Efficient Synthesis of Tertiary Alcohols: Highly Selective Alkylation to Ketones Catalyzed by Ate Complexes

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Chapter 1

Introduction and General Summary

1-1. Introduction

The synthesis of alcohols is one of the most fundamental and important reactions in organic chemistry.[1] Tertiary alcohols, along with primary and secondary alcohols, are key compounds in pharmaceuticals, natural products, and functional materials, as shown in Figure 1.[2]

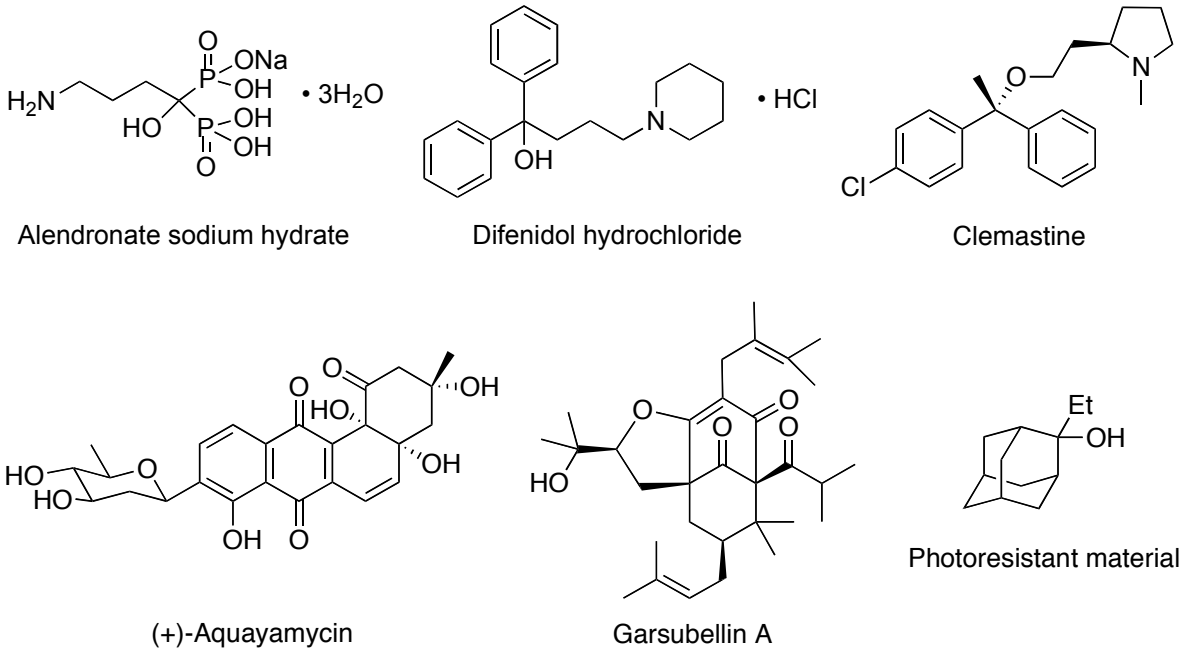
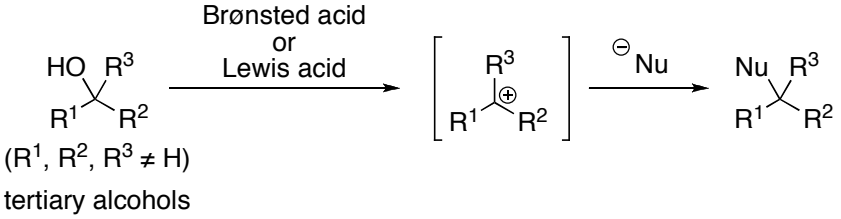


Figure 1. Tertiary alcohols used in pharmaceuticals, natural products, and functional materials.

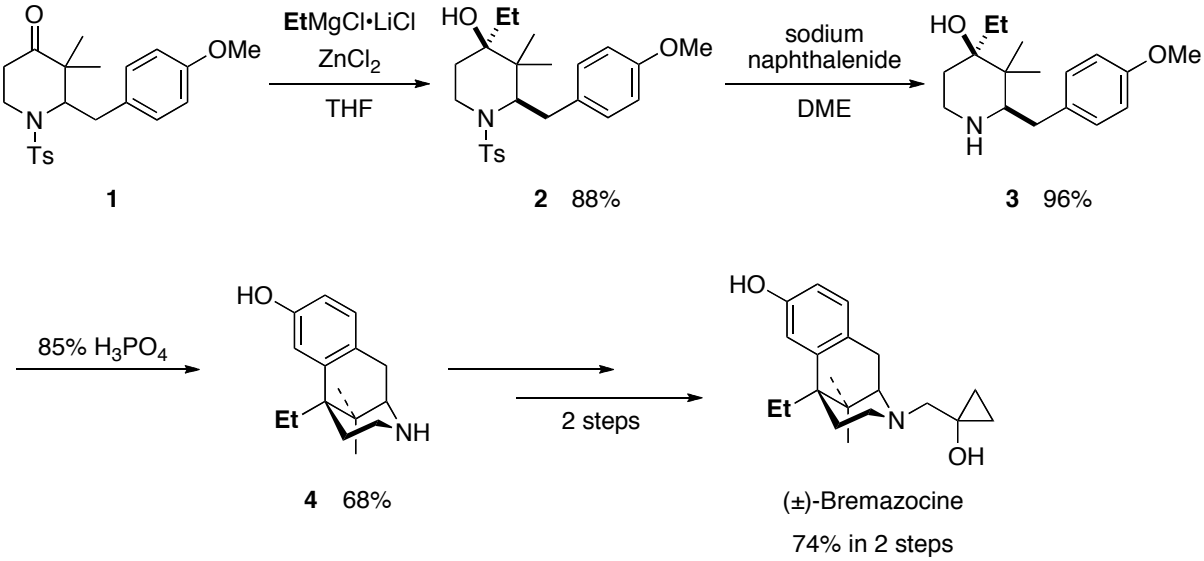
Furthermore, tertiary alcohols are also versatile intermediates for functionalized compounds, and allow us to take advantage of the reactive hydroxy group on tertiary carbon centers. Unlike those in primary and secondary alcohols, the hydroxy groups of tertiary alcohols can be directly substituted by nucleophiles (Nu) in the presence of a Brønsted acid or Lewis acid via the generation of a tertiary carbocation (Scheme 1).[3] In this transformation, functionalized tertiary carbon centers or even all-carbon quaternary carbon centers can be generated.

Scheme 1. Substitution Reactions of Tertiary Alcohols



As an example, Matsuo and co-workers recently reported the synthesis of (±)-Bremazocine (Scheme 2).[4] Ethylation to ketone **1** was a key reaction, and the corresponding tertiary alcohol **2** was obtained in 88% yield when EtMgCl·LiCl and $ZnCl_2$ were used. After deprotection of the *N*-Ts-group of **2**, tertiary alcohol **3** was transformed to benzomorphan **4** by treatment with H_3PO_4, which would promote the generation of a tertiary carbocation intermediate from **3**, and a subsequent intramolecular substitution reaction.

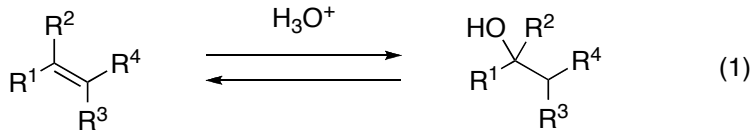
Scheme 2. Synthesis of (±)-Bremazocine



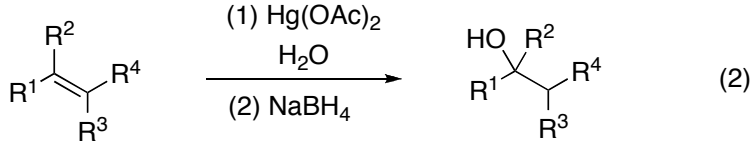
Basically, there are two major approaches for the synthesis of tertiary alcohols: a C–O bond-forming reaction (Schemes 3-1 and 3-2)[5,6] and a C–C bond-forming reaction (Schemes 3-3, 3-4, and 3-5).[1e,7,8]

Scheme 3. Traditional Approaches for the Synthesis of Tertiary Alcohols (R^1, $R^2 \neq H$)

(a) C–O bond-forming reactions

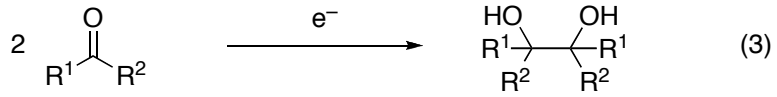


(1)

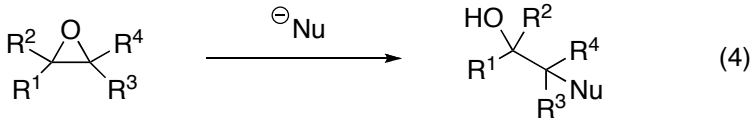


(2)

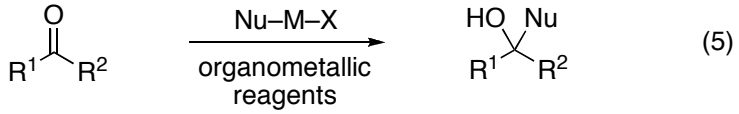
(b) C–C bond-forming reactions



(3)



(4)



(5)

The hydration and oxymercuration of olefins are well-known as traditional C–O bond-forming reactions (Schemes 3-1 and 3-2). These reactions give tertiary alcohols according to Markovnikov's rule. However, under acidic conditions, the starting olefins are sometimes recovered by retro-reaction from tertiary alcohols and/or polymerization of the starting olefins occurs. Moreover, in the case of oxymercuration, highly toxic mercury reagents are needed.

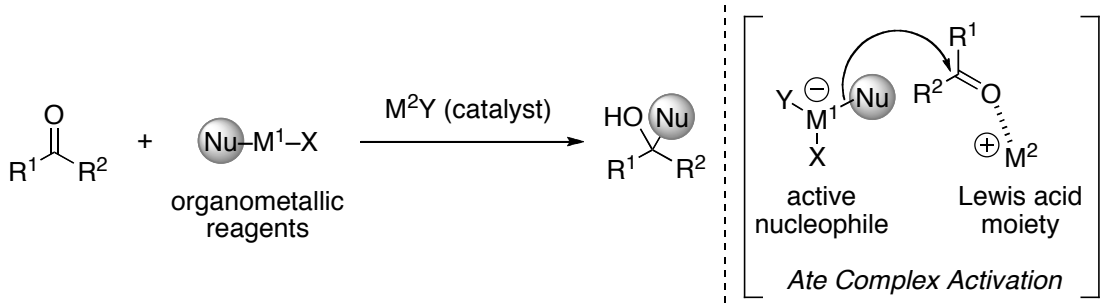
On the other hand, pinacol coupling reactions of ketones (Scheme 3-3), ring-opening

reactions of epoxide (Scheme 3-4), and nucleophilic addition of organometallic reagents to ketones (Scheme 3-5) are traditional C–C bond-forming reactions. Pinacol coupling reactions are usually limited to intermolecular homo coupling or intramolecular reactions. In contrast, various nucleophiles can be used in both the ring-opening reactions of epoxides and the nucleophilic addition of organometallic reagents to ketones. However, the starting epoxides are less available compared to ketones, and therefore the nucleophilic addition of organometallic reagents to ketones is one of the simplest and most convenient reactions for obtaining a variety of tertiary alcohols.

Traditional organometallic reagents, such as organolithium, organozinc, organomagnesium, and organosilicon reagents, are still powerful tools for constructing carbon–carbon bonds. In particular, the nucleophilic addition of traditional organometallic reagents to aldehydes proceeds smoothly, and a variety of secondary alcohols are obtained. However, ketones are much less-reactive than aldehydes due to steric and electronic constraints. Therefore, traditional organometallic reagents often cause serious problems when ketones are used as substrates: (1) these traditional organometallic reagents have weak nucleophilicity and/or strong basicity, and undesired side-reactions proceed, such as reduction, enolization, and retro reaction, (2) it is difficult to control the reactions even at –78 ºC, and (3) excess amounts of organometallic reagents are necessary. To overcome these problems, it is crucial to not only increase the nucleophilicity, but also to decrease the basicity of traditional organometallic reagents. For the selective addition of organometallic reagents to ketones, some effective stoichiometric and semi-stoichiometric additives have been developed.[1] However, to establish a more efficient and practical system for synthesizing tertiary alcohols, organometallic reagents should be controlled by a small amount of catalysts.

We found that organometallic ate complexes, which were generated in situ from organometallic reagents in the presence of catalytic amounts of metal salts, were effective for achieving the catalytic synthesis of tertiary alcohols (Scheme 4).[9] Through the generation of catalytic amounts of organometallic ate complexes, nucleophiles (Nu) would be activated and a carbon–carbon bond-forming reaction would proceed smoothly.

Scheme 4. Nucleophilic Addition to Ketones in the Presence of Ate Complex Catalysts

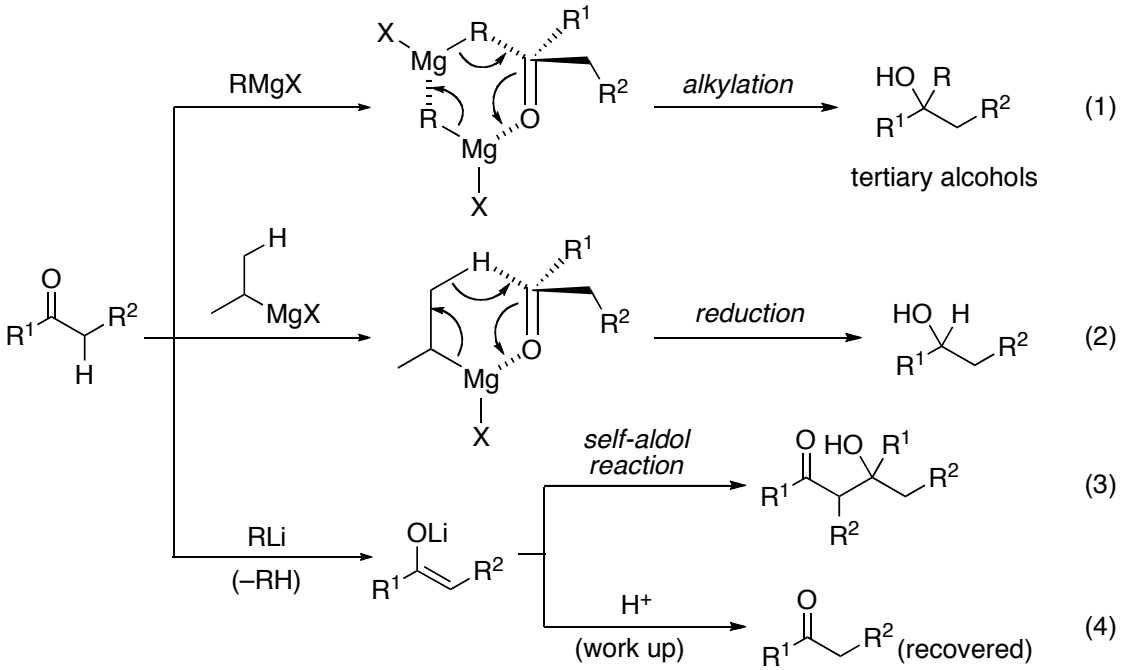


In Chapters 2 to 5, we report highly efficient methods for synthesizing tertiary alcohols catalyzed by organometallic ate complexes.

1-2. Grignard Addition with Stoichiometric Lanthanoid(III) Salts

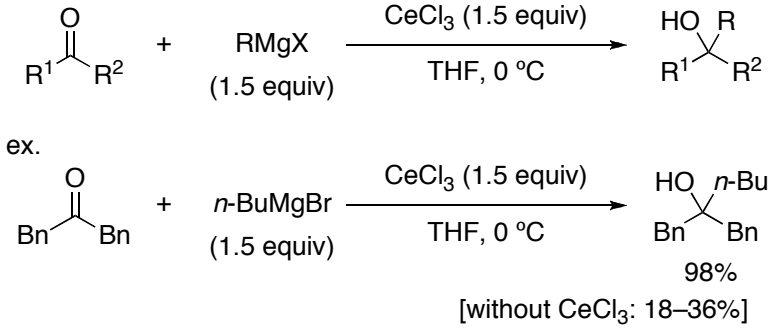
Grignard reagents (RMgX) and alkyllithium reagents (RLi) are common reagents for nucleophilic addition to ketones (Scheme 5-1). However, these reagents often give many undesired side products. In the case of Grignard reagents, reduction products are obtained due to β-hydride transfer (Scheme 5-2). In the case of alkyllithium reagents, self-aldol products and/or the starting ketones are obtained due to the enolization of ketones through the strong basicity of alkyllithium reagents (Schemes 5-3 and 5-4).

Scheme 5. Nucleophilic Addition of Alkyllithium Reagents and Grignard Reagents to Ketones



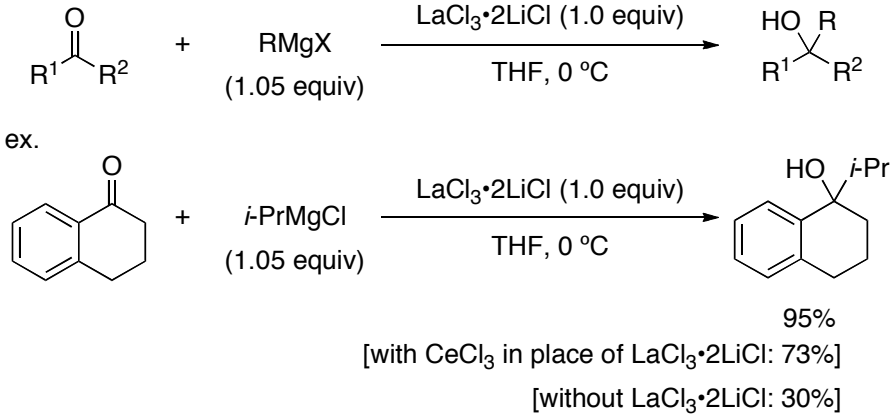
To overcome these problems, Imamoto and co-workers reported heterogeneous organocerium(III) complexes derived from Grignard reagents and stoichiometric $CeCl_3$ (Scheme 6).[10] These complexes underwent selective nucleophilic addition to ketones in THF at 0 °C. Even substrates that are susceptible to enolization could be used in this system. This is one of the pioneering developments in selective alkylation to ketones with Grignard reagents.

Scheme 6. Nucleophilic Addition of Grignard Reagents to Ketones with $CeCl_3$



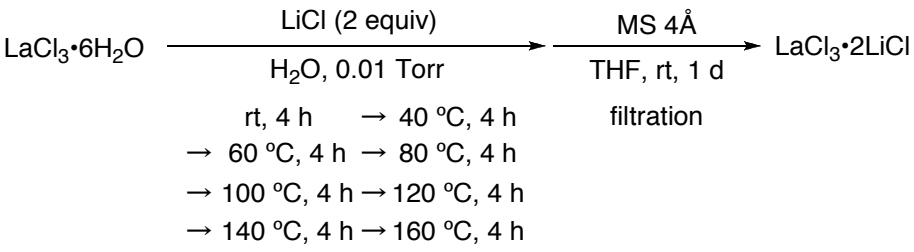
Later, Knochel and co-workers reported homogeneous organolanthanum(III) complexes derived from Grignard reagents and $LaCl_3 \cdot 2LiCl$ (Scheme 7).[11] A THF-soluble $LaCl_3 \cdot 2LiCl$ promoted the addition of Grignard reagents to various types of sterically hindered and/or enolable ketones.

Scheme 7. Nucleophilic Addition of Grignard Reagents to Ketones with $LaCl_3 \cdot 2LiCl$



However, before we can prepare these organolanthanoid(III) reagents, lanthanoid(III) chloride hydrates ($CeCl_3 \cdot 7H_2O$ and $LaCl_3 \cdot 6H_2O$) should be dried to the corresponding anhydrides in multi-step procedures at room temperature to 160 ºC under highly reduced pressure (<0.01 Torr) for a prolonged time (ca. 1–2 days) (Scheme 8).

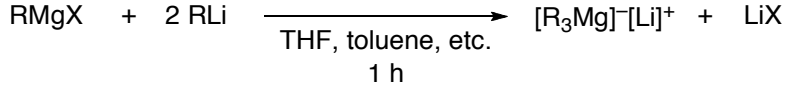
Scheme 8. Preparation of Lanthanoid(III) Anhydrides



1-3. Grignard Addition with Stoichiometric Magnesium(II) Ate Complexes

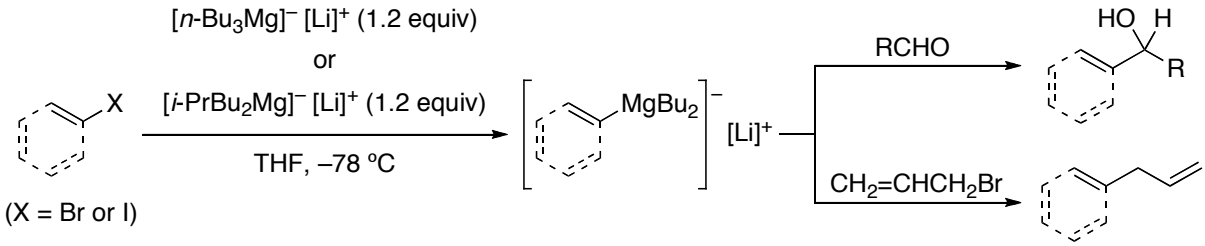
In sharp contrast to the organolanthanoid(III) reagents, magnesium(II) ate complexes as alkylating reagents were easily prepared in situ from Grignard reagents (1 equiv) and alkyllithium reagents (2 equiv) within 1 hour (Scheme 9).

Scheme 9. Preparation of Magnesium(II) Ate Complexes



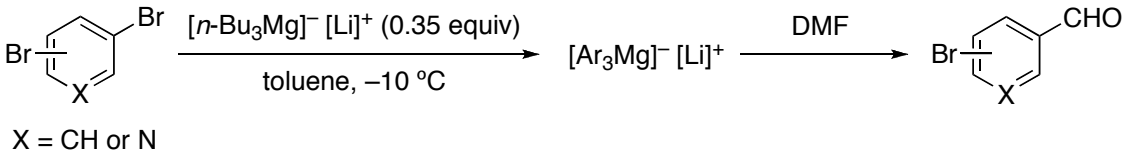
Oshima and co-workers reported arylation and alkenylation to electrophiles via a halogen-metal exchange reaction with trialkylmagnesium(II) ate complexes (Scheme 10).[12]

Scheme 10. Arylation and Alkenylation to Electrophiles via Halogen-Metal Exchange with Trialkylmagnesium(II) Ate Complexes



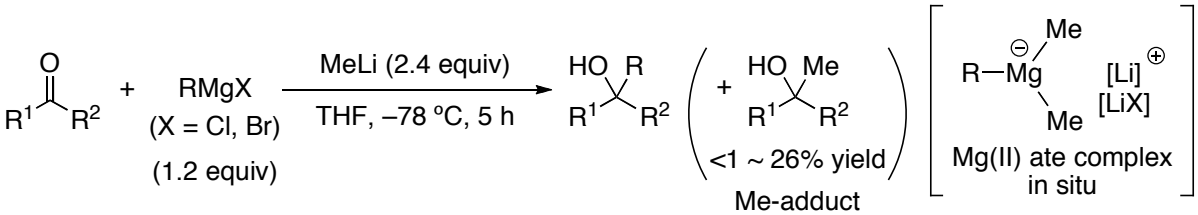
Moreover, Mase and co-workers reported the selective monosubstitution of dibromoarenes via a halogen-metal exchange reaction with tributylmagnesium(II) ate complex (Scheme 11).[13]

Scheme 11. Monosubstitution of Dibromoarenes via Halogen-Metal Exchange Reaction with Tributylmagnesium(II) Ate Complex



Later, our group found that trialkylmagnesium(II) ate complexes were effective for the selective alkylation of ketones (Scheme 12).[14] Magnesium(II) ate complexes have strong nucleophilicity and weak basicity compared to Grignard reagents and alkyllithium reagents. Nucleophilic addition to ketones proceeded smoothly at −78 ºC, and the desired tertiary alcohols were obtained in high yields. However, alkyllithium reagents are generally unstable, and only a few alkyllithium reagents are commercially available. Therefore, the desired *homo* trialkylmagnesium(II) ate complexes ($[R_3Mg]^-[Li]^+$) cannot always be prepared. To avoid the inconvenience of alkyllithium reagents, our group developed a selective alkylation with *hetero* trialkylmagnesium(II) ate complexes ($[RMe_2Mg]^-[Li]^+$), which gave R-adducts selectively in reactions with ketones. These *hetero* magnesium(II) ate complexes were easily prepared in situ from Grignard reagents (1.2 equiv) and commercially available methyllithium (2.4 equiv). However, a small amount of methyl-adducts were obtained as side products despite the high performance of magnesium(II) ate complexes.

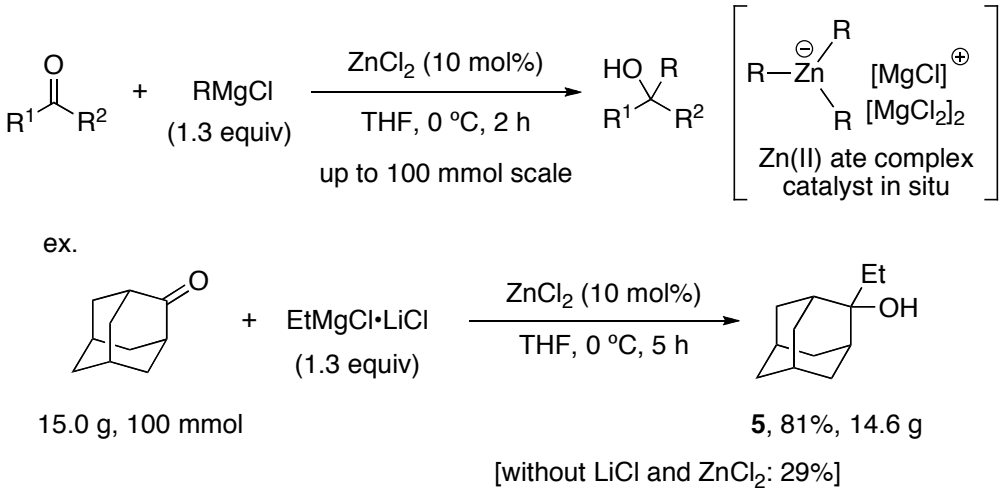
Scheme 12. Nucleophilic Addition to Ketones with *Hetero* Magnesium(II) Ate Complexes



1-4. Grignard Addition with Catalytic and Stoichiometric Zinc(II) Ate Complexes

Later, we found that zinc(II) ate complexes were also suitable for the selective alkylation of ketones (Scheme 13).[15] Zinc(II) ate complexes were easily prepared in situ from Grignard reagents and $ZnCl_2$ within 1 hour. The use of simple and inexpensive $ZnCl_2$ without further purification should offer a significant advantage over existing methods. Surprisingly, in the presence of 10 mol% of zinc chloride, the alkylation of ketones proceeded smoothly. Since catalytic amounts of zinc(II) ate complexes have stronger nucleophilicity than the original Grignard reagents, the desired tertiary alcohols were obtained in high yields with a minimum amount of byproducts. In addition, we tried a 100 mmol-scale synthesis of 2-ethyl-2-adamantanol (**5**), which was a useful photoresistant material. When only EtMgCl was used as an alkylating reagent, the desired tertiary alcohol **5** was obtained in 29% yield. In contrast, the yield was improved to 81% when $ZnCl_2$ catalyst was used.

Scheme 13. Catalytic Grignard Addition Reactions of Ketones with the Use of Zinc(II) Ate Complexes

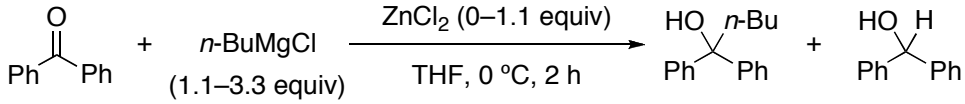


To the best of our knowledge, this is the first efficient catalytic system for Grignard addition reactions of ketones. In Chapter 2, we report a highly efficient alkylation of ketones and aldimines with Grignard reagents catalyzed by zinc(II) chloride.

