Aldol Reaction of Trimethylsilyl Enolate with Aldehyde Catalyzed by Pyridine *N*-Oxide as a Lewis Base Catalyst

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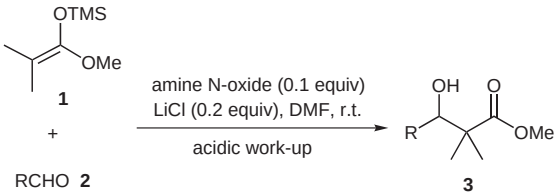
Abstract: Aldol reaction of trimethylsilyl enolate with aldehydes proceeded in the presence of a catalytic amount of a Lewis base, pyridine *N*-oxide, and lithium chloride in DMF at room temperature. Not only aryl aldehydes but also alkyl aldehydes provided the aldol products in satisfactory yields. The reaction was mild enough to apply to aldehydes having HO, AcO, THPO, TBDMSO, MeS, pyridyl, or olefinic groups.

Key words: aldol reactions, organomolecular catalysis, pyridine *N*-oxide, trimethylsilyl ketene acetal, Lewis base

The aldol reaction is a fundamental and important carbon–carbon bond-forming reaction.[1] However, due to its reversibility, either under basic or acidic reaction conditions, a classical aldol reaction could not equilibrate substrates into aldol products in satisfactory yields. The difficulty in generating an enol or an enolate quantitatively was the major reason for employing such reversible reaction conditions. This issue was solved by Mukaiyama, who developed the aldol reaction of trimethylsilyl enolate in the presence of a stoichiometric amount of $TiCl_4$.[2] In this reaction, the aldol acceptor is activated by coordination of the Lewis acid. The versatility of the reaction triggered numerous applications and variants.[1,2] Subsequently, Denmark et al. employed a different concept, which targeted activation of the silicone atom forming a hypervalent silicate intermediate. They demonstrated the utility of a more electropositive trichlorosilyl enol ether in the presence of phosphorane[3] or a more strained silacyclobutylketene acetal in the absence of Lewis acid.[4] Although the reaction conditions are efficient, use of the unstable or unusual silyl enol ether created some problems for practical application. Subsequently, this concept was further developed, and trimethylsilyl or dimethylsilyl enolates were employed in the presence of a catalytic amount of a Lewis base such as dimethylsulfoxide,[5] phosphine oxide,[6] or chloride ion[7] to activate silylenolate. Mukaiyama et al. also reported the reaction along this line employing lithium amide[8] or acetate as a catalyst.[9]

In order to develop more efficient and milder aldol reaction conditions, we focused on the catalytic activity of an amine *N*-oxide as an alternative candidate as an organomolecular Lewis basic catalyst in the reaction of easily available and stable trimethylsilyl enolate (Scheme 1). A simple amine *N*-oxide was chosen due to its economy, low toxicity, and availability as a chiral amine.[10]



Scheme 1 Aldol reaction of trimethylsilyl ketene acetal catalyzed by amine *N*-oxide

The optimum reaction conditions were examined employing the reaction of trimethylsilyl dimethylketene acetal **1** and benzaldehyde (**2**) (Table 1). The reaction was carried out at room temperature in the presence of 0.1 equivalents of amine *N*-oxide. The resulting silylether of **3** was hydrolyzed during work-up to give **3**. Among amine *N*-oxides investigated, pyridine *N*-oxide gave the best result (Table 1, entry 5).[11] The more nucleophilic DMAP *N*-oxide[12] gave capricious yields during repeated runs (Table 1, entry 7). Trimethylamine *N*-oxide suffered from poor yields probably due to its steric bulkiness (Table 1, entry 8).[13] The polarity of solvents did not influence the reaction (Table 1, entries 2 and 3). Among the solvents, DMF gave the best yield (Table 1, entry 5) due to its highly coordinating nature as exemplified by Mukaiyama et al.[8]

With the optimized amine *N*-oxide and solvent in hand, further effort was devoted to improving the reaction and the results are shown in Table 2. In order to enhance the rate of reaction (Table 2, entries 1 and 2), the effect of an auxiliary reagent was investigated. Fortunately, addition of a catalytic amount of lithium chloride was effective (Table 2, entry 3). Since lithium chloride alone provided poor yields (Table 2, entries 1, 4, and 5), lithium chloride and pyridine *N*-oxide might operate synergistically to drive the catalytic cycle. On the other hand, addition of Hünig's base, which was anticipated to remove *N*-oxide from the hypervalent alkoxysilicate intermediate in the allylation of allyltrichlorosilane,[14] was not satisfactory (Table 2, entry 7).

