,4,17] such as LiCl[3e,f,7c] in these catalytic reactions. In the catalytic reaction of **1b** with *i*-PrMgBr in the presence of $ZnCl_2$ and $TMSCH_2MgCl$, **2b** was obtained in 80% yield, and MgX_2 (X = Cl/Br) would be generated (entry 1 in Table 4; Scheme 3b). As an additive, LiCl was effective, and **2b** was obtained in 96% yield (entry 3 in Table 4; Scheme 3c). LiBr was not better than LiCl (entry 4 in Table 4). However, when *i*-PrMgCl was used in place of *i*-PrMgBr (Scheme 3d), both LiCl (entry 5 in Table 4; Scheme 3e) and LiBr (entry 6 in Table 4) were effective. On the basis of these results, we assumed that in situ-generated and/or additional salts might be responsible for the cation and halide effects (Scheme 3).

When LiX was added, the effect of Li^+ was generally observed in entries 3−6 in Table 4. According to the literature of Knochel et al.,[3f] the cation effect may involve the dissociation of oligomeric Grignard reagents (RMgX) to

(17) Salt effect of $MgBr_2$ in the stoichiometric addition of MeMgBr to biaryl ketones: (a) House, H. O.; Traficante, D. D. *J. Org. Chem.* **1963**, *28*, 355. (b) Bikales, N. M.; Becker, E. I. *Can. J. Chem.* **1963**, *41*, 1329. (c) Smith, S. G.; Su, G. *Tetrahedron Lett.* **1966**, *7*, 4417. Salt effect on the stereochemistry in the stoichiometric addition of organometallic reagents to ketones: (d) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. Salt effect on the reduction in the stoichiometric addition of dialkylmagnesium reagents to ketones: (e) Richey, H. G., Jr.; DeStephano, J. P. *J. Org. Chem.* **1990**, *55*, 3281.

SCHEME 2. Possible Stoichiometric Zinc(II) Ate Complexes



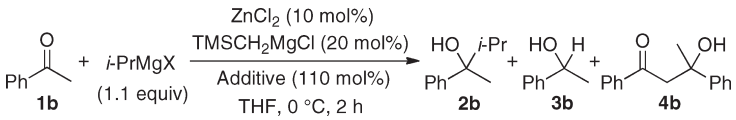
monomeric $[RMgX_2]^-[Li]^+$ (X = Cl/Br) due to the high polarity of Li^+ (Scheme 3a).[18] These polarized monomeric Li^+ species would be transformed to catalytic zinc(II) ate reagents in situ more smoothly than the original oligomeric Grignard reagents. Note that Li^+ additives were more favored than Na^+ and Mg^{2+} additives such as NaCl and $MgCl_2$ (entries 3−6 vs entries 7 and 8 in Table 4). With regard to the stoichiometric investigation above (i.e., Scheme 2; the cation effect is in the order $Li^+ > [MgCl]^+ > [MgBr]^+$), $[Li]^+[MgX_2]_m[LiX]_n$ but not $[MgX]^+[MgX_2]_m[LiX]_n$ is a likely active cation moiety of the zinc(II) ate complex.

Not only the effect of Li^+ but also the effect of Cl^- and Br^- should be considered. In particular, a Br^-/Cl^- combination such as *i*-PrMgBr/LiCl should involve a halide exchange between Cl^- and Br^- in situ. The existence of a Cl^- source to generate $MgCl_2$ via transmetalation might be important since the Lewis acidity is in the order $MgCl_2 > MgClBr > MgBr_2$ according to the large electronegativity of Cl^-. Therefore, particularly under the conditions of LiCl addition, the corresponding cationic part of the zinc(II) ate complex, namely $[Li]^+[MgX_2]_3[LiX]_n$ (X = Cl/Br), might be affected by added Cl^-.

