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A reliable method to create adjacent acid-base pair sites on silica through hydrolysis of pre-anchored amide

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A method to create adjacent acid-base pair sites, which are carboxyl and amino groups, respectively, on silica through hydrolysis of pre-anchored amide is proposed. This method can produce an adjacent acid-base pair sites. The catalyst showed excellent catalytic performance for aldol condensation of 4-nitrobenzaldehyde with acetone, overwhelming the catalyst having only amino group and an acid-base catalyst prepared in a conventional manner.

Keywords: Acid-base pair sites, Cooperative catalysis, Aldol condensation

Because acid and base in a solution unavoidably neutralize, they lose the acid and base functions and generally do not work as an efficient acid or base catalyst in the solution. On the other hand, some molecules having both acidic and basic groups enhance the reaction rates in the solution.[1–4] Proline is the representative molecule and efficiently promotes various carbon-carbon bond formation reactions.[5–7] It is pointed out that acidic and basic groups in such molecules cooperatively work for the reactions. The distance between acidic and basic groups in the molecule is important to determine the cooperative action as a catalyst. In fact, synergetic effect arising from the acidic and basic groups does not appear if they are placed away from each other in the molecule.[4] In other words, the molecule with the adjacent acidic and basic groups, namely acid-base pair, often show higher catalytic performance than distantly positioned analogs or those having either of the two.

In heterogeneous catalysts, some metal oxides including Al_2O_3, ZnO, Al_2O_3-ZnO, and ZrO_2-ZnO have both acid and base sites on the surface and they cooperatively promote the reactions.[8–11] However, the distance between the acid and base sites is widely distributed even for highly crystalline metal oxides, since the surface of the metal oxides is inhomogeneous at atomic level. In addition, the structure of the surface of the metal oxides is different depending on the crystal faces and correspondingly the non-uniform distance between the acid and base sites is unavoidable, while the distance is of critical importance to exert the synergetic effect.

Immobilization of organosilane with a basic group on metal oxides was proposed to control the distance between acid and base sites as well as the density of them.[12–15] Immobilization of (3-aminopropyl)triethoxysilane on SiO_2 is a typical example to create the acid-base pair sites by this approach, because silanol group on SiO_2 acts as an acid site.[12,13] The acid and base sites formed by this approach make the acid-base pair sites, working cooperatively, and thus effectively promotes the carbon-carbon bond formation reactions including aldol and Knoevenagel condensation reactions.[12–15] While silanol group on SiO_2 is weak Brønsted acid site, the acid-base pair sites comprising strong one is created by using silica alumina[16] and acidic montmorillonite[17] instead of SiO_2. In addition to the immobilization approach, co-condensation of aminoalkylsilane with tetraethyl orthosilicate has been extensively studied to synthesize the siliceous solids having the acid-base pair sites on the surface.[18]

As alternative approaches, acid-base pair sites on the surface can be created by the immobilizations of two different organosilanes on metal oxides or the co-condensation of the two.[19–26] This has a great advantage for installation of a variety of acid and base sites by simply changing acid and base attached to organosilanes.[21,23,24,26–28] However, the acidic and basic groups in silanes should be protected or silanes should have functional groups that are transformable to acidic and basic groups but not interactive each other to avoid neutralization during the synthesis,[19,21,22,27,28] requiring burdensome experimental processes to obtain the acidic and basic sites for the synthesis. In addition, this approach gives the randomly located acid and base sites, since no strong interaction works between the two reagents. Therefore, in this approach, it is hard to create a single acid-base pair sites with prescribed distance that exert the synergetic effect on catalysis.

