Communication

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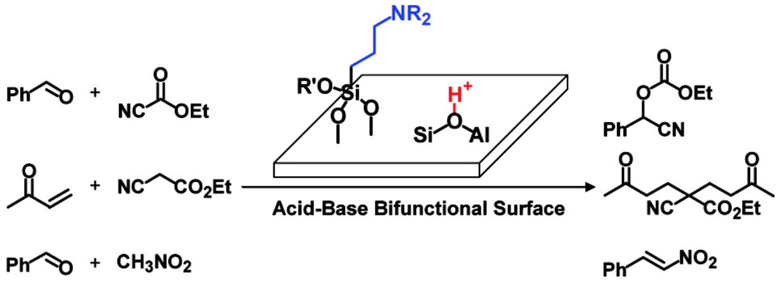

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Heterogeneous Organic Base-Catalyzed Reactions Enhanced by Acid Supports

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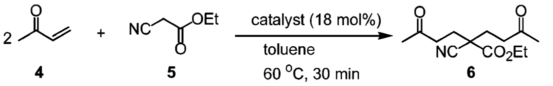
Development of multifunctional catalytic materials plays a pivotal role for achievement of highly efficient organic synthesis. Much attention has been paid to double catalytic activation of electrophiles and nucleophiles by acid and base functions, respectively.[1] However, most of these bifunctional catalyst systems are homogeneous ones, and recover and reuse of both acid and base catalysts are industrially problematic. In addition, a limited number of acid and base species can be used in the bifunctional systems because many types of homogeneous acids and bases neutralized readily in the same reactor. Immobilization of incompatible catalysts on separate solid supports has recently overcome these restrictions and realized one-pot acid−base reaction sequences,[2] and a few examples have also been reported for dual activation of electrophiles and nucleophiles by acid and base functions on the same solid surface in a single reaction.

The immobilization of both acid and base on a solid surface is one of the most effective procedures for the design of the bifunctional catalyst. The combinations of acids, such as hydrogen-bonding ureas, sulfonic acids, and surface silanol groups, and organic bases have been investigated;[3] however, satisfactory catalytic activity has not been achieved due to the random positioning of these two functions and/or weak acidity. As an alterative, our strategy for the design of an acid−base bifunctional catalyst surface focuses on the utilization of a *strong Brønsted acid site* derived from inorganic support surfaces. A major support previously reported for amine reagents is weak acid silica,[4] and there is no research for strong heterogeneous acids, such as amorphous silica-alumina (SA) and zeolites, as supports for basic amine immobilization. Herein, we present novel SA-supported organic amines (SA-NR_2) as nanostructured heterogeneous catalysts. The promising adjacent position of acid and base sites on the SA-NR_2 realized high catalytic activity for a variety of organic transformations, such as cyano-ethoxycarbonylation, Michael reaction, and nitro-aldol reactions.

The SA-supported 3-(diethylamino)propyl functional group (SA-NEt_2) was immobilized by treatment of amorphous silica-alumina (Nikki Chemical Co., SiO_2, 66.5; Al_2O_3, 25.1%, 380 m^2/g) with a toluene solution of 3-(diethylamino)propyltrimethoxysilane (DAPS) under reflux for 24 h. Then the solid was filtered and washed with dichloromethane, followed by drying under vacuum. The elemental analysis determined that the C/N ratio of the SA-NEt_2 was 7.7, and the amount of the amine group was 1.4 molecules/nm^2. The presence of the intact 3-(diethylamino)propyl group was indicated by the solid-state ^{13}C MAS NMR spectra (Supporting Information, SI). Solid-state ^{29}Si MAS NMR revealed that immobilized Si atoms exhibited chemical shifts due to the formation of Si−O bonds with the SA surface (SI). A SA-supported aminopropyl functional group (SA-NH_2) and other solid-supported amines (support-NR_2) were also synthesized and characterized by similar procedures. The elemental analysis of the SA-NH_2 showed 1.7 NH_2 per nm^2 on the SA surface.