Overall, based on the cation effect ($Li^+ > [MgCl]^+ > [MgBr]^+$) and the halide effect ($Cl^- > Br^-$) in the Zn(II)-catalyzed Grignard reaction with LiCl, the Lewis acidity of these cation moieties of zinc(II) ate complexes would be increased. As a result, a high predominance of alkylation to ketones should depend on the combination of RMgX/LiCl, as seen in the order $[R(TMSCH_2)_2Zn]^-[Li]^+[MgCl_2]_3[LiCl]_n$ (entry 5 in Table 4; Scheme 3e) > $[R(TMSCH_2)_2Zn]^-[Li]^+[MgX_2]_3[LiX]_n$ (X: Cl = <94%, Br = >6%)) (entry 3 in Table 4; Scheme 3c) > $[R(TMSCH_2)_2Zn]^-[MgCl]^+[MgCl_2]_2$ (entry 2 in Table 4; Scheme 3d) > $[R(TMSCH_2)_2Zn]^-[MgX]^+[MgX_2]_2$ (X: Cl = 80%, Br = 20%) (entry 1 in Table 4; Scheme 3b).

(18) LiCl-mediated formation of zinc(II) ate complexes: Koszinowski, K.; Böhrer, P. *Organometallics* **2009**, *28*, 771.

TABLE 4. Combination of Grignard Reagents (*i*-PrMgX) and Salts



			yield (%)		
entry	*i*-PrMgX	additive	**2b**	**3b**	**4b**
1	*i*-PrMgBr		80	8	6
2	*i*-PrMgCl		88	0	7
3	*i*-PrMgBr	LiCl	96	0	2
4	*i*-PrMgBr	LiBr	84	0	2
5	*i*-PrMgCl	LiCl	99	1	0
6	*i*-PrMgCl	LiBr	97	0	2
7	*i*-PrMgBr	NaCl	87	0	8
8	*i*-PrMgBr	$MgCl_2$	64	0	24

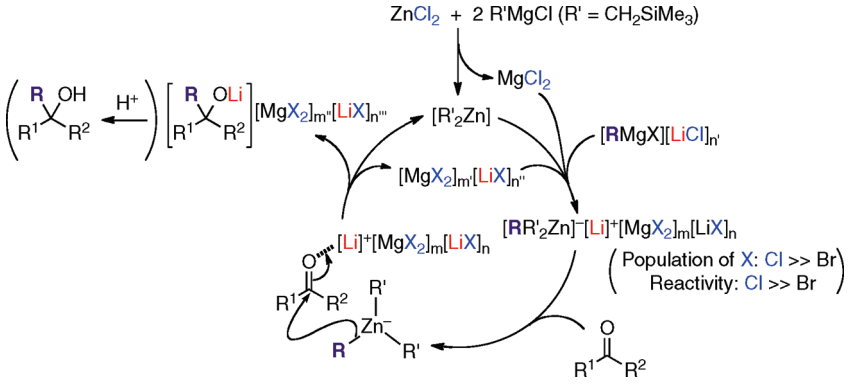
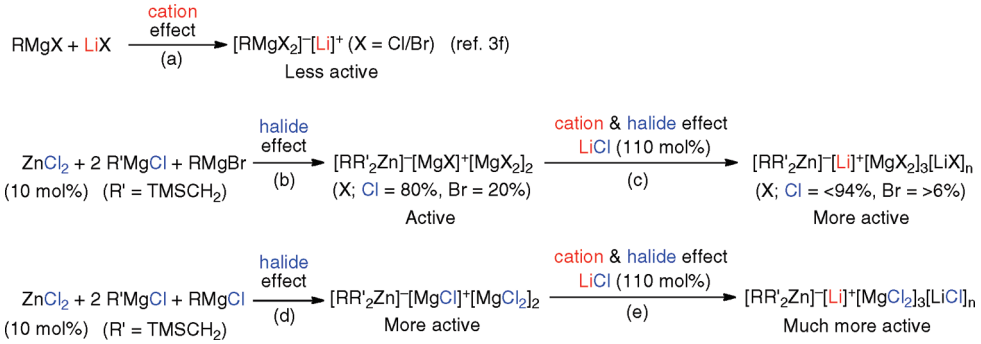


FIGURE 2. Proposed catalytic cycle.

