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Acid–Base Bifunctional Catalysis of Silica–Alumina-Supported Organic Amines for Carbon–Carbon Bond-Forming Reactions

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Abstract: Acid–base bifunctional heterogeneous catalysts were prepared by the reaction of an acidic silica–alumina (SA) surface with silane-coupling reagents possessing amino functional groups. The obtained SA-supported amines (SA–NR_2) were characterized by solid-state ^{13}C and ^{29}Si NMR spectroscopy, FT-IR spectroscopy, and elemental analysis. The solid-state NMR spectra revealed that the amines were immobilized by acid–base interactions at the SA surface. The interactions between the surface acidic sites and the immobilized basic amines were weaker than the interactions between the SA and free amines. The catalytic performances of the SA–NR_2 catalysts for various carbon–carbon bond-forming reactions, such as cyano-ethoxycarbonylation, the Michael reaction, and the nitro-aldol reaction, were investigated and compared with those of homogeneous and other heterogeneous catalysts. The SA–NR_2 catalysts showed much higher catalytic activities for the carbon–carbon bond-forming reactions than heterogeneous amine catalysts using other supports, such as SiO_2 and Al_2O_3. On the other hand, homogeneous amines hardly promoted these reactions under similar reaction conditions, and the catalytic behavior of SA–NR_2 was also different from that of MgO, which was employed as a typical heterogeneous base. An acid–base dual-activation mechanism for the carbon–carbon bond-forming reactions is proposed.

Keywords: acid–base interactions · amines · C–C coupling · heterogeneous catalysis · silica–alumina

Introduction

Immobilization of catalytically active species, or even almost inactive species, on solid materials enables not only the generation of recoverable and reusable catalysts but also remarkable catalytic performances compared with their homogeneous precursors before the immobilization owing to unique environments of the surfaces. Many reasons have been reported for the positive effects of immobilization: for example, the increasing stability of active structures by site isolation at surfaces, the creation of new geometric and electronic structures by surfaces, and the enhancement of substrate density around active sites by high surface polarities.[1] In addition to the increasing activity of the immobilized species, cooperative catalysis of the support surfaces with the immobilized species is another advantage of the use of supports.[2] The generation of multicatalytic functions on a solid surface realizes one-pot catalytic reaction sequences and double catalytic activation in a single reaction step for the improvement of the reaction rate and selectivity.[2,3]

Acid–base dual-activation catalysis has received much attention for highly efficient nucleophilic reactions, including carbon–carbon bond-forming reactions.[4] In base-catalyzed carbon–carbon couplings, nucleophilic precursors are activated by basic catalysts to generate nucleophiles by abstraction of their acidic parts, such as acyl groups and α-hydrogen atoms, and then, the nucleophiles attack electrophiles. On the other hand, decreasing the levels of the lowest-unoccupied molecular orbital (LUMO) of the electrophiles can be readily achieved by coordination activation of Brønsted or Lewis acidic catalysts. On the basis of these facts, it is expected that an ideal pathway for the carbon–carbon bond-forming reactions is dual activation of both the electrophiles and nucleophiles by acidic and basic functions of catalysts, respectively. Many types of homogeneous reaction systems with acid–base dual-activation have been developed, but with these homogeneous reagents, recovery and reuse of both acidic and basic catalysts are industrially problematic. In addition, strongly acidic and basic species in a single reactor induces neutralization immediately, thus affording inactive salts.

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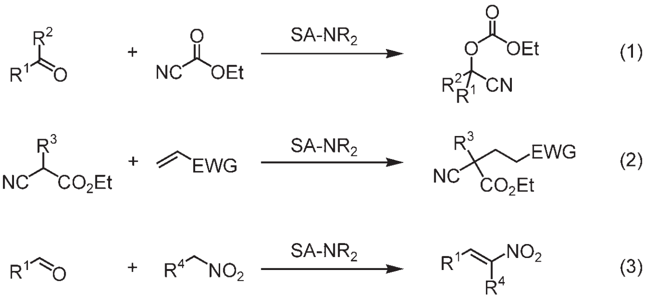
A possible solution to these problems is the utilization of heterogeneous catalysts that possess both acidic and basic functions on their surfaces. The immobilization of incompatible catalytic species on different solid supports has overcome the problem of neutralization and enabled acid–base one-pot reaction sequences.[5] A few examples of the generation of both acidic and basic functions on the same solid surface have been reported for the dual activation of electrophiles and nucleophiles.[6–9] Although primary alkylamines as basic immobilized groups and many types of acidic groups, such as, hydrogen-bonding urea,[6] sulfonic and carboxylic acids,[7] and surface silanols,[8] were found to have cocatalytic functions, these catalytic systems faced several problems, such as low catalytic activity due to weak acidity, significantly limited application in organic reactions, and complicated catalyst preparations.

Alternatively, we recently reported a new strategy for the design of acid–base bifunctional catalyst surfaces:[2] 1) the utilization of strong solid acids as supports for increased catalytic activity, 2) the immobilization of tertiary amines on these supports for the expansion of applicable catalytic reactions, and 3) the use of silane-coupling reactions between the amine reagents and acidic solid supports to simplify the catalyst preparation. Herein, we report detailed studies on the synthesis and characterization of amorphous silica–alumina-supported amine catalysts and their application to various catalytic organic reactions, such as cyano-ethoxycarbonylation, the Michael reaction, and the nitro-aldol reaction [Eqs. (1)–(3)].[10] We also present plausible mechanisms for the amine immobilization and acid–base bifunctional catalytic reactions.



Results and Discussion

Preparation and characterization of the catalysts: The amine catalysts supported on silica–alumina (SA) were prepared by a silane-coupling reaction mode. SA was heated at 120 °C under vacuum for 3 h, followed by reaction with silane-coupling reagents containing amine functional groups. A tertiary amine group was immobilized by reaction of SA (Nikki Chemical Co.; SiO_2 66.5, Al_2O_3 25.1 %; 380 $m^2 g^{-1}$) with a solution of 3-(diethylamino)propyltrimethoxysilane (DAPS) in toluene under reflux for 24 h. The reaction mixture was filtered, washed with dichloromethane, and dried under reduced pressure, thus affording the SA-supported amine catalyst (SA–NEt_2) as a white–yellow powder. Elemental analysis (%) of SA–NEt_2 revealed C 8.40, H 2.16, N 1.27, and the C/N ratio of 7.7:1 of SA–NEt_2 indicated a release of one or two methoxy groups in DAPS.

