Highly efficient synthesis of functionalized tertiary alcohols catalyzed by potassium alkoxide–crown ether complexes

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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.

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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 °C. 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. In this Letter, we 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.

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, KOt-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).

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 °C 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.
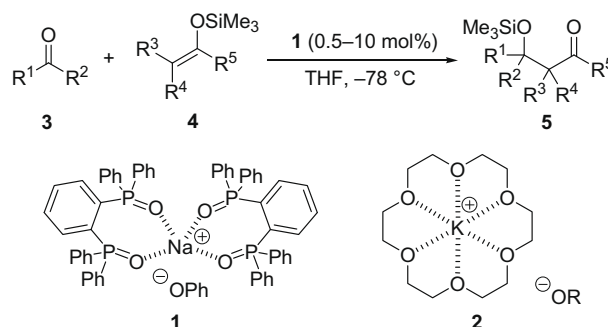
Scheme 1. Highly efficient Mukaiyama aldol reaction with ketones using Lewis base catalysts.

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*E-mail address:* ishihara@cc.nagoya-u.ac.jp (K. Ishihara).

Table 1
Mukaiyama aldol reaction of TMS enolate (**4a**) with benzophenone (**3a**) catalyzed by alkaline metal alkoxide–crown ether complexes


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	KOt-Bu–18-crown-6 (**2b**) [1]	15 min	11
7	**1** [1]	1 h	97

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.

As expected, a tandem lactonization proceeded between **3a** and the phenylester-derived TMS enolate **4b**, and **7** was obtained quantitatively (Eq. 1). 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 within 2 h at −78 °C (Eq. 2):

$$(1)$$

$$(2)$$
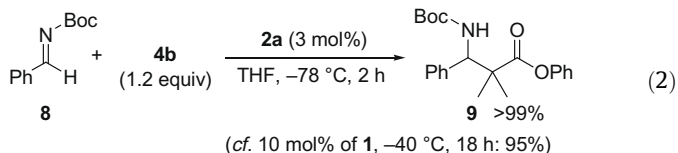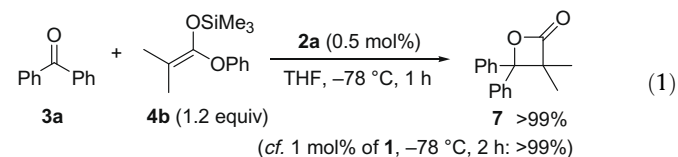
Other TMS reagents were also examined. With 5 mol % of **2a**, silyltrifluoromethylation with TMSCF$_3$ (**10**) (Eq. 3)[11] and silylcyanation with TMSCN (**12**) (Eq. 4)[12] proceeded with respective yields of >99% and 87%:

$$(3)$$

$$(4)$$
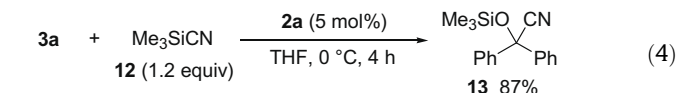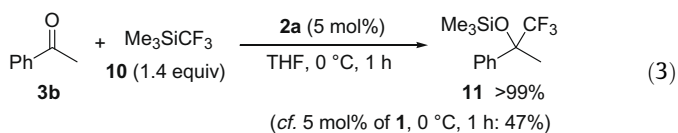
Next, we examined the Lewis base-catalyzed silylphosphonylation of ketones with dimethyl trimethylsilyl phosphite (**16**) (Table 3). The thermal silylphosphonylation of carbonyl compounds was first reported by Evans 30 years ago.[13] However, to the best of our knowledge, there has been no report on the catalytic silylphosphonylation of carbonyl compounds. The reaction between acetophenone (**3b**) and **16** proceeded successfully with 5 mol % of **2a** at 0 °C 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