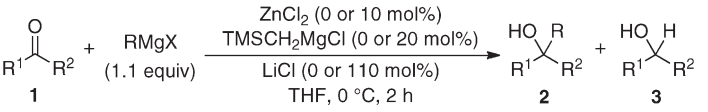
SCHEME 3. Possible Zinc(II) Ate Complexes and Salt Effect



Possible Catalytic Cycle. A possible catalytic cycle is shown in Figure 2. The key in this catalysis is a postulated active catalytic alkylating zinc(II) ate complex, $[R(TMSCH_2)_2Zn]^-[Li]^+[MgX_2]_m[LiX]_n$ (X = Cl, Br, or I), which is generated in situ from $(TMSCH_2)_2Zn$, RMgX (X = Cl, Br, or I), and LiCl reagents. In particular, the RMgBr−LiCl reagents described here may act as monomeric $[RMgX][LiCl]_{n'}$, which would easily be transformed to $[R(TMSCH_2)_2Zn]^-[Li]^+[MgX_2]_m[LiX]_n$ (X: Cl = <94%, Br = >6% when RMgBr and LiCl are used; see Scheme 3c) via transmetalation with $(TMSCH_2)_2Zn$. As discussed for stoichiometric/catalytic reactions, $[R(TMSCH_2)_2Zn]^-[Li]^+$ is the essential moiety of the active zinc(II) ate complexes. This could explain why not only RMgCl but also RMgBr and RMgI could be used in this catalytic system under the addition of LiCl. The alkylation step with the anionic $[R(TMSCH_2)_2Zn]^-$ moiety would also be accelerated by the Lewis acidic $[Li]^+[MgX_2]_m[LiX]_n$ (X: Cl > Br) moiety, and the products ($[R^1R^2RCOLi][MgX_2]_{m''}[LiX]_{n'''}$), $(TMSCH_2)_2Zn$, and $[MgX_2]_{m'}[LiX]_{n''}$ would be released.

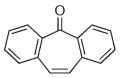
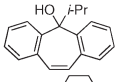
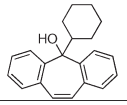
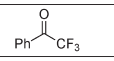
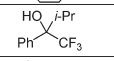
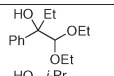
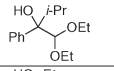
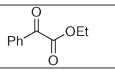
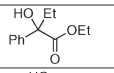
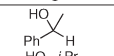
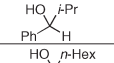
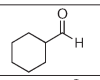
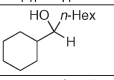
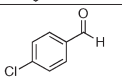
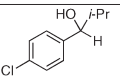
Zinc(II)-Catalyzed Addition of Grignard Reagents to Ketones and Aldehydes. We next demonstrated the catalytic addition of Grignard reagents (RMgCl, RMgBr, and MeMgI) to various ketones (Table 5, entries 1−31). With only $ZnCl_2$ catalyst or without $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ (i.e., traditional Grignard addition conditions), the yields of the desired tertiary alcohols were generally low to medium[9] due to side reactions and/or recovery of the starting material via enolization/protonation. In sharp contrast, in the presence of

TABLE 5. Addition of Grignard Reagents to Ketones and Aldehydes Catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