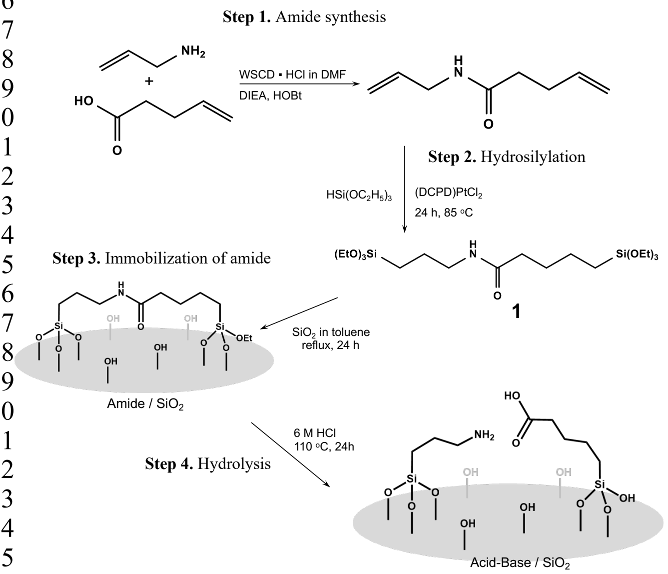

Figure 1. Synthetic procedure for adjacent acid-base pair sites on SiO_2 by use of hydrolysis of pre-anchored amide.

In the present study, we wish to propose a reliable method to definitely create adjacent acid-base pair sites on the surface through hydrolysis of secondary amide immobilized on SiO_2. In the method, the amide with trialkoxysilyl groups at both ends is immobilized on SiO_2 and subsequently is hydrolyzed to create the adjacent carboxyl and amino groups, namely the acid-base pair sites (Figure 1). The method has a great advantage to create only adjacent acid-base pair sites in principle. We furthermore demonstrate that the prepared catalyst exhibits excellent catalytic performance for aldol condensation.

5-(triethoxysilyl)pentanoic acid 3-(triethoxysilyl)propylamide (**1**) was synthesized from 3-amino-1-propene and 4-pentenoic acid by condensation, followed by hydrosilylation with triethoxysilane (Steps 1 and 2 in Figure 1). Structure and purity of **1** were confirmed by ^1H and ^{13}C solution NMR (Figure S1). Immobilization of **1** on SiO_2 (Nippon Aerosil Co., Ltd., AEROSIL® 300, 300 m^2 g^{-1}) was performed in toluene at reflux temperature for 24 h (Step 3 in Figure 1). To prevent multi-layer deposition of **1** on SiO_2, the density of **1** on SiO_2 was adjusted to 0.4 nm^{-2} with consideration for the molecular size of **1**. The obtained material is denoted as Amide/SiO_2. The IR spectrum of Amide/SiO_2 showed absorption bands assignable to amide at 1524 and 1652 cm^{-1} and methylene groups at 2800 – 2900 cm^{-1} (Figure 2(b) and 2(d)). The molar ratio of carbon to nitrogen (=C/N) determined by CHN elemental analysis for Amide/SiO_2 was 8.14 (Table S1), indicating that almost all ethoxy groups in **1** were eliminated by the reaction with silanol groups on SiO_2 to form Si-O-Si bonds. In fact, the decrease of silanol group on SiO_2 was confirmed as a sharp and intense negative band at 3740 cm^{-1} in the difference IR spectrum before and after the immobilization (Figure 2(d)). $^{13}C\{^1H\}$ CP/MAS NMR spectrum of Amide/SiO_2 was almost identical to ^{13}C solution NMR spectrum of **1** except for weakened peaks due to ethoxy group (Figure S2). These results demonstrated that **1** was successfully immobilized on SiO_2 as illustrated in Figure 1.