However, in the $ZnCl_2$-catalyzed system, the alkylation of bulky ketones with bulky Grignard reagents is sometimes difficult, and undesired reduction byproducts are obtained in significant yields due to competitive uncatalyzed side reactions with free Grignard reagents. For example, *n*-butylation of benzophenone with only *n*-BuMgCl gave undesired reduction byproduct **7** in 81% yield, and desired tertiary alcohol **6** was obtained in only 11% yield (Scheme 14). Moreover, in the $ZnCl_2$-catalyzed system, the yield of desired tertiary alcohol **6** was improved to 51%, although reduction byproduct **7** was generated in 49% yield through the competitive uncatalyzed pathway with free *n*-BuMgCl in a background reaction. In sharp contrast to the $ZnCl_2$-catalyzed system, a reaction with stoichiometric zinc(II) ate complexes provided **6** in 91% yield with a minimum amount of competitive uncatalyzed side reactions with free Grignard reagent.[16]

In Chapter 3, we report a highly chemoselective stoichiometric alkylation of ketones with Grignard reagent-derived zinc(II) ate complexes.

Scheme 14. *n*-Butylation of Benzophenone



	6	**7**
n-BuMgCl (1.1 equiv)	11%	81%
n-BuMgCl (1.3 equiv) + $ZnCl_2$ (0.1 equiv)	51%	49%
n-BuMgCl (3.3 equiv) + $ZnCl_2$ (1.1 equiv)	91%	9%

1-5. Extremely Active Zinc(II) Ate Catalysts for Grignard Addition Reactions of Ketones with RMgBr and RMgI

Unfortunately, in the catalytic and stoichiometric zinc(II) ate complex systems, Grignard reagents were limited to RMgCl (R = alkyl, but not aryl), and therefore RMgBr and RMgI could not be used effectively. To expand the utility of our catalytic system, not only RMgCl but also RMgBr and RMgI should be applied. Generally, RMgBr and RMgI are easier to obtain commercially than

RMgCl, since RBr and RI react with Mg more smoothly than RCl. Moreover, RBr and RI are easier to obtain commercially than RCl, since the former are more easily prepared than the latter via halogenation. However, RMgBr and RMgI are less-reactive than RMgCl. To develop more active zinc(II) ate catalysts for RMgBr and RMgI as well as RMgCl, we introduced nontransferable alkyl groups on zinc(II) ate complexes, which themselves do not transfer to carbonyl compounds (Figure 2).

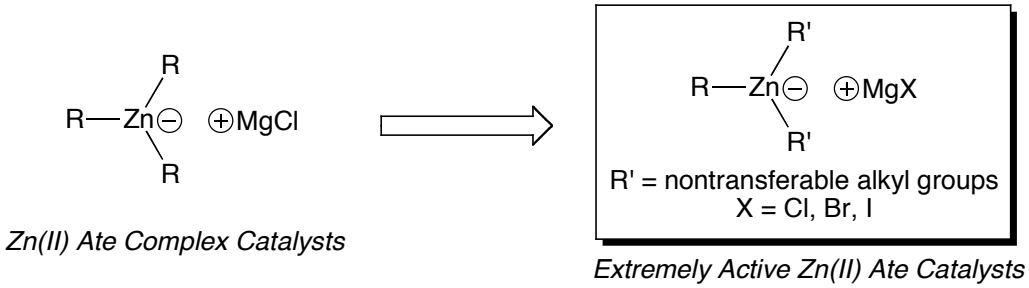
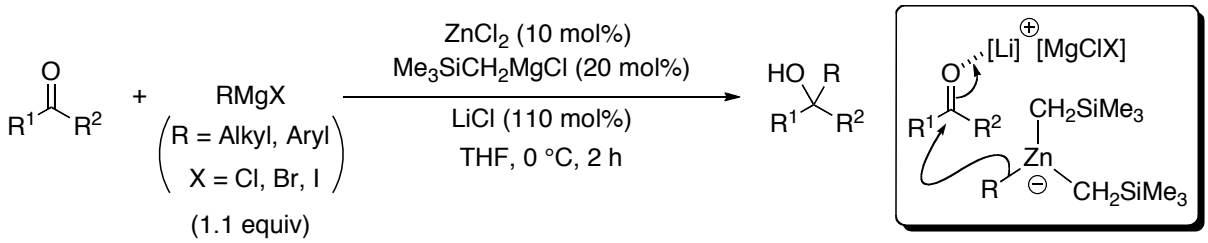


Figure 2. Design of more active zinc(II) ate complexes.

As a nontransferable ligand, we found that the Me_3SiCH_2 group was highly effective.[17–19] The corresponding zinc(II) ate complexes were prepared in situ from commercially available materials, such as $ZnCl_2$ (10 mol%), Me_3SiCH_2MgCl (20 mol%), and RMgX (X = Cl, Br, I). Moreover, we found that the addition of LiCl (110 mol%) was effective, and a variety of commercially available Grignard reagents RMgX (X = Cl, Br, I) could be used (Scheme 15). The activity of the Me_3SiCH_2-mixed zinc(II) ate complexes as catalytic alkylating reagents should increase with regard to the β-silyl effect and salt effect of LiCl.[20]

Scheme 15. Grignard Addition Reactions of Ketones Catalyzed by Extremely Active Zinc(II) Ate Complexes

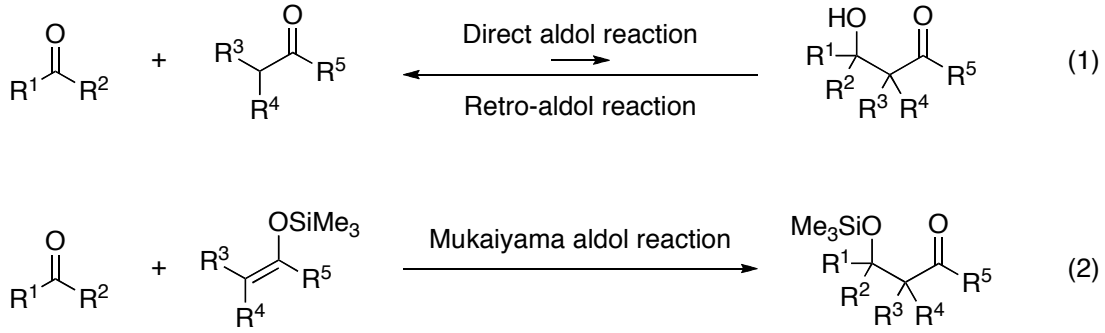


In Chapter 4, we report zinc(II)-catalyzed Grignard additions of RMgBr and RMgI to ketones. The mechanistic investigations are discussed based on a β-silyl effect and salt effect. In addition, to demonstrate the synthetic utility of this catalytic system, we synthesized cyproheptadine and a key intermediate of loratadine.[21]

1-6. Highly Efficient Synthesis of Functionalized Tertiary Alcohols Catalyzed by Potassium Alkoxide–Crown Ether Complexes

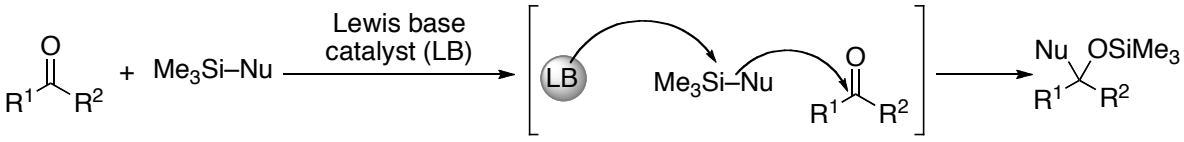
Grignard addition reactions are useful for synthesizing simple alcohols without functional groups. However, it is difficult, in principle, to synthesize functionalized alcohols in Grignard addition reactions, since the functional groups are often decomposed in the presence of reactive Grignard reagents. Alternatively, a catalytic direct aldol reaction is one of the most useful carbon–carbon bond-forming reactions for introducing functional groups in the corresponding alcohols (Scheme 16-1). However, when ketones are used as substrates, the equilibrium of the reaction significantly shifts to the starting materials under basic conditions due to rapid retro-aldol reaction, and the desired tertiary aldols are not obtained in high yields. In contrast to the direct aldol reaction, Mukaiyama aldol reactions with silyl enolates can minimize retro-aldol reactions by rapid protection with the silyl group (Scheme 16-2).

Scheme 16. Direct Aldol Reaction and Mukaiyama Aldol Reaction



Mukaiyama aldol reaction can be promoted by both Lewis acid catalysts and Lewis base catalysts. Lewis acid catalysts activate carbonyl compounds, and the Mukaiyama aldol reaction should proceed smoothly when aldehydes are used as substrates. However, sometimes they cannot activate less-reactive ketones in place of aldehydes sufficiently for the reaction to proceed smoothly. In sharp contrast, Lewis base catalysts (LB) activate organosilicon reagents, and thus generate reactive silicate complexes. Moreover, a nucleophile (Nu) attacks a carbonyl compound, and finally the silyl group is trapped by the corresponding alkoxide (Scheme 17).[22] As a silyl group, the trimethylsilyl (Me_3Si) group is attractive, since trimethylsilyl reagents are stable, easy to handle, and readily available. However, efficient Lewis base catalysts for trimethylsilyl reagents and ketones have not been well-developed, since trimethylsilyl reagents are less-reactive than trichlorosilyl reagents[22b] or trialkoxysilyl reagents.[23]

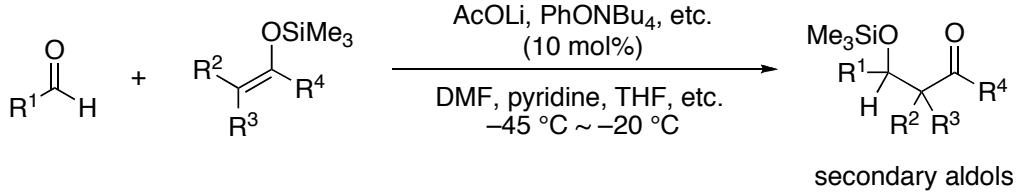
Scheme 17. Lewis Base-Catalyzed Addition of Organosilicon Reagents to Carbonyl Compounds



Mukaiyama and co-workers reported Lewis base catalysts for the Mukaiyama aldol reactions of aldehydes with trimethylsilyl enolates (Scheme 18).[22] As catalysts, they used simple lithium salts

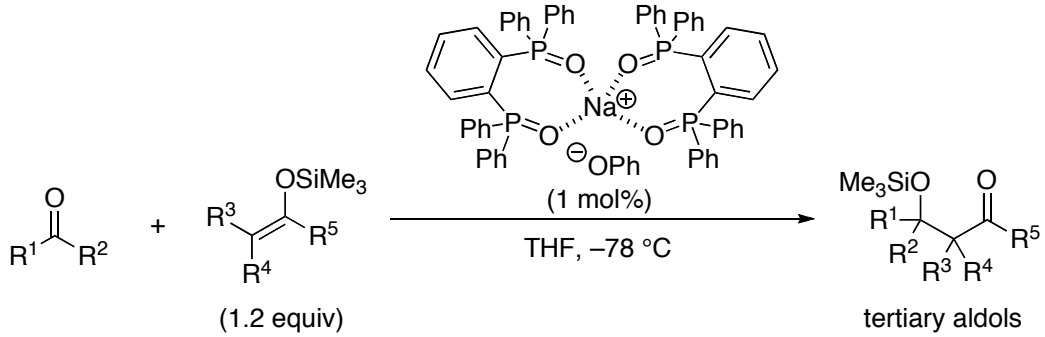
and ammonium salts such as AcOLi and $PhONBu_4$, respectively. However, the substrates were limited to aldehydes, and less-reactive ketones were not suitable for their catalysts.

Scheme 18. Mukaiyama Aldol Reactions with Simple Lewis Base Catalysts



Recently, our group developed sodium phenoxide–phosphine oxide complexes as Lewis base catalysts for Mukaiyama aldol reactions of ketones (Scheme 19).[24] The Na^+ moiety was surrounded by a catalytic amount of phosphine oxide, and the naked counter anion (PhO^-) was generated. This naked PhO^- could be an extremely active Lewis base catalyst, and activate trimethylsilyl enolates. In this catalytic system, Mukaiyama aldol reactions of ketones proceeded even at –78 ºC.

Scheme 19. Mukaiyama Aldol Reactions with Sodium Phenoxide–Phosphine Oxide Complexes



The sodium phenoxide–phosphine oxide complex was highly active, despite its bulkiness and high molecular weight. From the perspective of green chemistry, we should design more simple, more active, and smaller molecular catalysts. To activate trimethylsilyl reagents, generation of the naked PhO^- moiety is important. Therefore, the stronger trapping of alkaline metal ions would make

the naked PhO^- moiety a stronger Lewis base. In this regard, a simple multidentate-coordinative crown ether in place of bidentate-coordinative phosphine oxide might be attractive (Figure 3).

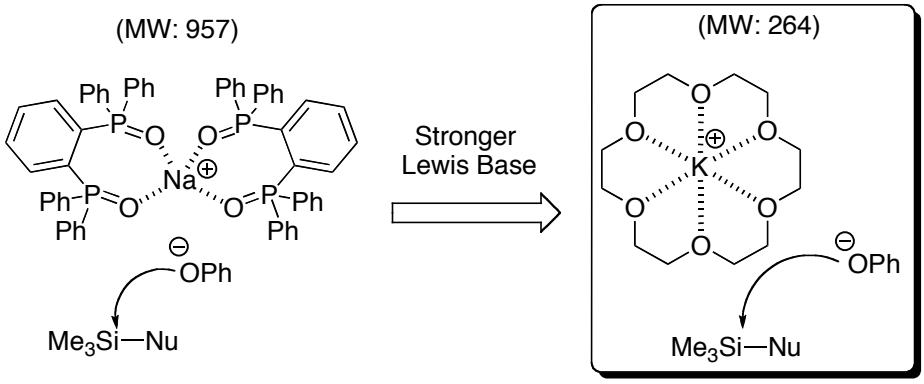
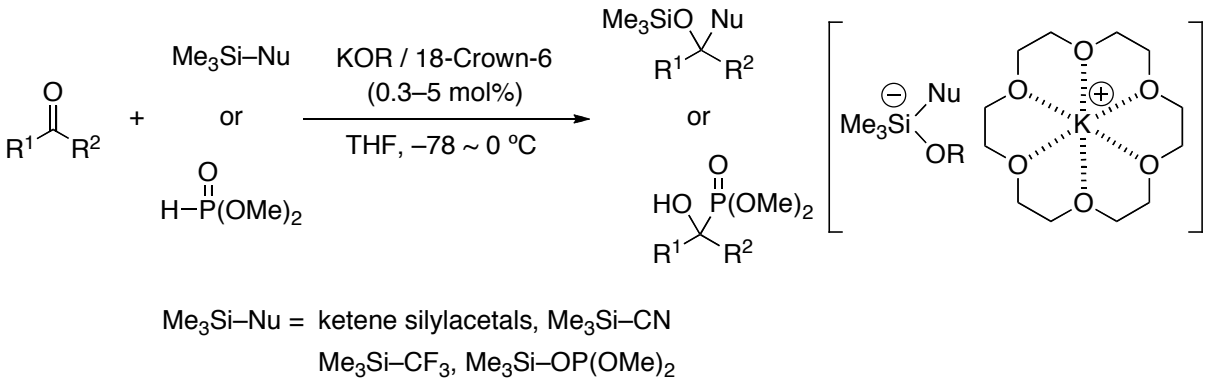


Figure 3. Development of stronger Lewis base catalysts.

As expected, Mukaiyama aldol reactions between ketones and trimethylsilyl enolates proceeded smoothly under mild conditions in the presence of potassium alkoxide–crown ether complexes as Lewis base catalysts (0.3–5 mol%) (Scheme 20).[25] Moreover, the catalytic activity of crown ether complexes was much higher than that of the previous phosphine oxide complexes, and the desired tertiary alcohols were obtained in higher yields. Potassium alkoxide–crown ether complexes also promoted other addition reactions of ketones with trimethylsilyl reagents such as silyltrifluoromethylation, silylcyanation, and silylphosphonylation. Interestingly, we found that they were also effective as Brønsted base catalysts for the direct hydrophosphonylation of ketones.

Scheme 20. Synthesis of Fuctionalized Tertiary Alcohols Catalyzed by Potassium Alkoxide–Crown Ether Complexes



$Me_3Si–Nu$ = ketene silylacetals, $Me_3Si–CN$
$Me_3Si–CF_3$, $Me_3Si–OP(OMe)_2$

In Chapter 5, we report a highly efficient synthesis of functionalized tertiary alcohols catalyzed by potassium alkoxide–crown ether complexes.

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Chapter 2

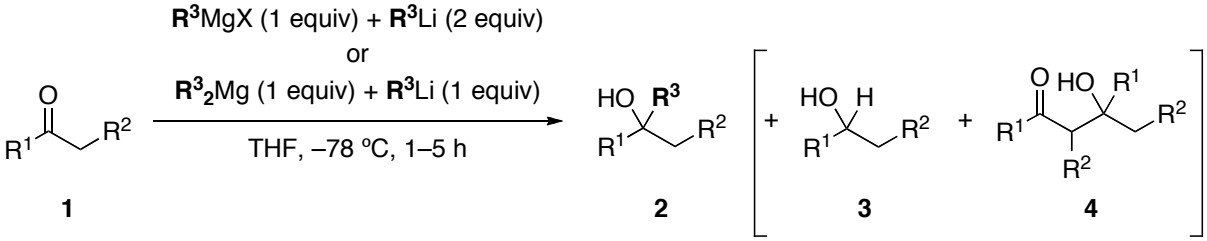
Highly Efficient Alkylation of Ketones and Aldimines with Grignard Reagents Catalyzed by Zinc(II) Chloride

Abstract: A highly efficient alkylation of ketones and aldimines with Grignard reagents in the presence of catalytic trialkylzinc(II) ate complexes derived from $ZnCl_2$ (10 mol%) in situ was developed. This simple Zn(II)-catalyzed alkylation could minimize the well-known but serious problems with the use of only Grignard reagents, which leads to reduction and aldol side products, and the yield of desired alkylation products could be improved.

2-1. Introduction

For carbon-carbon bond-forming reactions, the addition of organometallic 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 (Scheme 1).[3] Recently, the addition of stoichiometric or an excess amount of $CeCl_3$,[3] LiCl,[4] $LiClO_4$,[5] $FeCl_2$,[6] and $LaCl_3 \cdot 2LiCl$[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., $RCeCl_2$, $RMgCl_2 \cdot Li$, 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 of ketones (Scheme 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 of 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.

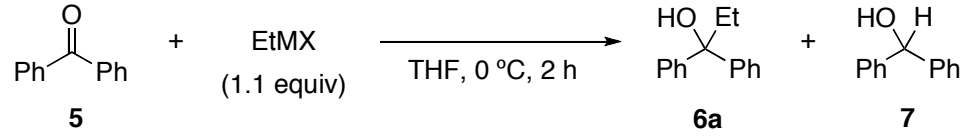
Scheme 1. Alkylation of Ketones with Trialkylmagnesium(II) Ate Complexes



2-2. Results and Discussion

First, ethylation of benzophenone (**5**) with organometallic 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 (**6a**) 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 **6a** 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 **6a** 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 **6a** 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).

Table 1. Ethylation of Benzophenone with Organometallic Reagents[a]



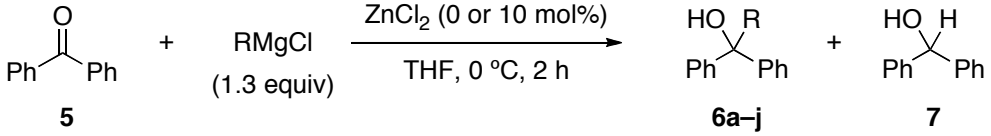
5 **6a** **7**

entry	EtMX	yield (%) of **6a** [**7**]	entry	EtMX	yield (%) of **6a** [**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.

Therefore, we next examined other alkylations of **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 **6a** but also Me, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu, and *c*-Hex adducts (**6b**–**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).

Table 2. Alkylation of Benzophenone Catalyzed by $ZnCl_2$

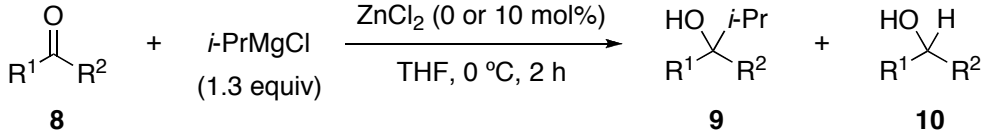


entry	R		yield (%) of **6** [**7**]		entry	R		yield (%) of **6** [**7**]	
			with Zn	without Zn				with Zn	without Zn
1	Et	**6a**	84 [15]	25 [72]	6	*s*-Bu	**6f**	50 [23]	43 [26]
2	Me	**6b**	94 [0]	91 [0]	7[a]	*c*-Hex	**6g**	57 [9]	51 [14]
3[a]	*n*-Pr	**6c**	71 [29]	14 [86]	8	vinyl	**6h**	96 [0]	92 [0]
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]

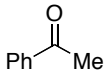
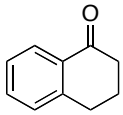
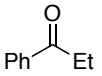
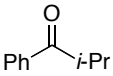
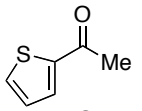
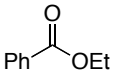
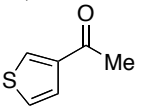
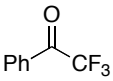
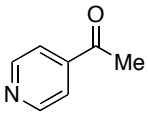
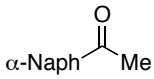
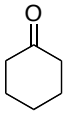
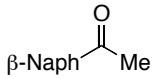
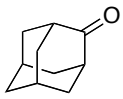
[a] Solvent was Et_2O. [b] $ZnCl_2$ (30 mol%) and *n*-BuMgCl (1.7 equiv) were used.

Next, isopropylation of ketones **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 of 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).

Table 3. Isopropylation of Ketones Catalyzed by $ZnCl_2$



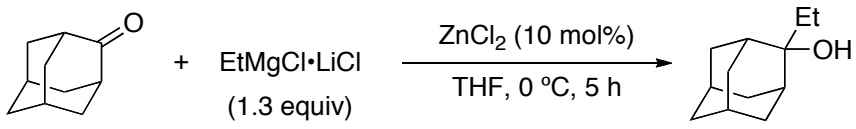
8 **9** **10**

entry	ketone (**8**)		yield (%) of **9** [**10**]			entry	ketone (**8**)		yield (%) of **9** [**10**]		
				with Zn	without Zn					with Zn	without Zn
1		**8a**	**9a**	85 [0]	31 [11]	8		**8g**	**9g**	80 [6]	20 [36]
2		**8b**	**9b**	95 [0]	56 [38]						
3		**8c**	**9c**	87 [12]	38 [59]	9		**8h**	**9h**	91 [0]	40 [0]
4[a]		–	**9c**	80 [12]	61 [29]	10		**8i**	**9i**	86 [0]	29 [8]
5		**8d**	**9d**	78[b] [20]	23[c] [73]	11		**8j**	**9j**	80 [7]	73 [11]
6		**8e**	**9e**	76 [0]	33 [12]	12		**8k**	**9k**	60 [–]	43 [–]
7		**8f**	**9f**	76 [0]	35 [12]	13		**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.

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

Scheme 2. Ethylation of 2-Adamantanone in 100 mmol-Scale



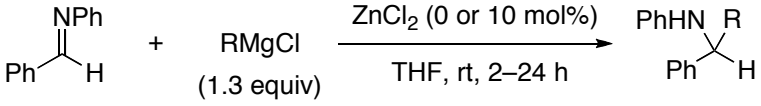
8l 15.0 g, 100 mmol

11 81%, 14.6 g

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

Encouraged by the efficient alkylation of 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 of *N*-Ts imines also proceeded selectively (entries 11 and 12).[15]

Table 4. Alkylation of Aldimine Catalyzed by $ZnCl_2$



12 **13**

entry	R		yield (%) of **13**		entry	R		yield (%) of **13**	
			with Zn	without Zn				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 $PhCH_2NHTs$.

Finally, a plausible catalytic cycle including transition-state assembly in this $ZnCl_2$-catalyzed alkylation of 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.

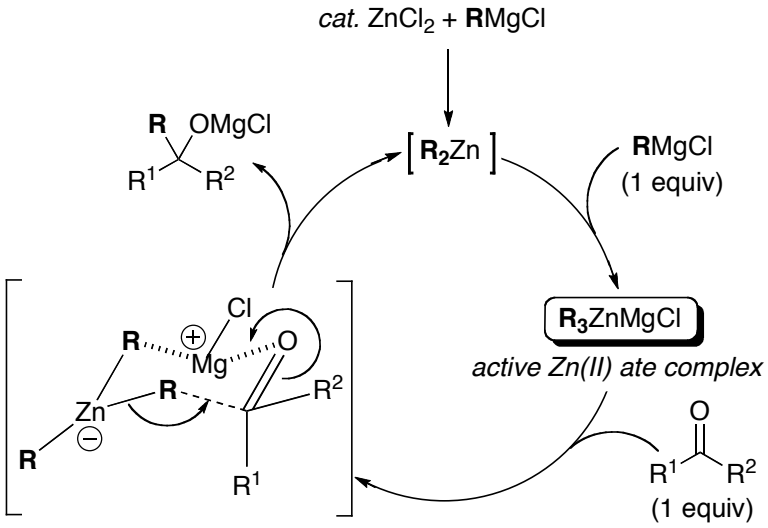


Figure 1. Proposed catalytic cycle and transition-state assembly.

2-3. Conclusion

In summary, we have developed a highly efficient alkylation of 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.

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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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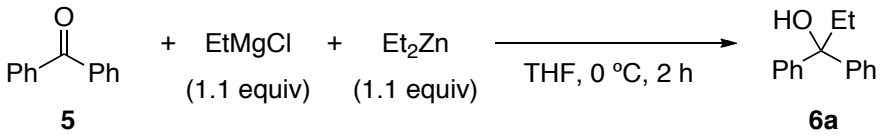
15. Et addition to less reactive PhCH=NBn proceeded in 27% yield with $ZnCl_2$ catalyst and in 12% yield without $ZnCl_2$.
16. When LiCl is used as a co-additive, the $[MgCl]^+$ moiety may change to $[Li]^+$. Further investigations for the mechanistic aspects are underway.
17. Six-membered ring assembly 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.

Experimental Section

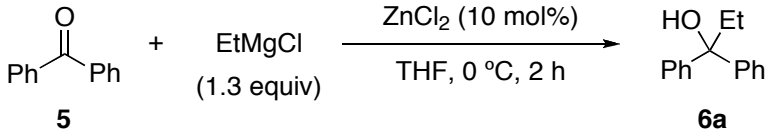
General Methods. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Mercury-300 (75 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{19}F NMR spectra were measured on Varian Mercury-300 (282 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (BTF at –63.24 ppm in deuterochloroform). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. The products were purified by neutral column chromatography on silica gel (Kanto Chemical Co., Inc. 37560). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. In experiments that required dry solvents, diethylether (dehydrate) and tetrahydrofuran (dehydrate) were purchased from Kanto Chemical Co., Inc. $ZnCl_2$ (Wako); LiCl (Wako), EtLi (0.5 *M* in benzene/cyclohexane, Aldrich); Et_2Zn (1.0 *M* in hexane, Kanto Chemical Co., Inc.); Me_2Zn (1.0 *M* in hexane, Kanto Chemical Co., Inc.); MeMgCl (3.0 *M* in THF, Aldrich); EtMgCl (1.0 *M* in THF, Kanto Chemical Co., Inc.); EtMgBr (1.0 *M* in THF, Kanto Chemical Co., Inc.); *n*-PrMgCl (2.0 *M* in Et_2O, Aldrich); *i*-PrMgCl (2.0 *M* in THF, Aldrich); *n*-BuMgCl (1.0 *M* in THF, Kanto Chemical Co., Inc.); *s*-BuMgCl (1.0 *M* in THF, Kanto Chemical Co., Inc.); *c*-HexMgCl (2.0 *M* in in Et_2O, Aldrich) *n*-OctMgCl (2.0 *M* in THF, Aldrich); (vinyl)MgCl (1.5 *M* in THF, Kanto Chemical Co., Inc.); (allyl)MgCl (2.0 *M* in THF, Aldrich); BnMgCl (1.0 *M* in THF, Kanto Chemical Co., Inc.) were used.