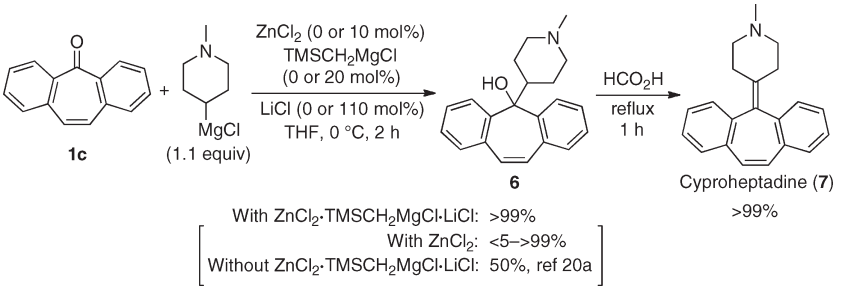
Entry	$R^1C(=O)R^2$ (**1**)	RMgX	Product (**2**)	Yield (%) of **2** (**3**) With $ZnCl_2$·$TMSCH_2MgCl$·LiCl	Yield (%) of **2** (**3**) With $ZnCl_2$	Yield (%) of **2** (**3**) Without $ZnCl_2$·$TMSCH_2MgCl$·LiCl
1		MeMgI		93 (0)		
2		*i*-PrMgCl		99 (1)		
3		*i*-PrMgBr		96 (0)		
4[a]		*i*-PrMgBr	(**2b**)	94 (0)		
5[b]	(**1b**)	*i*-PrMgI		>99 (0)		
6		4-FC_6H_4MgBr		92 (0)		
7		*i*-PrMgBr		94 (0)		
8		*i*-PrMgBr		95 (4)		
9		*i*-PrMgBr		81 (0)		
10		MeMgI		90 (0)		
11		EtMgBr		96 (0)	82 (8)	56 (13)
12		*i*-PrMgBr		85 (5)		
13		MeMgI		91 (0)		
14		EtMgBr		>99 (0)	85 (7)	75 (0)
15		*i*-PrMgBr		83 (0)		
16		*n*-OctylMgBr		>99 (0)		
17		*i*-PrMgBr		92 (0)		
18		*i*-PrMgBr		51		
19		EtMgBr		80 (16)		
20		*i*-PrMgBr		82 (0)		
21		1-NaphMgBr		82 (0)		
22		EtMgBr	(**2a**)	91 (9)	52 (42)	20 (78)
23	(**1a**)	$(CH_2)_2MgBr$		64 (32)		
24		EtMgBr		91 (9)	58 (36)	45 (49)

TABLE 5. Continued

Entry	$R^1C(=O)R^2$ (**1**)	RMgX	Product (**2**)	Yield (%) of **2** (**3**) With $ZnCl_2$·$TMSCH_2MgCl$·LiCl	With $ZnCl_2$	Without $ZnCl_2$·$TMSCH_2MgCl$·LiCl
25	 (**1c**)	*i*-PrMgBr		94 (6)		
26		*c*-HexMgBr		68 (24)		
27		*c*-HexMgCl		89 (0)	54 (41)	39 (61)
28[c]		*i*-PrMgBr		90 (10)		
29		EtMgBr		92 (8)	88 (12)	72 (21)
30		*i*-PrMgBr		72 (25)		
31		EtMgBr		71		
32		MeMgI		>99 (0)	98 (0)	58 (0)
33		*i*-PrMgBr		89 (11)	48 (51)	63 (37)
34		*n*-HexMgBr		>99 (0)	86 (0)	69 (0)
35		*i*-PrMgCl		89 (11)	75 (25)	55 (47)

[a] $TMSCH_2Li$ (20 mol %) was used in place of $TMSCH_2MgCl$. [b] Et_2O was used as a solvent. [c] 30 mol % of $ZnCl_2$, 60 mol % of $TMSCH_2MgCl$, 110 mol % of LiCl, and 1.1 equiv of *i*-PrMgBr were used.