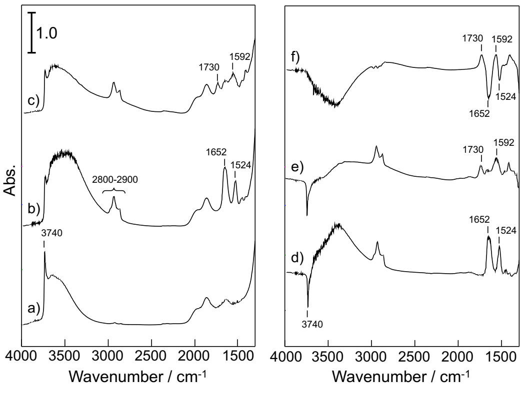

Figure 2. IR spectra for pristine (a) SiO_2, (b) Amide/SiO_2, (c) Acid-Base/SiO_2, and difference spectra obtained by (d) b–a, (e) c–a, and (f) c–b.

Finally, amide bond in Amide/SiO_2 was hydrolyzed in hydrochloric acid (6 mol L^{-1}) at reflux temperature for 12 h to form carboxyl and amino groups (Step 4 in Figure 1). The obtained material is denoted as Acid-Base/SiO_2. The amount of Cl remaining in Acid-Base/SiO_2 was below detection limit for elemental analysis. In the IR spectrum of Acid-Base/SiO_2, the absorption bands due to amide group were absent and instead, two new ones assignable to N-H deformation vibration of amino group and C=O stretching vibration of carboxyl one arose at 1592 and 1730 cm^{-1}, respectively (Figure 2(c) and 2(f)), which were identical to those observed for the samples in which each of 5-(triethoxysilyl)pentanoic acid and (3-aminopropyl)triethoxysilane was fixed on SiO_2 (Figure S3). The cleavage of amide bond was also confirmed by the peak shift of carbonyl group from176.6 to 182.3 ppm in $^{13}C\{^1H\}$ CP/MAS NMR spectra (Figure S2). There was no substantial shift in the other peaks in $^{13}C\{^1H\}$ CP/MAS NMR spectra with the hydrolysis. In addition, the contents of carbon and nitrogen as well as the C/N ratio for Acid-Base/SiO_2 were almost the same as those for Amide/SiO_2 (Table S1). Therefore, it was concluded that Acid-Base/SiO_2 was successfully synthesized as Figure 1 shows.

Next, we evaluated the catalytic performance of Acid-Base/SiO_2 for aldol condensation of 4-nitrobenzaldehyde with acetone and compared to the catalysts with only carboxyl (Acid/SiO_2) or amino group (Base/SiO_2). Acid/SiO_2 and Base/SiO_2 were prepared by the modifications of SiO_2 with 5-(triethoxysilyl)pentanoic acid and (3-aminopropyl)triethoxysilane, respectively, in a similar manner to that for Amide/SiO_2 (Details are shown in Supporting Information).

Base/SiO_2 showed catalytic activity for the aldol condensation reaction and the conversion at 24 h was 34% (Entry 3 in Table 1), while pristine SiO_2 (Entry 1) and Acid/SiO_2 (Entry 2) were completely inactive, indicating that the basic sites catalyzed the reaction as is reported.[29] In the experiment, we used Base/SiO_2 with the amino group density of 0.8 nm^{-2}, because it showed the highest catalytic activity among them with the various densities ranging from 0.1–2 nm^{-2}. To confirm the synergetic effect by silanol group on SiO_2 as an acid site, we carried out the reaction over Base/SiO_2 treated with 1,1,1,3,3,3-hexamethyldisilazane to cap remaining silanol group with trimethylsilyl group (Base/SiO_2(TMS)) and the conversion was only 9% (Entry 4), indicating that synergetic effect between the amino group and silanol on SiO_2 was present for Base/SiO_2. Amide/SiO_2 did not show any activity (Entry 5). It should be noted that Acid-Base/SiO_2 efficiently promoted the reaction and the conversion for Acid-Base/SiO_2 was much higher than that for Base/SiO_2 despite no difference in the number of the basic sites (Entry 6). We further confirmed that Acid-Base/SiO_2 with the density of 0.4 nm^{-2}, which was used here, was the most active catalyst among them with various acid-base pair site densities. Equimolar physical mixture of Acid/SiO_2 and Base/SiO_2 gave only low conversion (Entry 7). Therefore, we conclude that the adjacency of carboxyl group to amino one created by hydrolysis of the amide resulted in the excellent catalytic activity of Acid-Base/SiO_2 for the reaction.