One-pot catalytic cyanation-*O*-protection with a robust protecting group has been investigated as a novel synthetic pathway[5] because of the instability of cyanohydrins and highly toxicity of traditional cyanide sources, such as Me_3SiCN and HCN. Cyano-ethoxycarbonylation of benzaldehyde (**1**) with ethyl cyanoformate (**2**) was carried out using various heterogeneous and homogeneous acid and/or base catalysts, as shown in Table 1. Remarkably, the SA-NEt_2 was found to be an excellent catalyst for the reaction of **2** with **1**, affording **3** in a 95% yield (entry 1), while the reaction scarcely proceeded using either triethylamine (entry 8) or SA (entry 9) as a catalyst. The SA-NEt_2 catalyst also showed a higher catalytic activity than the mixture of triethylamine and SA (entry 7). The catalytic activity decreased by decreasing Al content in the SA support (entry 2). The activities of a SiO_2- and Al_2O_3-supported amine catalyst were lower than that of the SA-NEt_2 (entries 3 and 4). It is noted that this is the first report of the cyano-ethoxycarbonylation reaction using heterogeneous catalyst.



(1)

catalyst, Yield of **6**;
SA-NEt_2, 90; SiO_2-NEt_2, 43; SA+Et_3N (Mixture), 66; Et_3N, <1; SA, <1

Michael reaction of nitrile to α,β-unsaturated ketone using SA-supported amine catalysts was also investigated (eq 1). The SA-NEt_2 possessed high catalytic activity and selectivity in the addition reaction of ethyl cyanoacetate (**4**) to methyl vinyl ketone (**5**), giving 90% yield of 2-cyano-5-oxo-2-(3-oxobutyl)hexanoic acid ethyl ester (**6**). Notably, the reaction using a mixture of triethylamine and SA afforded lower yield of **6** compared to the SA-NEt_2 catalyst, and both triethylamine and SA showed no catalytic activity. In general, the conjugate addition of nitrile compounds to α,β-unsaturated ketones needs strong base or transition metal catalysts,[6] which faced difficulties for handling due to moisture sensitivity, deactivation by air containing carbon dioxide, and high toxicity. The use of the simple and stable alkyl amine as a heterogeneous catalyst meets the environmentally friendly organic synthesis.

The nitro-aldol reaction of **1** with nitromethane using various catalysts was examined, as shown in Table 2. The SA-NH_2 catalyst gave the highest yield of β-nitrostyrene (entry 1) and also showed a higher catalytic activity than the mixture of a primary amine and SA (entry 4). The reaction did not proceed using SA-NEt_2 (entry 2).[7] In the SA-NH_2-catalyzed reaction, the TON value based on the amine group reached up to 330, which is significantly higher than that for a previously reported MCM-41-supported amine catalyst (TON = 37).[4b]

After these reactions, both SA-NEt_2 and SA-NH_2 catalysts were separated from the reaction mixture easily and were able to be reused with retention of high catalytic activity and selectivity (SI).

The acid−base interaction between the Brønsted acid site on the SA surface and amine group was confirmed by the solid-state ^{13}C

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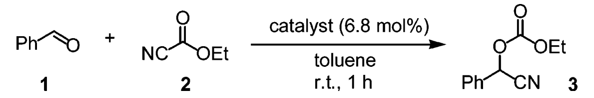
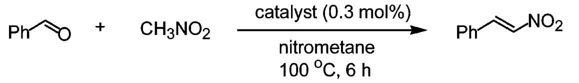
Table 1. Cyano-Ethoxycarbonylation on Various Catalysts[a]



entry	catalyst	yield (%)	entry	catalyst	yield (%)
1	SA-NEt_2	95	6	SA-NH_2	<1
2[b]	SA(L)-NEt_2	57	7	Et_3N + SA	70
3	SiO_2-NEt_2	17	8	Et_3N + p-TsOH·H_2O	<1
4	Al_2O_3-NEt_2	16	9	Et_3N	1
5	USY-NEt_2	3	10	SA	<1

[a] See SI for the reaction rate and detailed reaction conditions. [b] SA having low Al content (SA(L), SiO_2, 82.5; Al_2O_3, 12.6%) was used as a support.

Table 2. Nitro-Aldol Reaction on Various Catalysts[a]



entry	catalyst	yield (%)	entry	catalyst	yield (%)
1	SA-NH_2	99	5	n-$C_6H_{13}NH_2$ + p-TsOH·H_2O	<1
2	SA-NEt_2	<1	6	n-$C_6H_{13}NH_2$	13
3	SiO_2-NH_2	37	7	SA	<1
4	n-$C_6H_{13}NH_2$ + SA	12			

[a] See SI for the reaction rate and detailed reaction conditions.