SCHEME 4. Synthesis of Cyproheptadine

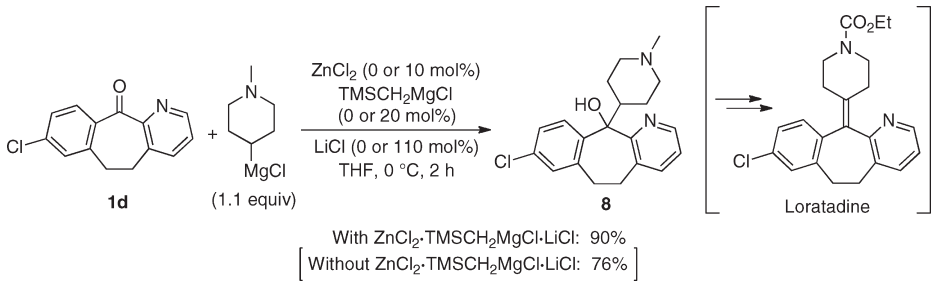


$ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ under homogeneous conditions, aromatic ketones (entries 1−3, 4−12),[19] heteroaromatic ketones (entries 13−17), aliphatic ketones (entries 18−21), and biaryl ketones (entries 22−27) gave the corresponding tertiary alcohols in high yields. The use of $TMSCH_2Li$ in place of $TMSCH_2MgCl$ was also effective (entry 4). Synthetically useful methylation with MeMgI (entries 1, 10, and 13) and arylation such as 4-fluorophenylation (entry 6) and 1-naphthylation (entry 9) also proceeded smoothly in the presence of $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$. Long-chain alkylation often provides undesired reduction product, but *n*-octylation in this catalysis gave the corresponding adduct quantitatively (entry 16). The desired α-functionalized tertiary alcohols were obtained in high yields without the decomposition of α-groups (entries 28−31). The cyclohexylation of bulky 5-dibenzosuberenone (**1c**) was difficult in the absence of catalysts or in the presence of $ZnCl_2$ even with the use of more-suitable *c*-HexMgCl instead of *c*-HexMgBr (entries 26 and 27). However, the yields were greatly improved when *c*-HexMgCl or *c*-HexMgBr was used in the presence of $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$. Moreover, this catalytic system could promote the reaction of aldehydes with Grignard reagents, and the desired secondary alcohols were obtained in high yields from aromatic and aliphatic aldehydes (entries 32−35). In addition to the alkyl magnesium bromides and iodides, an alkyl magnesium chloride could also be used with $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ more effectively than with $ZnCl_2$ or without catalysts.

Synthesis of Cyproheptadine. By taking advantage of the reactions of 5-dibenzosuberenone (**1c**) (Table 5, entries 24−27), we next examined the synthesis of cyproheptadine (**7**), which is both an antiserotonin drug and an antihistamine drug (Scheme 4).[20] Engelhardt et al. reported that a traditional Grignard addition to **1c** without catalysts gave tertiary alcohol **6** in 50% yield.[20a] However, we found that compound **6** was not obtained in reproductive yields even when $ZnCl_2$ was used, and the yields of **6** varied from < 5% to > 99% in several examinations. In sharp contrast, in the presence of $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$, the reaction of

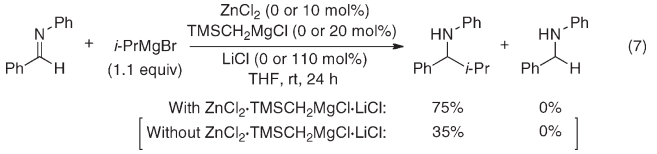
(19) A preliminary investigation of the isopropylation of acetophenone (**1b**) is described in the Supporting Information.

SCHEME 5. Synthesis of Loratadine Intermediate

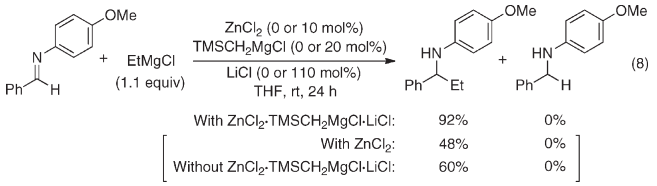


1c with (*N*-methylpiperidin-4-yl)magnesium chloride proceeded smoothly, and **6** was constantly obtained in >99% yield. We could readily transformed **6** to **7** in >99% yield by treatment with formic acid according to the literature.[21] Moreover, we also examined the synthesis of tertiary alcohol **8**, which is a key intermediate for loratadine, and the desired alkylation of **1d** proceeded smoothly (Scheme 5).[22]

