Ammonium Phenoxides-catalyzed syn-Selective Aldol Reaction Between an Aldehyde and an Trimethylsilyl Enolate

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Aldol reactions between aldehydes and trimethylsilyl enolates generated from ketones or thioesters proceeded smoothly in the presence of a Lewis base catalyst such as tetrabutylammonium phenoxide or *p*-methoxyphenoxide in THF to afford the corresponding aldols in high yields with high syn-selectivity.

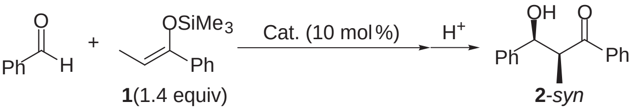
Aldol reaction is one of the most important and frequently employed tools for carbon–carbon bond formation.[1] In the course of our investigation on the Lewis base-catalyzed aldol reactions between aldehydes and trimethylsilyl (TMS) enolates, nitrogen- or oxygen-containing anions generated from amines, amides, imides, or carboxylic acids were found to behave as effective Lewis base catalysts.[2] It was also found that these Lewis base are also useful catalysts in Michael,[3] Mannich-type,[4] Strecker-type reactions,[5] and trifluoromethylation of aldehydes or aldimines.[6] Then, in order to extend further synthetic utilities of these Lewis base-catalyzed reactions, diastereoselective aldol reactions were examined. In this communication, we would like to report on tetrabutyl ammonium phenoxides-mediated syn-selective aldol reactions of aldehydes with TMS enolates generated from ketones or thioesters.

Lewis base catalysts were shown to be effective in promoting the reaction of ketene silyl acetals.[2] However, higher temperature was needed to complete the reaction since they were not reactive toward silyl enolate such as **1** at low temperature (Table 1, Entries 1–5).

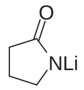
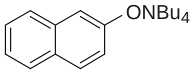
Then, Lewis base catalyst was screened in order to increase the reactivity and it was found that a lithium phenoxide (PhOLi) catalyst was successfully employed to promote the aldol reaction; that is, the reaction proceeded smoothly to afford the corresponding aldol in quantitative yield with moderate syn-selectivity[7] (syn:anti = 3:1) when the reaction was carried out by using 10 mol % of PhOLi in DMF at −45 °C (Entry 6). Further, higher yield and better syn-selectivities were attained when the reaction was carried out by using tetrabutylammonium phenoxide ($PhONBu_4$ **3**) in THF at −78 °C (Entry 8). Then, screening of the phenoxide anions revealed that the efficiency of this reaction was influenced by the catalysts employed, and **4** and **5** were also found to be effective catalysts for the above aldol reaction.

Next, the scope of acceptor aldehydes in the ammonium phenoxides-catalyzed aldol reaction was examined by using TMS enolate **1** in the presence of 10 mol % of **3**, **4**, or **5** in THF (Table 2). Various aldehydes smoothly reacted with TMS enolate **1** to afford the corresponding aldols in good to high yields with syn-selectivities. When aromatic aldehydes having electron-donating or -withdrawing group were used, the reactions proceeded smoothly to give the corresponding aldols in high yields with good syn-selectivities while the selectivity was moderate when 4-nitrobenzaldehyde was used. This reaction is also applicable to an aldehyde having a basic function (Entries 5 and 6). In the case when aliphatic aldehyde such as 3-phenylpropionaldehyde was used, the reaction proceeded to afford the corresponding aldols with moderate syn-selectivity. The yields were dependent on the nature of the catalysts employed, and **3** was found to be a favorable catalyst. Improved results were obtained when a more hindered aldehyde such as cyclohexanecarbaldehyde was used in the presence of **3**.

