A Catalytic Aldol Reaction between Ketene Silyl Acetals and Aldehydes Promoted by Lithium Amide under Non-acidic Conditions

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A catalytic aldol reaction between trimethylsilyl enol ethers and aldehydes by using lithium diphenylamide, a Lewis base catalyst, in DMF or pyridine solvent proceeded smoothly to afford the corresponding aldols under mild conditions.

Aldol reaction is one of the most important and frequently employed tools for carbon–carbon bond formation in synthetic organic chemistry. Ever since a crossed aldol reaction between aldehydes and silyl enol ethers promoted by Lewis acids was reported from our laboratory,[1] the aldol reaction of this type has become very popular. Then, the above combination of carbonyl compounds and silyl enol ethers was effectively employed: for example, the reactions *via* the metal enolates formed by transmetallation of silyl enol ethers with metal salts from original use of MeLi to recent catalytic use of transition metals[2] and also *via* the enolate anion generated by nucleophilic cleavage of the O–Si bond using a fluoride ion[3] or phosphines.[4] Further, respective reactions of silyl enol ethers such as trichlorosilyl enol ethers,[5] dimethyl(trifloxy)silyl enol ethers,[6] enoxysilacyclobutane[7] and dimethylsilyl enolates[8] derived from ketones with carbonyl compounds and of a combination of trichlorosilyl enol ethers and Lewis bases[5] with aldehydes were reported. Moreover, the reactions of silyl ketene acetals with aldehydes were carried out in water,[9] DMSO, DMF, and DME[10] or under high-pressure.[11]

Thus, it was considered important to explore a new and catalytic aldol reaction of the above combination which is to be carried out smoothly under non-acidic conditions. In this regard, Denmark *et al.* established a Lewis bases catalyzed aldol reaction using trichlorosilyl enol ethers and phosphoramides.[5] However, trichlorosilyl enol ethers were not prepared so conveniently, and thus to exprone a possibility of using simple enol ethers such as trimethylsilyl ether and a catalytic amount of Lewis bases was planned. In this communication, we would like to describe a new catalytic aldol reaction between trimethylsilyl enol ethers and aldehydes by using Lewis bases such as lithium amides.

Lithium amides which are derived from hindered amines such as lithium diisopropylamide (LDA) were known to behave as strong bases with low nucleophilicity, and were frequently employed in organic synthesis, *e.g.*, in the formation of enolates from carbonyl compounds or of lithiated carbon skeleton. To the best of our knowledge, such amides were used only as brønsted bases and never have they used as Lewis bases to activate silyl enol ethers by forming its hypervalent silicate.

Then effects of various lithium amides were examined by taking the reaction of benzaldehyde and trimethylsilyl enol ether derived from methyl isopropionate in THF as a model. Of the amides screened, lithium diphenylamide turned out to be the most effective promoter for the acceleration of the reaction as shown in Table 1.

Table 1.

Entry	Amine	Yield[a] /%	SMR[b] /%	H : TMS
1	-	36	n.d.	2 : 1
2	Et_2NH	35	6	3 : 1
3	$^iPro_2NH$	24	3	2 : 1
4	Piperidine	67	18	4 : 1
5	2,2,6,6,-Tetramethylpiperidine	35	8	2 : 1
6	1,1,1,3,3,3-Hexamethyldisilazane	trace	17	-
7	Ph_2NH	81	n.d.	2 : 1
8	$(p\text{-MeOC}_6H_4)_2NH$	62	5	3 : 2

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Starting material recovered.

When the reaction was carried out in THF, stoichiometric amount of lithium diphenylamide was required to complete the reaction. In order to establish a catalytic aldol reaction, it was needed that the aldol adducts were to be afforded selectively as *O*-silyl ether (R = TMS). But the adducts thus formed in THF were a mixture of aldol (R = H) and *O*-silyl ether. In addition, the amount of *O*-silyl ether was less than that of aldol, irrespective of the kind of lithium amides employed (Table 1). Then, in order to obtain better yields and higher ratios of *O*-silyl ether, the effect of solvents was examined by using lithium diphenylamide under the same conditions as shown in Table 1. Then, it was found that the aldol adduct was obtained in almost quantitative yields when DMF (H : TMS = 1 : 35) and pyridine (H : TMS = 1 : 6) were used. In these reactions, the major product was *O*-silyl ether which indicated the possibility to perform a catalytic cycle.