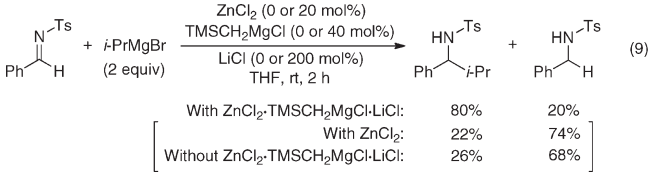
Zinc(II)-Catalyzed Addition of Grignard Reagents to Aldimines. The alkylations of less-reactive aldimines with Grignard reagents[23] were also explored (eqs 7−9). Without the catalysts or with $ZnCl_2$ catalyst, the alkylation of *N*-arylaldimines was generally slow even at room temperature, although reduction byproducts were not observed (eqs 7 and 8). In contrast, $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ promoted the reactions of *N*-arylaldimines with *i*-PrMgBr and EtMgCl, and the corresponding secondary amines were obtained in much improved yields. Moreover, isopropylation of an *N*-Ts aldimine without the catalysts or with $ZnCl_2$ catalyst gave a significant amount of the undesired reduction byproduct in yields of 68% and 74%, respectively (eq 9). However, $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ improved the predominance of the desired isopropylation, and the corresponding product was obtained in 80% yield.



(7)



(8)



(9)

Conclusion

In summary, we have developed highly efficient alkylation and arylation reactions to ketones, aldehydes, and aldimines with Grignard reagents (RMgX: R = alkyl, aryl; X = Cl, Br, I)/LiCl using catalytic $ZnCl_2$ and $TMSCH_2MgCl$. The postulated active species are in situ prepared $[R(TMSCH_2)_2Zn]^-[Li]^+[MgX_2]_m[LiX]_n$ (X is preferentially Cl under the addition of LiCl), which were designed based on the β-silyl effect, the cation effect of Li^+, and halide effect of Cl^-. $[R(TMSCH_2)_2Zn]^-[Li]^+[MgX_2]_m[LiX]_n$ can act as both a catalytic alkylating reagent with increased nucleophilicity in the anion part ($[R(TMSCH_2)_2Zn]^-$) and also as an activator of carbonyl compounds in the Lewis acidic cation part ($[Li]^+[MgX_2]_m[LiX]_n$). In this catalysis, the desired alkyl or aryl adducts were obtained in high yields, while minimizing undesired side products by reduction via β-H transfer of Grignard reagents and/or enolization due to the strong basicity of Grignard reagents. In particular, to demonstrate the synthetic utility, the tertiary alcohols that are the key intermediates of cyproheptadine and loratadine were prepared in 90− >99% yields by using the homogeneous $ZnCl_2 \cdot TMSCH_2MgCl \cdot LiCl$ system. This simple and robust catalytic system should represent a breakthrough in the efficient alkylation of carbonyl compounds since a variety of commercially available Grignard reagents can be used.

Experimental Section

Representative procedure for $ZnCl_2-TMSCH_2MgCl-LiCl$-Catalyzed Grignard Reaction of Ketones (Entries 1−31 in Table 5). To a Pyrex Schlenk tube was added $ZnCl_2$ (40.8 mg, 0.30 mmol), which was then melt-dried by a heat gun under reduced pressure (< 5 Torr) within 5 min. LiCl (139.9 mg, 3.3 mmol) was added to the Pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again, the mixture was partially melt-dried by a heat gun under reduced pressure (< 5 Torr) within 5 min. To the mixture was added (trimethylsilyl)methylmagnesium chloride (1.0 M in Et_2O, 0.60 μL, 0.60 mmol) at room temperature. This mixture was stirred at that temperature for 15 min. *i*-PrMgBr (0.7 *M* in THF, 4.71 mL, 3.3 mmol) was added, and the solution was stirred at that temperature for 45 min. Then, the solution was cooled at 0 °C, and acetophenone (**1b**) (350 μL, 3.0 mmol) was added over 1 h by a syringe pump. The mixture was stirred at 0 °C for 2 h.

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The resulting mixture was quenched by saturated aqueous NH_4Cl (10 mL), extracted with AcOEt (10 mL × 3), and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane/AcOEt, v/v = 10/1−5/1) to give the desired product (**2b**) (474 mg, 96%).

