DOI: 10.1002/chem.200701129

Noncovalently Supported Heterogeneous Chiral Amine Catalysts for Asymmetric Direct Aldol and Michael Addition Reactions

Sanzhong Luo,*[a] Jiuyuan Li,[a] Long Zhang,[b] Hui Xu,[a] and Jin-Pei Cheng*[b]

Abstract: A new strategy for the immobilization of asymmetric organocatalysts by combining polystyrene (PS)/sulfonic acids and chiral amines in situ through acid–base interactions is presented. The PS/sulfonic acids play a dual role as catalyst anchors and modulators for activity and stereoselectivity. Different types of polymeric sulfonic acids were examined and 1% divinylbenzene (DVB) cross-linked PS/sulfonic acid **1e** with a medium loading of sulfonic acid moieties was found to be the optimal support. Furthermore, the noncovalency of this system allows combinatorial screening of optimal catalysts for the targeted reactions. In this regard, highly efficient and enantioselective heterogeneous catalysts were identified for the asymmetric direct aldol and Michael addition reactions. The catalysts could be easily recovered by filtration and reused for six cycles with similar stereoselectivity but slightly decreased activity. Significantly, the deactivated catalysts could be regenerated following an acidic washing/amine recharging procedure.

Keywords: aldol reaction · heterogeneous catalysis · Michael addition · noncovalent immobilization · organocatalysis

Introduction

Organocatalysis is increasingly recognized as the third important kind of asymmetric catalysis, thus complementing the well-established asymmetric transition-metal and enzyme catalysis processes.[1] Unlike transition-metal catalysts, organocatalysts typically do not use metals, therefore giving them greater potential in pharmaceutical processes in which metal contaminations are problematic. Furthermore, organocatalysts are also much cheaper and easier to handle than their transition-metal and enzyme counterparts. These properties have propelled the explosive development of organocatalysts for a wide variety of fundamental transformations.[1] However, organocatalysis has also been considered to be of low efficiency as a result of the high catalyst loadings and the difficulties in catalyst separation and recycling. The heterogenization of organocatalysts may provide potential solutions to these challenges.[2] Indeed, this strategy has been attempted for organocatalysts ever since their debut in similar ways to the heterogenization of homogeneous transition-metal catalysts and enzymes.[2,3] In this regard, heterogenization is commonly achieved by covalent attachment to solid supports such as PS, poly(ethylene glycol) (PEG), dendrimers, and inorganic materials (Figure 1, **I**).[4] However, the heterogeneous organocatalysts obtained in these cases have the disadvantages that 1) the catalysts are less effective than their nonsupported homogeneous counterparts; 2) as a result of being less effective, high loading (both w/w% and mol%) of the catalysts is normally employed to achieve reasonable yields; and 3) multiple synthetic manipulations are required to achieve the covalent immobilizations.

For the reason of practicality, the noncovalent immobilization of homogeneous catalysts is highly desirable since modifications of the parent catalysts are generally minimized and the strategy is also quite facile and modular, thus allowing fine-tuning of the support structure and the homogeneous catalyst and their combination.[5] Accordingly, noncovalently supported organocatalysts have been developed through physical adsorption (Figure 1, **II**)[6] and biphasic technology (Figure 1, **III**).[7] Although high activities and ex-

[a] Prof. Dr. S. Luo, J. Li, H. Xu
Beijing National Laboratory for Molecular Sciences
Center for Chemical Biology
Institute of Chemistry and Graduate School
Chinese Academy of Sciences, Beijing, 100080 (China)
Fax: (+86) 10-6255-4449
E-mail: luosz@iccas.ac.cn

[b] L. Zhang, Prof. Dr. J.-P. Cheng
Department of Chemistry and State Key Laboratory of Elemento-organic Chemistry
Nankai University, Tianjin, 300071 (China)
Fax: (+86)
E-mail: chengjp@mail.most.gov.cn

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

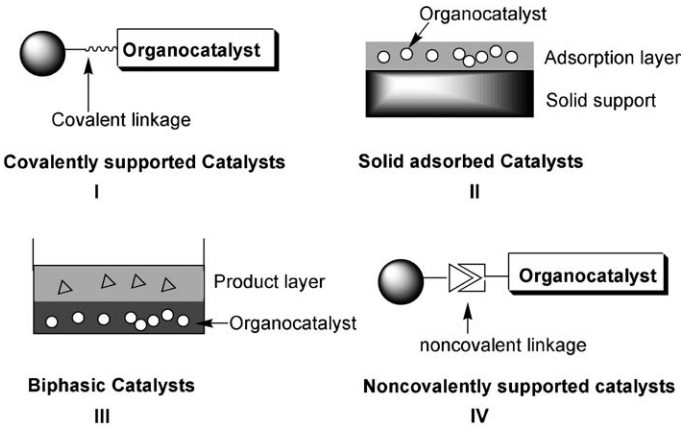
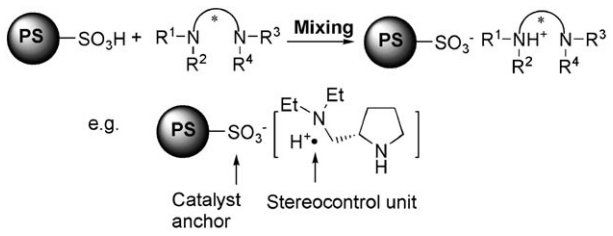


Figure 1. Current immobilization strategies (I–III) for organocatalysts and our noncovalent strategy (IV).

cellent enantioselectivities were achieved in some of these examples,[8] the issue of catalyst recycling and reuse still remains to be addressed. A noncovalent linkage of reasonable strength should solve these problems.

