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Practical aldol reaction of trimethylsilyl enolate with aldehyde catalyzed by *N*-methylimidazole as a Lewis base catalyst

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Abstract—Aldol reaction of trimethylsilyl enolate with aldehyde proceeded in the presence of a catalytic amount of a Lewis base, *N*-methylimidazole, and lithium chloride in DMF at room temperature. Not only aryl aldehyde but also alkyl aldehyde provided the aldol product in satisfactory yields. The reaction was mild enough to apply to the aldehyde having HO, AcO, THPO, TBDMSO, MeS, pyridyl or olefinic group. Microwave irradiation accelerated the reaction.

The aldol reaction is one of the most fundamental and important carbon–carbon bond-forming reactions.[1] The most prominent development in the reaction is the use of a stable metal enolate such as trimethylsilyl enolate by activation of the carbonyl group with Lewis acid, which was invented by Mukaiyama and has been highly successful.[2] However, there are several limitations in choosing substrates due to the presence of a strong Lewis acid such as titanium tetrachloride. Denmark et al. focused on an alternative concept, an activation of the silicone atom to form a hypervalent silicate intermediate. They investigated the reaction of a more electropositive trichlorosilylenol ether in the presence of phosphorane[3] or a more strained silacyclobutylketene acetal in the absence of Lewis acid,[4] though the use of the moisture-sensitive or unusual silylenol ether was not suitable for practical application. This concept was further revised to employ easily available and more stable trimethylsilyl or dimethylsilyl enolate in the presence of a Lewis base such as dimethylsulfoxide,[5] phosphine oxide[6] or chloride ion[7] to activate the silylenolate as a hypervalent silicate intermediate. Subsequently, Mukaiyama et al. reported the reaction along the concept employing lithium amide[8] or lithium acetate as a catalyst.[9]

With an intention to develop more efficient and milder aldol reaction conditions, we focused on catalytic activity of an amine N-oxide as an alternative candidate of an organomolecular Lewis basic catalyst in the reaction of trimethylsilyl enolate, due to its economy, less toxicity and availability of a chiral amine,[10] and reported previously that pyridine-N-oxide catalyzed the reaction efficiently.[11] Although the reaction conditions were so mild that various functional groups could tolerate under the reaction conditions, it was much desired that the reaction completed in a shorter time with improved yield.

In order to respond to the issue above, we turned to nitrogen aromatic heterocycles as an alternative catalyst. Among common and easily available heterocycles, *N*-methylimidazole and *N*,*N*-dimethylaminopyridine (DMAP) were focused on, which were expected to form a hypervalent silicate intermediate.[12]

The reaction was carried out in a similar manner as our previous report,[11] employing trimethylsilyl dimethylketene acetal **1** with benzaldehydes **2** in the presence of nitrogen heterocycles (0.1 equiv) and LiCl (0.2 equiv) in DMF at room temperature.[13] The resulting silylether of **3** was hydrolyzed during weakly acidic work-up to give **3** (Scheme 1).

Among catalysts investigated, *N*-methylimidazole (Table 1, entry 4) was superior compared to LiCl,[7]

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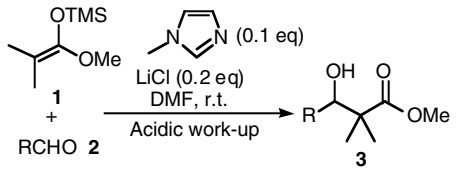


Scheme 1. Aldol reaction of trimethylsilyl ketene acetal catalyzed by *N*-methylimidazole.

Table 1. Investigation of the optimized amine catalyst for the Lewis base-catalyzed aldol reaction[a]

Entry	Amine	Yield[b] (%)
1	—[c]	44
2	Pyridine-N-oxide	76
3	*N*,*N*-Dimethylaminopyridine	74
4	*N*-Methylimidazole	90
5[d]		68
6[e]		71

[a] The reaction of trimethylsilyl dimethylketene acetal **1** (1.5 equiv) with benzaldehyde **2** was carried out in the presence of amine (0.1 equiv) and LiCl (0.2 equiv) in DMF at room temperature for 3 h.
[b] Yield of the isolated pure product based on aldehyde **2**.
[c] The reaction was carried out only with LiCl (0.2 equiv).
[d] The reaction was carried out only with *N*-methylimidazole (0.1 equiv).
[e] The reaction was carried out only with *N*-methylimidazole (0.3 equiv).

pyridine-N-oxide or *N*,*N*-dimethylaminopyridine. In order to realize high yield, addition of LiCl was effective (Table 1, entries 1, 4 and 5) as previously reported in the reaction catalyzed by pyridine-N-oxide.[11] Synergistic role of both *N*-methylimidazole and LiCl are suggested to accelerate the catalytic cycle, since even 0.3 equiv of *N*-methylimidazole gave moderate yield in the absence of LiCl (Table 1, entries 5 and 6). Major by product in Table 1 was benzaldehyde.

