Sodium Phenoxide—Phosphine Oxides as Extremely Active Lewis Base Catalysts for the Mukaiyama Aldol Reaction with Ketones

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ABSTRACT



A highly efficient Mukaiyama aldol reaction between ketones and trimethylsilyl enolates catalyzed by sodium phenoxide–phosphine oxides as simple homogeneous Lewis base catalysts (0.5–10 mol %) was developed, which minimized competing retro-aldol reaction. For a variety of aromatic ketones and aldimines, aldol and Mannich-type products with an α -quaternary carbon center were obtained in good to excellent yields. Up to 100 mmol scale of benzophenone and trimethylsilyl enolate with 0.5 mol % of catalyst was established in 97% yield (34.8 g).

The catalytic aldol reaction is one of the most important and useful reactions for synthesizing a β -hydroxy carbonyl structural scaffold, which is often found in natural products and pharmaceuticals.¹ Remarkably, however, an efficient synthesis of tertiary aldols (aldol adducts of enolates with ketones) is still limited.² This is because (1) the reactivity of ketones is low due to electronic and steric reasons and (2) the intrinsic retro-aldol reactions are generally rapid.^{2b,d} Actually, according to our preliminary experiments, the direct aldol reaction of Na enolate (**2**)³ with benzophenone (**1a**) gave the desired product (**3a-OH**) in only 1% yield (eq 1).

(2) Cl₃Si- or (RO)₃Si enolates with ketones: (a) Denmark, S. E.; Fan,
Y. J. Am. Chem. Soc. 2002, 124, 4233. (b) Oisaki, K.; Suto, Y.; Kanai, M.;
Shibasaki, M. J. Am. Chem. Soc. 2003, 125, 5644. (c) Denmark, S. E.;
Fan, Y.; Eastgate, M. D. J. Org. Chem. 2005, 70, 5235. (d) Oisaki, K.;
Zhao, D.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2006, 128, 7164.
(3) Lochmann, L.; Trekoval, J. J. Organomet. Chem. 1975, 99, 329.

Surprisingly, 87% of the corresponding Na aldolate quickly decomposed to **1a** within 1 min due to the rapid retro-aldol reaction even at -78 °C (eq 2). Moreover, a poor result (0% yield) was obtained in an exemplary Lewis acid-catalyzed Mukaiyama aldol reaction between **1a** and trimethylsilyl (TMS) enolate (**4a**) by using 10 mol % of TMSOTf even at 60 °C (eq 3).⁴ Thus, there are many difficulties in tertiary aldol synthesis from, particularly, diaryl ketones. However, we considered that, in principle, rapid TMS protection to the corresponding tertiary aldolate via anionic activation to TMS enolate by Lewis base catalysts might minimize the retro-aldol reaction (eq 4). We report here, for the first time, simple and highly effective Lewis base catalysts such as

^{(1) (}a) Nelson, S. G. Tetrahedron: Asymmetry **1998**, *9*, 357. (b) Mahrwald, R. Chem. Rev. **1999**, *99*, 1095. (c) Machajewski, T. D.; Wong, C.-H. Angew. Chem., Int. Ed. **2000**, *39*, 1352. (d) Palomo, C.; Oiarbide, M.; García, J. M. Chem. Soc. Rev. **2004**, *33*, 65. (e) Mahrwald, R. Modern Aldol Reactions; Wiley-VCH: Weinheim, Germany, 2004. (f) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. Chem. Rev. **2006**, *106*, 2734.

⁽⁴⁾ Pioneering Lewis acid or Lewis base catalysis with Si enolates with aldehydes: (a) Mukaiyama, T.; Narasaka, K.; Banno, K. Chem. Lett. **1973**, 1011. (b) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. J. Am. Chem. Soc. **1996**, 118, 7404. (c) Matsukawa, S.; Okano, N.; Imamoto, T. Tetrahedron Lett. **2000**, 41, 103. (d) Fujisawa, H.; Mukaiyama, T. Chem. Lett. **2002**, 31, 182. (e) Nakagawa, T.; Fujisawa, H.; Nagata, Y.; Mukaiyama, T. Bull. Chem. Soc. Jpn. **2004**, 77, 1555. (f) Fujisawa, H.; Nakagawa, T.; Fujisawa, H.; Nakagawa, T.; Fujisawa, H.; Nagata, Y.; Mukaiyama, T. Adv. Synth. Catal **2004**, 346, 1241. (g) Nakagawa, T.; Fujisawa, H.; Nagata, Y.; Mukaiyama, T. Bull. Chem. Soc. Jpn. **2005**, 78, 236.

sodium phenoxide (**5b**) with phosphine oxides (**L**) (eqs 4 and 5), which were designed for tertiary aldol syntheses with an α -quaternary carbon center between ketones and easily available TMS enolates.