The IR spectra of SA–NEt_2 showed absorption bands characteristic of the parent DAPS (ν(C–H) = 2990–2850, δ_s-(CH_2) = 1370–1480, and ρ(CH_2) = 765 cm^{-1}).[11] Figure 1 C shows a solid-state ^{13}C CP/MAS NMR spectrum of SA–NEt_2, with signals at δ = 4.0–13.0, 19.6, 43.0–53.0, and 55.6 ppm, assignable, respectively, to the carbon atom next to the silicon and terminal carbon atoms of the amino group, the central carbon atom in the propyl chain, the carbon atom in the methoxy groups and next to the nitrogen atom in the ethyl groups, and the carbon atom next to the nitrogen atom in the propyl chain. These signal positions are similar to those of the parent DAPS (Figure 1 A) and a SiO_2-supported amine catalyst SiO–NEt_2 (Figure 1 B). These IR and ^{13}C NMR spectroscopic data demonstrate that the main structure of the DAPS skeleton is retained in SA–NEt_2. In the ^{29}Si MAS NMR spectrum of SA–NEt_2 (Figure 2 D), the Q sites were observed at around $\delta = -100$ ppm and new signals appeared at $\delta = -48$ and -56 ppm, which are assignable to T^1 and T^2 organosilica species, respectively ($T^m = RSi(OSi)_m(OMe)_{3-m}$, $m = 1, 2$).[12] As a consequence, the amino group was immobilized on the SA surface by a condensation reaction between the surface silanol groups of SA and the methoxy groups of DAPS to form a covalent Si-O-Si linkage while maintaining the tertiary amine skeleton of DAPS. Other solid-supported tertiary amines (support–NEt_2) were synthesized and characterized by using the same procedures. *n*-Octyl groups were also immobilized on SA by

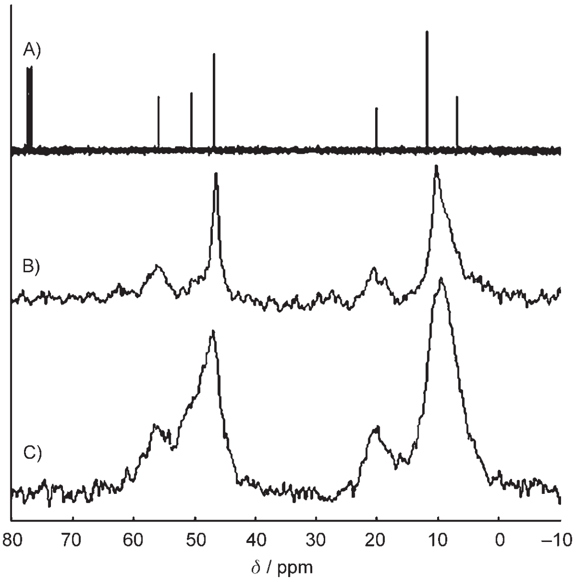


Figure 1. A) ^{13}C NMR spectra of DAPS in $CDCl_3$ (the signals around δ = 77 ppm are assignable to TMS as the internal standard). Solid-state ^{13}C CP/MAS NMR spectra of B) SiO_2–NEt_2 and C) SA–NEt_2.

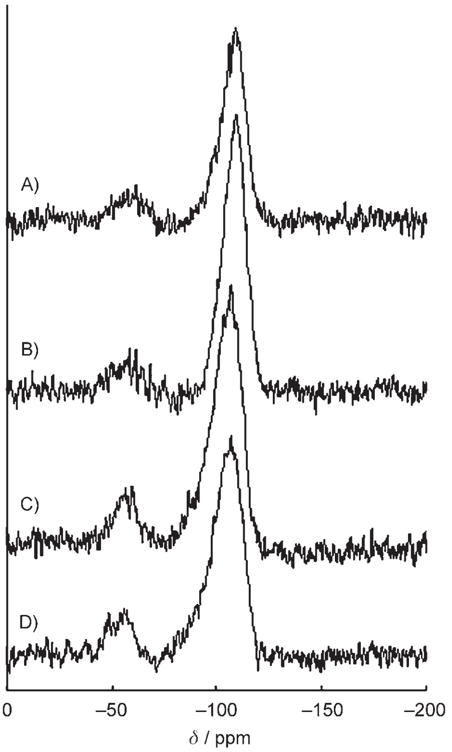


Figure 2. Solid-state ^{29}Si MAS NMR spectra for A) SiO_2–NH_2, B) SiO_2–NEt_2, C) SA–NH_2, and D) SA–NEt_2.

reaction of *n*-octyltrimethoxysilane with SA in a similar procedure (SA–octyl).

The SA-supported primary amine catalyst (SA–NH_2) was also synthesized by modification of the SA surface with 3-aminopropyltriethoxysilane in solution with toluene under reflux conditions. The result of the elemental analysis (%) of SA–NH_2 was C 6.41, H 1.99, N 1.57. The IR spectra of SA–NH_2 showed peaks assignable to 3-aminopropyltriethoxysilane (ν(C–H) = 2980–2880 and $\delta_s(CH_2)$ = 1450–1480 cm^{-1}).[13] The solid-state ^{13}C CP/MAS NMR spectroscopic analysis showed the retention of the primary amine structure (Figure 3): δ = 10.0, 16.5, 21.0–27.0, 44.3, and 57.7 ppm, assignable, respectively, to the carbon atom next to the silicon atom, the terminal carbon atom in the ethoxy groups, the central carbon atom of the propyl chain, the carbon atom next to the nitrogen atom, and the carbon atoms next to the oxygen atoms. The T sites were also observed in the solid-state ^{29}Si MAS NMR spectra of SA–NH_2 (Figure 3 C). These results suggest that the primary amine groups were immobilized on the SA surface by the formation of the Si-O-Si covalent bonds, similar to the above tertiary amine groups.

The acid density of the SA and SA–NEt_2 surfaces was determined from the amount of adsorbed 4-dimethylaminopyridine (DMAP) in the liquid phase. After the amine immobilization onto the SA surface, the amount of acidic sites did not change significantly (see Table 1, entry 1 vs. 3). On the other hand, the acid density of SA decreased with the immobilization of *n*-octyltrimethylsilane.

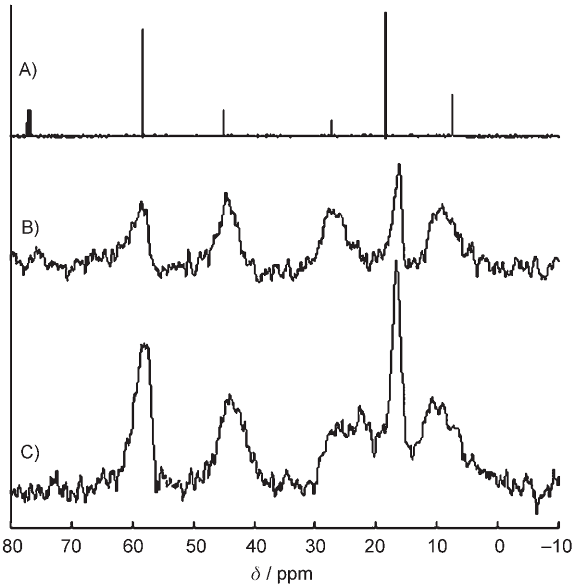


Figure 3. A) ^{13}C NMR spectra of aminopropyltriethoxysilane in $CDCl_3$ (the signals around δ = 77 ppm are assignable to TMS as the internal standard). Solid-state ^{13}C CP/MAS NMR spectra for B) SiO_2–NH_2 and C) SA–NH_2.

Table 1. Amount of DMAP adsorbed on functionalized SA.