Herein, we present a new strategy for noncovalent immobilization through acid–base interactions (Figure 1, **IV**). Our immobilization strategy employs readily available chiral diamines and solid acids, such as PS/sulfonic acids. The immobilization is simply carried out by mixing the two reagents together without any pretreatment and additional modification to the parent catalyst. The resultant acid–base linkage, that is, electrostatic interaction through ion pairs, would suffice for good recyclability and reusability as a result of the reasonably high strength of the linkage. In fact, a similar strategy of noncovalently attaching transition-metal catalysts onto solid supports has been previously well explored with good activity and reusability.[9] Recently, an acid–base strategy was applied to immobilize ruthenium cross-metathesis catalysts, thus leading to enhanced activity.[10] Our design herein is distinct from these previous reports as a result of the dual functions of the solid-acid supports: first, they act as an anchor for the chiral diamines and second they act as a critical modulator for the catalytic activity and stereoselectivity (Scheme 1). We report herein the development of noncovalently supported chiral amine catalysts as asymmetric heterogeneous organocatalysts for asymmetric direct aldol and Michael addition reactions.



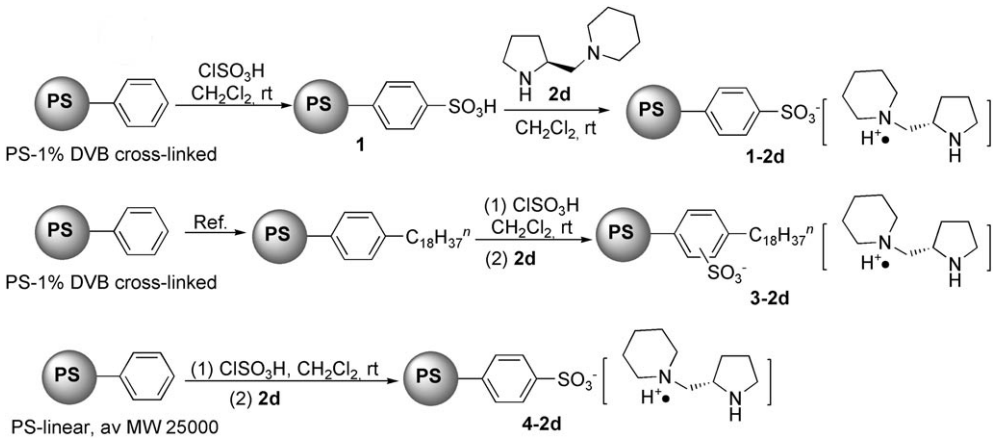
Scheme 1. Immobilization strategy through acid–base interactions.

Results and Discussion

Design principle for the immobilization of chiral amines: Chiral amines are a recent focus in research into organocatalysis because of their divergent nature, which results in the formation of either nucleophilic enamines or electrophilic imminium ions, and their structural modifiability to ease the discovery of diversity-oriented catalysts.[11] The immobilization of the chiral amine catalysts normally requires additional manipulations with the original or newly installed functional groups. These procedures are somewhat tedious and also introduce marked perturbations to the original small molecular skeletons, consequently leading to varied catalytic outcomes.[2] The acid–base assembly of chiral amines has proven to be one of the most efficient bifunctional enamine catalysts.[12] The acids used in these cases were essential units that dramatically impacted the catalytic activity and stereoselectivity.[13] Taking advantage of this strategy, we developed a noncovalent immobilization strategy by utilizing solid acids (Scheme 1). Besides their similar roles to homogeneous acids, the acidic units in the solid acids also serve as anchors for the chiral amines, thus resulting in heterogeneous acid/chiral amine assemblies that may work as asymmetric heterogeneous enamine-type organocatalysts. Although the structure and acidity of the solid acids and the nature of the chiral diamines are key issues that relate to the performance of the obtained heterogeneous catalysts, the modular and combinatorial features of the current strategy should provide a great opportunity to find optimal catalysts for the reactions studied.

Construction of heterogeneous chiral amine catalysts: We started with PS as our selected solid support since PS is frequently employed in solid-supported organic synthesis and catalysis.[14] With commercially available PS (1% divinylbenzene (DVB) cross-linked, 200–400 mesh), the corresponding PS/sulfonic acids **1** were obtained by simple treatment with chlorosulfonic acid (Scheme 2). The loading of the acid units could be adjusted by using different quantities of chlorosulfonic acid (Table 1). PS/sulfonic acids with hydrophobic groups and linear PS/sulfonic acids were prepared using similar procedures.