First of all, Mukaiyama aldol reactions between **1a** and TMS enolate (**4a**) were examined in the presence of alkaline metal phenoxide (PhOM, **5**) as a Lewis base catalyst.^{5,6} We found that the co-presence of phosphine oxides, especially bidentate $1,2-(O=PPh_2)_2C_6H_4$ (**L**), remarkably increased the activity of the catalysts. Table 1 shows the results with simply mixed homogeneous catalysts of **5** and **L** in TMS aldol (**3a**) syntheses from **1a** and 1.2 equiv of **4a** in THF at -78 °C for 5 min-2 h. With 10 mol % each of **5** and **L**, PhONa (**5b**) showed high reactivity among alkaline metal phenoxides

Table 1. Mukaiyama Aldol Reactions of **4a** withBenzophenone (**1a**) Catalyzed by Alkaline MetalPhenoxide-Phosphine Oxides ($5\cdot L_n$)

	1a . 4a	-10 mol %) (L) (0–10 mol %	6)	30			
	1a + 4a (1.2 equ	THF, –78 °C, 2 h				Ja	
entry	5 [M] ^a	\mathbf{L}^{a}	\mathbf{yield}^b	entry	5 [M] ^{<i>a</i>}	\mathbf{L}^{a}	yield ^{b}
1	5a [Li], 10	10	69 [40] ^c	6	5b [Na], 10	0	0
2	5b [Na], 10	10	84 [86] ^c	7	-, 0	10	0
3	5c [K], 10	10	80 [79] ^c	8	5b [Na], 1	1	92 [22] ^a
4	5d [Rb], 10	10	76	9	5b [Na], 1	2	97 [34] ^a
5	5e [Cs], 10	10	73	10	5b [Na], 1	3	89 [38] ^a

 a Units: mol %. b Units: %. c Reaction time was 15 min. d Reaction time was 5 min.

(entries 1-5).⁷ The reactions did not proceed in the absence of either **5b** or **L** (entries 6 and 7). To our delight, the reaction proceeded with 1 mol % of **5b** and 1-3 mol % of **L** (entries 8-10).

Under the optimized reaction conditions, a 100 mmol scale amount of the desired tertiary aldol **3a** with an α -quaternary carbon center was obtained in 97% yield (34.8 g) from **1a** and **4a** with 0.5 mol % of **5b·L**₂ in THF at -78 °C for 6 h (eq 6).



Next, we examined the aldol synthesis of other TMS enolates (4a-h) with 1a in the presence of a mixed catalyst $5b\cdot L_2$ (1 mol %) in THF at -78 °C for 2 h, in which tertiary aldols with an α -quaternary or α -tertiary carbon would be formed (Table 2). In particular, the reaction of α, α -



^a 5 mol % of 5b·L₂ was used.

disubstituted TMS ketene acetals with 1a proceeded with yields of 87–99% in 3a–d. β -Lactone 3g' was obtained in

⁽⁵⁾ Ba(OPh)₂-catalyzed direct aldol reactions: Saito, S.; Kobayashi, S. J. Am. Chem. Soc. **2006**, 128, 8704.

>99% yield from the phenyl ester-derived enolate. *O*-TMS *N*,*O*-ketene acetal also reacted with **1a**, and **3h** was obtained in 86% yield. Encouraged by the good reactivities for commonly used TMS enolates with **1a**, we further examined the reactions between other ketones and **4a** or **4h** by using $1-10 \mod \%$ of **5b**·L₂ (Table 3). Unfortunately, the reactivity



^{*a*} 1 mol % of **5b·L**₂ was used. ^{*b*} 5 mol % of **5b·L**₂ was used. ^{*c*} 10 mol % of **5b·L**₂ was used.

of acetophenone with enolizable α -proton was not high, probably due to the basicity of the catalyst, and **3i** was obtained in moderate yield (entry 1). In sharp contrast, diphenylpropynone, enolizable heteroaromatic ketones, diaryl ketones, and ferrocenyl ketone provided the desired corresponding aldols in 71–99% yield (entries 2–7). An α -diketone and an α -ketoester also reacted with **4**, and polyfunctionalized aldol compounds (**3p** and **3q**) with vicinal quaternary carbon centers were obtained in 83% and 92% yield, respectively (entries 8 and 9).

We next examined aldimines (6) with TMS enolates (4) in the presence of $5-10 \mod \%$ of $5b \cdot L_2$ (Table 3). In principle, aldimines are not much reactive due to their weak electrophilic nature, and moreover, deactivation was expected particularly in the case of Lewis acid catalysts because of the increasing basicity of the corresponding products. Anionic Lewis base catalyst $5b \cdot L_2$, however, showed high catalytic activities with *N*-Bz, *N*-Boc, and *N*-Cbz protected aldimines (**6a**-**c**) in Mannich-type reactions with **4**, and the corre-