Entry	Solid	Amount of adsorbed DMAP [mmol g^{-1}]
1	SA–NEt_2	2.25
2	SA-octyl	1.78
3	SA	2.30

Interaction between the amines and acidic sites: The IR spectra for SA–NEt_2, NEt_3 adsorbed on SA, and DAPS are shown in Figure 4, and the peak positions are listed in Table 2. In the case of NEt_3 adsorbed on a SA surface, the N–H stretching vibrations of the protonated amines were observed at $\tilde{\nu}$ = 2804, 2746, 2689, and 2497 cm^{-1} (Table 2),[14] whereas these peaks were definitely not observed for the immobilized catalyst SA–NEt_2. These results suggest that the interaction between the immobilized NEt_2 groups and the acidic sites on the SA surface is much weaker than the direct interaction between the free amines and the acidic sites on the SA surface.

We also recorded solid-state ^{13}C NMR spectra to examine the surface acid–base interactions between the acidic sites of SA and the immobilized tertiary amine groups. It is well known that the ^{13}C NMR signal of the terminal carbon atom of the ethyl amino group shifts upfield through the interaction between the acidic species and the nitrogen atom. Figure 5 shows the ^{13}C NMR signals assignable to the terminal carbon atom of the free or immobilized diethyl amino groups. The signals of immobilized amines on Al_2O_3, SiO_2, and SA shifted upfield (δ = 11.0, 10.0, and 9.4 ppm, respectively; Figures 5 B–D) relative to the signal of DAPS in solution (δ = 11.9 ppm; Figure 5 A). The larger shift for SA–NEt_2 than those for Al_2O_3–NEt_2 and SiO_2–NEt_2 may be de-

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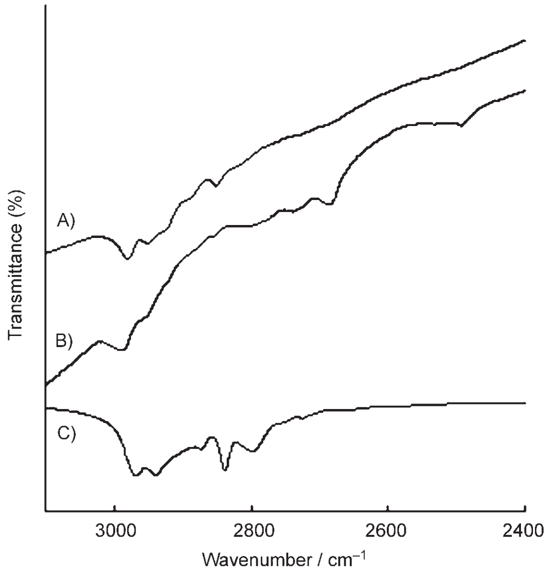


Figure 4. IR spectra of A) SA–NEt$_2$, B) NEt$_3$ adsorbed on SA, and C) DAPS. These spectra were recorded at room temperature in a transmission mode. The solid samples were pressed into a disk with KBr.

Table 2. IR vibration absorptions of SA–NEt$_2$, triethylamine adsorbed on SA, DAPS, triethylamine, and triethylamine hydrochloride.

Sample	ν(C–H) [cm^{-1}]	ν(N–H) [cm^{-1}]
SA–NEt$_2$	2986, 2954, 2855	(negligible)
SA+NEt$_3$	2996, 2963	2804, 2746, 2693, 2497
DAPS	2974, 2946, 2843	–
NEt$_3$[a]	2971, 2936, 2798	–
NEt$_3$·HCl[a]	3000, 2976, 2938	2803, 2739, 2678, 2492

[a] Data from ref. [14]

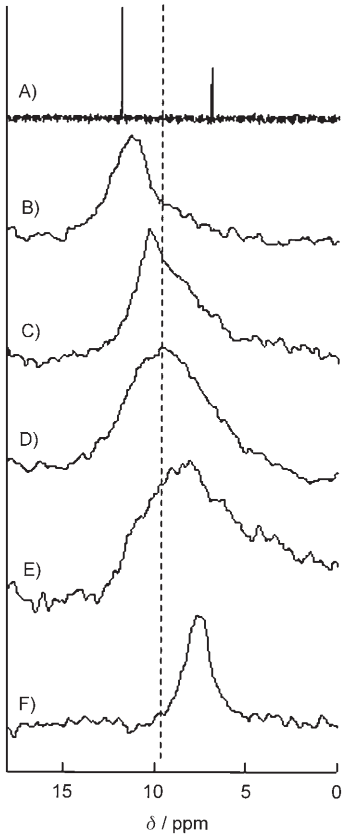


Figure 5. A) ^{13}C NMR spectra of DAPS in CDCl$_3$. Solid-state ^{13}C CP/MAS NMR spectra for B) Al$_2$O$_3$–NEt$_2$, C) SiO$_2$–NEt$_2$, D) SA–NEt$_2$, E) SA treated with a solution of DAPS in toluene for 5 min at room temperature (SA+DAPS), and F) triethylamine adsorbed at the terminal carbon atoms of the amino groups on the SA surface.

rived from the stronger Brønsted acidity of the SA surface. The signals from mixtures of SA and free DAPS or triethylamine appeared more upfield than that for SA–NEt$_2$. For example, the signal for triethylamine (NEt$_3$) adsorbed on the SA surface showed the largest upfield shift (from $\delta = 11.8$ (free NEt$_3$) to 7.5 ppm; Figure 5F). This outcome is in agreement with the above IR results: a weak acid–base interaction with the immobilized SA–NEt$_2$.

Proposed mechanism for amine immobilization: The SA surface was treated with a solution of DAPS in toluene for 5 min at room temperature, followed by filtration. The obtained solid (SA+DAPS) was subjected to solid-state ^{13}C and ^{29}Si NMR spectroscopic analysis. A ^{13}C NMR peak assignable to the terminal carbon atom of adsorbed DAPS was observed at around $\delta = 8.0$ ppm (Figure 5E), which indicates that the acid–base interactions are stronger than those in SA–NEt$_2$ after complete immobilization under reflux for 24 h ($\delta = 9.4$ ppm; Figure 5D). Figure 6 shows the ^{29}Si NMR spectra for the T^m sites in SA–NEt$_2$ and SA+DAPS, in which the ^{29}Si NMR spectra are noisy as a result of the small amount of the T^m sites at the surface. In the case of SA+DAPS, the T^1 site was observed at $\delta = -49$ ppm as a main signal (Figure 6B), whereas the majority of sites in SA–NEt$_2$ were T^2 sites (Figure 6A). From these results, the mechanism for amine immobilization on the SA surface is proposed to be as follows (Scheme 1): i) the nitrogen atom of free DAPS interacts with the strong Brønsted acid on the SA surface, ii) one Si−OMe bond of DAPS reacts with the surface Si−OH species near the strongly acidic site to form a covalent Si-O-Si(surface) bond, and iii) another Si−OMe species further reacts with a neighboring Si−OH bond on heating, thus resulting in decreased acid–base interactions between the strongly acidic site and the nitrogen atom. The formation of a T^2 silicon species with two covalent Si-O-Si-(surface) bonds tends to increase the distance between the amine group and the acidic site, which induces a decrease in the acid–base interactions. The silane-coupling reaction of the Brønsted acid with the alkoxysilane, which maintains the quantity of strongly acidic sites (Table 1), is prevented from proceeding by these acid–base interactions. In the solid-state ^{29}Si NMR spectra of SA–octyl, the formation of not only T^2 but also T^3 sites was observed in the absence of basic amino groups (Figure 6C), which suggests that the alkoxysilane groups randomly reacted with two or three surface hydroxy groups, including the strongly acidic sites. The ability of the acid–base to coexist on the SA–NR$_2$ surface