3-Methyl-2-phenylbutan-2-ol (2b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 1.53 (s, 3H), 1.56 (s, 1H), 2.02 (septet, J = 6.9 Hz, 1H), 7.20−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 17.4, 26.7, 38.6, 77.8, 125.2, 126.4, 127.8, 147.8; HRMS (FAB+) calcd for $C_{11}H_{15}$ $[M - OH]^+$ 147.1174, found 147.1170.

Representative Procedure for $ZnCl_2$−$TMSCH_2MgCl$−LiCl-Catalyzed Grignard Reaction of Aldehydes (Entries 32−35 in Table 5). To a Pyrex Schlenk tube was added $ZnCl_2$ (40.8 mg, 0.30 mmol), which was then melt-dried by a heat gun under reduced pressure (< 5 Torr). LiCl (139.9 mg, 3.3 mmol) was added to the Pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again the mixture was partially melt-dried by a heat gun under reduced pressure (< 5 Torr). To the mixture was added (trimethylsilyl)methylmagnesium chloride (1.0 M in Et_2O, 0.60 μL, 0.60 mmol) at room temperature. This mixture was stirred at that temperature for 15 min. *i*-PrMgBr (0.7 M in THF, 4.71 mL, 3.3 mmol) was added, and the solution was stirred at that temperature for 45 min. Then, the solution was cooled at 0 °C, and benzaldehyde (305 μL, 3.0 mmol) was added over 1 h by a syringe pump. The mixture was stirred at 0 °C for 2 h. The resulting mixture was quenched by saturated aqueous NH_4Cl (10 mL), extracted with AcOEt (10 mL × 3), and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane/Et_2O, v/v = 10/1−3/1), to give the desired product (402 mg, 89%).

2-Methyl-1-phenylpropan-1-ol (entry 33 in Table 5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.92 (septet, J = 6.6 Hz, 1H), 2.26 (bs, 1H), 4.31 (d, J = 6.9 Hz, 1H), 7.22−7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 19.0, 35.2, 80.0, 126.5, 127.3, 128.1, 143.6; HRMS (FAB+) calcd for $C_{10}H_{13}$ $[M - OH]^+$ 133.1017, found 133.1020.

Synthesis of 5-(1-Methyl-4-piperidyl)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (6, Scheme 4). To a Pyrex Schlenk tube were added magnesium turnings (365 mg, 15 mmol), which were dried by a heat gun under reduced pressure (< 5 Torr). N_2 was charged into the Pyrex Schlenk tube, and a piece of I_2 (< 5 mg) was added. The mixture was vigorously stirred at room temperature for 2 h. Then THF (30 mL) and 4-chloro-1-methylpiperidine (2.0 g, 15 mmol) were added. The mixture was heated at reflux temperature for 5 h. The solution of (1-methylpiperidin-4-yl)-magnesium chloride was titrated prior to use against a solution of 1,10-phenanthoroline/*n*-BuLi/*s*-BuOH in benzene. To a Pyrex Schlenk tube was added $ZnCl_2$ (40.8 mg, 0.30 mmol), which was melt-dried by a heat gun under reduced pressure (< 5 Torr) within 5 min. LiCl (139.9 mg, 3.3 mmol) was added to the Pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again the mixture was partially melt-dried by a heat gun under reduced pressure (< 5 Torr) within 5 min. To the mixture was added (trimethylsilyl)methylmagnesium chloride (1.0 M in Et_2O, 0.60 μL, 0.60 mmol) at room temperature. This mixture was stirred at that temperature for 15 min. (1-Methylpiperidin-4-yl)-magnesium chloride (0.5 M in THF, 6.6 mL, 3.3 mmol) was added, and the solution was stirred at that temperature for 45 min. Then, the solution was cooled at 0 °C, and 5-dibenzosuberenone (**1c**) (619 mg, 3.0 mmol) was added in one portion. The mixture was stirred at 0 °C for 2 h. The resulting mixture was quenched by saturated aqueous NH_4Cl (10 mL), extracted with AcOEt (10 mL × 3), and washed by brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by basic silica gel column chromatography (eluent: chloroform/MeOH, v/v = 20/1) to give the desired product (**6**) (916 mg, > 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, J = 12.8 Hz, 2H), 1.31 (m, 2H), 1.62 (td, J = 12.0, 2.7 Hz, 2H), 2.14 (s, 3H), 2.51 (m, 1H), 2.58 (s, 1H), 2.68 (d, J = 11.1 Hz, 2H), 6.95 (s, 2H), 7.25 (td, J = 7.5, 1.2 Hz, 2H), 7.32 (dd, J = 7.5, 1.5 Hz, 2H), 7.40 (td, J = 8.1, 1.5 Hz, 2H), 7.91 (dd, J = 8.1, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 36.1, 46.2, 55.8, 78.3, 125.1, 126.4, 128.6, 129.5, 131.5, 132.3, 141.8; IR (KBr) 3341, 2931, 2795, 1434, 1377, 1277, 1141 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{22}N$ $[M - OH]^+$ 288.1752, found 288.1758.