Table 4	4. Mannio	ch-Type	Reac	tions of 4 with Aldim	ine 6
N Ph 6a—c (2 mmo	X + R ¹ H s; ol) (1.	OTMS R ² 4 2 equiv)	5I 	X →L ₂ (5–10 mol %) → Ph HF, -40 °C, 18 h	$ \begin{array}{c c} $
entry	imine	(6)	4	product (7)	yield (%)
1 ^{<i>a,b</i>}	Ph H	(6a)	4 a	Bz NH O Ph S OMe (7a)	>99
2^c	Ph H	(6b)	4 a	Boc NH O Ph S OMe (7b)	94
3 ^c	Ph H	(6b)	4b	Ph v OEt (7c)	98
4 ^b	Ph H	(6b)	4c	$ \begin{array}{c} Boc \\ NH & O \\ Ph & OPr^i \end{array} (7d) $	88
5 ^b	Ph H	(6b)	4d	$\begin{array}{c} \text{Boc} \\ \text{NH} & \text{O} \\ \\ \text{Ph} & \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	>99
6 ^b	Ph H	(6b)	4g	Ph C OPh (7f)	95
7 ⁶	Ph H	(6b)	4h	$\begin{array}{c} Boc_{NH} & O \\ H & S \\ Ph & S \\ NMe_2 \end{array} (7g)$	89
8 ^b	N ^{-Cbz}	(6c)	4a	Cbz NH O Ph & OMe (7h)	70

^{*a*} Reaction was examined at 0 °C for 2 h. ^{*b*} 10 mol % of $5b\cdot L_2$ was used. ^{*c*} 5 mol % of $5b\cdot L_2$ was used.

sponding adducts (7) were obtained in up to >99% yield. Deprotection of the *N*-Boc product **7b** smoothly proceeded under AcCl–MeOH conditions to give the primary amine compound in quantitative yield.

Finally, we turned our attention to the study of the active catalysts. When **3a-OH** (10 mol %), NaN(SiMe₃)₂ (10 mol %), and L (20 mol %) were used, **3a** was obtained in only 8% yield while an estimated maximum yield was 110% (eq 7). Therefore, the possibility of self-catalysis by the corresponding aldolate (**3a-O**⁻) was denied.^{4f} However, addition

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⁽⁷⁾ AcONa• L_2 or *t*-BuONa• L_2 (10 mol %) with low solubility showed no catalytic activity under the same reaction conditions.



of 10 mol % of PhOTMS under the same conditions promoted the reaction, and **3a** was obtained quantitatively (eq 7). These results show the importance of the PhO⁻ moiety in situ. Fortunately, a single crystal could be obtained for X-ray analysis of tetrahedral Li complex ($8\cdot OH$) bearing Li⁺ and L₂ as a cation moiety and HO⁻ as an anion moiety (Figure 1).⁸ As an analogy from $8\cdot OH$ in the X-ray analysis,



Figure 1. ORTEP drawing of the cationic moiety of Li complex **(8·OH)**.

we can predict the structure of $5b\cdot L_2$ as a possible active catalyst,⁹ although **8·OH** should not be the active species because no catalytic activity was observed by LiOH·L₂ or NaOH·L₂ in the reaction of **1a** and **4a**. In particular, for **5b·L**₂, the Na⁺ moiety wrapped by L₂ should make the counteranion (i.e., PhO⁻) naked and hypervalent silicate **9** would be generated (Figure 2).^{10,11} Thus, activated enolate **9** could ultimately increase the nucleophilicity enough to attack even ketones. Presumably, the naked PhO⁻ as **5b·L**₂ could be regenerated from PhOTMS in continuous catalytic cycles (see also eq 7).¹²



Figure 2. Postulated catalytic cycle including initial precursor 5b·L₂.

In summary, we have developed a highly efficient Mukaiyama aldol reaction between ketones and TMS enolates catalyzed by sodium phenoxide—phosphine oxides as a simple Lewis base. Aldol products with an α -quaternary carbon center were obtained in high yields with prevention of the serious retro-aldol reactions, by rapidly protecting the corresponding aldolates with TMS. Further studies of the application to other catalyses and a challenge toward enantioselective catalyses, are now underway.

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Supporting Information Available: Experimental procedures and spectral data, as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽⁸⁾ Due to adventitious water during the recrystallization of $5a \cdot L_2$, the phenol moiety was interchanged by hydroxide in the crystal structure. (9) HRMS(FAB+) analysis of $5b \cdot L_2$ also assisted in determining the

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⁽c) Orito, Y.; Nakajima, M. Synthesis 2006, 1391.
(11) Anionic fluoride-promoted reactions with RSi(OMe)₃ or RSiMe₃:

⁽¹¹⁾ Anionic Huorde-promoted reactions with RSI(OMe)₃ or RSIMe₃:
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(b) Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 676. (c) Biddle, M. M.; Reich, H. J. J. Org. Chem. **2006**, *71*, 4031.

⁽¹²⁾ Addition of PhOTMS (1 mol %) in the presence of 2 mol % of L was not effective in the reaction between **1a** and **2**, and therefore, PhO^- is essential for the activation of TMS enolates but *not* Na enolates.