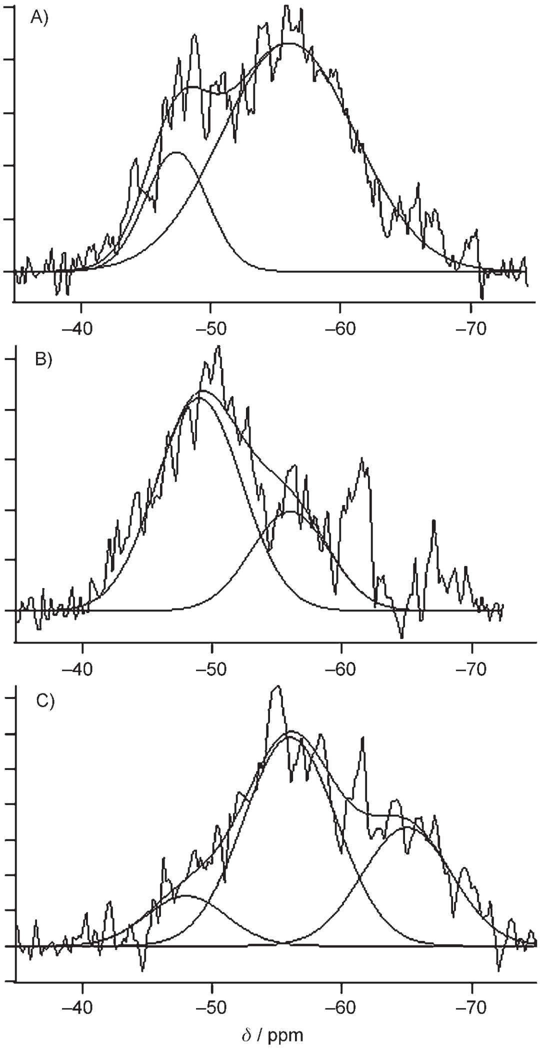


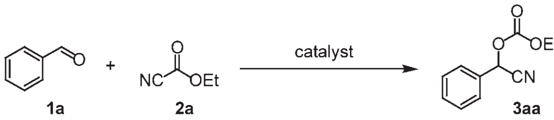
Figure 6. Solid-state ^{29}Si MAS NMR spectra of T^m sites. A) SA–NEt$_2$, B) SA treated with a solution of DAPS in toluene for 5 min at room temperature (SA+DAPS), and C) SA–octyl.

without neutralization tempted us to envisage that SA–NR$_2$ could act as a heterogeneous acid–base bifunctional catalyst for efficient organic syntheses.

Catalysis of the amine-immobilized solid acid: Cyanohydrins are important building blocks in synthetic organic chemistry,[15] and they have been synthesized by the cyanation of carbonyl compounds with HCN or trimethysilyl cyanide.[16] However, HCN and trimethylsilyl cyanide are toxic, unstable, and expensive; hence, the use of alternative cyanation reagents is desirable. Recently, one-pot catalytic cyanation/*O*-protection with cyanoformic esters has been investigated as a novel synthetic pathway.[17] Although several examples of the cyanation/*O*-protection reactions by homogenous acid–base bifunctional catalysts have been demonstrated,[17c–f,i] heterogeneous catalysts for the cyanation reaction have not yet been reported. We found that our heterogeneous acid–base bifunctional catalysts were active towards cyanation/*O*-protection with a cyanoformic ester as a cyanation regent.

First, the cyano-ethoxycarbonylation of benzaldehyde (**1a**) with ethyl cyanoformate (**2a**) was studied in the presence of heterogeneous and homogeneous catalysts (Table 3).

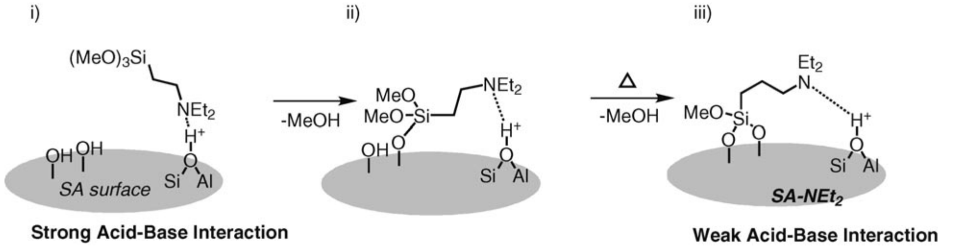
Table 3. Cyano-ethoxycarbonylation using various catalysts.[a]



Entry	Catalyst	Yield [%][b]
1	SA–NEt$_2$	95
2[c]	SA–NEt$_2$	57
3	SiO$_2$–NEt$_2$	17
4	Al$_2$O$_3$–NEt$_2$	16
5	H-USY–NEt$_2$	3
6	SA–NH$_2$	trace
7[d,e]	Et$_3$N+SA	70
8[d,f]	Et$_3$N+p-TsOH·H$_2$O	trace
9[d]	Et$_3$N	1
10[g]	DAPS	1
11[e]	SA	trace
12[e]	SiO$_2$	trace
13[e]	Al$_2$O$_3$	trace
14[e]	MgO	trace
15	none	trace

[a] Reagents and conditions: catalyst (0.034 mmol of amine), **1a** (0.5 mmol), **2a** (1.0 mmol), toluene (5 mL), room temperature, 1 h. [b] Determined by GC, based on **1a**. [c] SA (SiO$_2$: 82.5; Al$_2$O$_3$: 12.6%) was used as a support. [d] Triethylamine (0.034 mmol). [e] Catalyst (0.038 g). [f] p-TsOH (0.034 mmol). [g] DAPS (0.034 mmol).

Among the amine-immobilized catalysts, the SA-supported tertiary amine catalyst showed the highest performance to afford cyanophenylmethyl ethyl carbonate (**3aa**) in an excellent yield (Table 3, entry 1). A decrease in the Al content in SA induced a decrease in the activity of the cyanation reaction (Table 3, entry 2). Other solid-



Scheme 1. Proposed mechanism for amine immobilization on the SA surface. i) Interaction between the nitrogen atom of free DAPS with a Brønsted acid, ii) formation of a covalent Si-O-Si(surface) bond, and iii) decreased acid–base interactions between the strongly acidic site and the nitrogen atom as a result of another Si–OMe species reacting with a neighboring Si–OH bond.