Representative procedure for alkylation to ketones with stoichiometric $Et_3ZnMgCl$ (Table 1, entry 10).



To a solution of EtMgCl (1.0 *M* in THF, 3.30 mL, 3.30 mmol) was added Et_2Zn (1.0 *M* in hexane, 3.30 mL, 3.30 mmol) at room temperature under nitrogen atmosphere. This solution was stirred at that temperature for 1 h. Then, the solution was cooled to 0 °C, and benzophenone (**5**) (546 mg, 3.00 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h, and the reaction was monitored by TLC. The resulting mixture was quenched by saturated aqueous NH_4Cl (5 mL), extracted with AcOEt (10 mL × 3), and washed by brine (5 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: hexane/EtOAc), to give the desired product (**6a**) (541 mg, 85% yield).

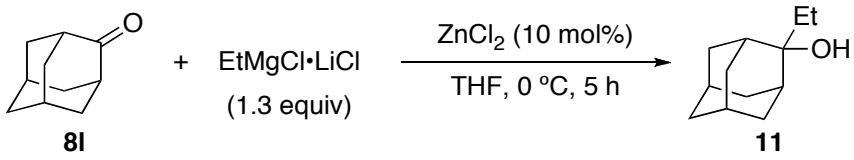
Representative procedure for $ZnCl_2$-catalyzed alkylation to ketones with Grignard reagents (Table 1, entry 11).



To a solution of EtMgCl (1.0 *M* in THF, 3.90 mL, 3.90 mmol) was added $ZnCl_2$ (40.8 mg, 0.30 mmol) at room temperature under nitrogen atmosphere. This solution was stirred at that temperature for 1 h. Then, the solution was cooled to 0 °C, and benzophenone (**5**) (546 mg, 3.00 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h, and the reaction was monitored

by TLC. The resulting mixture was quenched by saturated aqueous NH_4Cl (5 mL), extracted with AcOEt (10 mL × 3), and washed by brine (5 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: hexane/EtOAc), to give the desired product (**6a**) (535 mg, 84% yield).

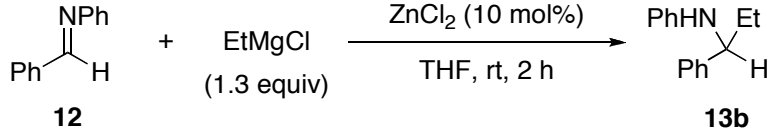
Representative procedure for $ZnCl_2$-catalyzed alkylation to 2-adamantanone with Grignard reagents.



8l **11**

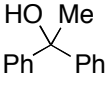
To a solution of EtMgCl (1.0 *M* in THF, 130 mL, 130 mmol) was added $ZnCl_2$ (1.33 g, 10.0 mmol) and LiCl (5.49 g, 130 mmol) at room temperature under nitrogen atmosphere. This solution was stirred at that temperature for 1 h. Then, 2-adamamthanone (**8l**) (15.0 g, 100 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 5 h, and the reaction was monitored by TLC. The resulting mixture was quenched by saturated aqueous NH_4Cl (100 mL), extracted with AcOEt (100 mL × 3), and washed by brine (100 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: hexane/EtOAc), to give the desired product (**11**) (14.8 g, 81% yield).

Representative procedure for $ZnCl_2$-catalyzed alkylation to aldimine with Grignard reagents (Table 4, entry 1).

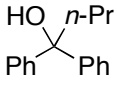


To a solution of EtMgCl (1.0 *M* in THF, 3.90 mL, 3.90 mmol) was added $ZnCl_2$ (40.8 mg, 0.30 mmol) at room temperature under nitrogen atmosphere. This solution was stirred at that temperature for 1 h. Then, *N*-phenylbenzylideneamine (**12**) (547 mg, 3.00 mmol) was added at room temperature. The mixture was stirred for 2 h, and the reaction was monitored by TLC. The resulting mixture was quenched by saturated aqueous NH_4Cl (5 mL), extracted with AcOEt (10 mL × 3), and washed by brine (5 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: hexane/EtOAc), to give the desired product (**13b**) (513 mg, 81% yield).

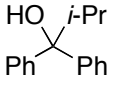
1,1-Diphenyl-1-propanol (6a):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 2.05 (bs ,1H), 2.32 (q, *J* = 7.2 Hz, 2H), 7.18-7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 34.4, 78.4, 126.1, 126.7, 128.1, 146.9.



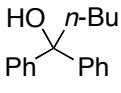
1,1-Diphenyl-1-ethanol (6b):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.18 (bs, 1H), 7.20-7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 76.1, 125.7, 126.8, 128.0, 147.9.



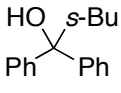
1,1-Diphenyl-1-butanol (6c):[1,3,4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.30 (m, 2H), 2.08 (bs, 1H), 2.25 (m, 2H), 7.18-7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 17.2, 44.5, 78.5, 126.2, 126.8, 128.1, 147.4.



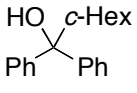
2-Methyl-1,1-diphenyl-1-propanol (6d):[1,3,5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 1.53 (bs, 1H), 2.02 (m, 1H), 7.20-7.42 (m, 10H).



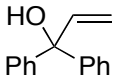
1,1-Diphenyl-1-pentanol (6e):[1,6,7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.20-1.42 (m, 4H), 2.09 (bs, 1H), 2.27 (m, 2H), 7.15-7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.1, 26.1, 41.9, 78.4, 126.2, 126.8, 128.2, 147.4.



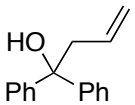
2-Methyl-1,1-diphenyl-1-butanol (6f):[8,9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 1.40-1.70 (m, 2H), 2.01 (bs, 1H), 2.53 (m, 1H), 7.10-7.54 (m, 10H).



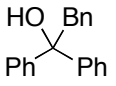
Cyclohexyldiphenylmethanol (6g):[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.80 (m, 10H), 2.06 (s, 1H), 2.43 (m, 1H), 7.13-7.34 (m, 6H), 7.48 (d, *J* = 7.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 26.9, 27.5, 46.1, 80.5, 126.0, 127.3, 128.1, 146.7.



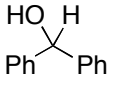
1,1-Diphenyl-2-propen-1-ol (6h):[11,12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (bs, 1H), 5.32 (d, *J* = 11.4 Hz, 1H), 5.33 (d, *J* = 16.2 Hz, 1H), 6.51 (dd, *J* = 15.9, 11.7 Hz, 1H), 7.20-7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.4, 114.0, 126.9, 127.3, 128.2, 143.6, 145.8.



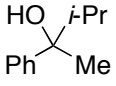
1,1-Diphenyl-3-buten-1-ol (6i):[13,14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (bs, 1H), 3.08 (d, *J* = 7.5 Hz, 2H), 5.18 (d, *J* = 10.2 Hz, 1H), 5.25 (d, *J* = 17.4 Hz, 1H), 5.66 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 4H), 7.45 (d, *J* = 7.8 Hz, 4H).



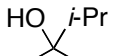
1,1,2-Triphenyl-1-ethanol (6j):[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 1H), 3.64 (bs, 2H), 6.86-6.92 (m, 2H), 7.10-7.34 (m, 9H), 7.40-7.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.8, 77.9, 126.1, 126.7, 126.8, 127.9, 128.0, 130.8, 135.7, 146.5.



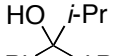
Diphenylmethanol (7):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (bs, 1H), 5.80 (bs, 1H), 7.20-7.43 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.3, 126.6, 127.6, 128.5, 143.8.



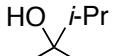
3-Methyl-2-phenyl-2-butanol (9a):[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 1.53 (s, 3H), 1.63 (s, 1H), 2.02 (m, 1H), 7.20-7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 17.4, 26.7, 38.6, 77.8, 125.2, 126.4, 127.8, 147.8.



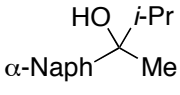
2-Methyl-3-phenyl-3-pentanol (9b):[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (t, *J* = 7.2 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.58 (s, 1H), 1.89 (q, *J* = 6.9 Hz, 2H), 2.05 (m, 1H), 7.18-7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 16.6, 17.5, 32.0, 37.5, 79.3, 125.9, 126.1, 127.7, 145.0.



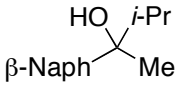
2,4-Dimethyl-3-phenyl-3-pentanol (9c):[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 6H), 1.50 (s, 1H), 2.31 (m, 2H), 7.22-7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 17.4, 33.7, 80.9, 126.1, 126.6, 127.2, 142.8.



1,1,1-Trifluoro-3-methyl-2-phenylbutan-2-ol (9d):[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 2.39 (bs, 1H), 2.51 (m, 1H), 7.30-7.45 (m, 3H), 7.54 (d, *J* = 7.2 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.2.

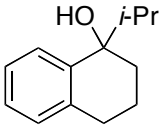


3-Methyl-2-(1-naphthalenyl)-2-butanol (9e):[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.74 (s, 3H), 1.93 (bs, 1H), 2.81 (m, 1H), 7.00-8.05 (m, 6H), 8.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 18.2, 25.1, 36.1, 78.9, 124.2, 124.5, 124.9, 127.1, 128.3, 129.1, 130.8, 135.0, 143.2.

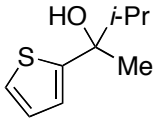


3-Methyl-2-(2-naphthalenyl)-2-butanol (9f):[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.62 (bs, 3H), 1.73 (bs, 1H), 2.15 (m, 1H), 7.40-7.95

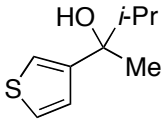
(m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 17.6, 26.9, 38.5, 76.9, 123.7, 124.1, 125.6, 125.9, 127.4, 127.5, 128.2, 132.3, 133.2, 145.5.



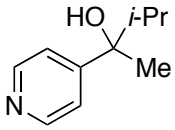
1-Isopropyl-1,2,3,4-tetrahydro-1-naphthol (9g):[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.68-1.94 (m, 4H), 2.40 (m, 1H), 2.60-2.84 (m, 2H), 7.09 (d, *J* = 6.9 Hz, 1H), 7.12-7.26 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 1H).



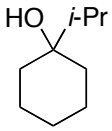
3-Methyl-2-(2-thienyl)-2-butanol (9h):[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 1.53 (s, 3H), 1.92 (s, 1H), 2.05 (m, 1H), 6.90 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.95 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.20 (dd, *J* = 4.8, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 17.6, 26.8, 39.7, 76.4, 122.7, 123.6, 126.5, 153.1.



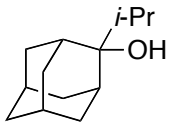
3-Methyl-2-(3-thienyl)-2-butanol (9i):[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 1.51 (s, 3H), 1.71 (s, 1H), 2.00 (m, 1H), 7.04 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.13 (d, *J* = 3.3, 1.5 Hz, 1H), 7.26 (d, *J* = 5.1, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 17.5, 26.3, 38.6, 76.1, 119.8, 125.2, 126.1, 149.6.



3-Methyl-2-(4-pyridinyl)-2-butanol (9j):[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.51 (s, 3H), 1.72, (bs, 1H), 1.99 (m, 1H), 7.33 (d, *J* = 6.3 Hz, 2H), 8.53 (d, *J* = 6.3 Hz, 2H).



1-Isopropyl-1-cyclohexanol (9k):[26,27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.9 Hz, 6H), 1.07 (s, 1H), 1.20-1.65 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 22.0, 26.0, 34.2, 37.6, 73.1.

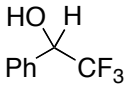


2-Isopropyl-2-adamantanol (9l):[28,29] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.9 Hz, 6H), 1.17 (s, 1H), 1.40-2.20 (14H), 2.30 (m, 1H).

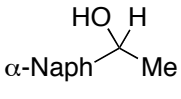
1-Phenylethanol (10a):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J = 6.6 Hz, 3H), 4.40 (bs, 1H), 4.76 (q, J = 6.6 Hz, 1H), 7.18 (m, 1H), 7.24-7.32 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 70.3, 125.3, 127.3, 128.3, 145.8.

1-Phenyl-1-propanol (10b):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3H), 1.67 (m, 2H), 2.94 (bs, 1H), 4.41 (t, J = 6.3 Hz, 1H), 7.16-7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 31.9, 75.9, 125.9, 127.4, 128.3, 144.6.

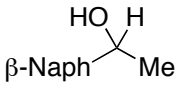
2-Methyl-1-phenyl-1-propanol (10c):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H,), 1.92 (m, 1H), 2.26 (bs, 1H), 4.31 (d, J = 6.9 Hz, 1H), 7.22-7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 19.0, 35.2, 80.0, 126.5, 127.3, 128.1, 143.6.



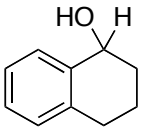
2,2,2-Trifluoro-1-phenylethanol (10d):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (bs, 1H), 4.93 (q, J = 6.9 Hz, 1H), 7.25-7.50 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.8 (q, J = 31.5 Hz), 124.2 (q, J = 285 Hz), 127.4, 128.6, 129.5, 133.8.



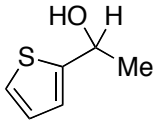
1-(1-Naphthyl)-1-ethanol (10e):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, J = 6.6 Hz, 3H), 3.32 (bs, 1H), 5.35 (q, J = 6.6 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.33-7.36 (m, 2H), 7.48 (d, J = 6.9 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.72 (m, 1H), 7.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 62.8, 123.6, 125.4, 125.5, 125.9, 127.0, 127.2, 128.8, 132.0, 133.9, 134.4.



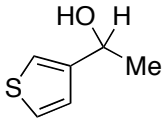
1-(2-Naphthyl)-1-ethanol (10f):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (d, J = 6.3 Hz, 3H), 2.33 (bs, 1H), 5.54 (m, 1H), 7.25-7.50 (m, 3H), 7.59 (d, J = 6.9 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.78-7.84 (m, 1H), 7.98-8.04 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.2, 63.4, 125.3, 126.0, 127.3, 127.4, 127.4 127.5, 128.1, 132.1, 133.4, 135.9.



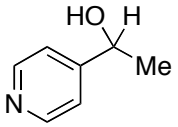
1,2,3,4-Tetrahydro-1-naphthol (10g):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-2.00 (m, 4H), 2.17 (d, J = 6.0 Hz, 1H), 2.61-2.75 (m, 2H), 4.71 (m, 1H), 7.07 (m, 1H), 7.12-7.23 (m, 2H), 7.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 29.2, 32.2, 68.0, 126.0, 127.4, 128.6, 128.9, 137.0, 138.7.



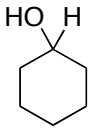
1-(2-Thienyl)-1-ethanol (10h):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* = 6.3 Hz, 3H), 2.09 (d, *J* = 4.2 Hz, 1H), 5.12 (dd, *J* = 6.3, 4.2 Hz, 1H), 6.98-6.93 (m, 2H), 7.23 (dd, *J* = 4.5, 1.5 Hz, 1H).



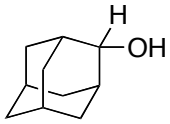
1-(3-Thienyl)-1-ethanol (10i):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.6 Hz, 3H), 3.19 (d, *J* = 3.9 Hz, 1H), 4.87 (m, 1H), 7.05 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.12 (m, 1H), 7.25 (dd, *J* = 5.1, 3.0 Hz, 1H).



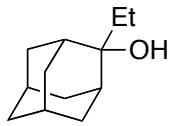
1-(4-Pyridinyl)-1-ethanol (10j):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.6 Hz, 3H), 4.10 (bs, 1H), 4.88 (q, *J* = 6.6 Hz, 1H), 7.30 (dd, *J* = 4.8, 1.5 Hz, 2H), 8.44 (dd, *J* = 4.5, 1.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 68.1, 120.7, 149.0, 156.1.



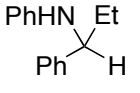
Cyclohexanol (10k):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.37 (m, 5H), 1.55 (m, 1H), 1.65-1.80 (m, 2H), 1.82-1.96 (m, 2H), 2.21 (bs, 1H), 3.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.5, 35.5, 70.2.



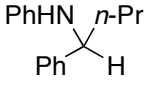
2-Adamanthanol (10l):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, *J* = 12.6 Hz, 2H), 1.60-1.95 (m, 11H), 2.07 (d, *J* = 12.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 27.5, 31.0, 34.6, 36.5, 37.6, 74.5.



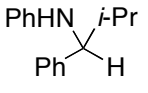
2-Ehtyl-2-adamantanol (11):[31] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 7.8 Hz, 3H), 1.69 (d, *J* = 7.5 Hz, 2H), 1.32 (s, 1H), 1.50-2.25 (14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.3, 27.5, 30.6, 33.2, 34.7, 36.8, 38.5, 39.4, 74.9.



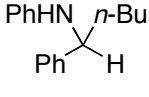
***N*-Phenyl-(1-phenylpropyl)amine (13a):**[31,32,33,34] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 6.9 Hz, 3H), 1.85 (m, 2H), 4.07 (bs, 1H), 4.24 (t, *J* = 6.9 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 2H), 6.63 (t, *J* = 7.5 Hz, 1H), 7.04-7.11 (m, 2H), 7.18-7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 31.8, 59.9, 113.4, 117.3, 126.7, 127.0, 128.7, 129.2, 144.4, 147.7.



***N*-Phenyl-(1-phenylbutyl)amine (13b):**[33,34,35] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.26-1.50 (m, 2H), 1.66-1.82 (m, 2H), 4.06 (bs, 1H), 4.30 (t, *J* = 6.9 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.61 (t, *J* = 7.5 Hz, 1H), 7.06 (m, 2H), 7.18-7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.6, 41.2, 58.1, 113.3, 117.2, 126.4, 126.9, 128.5, 129.1, 144.4, 147.6.

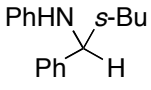


***N*-Phenyl-(2-methyl-1-phenylpropyl)amine (13c):**[33,34] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 2.03 (m, 1H), 4.11 (bs, 1H), 4.80 (bs, 1H), 6.50 (d, *J* = 7.5 Hz, 2H), 6.60 (t, *J* = 7.5 Hz, 1H), 7.02-7.10 (m, 2H), 7.18-7.36 (m, 5H).

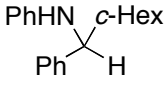


***N*-Phenyl-(1-phenylpentyl)amine (13d):**[32,33,35] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 3H), 1.20-1.46 (m, 4H), 1.79 (m, 2H), 4.05 (bs, 1H), 4.28 (t, *J* = 6.6 Hz, 1H), 6.51 (d, *J* = 8.4 Hz,

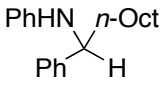
2H), 6.61 (t, J = 7.5 Hz, 1H), 7.02-7.12 (m, 2H), 7.16-7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.6, 28.5, 38.7, 58.2, 113.2, 117.1, 126.4, 126.8, 128.5, 129.1, 144.1, 147.5.



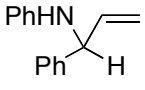
***N*-Phenyl-(1-phenyl-2-methylbutyl)amine (13e, ca. 3:2 diastereomer mixture):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.9 Hz, 3H-a), 0.90 (d, J = 6.9 Hz, 3H-b), 0.91 (t, J = 7.5 Hz, 3H-a), 0.94 (t, J = 7.2 Hz, 3H-b), 1.06-1.88 (m, 3H), 4.10 (bs, 1H), 4.19 (m, 1H-a), 4.29 (m, 1H-b), 6.49 (d, J = 7.5 Hz, 2H), 6.60 (t, J = 6.9 Hz, 1H), 7.05 (m, 2H), 7.16-7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) a: δ 11.8, 16.1, 25.4, 41.4, 62.7, 113.3, 117.0, 126.8, 127.4, 128.2, 129.1, 142.4, 147.8; b: δ 12.0, 14.5, 25.7, 41.9, 61.6, 113.2, 117.0, 126.7, 127.0, 128.2, 128.3, 143.1, 147.8.



***N*-Phenyl-(1-phenyl-1-cyclohexylmethyl)amine (13f):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90-1.94 (m, 11H), 4.09 (d, J = 6.3 Hz, 1H), 4.11 (bs, 1H), 6.47 (d, J = 7.8 Hz, 2H), 6.59 (t, J = 7.5 Hz, 1H), 7.05 (m, 2H), 7.18-7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 29.5, 30.3, 45.0, 63.5, 113.2, 117.0, 126.7, 127.2, 128.2, 129.0, 142.7, 147.8.

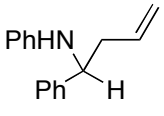


***N*-Phenyl-(1-phenylnonyl)amine (13g):** ^{1}H NMR (300 MHz, CDCl3) δ 0.80-1.90 (m, 17H), 4.05 (bs, 1H), 4.28 (bs, 1H), 6.50 (d, J = 7.2 Hz, 2H), 6.18 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.5 Hz, 2H), 7.20-7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.7, 26.4, 29.2, 29.5, 29.6, 31.9, 39.0, 58.6, 113.5, 117.3, 126.5, 126.9, 128.6, 129.1, 144.5, 147.8.

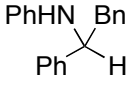


***N*-Phenyl-(1-phenylallyl)amine (13h):**[36] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (bs, 1H), 4.93 (bs, 1H), 5.22 (d, J = 10.2 Hz, 1H), 5.27 (d, J = 17.4 Hz, 1H), 6.04 (ddd, J = 17.1, 10.2, 6.3

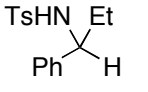
Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.20-7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.9, 113.6, 116.1, 117.7, 127.2, 127.5, 128.8, 129.1, 139.1, 141.9, 147.3.



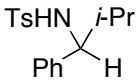
***N*-Phenyl-(1-phenyl-3-butenyl)amine (13i):**[37,38,39] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42-2.68 (m, 2H), 4.15 (bs, 1H), 4.37 (m, 1H), 5.14 (d, *J* = 8.4 Hz, 1H), 5.18 (d, *J* = 16.8 Hz, 1H), 5.75 (m, 1H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.39 (d, *J* = 7.5 Hz, 1H), 7.07 (m, 2H), 7.20-7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.3, 57.1, 113.4, 117.3, 118.3, 126.2, 126.9, 128.6, 129.0, 134.6, 143.5, 147.3.



***N*-Phenyl-(1,2-diphenylethyl)amine (13j):**[40] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (dd, *J* = 13.8, 8.4 Hz, 1H), 3.14 (dd, *J* = 14.1, 5.7 Hz, 1H), 4.12 (bs, 1H), 4.57 (m, 1H), 6.45 (d, *J* = 7.8 Hz, 2H), 6.62 (t, *J* = 6.9 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 6.3 Hz, 2H), 7.15-7.35 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.0, 59.5, 113.9, 117.8, 126.5, 126.7, 127.1, 128.5, 128.5, 129.0, 129.2, 137.6, 143.1, 146.9.



4-Methyl-*N*-(1-phenylpropyl)benzenesulfonamide (14):[41] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.5 Hz, 3H), 1.79 (m, 2H), 2.38 (s, 3H), 4.20 (m, 1H), 5.49 (bs, 1H), 7.01 (m, 2H), 7.16 (m, 5H), 7.55 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 21.3, 30.5, 59.7, 126.5, 126.9, 127.0, 128.2, 129.1, 137.6, 140.6, 142.7.



4-Methyl-*N*-(2-methyl-1-phenylpropyl)benzenesulfonamide (15):[42] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, *J* = 6.6 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 1H), 1.92 (m, 1H), 2.31 (s, 3H), 4.02 (m, 1H), 5.66 (bs, 1H), 6.95-7.52 (m, 7H), 7.49 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 19.2, 21.2, 34.2, 64.1, 126.7, 126.8, 126.9, 127.8, 128.9, 137.5, 139.8, 142.5.

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Chapter 3

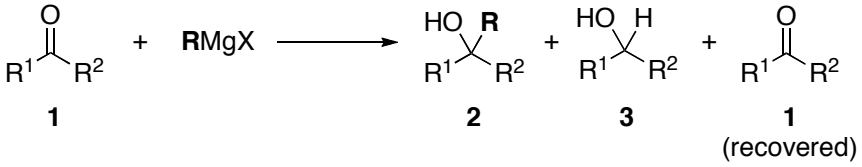
Highly Chemoselective Stoichiometric Alkylation of Ketones with Grignard Reagent-Derived Zinc(II) Ate Complexes

Abstract: A highly chemoselective alkylation of ketones with Grignard reagent-derived stoichiometric zinc(II) ate complexes was developed. Zinc(II) ate complexes are readily prepared at room temperature within one hour in situ from $ZnCl_2$ and Grignard reagents without unstable alkyllithium reagents. The desired tertiary alcohols were obtained in much improved yields due to the minimization of background reactions with free Grignard reagents.

3-1. Introduction

Traditional Grignard reagents have been widely used as alkylating reagents and organometallic bases for over a hundred years.[1] Since Grignard reagents are both readily commercially available (over 200 can be purchased) and easy to prepare, the addition of Grignard reagents to carbonyl compounds is the most fundamental carbon–carbon bond-forming reaction in organic chemistry to give the corresponding alkylated alcohols (Scheme 1). Over the past decade, efficient nonasymmetric and asymmetric syntheses of tertiary alcohols from ketones and organometallic reagents have been studied.[2] Nevertheless, with regard to Grignard addition to ketones, there have been only a few reports, by Imamoto et al.,[3] Knochel et al.,[4] Ishihara et al.,[5] and other groups.[6] An inherent difficulty in the Grignard addition to ketones **1** is that reduction of byproducts **3** and the starting ketone/self-aldol adducts are often obtained in addition to the desired alcohols **2** due to a competing enolization (Scheme 1). To overcome this serious problem, increased nucleophilicity and decreased basicity of the alkylating reagents are needed. We report here a highly chemoselective alkylation of ketones with Grignard reagent-derived stoichiometric zinc(II) ate complexes which minimizes undesired side products.[7]

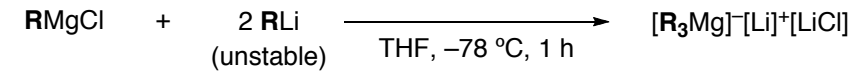
Scheme 1. Traditional Grignard Addition to Ketones to Provide Tertiary Alcohols



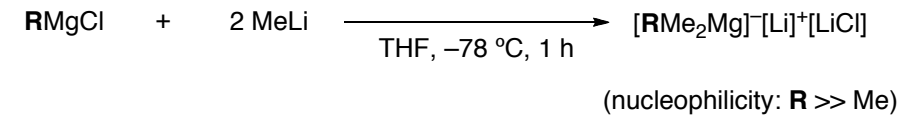
3-2. Results and Discussion

Scheme 2. Preparation of Magnesium(II) and Zinc(II) Ate Complexes from Grignard Reagents in Situ

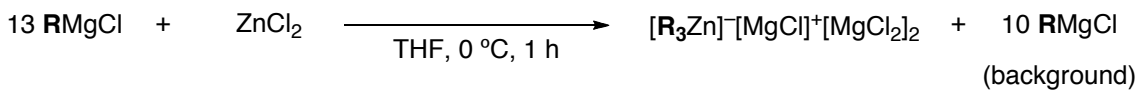
(a) stoichiometric *homo* Mg(II) ate complexes (ref. 5a)



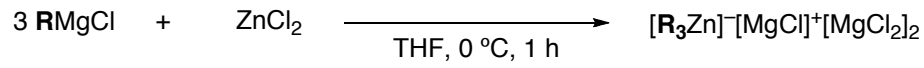
(b) stoichiometric *hetero* Mg(II) ate complexes (ref. 5a)



(c) catalytic Zn(II) ate complexes (ref. 5b)



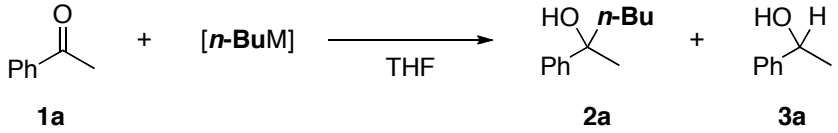
(d) stoichiometric Zn(II) ate complexes



We previously developed a stoichiometric alkylation of ketones with magnesium(II) ate complexes derived from Grignard reagents and alkyllithium reagents.[5a] In that study, we found that enolizable acetophenone (**1a**) was easily deprotonated by basic and less nucleophilic organometallic reagents, such as *n*-BuMgCl and *n*-BuLi, and the yield of the desired *n*-Bu-adduct **2a** was not good due to the recovery of the starting material **1a** after acidic workup of Li enolate (Table 1, entries 1 and 2). In contrast, the mixture prepared from *n*-BuMgCl (1 equiv) and *n*-BuLi (2 equiv) at –78 °C within 1 hour, which would lead to the magnesium(II) ate complex [*n*-$Bu_3Mg]^-[Li]^+$[LiCl] in situ (Scheme 2a), dramatically improved the chemoselectivity of the *n*-butylation of **1a**, and the desired *n*-Bu adduct **2a** was obtained in 99% yield (entry 3). Despite the high performance of

magnesium(II) ate complexes, however, alkyllithium reagents other than MeLi, (*n*, *sec*, *tert*)-BuLi, and *n*-HexLi are usually unstable and commercially unavailable, and the preparation of *homo* magnesium(II) ate complexes with $[R_3Mg]^-$ is limited in principle. Our previously reported *hetero* magnesium(II) ate complexes [*n*-$BuMe_2Mg]^-[Li]^+[LiCl]$, which were prepared from *n*-BuMgCl (1 equiv) and MeLi (2 equiv, Scheme 2b),[5a] gave **2a** as a major product but with the undesired Me-adduct (26%, entry 4). Meanwhile, zinc(II) ate complexes could be prepared in situ from Grignard reagents (3 equiv) and $ZnCl_2$ (1 equiv) at room temperature within 1 hour, and thus do not require alkyllithium reagents (Scheme 2d). Fortunately, for both laboratory and industrial applications, zinc(II) ate complexes are more stable than magnesium(II) ate complexes, and the reaction can proceed at temperatures ranging from room temperature to 0 °C. Thus, the mixture of *n*-BuMgCl (3.3 equiv) and $ZnCl_2$ (1.1 equiv), which would lead to the zinc(II) ate complex [*n*-$Bu_3Zn]^-[MgCl]^+[MgCl_2]_2$ in situ, provided the desired *n*-Bu-adduct **2a** in 98% yield (entry 5). $ZnCl_2$ catalysis with catalytic zinc(II) ate reagents[5b] (Scheme 2c) was effective in this case, and **2a** was obtained in 98% yield (entry 6).