Some representative chiral diamines are shown in Scheme 3. To illustrate the synthesis of the supported catalysts, chiral diamine **2d** was selected as a model catalyst. The PS/sulfonic acids were treated with approximately 1.2 equivalents of **2d** in CH_2Cl_2, the reaction mixture was then filtered and washed with CH_2Cl_2 and ethanol. The final PS/sulfonic acid/**2d** hybrids are insoluble in most organic solvents and readily obtained by filtration. An exception was observed with PS/sulfonic acid **1f**, which has a high loading of sulfonic acid (2.75 mmol g^{-1}). In this case, the high density of chiral amine **2d** dramatically changed the physical properties of the resultant hybrid solid, thus making the filtration difficult and excluding its further application in heterogeneous applications (see below). The content of **2d** in the supported catalysts was determined by ele-

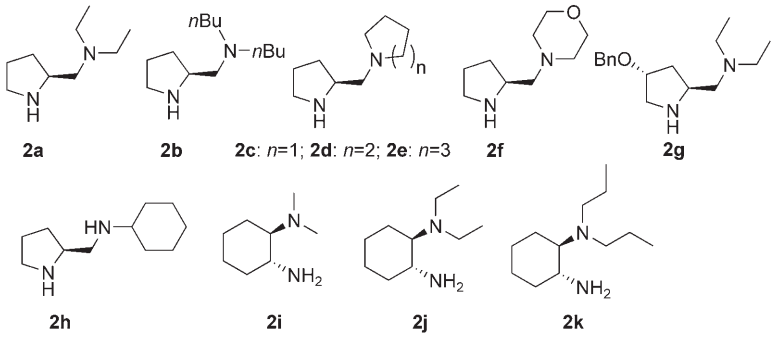


Scheme 2. Synthesis of PS/sulfonic acids and their chiral amine hybrids.

Table 1. Elemental analysis of the supported chiral amines.

PS/sulfonic acids	Loading of SO_3H [mmol g]$^{-1}$	Loading of **2d** [mmol g]$^{-1}$	
		calculated	determined
1a	0.31	0.29	0.29
1b	0.60	0.55	0.55
1c	1.05	0.91	0.90
1d	1.19	1.02	1.00
1e	1.39	1.11	1.09
1f	2.75	n.d.[a]	n.d.
3a	0.31	0.30	0.30
3b	0.54	0.50	0.50
3c	0.85	0.76	0.75
4	0.95	0.84	0.90

[a] n.d. = not determined.



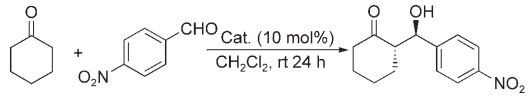
Scheme 3. Library of selected chiral diamines.

mental analysis. The loading of **2d** was in good agreement with calculated data based on the loading of the sulfonic acid (Table 1), except in the case of linear PS/sulfonic acid **4**, in which a slightly higher loading than expected was observed, probably because of the cross-linking between the linear polymeric acids with the diamine **2d**. These results suggest that the active sites in the DVB cross-linked PS/sulfonic acids (**1** and **3**) were fully accessible.

Heterogeneous chiral amine catalysts for the asymmetric direct aldol reaction: The asymmetric direct aldol reaction was selected as a benchmark for testing our noncovalently supported catalysts. The direct aldol reaction is one of the most extensively explored organocatalytic enamine-based transformations catalyzed by chiral amines.[15] Although a number of solid-supported chiral amine catalysts have been developed for these reactions, only a few of them have shown good stereoselectivity under heterogeneous conditions.[4n] The chiral amine **2d** supported on PS/sulfonic acids was submitted to the model reaction of cyclohexanone and *para*-nitrobenzaldehyde. To our delight, the reaction proceeded smoothly in the presence of 10 mol% of supported chiral amine **2d** (Table 2). Both the activity and stereoselectivity demonstrated clear dependence on the loading of **2d** on the polymer (Table 2). The catalyst **1e**/**2d** with a medium loading of 1.09 mmol g^{-1} gave the best enantioselectivity (Table 2, entry 5). In contrast, either a lower or higher loading led to inferior results in terms of activity and enantioselectivity (Table 2, entries 1–4). The catalyst with a high loading of 2.75 mmol g^{-1} was totally inactive (Table 2, entry 7). Other types of PS/sulfonic acids, such as **3** appended with a long alkyl chain and linear **4**, gave poor results (Table 2, entries 8–11). Notably, the catalysis of **1e**/**2d** could be significantly accelerated using much less solvent (Table 1, entry 6 versus 5). Based on these results, PS/sulfonic acid **1e** was selected as our optimal support for further development.

The solvent effect was briefly examined with **1e**/**2d** as a representative catalyst (Table 3). As is well known, the swelling of a polymer resin has a significant influence on the corresponding supported catalyst.[14a] While the reactions showed consistently high activities in all the solvents examined, there was an obvious solvent effect on the stereoselec-

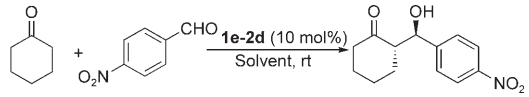
Table 2. The effect of catalyst loading in asymmetric direct aldol reactions.