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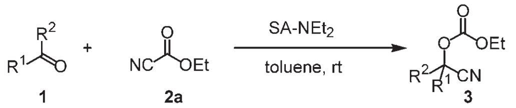
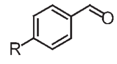
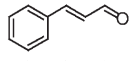
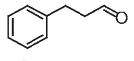
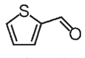
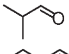
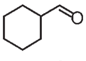
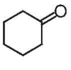
supported tertiary amine catalysts, such as SiO_2–NEt_2 and Al_2O_3–NEt_2, were much less active (Table 3, entries 3–5). These results suggest that the stronger surface acidic sites of SA play a pivotal role in the promotion of cyano-ethoxycarbonylation. Interestingly, the reaction scarcely proceeded with either homogeneous amines (Table 3, entries 9 and 10) or acidic solid supports (Table 3, entries 11–13). The mixture of triethylamine and SA showed catalytic activity, but the product yield was lower than for SA–NEt_2 under the same reaction conditions (Table 3, entry 7). When the acidic support SA was replaced by *para*-toluenesulfonic acid (*p*-TsOH) in a homogeneous system, the reaction did not occur (Table 3, entry 8). A poor result was obtained with MgO as a typical heterogeneous base (Table 3, entry 9). These results suggest that both the acidic and basic functions on the surface are highly efficient for the promotion of cyano-ethoxycarbonylation.

The high performances of the SA–NEt_2 catalyst for the cyano-ethoxycarbonylation of various carbonyl compounds are shown in Table 4. Both electron-rich and electron-deficient benzaldehydes acted as good substrates, thus giving the corresponding *O*-protected cyanohydrin derivatives in excellent yields (Table 4, entries 1–5). An allylic aldehyde, such as cinnamaldehyde, also underwent a reaction with **2a** in the presence of SA–NEt_2 (Table 4, entry 6). A sulfur heteroatom did not affect the reaction rate: the cyanation reaction of 2-thiophenecarboxyaldehyde took place readily (Table 4, entry 8). Notably, many types of aliphatic aldehydes, such as acyclic, branched, and cyclic aldehydes, underwent a reaction with **2a**, affording excellent yields of the corresponding products (Table 4, entries 9–11). To extend the scope of the carbonyl substrates, the use of ketones was also examined. Cyanoformic ester **2a** underwent a reaction with cyclohexenone to afford the corresponding product in 88 % yield after a prolonged reaction time (Table 4, entry 12). To the best of our knowledge, this report is the first of a one-pot cyano/*O*-protection of carbonyl compounds with cyanoformic ester using a heterogeneous catalyst.

Table 4. Cyano-ethoxycarbonylation using SA–NEt_2.[a]



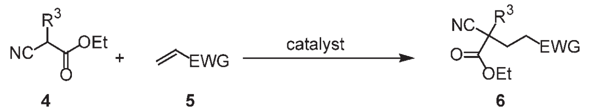
Entry	Carbonyl		Time [h]	Conversion [%][b]	Yield [%][b]
					
1	R=H	**1a**	1	>99	98
2	R=H	**1a**	1	>99	97[c]
3	R=Cl	**1b**	3	>99	99
4	R=Me	**1c**	1	>99	99
5	R=OMe	**1d**	3	>99	98
6		**1e**	2	>99	91
7		**1f**	1	>99	99
8		**1g**	1	>99	98
9		**1h**	1	>99	99
10		**1I**	1	>99	92
11		**1j**	1	>99	99
12		**1k**	48	90	88

[a] Reagents and conditions: **1** (0.5 mmol), **2a** (0.6 mmol), toluene (1 mL), SA–NEt_2 (0.038 g; N: 0.034 mmol), room temperature. [b] Determined by GC and ^{1}H NMR spectroscopic analysis, based on **1**. [c] Reuse experiment.

After the first run of the cyano-ethoxycarbonylation reaction was completed, the SA–NEt_2 catalyst was separated from the reaction mixture and was reusable with retention of the high catalytic activity and selectivity (Table 4, entry 2). The ^{1}H NMR spectroscopic analysis of the filtrate showed no leaching of the immobilized amine compounds, and the elemental analysis of the recovered catalyst also indicated no decrease in the amount of the amino group. These facts rule out any contribution of the amines to the carbon–carbon bond-forming reaction by leaching into the reaction solution.

This amine-immobilized solid acid catalyst was applicable to the Michael reaction of nitrile compounds **4** with electron-deficient alkenes **5** (Table 5). The SA–NEt_2 catalyst showed the highest catalytic activity for the Michael reaction of ethyl 2-cyanopropionate (**4a**) with ethyl acrylate (**5a**) to afford 2-cyano-2-methyl glutaric acid diethyl ester in 94 % yield (Table 5, entry 1). The reaction did not proceed in the case of the SA-supported primary amine (SA–NH_2; Table 5, entry 3). Other solid supports, such as SiO_2, were less active (Table 5, entry 2), and neither triethylamine nor SA promoted the desired addition reaction (Table 5, en-

Table 5. Michael reaction of α-substituted ethyl cyanoacetates with electron-deficient alkenes.[a]



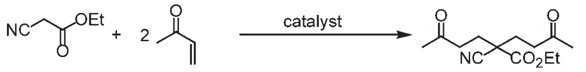
Entry	Catalyst	R^3	EWG	Yield [%][b]
1	SA–NEt_2	Me (**4a**)	CO_2Et (**5a**)	94
2	SiO_2-NEt_2	Me	CO_2Et	9
3	SA–NH_2	Me	CO_2Et	trace
4[c,d]	Et_3N+SA	Me	CO_2Et	5
5[c]	Et_3N	Me	CO_2Et	3
6[c]	SA	Me	CO_2Et	1
7[e,f]	SA–NEt_2	Ph (**4b**)	CO_2Me (**5b**)	99
8[e,f]	SA–NEt_2	Ph	CO_2Me	99[g]
9[e,f]	SA–NEt_2	Ph	CO_2Me	94[h]
10[e]	SA–NEt_2	Me	CN (**5c**)	95
11[e,f]	SA–NEt_2	Me	CN	66
12[e,f]	Et_3N	Me	CN	17

[a] Reagents and conditions: catalyst (0.09 mmol of amine), **4** (1.0 mmol), **5** (3 mmol), toluene (1 mL), 90 °C, 24 h. [b] Determined by GC and ^{1}H NMR spectroscopic analysis, based on **4**. [c] Triethylamine (0.09 mmol). [d] Catalyst (0.05 g). [e] Catalyst (0.045 mmol of amine); 60 °C. [f] Reaction time: 3 h. [g] Second reuse experiment. [h] Fourth reuse experiment. EWG = electron-withdrawing group.

tries 5 and 6). In addition, the reaction scarcely proceeded in the presence of the mixture of triethylamine and SA (Table 5, entry 4). Notably, the SA–NEt$_2$-catalyzed reaction of ethyl phenylcyanoacetate (**4b**) with methyl acrylate (**5b**) successfully proceeded to give 2-cyano-2-phenyl glutaric acid 1-ethyl-5-methyl ester, which is a highly useful intermediate for glutarimide synthesis (Table 5, entry 7).[18] The SA–NEt$_2$ catalyst was reusable at least four times with retention of its high catalytic activity and selectivity in the Michael reaction (Table 5, entries 8 and 9). In addition, SA–NEt$_2$ showed higher catalytic activity for the reaction of **4a** with acrylonitrile (**5c**; Table 5, entries 10 and 11) than the homogeneous amine (Table 5, entry 12).