Table 1. *n*-Butylation of Acetophenone (**1a**)



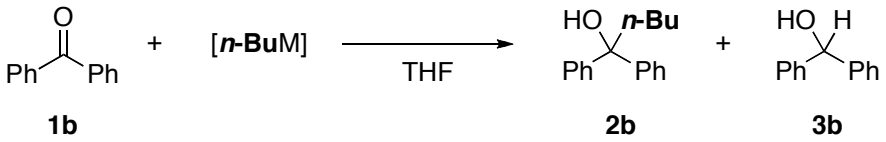
1a **2a** **3a**

entry	reagents [*n*-BuM] (equiv)	conditions	yield of **2a** (%)	yield of **3a** (%)	recovery of **1a** (%)
1	***n*-Bu**MgCl (1)	–78 °C, 5 h	50	8	33
2	***n*-Bu**Li (1)	–78 °C, 5 h	62	0	31
3	***n*-Bu**MgCl (1) + ***n*-Bu**Li (2)	–78 °C, 5 h	99	0	0
4[a]	***n*-Bu**MgCl (1) + MeLi (2)	–78 °C, 5 h	72	0	0
5	***n*-Bu**MgCl (3.3) + $ZnCl_2$ (1.1)	0 °C, 2 h	98	0	2
6	***n*-Bu**MgCl (1.3) + $ZnCl_2$ (0.1)	0 °C, 2 h	98	0	2

[a] Me-adduct was obtained in 26% yield.

In another investigation, *n*-butylation was examined with benzophenone (**1b**), which often provides reduction byproducts in alkylation (Table 2). *n*-BuMgCl, *n*-BuMgCl/LiCl, and *n*-BuLi gave the reduction compound **3b** as a major product (entries 1–4), while magnesium(II) ate complex provided the desired product **2b** in 95% yield (entry 5). *Hetero* magnesium(II) ate complexes prepared from *n*-BuMgCl (1.2 equiv) and MeLi (2.4 equiv) gave **2a** selectively in 92% yield, although the Me-adduct was also provided in 8% yield (entry 6). A previously established $ZnCl_2$-catalyzed system also improved the yield of **2b**, but **3b** was generated in 49% yield through the uncatalyzed pathway with free *n*-BuMgCl in the background (entry 7). In contrast, the stoichiometric zinc(II) ate complex {[*n*-Bu_3Zn]$^-$[MgCl]$^+$[$MgCl_2$]$_2$ in situ} provided **2b** in good yield (91%) compared to the stoichiometric magnesium(II) ate complex (entry 8 vs. entries 5 and 6). Moreover, the yield of **2b** was improved to 97% in the presence of 1 equivalent amount of LiCl[8] (entry 9). The enhanced chemoselectivity of the *n*-butylation with LiCl is probably due to a salt effect, which, as proposed by Knochel et al., may involve the dissociation of polymeric Grignard reagents to monomeric RMgCl·LiCl or [$RMgCl_2$]$^-$[Li]$^+$.[8] The corresponding zinc(II) ate complexes [R_3Zn]$^-$[MgCl]$^+$[$MgCl_2$]$_2$[LiCl] or [R_3Zn]$^-$[Li]$^+$[$MgCl_2$]$_3$ generated in situ might be more polarized than [R_3Zn]$^-$[MgCl]$^+$[$MgCl_2$]$_2$, and the nucleophilicity of R could be increased effectively to promote chemoselective alkylation. Meanwhile, the halogenated pseudo magnesium(II) ate complex [*n*-$BuMgCl_2$]$^-$[Li]$^+$ (entry 3) was much less nucleophilic toward the inactive ketone **1b** than Li^+-polarized [*n*-Bu_3Mg]$^-$[Li]$^+$[LiCl] (entry 5) and [*n*-Bu_3Zn]$^-$[Li]$^+$[$MgCl_2$]$_3$ (entry 9), and the yield of **2b** with *n*-BuMgCl/LiCl was not as good as expected (entry 3). LiBr and LiCl had almost the same effect in improving the yield of **2b** (entry 10), and this result strongly supported the generation of Li^+-polarized zinc(II) ate complexes [*n*-Bu_3Zn]$^-$[Li]$^+$[MgX_2]$_3$ (X = Cl/Br).

Table 2. *n*-Butylation of Benzophenone (**1b**)



1b **2b** **3b**

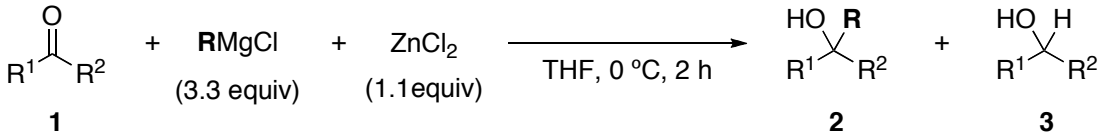
entry	reagents [*n*-BuM] (equiv)	conditions	yield of **2b** (%)	yield of **3b** (%)
1	***n*-Bu**MgCl (1.2)	–78 ºC, 2 h	0	56
2	***n*-Bu**MgCl (1)	0 ºC, 2 h	11	81
3	***n*-Bu**MgCl (1.1) + LiCl (1.1)	0 ºC, 2 h	12	78
4	***n*-Bu**Li (1)	–78 ºC, 5 h	58	38
5	***n*-Bu**MgCl (1) + ***n*-Bu**Li (2)	–78 ºC, 2 h	95	5
6[a]	***n*-Bu**MgCl (1) + MeLi (2)	–78 ºC, 2 h	92	0
7	***n*-Bu**MgCl (1.3) + $ZnCl_2$ (0.1)	0 ºC, 2 h	51	49
8	***n*-Bu**MgCl (3.3) + $ZnCl_2$ (1.1)	0 ºC, 2 h	91	9
9	***n*-Bu**MgCl (3.3) + $ZnCl_2$ (1.1) + LiCl (1.1)	0 ºC, 2 h	97	3
10	***n*-Bu**MgCl (3.3) + $ZnCl_2$ (1.1) + LiBr (1.1)	0 ºC, 2 h	95	5

[a] Me-adduct was obtained in 8% yield.

Next, we examined various stoichiometric alkylations of ketones with zinc(II) ate complexes, $[R_3Zn]^-[MgCl]^+[MgCl_2]_2$, which were prepared in situ from Grignard reagents and $ZnCl_2$ (Table 3). As an alkyl moiety (R), we examined Et, *n*-Pr, *i*-Pr, and *c*-Hex, whose lithium reagents (RLi) are significantly unstable and thus expensive if obtained commercially, since the corresponding magnesium(II) ate complexes would not be readily provided from RMgX and RLi. Greatly improved results may be expected compared to the $ZnCl_2$-catalysis because the stoichiometric addition of zinc(II) ate complexes may not include the background reaction with free Grignard reagents. Isopropylation is one of the most difficult alkylations, and the mixture of *i*-PrMgCl and $ZnCl_2$ was highly effective for 1-acetonaphthone (**1c**), 2-acetonaphthone (**1d**), and α-tetralone (**1e**, entries 1–3). Isopropylation, *n*-propylation, and cyclohexylation of benzophenone (**1b**) proceeded

smoothly, and the desired corresponding products were obtained in 81–90% yields (entries 4–6). Isopropylation of aliphatic ketones such as 2-adamantanone (**1f**) gave the desired product in improved yield (67%, entry 7).[9] Ethylation of ethyl benzoylformate (**1g**) as an α-ketoester gave a single product via selective keto-ethylation without any side reactions (entry 8). Isopropylation of an α-functionalized ketone such as trifluoroacetophenone (**1h**) gave the product in much improved yield (85%, entry 9). Aldehydes **1i** and **1j** were also examined, and the reactions with stoichiometric zinc(II) ate complexes were found to be effective (entries 10 and 11). $ZnCl_2$ catalysis {data in brackets, '[xx]'} also considerably improved the traditional Grignard addition in which no additives were used [data in parentheses, '(xx)'], but the background pathway with free Grignard reagents could not be effectively excluded.

Table 3. Alkylation of Ketones with Zinc(II) Ate Complexes Derived from Grignard Reagents[a,b]



1 **2** **3**

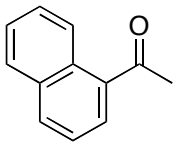
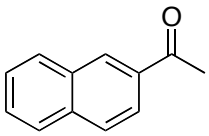
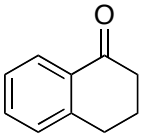
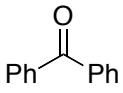
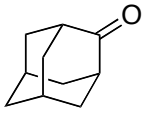
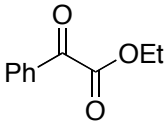
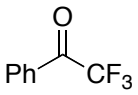
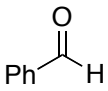
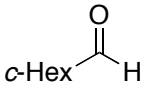
entry	ketone (**1**)[c]		**R**	yield of **2** (%)	yield of **3** (%)	recov. of **1** (%)
1		**1c**	*i*-Pr	96 [76] (33)	0 [0] (12)	4 [10] (13)
2		**1d**	*i*-Pr	81 [76] (35)	0 [0] (12)	 (11)
3		**1e**	*i*-Pr	91 [80] (20)	0 [6] (36)	9 [14] (30)
4		**1b**	*i*-Pr	90 [75] (62)	3 [10] (14)	7 [0] (0)
5		**1b**	*n*-Pr	81 [71] (14)	17 [29] (86)	2 [0] (0)
6		**1b**	*c*-Hex	81 [57] (51)	6 [9] (14)	13 [0] (0)
7		**1f**	*i*-Pr	67[d] [45][d] (16)[d]	24[d] [51][d] (78)[d]	9[d] [4][d] (6)[d]
8		**1g**	Et	100[d] [71][d] (33)[d]	0	0

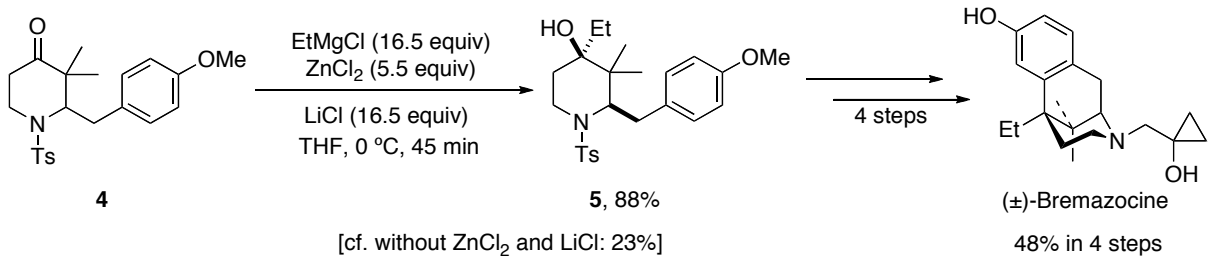
Table 3. Continued

entry	ketone (**1**)[c]		**R**	yield of **2** (%)	yield of **3** (%)	recov. of **1** (%)
9		**1h**	*i*-Pr	85[d] [17] (23)[d]	15[d] [80] (73)[d]	0[d] [3] (4)[d]
10		**1i**	*i*-Pr	95 [76] (67)	5 [23] (32)	0 [1] (1)
11		**1j**	*i*-Pr	98 [88] (86)	2 [12] (14)	0 [1] (0)

[a] Data in brackets '[xx]' are the yields when 10 mol% of $ZnCl_2$ and 1.3 equiv of Grignard reagent were used. [b] Data in parentheses '(xx)' are the yields when only Grignard reagent (1.1 equiv) was used. [c] Aldehydes were used in entries 10 and 11. [d] LiCl (1.1 equiv) was added.

Taking advantage of our highly chemoselective stoichiometric alkylation of ketones with Grignard reagent-derived zinc(II) ate complexes, Matsuo et al. recently reported the synthesis of (±)-Bremazocine which is a κ-opiloid agonist (Scheme 3).[10] To synthesize tertiary alcohol **5** as a key intermediate, they examined a Grignard addition reaction with EtMgCl to ketone **4**. However, the desrired tertiary alcohol **5** was obtained in 23% yield along with undesired reduction byproduct. In sharp contrast, the combined use of EtMgCl, $ZnCl_2$, and LiCl could improve the yield of **5** to 88%.

Scheme 3. Synthesis of the (±)-Bremazocine



3-3. Conclusion

In summary, a highly chemoselective alkylation to ketones with Grignard reagent-derived zinc(II) ate complexes was developed. Desired tertiary alcohols were obtained in much improved yields due to minimization of the competitive background reaction with free Grignard reagents. In sharp contrast to magnesium(II) ate complexes prepared from Grignard reagents and alkyllithium reagents at –78 °C for one hour, zinc(II) ate complexes can be more easily prepared in situ at room temperature for one hour from $ZnCl_2$ and Grignard reagents. Since the stable zinc(II) ate complexes can be handled under conditions ranging from room temperature to 0 °C without unstable alkyllithium reagents, this stoichiometric alkylation system should be highly useful for both laboratory and industrial applications.

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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) Gosselin, F.; Britton, R. A.; Mowat, J.; O'Shea, P. D.; Davies, I. W. *Synlett* **2007**, 2193. (h) Nobuto, D.; Uchiyama, M. *J. Org. Chem.* **2008**, *73*, 1117. (i) Murakami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2009**, *74*, 1415.

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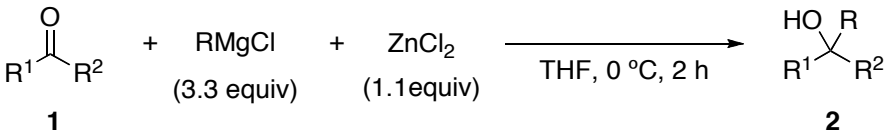
9. In general, for aliphatic ketones, in sharp contrast to aromatic ketones, even stoichiometric zinc(II) ate reagents provided small improvements for selective alkylations.
10. Matsuo, J.; Okado, R.; Ishibashi, H. *Org. Lett*. **2010**, *12*, 3266.

Experimental Section

General Methods. ^{1}H NMR spectra were measured on a 300 MHz or a 400 MHz spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a 75 MHz or a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.1 ppm). For thin-layer chromatography (TLC) analysis throughout this work, TLC plates (silica gel 60 F254) were used. The products were purified by neutral column chromatography on silica gel. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Tetrahydrofuran was distilled from sodium/benzophenone in prior to use. $ZnCl_2$, LiCl, EtMgCl (2.0 *M* in THF), *i*-PrMgCl (2.0 *M* in THF), *n*-PrMgCl (2.0 *M* in Et_2O), *n*-BuMgCl (1.0 *M* in THF), *c*-HexMgCl (2.0 *M* in Et_2O), were commercially available. All the Grignard reagents were titrated prior to use against a solution of 1,10-phenanthoroline/*n*-BuLi/*s*-BuOH in benzene.

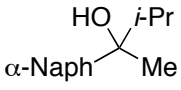
General procedure for the stoichiometric alkylation of ketones with Grignard reagent-derived zinc(II) ate complexes.



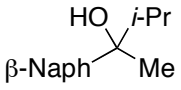
1 **2**

To a pyrex Schlenk tube, $ZnCl_2$ (145 mg, 1.1 mmol) was added and melt-dried (>300 °C) by a heat gun under reduced pressure (<5 Torr) for 5 min. RMgCl (2 *M* in THF or Et_2O, 3.3 mmol) and THF were added to keep the concentration at ca. 1.5 *M*, and the solution was stirred at that temperature for 1 h. The solution was then cooled at 0 °C, and ketone **1** (1 mmol) was added (if the ketone was in a solid state, a THF solution (ca. 0.5–1 mL) was prepared in advance). The mixture was stirred at 0 °C for 2 h. The resulting mixture was quenched with sat. aq NH_4Cl (20 mL),

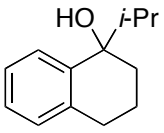
extracted with EtOAc (3 × 30 mL), and washed with brine (30 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: hexane–EtOAc), to give the desired product **2**.



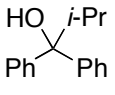
3-Methyl-2-(1-naphthalenyl)-2-butanol (Entry 1 in Table 3):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.74 (s, 3H), 1.93 (bs, 1H), 2.81 (m, 1H), 7.00-8.05 (m, 6H), 8.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 18.2, 25.1, 36.1, 78.9, 124.2, 124.5, 124.9, 127.1, 128.3, 129.1, 130.8, 135.0, 143.2.



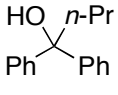
3-Methyl-2-(2-naphthalenyl)-2-butanol (Entry 2 in Table 3):[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 1.62 (bs, 3H), 1.73 (bs, 1H), 2.15 (m, 1H), 7.40-7.95 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 17.6, 26.9, 38.5, 76.9, 123.7, 124.1, 125.6, 125.9, 127.4, 127.5, 128.2, 132.3, 133.2, 145.5.



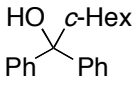
1-Isopropyl-1,2,3,4-tetrahydro-1-naphthol (Entry 3 in Table 3):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.68-1.94 (m, 4H), 2.40 (m, 1H), 2.60-2.84 (m, 2H), 7.09 (d, J = 6.9 Hz, 1H), 7.12-7.26 (m, 2H), 7.52 (d, J = 7.5 Hz, 1H).



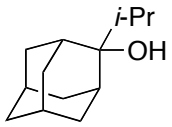
2-Methyl-1,1-diphenyl-1-propanol (Entry 4 in Table 3):[1–3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 1.53 (bs, 1H), 2.02 (m, 1H), 7.20-7.42 (m, 10H).



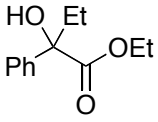
1,1-Diphenyl-1-butanol (Entry 5 in Table 3):[1,3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.30 (m, 2H), 2.08 (bs, 1H), 2.25 (m, 2H), 7.18-7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 17.2, 44.5, 78.5, 126.2, 126.8, 128.1, 147.4.



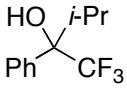
Cyclohexyldiphenylmethanol (Entry 6 in Table 3):[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.80 (m, 10H), 2.06 (s, 1H), 2.43 (m, 1H), 7.13-7.34 (m, 6H), 7.48 (d, *J* = 7.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 26.9, 27.5, 46.1, 80.5, 126.0, 127.3, 128.1, 146.7.



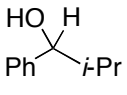
2-Isopropyl-2-adamantanol (Entry 7 in Table 3):[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.9 Hz, 6H), 1.17 (s, 1H), 1.40-2.20 (14H), 2.30 (m, 1H).



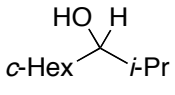
Ethyl 2-hydroxy-2-phenylbutanoate (Entry 8 in Table 3):[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.01 (dq, *J* = 14.7, 7.2 Hz, 1H), 2.24 (dq, *J* = 14.7, 7.2 Hz, 1H), 3.77 (s, 1H), 4.19 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.29 (dq, *J* = 10.8, 7.2 Hz, 1H), 7.24-7.40 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 14.1, 32.7, 62.4, 78.6, 125.6, 127.6, 128.2, 141.9, 175.4.



1,1,1-Trifluoro-3-methyl-2-phenylbutan-2-ol (Entry 9 in Table 3):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 2.39 (bs, 1H), 2.51 (m, 1H), 7.30-7.45 (m, 3H), 7.54 (d, *J* = 7.2 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.2.



2-Methyl-1-phenyl-1-propanol (Entry 10 in Table 3):[1,4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H,), 1.92 (m, 1H), 2.26 (bs, 1H), 4.31 (d, *J* = 6.9 Hz, 1H), 7.22-7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 19.0, 35.2, 80.0, 126.5, 127.3, 128.1, 143.6.



1-Cyclohexyl-2-methylpropan-1-ol (Entry 11 in Table 3):[4] ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.95-1.92 (m, 13H), 3.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 19.9, 26.2, 26.4, 26.5, 27.7, 29.7, 29.9, 40.6, 81.1.

References

1. Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998.
2. Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun*. **2010**, *46*, 2674.
3. Hatano, M.; Matsumura, T.; Ishihara, K. *Org. Lett.* **2005**, *7*, 573.
4. Hatano, M.; Mizuno, T.; Ishihara, K. *Chem. Commun.* **2010**, *46*, 5443.

Chapter 4

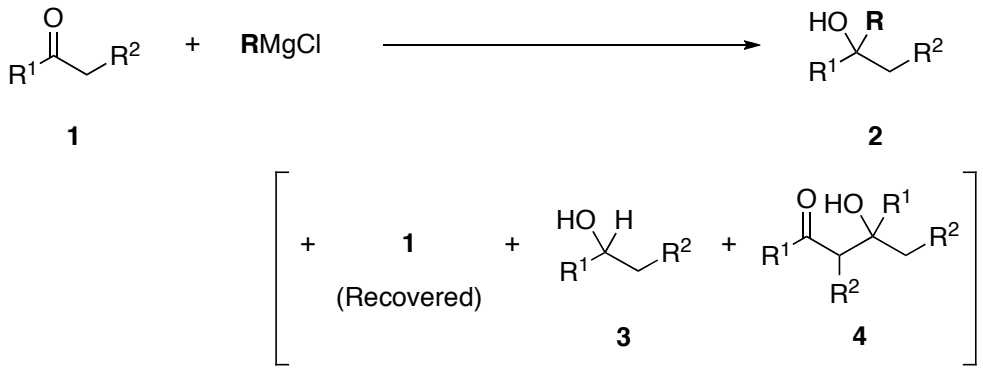
Extremely Active Zinc(II)-Catalyzed Grignard Additions to Ketones with RMgBr and RMgI

Abstract: 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.

4-1. Introduction

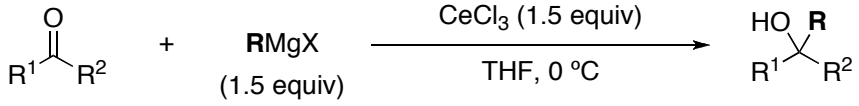
Over the past century, the addition of Grignard reagents to ketones and aldehydes has been a versatile method for synthesizing tertiary and secondary alcohols via carbon–carbon bond formation.[1,2] However, the reaction of carbonyl compounds with Grignard reagents often gives undesired side products,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

Scheme 1. Grignard Addition to Carbonyl Compounds

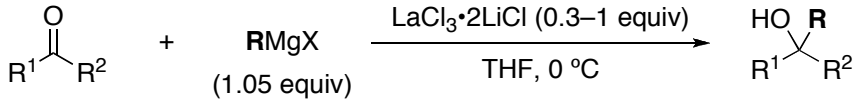


To avoid these problems, some progress has been achieved through the use of stoichiometric or excess amounts of inorganic additives.[3] Imamoto et al.[4a] developed highly useful heterogeneous stoichiometric organocerium(III) complexes (Scheme 2), and later Knochel et al.[4b,c] developed homogeneous[5] stoichiometric and semistoichiometric organolanthanum(III) complexes (Scheme 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 ºC under reduced pressure for a prolonged time (ca. 1–2 days) (Scheme 4).[4b]

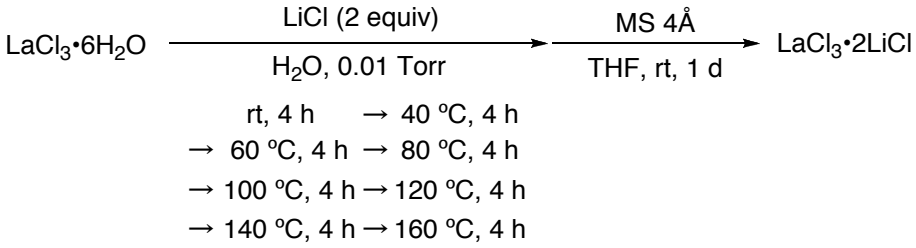
Scheme 2. Grignard Addition to Ketones with $CeCl_3$



Scheme 3. Grignard Addition to Ketones with $LaCl_3$·2LiCl

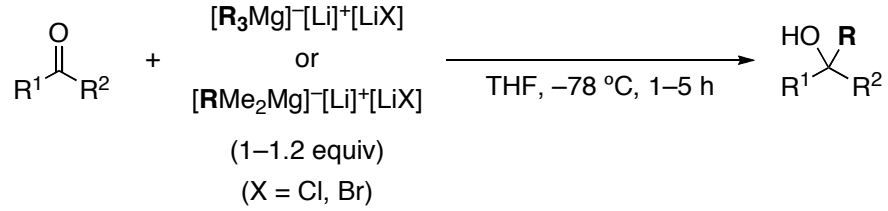


Scheme 4. Preparation of lanthanoid(III) anhydrides

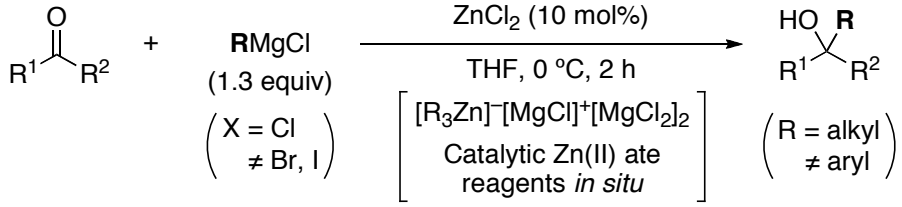


In sharp contrast to complicated procedures involving these lanthanoid(III) reagents, we have developed a homogeneous stoichiometric alkylation to ketones with trialkylmagnesium(II) ate complexes ($[R_3Mg]^-[Li]^+[LiX]$ or $[RMe_2Mg]^-[Li]^+[LiX]$), which were prepared from RMgX/RLi or RMgX/MeLi (X = Cl, Br) (Scheme 5).[7a] After that report, we also developed a homogeneous $ZnCl_2$-catalyzed alkylation to ketones with RMgCl via trialkylzinc(II) ate complexes $[R_3Zn]^-[MgCl]^+[MgCl_2]_2$ (Scheme 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 ºC. 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]

Scheme 5. Stoichiometric Grignard Addition to Ketones with Magnesium(II) Ate Complexes



Scheme 6. Catalytic Grignard Addition to Ketones with Zinc(II) Ate Complexes



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.[9]

Moreover, mechanistic details were investigated through the catalytic and stoichiometric $ZnCl_2$·$TMSCH_2MgCl$·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 $ZnCl_2$·$TMSCH_2MgCl$·LiCl catalysis in all cases, were sometimes ineffective, particularly with RMgBr and RMgI.