With the appropriate catalytic system in hand, the reactions with various aldehyde **2** were compiled in Table 2. Aldehydes **2** having acid- (entries 7 and 8) or base-sensitive (entry 6) protecting groups, and having highly coordinating groups such as pyridyl (entry 10) or sulfide (entry 9) groups provided successfully the desired aldol product **3**. It is interesting to note that aldehyde **2** having an acidic proton provided aldol product **3** in satisfactory yield even in the presence of a basic amine catalyst (entry 5). In most entries, reactions completed in higher yields within a shorter period of time than the reactions catalyzed by pyridine-N-oxide, which exemplify the better catalytic efficiency of *N*-methylimidazole than that of pyridine-N-oxide. Especially, in entries 1, 3, 4, 5 and 8, yields increased more than 10%.

Generality of the present protocol was further demonstrated by the reaction of trimethylsilyl enolate **4** (Scheme 2 and Table 2, entries 15–17).

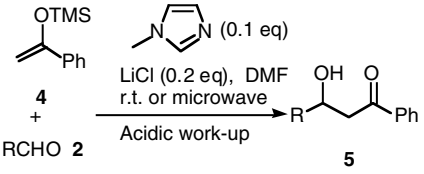
In order to accelerate the reaction, internal heating by irradiation of multi-mode microwave (100 W) was applied (Table 3). The reaction temperature was ramped to room temperature to 90 °C and maintained at that temperature for 30 min. The irradiation was repeated once again for 30 min. The reactions terminated apparently in shorter time. The yields are comparable to these of reactions at room temperature, with considerable improvement in the reaction with citronellal (Table 2, entry 17 and Table 3, entry 6). It is worthy to note that dehydration to give chalcones did not proceed even under elevated temperature (entries 4 and 5).

In summary, we have developed an alternative catalyst, *N*-methylimidazole, for the aldol reaction of easily available trimethylsilyl enolate in the presence of lithium chloride in DMF at room temperature. The reaction conditions are so mild that the base- or acid-sensitive protecting groups in aldehydes **2** remained intact. Moreover, the reaction was accelerated by microwave irradiation. The present reaction is practical, environmentally benign, and less toxic compared to existing methods,

Table 2. Reaction of silyl enolate **1** or **4** with a variety of aldehydes **2**[a]

Entry	Aldehyde **2**	Enolate (equiv)	Time (h)	Yield[b] (%)
1	Benzaldehyde	**1** (1.5)	10	91
2	*p*-Nitrobenzaldehyde		10	87
3	*p*-Chlorobenzaldehyde		10	94
4	*p*-Anisaldehyde		10	79
5	*p*-Hydroxybenzaldehyde	**1** (2)	8	71
6	*p*-Acetoxybenzaldehyde		8	83
7	*p*-Tetrahydropyranyloxybenzaldehyde		10	80
8	*p*-(*t*-Butyldimethylsiloxy)benzaldehyde		10	72
9	*p*-Methylthiobenzaldehyde		7	87
10	5-Methylpyridine-2-carboxaldehyde		10	92
11	Hydrocinnamaldehyde	**1** (3)	4.5	87
12	Citronellal		5	86
13	1-Decanal		5	90
14	Perillaldehyde		10	90
15	Benzaldehyde	**4** (5)	15	83
16	*p*-Chlorobenzaldehyde		20	83
17	Citronellal		23	44

[a] The reaction of trimethylsilyl dimethylketene acetal **1** with aldehyde **2** was carried out in the presence of *N*-methylimidazole (0.1 equiv) and LiCl (0.2 equiv) in DMF at room temperature.
[b] Yield of the isolated pure product based on aldehyde **2**.



Scheme 2. Aldol reaction of trimethylsilyl enolates catalyzed by *N*-methylimidazole.

Table 3. Reaction of silyl enolate **1** or **4** with a variety of aldehydes **2**[a] under microwave heating

Entry	Enolate (equiv)	Aldehyde **2**	Yield[b] (%)
1	**1** (1.5)	Benzaldehyde	82
2		*p*-Anisaldehyde	85
3		Hydrocinnamaldehyde	74
4	**4** (5)	Benzaldehyde	88
5		*p*-Chlorobenzaldehyde	78
6		Citronellal	77

[a] The reaction was carried out in the presence of *N*-methylimidazole (0.1 equiv) and LiCl (0.2 equiv) in DMF under microwave irradiation. The temperature ramped from room temperature to 90 °C and kept at the temperature for 30 min. The irradiation was repeated once again for 30 min. The temperature was monitored by radiation thermometer.

[b] Yield of the isolated pure product based on aldehyde **2**.

which would be useful not only for large-scale preparation but also for transformation of multifunctional substrates for natural products syntheses.

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13. Typical experimental procedure: To a stirred solution of *N*-methylimidazole (5 μL, 0.045 mmol) and anhydrous LiCl (4 mg, 0.08 mmol) in DMF (1.5 mL) were added benzaldehyde **2** (R = Ph) (42 μL, 0.4 mmol) and trimethylsilyl ketene acetal **1** (125 μL, 0.6 mmol) at room temperature under nitrogen atmosphere. After being stirred for 10 h, the reaction was quenched by the addition of a little amount of 1 N aq HCl. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and evaporated to dryness. The residue was purified by medium-pressure LC (eluent: ethyl acetate–*n*-hexane = 1:2) to afford aldol product **3** (R = Ph) (78 mg, 91%) as a solid.