Entry[a]	Cat. (10 mol%)	Loading [mmol g^{-1}]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d] *anti*/*syn*
1	**1a**/**2d**	0.29	46	89:11	55:78
2	**1b**/**2d**	0.55	65	86:14	55:53
3	**1c**/**2d**	0.90	75	81:19	40:58
4	**1d**/**2d**	1.00	63	84:16	46:51
5	**1e**/**2d**	1.09	51	84:16	62:83
6[e]	**1e**/**2d**	1.09	97	80:20	75:63
7[f]	**1f**/**2d**	2.75	trace	n.d.	n.d.
8	**3a**/**2d**	0.30	54	64:36	3:58
9	**3b**/**2d**	0.50	59	70:30	3:64
10	**3c**/**2d**	0.75	44	74:26	9:66
11	**4**/**2d**	0.90	trace	n.d.	n.d.

[a] Reactions conditions: aldehyde = 0.25 mmol, cyclohexanone = 1.0 mmol, CH_2Cl_2 = 500 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC. [e] The reaction was carried out in CH_2Cl_2 (100 μL) over 12 h. [f] The catalyst was prepared in situ.

Table 3. Solvent effect in asymmetric direct aldol reactions catalyzed by **1e**/**2d**.



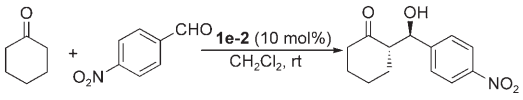
Entry[a]	Solvent	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d] *anti*/*syn*
1	dioxane	12	98	78:22	50:60
2	toluene	12	94	80:20	59:66
3	methanol	12	97	62:38	41:56
4	THF	12	95	79:21	54:62
5	CH_2Cl_2	12	97	80:20	75:63
6	CH_3CN	12	95	84:16	55:65
7	ethyl acetate	12	98	76:24	40:42.
8	$CHCl_3$	12	97	83:17	54:57
9	H_2O	12	97	79:21	62:45
10	neat	6	97	80:20	55:41

[a] Reactions conditions: aldehyde = 0.25 mmol, cyclohexanone = 1.0 mmol, solvent = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC.

tivity. The best enantioselectivity (75% *ee* for the major *anti* isomer) was achieved in CH_2Cl_2 (Table 3, entry 5). A control reaction was carried out in the presence of *para*-toluenesulfonic acid instead of the polymeric sulfonic acid **1e** with an enantiomeric excess of 54% *ee* being obtained for the major *anti* isomer (*anti*/*syn* = 74:26), thus highlighting the importance of the role of the polymeric acid on enantioselectivity.

To further improve the stereoselectivity, two strategies were applicable: The first was to increase the acidity of the polymeric acids; previous studies have shown that the combination of stronger acids with chiral diamines, such as **2d**, give a better stereoselectivity.[13a,16] The second strategy was to screen a library of chiral amines. Since libraries of chiral amines were readily available to us, the latter strategy was followed. For convenience, the supported chiral amine catalysts were prepared in situ by simply mixing **1e** and chiral diamines **2** in 1:1 molar ratio. A quick screening identified primary/tertiary diamines **2i** and **2k** as promising candidates. We previously showed that this type of diamine combined with a Brønsted acid was a highly effective enantioselective catalyst for direct aldol reactions.[13f] In the presence of 10 mol% of **1e**/**2k**, the product was obtained in 95% yield with 95:5 d.r. and 94% *ee* over 19 h (Table 4, entry 8). The

Table 4. Screening of chiral amines **2**.



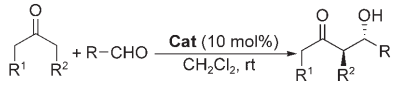
Entry[a]	Chiral amine	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d] *anti*/*syn*
1	**2a**	12	97	79:21	46:52
2	**2b**	12	58	83:17	52:39
3	**2c**	12	95	64:36	60:73
4	**2d**	12	97	72:28	75:63
5	**2h**	12	17	78:22	85:69
6	**2i**	24	97	91:9	97:57[e]
7	**2j**	24	92	90:10	94:80[e]
8	**2k**	19	95	95:5	94:14[e]

[a] Reactions conditions: aldehyde = 0.25 mmol, cyclohexanone = 1.0 mmol, CH_2Cl_2 = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC. [e] The products had a 1′*S*,2*R* configuration, which is opposite to the products in the catalysis of **2a**/**2h** (as shown above).

reaction with **2i** provided equally good results (Table 4, entry 6) and these two chiral diamines were thus selected for further investigation. To the best of our knowledge, these represent the first examples of supported chiral primary amine catalysts.