4-2. Results and Discussion

Design of Extremely Active Zn(II) Ate Complexes

The key to the design of further active catalytic zinc(II) ate reagents is the use of nontransferable alkyl groups, which themselves do not transfer to substrates on alkylation (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, 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_{z^2}(Zn)–σ^*(C–Si) overlaps (Figure 1c).[15]

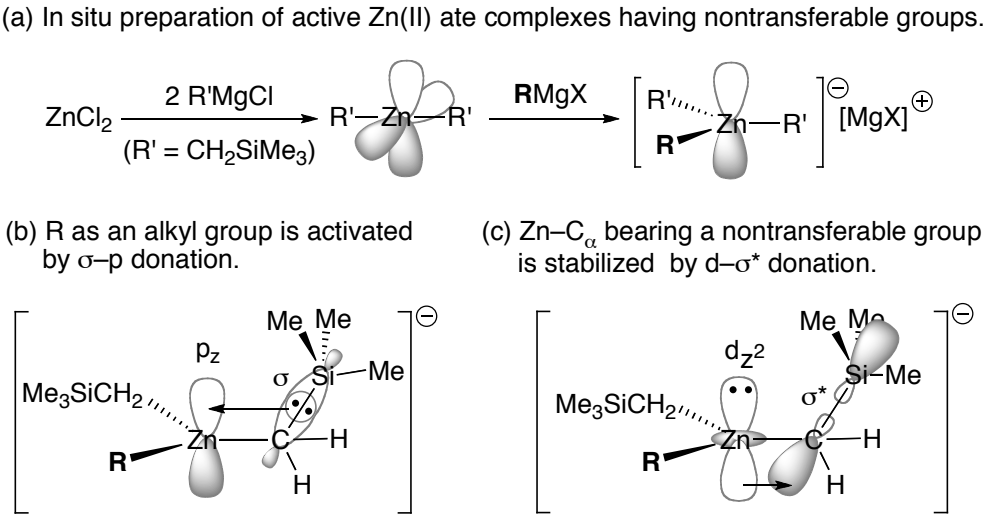
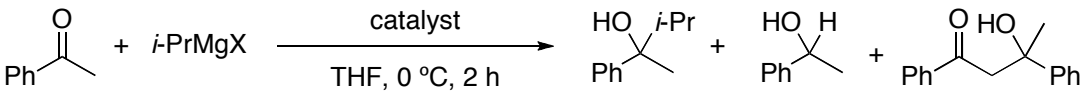


Figure 1. Design of catalytic zinc(II) ate reagents in situ.

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 with *i*-PrMgCl, *i*-PrMgBr, and *i*-PrMgBr·LiCl in the absence of catalysts gave mixtures of the desired

product (**2a**) and byproducts (**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.[7b] 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),[3f] 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 nontransferable group.

Table 1. Isopropylation of Acetophenone (**1a**) Catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



1a **2a** **3a** **4a**

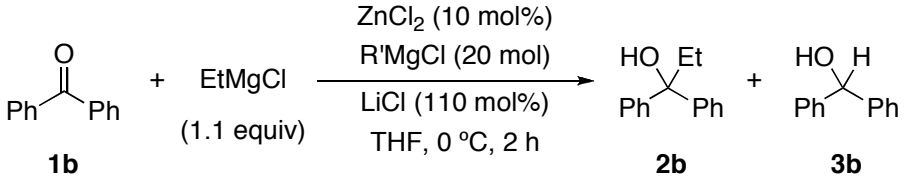
entry	*i*-PrMgX [equiv]	$ZnCl_2$ (mol%)	$TMSCH_2MgCl$ (mol%)	LiCl (mol%)	yield (%) of **2a**	**3a**	**4a**
1	*i*-PrMgCl [1.1]	–	–	–	31	11	6
2	*i*-PrMgBr [1.1]	–	–	–	29	24	12
3	*i*-PrMgBr [1.1]	–	–	110	42	16	17
4	*i*-PrMgCl [1.3]	10	–	–	85	0	7
5	*i*-PrMgBr [1.3]	10	–	–	48	9	19
6	*i*-PrMgBr [1.1]	10	20	–	80	8	6
7	*i*-PrMgBr [1.3]	10	–	110	84	5	8
8	*i*-PrMgBr [1.1]	10	20	110	96	0	2
9	*i*-PrMgCl [1.1]	10	20	110	99	1	0
10[a]	*i*-PrMgI [1.1]	10	20	110	>99	0	0

[a] Et_2O was used as a solvent.

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 (**1b**) with EtMgCl (Table 2). The use of R'MgCl decreased the reduction compound (**3b**) (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 2. Effect of Nontransferable β-Silylalkyl Groups



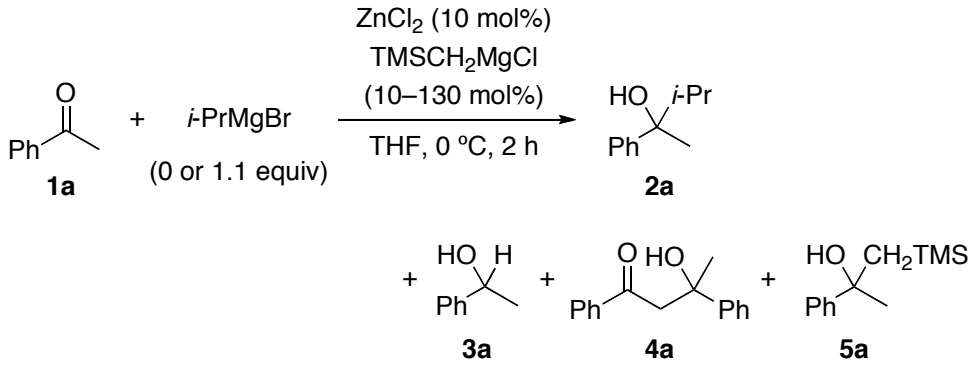
entry	R'MgCl	yield (%)	
		2b	**3b**
1[a]		20	78
2		88	12
3	$TMSCH_2MgCl$	94	4
4	$Me_2PhSiCH_2MgCl$	93	7
5	$(i\text{-PrO})Me_2SiCH_2MgCl$	90	7
6	$(TMS)_2CHMgCl$	76	11
7	Me_3CCH_2MgCl	83	11

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

Next, the optimal amount of $TMSCH_2MgCl$ was investigated (Table 3).[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 (**1a**) with *i*-PrMgBr, the yield of the product (**2a**) 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 (**5a**) (entry 3). This interesting result prompted us to investigate the trimethylsilylmethylation of **1a** 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 **5a** (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 **1a** 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 (**2a**)

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.

Table 3. Amount of $TMSCH_2MgCl$



entry	*i*-PrMgBr (equiv)	$TMSCH_2MgCl$ (mol%)	yield (%)			
			2a	**3a**	**4a**	**5a**
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

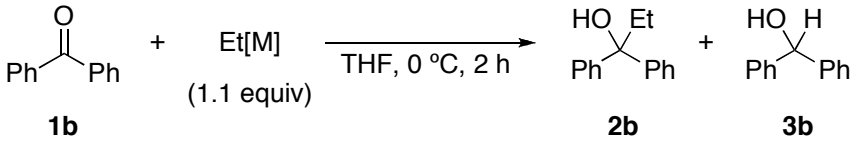
[a] In the absence of $ZnCl_2$.

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 **1b** with EtMgX or EtLi (1.1 equiv) and Et_2Zn (1.1 equiv) (Table 4). 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 (**3b**), and **2b** was obtained in only 54% yield (entry 1). In sharp contrast, the

combination of EtMgCl and Et_2Zn improved the yield of **2b** (81%) with a decrease in **3b** (14%) (entry 2). Moreover, the combination of EtLi and Et_2Zn greatly improved the yield of **2b** (94%) while significantly minimizing **3b** (1%) (entry 3). Therefore, the preferred cation moiety of zinc(II) ate complexes is in the order $Li^+ > [MgCl]^+ > [MgBr]^+$ (Scheme 7), and this order may be applied in catalytic reactions.

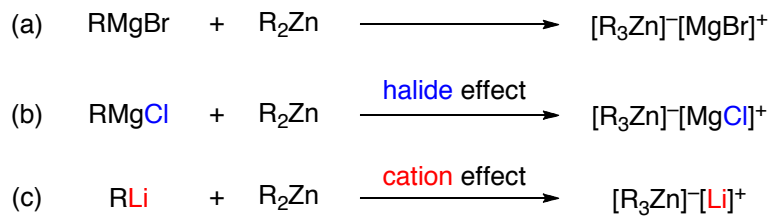
Table 4. Effect of the Cation Moiety of Zinc(II) Ate Complexes in Stoichiometric Reactions



1b **2b** **3b**

entry	reagent Et[M] (equiv)	yield (%)		
		2b	**3b**	**1b**
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

Scheme 7. Possible Stoichiometric Zinc(II) Ate Complexes



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 **1a** with *i*-PrMgBr in the presence of $ZnCl_2$ and $TMSCH_2MgCl$, **2a** was obtained in 80% yield, and MgX_2 (X = Cl/Br) would be generated (entry 1 in Table 5; Scheme 8b). As an additive, LiCl was effective, and **2a** was obtained in 96% yield (entry 3

in Table 5; Scheme 8c). LiBr was not better than LiCl (entry 4 in Table 5). However, when *i*-PrMgCl was used in place of *i*-PrMgBr (Scheme 8d), both LiCl (entry 5 in Table 5; Scheme 8e) and LiBr (entry 6 in Table 5) 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 8).

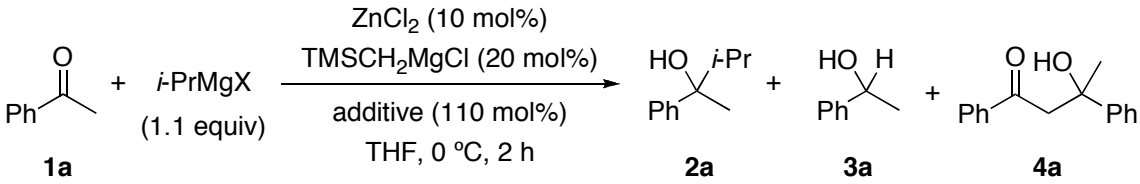
When LiX was added, the effect of Li^+ was generally observed in entries 3–6 in Table 5. According to the literature of Knochel et al.,[3f] the cation effect may involve the dissociation of oligomeric Grignard reagents (RMgX) to monomeric $[RMgX_2]^-[Li]^+$ (X = Cl/Br) due to the high polarity of Li^+ (Scheme 8a).[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 5). With regard to the stoichiometric investigation above (i.e., Scheme 7; 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 5; Scheme 8e) >

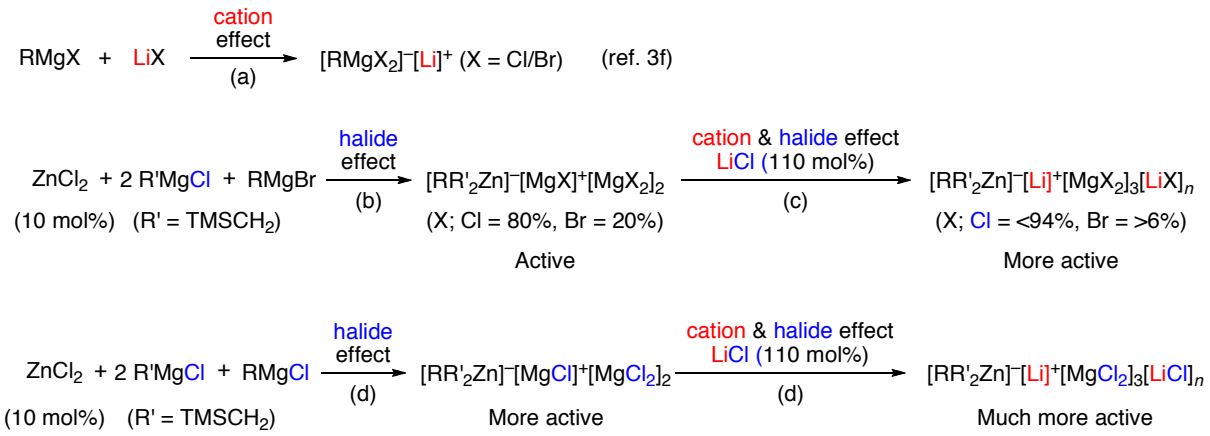
$[R(TMSCH_2)_2Zn]^-[Li]^+[MgX_2]_3[LiX]_n$ (X: Cl = <94%, Br = >6%) (entry 3 in Table 5; Scheme 8c) > $[R(TMSCH_2)_2Zn]^-[MgCl]^+[MgCl_2]_2$ (entry 2 in Table 5; Scheme 8d) > $[R(TMSCH_2)_2Zn]^-[MgX]^+[MgX_2]_2$ (X: Cl = 80%, Br = 20%) (entry 1 in Table 5; Scheme 8b).

Table 5. Combination of Grignard Reagents (*i*-PrMgX) and Salts



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

Scheme 8. 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 8c) 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.

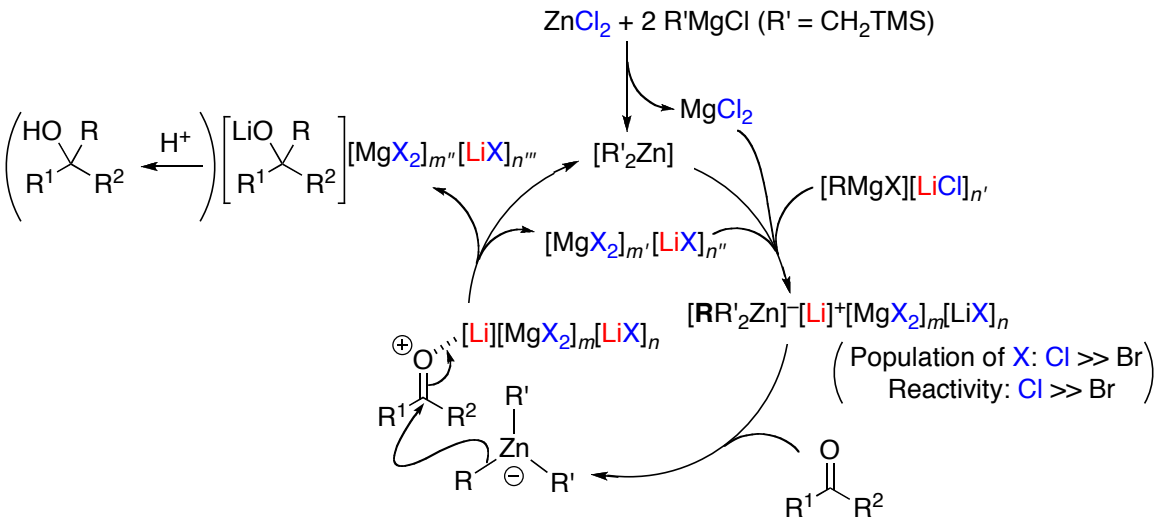
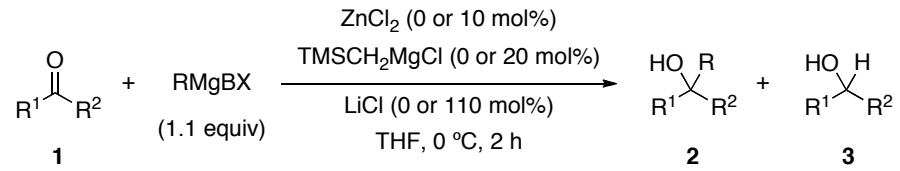


Figure 2. Proposed catalytic cycle.

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 6, entries 1–31). With only $ZnCl_2$ catalyst or without $ZnCl_2$·$TMSCH_2MgCl$·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 $ZnCl_2$·$TMSCH_2MgCl$·LiCl under homogeneous conditions, aromatic ketones (entries 1–3, 4–12), 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 $ZnCl_2$·$TMSCH_2MgCl$·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 $ZnCl_2$·$TMSCH_2MgCl$·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 $ZnCl_2$·$TMSCH_2MgCl$·LiCl more effectively than with $ZnCl_2$ or without catalysts.

Table 6. Addition of Grignard Reagents to Ketones and Aldehydes Catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



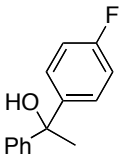
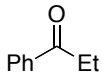
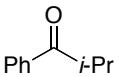
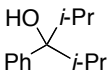
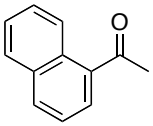
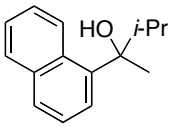
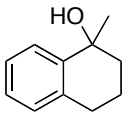
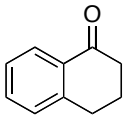
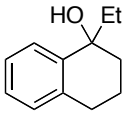
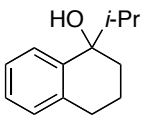
entry	$R^1C(=O)R^2$ (**1**)	RMgX	product (**2**)	yield (%) of **2** (**3**)		
				with $ZnCl_2$ •$TMSCH_2MgCl$•LiCl	with $ZnCl_2$	without $ZnCl_2$ •$TMSCH_2MgCl$•LiCl
1	 (**1a**)	MeMgI		93 (0)	58 (0)	40 (0)
2		*i*-PrMgCl	 (**2a**)	99 (1)	85 (0)	31 (11)
3		*i*-PrMgBr		96 (0)	48 (9)	29 (24)
4[a]		*i*-PrMgBr		94 (0)	48 (9)	29 (24)
5[b]		*i*-PrMgI		99 (1)	–	–
6		4-FC_6H_4MgBr		92 (0)	88 (0)	86 (0)
7		*i*-PrMgBr		94 (0)	75 (11)	36 (17)
8		*i*-PrMgBr		95 (4)	78 (14)	25 (50)
9		*i*-PrMgBr		81 (0)	56 (0)	51 (0)
10		MeMgI		90 (0)	59 (0)	42 (0)
11		EtMgBr		96 (0)	82 (8)	56 (13)
12		*i*-PrMgBr		85 (5)	55 (19)	16 (36)

Table 6. Continued

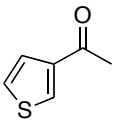
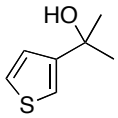
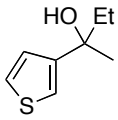
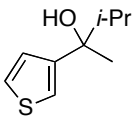
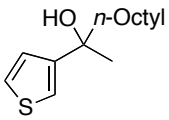
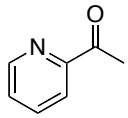
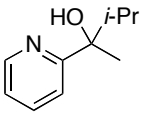
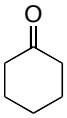
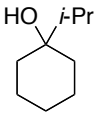
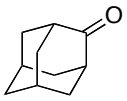
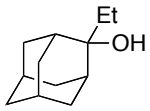
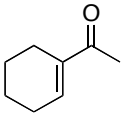
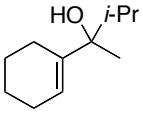
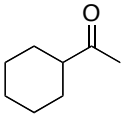
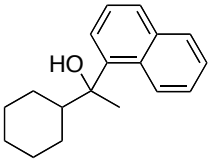
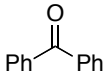
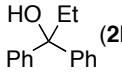
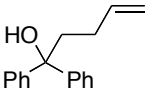
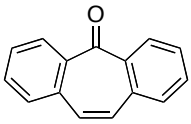
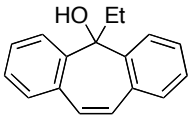
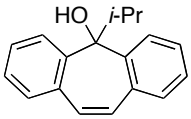
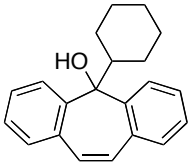
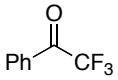
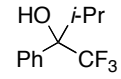
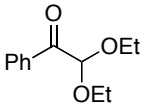
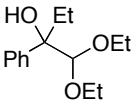
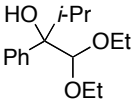
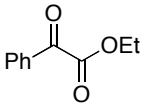
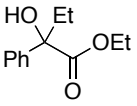
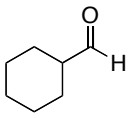
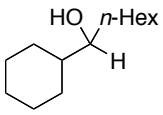
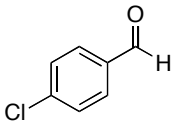
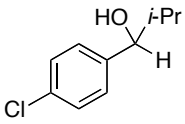
entry	$R^1C(=O)R^2$ (**1**)	RMgX	product (**2**)	yield (%) of **2** (**3**)		
				with $ZnCl_2$ •$TMSCH_2MgCl$•LiCl	with $ZnCl_2$	without $ZnCl_2$ •$TMSCH_2MgCl$•LiCl
13		MeMgI		91 (0)	62 (0)	48 (0)
14		EtMgBr		>99 (0)	85 (7)	75 (0)
15		*i*-PrMgBr		83 (0)	55 (0)	30 (2)
16		*n*-OctylMgBr		>99 (0)	90 (5)	91 (7)
17		*i*-PrMgBr		92 (0)	73 (0)	76 (0)
18		*i*-PrMgBr		51	25	27
19		EtMgBr		80 (16)	28 (65)	18 (80)
20		*i*-PrMgBr		82 (0)	49 (0)	41 (0)
21		α-NaphMgBr		82 (0)	39 (0)	49 (0)
22	 (**1b**)	EtMgBr	 (**2b**)	91 (9)	52 (42)	20 (78)
23		$(CH_2)_2MgBr$		64 (32)	15 (42)	11 (89)

Table 6. Continued

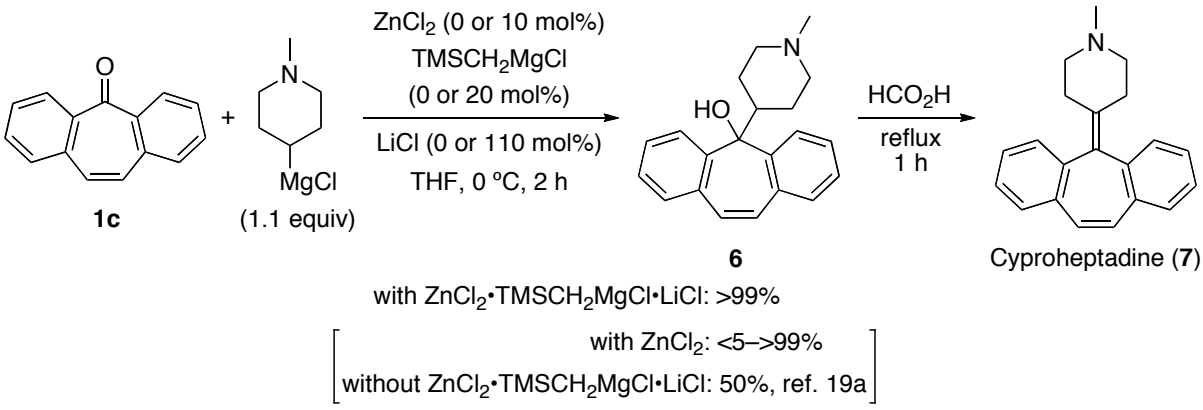
entry	$R^1C(=O)R^2$ (**1**)	RMgX	product (**2**)	yield (%) of **2** (**3**)		
				with $ZnCl_2$ •$TMSCH_2MgCl$•LiCl	with $ZnCl_2$	without $ZnCl_2$ •$TMSCH_2MgCl$•LiCl
24	 (**1c**)	EtMgBr		91 (9)	58 (36)	45 (49)
25		*i*-PrMgBr		94 (6)	37 (41)	11 (89)
26		*c*-HexMgBr		68 (24)	38 (59)	37 (58)
27		*c*-HexMgCl		89 (0)	54 (41)	39 (61)
28		*i*-PrMgBr		90 (10)[c]	17 (82)[d]	15 (85)
29		EtMgBr		92 (8)	88 (12)	72 (21)
30		*i*-PrMgBr		72 (25)	39 (58)	30 (65)
31		EtMgBr		71	69	45
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 (45)

[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. [d] 30 mol% of $ZnCl_2$ and 1.7 equiv. of *i*-PrMgBr were used.

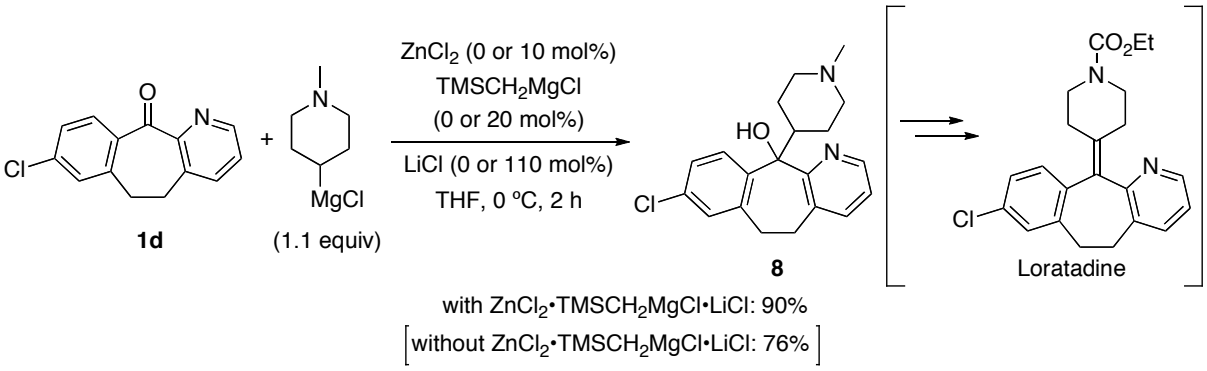
Synthesis of Cyproheptadine

By taking advantage of the reactions of 5-dibenzosuberenone (**1c**) (Table 6, entries 24–27), we next examined the synthesis of cyproheptadine (**7**), which is both an antiserotonin drug and an antihistamine drug (Scheme 9).[19] Engelhardt et al. in Merck reported that a traditional Grignard addition to **1c** without catalysts gave tertiary alcohol **6** in 50% yield.[19a] 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 $ZnCl_2$·$TMSCH_2MgCl$·LiCl, the reaction of **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.[20] 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 10).[21]

Scheme 9. Synthesis of Cyproheptadine



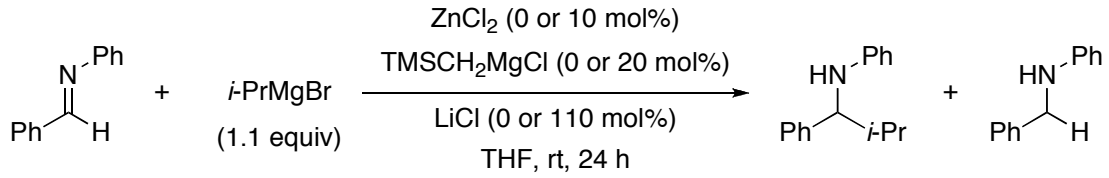
Scheme 10. Synthesis of Loratadine



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

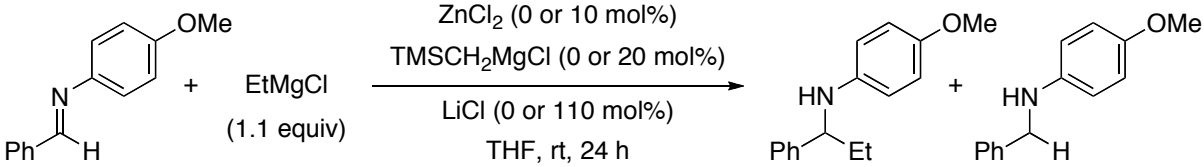
The alkylations of less-reactive aldimines with Grignard reagents[22] were also explored (Schemes 11–13). Without the catalysts or with $ZnCl_2$ catalyst, the alkylation of *N*-arylaldimines was generally slow even at room temperature, although reduction byproducts were not observed (Schemes 11 and 12). In contrast, $ZnCl_2$·$TMSCH_2MgCl$·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 (Scheme 13). However, $ZnCl_2$·$TMSCH_2MgCl$·LiCl improved the predominance of the desired isopropylation, and the corresponding product was obtained in 80% yield.

