

Self-aldol condensation of unmodified aldehyde in supercritical carbon dioxide catalyzed by amine grafted on silica

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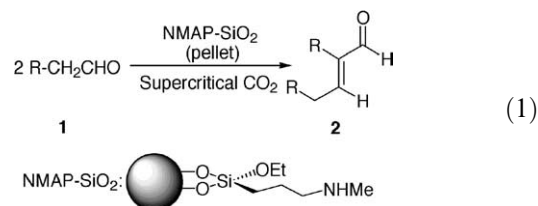
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Abstract—Self-aldol condensation of an unmodified aldehyde has been effected by 3-*N*-methylaminopropylated silica as a catalyst in supercritical carbon dioxide, to give an α,β -unsaturated aldehyde (enal). Aldehydes having acid or base-sensitive substituents provided desired enals.

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In producing organic molecules, there is increasing demand for an environmentally friendly and sustainable process.¹ In order to achieve this process, catalytic reactions of higher atom economy² are desirable along with simple operation, simple work-up, and simple purification. Among catalytic reactions, homogeneous transition metal catalysts have played important roles. However, drawbacks of the catalysts are easy deterioration forming metal clusters, dependence of supply of metals on natural resources and pollution by leaching out of the metals. On the other hand, organomolecular catalysts have a complementary character to metal catalysts and are currently attracting considerable interest³ as environmentally more benign catalysts, because they do not involve metals. The catalysts are easily reproducible and their reactivity is tunable by structure modification. One shortcoming of the catalyst is the lack of stability for repeated use, which would be solved by immobilization on solid supports. Furthermore, a combination of the immobilized organomolecular catalysts and environmentally benign organic reaction media is expected to provide an attractive protocol for catalytic organic syntheses.

As a part of our ongoing efforts in this area, we have recently developed a mild and sustainable nucleophilic reaction of unmodified aldehyde in an ionic liquid catalyzed by amine grafted on silica, in which the heterogeneous catalyst and the solvent could be recycled.⁴



An alternative 'green solvent' is supercritical carbon dioxide (scCO₂). Not only as a surrogate of conventional organic solvents but also as an environmentally benign solvent, importance of scCO₂ is increasing due to its less expensive, less toxic, inflammable and easily removable nature.⁵ Another advantage is that CO₂ reaches easily to its critical point under relatively mild conditions ($T_c = 31.1\text{ }^\circ\text{C}$, $P_c = 7.4\text{ MPa}$). Thus, use of scCO₂ has been attracting much attention in contemporary synthetic organic chemistry.⁶

The self-aldol condensation of an unmodified aldehyde **1** is still not a trivial process due to higher reactivity of the formyl group to give many by-products, in spite of several successful methods reported so far.⁷ Since the product enal **2** is a versatile intermediate for organic syntheses, a more efficient catalyst and an environmentally benign process have been desired. Recently,

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Kawanami and co-workers reported a self-aldol condensation of propanal **1** ($R = CH_3$) catalyzed by MgO under supercritical conditions, in which the selectivity of aldol and enal **2** ($R = CH_3$) was tunable simply by adjusting the pressure of CO_2 .⁸ This result prompted us to report our independent findings on a self-aldol condensation of an unmodified aldehyde **1** catalyzed by aminopropylated silica in $scCO_2$, leading to an α,β -unsaturated aldehyde (enal) **2** (Eq. 1). The aminopropylated silica is expected to be a mild organomolecular catalyst, which could be applicable to a variety of aldehyde **1**.

One major issue incurred in employing amine catalysts in $scCO_2$ was the formation of carbamic acid⁹ to decrease catalytic activity. In the amine catalyst grafted on silica gel, a large amount of silanols exists on the surface of the silica gel compared to the amine residue. Since silanols were not end-capped and Brønsted acidity of silanol is estimated to be pK_a 6,¹⁰ the amino residues might be protonated by silanols close by. This idea suggests that the formation of carbamic acid might be suppressed. A mixture of an equivalent amount of a Brønsted base and an acid is known to be effective as a catalyst for self-aldol condensation of aldehydes **1**.^{6c} To this end, an amine catalyst grafted on silica gel is expected to be a potential catalyst.

Employing self-aldol condensation of *n*-decanal **1** ($R = C_8H_{17}$) as a probe, optimum reaction conditions (Eq. 1, Table 1) were investigated with the catalysts, which were grafted primary (NAP = aminopropylated), secondary (NMAP = *N*-methylaminopropylated) or tertiary aminopropyl residues (NDEAP = *N,N*-diethylaminopropylated) on amorphous silica. In order to make handling of the catalysts easier, the aminopropyl residues were grafted on cylindrical pellets (3×2.5 mm OD) of silica by the post-modification method.⁴ Amounts of amine residues grafted were determined by combustion analyses.