The present reaction conditions (Table 2, entry 3) can be applied to various aldehydes as shown in Table 3. Not

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Table 1 Investigation of the Optimized Reaction Conditions for the Lewis Base Catalyzed Aldol Reaction[a]

Entry	Amine *N*-oxide	Solvent	Time (h)	Yield[b] (%)
1	Pyridine *N*-oxide	CH_2Cl_2	24	0
2	Pyridine *N*-oxide	$MeNO_2$	5	13
3	Pyridine *N*-oxide	[bmim]PF_6	18	32
4	Pyridine *N*-oxide	DMI[c]	5	36
5	Pyridine *N*-oxide	DMF	5.5	55
6	–	DMF	5	25
7	DMAP *N*-oxide	DMF	5	60
8	Me_3N *N*-oxide	DMF	9	18

[a] The reaction of trimethylsilyl dimethylketene acetal (**1**, 1.3 equiv) with benzaldehyde (**2**) was carried out in the presence of amine *N*-oxide (0.1 equiv) at r.t.
[b] Yield of the isolated pure product.
[c] 1,3-Dimethyl-2-imidazolidinone.

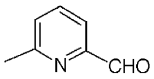
only arylaldehydes (Table 3, entries 1–10) but also alkylaldehydes (Table 3, entries 11–17) provided the aldol products; to date alkylaldehyde had not been a good aldol partner compared to arylaldehyde under either Lewis acid or base reaction conditions.[2,5,6,8] It is interesting to note that the reaction proceeded in the absence of lithium chloride without protection of the acidic phenol (Table 3, entry 5). Addition of excess trimethylsilyl dimethylketene acetal (**1**) accelerated the reaction (Table 3, entries 12, 14, and 16). The mild nature of the present reaction conditions is apparent from the successful reactions of aldehydes **2** having acid or base-sensitive protecting groups (Table 3, entries 6–8). Moreover, pyridinecarboxaldehyde provided the aldol product (Table 3, entry 10), which hitherto was not a suitable substrate under Lewis acid reaction conditions due to its highly coordinating character. The sulfide or double bond remained intact even in the presence of pyridine *N*-oxide (Table 3, entries 9, 13, and 17).

Table 2 Effect of an Additive[a]

Entry	Amine *N*-oxide and additive	Time (h)	Yield[b] (%)
1	No additive	5.5	55
2	No additive	23	81
3	LiCl (0.2 equiv)	5	83
4	LiCl (0.2 equiv)[c]	5	32
5	LiCl (1.2 equiv)[c]	5	41
6	$CaCl_2$ (0.2 equiv)	9	42
7	(*i*-Pr)$_2$NEt (0.1equiv)	9	59

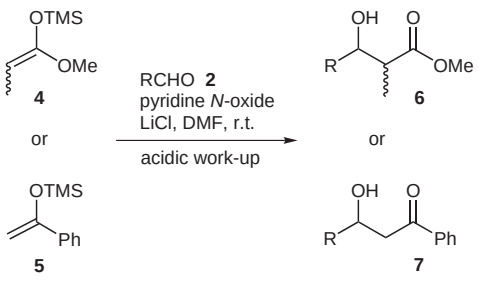
[a] The reaction of trimethylsilyl dimethylketene acetal (**1**, 1.3 equiv) with benzaldehyde (**2**) was carried out in the presence of pyridine *N*-oxide (0.1 equiv) and the additive in DMF at r.t.
[b] Yield of the isolated pure product.
[c] Pyridine *N*-oxide was not added.