With the identified optimal catalysts, the major concerns were then their recyclability, reusability, and applicability. The supported catalysts **1e**/**2i** and **1e**/**2k** had shown that they were suitable for a range of ketone donors and aldehyde acceptors (Table 5). In all the cases examined, the reactions demonstrated reasonably high activity and the products were afforded in up to 99% yield with 96:4 d.r. and 99% *ee*. Catalyst **1e**/**2k** provided a better diastereoselectivity than catalyst **1e**/**2i** in several cases (Table 5, entries 5, 7, 9, 11, and 13). The recyclability and reusability of catalyst **1e**/**2i** was examined in the model reaction of cyclohexanone and *para*-nitrobenzaldehyde (Table 6). On completion of the reaction, the catalyst was simply filtered off and washed with diethyl ether. The dried catalyst was then subjected to the next run. The thus-recycled catalyst showed unchanged activity and stereoselectivity in the first three rounds of reuse. Decreased activity was observed in the subsequent fourth and fifth rounds of reuse, but the stereoselectivity was essentially maintained (Table 6, entries 4 and 5). Significantly, the deactivated catalyst could be reactivated by washing with HCl/dioxane and recharging with chiral diamine **2i**. The activity was recovered to the same level as the

Table 5. Applications of catalysts **1e/2i** and **1e/2k** in asymmetric direct aldol reactions.



Entry[a]	R^1, R^2	R	Cat.	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	 **5**	4-NO_2Ph	**1e/2i**	24	97	91:9	97
2	**5**	3-NO_2Ph	**1e/2i**	19	95	91:9	99
3	**5**	2-NO_2Ph	**1e/2i**	22	97	96:4	96
4	**5**	4-CF_3Ph	**1e/2i**	40	99	83:17	95
5	**5**	4-CF_3Ph	**1e/2k**	30	97	93:7	96
6	**5**	4-CNPh	**1e/2i**	19	98	81:19	94
7	**5**	4-CNPh	**1e/2k**	24	97	93:7	95
8	**5**	4-ClPh	**1e/2i**	96	90	77:23	89
9	**5**	4-ClPh	**1e/2k**	96	89	92:8	91
10	**5**	Ph	**1e/2i**	96	86	68:32	90
11	**5**	Ph	**1e/2k**	96	48	81:19	94
12	**5**	1-naph	**1e/2i**	48	67	78:22	89
13	**5**	1-naph	**1e/2k**	72	60	85:15	95
14	 **6**	2-NO_2Ph	**1e/2i**	20	91	68:32	94
15	H, H (**7**)	4-NO_2Ph	**1e/2i**	60	83	–	76
16	**7**	3-NO_2Ph	**1e/2k**	72	88	–	83
17	**7**	2-NO_2Ph	**1e/2k**	72	80	–	81
18	**7**	4-CF_3Ph	**1e/2k**	72	87	–	77
19	**7**	4-CNPh	**1e/2k**	72	88	–	77
20	**7**	3-BrPh	**1e/2k**	72	72	–	77
21	**7**	2-ClPh	**1e/2k**	72	82	–	83

[a] Reactions conditions: aldehyde = 0.25 mmol, ketone = 1.0 mmol, CH_2Cl_2 = 100 μL; entries 15–21: reaction in neat acetone (200 μL). [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC. 1-naph = 1-naphthalene.

Table 6. Recycle and reuse of **1e/2i** in the reaction of cyclohexanone with *para*-nitrobenzaldehyde.

Entry[a]	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d] *anti*/*syn*
1	24	97	91:9	97:57
2	24	97	89:11	97:60
3	26	98	88:12	97:66
4	34	95	92:8	98:67
5	48	53	92:8	96:20
6[e]	24	92	86:14	89:26

[a] Reactions conditions: aldehyde = 0.25 mmol, cyclohexanone = 1.0 mmol, CH_2Cl_2 = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC. [e] The catalyst was reactivated.

fresh catalyst; however, the enantioselectivity was decreased slightly (Table 6, entry 6).

To probe the heterogeneous nature of the noncovalently supported catalysts, the model reaction of cyclohexanone and *para*-nitrobenzaldehyde was allowed to carry on until approximately 50% conversion was reached. The catalyst **1e/2i** was then filtered off. The reaction in the homogeneous filtrate was monitored by ^{1}H NMR spectroscopic analysis, which showed less than 3% conversion over 24 h after filtration of the catalyst (Figure 2). This behavior suggests homogeneous catalysis arising from the dissociated chiral amine was insignificant and the reaction mainly occurred under heterogeneous conditions.

Heterogeneous chiral amine catalysts for an asymmetric Michael reaction: The Michael reaction is one of the basic C–C bond-forming reactions, and its versatile utility in organic synthesis has stimulated tremendous research interest in the development of asymmetric Michael catalysts, especially metal-free organocatalysts.[17] To address the issue of catalyst recycling and reuse, the use of several supported chiral amines has been explored for asymmetric Michael additions to nitroolefins. Using biphasic technology, recyclable chiral amine catalysts supported by a fluorous phase[7j,k] and dendrimers[4t] were developed for the asymmetric Michael addition of aldehydes to nitrostyrenes. The catalysts offered high enantioselectivity but limited reusability. PEG-supported chiral amines were also tried for the Michael addition of ketones, but showed poor stereoselectivity.[4e,18] Previously, we developed functionalized chiral ionic liquids (FCILs) as new types of recyclable and reusable small-molecular catalysts