Table 1. Effect of catalysts in self-aldol condensation of *n*-decanal **1** in $scCO_2$ ^a

Entry	Catalyst	Pressure (MPa)	Yield (%) ^b
1	SiO ₂	21.5	0
2	NDEAP	22.1	16
3	NAP	23.0	41
4	NMAP ^c	22.0	59
5	MS-4 Å	20.0	59
6	NMAP ^d	19.5	61
7	NMAP	23.0	86
8 ^e	NMAP	—	42
9 ^f	NMAP	—	38

^a The reaction was carried out in the presence of 0.2–0.4 equiv of catalyst and MS-4 Å pellets at 80 °C for 15 h under the pressure indicated.

^b The yields were for isolated pure products after extraction with diethylether followed by medium-pressure LC.

^c NMAP coated with [bmim]PF₆ was employed.

^d MS-4 Å was not added.

^e The reaction was carried out in refluxing *n*-hexane under nitrogen atmosphere.

^f The reaction was carried out in refluxing *n*-hexane under CO_2 atmosphere.

Table 2. Self-aldol condensation of some representative aldehydes **1**^a

Entry	R	Pressure (MPa)	Yield (%) ^b
1	C ₄ H ₉	22.9	88
2	PhCH ₂	26.5	83
3	PhCH ₂	24.8	64
4	TBSO(CH ₂) ₉	30.5	59
5	TBSO(CH ₂) ₉	27.0	50
6	THPO(CH ₂) ₉	28.5	56
7	THPO(CH ₂) ₉	22.0	44
8	AcO(CH ₂) ₉	22.6	53

^a The reaction was carried out in the presence of 0.2–0.4 equiv of NMAP and MS-4 Å pellets at 80 °C for 15 h under the pressure indicated.

^b The yields were for isolated pure products after extraction with diethylether followed by medium-pressure LC.

The aldehyde **1** was placed in an inner glass tube to avoid direct contact with the catalysts and the metal surface of a stainless steel autoclave.¹¹ Judging from the complete transfer of the aldehyde **1** from the glass tube after the reaction, the aldehyde **1** dissolved cleanly in $scCO_2$ and was transferred from the glass tube. Among the catalysts investigated, secondary amino residue grafted on silica, NMAP, gave the highest yields (Table 1, entries 2, 3 and 7). Silica gel did not catalyze the reaction (Table 1, entry 1). In the absence of molecular sieves 4 Å (MS-4 Å), the yield was moderate (entry 6), which indicates an important role of MS-4 Å to make the reaction irreversible. Super critical CO_2 was apparently superior reaction media compared to *n*-hexane, which has similar solvent polarity as $scCO_2$ (entries 8 and 9).

Based on the reaction conditions cited in Table 1, entry 7,¹¹ several examples of the self-aldol condensation of representative aldehydes **1** with NMAP catalyst are summarized in Table 2. As shown in entries 2, 4, 6 in Table 2, higher pressure provided higher yields. At lower pressure, aldehyde **1** was recovered predominantly and aldol product was not isolated different from the observation of Kawanami and co-workers.⁸ Even aldehydes **1** having an acid (entries 4–7) or a base-sensitive protecting group (entry 8) provided the enals **2** without any decomposition or deprotection, which could not be realized by other methods.^{7,8} The mild and general nature of the present procedure was exemplified.

In summary, we have demonstrated that in $scCO_2$ NMAP catalyzed the self-aldol condensation of unmodified aldehydes **1** leading to enals **2**. The reaction could be realized by amine grafted on silica gel. Characteristic features of the reaction are mild nature, simple, easy and clean operation as well as work-up. By circulation of $scCO_2$ through a column, which was packed NMAP, a continuously reacting system could be designed for a larger scale preparation.

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11. Typical experimental procedure: In a 35 mL stainless steel autoclave were placed NMAP pellets (280 mg, 0.2 mmol), MS-4 Å pellets (1 g) and a glass tube containing *n*-decanal **1** (95 μ L, 0.51 mmol) to prevent neat exposition to inorganic surfaces. Desired amount of CO₂ was charged directly from the cylinder with the use of a plunger pump at room temperature. The autoclave was set in a thermostated air bath and heated at 80 °C for 15 h. The pressure in the autoclave was measured and found to be 23 MPa with the bourdon tube gauge connected to the autoclave. After the reaction, CO₂ was released through diethylether. The autoclave was rinsed with diethylether. The combined ether layer was evaporated to dryness and the residue was purified by medium-pressure LC to afford the enal **2**⁴ (62 mg, 88%).