Table 1. Screening of the catalyst on aldol reaction of PhCHO with TMS enolate **1**



1(1.4 equiv) **2**-*syn*

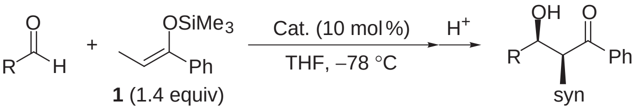
Entry	Catalyst	Solv.	Temp. /°C	Time /h	Yield[a] /%	syn : anti[b]
1	AcOLi	DMF	0 to rt	6	87	63:37
2	AcOLi	DMF	–45	6	n.d.[c]	—
3	$AcONBu_4$	DMF	–45	6	n.d.[c]	—
4		DMF	–45	3	25	50:50
5	BnOLi	DMF	–45	6	n.d.[c]	—
6	PhOLi	DMF	–45	5	98	75:25
7	$PhONBu_4$ (**3**)	THF	–45	1	95	78:22
8	$PhONBu_4$	THF	–78	3	92	91:9
9	$2\text{-}MeOC_6H_4ONBu_4$	THF	–78	1	79	94:6
10	$3\text{-}MeOC_6H_4ONBu_4$	THF	–78	1	23	94:6
11	$4\text{-}MeOC_6H_4ONBu_4$ (**4**)	THF	–78	1	quant.	95:5
12	$4\text{-}ClC_6H_4ONBu_4$	THF	–78	3	15	96:4
13	 (**5**)	THF	–78	1	91	94:6

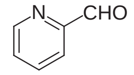
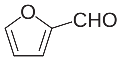
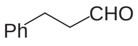
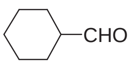
[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]The ratio was determened by ^1H NMR. [c]n.d.; not detected.

Silyl enolates generated from thioesters were further applied to this reaction (Table 3). When TMS enolate **6** having *S*-*t*-butyl substituent was used, the aldol adducts were obtained in good yields with moderate selectivities. On the other hand, good yields and high selectivities were attained by using TMS enolates such as **7**, **8**, or **9**. Especially, it was observed that the TMS enolate **8** and **9** gave the aldols in good yield with high syn-selectivity irrespective of the geometry of the enolates (Entries 4 and 5). These results indicated that the reaction proceeded via the acyclic transition states.[2c]

Thus, phenoxide anions are proved to be good Lewis base catalysts to promote aldol reactions and syn-selective aldol

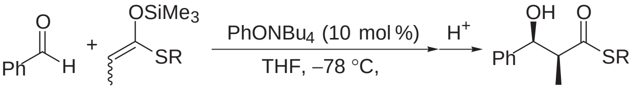
Table 2. Tetrabutylammonium phenoxides-catalyzed syn-selective aldol reaction of various aldehydes with **1**

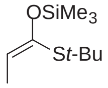
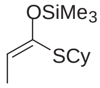
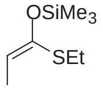
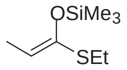


Entry	Aldehyde	Cat.	Time /h	Yield[a] /%	syn : anti[b]
1	4-MeC_6H_4CHO	**3**	2	quant.[c]	95:5
2	4-MeC_6H_4CHO	**4**	2	quant.	91:9
3	4-$NO_2C_6H_4CHO$	**3**	3	87[c]	74:26
4	4-$NO_2C_6H_4CHO$	**4**	2	93	76:24
5		**3**	5	84[c]	94:6
6		**4**	2	quant.	94:6
7		**3**	4	82[c]	96:4
8		**4**	2	quant.[c]	97:3
9		**3**	4	56	77:23
10		**4**	3	44	74:26
11		**5**	5	52	81:19
12		**3**	2	69	91:9
13		**4**	3	51	93:7
14		**5**	5	34	73:27

[a]Isolated yield. [b]The ratio was determined by ^1H NMR. [c]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Table 3. $PhONBu_4$-catalyzed aldol reaction of PhCHO with TMS enolate genarated from thioesters



Entry	Silyl enolates	Equiv	Time /h	Yield[a] /%	syn : anti[b]
1	 (**6**)	1.4	3	82	62:38
2	 (**7**)	2	2	70	92:8
3		3	2	84	93:7
4	 (**8**)	2	1.5	78	93:7
5	 (**9**)	2	1	88	94:6

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]The ratio was determined by ^1H NMR.

reaction between TMS enolates and aldehydes was established by using a catalytic amount of $PhONBu_4$ or 4-$MeOC_6H_4ONBu_4$ in THF. Further study on this reaction is now in progress.

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