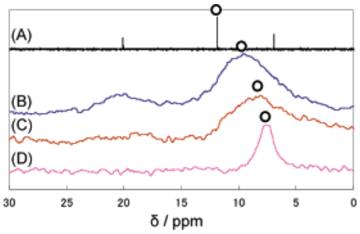
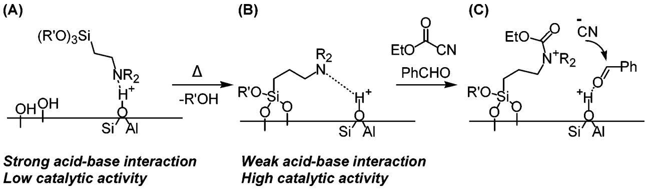


Figure 1. (A) ^{13}C NMR spectra of DAPS in $CDCl_3$. (B−D) Solid-state ^{13}C MAS NMR spectra of (B) the SA-NEt_2, (C) the SA treated with a toluene solution of DAPS (room temp, 5 min), and (D) triethylamine adsorbed on SA. ○: signal assignable to the terminal carbon of amine.

Scheme 1



NMR chemical shifts of the terminal carbon of amine. After the immobilization of the 3-(diethylamino)propane functional group on the SA surface, the upfield shift of the terminal carbon was observed (from 11.9 to 9.5 ppm, Figure 1A,B). In comparison, the signal assignable to the terminal carbon of triethylamine adsorbed on the SA surface showed larger upfield shift (from 11.8 to 7.5 ppm, Figure 1D). These results indicate that the acid-buffering effect to the basic amine of the SA-supported catalyst is smaller than that of the mixture of SA and free amine,[8,9] which agrees with the higher catalytic activity of the immobilized catalyst compared to that of the mixture. To monitor the generation process of the surface active site, the solid SA was separated from the toluene solution of DAPS before heat treatment in the SA-NEt_2 catalyst preparation, and then we conducted the ^{13}C solid-state NMR analysis: the large upfield shift of the terminal carbon of amine was also observed (~8.0 ppm, Figure 1C). The immobilization process is proposed, as shown in Scheme 1: (A) an amine group adsorbs on the surface acid site with strong acid−base interaction; (B) the amine is immobilized to the neighbor of the acid site by silane-coupling reaction, and the acid−base interaction decreases.

Among the solvents examined in the Michael reaction using SA-NEt_2, nonpolar solvents, such as toluene and diethyl ether, were good solvents, whereas polar solvents DMF and DMSO gave poor results with respect to conversion of the enone (SI). Interestingly, this solvent effect of the SA-NEt_2-catalyzed reaction shows a sharp contrast to that using MgO as a typical solid base catalyst (SI), and it is suggested that the Brønsted acid site on the SA surface, which is deactivated by electron-donating solvents, plays a crucial role in the catalysis of the SA-NR_2. On the basis of these results, a proposed reaction mechanism involves the dual activation of donor and acceptor substrates at the amine base site and the neighboring Brønsted acid site on the SA surface, respectively (Scheme 1C). Initial rate kinetics of triethylamine-catalyzed cyanation of **1** with **2** indicates first-order dependence on the concentration of **1** and zero-order dependence on **2**, and the rate-determining step is the carbon−carbon bond-forming step. On the other hand, the initial rate in the SA-NR_2-catalyzed reaction is zero-order dependence on both **1** and **2**. Activation of **1** by the acid site accelerated the carbon−carbon bond-forming step, and another step in the catalytic cycle became the new rate-determining step.

In summary, the use of acidic silica-alumina as a support for basic amine catalyst enables coexistence of strong acid and base sites on the solid surface with suitable distance. This SA-NR_2 catalyst possessed high catalytic activities for various carbon−carbon bond-forming reactions. The advanced solid-state NMR analyses revealed that the basic amine groups were immobilized at the neighboring position of the surface acid site without strong acid−base interaction. This concept, a novel design method of acid−base bifunctional solid surface, can be applied to creation of new heterogeneous catalysts for efficient organic synthesis.

Supporting Information Available: Details of experimental procedures and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The ^{13}C NMR signal of the terminal carbon of triethylamine shifts upfield by protonation, for example, 11.8 (free NEt_3) to 8.84 ppm (NEt_3·HCl).
(9) The IR spectra of catalysts also indicate weak interaction of immobilized amines and surface acid sites (SI), which suggests that the surface acid sites on the SA act as active sites.

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