Table 3 Reaction with a Variety of Aldehydes[a]

Entry	Aldehyde **2**	Acetal **1** (equiv)	Time (h)	Yield[b] (%)
1	*p*-Nitrobenzaldehyde	1.5	23	87
2	*o*-Chlorobenzaldehyde	1.5	12	65
3	*p*-Chlorobenzaldehyde	1.5	10	77
4	*p*-Anisaldehyde	1.5	10	44
5[c]	*p*-Hydroxybenzaldehyde	3	21	96
6	*p*-Acetoxybenzaldehyde	3	15	80
7	*p*-Tetrahydropyranyloxy-benzaldehyde	3	15	79
8	*p*-(*tert*-Butyldimethyl-siloxy)benzaldehyde	1.5	10	62
9	*p*-Methylthiobenzaldehyde	1.5	21	87
10		3	15	87
11	Hydrocinnamaldehyde	1.5	10	44
12	Hydrocinnamaldehyde	4.5	5	80
13	Citronellal	1.5	13	44
14	Citronellal	4	5	81
15	1-Decanal	1.5	20	43
16	1-Decanal	5	7	78
17	Perillaldehyde	3	10	91

[a] The reaction of trimethylsilyl dimethylketene acetal **1** with aldehyde **2** was carried out in the presence of pyridine *N*-oxide (0.1 equiv) and LiCl (0.2 equiv) in DMF at r.t.
[b] Yield of the isolated pure product.
[c] Lithium chloride was not added.

The generality of the present protocol was further demonstrated by the reaction of trimethylsilyl enolate of methyl propanoate (**4**) or acetophenone (**5**) (Scheme 2, Table 4).



Scheme 2 Aldol reaction of trimethylsilyl enolate catalyzed by pyridine *N*-oxide.

Table 4 Reaction with Trimethylsilyl Enolates **4** and **5**[a]

Entry	Aldehyde **2**	Silyl enolate **4** or **5** (equiv)	Time (h)	Yield[b] (%)
1	Benzaldehyde	**4** (5)[c]	6	85 (56:44)[c]
2	*p*-Nitrobenz-aldehyde	**4** (5)	5	95 (54:46)[d]
3	*p*-Anisaldehyde	**4** (5)	12	99 (51:49)[d]
4	Citronellal	**4** (5)	15	45[e]
5	Benzaldehyde	**5** (5)	24	96
6	*p*-Nitrobenz-aldehyde	**5** (4.5)	21	56
7	*p*-Tetrahydropyran-yloxybenzaldehyde	**5** (5)	24	57
8	Citronellal	**5** (5)	23	60

[a] The reaction of trimethylsilyl enolate **4** or **5** with aldehyde **2** was carried out in the presence of pyridine *N*-oxide (0.1 equiv) and LiCl (0.2 equiv) in DMF at r.t.
[b] Yield of the isolated pure product.
[c] Ratio *E*/*Z*, 79:21.[18]
[d] Ratio *syn*/*anti*.
[e] An inseparable mixture of diastereomers.

The present reaction could proceed via the same catalytic cycle proposed by Denmark[3] or Mukaiyama.[8] After coordination of pyridine *N*-oxide and DMF to the silicone atom[15] of the silyl ketene acetal to form a hexa-coordinated hypervalent silicate intermediate, addition to the aldehyde proceeded to provide a hypervalent alkoxysilicate intermediate, from which pyridine *N*-oxide was pushed out by lithium chloride and re-used in the catalytic cycle.

In summary, we have developed a new protocol for a Lewis base catalyzed aldol reaction of trimethylsilyl enolate employing a catalytic amount of pyridine *N*-oxide and lithium chloride in DMF at room temperature.[16,17] The present reaction proceeds via stable trimethylsilyl enolate, which is the major advantage compared to the previous works employing trichlorosilyl- or silacyclobutylenolate. The reaction conditions are so mild that the base- or acid-sensitive protecting groups on aldehydes **2** survived. Pyridine *N*-oxide did not oxidize the sulfide or double bond. The present reaction is mild, practical, environmentally benign, and less toxic than existing methods, which would be useful not only for large-scale preparation but also manipulation of multifunctional substrates for natural product syntheses.

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(16) Typical experimental procedure: To a stirred solution of pyridine *N*-oxide (3.8 mg, 0.04 mmol) and LiCl (3.4 mmol, 0.08 mmol) in DMF (1.5 mL) were added benzaldehyde **2** (R = Ph) (42 μL, 0.4 mmol) and trimethylsilyl ketene acetal **1** (105 μL, 0.52 mmol) at r.t. under a nitrogen atmosphere. After stirring for 5 h, the reaction was quenched by the addition of 1 N aq HCl. The product was extracted with EtOAc twice. The combined organic layer was washed with water, brine, and evaporated to dryness. The residue was purified by medium-pressure LC (EtOAc–hexane, 1:2) to afford aldol product **3** (R = Ph) (92 mg, 81%) as a solid.
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