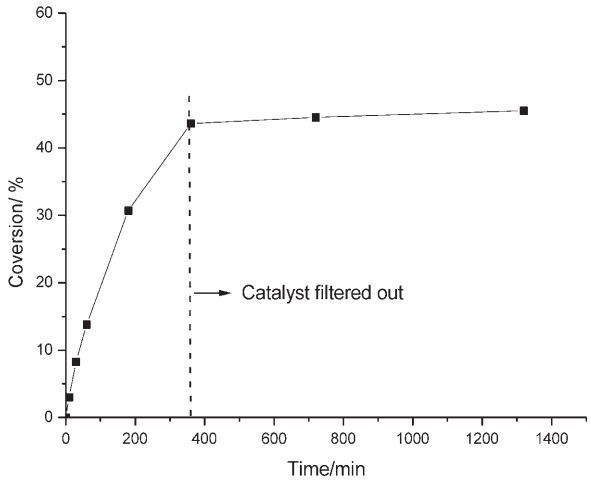
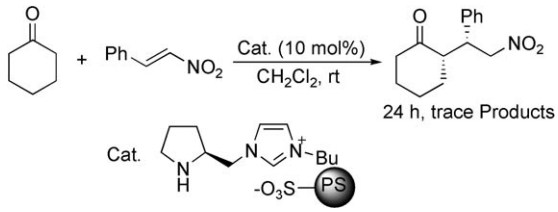


Figure 2. Reaction progress before and after filtration of the catalysts **1e/2i**.

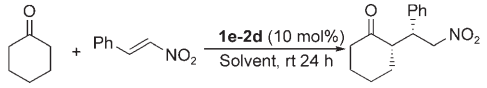
for asymmetric Michael additions to nitroolefins.[8a] The FCILs catalyzed the reaction in high yields and with excellent stereoselectivity, could be recycled by precipitation with diethyl ether and could be reused for four times. To further enhance their recyclability, heterogeneous FCILs were prepared by noncovalent immobilization through ion pairing using a PS/sulfonic anion. Unfortunately, the heterogeneous FCILs were nearly inactive for the catalysis of the same reaction (Scheme 4).



Scheme 4. Heterogeneous FCIL-catalyzed asymmetric Michael addition.

We then tested noncovalently supported chiral amine catalysts in Michael addition reactions. To our delight, this type of catalyst could effectively catalyze the Michael additions. In the catalytic processes using **1e**/**2d**, the reactions proceeded smoothly in organic solvents, but hardly occurred under neat conditions (Table 7, entry 1). The reactions in

Table 7. Solvent effect in asymmetric Michael addition reactions catalyzed by **1e**/**2d**.

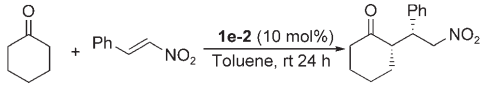


Entry[a]	Solvent	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	neat	trace	–	–
2	toluene	81	94:6	83
3	methanol	85	91:9	85
4	THF	77	93:7	78
5	CH_2Cl_2	67	96:4	84
6	CH_3CN	74	93:7	80
7	ethyl acetate	66	94:6	85
8	$CHCl_3$	73	95:5	84

[a] Reaction conditions: nitrostyrene = 0.25 mmol, cyclohexanone = 1.0 mmol, solvent = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC.

methanol and toluene produced the best results in terms of both activity and stereoselectivity (Table 7, entries 2 and 3). Toluene was selected for further experiments to balance activity and stereoselectivity. A small library of chiral amines was then evaluated in the noncovalently supported catalytic systems (Table 8), and chiral diamine **2e** was found to be an optimal choice (Table 8, entry 5). With 10 mol% of **1e**/**2e**, the product was obtained in 94% yield with 94:6 d.r. and 87% *ee* over 24 h. These results showed significant improvement in activity relative to the nonsupported catalyst **2e** (20 mol% of **2d**, 22 h, 93% yield).[17z] Finally, chiral primary

Table 8. Screening of chiral amines **2** in the Michael addition reaction.



Entry[a]	Chiral amine	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**2a**	24	77	94:6	82
2	**2b**	24	84	94:6	88
3	**2c**	24	89	94:6	87
4	**2d**	24	81	94:6	83
5	**2e**	24	94	94:6	87
6	**2f**	48	30	89:11	81
7	**2g**	48	30	86:14	67
8	**2h**	48	56	92:8	85

[a] Reaction conditions: nitrostyrene = 0.25 mmol, cyclohexanone = 1.0 mmol, CH_2Cl_2 = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC.

amines such as **2i**–**2k** were also examined but were found to be ineffective for the catalysis of the Michael addition reactions.

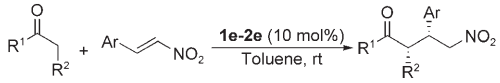
With the optimal catalyst **1e**/**2e**, we investigated the heterogeneous catalysis of the Michael addition reaction of a wide range of Michael donors and nitrostyrenes. The reaction proceeded well with cyclohexanone. In all cases, the desired Michael adducts were obtained in good diastereo- and enantioselectivities (up to 96:4 d.r. and 90% *ee*, respectively). Moreover, the reactions tolerated a variety of nitrostyrenes possessing either electron-withdrawing or -donating substitutents and various substitution patterns (*para*-, *meta*-, *ortho*-, and bis-). Cyclopentanone and acetone were also tested under these conditions, but low yields and poor stereoselectivity were obtained (Table 9, entries 13 and 14). The heterogeneous catalyst **1e**/**2e** also worked with aldehyde donors, such as isobutyraldehyde, thus affording 69% yield and 83% *ee* in 36 hours.