Scheme 11. Addition of Grignard Reagents to *N*-Ph Aldimine Catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



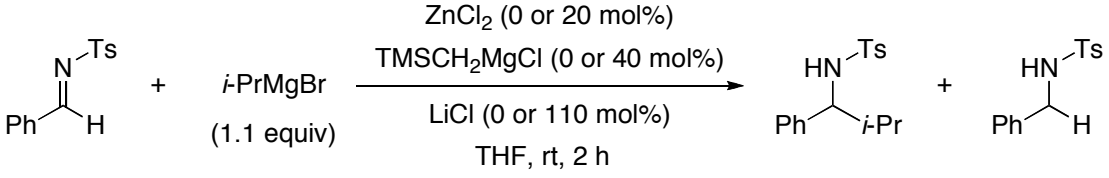
with $ZnCl_2$•$TMSCH_2MgCl$•LiCl:	75%	0%
[without $ZnCl_2$•$TMSCH_2MgCl$•LiCl:	35%	0%]

Scheme 12. Addition of Grignard Reagents to *N*-Arylaldimine Catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



with $ZnCl_2$•$TMSCH_2MgCl$•LiCl:	92%	0%
[with $ZnCl_2$:	48%	0%
without $ZnCl_2$•$TMSCH_2MgCl$•LiCl:	60%	0%]

Scheme 13. Addition of Grignard Reagents to *N*-Ts Aldimine Catalyzed by $ZnCl_2$, $TMSCH_2MgCl$, and LiCl



with $ZnCl_2$•$TMSCH_2MgCl$•LiCl:	80%	20%
[with $ZnCl_2$:	22%	74%
without $ZnCl_2$•$TMSCH_2MgCl$•LiCl:	26%	78%]

4-3. 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.

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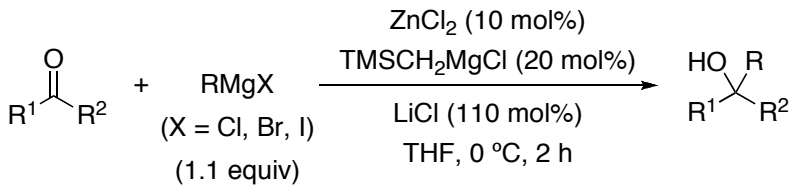
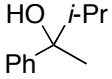
Experimental Section

General Methods. ^{1}H NMR spectra were measured on a 300 MHz or a 400 MHz spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a 75 MHz or a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.1 ppm). For thin-layer chromatography (TLC) analysis throughout this work, TLC plates (silica gel 60 F254) were used. The products were purified by neutral column chromatography on silica gel. IR spectra were determined by a FT-IR spectrometer. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Tetrahydrofuran was distilled from sodium/benzophenone in prior to use. $ZnCl_2$, LiCl, $TMSCH_2MgCl$ (1.0 *M* in Et_2O), $TMSCH_2Li$ (1.0 *M* in pentane), MeMgI (3.0 *M* in Et_2O), EtMgBr (1.0 *M* in THF), EtMgCl (2.0 *M* in THF), *i*-PrMgCl (2.0 *M* in THF), *i*-PrMgBr (0.7 *M* in THF), $CH_2=CH(CH_2)_2MgBr$ (0.5 *M* in THF), *n*-HexMgBr (2.0 *M* in Et_2O), *c*-HexMgBr (1.0 *M* in THF), $4\text{-}FC_6H_4MgBr$ (1.0 *M* in THF), *n*-OctylMgBr (2.0 *M* in Et_2O), magnesium turnings, were commercially available. α-NaphMgBr (1.0 *M* in THF), $Me_2PhSiCH_2MgCl$ (1.0 *M* in THF), (*i*-PrO)Me_2SiCH_2MgCl (1.0 *M* in THF), $(Me_3Si)_2CHMgCl$ (1.0 *M* in THF), Me_3CCH_2MgCl (1.0 *M* in THF), were prepared from the halide compounds and magnesium turnings. All the Grignard reagents were titrated prior to use against a solution of 1,10-phenanthoroline/*n*-BuLi/*s*-BuOH in benzene.

General procedure for $ZnCl_2$–$TMSCH_2MgCl$–LiCl-catalyzed Grignard reaction of ketones (Entries 1–31 in Table 6).



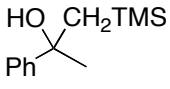
To a pyrex Schlenk tube, $ZnCl_2$ (40.8 mg, 0.30 mmol) was added and melt-dried by a heat gun under reduced pressure (<5 Torr) within 5 min. LiCl (139.9 mg, 3.3 mmol) was added to the pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again the mixture was partially melt-dried by a heat gun under reduced pressure (<5 Torr) within 5 min. To the mixture, $TMSCH_2MgCl$ (1.0 *M* in Et_2O, 0.60 mL, 0.60 mmol) was added at room temperature. This mixture was stirred at that temperature for 15 min. RMgX (0.5–2.0 *M* in THF or Et_2O, 3.3 mmol) was added, and the solution* was stirred at that temperature for 45 min (*If a Grignard reagent is >1 *M*, the solution of the Grignard reagent is diluted with THF to 1 *M* in situ. If a Grignard reagent is <1 *M*, the solution is used as it is.). Then, the solution was cooled at 0 °C, and ketone (**1**) (3.0 mmol) was added over 1 h by a syringe pump (If a ketone is solid state, a THF solution (ca. 2 mL) is prepared in advance.). The mixture was stirred at 0 °C for 2 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 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 = 20/1–3/1), to give the desired product.



3-Methyl-2-phenylbutan-2-ol (2a, Tables 1, 3, and 5 Entries 2–5 in Table 6):[1,3] ^{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,

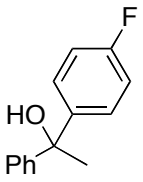
38.6, 77.8, 125.2, 126.4, 127.8, 147.8. HRMS (FAB+) calcd for $C_{11}H_{15}$ $[M–OH]^+$ 147.1174, found 147.1170.

1,1-Diphenyl-1-propanol (2b, Tables 2 and 4, Entry 22 in Table 6):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 2.05 (bs ,1H), 2.32 (q, *J* = 7.2 Hz, 2H), 7.18-7.35 (m, 6H), 7.38-7.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 34.4, 78.4, 126.1, 126.7, 128.1, 146.9. HRMS (FAB+) calcd for $C_{15}H_{15}$ $[M–OH]^+$ 195.1174, found 195.1177.



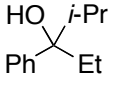
2-Phenyl-1-(trimethylsilyl)propan-2-ol (5a, Table 3):[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.14 (s, 9H), 1.38 (s, 2H), 1.57 (s, 1H), 1.63 (s, 3H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0, 33.7, 35.0, 75.1, 124.5, 126.5, 128.1, 149.8. HRMS (FAB+) calcd for $C_{12}H_{19}Si$ $[M–OH]^+$ 191.1256, found 191.1261.

2-Phenylpropan-2-ol (Entry 1 in Table 6):[2,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 3H), 1.76 (s, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.49 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 72.5, 124.4, 126.7, 128.2, 149.1. HRMS (FAB+) calcd for $C_9H_{12}NaO$ $[M+Na]^+$ 159.0786, found 159.0789.

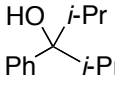


1-(4-Fluorophenyl)-1-phenylethanol (Entry 6 in Table 6):[3,5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.17 (s, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.20-7.43 (m, 7H). ^{13}C NMR (100

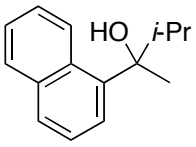
MHz, $CDCl_3$) δ 31.0, 76.7, 114.9 (d, J = 20.9 Hz), 125.8, 127.1, 127.6 (d, J = 7.6 Hz), 128.3, 143.8, 147.7, 161.7 (d, J = 244 Hz). HRMS (FAB+) calcd for $C_{14}H_{12}F$ $[M–OH]^+$ 199.0923, found 199.0925.



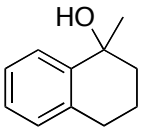
2-Methyl-3-phenyl-3-pentanol (Entry 7 in Table 6):[1–3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (t, J = 6.9 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 1.58 (s, 1H), 1.89 (q, J = 6.9 Hz, 2H), 2.05 (septet, J = 6.9 Hz, 1H), 7.18-7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 16.6, 17.5, 32.0, 37.5, 79.3, 125.9, 126.1, 127.7, 145.0. HRMS (FAB+) calcd for $C_{12}H_{17}$ $[M–OH]^+$ 161.1330, found 161.1326.



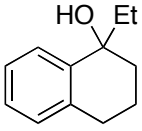
2,4-Dimethyl-3-phenyl-3-pentanol (Entry 8 in Table 6):[1,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.6 Hz, 6H), 0.84 (d, J = 6.6 Hz, 6H), 1.50 (s, 1H), 2.31 (m, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 17.4, 33.7, 80.9, 126.1, 126.6, 127.2, 142.8. HRMS (FAB+) calcd for $C_{13}H_{19}$ $[M–OH]^+$ 175.1487, found 175.1487.



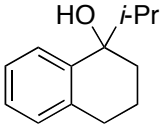
3-Methyl-2-(naphthalen-1-yl)butan-2-ol (Entry 9 in Table 6):[1,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.74 (s, 3H), 1.93 (bs, 1H), 2.81 (m, 1H), 7.00-8.05 (m, 6H), 8.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 18.2, 25.1, 36.1, 78.9, 124.2, 124.5, 124.9, 127.1, 128.3, 129.1, 130.8, 135.0, 143.2. HRMS (FAB+) calcd for $C_{15}H_{17}$ $[M–OH]^+$ 197.1330, found 197.1333.



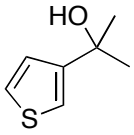
1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol (Entry 10 in Table 10):[3,6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.74 (s, 1H), 1.77-2.24 (m, 4H), 2.70-2.88 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 30.0, 30.8, 39.9, 70.6, 126.3, 126.4, 127.1, 128.9, 136.3, 142.9. HRMS (FAB+) calcd for $C_{11}H_{13}$ $[M–OH]^+$ 145.1017, found 145.1020.



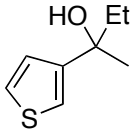
1-Ethyl-1,2,3,4-tetrahydronaphthalen-1-ol (Entry 11 in Table 6):[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.75-2.15 (m, 4H), 1.71 (s, 1H), 1.87 (q, *J* = 7.2 Hz, 2H), 2.60-2.90 (m, 2H), 7.07 (m, 1H), 7.16 (td, *J* = 7.2, 1.8 Hz, 1H), 7.19 (td, *J* = 7.2, 1.8 Hz, 1H), 7.52 (dd, *J* = 7.2, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 19.8, 30.0, 34.9, 35.4, 72.7, 126.3 (2C) 127.0, 128.9, 136.9, 142.3. HRMS (FAB+) calcd for $C_{12}H_{15}$ $[M–OH]^+$ 159.1174, found 159.1174.



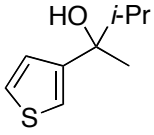
1-Isopropyl-1,2,3,4-tetrahydro-1-naphthol (Entry 12 in Table 6):[1,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.68-1.94 (m, 4H), 2.40 (septet, *J* = 6.9 Hz, 1H), 2.60-2.84 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.12-7.26 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 18.4, 19.2, 30.4, 30.9, 37.4, 74.4, 126.2, 126.4, 126.9, 129.0, 137.9, 141.6. HRMS (FAB+) calcd for $C_{13}H_{17}$ $[M–OH]^+$ 173.1330, found 173.1335.



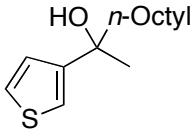
2-(Thiophen-3-yl)propan-2-ol (Entry 13 in Table 6):[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 6H), 1.82 (s, 1H), 7.13 (dd, J = 5.1, 1.2 Hz, 1H), 7.18 (dd, J = 3.0, 1.2 Hz, 1H), 7.28 (dd, J = 5.0, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 71.0, 118.8, 125.7, 125.8, 151.0. HRMS (FAB+) calcd for C_7H_9S $[M–OH]^+$ 125.0425, found 125.04246.



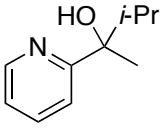
2-(Thiophen-3-yl)butan-2-ol (Entry 14 in Table 6):[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 1.28 (s, 1H), 1.54 (s, 3H), 1.83 (q, J = 7.5 Hz, 2H), 7.04 (dd, J = 5.1, 1.2 Hz, 1H), 7.15 (dd, J = 3.0, 1.2 Hz, 1H), 7.28 (dd, J = 5.1, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 29.2, 36.5, 73.9, 119.5, 125.7, 125.8, 149.9. HRMS (FAB+) calcd for $C_8H_{11}S$ $[M–OH]^+$ 139.0581, found 139.0579.



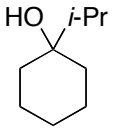
3-Methyl-2-(3-thienyl)-2-butanol (Entry 15 in Table 6):[1,3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 1.51 (s, 3H), 1.71 (s, 1H), 2.00 (septet, J = 6.9 Hz, 1H), 7.04 (dd, J = 5.1, 1.5 Hz, 1H), 7.13 (d, J = 3.3, 1.5 Hz, 1H), 7.26 (d, J = 5.1, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 17.5, 26.3, 38.6, 76.1, 119.8, 125.2, 126.1, 149.6. HRMS (FAB+) calcd for $C_9H_{13}S$ $[M–OH]^+$ 153.0738, found 153.0734.



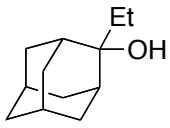
2-(Thiophen-3-yl)decan-2-ol (Entry 16 in Table 6):[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.23 (m, 12H), 1.54 (s, 3H), 1.77 (m, 2H), 1.79 (s, 1H), 7.04 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 (dd, *J* = 3.3, 1.2 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 24.1, 29.3, 29.5, 29.6, 29.9, 31.9, 43.9, 73.7, 119.3, 125.7, 125.8, 150.1. HRMS (FAB+) calcd for $C_{14}H_{23}S$ $[M–OH]^+$ 223.1520, found 223.1518.



3-Methyl-2-(pyridin-2-yl)butan-2-ol (Entry 17 in Table 6):[3,7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.49 (s, 3H), 1.97 (septet, *J* = 6.9 Hz, 1H), 5.19 (s, 1H), 7.19 (dd, *J* = 6.0, 4.6 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.69 (dd, *J* = 7.8, 6.0 Hz, 1H), 7.19 (d, *J* = 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 17.1, 26.2, 38.5, 75.3, 119.5, 121.6, 136.6, 146.9, 165.0. HRMS (FAB+) calcd for $C_{10}H_{14}N$ $[M–OH]^+$ 148.1126, found 148.1125.

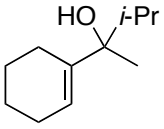


1-Isopropyl-1-cyclohexanol (Entry 18 in Table 6):[1,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.9 Hz, 6H), 1.07 (s, 1H), 1.20-1.65 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 22.0, 26.0, 34.2, 37.6, 73.1. HRMS (FAB+) calcd for C_9H_{17} $[M–OH]^+$ 125.1330, found 125.1327.

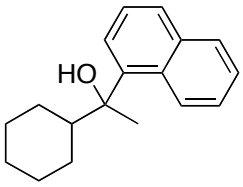


2-Ethtyl-2-adamantanol (Entry 19 in Table 6):[1,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.8 Hz, 3H), 1.32 (s, 1H), 1.69 (d, *J* = 7.5 Hz, 2H), 1.50-2.25 (m, 14H). ^{13}C NMR (100

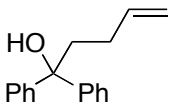
MHz, $CDCl_3$) δ 6.5, 27.3, 27.5, 30.5, 33.0, 34.6, 36.6, 38.4, 74.9. HRMS (FAB+) calcd for $C_{12}H_{19}$ $[M–OH]^+$ 163.1487, found 163.1485.



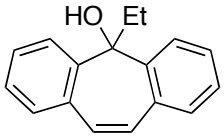
2-Cyclohexenyl-3-methylbutan-2-ol (Entry 20 in Table 6):[3] ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3 H), 1.21 (s, 3H), 1.49-1.66 (m, 4H), 1.83 (septet, J = 6.9 Hz, 1H), 1.95 (m, 2H), 2.03-2.10 (m, 3H), 5.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 22.4, 23.1, 23.8, 24.7, 25.1, 34.0, 77.0, 119.7, 142.7. HRMS (FAB+) calcd for $C_{11}H_{19}$ $[M–OH]^+$ 151.1487, found 151.1486.



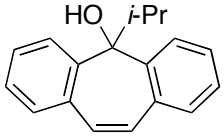
1-Cyclohexyl-1-(naphthalen-1-yl)ethanol (Entry 21 in Table 6):[3,8] ^1H NMR (400 MHz, $CDCl_3$) δ 1.00-1.90 (m, 10H), 1.75 (s, 3H), 1.94 (bs, 1H), 2.37 (m, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.42-7.50 (m, 2H), 7.53 (d, J = 6.3 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.85 (m, 1H), 8.77 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.5, 26.7, 26.8, 27.2, 28.3, 46.8, 79.0, 124.5, 124.6, 125.0, 125.1, 127.2, 128.3, 129.2, 130.9, 134.9, 143.1. HRMS (FAB+) calcd for $C_{18}H_{21}$ $[M–OH]^+$ 237.1643, found 237.1641.



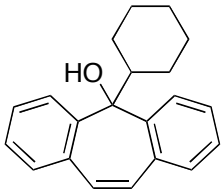
1,1-Diphenylpent-4-en-1-ol (Entry 23 in Table 6):[3,9] ^1H NMR (400 MHz, $CDCl_3$) δ 2.02-2.10 (m, 2H), 2.17 (s, 1H), 2.35-2.43 (m, 2H), 4.95 (d, J = 9.9 Hz, 1H), 5.00 (d, J = 17.4 Hz, 1H), 5.85 (ddt, J = 17.4, 9.9, 6.9 Hz, 1H), 7.22 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 4H), 7.41 (t, J = 7.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 41.2, 78.5, 114.9, 126.2, 127.1, 128.4, 138.9, 147.1. HRMS (FAB+) calcd for $C_{17}H_{17}$ $[M–OH]^+$ 221.1330, found 221.1329.



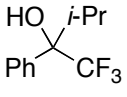
5-Ethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (Entry 24 in Table 6):[10,11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.50 (t, *J* = 7.2 Hz, 3H), 1.97 (d, *J* = 7.2 Hz, 2H), 2.26 (s, 1H), 6.96 (s, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 28.9, 77.3, 124.3, 126.5, 128.6, 129.5, 131.5, 132.6, 142.5. HRMS (FAB+) calcd for $C_{17}H_{15}$ $[M–OH]^+$ 219.1174, found 219.1177.



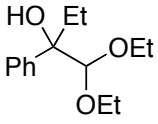
5-Isopropyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (Entry 25 in Table 6):[3,12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.47 (d, *J* = 6.9 Hz, 6H), 2.31 (s, 1H), 2.88 (septet, *J* = 6.9 Hz, 1H), 6.92 (s, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.91 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 28.0, 79.2, 124.7, 126.3, 128.4, 129.4, 131.4, 132.3, 142.5. HRMS (FAB+) calcd for $C_{18}H_{17}$ $[M–OH]^+$ 233.1330, found 233.1329.



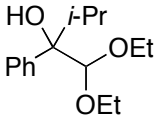
5-Cyclohexyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (Entries 26 and 27 in Table 6):[3,13] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76-1.06 (m, 10H), 2.38 (s, 1H), 2.52 (m, 1H), 6.95 (s, 2H), 7.26 (td, *J* = 7.5, 1.2 Hz, 2H), 7.32 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.41 (td, *J* = 8.1, 1.5 Hz, 2H), 7.92 (dd, *J* = 8.1, 1.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.5, 26.8, 38.3, 79.2, 124.8, 126.2, 128.3, 129.4, 131.4, 132.3, 142.2. HRMS (FAB+) calcd for $C_{21}H_{21}$ $[M–OH]^+$ 273.1643, found 273.1642.



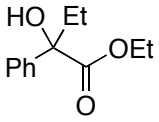
1,1,1-Trifluoro-3-methyl-2-phenylbutan-2-ol (Entry 28 in Table 6):[1,3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 2.39 (bs, 1H), 2.51 (septet, J = 6.9 Hz, 1H), 7.30-7.45 (m, 3H), 7.50-7.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 17.2, 33.7, 79.6 (q, J = 26.9 Hz), 125.6, 126.0 (q, J = 285.5), 128.1, 128.2, 137.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.2. HRMS (FAB+) calcd for $C_{11}H_{13}F_3O$ $[M]^+$ 218.0918, found 218.0914.



1,1-Diethoxy-2-phenylbutan-2-ol (Entry 29 in Table 6): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, J = 7.8 Hz, 3H), 1.11 (t, J = 6.9 Hz, 3H), 1.16 (t, J = 6.9 Hz, 3H), 1.93 (m, 1H), 2.02 (m, 1H), 2.59 (s, 1H), 3.35 (m, 2H), 3.71 (m, 2H), 4.35 (s, 1H), 7.18-7.36 (m, 3H), 7.45-7.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1, 15.2, 15.3, 28.1, 65.8, 65.9, 78.5, 108.3, 126.5, 126.6, 127.7, 142.1. IR (neat) 3568, 2975, 1448, 1372, 1061 cm^{-1}. HRMS (FAB+) calcd for $C_{14}H_{21}O_2$ $[M–OH]^+$ 221.1542, found 221.1543. Elemental anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30; found C, 70.23; H, 9.15.

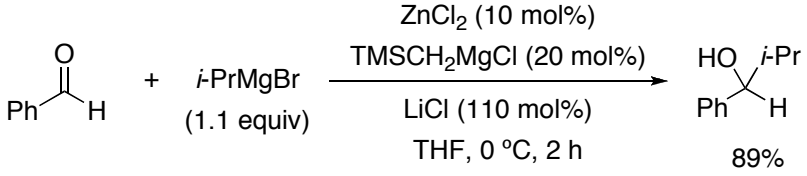


1,1-Diethoxy-3-methyl-2-phenylbutan-2-ol (Entry 30 in Table 6):[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 1.10 (t, J = 6.9 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H), 2.36 (septet, J = 6.9 Hz, 1H), 2.69 (s, 1H), 3.38-3.60 (m, 2H), 3.60-3.90 (m, 2H), 4.68 (s, 1H), 7.18-7.34 (m, 3H), 7.47-7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 15.4, 16.9, 17.5, 33.7, 65.3, 66.0, 79.6, 106.6, 126.2, 126.3, 127.3, 142.7. HRMS (FAB+) calcd for $C_{15}H_{23}O_2$ $[M–OH]^+$ 235.1698, found 235.1702.



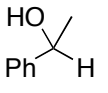
Ethyl 2-hydroxy-2-phenylbutanoate (Entry 31 in Table 6):[1,3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.01 (dq, *J* = 14.7, 7.2 Hz, 1H), 2.24 (dq, *J* = 14.7, 7.2 Hz, 1H), 3.77 (s, 1H), 4.19 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.29 (dq, *J* = 10.8, 7.2 Hz, 1H), 7.24-7.40 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 14.1, 32.7, 62.4, 78.6, 125.6, 127.6, 128.2, 141.9, 175.4. HRMS (FAB+) calcd for $C_{12}H_{15}O_2$ $[M–OH]^+$ 191.1072, found 191.1072.

Representative procedure for $ZnCl_2$–$TMSCH_2MgCl$–LiCl-catalyzed Grignard reaction of aldehydes (Entries 32–35 in Table 6).

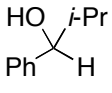


To a pyrex Schlenk tube, $ZnCl_2$ (40.8 mg, 0.30 mmol) was added and melt-dried by a heat gun under reduced pressure (<5 Torr). LiCl (139.9 mg, 3.3 mmol) was added to the pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again the mixture was partially melt-dried by a heat gun under reduced pressure (<5 Torr). To the mixture, $TMSCH_2MgCl$ (1.0 *M* in Et_2O, 0.60 mL, 0.60 mmol) was added at room temperature. This mixture was stirred at that temperature for 15 min. *i*-PrMgBr (0.7 *M* in THF, 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, 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 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

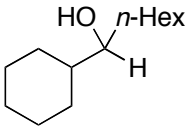
neutral silica gel column chromatography (eluent: *n*-hexane/AcOEt, v/v = 10/1–3/1), to give the desired product (402 mg, 89%).



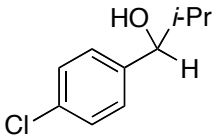
1-Phenylethanol (Entry 32 in Table 6):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, J = 6.4 Hz, 3H), 1.85 (br, 1H), 4.89 (m, 1H), 7.23-7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 70.2, 125.3, 127.3, 128.3, 145.7. HRMS (FAB+) calcd for $C_8H_{10}O$ $[M]^+$ 122.0732, found 122.0730.



2-Methyl-1-phenylpropan-1-ol (Entry 33 in Table 6):[1] ^{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.



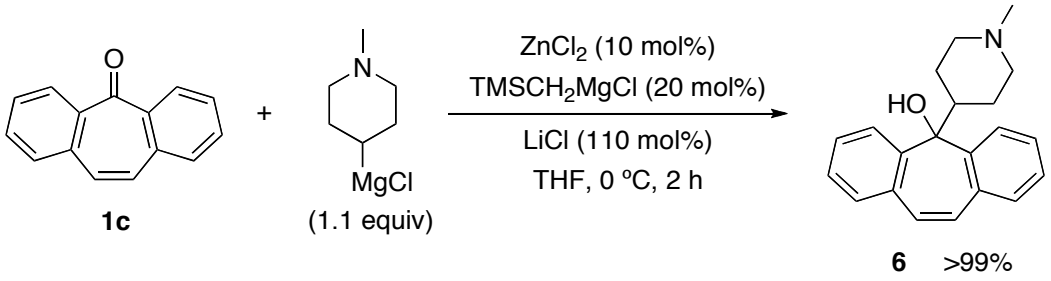
1-Cyclohexylheptan-1-ol (Entry 34 in Table 6):[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 0.93-1.55 (m, 17H), 1.56-1.84 (m, 5H), 3.34 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.8, 26.2, 26.3, 26.5, 27.6, 29.2, 29.4, 31.8, 34.1, 43.5, 76.1. HRMS (FAB+) calcd for $C_{13}H_{25}$ $[M–OH]^+$ 181.1956, found 181.1952.



1-(4-Chlorophenyl)-2-methylpropan-1-ol (Entry 35 in Table 6):[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 1.82 (d, J = 3.2 Hz, 1H), 1.91 (octet, J = 6.9 Hz, 1H), 4.36 (dd, J = 6.6, 3.2 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz,

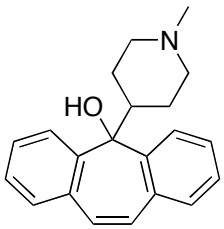
2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 18.9, 35.3, 79.2, 127.9, 128.3, 133.0, 142.1. HRMS (FAB+) calcd for $C_{10}H_{12}Cl$ $[M–OH]^+$ 167.0628, found 167.0627.

Synthesis of 5-(1-Methyl-4-piperidyl)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (6, Scheme 9).



To a pyrex Schlenk tube, magnesium turnings (365 mg, 15 mmol) was added, and 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, $ZnCl_2$ (40.8 mg, 0.30 mmol) was added and 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, $TMSCH_2MgCl$ (1.0 *M* in Et_2O, 0.60 mL, 0.60 mmol) was added 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

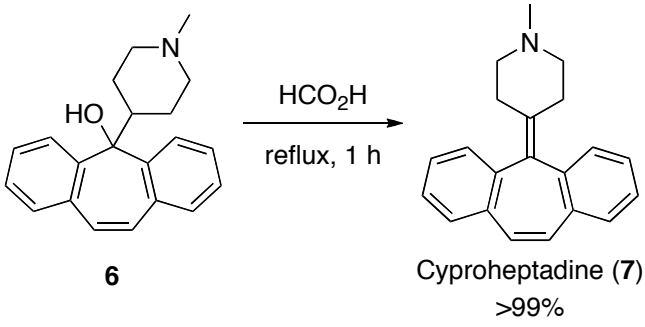
dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the resultant residue was purified by basic silica gel column chromatography (eluent: chloroform/MeOH, v/v = 20/1), to give the desired product (**6**) (916 mg, >99%).