Table 1. Comparison of catalytic activities for aldol condensation of 4-nitrobenzaldehyde with acetone.

Entry	Catalyst	Conv.[a] /%
1	SiO_2	0
2	Acid/SiO_2	0
3	Base/SiO_2	34
4	Base/SiO_2(TMS)	9
5	Amide/SiO_2	0
6	Acid-Base/SiO_2	66 (61, 63)[b]
7	Acid/SiO_2 + Base/SiO_2	8
8	Acid-Base(CV)/SiO_2	42
9	Propylamine[c]	22
10	Propylamine + Pentanoic acid[d]	12

Reaction conditions: 4-nitrobenzaldehyde, 0.5 mmol; acetone, 1.5 mmol; catalyst, 0.025 mmol; toluene (solvent), 10 mL; temperature, 50°C; time, 24 h. The amount of the catalyst was defined according to the number of base sites estimated by titration. In entries 1 and 2, 0.05 g of the catalysts were used. In entry 5, 0.10 g of the catalyst was used. [a]Conversion of 4-nitrobenzaldehyde. [b]The data in parenthesis are the conversions for 1st and 2nd reuses. [c]Homogeneous catalyst. [d]Mixture.

At 10 h for the reaction over Acid-Base/SiO_2, the catalyst was removed by filtration and the obtained solution was further heated again at 50°C. No significant increase in the conversion was observed (Figure 3), indicating that the reaction proceeded over Acid-Base/SiO_2. In addition, Acid-Base/SiO_2 was reusable for the reaction. After the reaction for 24 h, the catalyst was collected by a centrifugation and washed with toluene and ethanol, followed by drying at 60°C overnight. Then, the catalyst was afforded to the second reaction under the same reaction conditions. It was found that Acid-Base/SiO_2 was reusable without any significant loss of activity for at least 2 times reuse (Entry 6 in Table 1).

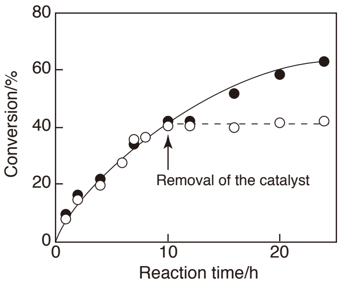

Figure 3. Hot-filtration experiment for the aldol condensation over Acid-Base/SiO_2. (●) without removal of the catalyst and (○) the catalyst was removed at 10 h.

To highlight the superiority of our proposed method, we further compared Acid-Base/SiO_2 with another acid-base SiO_2 catalyst (Acid-Base(CV)/SiO_2) that was prepared by a conventional manner[25,26] and a homogeneous base catalyst. Acid-Base(CV)/SiO_2 was prepared by immobilizing *tert*-butoxycarbonyl (Boc)-protected 3-(triethoxysilyl)propylamine and 5-(triethoxysilyl)pentanoic acid on SiO_2, followed by deprotection of Boc to give the catalyst that had both acid and base sites (Details are shown in Supporting Information). Acid-Base(CV)/SiO_2 was less active than Acid-Base/SiO_2 (Entry 8), while the number of the base sites for Acid-Base(CV)/SiO_2 determined by titration (0.16 mmol g^{-1}) was almost the same as that for Acid-Base/SiO_2 (0.14 mmol g^{-1}). We presumed that the low activity of Acid-Base(CV)/SiO_2 was due to the presence of the less active amino group that was not adjacent to carboxylic acid. In other word, our proposed method can create efficiently the adjacent acid-base pair sites showing the high catalytic activity. Jones and co-workers reported that the modification of Base/SiO_2 with methacrylic acid, which was formed by deprotection of *tert*-butylmethacrylate fixed in advance, to make acid-base pair sites lower the catalytic activity for the aldol condensation[22] unlike Acid-Base(CV)/SiO_2. The carboxyl group in Acid-Base(CV)/SiO_2 is more flexible than that in their catalyst because of the longer (C_4) methylene chain, which probably makes the distance of acid-base pair sites appropriate for the activation of the reactants. It is interesting that the adjacent acid-base pair sites on Acid-Base/SiO_2 was more active than the corresponding propylamine (Entry 9) that acted as a homogenous catalyst and a mixture of propylamine and pentanoic acid (Entry 10).