Synthesis of Cyproheptadine (7, Scheme 4). To a 30 mL round flask were added **6** (610 mg, 2.0 mmol) and formic acid (3 mL). The mixture was heated at 100 °C for 2 h. The resulting mixture was cooled to 0 °C, diluted with AcOEt (15 mL), and quenched by aqueous 1 M NaOH. The mixture was extracted with AcOEt (20 mL × 3) and washed with brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by basic silica gel column chromatography (eluent: chloroform/MeOH, v/v = 20/1) to give the desired product (**7**) (575 mg, > 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (m, 2H), 2.16 (m, 2H), 2.23 (s, 3H), 2.35 (m, 2H), 2.51 (m, 2H), 6.91 (s, 2H), 7.16−7.26 (m, 4H), 7.27−7.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 46.0, 57.2, 126.2, 127.7, 128.1, 128.4, 130.9, 133.3, 134.7, 135.1, 139.1; HRMS (FAB+) calcd for $C_{21}H_{21}NNa$ $[M + Na]^+$ 310.1572, found 310.1570.

Representative Procedure for $ZnCl_2$−$TMSCH_2MgCl$−LiCl-Catalyzed Grignard Reaction of Aldimines (eqs 7−9). To a Pyrex Schlenk tube was added $ZnCl_2$ (40.8 mg, 0.30 mmol), which was melt-dried by a heat gun under reduced pressure (< 5 Torr). LiCl (139.9 mg, 3.3 mmol) was added to the Pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again the mixture was partially melt-dried by a heat gun under reduced pressure (< 5 Torr). To the mixture was added (trimethylsilyl)methylmagnesium chloride (1.0 M in Et_2O, 0.60 μL, 0.60 mmol) at room temperature. This mixture was stirred at that temperature for 15 min. *i*-PrMgBr (0.7 M in THF, 4.71 mL, 3.3 mmol) was added, and the solution was stirred at that temperature for 45 min. Under N_2 flow conditions, *N*-phenylbenzylideneamine (547 mg, 3.0 mmol) was added. The mixture was stirred at room temperature for 24 h, and the reaction was monitored by TLC. The resulting mixture was quenched by saturated aqueous NH_4Cl (10 mL), extracted with AcOEt (10 mL × 3), and washed with brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane/Et_2O, v/v = 25/1−10/1) to give the desired product (507 mg, 75%).

***N*-(2-Methyl-1-phenylpropyl)aniline (eq 7):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 2.03 (octet, J = 6.9 Hz, 1H), 4.12 (br, 2H), 6.49 (d, J = 7.2 Hz, 2H), 6.60 (t, J = 7.2 Hz, 1H), 7.05 (t, J = 7.2 Hz, 2H), 7.17−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.6, 34.8, 63.6, 113.1, 116.9, 126.7, 127.1, 128.1, 129.0, 142.5, 147.6; HRMS (FAB+) calcd for $C_{16}H_{19}NNa$ $[M + Na]^+$ 248.1415, found 248.1416.

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Supporting Information Available: General information, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.