Table 2
2a-catalyzed Mukaiyama aldol reaction

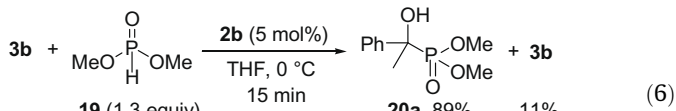| Entry	Product (**5**)	X[a] (mol %)	Yield[a] (%)
1[b]	(**5a**)	0.3 (1)	>99 (97)
2	(**5b**)	0.5 (1)	98 (87)
3	(**5c**)	0.5 (1)	>99 (75)
4	(**5d**)	1 (5)	90 (86)
5	(**5e**)	5 (5)	>99 (71)
6	(**5f**)	5 (5)	93 (83)

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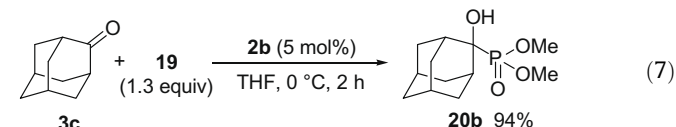[b] Reaction time was 1 h.

to excellent yields (56~>99%). Furthermore, silylphosphonylation of aldimine **8** also provided the corresponding adduct **18** in 83% yield (Eq. 5):

$$(5).$$
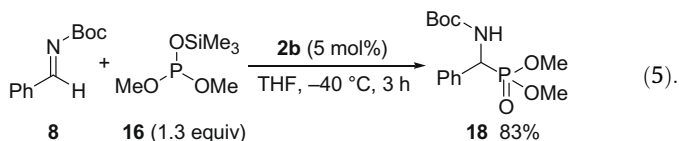
Interestingly, **2b** was as an effective Brønsted base catalyst for the direct hydrophosphonylation of ketones. Direct hydrophosphonylation of **3b** with dimethyl phosphite (**19**) was examined in the presence of 5 mol % of **2b** in THF at 0 °C for 15 min, and the corresponding tertiary alcohol (**20a**) was obtained in 89% yield (Eq. 6). While this type of reaction usually proceeds slowly under basic conditions with a stoichiometric or excess amount of alkaline metal salts (Eq. 6, 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 Eq. 7, although silylphosphonylation for the synthesis of **17e** was not easy (Table 3, entry 5):

$$(6)$$

$$(7)$$

Table 3
2b-catalyzed silylphosphonylation of ketones

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.

We then turned our attention to mechanistic aspects of silylphosphonylation and direct hydrophosphonylation in comparison to the Mukaiyama aldol reaction and direct aldol reaction (Fig. 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 (Fig. 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 (Fig. 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 (Figs. 1a and c). Therefore, strong Lewis Base catalyst **2a** or **2b** could efficiently promote the Mukaiyama aldol reaction and silylphosphonylation.

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.

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. Further studies on the application of this method to asymmetric catalyses are now underway.

Figure 1. Retro-reactions and equilibriums in tertiary alcohol syntheses.
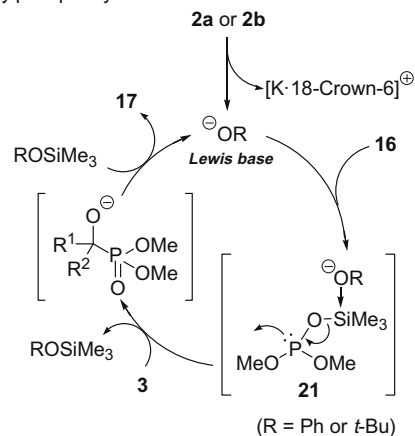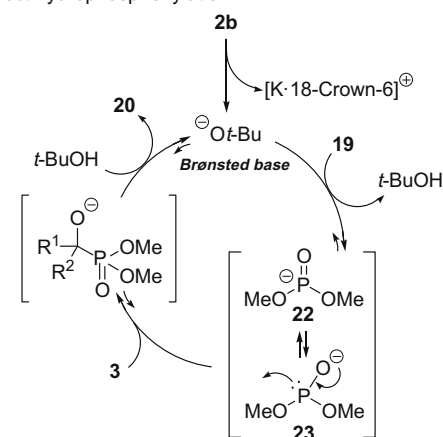
Figure 2. Possible catalytic cycles of silylphosphonylation (a) and direct hydrophosphonylation (b).

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.028.

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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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