5-(1-Methyl-4-piperidyl)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (6, Scheme 9):[16]

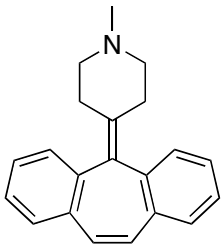
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, *J* = 12.8 Hz, 2H), 1.31 (m, 2H), 1.62 (td, *J* = 12.0, 2.7 Hz, 2H), 2.14 (s, 3H), 2.51 (m, 1H), 2.58 (s, 1H), 2.68 (d, *J* = 11.1 Hz, 2H), 6.95 (s, 2H), 7.25 (td, *J* = 7.5, 1.2 Hz, 2H), 7.32 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.40 (td, *J* = 8.1, 1.5 Hz, 2H), 7.91 (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 9).[17]



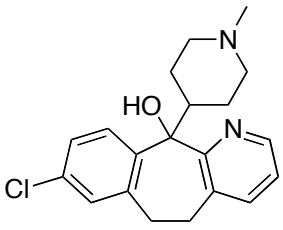
To a 30 mL round flask, **6** (610 mg, 2.0 mmol) and formic acid (3 mL) were added. The mixture was heated at 100 °C for 2 h, and the reaction was monitored by TLC. The resulting mixture was cooled to 0 °C, and diluted with AcOEt (15 mL), and quenched by aqueous 1 *M* NaOH. The mixture was extracted with AcOEt (20 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 (**7**) (575 mg, >99%).



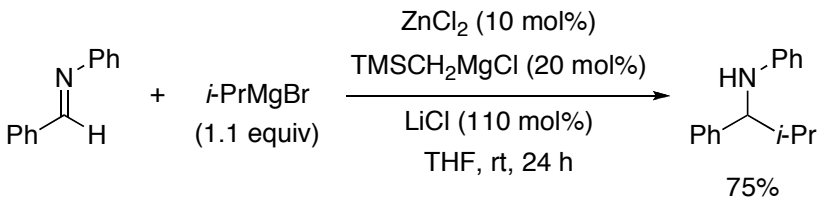
Cyproheptadine (7, Scheme 9):[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (m, 2H), 2.16 (m, 2H), 2.23 (s, 3H), 2.35 (m, 2H), 2.51 (m, 2H), 6.91 (s, 2H), 7.16-7.26 (m, 4H), 7.27-7.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 46.0, 57.2, 126.2, 127.7, 128.1, 128.4, 130.9, 133.3, 134.7, 135.1, 139.1. HRMS (FAB+) calcd for $C_{21}H_{21}NNa$ $[M+Na]^+$ 310.1572, found 310.1570.

Synthesis of loratadine intermediate (8, Scheme 10).

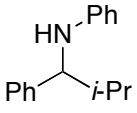


8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidinyl)-5*H*-Benzo[5,6]cyclo hepta[1,2-*b*]pyridin-11-ol (8, Scheme 10):[19,20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (m, 1H), 1.17 (m, 1H), 1.53-1.82 (m, 5H), 2.18 (s, 3H), 2.31 (m, 1H), 2.74-2.85 (m, 2H), 2.90-3.40 (m, 2H), 3.44-3.63 (m, 2H), 7.09 (d, J = 2.4 Hz, 1H), 7.15-7.20 (m, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 8.35 (dd, J = 4.5, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.2, 31.5, 32.5, 44.8, 46.3, 56.0, 56.3, 77.9, 122.8, 125.8, 129.7, 129.9, 132.4, 132.9, 137.8, 139.2, 141.4, 143.9, 158.3. IR (neat) 3266, 2935, 2782, 2676, 2176, 1591, 1454, 1279 cm^{-1}. HRMS (FAB+) calcd for $C_{20}H_{24}ClN_2O$ $[M+H]^+$ 343.1577, found 343.1578.

Representative procedure for $ZnCl_2$–$TMSCH_2MgCl$–LiCl-catalyzed Grignard reaction of aldimines (Schemes 11–13).

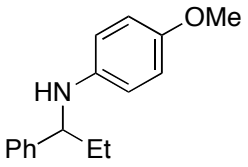


To a pyrex Schlenk tube, $ZnCl_2$ (40.8 mg, 0.30 mmol) was added and melt-dried by a heat gun under reduced pressure (<5 Torr). LiCl (139.9 mg, 3.3 mmol) was added to the pyrex Schlenk tube containing melt-dried $ZnCl_2$, and again the mixture was partially melt-dried by a heat gun under reduced pressure (<5 Torr). To the mixture, $TMSCH_2MgCl$ (1.0 *M* in Et_2O, 0.60 mL, 0.60 mmol) was added at room temperature. This mixture was stirred at that temperature for 15 min. *i*-PrMgBr (0.7 *M* in THF, 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 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 = 25/1–10/1), to give the desired product (507 mg, 75%).

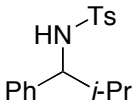


***N*-(2-Methyl-1-phenylpropyl)aniline (Scheme 11):**[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 2.03 (octet, *J* = 6.9 Hz, 1H), 4.12 (br, 2H), 6.49 (d, *J* = 7.2 Hz, 2H), 6.60 (t, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 2H), 7.17-7.34 (m, 5H). ^{13}C 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.



***N*-(4-Methoxyphenyl)-1-phenylpropan-1-amine (Scheme 12):**[21] ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 7.8 Hz, 3H), 1.70-1.90 (m, 2H), 3.68 (s, 3H), 3.81 (br, 1H), 4.15 (t, J = 6.7 Hz, 1H), 6.46 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 7.17-7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 31.6, 55.6, 60.4, 114.3, 114.7, 126.4, 126.7, 128.4, 141.7, 144.1, 151.7. HRMS (FAB+) calcd for $C_{16}H_{19}NO$ $[M]^+$ 241.1467, found 241.1465.



4-Methyl-*N*-(2-methyl-1-phenylpropyl)benzenesulfonamide (Scheme 13):[1] ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, J = 6.9 Hz, 1H), 0.94 (d, J = 6.9 Hz, 1H), 1.92 (octet, J = 6.9 Hz, 1H), 2.31 (s, 3H), 4.02 (t, J = 7.8 Hz, 1H), 5.04 (d, J =8.1 Hz 1H), 6.88-6.95 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 7.07-7.14 (m, 3H), 7.47 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.4, 21.4, 34.4, 64.2, 126.9, 127.0, 127.1, 128.0, 129.1, 137.7, 140.0, 142.7. HRMS (FAB+) calcd for $C_{17}H_{22}NO_2S$ $[M+H]^+$ 304.1371, found 304.1372.

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Chapter 5

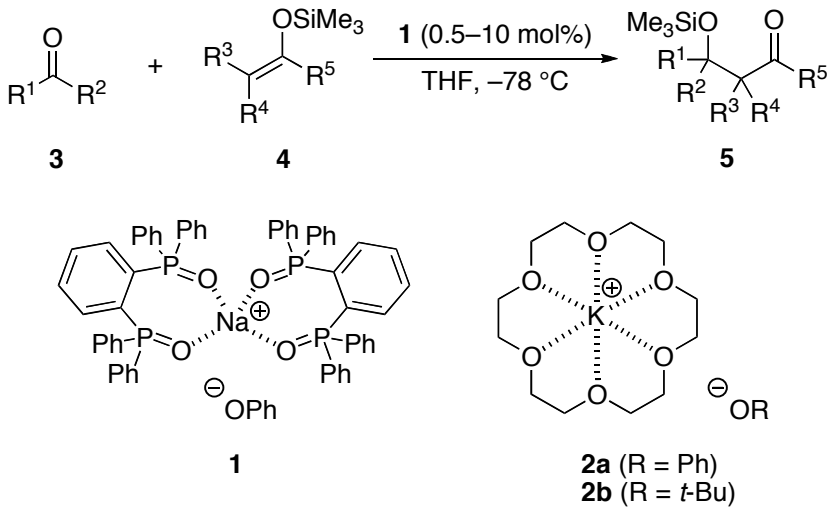
Highly Efficient Synthesis of Functionalized Tertiary Alcohols Catalyzed by Potassium Alkoxide–Crown Ether Complexes

Abstract: A highly efficient Mukaiyama aldol reaction between ketones and trimethylsilyl enolates in the presence of potassium alkoxide–crown ether complexes as Lewis base catalysts (0.3–5 mol%), which minimized the competing retro-aldol reaction, was developed. These catalysts promoted other addition reactions of trimethylsilyl reagents to ketones and aldimines, such as silyltrifluoromethylation, silylcyanation, and silylphosphonylation. A direct hydrophosphonylation of ketones also proceeded when the catalysts were used as a Brønsted base under mild reaction conditions.

5-1. Introduction

The efficient synthesis of tertiary alcohols using catalytic methodologies is currently one of the most rapidly advancing fields in organic chemistry. In particular, a carbon–carbon bond-forming reaction between ketones and organometallic reagents is an important strategy for synthesizing functionalized tertiary alcohols, which are versatile building blocks for the synthesis of natural products and pharmaceuticals.[1,2] Organosilicon compounds are quite useful reagents for synthesizing functionalized tertiary alcohols, particularly in the Mukaiyama aldol reaction, since Lewis acid and/or Lewis base can promote reactions with carbonyl compounds under mild reaction conditions.[3] However, due to the retro-aldol reaction, the synthesis of tertiary aldols from ketones and enolates has been limited,[4] which is in sharp contrast to the synthesis of secondary aldols from aldehydes and enolates.[5] Recently, we reported an efficient Mukaiyama aldol reaction with ketones using sodium phenoxide–phosphine oxides (**1**) as a Lewis base catalyst (Scheme 1).[6] The desired tertiary aldols, particularly with an α-quaternary or α-tertiary carbon, were obtained in high yields from a variety of ketones in the presence of 0.5–10 mol% of **1** in THF at –78 ºC. In this reaction, the naked PhO^- should act as an active Lewis base species to activate a trimethylsilyl (TMS) moiety to form the hypervalent silicate.[7,8] With this catalytic methodology, the activity should depend on the strength of the basicity. We here describe a potassium alkoxide–crown ether complex (**2**) as an extremely active Lewis base catalyst[9] for the highly efficient Mukaiyama aldol reaction with ketones (Scheme 1). Other reactions such as silyltrifluoromethylation, silylcyanation, and silylphosphonylation with the corresponding TMS reagents and ketones were also examined to afford a variety of functionalized tertiary alcohols under mild reaction conditions.

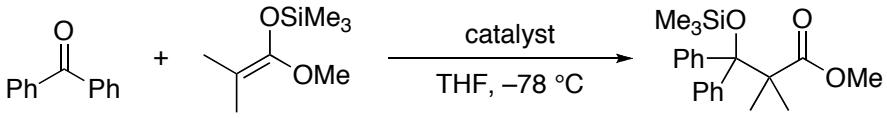
Scheme 1. Highly Efficient Mukaiyama Aldol Reaction with Ketones Using Lewis Base Catalysts



5-2. Results and Discussion

First, we examined the Mukaiyama aldol reaction between benzophenone (**3a**) and TMS enolate (**4a**) in the presence of alkaline metal alkoxide–crown ether complex as a Lewis base catalyst (Table 1). As expected, the reactivity was in the order KOPh–18-crown-6 (**2a**) > NaOPh–15-crown-5 >> LiOPh–12-crown-4 (entries 1–3). The reaction proceeded with 0.3 mol% of catalyst **2a**, and the tertiary aldol (**5a**) was obtained quantitatively within 1 h (entry 4). Low reactivity was observed without 18-crown-6 (entry 5). Interestingly, however, KO*t*-Bu–18-crown-6 (**2b**) showed much less reactivity than **2a** (entry 6).[10] As a comparison, 1 mol% of **1** was necessary to give **5a** in 97% yield in 1 h (entry 7).

Table 1. Mukaiyama Aldol Reaction of TMS Enolate (**4a**) with Benzophenone (**3a**) Catalyzed by Alkaline Metal Alkoxide–Crown Ether Complexes

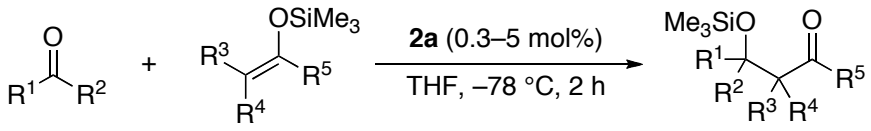


3a **4b** (1.2 equiv) **5a**

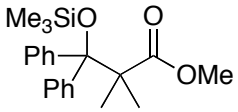
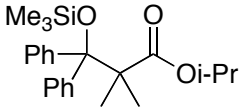
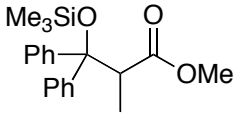
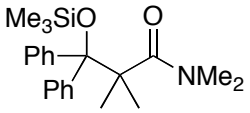
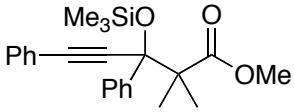
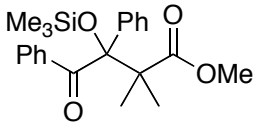
entry	catalyst (mol%)	reaction time	yield (%)
1	LiOPh–12-crown-4 [10]	30 min	0
2	NaOPh–15-crown-5 [10]	30 min	82
3	KOPh–18-crown-6 (**2a**) [1]	15 min	>99
4	**2a** [0.3]	1 h	>99
5	KOPh	2 h	6
6	KO*t*-Bu–18-crown-6 (**2b**) [1]	15 min	11
7	**1** [1]	1 h	97

Under the optimized reaction conditions, we next examined the tertiary aldol synthesis of other TMS enolates with ketones in the presence of **2a** (0.3–5 mol%) in THF at –78 ºC for 2 h, in which tertiary aldols with an α-quaternary or α-tertiary carbon center would be formed (Table 2). The catalytic activity of **2a** was much higher than that of **1**, and the desired tertiary alcohols were obtained in 90–>99% yields with less catalyst for **2a** than for **1**. *O*-TMS *N,O*-ketene acetal also reacted with **3a** in 90% yield when 1 mol% of **2a** was used (entry 4). Diphenylpropynone (entry 5) and α-diketone (entry 6) also reacted with TMS enolate, and the functionalized tertiary aldols were obtained in high yield.

Table 2. **2a**-Catalyzed Mukaiyama Aldol Reaction



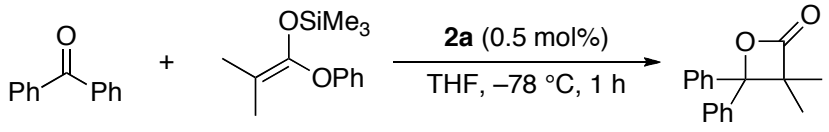
3 **4** (1.2 equiv) **5**

entry	product (**5**)		X[a] (mol%)	yield[a] (%)
1[b]		(**5a**)	0.3 (1)	>99 (97)
2		(**5b**)	0.5 (1)	89 (87)
3		(**5c**)	0.5 (1)	>99 (75)
4		(**5d**)	1 (5)	90 (86)
5		(**5e**)	5 (5)	>99 (71)
6		(**5f**)	5 (5)	93 (83)

[a] The results of catalyst **1** in place of **2a** are shown in parentheses.
[b] Reaction time was 1 h.

As expected, a tandem lactonization proceeded between **3a** and the phenylester-derived TMS enolate **4b**, and **7** was obtained quantitatively (Scheme 2). Catalyst **2a** was also highly effective in the Mannich-type reaction between *N*-Boc aldimine **8** and **4b,** and the adduct (**9**) was obtained quantitatively at –78 ºC within 2 h (Scheme 3).

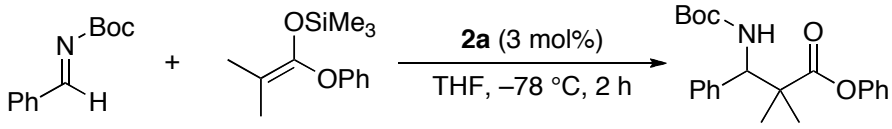
Scheme 2. **2a**-Catalyzed Tandem Lactonization



3a **4b** (1.2 equiv) **7** >99%

(*cf.* 1 mol% of **1**, –78 °C, 2 h: >99%)

Scheme 3. **2a**-Catalyzed Mannich-Type Reaction

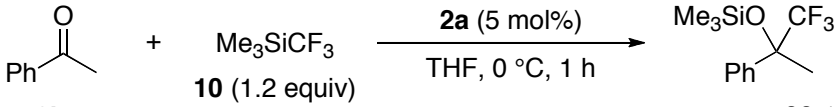


8 **4b** (1.2 equiv) **9** >99%

(*cf.* 10 mol% of **1**, –40 °C, 18 h: 95%)

Other TMS reagents were also examined. With 5 mol% of **2a**, silyltrifluoromethylation with $TMSCF_3$ (**10**) (Scheme 4)[11] and silylcyanation with TMSCN (**12**) (Scheme 5)[12] proceeded with respective yields of >99% and 87%.

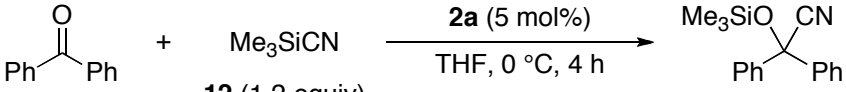
Scheme 4. **2a**-Catalyzed Silyltrifluoromethylation



3b **11** >99%

(*cf.* 5 mol% of **1**, 0 °C, 1 h: 47%)

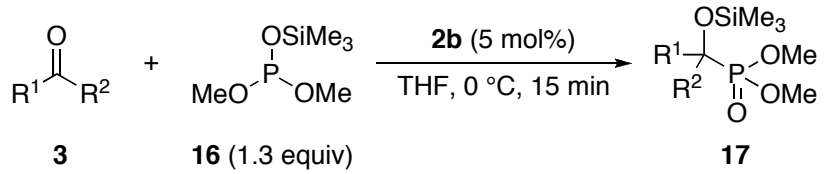
Scheme 5. **2a**-Catalyzed Silylcyanation



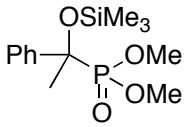
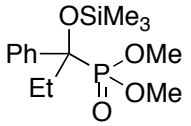
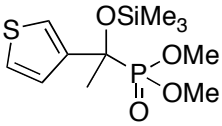
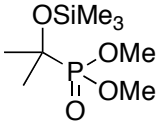
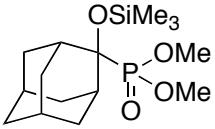
3a **13** 87%

Next, we examined the Lewis base-catalyzed silylphosphonylation of ketones with dimethyl trimethylsilyl phosphite (**16**) (Table 3). The thermal silylphosphonylation of carbonyl compounds was first reported by Evans 30 years ago.[13] However, to the best of our knowledge, there has been no report on the catalytic silylphosphonylation of carbonyl compounds. The reaction between acetophenone (**3b**) and **16** proceeded successfully with 5 mol% of **2a** at 0 ºC for 15 min (entry 1, parentheses).[14] Fortunately, the reaction also proceeded smoothly with commercially available **2b** (entry 1).[15] With 5 mol% of **2b**, other ketones, such as propiophenone (entry 2), 3-acetylthiophene as a heteroaromatic ketone (entry 3), acetone as a small aliphatic ketone (entry 4), and 2-adamantanone as a bulky aliphatic ketone (entry 5), also reacted, and the corresponding functionalized tertiary alcohols were obtained in good to excellent yields (56–>99%).

Table 3. **2b**-Catalyzed Silylphosphonylation of Ketones



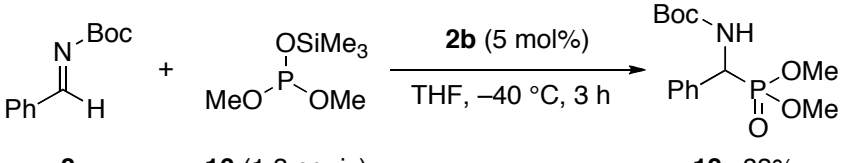
3 **16** (1.3 equiv) **17**

entry	product (**17**)		reaction time	yield (%)
1		(**17a**)	15 min (15 min)[a]	>99 (>99)[a]
2		(**17b**)	1 h	>99
3		(**17c**)	1 h	>99
4		(**17d**)	2 h	77
5		(**17e**)	2 h	56

[a] The results of catalyst **2a** in place of **2b** are shown in parentheses.

Furthermore, silylphosphonylation of aldimine **8** also provided the corresponding adduct **18** in 83% yield (Scheme 6).

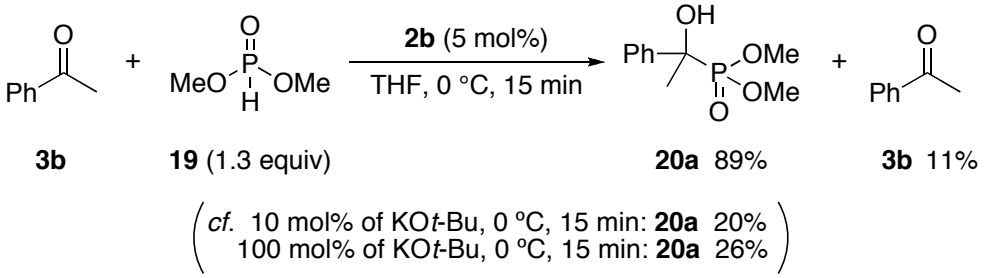
Scheme 6. **2b**-Catalyzed Silylphosphonylation of Aldimine **8**



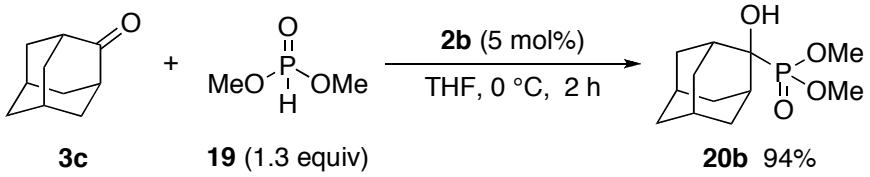
8 **16** (1.3 equiv) **18** 83%

Interestingly, **2b** was as an effective Brønsted base catalyst for the direct hydrophosphonylation of ketones. Direct hydrophosphonylation of **3b** with dimethyl phosphite (**19**) was examined in the presence of 5 mol% of **2b** in THF at 0 ºC for 15 min, and the corresponding tertiary alcohol (**20a**) was obtained in 89% yield (Scheme 7). While this type of reaction usually proceeds slowly under basic conditions with a stoichiometric or excess amount of alkaline metal salts (Scheme 7, parentheses),[16] we found that catalyst **2b** efficiently promoted the reaction. Remarkably, the reaction of 2-adamantanone (**3c**) with **19** proceeded smoothly, and the corresponding adduct (**20b**) was obtained in 94% yield (Scheme 8), although silylphosphonylation for the synthesis of **17e** was not easy (Table 3, entry 5).

Scheme 7. **2b**-Catalyzed Direct Hydrophosphonylation of Acetophenone



Scheme 8. **2b**-Catalyzed Direct Hydrophosphonylation of 2-Adamantanone



We then turned our attention to mechanistic aspects of silylphosphonylation and direct hydrophosphonylation in comparison to the Mukaiyama aldol reaction and direct aldol reaction (Figure 1). The key to clarifying these reactions is the retro-reactions and their equilibriums. In fact, the retro-reactions from tertiary alcohols **20** to ketones appeared to be slow.[17] Therefore, we can

conclude that strong Brønsted base catalysts such as **2b** promote deprotonation of the reagent (**19**) and accelerate the desired direct hydrophosphonylation with essentially minimal retro-reactions (Figure 1d). However, it is difficult to synthesize tertiary aldols from ketones and carbonyl compounds because the equilibrium of direct aldol reactions significantly shifts to the starting materials under basic conditions (Figure 1b).[6] In sharp contrast to these direct reactions, the TMS protection of tertiary alcohols is extremely effective for stopping or minimizing the undesired retro-reactions (Figures 1a and 1c). Therefore, strong Lewis Base catalyst **2a** or **2b** could efficiently promote the Mukaiyama aldol reaction and silylphosphonylation.

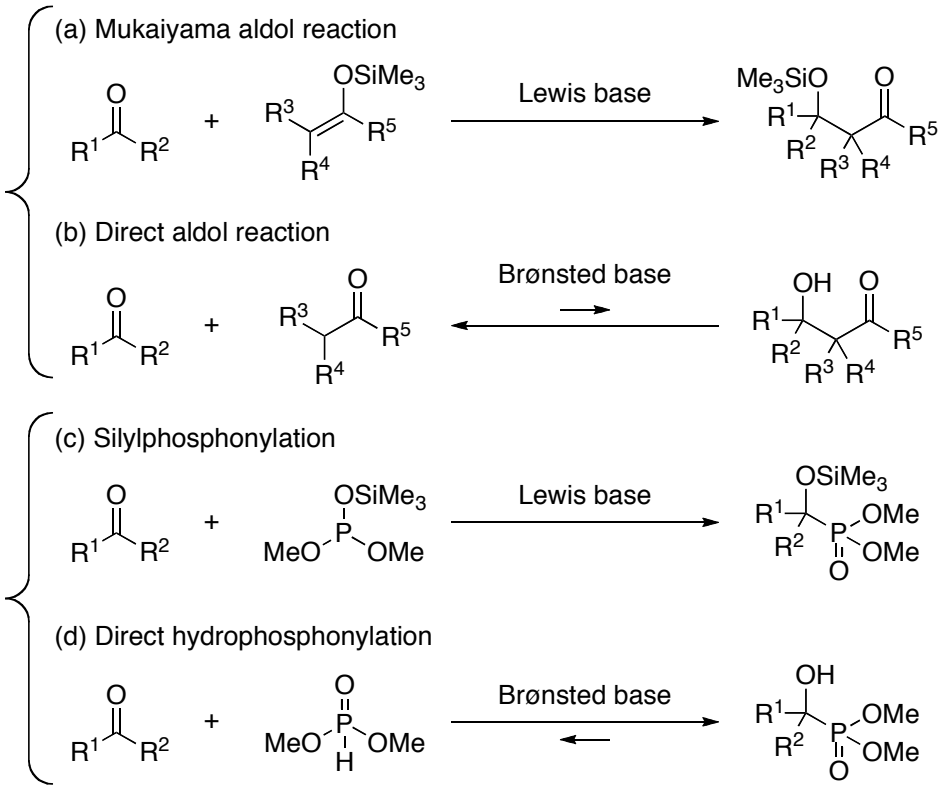


Figure 1. Retro-reactions and equilibriums in tertiary alcohol syntheses.

Finally, postulated catalytic cycles are shown in Figure 2.[18] In silylphosphonylation, **2a** or **2b** should be a Lewis base catalyst. A naked counter anion RO^- (R = Ph or *t*-Bu) would activate **16** to generate hypervalent silicate (**21**). Next, after P–C bond formation, RO^- could be regenerated from

ROTMS as a possible catalytic cycle. In direct hydrophosphonylation, **2b** should be a Brønsted base catalyst. After the deprotonation of **19** by naked *t*-BuO$^-$, a tautomeric equilibrium would be formed between phosphonate **22** and phosphite **23**.[19] These intermediates could react with **3** to generate the product via protonation by *t*-BuOH, accompanied by regeneration of the active *t*-BuO$^-$ moiety.