To investigate the heterogeneous nature of the Michael addition reactions, the supernatant of **1e**/**2e** in the model reaction (as shown in Table 10) at approximately 50% conversion was monitored by ^{1}H NMR spectroscopic analysis. There was approximate 10% further conversion observed over 10 h, thus suggesting the leaching of chiral amine **2e**. This leaching could be diminished by diluting the reaction mixture with hexane or diethyl ether before filtration. Following this procedure, we found the catalyst could be reused for six cycles, thus maintaining the same activity as the first three cycles (Table 10). A significant decrease in activity was only observed in the sixth cycle. At this stage, the catalyst could be reactivated by washing with HCl/dioxane and recharging with fresh **2e** (Table 10, entry 7), again highlighting the advantages of noncovalent immobilization.

Conclusion

We have developed a new and very facile approach for the development of heterogeneous asymmetric organocatalysts

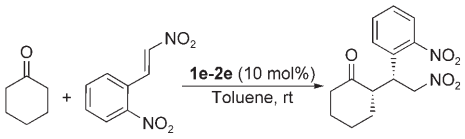
Table 9. Applications of catalysts **1e**/**2e** in asymmetric Michael addition reactions.



Entry[a]	R^1, R^2	Ar	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	 **5**	Ph	24	94	94:6	87
2	**5**	4-MeOPh	24	97	94:6	82
3	**5**	1-naph	24	97	95:5	89
4	**5**	4-MePh	30	91	95:5	89
5	**5**	4-PhPh	30	88	96:4	80
6	**5**	4-ClPh	20	56	94:6	88
7	**5**	4-NO_2Ph	8	80	96:4	88
8	**5**	2-NO_2Ph	6	95	95:5	84
9	**5**	3-NO_2Ph	12	77	95:5	90
10	**5**	2-ClPh	15	96	95:5	89
11	**5**	piperal	24	70	93:7	68
12	**5**	2,4,-$(MeO)_2$Ph	24	78	94:6	87
13	 **6**	Ph	24	39	70:30	62
14	Me,H **7**	Ph	36	21	–	20
15	isobutyraldehyde **8**	Ph	36	69	–	83

[a] Reactions conditions: nitrostyrene = 0.25 mmol, ketone = 1.0 mmol, toluene = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC.

Table 10. Recycle and reuse of **1e**/**2e** in asymmetric Michael additions.



Entry[a]	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	6	95	95:5	84
2	6	98	95:5	83
3	6	91	96:4	84
4	10	93	95:5	84
5	13	89	95:5	81
6	21	77	94:6	80
7 [e]	6	89	95:5	81

[a] Reaction conditions: nitrostyrene = 0.25 mmol, ketone = 1.0 mmol, toluene = 100 μL. [b] Yield of the isolated products. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral HPLC. [e] The catalyst was reactivated.

through the complexation of PS/sulfonic acids and chiral amines in situ through acid–base interactions. PS/sulfonic acids were shown to not only act as the anchor for the catalyst, but they also played critical roles in affecting the catalytic activity and stereoselectivity. The structure and the density of the sulfonic acid groups were found to have a marked impact on the performance of the supported catalysts. PS/sulfonic acid **1e** with 1% DVB cross-linking and a medium loading of sulfonic acid was identified as the optimal support. Furthermore, the noncovalent feature allowed for combinatorial screening of the desired heterogeneous asymmetric organocatalysts for the targeted reactions. In this regard, **1e**/**2i** and **1e**/**2e** were identified from a library of readily available chiral amines as the optimal catalysts for asymmetric direct aldol and Michael addition reactions, respectively. These catalysts demonstrated comparable or even better activity and stereoselectivity than their nonsupported homogeneous catalyst counterparts.

The heterogeneous nature of the noncovalently supported catalysts facilitates easy recycling of the catalysts through filtration; furthermore, the catalysts could be reused six times with similar stereoselectivity, although slightly decreased activity. Significantly, the recycled catalysts could be reactivated following an acidic washing/recharging procedure. Overall, the noncovalency of our heterogenization strategy enables simple catalyst preparation, combinatorial screening, and facile catalyst reuse and reactivation. Since many kinds of solid acids, such as sulfonated PSs, are commercially available, this strategy may thus provide a new solution to the development of recoverable and reusable asymmetric organocatalysts.[19] Ongoing investigations include the design of heterogeneous acids with enhanced acidity,[16] applications to other organocatalytic transformations, and the development of a flow catalytic system.