It is noteworthy that the SA–NEt$_2$ catalyst also showed excellent performance for the bis-substitution reaction of ethyl cyanoacetate (**4c**) with methyl vinyl ketone (**5d**), thus producing 5-carboethoxy-5-cyano-2,8-nonanedione (**6 cd**) in 90 % yield within 30 minutes (Table 6, entry 1). A SiO$_2$-supported tertiary amine catalyst also gave **6 cd** in a moderate yield of 43 % (Table 6, entry 2). Neither triethylamine nor SA produced **6 cd** (Table 6, entries 5 and 6), whereas the mixture of triethylamine and SA gave a 66 % yield of **6 cd** (Table 6, entry 4). A typical heterogeneous base of MgO also gave the corresponding product (Table 6, entry 8), but the catalytic activity was lower than for the same weight of SA–NEt$_2$. Generally, strong bases or transition-metal catalysts are needed for the 1,4-addition of nitrile compounds to electron-deficient alkenes.[19] However, these reaction systems present difficulty in their handling as a result of moisture sensitivity and deactivation by air containing carbon dioxide. The present SA–NEt$_2$ catalyst can solve these problems because of the use of the simple and stable alkylamines immobilized on the stable SA as a heterogeneous catalyst, which contributes to environmentally friendly organic syntheses.

Table 6. Michael reaction of **4c** with **5d** using various catalysts.[a]



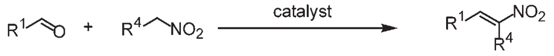
4c **5d** **6cd**

Entry	Catalyst	Conversion [%][b]	Yield [%][b]
1	SA–NEt$_2$	>99	90
2	SiO$_2$–NEt$_2$	83	43
3	SA–NH$_2$	<1	<1
4[c,d]	Et$_3$N+SA	90	66
5[c]	Et$_3$N	<1	<1
6[d]	SA	<1	<1
7[d]	SiO$_2$	<1	<1
8[d]	MgO	82	52
9	None	<1	<1

[a] Catalyst (0.091 mmol of amine), **5d** (1.5 mmol), **4c** (0.5 mmol), toluene (1 mL), 60 °C, 30 min. [b] Determined by GC, based on **4c**. [c] Triethylamine (0.091 mmol). [d] Catalyst (0.1 g).

The condensation reaction of nitroalkanes with carbonyl compounds, namely, the nitro-aldol reaction, is one of the most powerful procedures for the production of α,β-unsaturated nitro compounds, which are important building blocks in the synthesis of pharmaceutical products.[20] The α-hydrogen atom of a nitroalkane can be abstracted by strong bases owing to its acidity, but the selective production of a nitroalkene using conventional strong bases is generally difficult because the side reaction of a conjugate addition of the nitroalkane to the carbon–carbon double bond of the nitroalkene occurs to give a bis(nitro) compound.[21] Because of the highly useful nature of nitroalkenes, the nitro-aldol reaction of nitroalkanes with aldehydes was also investigated (Table 7).[22] The SA–NH$_2$ catalyst gave a quantitative yield of β-nitrostyrene from **1a** and nitromethane (**7a**; Table 7, entry 1). The homogeneous primary amine was much less active (Table 7, entry 5) and the low catalytic activity was not improved by the addition of SA (Table 7, entry 3). Notably, the reaction hardly proceeded using SA–NEt$_2$ instead of SA–NH$_2$ (Table 7, entry 2). In the case of the SA–NH$_2$-catalyzed reaction of **7a** with **1a**, the turnover number (TON) based on the amine reached up to 330. This value is significantly higher than that of the previously reported amine catalysts: MCM-41-supported amine (TON = 37),[22c] aminopropylsilica (TON = 17),[22d] and a silica-supported urea–amine bifunctional catalyst (TON = 125).[6] The SA–NH$_2$ catalyst was found to be applicable to the nitro-aldol reaction of other aldehydes with nitroalkanes. The reaction of aliphatic aldehydes, such as cyclohexanecarboxyaldehyde (**1j**) and *n*-octylaldehyde (**1h**), produced the corresponding nitroalkenes in excellent yields (Table 7, entries 8 and 9). Nitroethane (**7b**) also acted as a good donor substrate (Table 7, entry 10). After the nitro-aldol reaction of **7a** with **1a**, the recovered SA–NH$_2$ catalyst was washed with toluene and reusable under the same reaction conditions: the first and

Table 7. Nitro-aldol reaction of aldehydes with nitroalkanes using various catalysts.[a]



1 **7** **8**

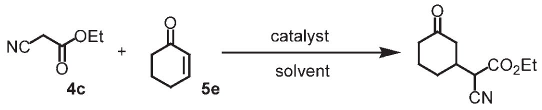
Entry	Catalyst	R^1	R^4	Time [h]	Yield [%][b]
1	SA–NH$_2$	Ph (**1a**)	H (**7a**)	6	99 (97)[c]
2	SA–NEt$_2$	Ph	H	6	<1
3[d,e]	*n*-hexylamine + SA	Ph	H	6	12
4[d,f]	*n*-hexylamine + *p*-TsOH·H$_2$O	Ph	H	6	<1
5[d]	*n*-hexylamine	Ph	H	6	13
6[e]	SA	Ph	H	6	<1
7[e,f]	none	Ph	H	6	<1
8[g]	SA–NH$_2$	*c*-hexyl (**1j**)	H	2	88
9[g]	SA–NH$_2$	*n*-octyl (**1h**)	H	2	88
10[g]	SA–NH$_2$	Ph	Me (**7b**)	4	90

[a] Reagents and conditions: catalyst (0.015 mmol of amine), **1** (5.0 mmol), **7** (2 mL), 100 °C. [b] Determined by GC, based on **1**. [c] Fourth reuse experiment. [d] *n*-Hexylamine (0.015 mmol). [e] Catalyst (0.0145 g). [f] *p*-TsOH acid (0.015 mmol). [g] Aldehyde (1 mmol); SA–NH$_2$ (0.056 mmol).

second runs afforded product yields of 99 and 97 %, respectively.

Proposed catalytic reaction mechanism: Table 8 shows the effect of solvents on the performances of the catalysts, and the dielectric constant values ε of the solvents as a criterion of polarity are also listed. Toluene was the most effective solvent among the solvents for the Michael reaction of **4c** with 2-cyclohexen-1-one (**5e**; Table 8, entry 2), whereas dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were substantially less active (Table 8, entries 4 and 5). *n*-Heptane allowed an excellent conversion of **4c** to be obtained, but the selectivity was low (Table 8, entry 1). These results suggest that nonpolar solvents with low dielectric constants are good media for the Michael reaction and that polar and electron-donating solvents with higher dielectric constants resulted in lower reaction rates. On the other hand, a polar solvent, DMF, gave a good result relative to toluene when MgO, as a typical heterogeneous base, was used as a catalyst for the Michael reaction (Table 8, entry 6 vs. 7).