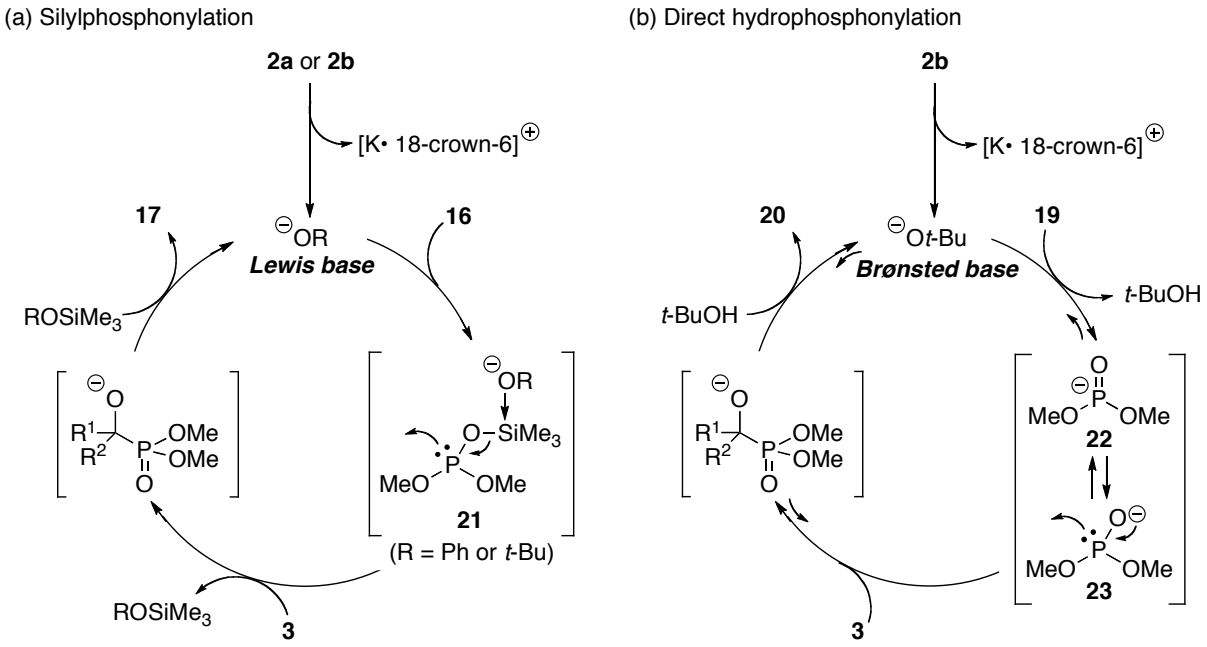


Figure 2. Possible catalytic cycles of silylphosphonylation (a) and direct hydrophosphonylation (b).

5-3. Conclusion

In summary, we have developed a highly efficient Mukaiyama aldol reaction between ketones and trimethylsilyl enolates catalyzed by potassium alkoxide–crown ether complex as a Lewis base. The Lewis base catalyst could successfully promote other addition reactions such as silyltrifluoromethylation, silylcyanation, and silylphosphonylation. Catalytic direct hydrophosphonylation was also promoted by the same complex as an effective Brønsted base. In these reactions, the corresponding functionalized tertiary alcohols could be obtained in high to excellent yields.

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14. Catalyst **1** was less active than **2a** or **2b**. In the reaction between **3b** and **16**, both **17a** and deprotected product **20a** were obtained in 92% yield (**17a**:**20a** = ca. 4:1).

15. This result was in sharp contrast to that with the Mukaiyama aldol reaction (see Table 1). Other catalysts such as KOAc–18-crown-6 and KF–18-crown-6 showed almost no reactivity under the same reaction conditions. KOPh or KO*t*-Bu without 18-crown-6 also showed no reactivity.

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17. From **20a**, **3b** was obtained in yields of only 19–20% in THF at 0 ºC for 2 h with the use of 5 mol% of KO*t*-Bu or 5 mol% of catalyst **2b**.

18. With these preliminary results to date, we cannot exclude the possibility of competitive self-catalysis by tertiary alkoxide intermediates.

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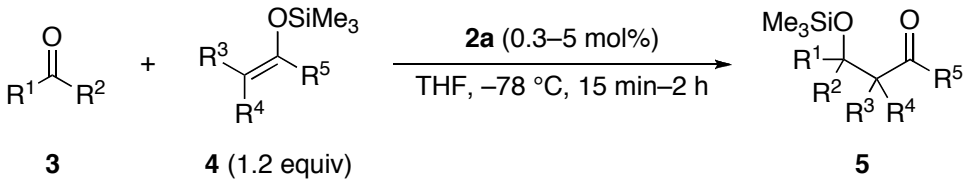
Experimental Section

General Methods. ^{1}H NMR spectra were measured on a Varian Mercury-300 (300 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; sept = septet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Mercury-300 (75 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{19}F NMR (282 MHz) spectra were measured on a 300 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (BTF at –63.24 ppm in deuterochloroform). ^{31}P NMR spectra were measured on Varian Mercury-300 (121 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (H_3PO_4 at 0 ppm). High resolution mass spectral analyses (HRMS) were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. The products were purified by neutral column chromatography on silica gel (Kanto Chemical Co., Inc. 37560) or NH silica gel column chromatography (Fuji Silysia Chemical LTD. Chromatorex-NH DM1020). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. In experiments that required dry solvents, diethylether (dehydrate), tetrahydrofuran (dehydrate), toluene (dehydrate) were distilled in prior to use.

Preparation of potassium phenoxides.[1]

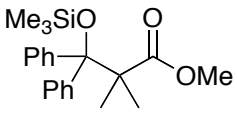
Phenol (338 mg, 3.6 mmol) was dissolved in 6 mL of aqueous solution of alkali metal hydroxide (3 mmol). Water was evaporated, and further dried in vacuo (3–5 Torr) at 120–130 °C for 1 h to remove excess phenol. The prepared alkali metal phenoxides were ground to fine powder in dry box under nitrogen atomosphere.

General procedure for 2a-catalyzed Mukaiyama aldol reaction with ketones.

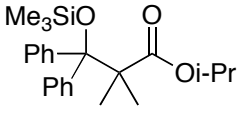


3 **4** (1.2 equiv) **5**

Freshly distilled THF (5 mL) was injected at room temperature under nitrogen into pyrex Schrenk tube containing potassium phenoxide (3.3 mg, 0.025 mmol) and 18-crown-6 (6.6 mg, 0.025 mmol). The mixture was stirred for 10 min at that temperature, and then this colorless solution was cooled to –78 °C and stirred for 5 min at that temperature. Ketone (2.5 mmol), and then trimethylsilyl enolate (3.0 mmol) were added. The pale yellow solution was stirred at –78 °C for 15 min–2 h by monotoring with TLC, and the reaction mixture was diluted with sat. $NaHCO_3$ aqueous solution (10 mL). The mixture was extracted with ethyl acetate (15 mL × 2), and the combined organic layer was washed by brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the aldol product which was purified by flash neutral silica gel column chromatography (hexane/AcOEt = 50/1–1/1).

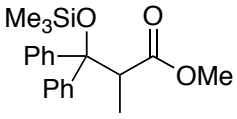


Methyl 2,2-dimethyl-3,3-diphenyl-3-(trimethylsilyloxy)propanoate (5a):[2]
^{1}H NMR (300 MHz, $CDCl_3$) δ –0.16 (s, 9H), 1.26 (s, 6H), 3.65 (s, 3H), 7.18-7.27 (m, 6H), 7.30-7.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.8, 24.4, 50.6, 51.7, 85.9, 126.9, 127.0, 129.8, 145.6, 178.3. IR(film) 2950, 1735, 1720, 1445, 1249, 1146, 1107, 1078 cm^{-1}. HRMS(FAB+) calcd for $C_{21}H_{28}NaO_3Si$ $[M+Na]^+$ 379.1705, found 379.1711.

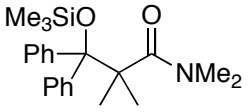


Isopropyl 2,2-dimethyl-3,3-diphenyl-3-(trimethylsilyloxy)propanoate (5b):[2]
^{1}H NMR (300 MHz, $CDCl_3$) δ –0.15 (s, 9H), 1.20 (d, J = 6.3 Hz, 6H), 1.27 (s, 6H), 4.99 (sept, J = 6.3

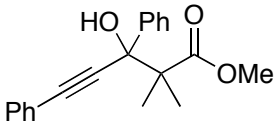
Hz, 1H), 7.20-7.28 (m, 6H), 7.34-7.41 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.0, 21.7, 24.6, 50.7, 67.8, 86.0, 126.8, 126.9, 129.9, 145.5, 176.4. IR(film) 2978, 2955, 1726, 1249, 1140, 1105, 1077 cm^{-1}. HRMS(FAB+) calcd for $C_{23}H_{32}NaO_3Si$ $[M+Na]^+$ 407.2018, found 407.2025.



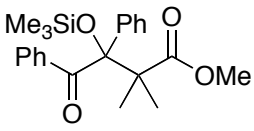
Methyl 2-methyl-3,3-diphenyl-3-(trimethylsilyloxy)propanoate (5c):[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.12 (s, 9H), 1.15 (d, *J* = 7.2 Hz, 3H), 3.55 (s, 3H), 3.74 (q, *J* = 7.2 Hz, 1H), 7.20-7.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.8, 14.4, 48.4, 51.3, 82.7, 127.0, 127.1, 127.5, 127.6, 128.3, 128.5, 144.4, 174.1. IR(film) 2950, 1746, 1446, 1249, 1196, 1157, 1089, 1070 cm^{-1}. HRMS(FAB+) calcd for $C_{20}H_{26}NaO_3Si$ $[M+Na]^+$ 365.1549, found 365.1545.



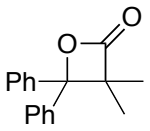
***N*,*N*,2,2-Tetramethyl-3,3-diphenyl-3-(trimethylsilyloxy)propanamide (5d):**[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.17 (s, 9H), 1.39 (s, 6H), 2.93 (s, 6H), 7.22-7.35 (m, 6H), 7.53-7.62 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.0, 27.2, 39.3, 54.5, 87.4, 127.1, 127.3, 129.4, 143.8, 176.3. IR(film) 2951, 1617, 1491, 1364, 1251, 1111, 1067 cm^{-1}. HRMS(FAB+) calcd for $C_{22}H_{31}NNaO_2Si$ $[M+Na]^+$ 392.2022, found 392.2021.



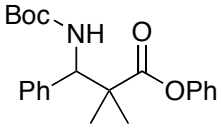
Methyl 3-hydroxy-2,2-dimethyl-3,5-diphenylpent-4-ynoate (5e'):[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.27 (s, 3H), 3.76 (s, 3H), 5.29 (s, 1H), 7.20-7.50 (m, 8H), 7.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) 20.5, 22.0, 51.7, 52.5, 77.1, 85.7, 90.7, 122.5, 127.3,128.0. 128.3, 128.5, 131.7, 139.0, 178.6. IR(film) 3447, 2988, 2949, 1731, 1701, 1490, 1448, 1284, 1145, 1057 cm^{-1}. HRMS(FAB+) calcd for $C_{20}H_{20}NaO_3$ $[M+Na]^+$ 331.1310, found 331.1312.



Methyl 2,2-dimethyl-4-oxo-3,4-diphenyl-3-(trimethylsilyloxy)butanoate (5f):[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.18 (s, 3H), 1.19 (s, 3H), 3.71 (s, 3H), 4.34 (m, 2H), 7.15-7.70 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.6, 22.2, 24.8, 49.8, 51.7, 89.2, 127.5, 127.5, 127.6, 127.7, 131.2, 132.3, 135.5, 140.7, 177.4, 199.0. IR(film) 2953, 1732, 1687, 1272, 1250, 1147, 1130, 1081 cm^{-1}. HRMS(FAB+) calcd for $C_{22}H_{28}NaO_4Si$ $[M+Na]^+$ 407.1655, found 407.1660.

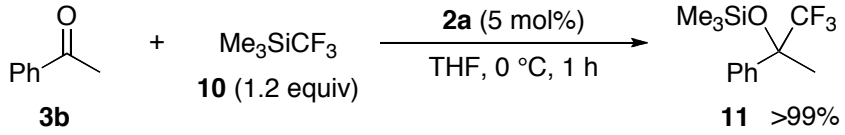


3,3-Dimethyl-4,4-diphenyloxetan-2-one (7):[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 6H), 7.27 (t, J = 7.2 Hz, 2H), 7.36 (t, J = 6.9 Hz, 4H), 7.48 (d, J = 6.9 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 59.8, 88.5, 125.6, 127.8, 128.4, 139.7, 175.0. IR(KBr) 3071, 2984, 1820, 1492, 1448, 1389, 1184 cm^{-1}. HRMS(FAB+) calcd for $C_{17}H_{17}O_2$ $[M+H]^+$ 253.1229, found 253.1229.

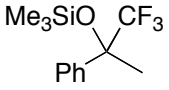


Phenyl 3-(*tert*-butoxycarbonylamino)-2,2-dimethyl-3-phenylpropanoate (9):[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.39 (s, 9H), 1.44 (s, 3H), 4.92 (d, J = 9.6 Hz, 1H), 5.94 (d, J = 9.6 Hz, 1H), 6.98 (d, J = 7.2 Hz, 2H), 7.20-7.42 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 24.5, 28.3, 47.1, 61.2, 79.5, 121.5, 125.9, 127.6, 128.0, 128.1, 129.4, 139.1, 150.5, 155.2, 175.2. IR(KBr) 3364, 2979, 1741, 1700, 1519, 1366, 1242, 1192, 1168, 1114 cm^{-1}. HRMS(FAB+) calcd for $C_{22}H_{28}NO_4$ $[M+H]^+$ 370.2018, found 370.2017.

Procedure for 2a-catalyzed silyltrifluoromethylation with $TMSCF_3$.

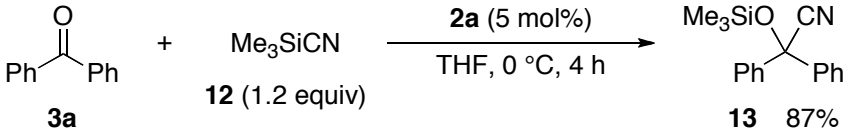


Freshly distilled THF (2 mL) was injected at room temperature under nitrogen into pyrex Schrenk tube containing potassium phenoxide (6.6 mg, 0.05 mmol) and 18-crown-6 (13.2 mg, 0.05 mmol). The mixture was stirred for 10 min at that temperature, and then this colorless solution was cooled to 0 °C and stirred for 5 min at that temperature. Acetophenone (**3b**) (117 μL, 1.0 mmol), and then trimethyl(trifluoromethyl)silane (**10**) (207 μL, 1.4 mmol) were added. The colorless solution was stirred at 0 °C for 1 h by monotoring with TLC, and the reaction mixture was diluted with water (10 mL). The mixture was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was washed by brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the product (**11**) which was purified by flash neutral silica gel column chromatography (hexane/AcOEt = 30/1) (262 mg, >99% yield).

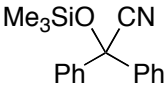


Trimethyl-(2,2,2-trifluoro-1-methyl-1-phenyl-ethoxy)-silane (11):[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.83 (q, J = 0.9 Hz, 3H), 7.35-7.41 (m, 3H), 7.53-7.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.1, 22.8, 125.4 (q, J = 283.9 Hz), 126.9, 128.1, 128.4, 140.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ –82.0. IR(film) 2961, 1448, 1380, 1296. 1255, 1170, 1105. 1073 cm^{-1}. HRMS(FAB+) calcd for $C_{11}H_{17}OSi$ $[M–CF_3]^+$ 193.1049, found 193.1053.

Procedure for 2a-catalyzed silylcyanation with TMSCN.

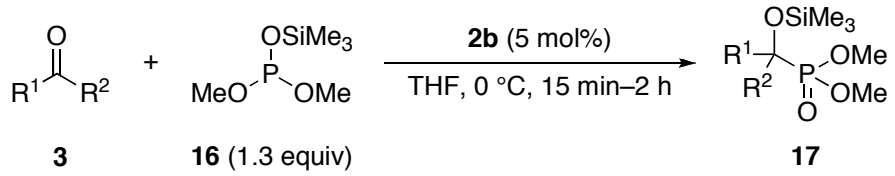


Freshly distilled THF (2 mL) was injected at room temperature under nitrogen into pyrex Schrenk tube containing potassium phenoxide (6.6 mg, 0.05 mmol) and 18-crown-6 (13.2 mg, 0.05 mmol). The mixture was stirred for 10 min at that temperature, and then this colorless solution was cooled to 0 °C and stirred for 5 min at that temperature. Benzophenone (**3a**) (182.2 mg, 1.0 mmol), and then TMSCN (**12**) (150 μL, 1.2 mmol) were added. The colorless solution was stirred at 0 °C for 4 h by monotoring with TLC, and the reaction mixture was diluted with water (10 mL). The mixture was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was washed by brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the product (**13**) which was purified by flash neutral silica gel column chromatography (hexane/AcOEt = 50/1) (245 mg, 87% yield).



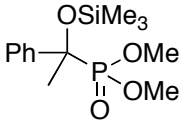
Diphenyl-trimethylsilanyloxy-acetonitrile (13):[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 9H), 7.28-7.36 (m, 6H), 7.46-7.49 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.1, 76.4, 120.7, 125.9, 128.5, 128.6, 141.9. IR(film) 2959, 1490, 1450, 1254, 1193, 1120, 1100 cm^{-1}. HRMS(FAB+) calcd for $C_{17}H_{19}NOSi$ $[M]^+$ 281.1236, found 281.1238.

General procedure for 2b-catalyzed silylphosphonylation.

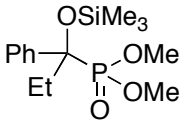


3 **16** (1.3 equiv) **17**

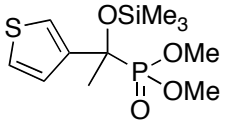
Freshly distilled THF (2 mL) was injected at room temperature under nitrogen into pyrex Schrenk tube containing potassium *tert*-butoxide (5.6 mg, 0.05 mmol) and 18-crown-6 (13.2 mg, 0.05 mmol). The mixture was stirred for 10 min at that temperature, and then this colorless solution was cooled to 0 °C and stirred for 5 min at that temperature. Ketone (**3**) (1.0 mmol), and then dimethyl trimethylsilyl phosphite (**16**) (248 μL, 1.3 mmol) were added. The colorless solution was stirred at 0 °C for 15 min–2 h by monotoring with TLC, and the reaction mixture was diluted with sat. $NaHCO_3$ aqueous solution (10 mL). The mixture was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was washed by brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the product (**17**) which was purified by flash neutral silica gel column chromatography (hexane/AcOEt = 1/1 to AcOEt only).



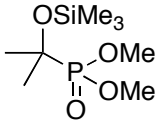
(1-Phenyl-1-trimethylsilanyloxy-ethyl)-phosphonic acid dimethyl ester (17a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.93 (d, J_{HP} = 16.5 Hz, 3H), 3.57 (d, J_{HP} = 10.2 Hz, 3H), 3.63 (d, J_{HP} = 10.2 Hz, 3H), 7.27-7.39 (m, 3H), 7.54-7.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.4, 24.7, 54.1, 77.4 (d, J_{CP} = 169.4 Hz), 126.7 (d, J_{CP} = 4.6 Hz), 127.6, 127.9, 142.0. ^{31}P NMR (121 MHz, $CDCl_3$) δ 24.5. IR(film) 2954, 1447, 1251, 1153, 1128, 1073, 1053, 1030 cm^{-1}. HRMS(FAB+) calcd for $C_{13}H_{24}O_4PSi$ $[M+H]^+$ 303.1182, found 303.1176.



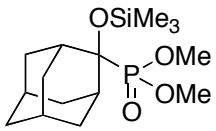
(1-Phenyl-1-trimethylsilanyloxy-propyl)-phosphonic acid dimethyl ester (17b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 0.71 (t, J = 7.5 Hz, 3H), 2.18-2.34 (m, 2H), 3.38 (d, J_{HP} = 10.2 Hz, 3H), 3.72 (d, J_{HP} = 10.2 Hz, 3H), 7.24-7.38 (m, 3H), 7.57-7.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.2, 6.8 (d, J_{CP} = 11.5 Hz), 29.2, 52.9, 53.9, 80.4 (d, J_{CP} = 160.2 Hz), 126.8 (d, J_{CP} = 4.6 Hz), 127.2, 127.9, 140.0. ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.9. IR(film) 2975, 2954, 1447, 1290, 1249, 1155, 1077, 1054, 1031 cm^{-1}. HRMS(FAB+) calcd for $C_{14}H_{26}O_4PSi$ $[M+H]^+$ 317.1338, found 317.1335.



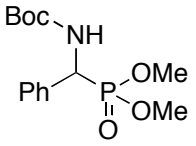
(1-Thiophen-3-yl-1-trimethylsilanyloxy-ethyl)-phosphonic acid dimethyl ester (17c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.90 (d, J_{HP} = 16.2 Hz, 3H), 3.65 (d, J_{HP} = 10.2 Hz, 3H), 3.73 (d, J_{HP} = 10.2 Hz, 3H), 7.21-7.24 (m, 1H), 7.26-7.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.3, 25.0, 54.0 (d, J_{CP} = 6.8 Hz), 75.7 (d, J_{CP} = 173.1 Hz), 122.3 (d, J_{CP} = 8.0 Hz), 125.2, 127.4 (d, J_{CP} = 3.3 Hz), 143.5. ^{31}P NMR (121 MHz, $CDCl_3$) δ 24.0. IR(film) 2954, 1251, 1234, 1186, 1148, 1117, 1054, 1031 cm^{-1}. HRMS(FAB+) calcd for $C_{11}H_{22}O_4PSSi$ $[M+H]^+$ 309.0746, found 309.0746.



(1-Methyl-1-trimethylsilanyloxy-ethyl)-phosphonic acid dimethyl ester (17d):[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.48 (d, J_{HP} = 15.9 Hz, 6H), 3.80 (d, J_{HP} = 9.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.6, 26.2 (d, J_{CP} = 3.4 Hz), 53.7, 73.8 (d, J_{CP} = 172.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.9. IR(film) 2956, 1465, 1252, 1203, 1178, 1064, 1037 cm^{-1}. HRMS(FAB+) calcd for $C_8H_{22}O_4PSi$ $[M+H]^+$ 241.1025, found 241.1025.

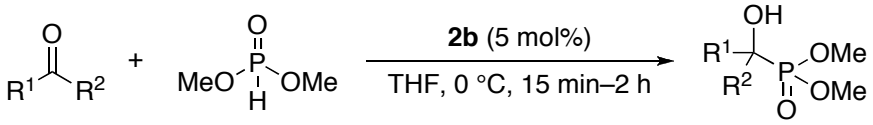


(2-Trimethylsilanyloxy-adamantan-2-yl)-phosphonic acid dimethyl ester (17e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.46-2.18 (m, 12H), 2.54 (d, J = 12.9 Hz, 2H), 3.75 (d, J = 10.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.3, 26.7, 27.3, 33.0 (d, J_{CP} = 11.4 Hz), 33.8, 34.8 (d, J_{CP} = 3.4 Hz), 52.5, 80.7 (d, J_{CP} = 159.4 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.3. IR(KBr) 2905, 2854, 1451, 1248, 1234, 1124, 1059, 1026 cm^{-1}. HRMS(FAB+) calcd for $C_{15}H_{30}O_4PSi$ $[M+H]^+$ 333.1651, found 333.1654.



Carbamic acid, *N*-[(dimethoxyphosphinyl)phenylmethyl]-1,1-dimethylethyl ester (18):[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 3.51 (d, J_{HP} = 10.8 Hz, 3H), 3.77 (d, J_{HP} = 10.5 Hz, 3H), 5.15 (dd, J = 9.6 Hz, 21.5 Hz, 1H), 5.48 (br, 1H), 7.29-7.43 (m. 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 51.5 (d, J_{CP} = 152.2 Hz), 53.6 (d, J_{CP} = 6.9 Hz), 53.8 (d, J_{CP} = 6.8 Hz), 80.5, 127.8 (d, J_{CP} = 5.8 Hz), 128.2 (d, J_{CP} = 2.3 Hz), 128.8, 135.2, 155.0. ^{31}P NMR (121 MHz, $CDCl_3$) δ 24.7. IR(KBr) 3252, 2972, 1693, 1535, 1296, 1249, 1167, 1046 cm^{-1}. HRMS(FAB+) calcd for $C_{14}H_{23}NO_5P$ $[M+H]^+$ 316.1314, found 316.1311.

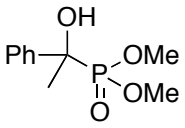
General procedure for 2b-catalyzed hydophosphonylation.



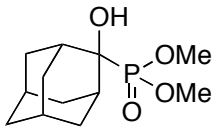
3 **19** (1.3 equiv) **20**

Freshly distilled THF (2 mL) was injected at room temperature under nitrogen into pyrex Schrenk tube containing potassium *tert*-butoxide (5.6 mg, 0.05 mmol) and 18-crown-6 (13.2 mg, 0.05

mmol). The mixture was stirred for 10 min at that temperature, and then this colorless solution was cooled to 0 °C and stirred for 5 min at that temperature. Ketone (**3**) (117 μL, 1.0 mmol), and then dimethyl phosphite (**19**) (119 μL, 1.3 mmol) were added. The colorless solution was stirred at 0 °C for 15 min by monotoring with TLC, and the reaction mixture was diluted with sat. NH_4Cl aqueous solution (10 mL). The mixture was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was washed by brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the product (**20**) which was purified by flash neutral silica gel column chromatography (hexane/AcOEt = 1/1 to AcOEt only).



(1-Hydroxy-1-phenyl-ethyl)-phosphonic acid dimethyl ester (20a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J_{HP} = 15.6 Hz, 3H), 2.91 (br, 1H), 3.56 (d, J_{HP} = 10.2 Hz, 3H), 3.74 (d, J_{HP} = 10.2 Hz, 3H), 7.27-7.41 (m, 3H), 7.59-7.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 54,2, 73.8 (d, J_{CP} = 159.1 Hz), 125.8, 127.6, 128.2, 140.9. ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.5. IR(KBr) 3282, 2954, 2926, 1735, 1449, 1229, 1069, 1027 cm^{-1}. HRMS(FAB+) calcd for $C_{10}H_{14}O_3P$ $[M–OH]^+$ 213.0681, found 213.0686.



(2-Hydroxy-adamantan-2-yl)-phosphonic acid dimethyl ester (20b): ^{1}H NMR (300 MHz, CDCl3) δ 1.49-2.39 (m, 15H), 3.81 (d, J_{HP} = 10.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.3, 32.3 (d, J_{CP} = 11.4 Hz), 34.0, 34.3, 38.3, 53.5 (d, J_{CP} = 8.0 Hz), 77.4 (d, J_{CP} = 156.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.1. IR(KBr) 3270, 2955, 2905, 1454, 1231, 1215, 1055, 1025 cm^{-1}. HRMS(FAB+) calcd for $C_{12}H_{20}O_3P$ $[M–OH]^+$ 243.1150, found 243.1151.

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Publication List

Communications

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

   Manabu Hatano, Shinji Suzuki, Kazuaki Ishihara

   J. Am. Chem. Soc. **2006**, *128*(31), 9998–9999.

   Rank in Most Accessed Articles, July–September, 2006.

   Highlighted in *Synfacts* **2006**, 1166.

   Highlighted in *Organic Chemistry Portal,* Germany. (http://www.organic-chemistry.org/)

2. "Highly Efficient Synthesis of Functionalized Tertiary Alcohols Catalyzed by Potassium Alkoxide–Crown Ether Complexes"

   Tetrahedron Lett. **2009**, *50*(26), 3171–3174.

   Manabu Hatano, Shinji Suzuki, Eri Takagi, Kazuaki Ishihara

3. "Highly Chemoselective Stoichiometric Alkylation of Ketones with Grignard Reagent Derived Zinc(II) Ate Complexes"

   Synlett **2010**, 321–324.

   Manabu Hatano, Shinji Suzuki, Kazuaki Ishihara

4. "Zinc(II)-Catalyzed Grignard Additions to Ketones with RMgBr and RMgI"

   Chem. Commun. **2010**, *46*(15), 2674–2676.

   Manabu Hatano, Orie Ito, Shinji Suzuki, Kazuaki Ishihara

   Highlighted in *Synfacts* **2010**, 819.

Article

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

   J. Org. Chem. **2010**, *75*(15), 5008–5016.

   Manabu Hatano, Orie Ito, Shinji Suzuki, Kazuaki Ishihara

   Rank in Most Accessed Articles, June, 2010.

Review

6. "Challenge of Preparation of Ideal Alkylation Reagents – Development of the Most Efficient Reaction to Synthesize Tertiary Alcohols"

   Kagaku **2007**, *62*(3), 16–20.

   Manabu Hatano, Shinji Suzuki, Kazuaki Ishihara

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January 2011

Shinji Suzuki