In the aldol condensation catalyzed by primary amine, it is proposed based on the spectroscopic analyses with IR, Raman and ^{13}C CP/MAS NMR that the reaction proceeds through the formation of enamine intermediate between ketone and amine,[30,31] while imine formation inhibits the reaction.[31] In this process, it is assumed that enough nucleophilicity of amine is required for the addition to carbonyl group. Thus, higher the nucleophilicity of amine on the catalyst is, more the reaction is enhanced. To get information on the nucleophilicity, we measured N 1s XPS spectra for Base/SiO_2 and Acid-Base/SiO_2 (Figure S4). The both catalysts gave the peaks with almost the same binding energy, indicating similar nucleophilicity between Acid-Base/SiO_2 and Base/SiO_2 having no carboxyl group for neutralization of amino group.

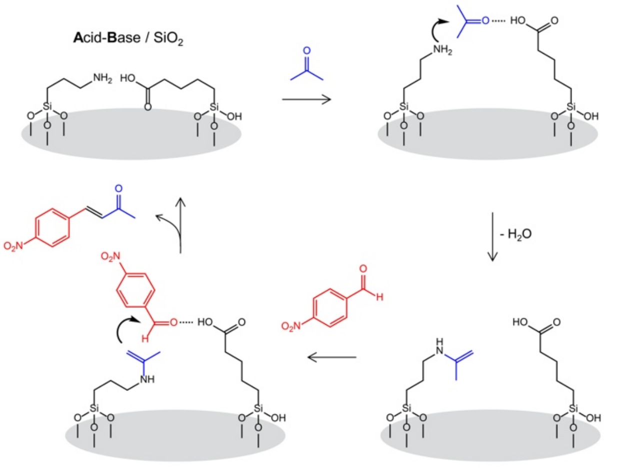

Figure 4. Plausible mechanism for the acceleration of aldol condensation over the adjacent acid-base pair sites on SiO_2.

The other possibility is that the acid and base sites on Acid-Base/SiO_2 cooperatively activate the reactants (Figure 4).[30,31] In acid-base cooperative mechanism for the aldol condensation, an enamine derived from acetone and amino group in Acid-Base/SiO_2 is first generated by the assistance of carboxyl group. Subsequently, nucleophilic addition of the enamine to the aldehyde smoothly occurs through activation of the aldehyde by the carboxyl group to form the carbon-carbon bond. Under these processes, the higher acidity of the carboxyl group than the silanol and the appropriate adjacency between the carboxyl and amino groups are thought to be important for the potent catalytic activity of Acid-Base/SiO_2. We are now investigating kinetic and spectroscopic studies to reveal how the acid-base pair sites on Acid-Base/SiO_2 catalyze the reaction and thus will report them in the near future.

In conclusion, we have shown the excellent catalytic performance of the present catalyst having adjacent acid-base pair sites for the aldol condensation of 4-nitrobenzaldehyde with acetone. The acid-base pair was closely arranged by hydrolysis of amide immobilized on SiO_2, exhibiting much higher catalytic activity than other catalysts examined such as only acid or base sites on SiO_2. This method enabled close proximity between acid and base and further applicable to create acid-base pair sites with precisely controlled distance by hydrolysis of amide including linker moiety. (Figure S5)

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Supporting Information is available on https://doi.org/????????.

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