Table 8. Solvent effect on the Michael reaction.[a]



Entry	Catalyst	Solvent (dielectric constant (ε))	Conversion [%][b]	Yield [%][b]
1	SA–NEt_2	*n*-heptane (1.9)	>99	32
2	SA–NEt_2	toluene (2.4)	88	64
3	SA–NEt_2	Et_2O (4.2)	86	56
4	SA–NEt_2	DMSO (47.2)	20	20
5	SA–NEt_2	DMF (36.7)	8	<1
6	MgO	toluene (2.4)	33	33
7	MgO	DMF (36.7)	58	46

[a] Reagents and conditions: catalyst (0.1 g), **5e** (0.75 mmol), **4c** (0.5 mmol), solvent (1 mL), 60 °C, 3 h. [b] Determined by ^{1}H NMR spectroscopic analysis, based on **4c**.

From these contrary results, it is reasonable to conclude that the Brønsted acidic sites on the SA surface, which can be deactivated by electron-donating solvents, play a crucial role in the catalytic mechanism of SA–NEt_2.[23] After the treatment of SA–NEt_2 with **2a**, the ν(CN) peak for **2a** appeared at 2221 cm^{-1} (Figure 7B),[24] which is lower than that for free **2a** (2247 cm^{-1}; Figure 7D). The shifted ν(CN) absorption band disappeared on treatment with **1a**, accompanied with the production of **3aa** (Figure 7A). This peak shift was not observed when the SA surface was treated with **2a** (Figure 7C). These results indicate that the nucleophilic CN species forms through interaction with the surface tertiary amine group. As consequence, we proposed a reaction mechanism for the SA–NEt_2-catalyzed reactions involving the dual activation of the donor and acceptor substrates at the basic amine site and the neighboring Brønsted acidic site on the SA surface, respectively (Scheme 2). The initial rate of the triethylamine-catalyzed cyanation of **1a** with **2a** is first-order with respect to the concentration of **1a** and zero-order with respect to the concentration of **2a**, thus indicating that the rate-determining step is the carbon–carbon bond-forming step. On the other hand, the initial reaction kinetics in the SA–NR_2-catalyzed reaction shows zero-order dependence with respect to both **1a** and **2a**. It is suggested

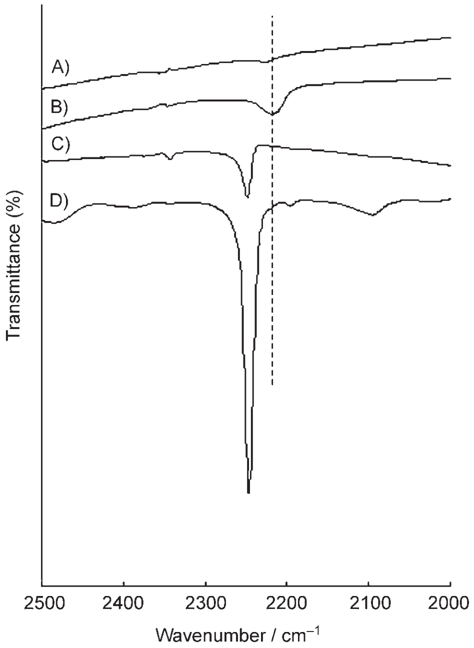
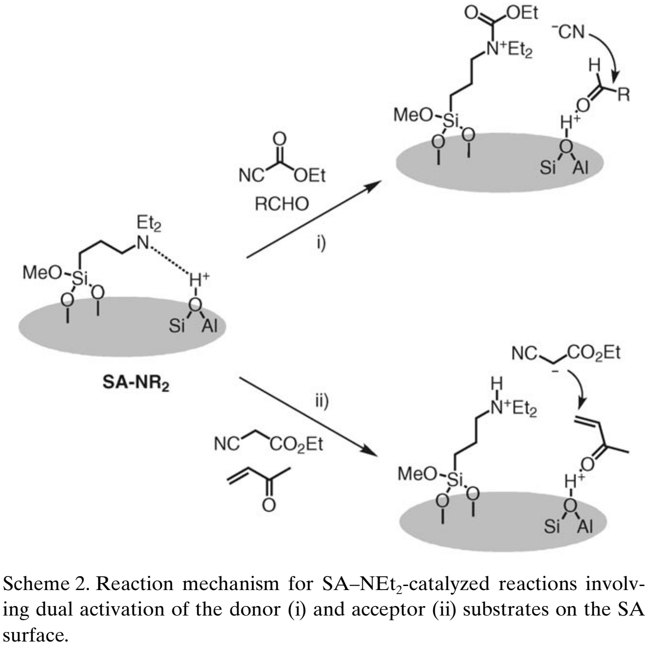


Figure 7. IR spectra of A) SA–NEt_2+**2a** after treatment with **1a**, B) SA–NEt_2+**2a**, C) SA+**2a**, and D) free **2a**. These spectra were measured at room temperature in transmission mode. The solid samples were pressed into a disk with KBr.



Scheme 2. Reaction mechanism for SA–NEt_2-catalyzed reactions involving dual activation of the donor (i) and acceptor (ii) substrates on the SA surface.

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that the electron-withdrawing activation of a carbonyl compound by surface acidic sites is a new and very fast reaction step.

Table 7 and several previous reports[22b] show the substantially low catalytic activity of tertiary amine catalysts for the nitro-aldol reaction relative to primary amine catalysts in spite of the larger electron-donating effect of tertiary amine groups as a result of alkyl moieties. To determine the reaction intermediate, IR spectra of the SA–NH_2 catalyst after treatment with a solution of **1a** in toluene were recorded (Figure 8). New peaks appeared at 1650 and 1457 cm^{-1}, which are assignable to the C=N stretching and C–C vibration modes in a benzylimine species, respectively (Figure 8).[25] From these results and previously reported data, the reaction mechanism for the SA–NH_2-catalyzed nitro-aldol reaction is proposed in Scheme 3: 1) an aldehyde is activated by a surface acidic site and the immobilized NH_2 group attacks the carbonyl carbon atom in the aldehyde, 2) a dehydration reaction occurs so that a surface imine species forms, and a nitroalkane moiety reacts with the activated imine to afford the nitroalkene product.