Recently, Génisson *et al.* reported that the aldol reaction of this combination proceeded "spontaneously" in DMSO, DME and DMF at room temperature.[10] Then, in order to examine the effect of

Table 2.

Entry	Solvent	Time /h	Temp. /°C	Yield[a] /%
1	DMF	1	0	84
2	DMF	1	-19	43
3	DMF	1	-45	trace
4	DMF	1	-78	trace
5	Pyridine	4	0	n.d.

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

lithium diphenylamide, the above reaction was tried under the conditions in which the above solvents would not behave as effective promoters. As a result, it was found that the reaction was not promoted in DMF when the temperature was below −45 °C and also in pyridine at 0 °C.

The same reaction was carried out by adding 5 mol% of lithium diphenylamide at −45 °C in DMF and the desired aldol was then obtained in 80% yield along with the recovery of 18% of the starting material. Likewise, the aldol adduct was obtained in quantitative yield when the reaction was carried out at 0 °C by using 20 mol% of lithium diphenylamide in pyridine. These results clearly indicated that lithium diphenylamide did behave as an effective catalyst to promote the present aldol reaction in DMF or in pyridine.

Table 3.

| Entry	Aldehyde	Solv	Time /h	Temp /°C	Yield[a] /%
1		DMF	1	-45	96
2		Pyridine	7	0	98
3	MeO-C6H4-CHO	DMF	1	-45	98
4		Pyridine	1	0	97
5[b]	NpCHO	DMF	1	-45	97
6[b]		Pyridine	6	0	95
7	O2N-C6H4-CHO	DMF	3	-45	60
8	Ph-CH=CH-CHO	DMF	1	-45	99(12 : 1)[c,d]
9		Pyridine	6	0	96(100 : 0)[c,d]
10	Ph-CH2CH2-CHO	DMF	2	-45	60
11	2-pyridyl-CHO	DMF	1.5	-45	67

[a]Isolated yield. [b]NpCHO : 1-Naphthaldehyde. [c]1,2 : 1,4. [d]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Taking these results into consideration, aldol reactions using other aldehydes were tried and their consequence are summarized in Table 3. Here, Trimethylsilyl enol ether derived from methyl isopropionate smoothly reacted with various aromatic aldehyde to give the corresponding aldols in high yields. Aromatic aldehyde with electron withdrawing group such as p-nitrobenzaldehyde and aliphatic aldehyde also afforded aldol adducts in moderate yields. When conjugated aldehyde was used, 1,2- and 1,4-addition reactions took place simultaneously in DMF while aldol adduct was selectively obtained in high yield without accompanying 1,4-adduct when the reaction was carried out in pyridine.
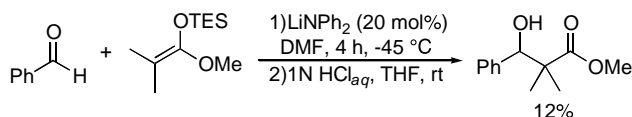
It is assumed that the reaction proceeded *via* the activation of trimethylsilyl enol ether by forming a hypervalent silicate between lithium diphenylamide and silicon atom of the enolate. This hypothesis was supported by the actual prevention of the above reaction *via* the activated intermediate to be formed from hindered enol ether derived from methyl isopropionate, such as triethylsilyl one.
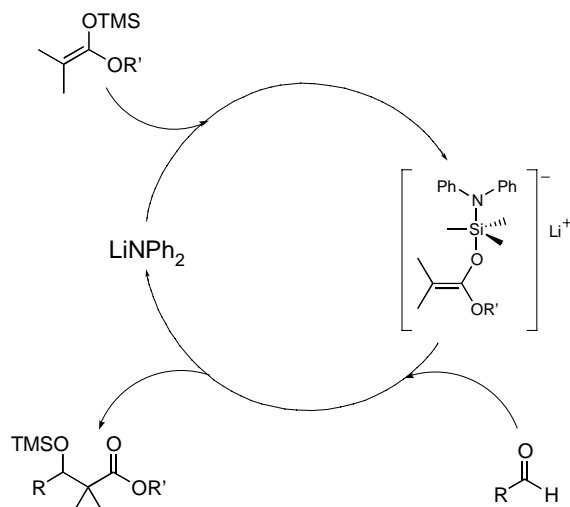
Scheme 1.

Thus, a new catalytic aldol reaction between trimethylsilyl enol ethers and aldehydes was established under non-acidic conditions by using lithium diphenylamide in DMF or pyridine solvent. Further extension of this reaction is now in progress.

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