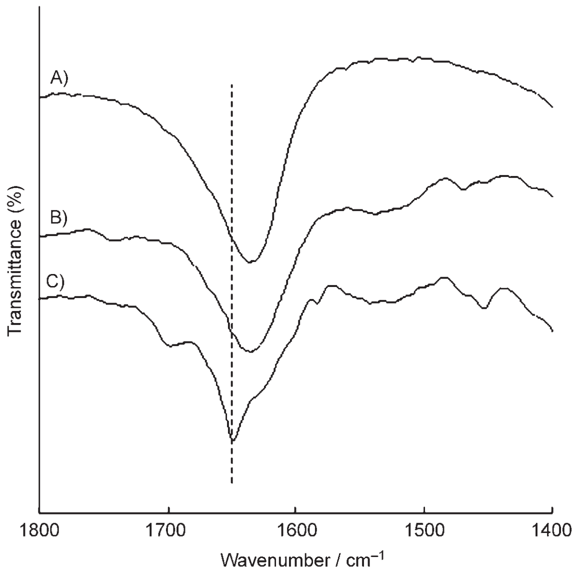
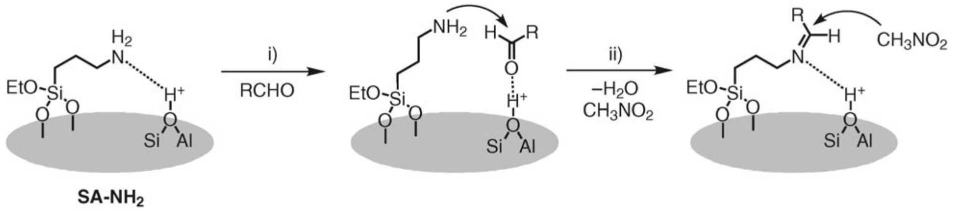


Figure 8. IR spectra for A) SA, B) SA–NH_2, and C) SA–NH_2 treated with benzaldehyde. These spectra were measured at room temperature in transmission mode. The solid samples were pressed into a disk with KBr.



Scheme 3. Reaction mechanism for the SA–NH_2-catalyzed nitro-aldol reaction. i) Attack on the carbonyl carbon atom by the immobilized NH_2 group and ii) a dehydration reaction followed by the formation of the nitroalkene product.

Conclusion

Silica–alumina was used as a support for basic amines in the development of acid–base bifunctional catalysts (SA–NEt_2 and SA–NH_2) in carbon–carbon bond-forming reactions for the first time. The amine-immobilization process on the SA surface was examined by solid-state NMR spectroscopic analysis, which revealed a weak acid–base interaction between the amine and the acidic site of SA–NEt_2. The coexistence of both a moderately acidic site and an amine base at the same solid surface without neutralization realized the acid–base bifunctional catalyst with a high performance: the SA–NR_2 surface was found to be an extremely active heterogeneous catalyst for carbon–carbon bond-forming reactions, such as cyano-ethoxycarbonylation, the Michael reaction, and the nitro-aldol reaction. Refinement of multifunctional solid surfaces may achieve highly efficient organic synthesis including brand new reactions.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on a JNM-AL400 spectrometer at 400 MHz using $CDCl_3$ as the solvent and trimethylsilane (TMS) as an internal standard. Solid state ^{13}C and ^{29}Si MAS NMR spectra (MAS rate: 4 kHz) were recorded on a Chemagnetics CMX-300 spectrometer operating at 75.5 and 59.7 MHz, respectively. ^{13}C MAS NMR spectra with cross polarization (CP) were acquired at a contact time of 5.0 ms. ^{29}Si NMR spectra were measured by a single-pulse detection method with hydrogen decoupling (pulse duration: 1.5 μs, rotor-spin rate: 4 kHz, delay time: 15 (^{13}C) and 20 s (^{29}Si). Hexamethylbenzene (^{13}C: $\delta =$ 17.17 and 176.46 ppm) and TMS (^{29}Si: $\delta = 0$ ppm) were used as external standards for the calibration of the chemical shifts. The accumulation numbers were fixed at about 20000 (^{13}C) and 10000 (^{29}Si). The IR spectra were recorded on a JASCO FTIR-410 spectrometer. Analytical GLC and GLC–MS were carried out on a Shimadzu GC-2010 machine with a flame ionization detector equipped using a silicon SE-30 column.

Unless otherwise noted, the materials were purchased from Wako Pure Chemicals (Tokyo Kasei Co.) and Aldrich Inc. and were used after appropriate purification. Amorphous silica–alumina (SA) N633HN (SiO_2, 66.5; Al_2O_3, 25.1 %; 380 $m^2 g^{-1}$) was purchased from Nikki Chemical Co. SA containing a lower Al content (N633 L; SiO_2, 82.5; Al_2O_3, 12.6 %; 429 $m^2 g^{-1}$) was also obtained from Nikki Chemical Co. Silica (Aerosil 300; 300 $m^2 g^{-1}$), alumina (γ-Al_2O_3; Soekawa Chemicals), and H-USY (Tosoh Co. HSZ-330HUA; Si/Al = 3.17:1; 626 $m^2 g^{-1}$) were used as supports. The products were confirmed by comparison with reported mass spectrometric and NMR spectroscopic data.

Preparation of the SA–NEt_2 surface: SA was pretreated at 393 K for 3 h under vacuum. SA (1.0 g) was added to a solution of 3-(diethylamino)-propyl trimethoxysilane (2 mmol) in toluene (20 mL). The reaction mixture was heated to reflux for 24 h. The solvent was removed by filtration, and the obtained functionalized SA was washed with dichloromethane, followed by drying under vacuum. Elemental analysis (%) of SA–NEt_2: C 8.40, H 2.16, N 1.27. Other supported amines (support–NR_2) were also prepared by using similar procedures. Elemental analysis (%) for SA–NH_2: C 6.41, H 1.99, N 1.57; SA(lower Al)–NEt_2: C 8.49, H 2.08, N 1.17; SiO_2–NEt_2: C 6.58, H 1.42, N 0.99; Al_2O_3–NEt_2: C 4.07, H 1.26, N 0.54; H-USY–NEt_2: C 7.38, H 2.19, N 0.63.

Cyano-ethoxycarbonylation using the SA–NEt_2 surface: SA–NEt_2 (0.038 g, 0.034 mmol), toluene (5 mL), ethyl cyanoformate (1.0 mmol), and benzaldehyde (0.5 mmol) were placed in a pyrex glass reactor. The resulting mixture was vigorously stirred at room temperature under N_2, and the catalyst was separated by filtration after 1 h. GC analysis of the filtrate showed 95 % yield of the addition product.

Michael reaction using the SA–NEt_2 surface: SA–NEt_2 (0.1 g, 0.091 mmol), toluene (1 mL), ethyl cyanoacetate (0.5 mmol), and methyl vinyl ketone (1.5 mmol) were placed in a pyrex glass reactor. The resulting mixture was vigorously stirred at 60 °C, and the catalyst was separated by filtration after 30 min. GC analysis of the filtrate showed a quantitative conversion of ethyl cyanoacetate and 90 % yield of the bisaddition product.

Nitro-aldol reaction using the SA–NH_2 surface: SA–NH_2 (0.0135 g, 0.015 mmol), nitromethane (2 mL), and benzaldehyde (5.0 mmol) were placed in a pyrex glass reactor. The resulting mixture was vigorously stirred at 100 °C, and the catalyst was separated by filtration after 6 h. GC analysis of the filtrate showed 99 % yield of the β-nitrostyrene product.

IR spectroscopic analysis: After exposure of the SA, SA–NEt_2, and SA–NH_2 surfaces to the substrates in toluene, the solid catalysts were filtered, dried under atmospheric pressure, and pressed into a disk with KBr.

Acknowledgement

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