Experimental Section

General methods: Commercial reagents were used as received, unless otherwise indicated. Visualization of the developed chromatograms was performed by fluorescence quenching or staining with $KMnO_4$ and *para*-anisaldehyde. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 300-MHz spectrometer at 25 °C and the chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The IR spectra were recorded on a FT-IR instrument and are reported in cm^{-1}. HPLC analysis was performed using Chiralcel AD-H, OD-H, AS-H, and OJ-H columns. The absolute configurations were determined by correlation to reported results. Elemental analysis was obtained from ThermoQuest. Polystyrene (1% DVB cross-linked) and linear polystyrene (MW = 25000) were commercial available (Acros). Polystyrene appended with long alkyl chains was synthesized following a reported procedure.[20]

Typical procedure for the synthesis of PS/sulfonic acid 1e: PS-supported sulfonic acid was synthesized according to a reported procedure with

minor modifications:[19] Chlorosulfonic acid (0.4 mL) was slowly added to a suspension of PS (3.0 g, 1% DVB cross-linked, 200–400 mesh) in CH_2Cl_2 (60 mL) at 0 °C, and the reaction mixture was stirred for 6 h. THF/water (5:1, 60 mL) was added and after 1 h the resin was collected on a glass filter, rinsed with water (3×50 mL), THF/water (5:1, 3× 50 mL), and dichloromethane (3×50 mL) and then dried under vacuum to give resin **1e**. From the result of elemental analysis (%) found: S 4.44; thus, the sulfonic acid content was estimated to be 1.39 mmol g^{-1}.

Typical procedure for the synthesis of catalyst 1e/2d: PS/sulfonic acid **1e** (1.0 g, 1.39 mmol) was suspended in CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 15 min at room temperature. Chiral amine **2d** (280 mg, 1.8 mmol) was then added and the resultant mixture was stirred for 2 h at room temperature. The catalyst was separated by filtration and washed sequentially with CH_2Cl_2, ethanol, and CH_2Cl_2. The solid was dried in vacuo at room temperature over night to give **1e/2d** in quantitative yield. Elemental analysis (%) found: N 3.05, equal to 1.09 mmol g^{-1} of **2d**; IR (KBr): $\tilde{\nu}$ = 3446, 3026, 2922, 2777, 2472, 1945, 1630, 1489, 1447, 1382, 1116, 835, 758, 696, 541 cm^{-1}.

The other catalysts were prepared using similar procedures.

Catalyst 1e/2e: Elemental analysis (%) found: N 3.06, therefore the loading of **2e** was estimated to be 1.09 mmol g^{-1}; IR (KBr): $\tilde{\nu}$ = 3445, 3026, 2920, 1946, 1631, 1488, 1448, 1380, 1116, 834, 757, 696, 544 cm^{-1}.

Catalyst 1e/2i: Elemental analysis (%) found: N 3.08, therefore the loading of **2i** was estimated to be 1.10 mmol g^{-1}. IR (KBr): $\tilde{\nu}$ = 3442, 3027, 2921, 1947, 1634, 1488, 1449, 1380, 1164, 1116, 834, 756, 695, 537 cm^{-1}.

Catalyst 1e/2k: Elemental analysis (%) found: N 3.06, therefore the loading of **2k** was estimated to be 1.09 mmol g^{-1}; IR (KBr): $\tilde{\nu}$ = 3441, 3027, 2922, 1947, 1631, 1487, 1449, 1381, 1160, 1115, 834, 756, 696, 538 cm^{-1}.

Typical procedure for the asymmetric direct aldol reaction: Catalyst **1e/2i** (22 mg, 0.025 mmol) was added to a solution of cyclohexanone (0.1 mL) in CH_2Cl_2 (0.1 mL). The heterogeneous solution was stirred for 10 min and then 4-nitrobenzaldehyde (38 mg, 0.25 mmol) was added. The resulting mixture was stirred at room temperature until no 4-nitrobenzaldehyde could be detected. The catalyst was filtered and washed with diethyl ether (3×5 mL). The catalyst could be directly used after removing the residue volatile under vacuum. The organic portions were combined and concentrated. The residue was purified by column chromatography on silica gel to afford the desired product (61 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32–1.46 (1H, m), 1.46–1.76 (2H, m), 1.76–1.91 (1H, m), 2.04–2.19 (1H, m), 2.28–2.44 (1H, m), 2.44–2.72 (2H, m), 4.00–4.16 (1H, d, J = 3.0 Hz), 4.81–4.03 (1H, dd, J = 3.0, 3.2 Hz, 8.3 Hz), 7.43–7.67 (2H, m), 8.10–8.37 (2H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.7, 27.6, 30.7, 42.6, 57.1, 74.0, 123.5, 127.8, 147.6, 148.3, 214.6 ppm; the enantiomeric excess was determined by HPLC on an AD-H column at 254 nm (2-propanol/hexane 20:80), 25 °C, 0.5 mL min^{-1}; t_R = 22.44 (major), t_R = 28.60 (minor).

All the aldol products in Table 5 are known products.[4r,13]

Typical procedure for asymmetric Michael reaction: Catalysts **1e/2d** (22 mg, 0.025 mmol) were added to a solution of cyclohexanone (0.1 mL) in toluene (0.1 mL). The heterogeneous mixture was stirred for 10 min and β-nitrostyrene (37 mg, 0.25 mmol) was added. The resultant mixture was stirred at room temperature until no β-nitrostyrene could be detected. Ethyl ether was then added to the reaction mixture. The product layer was separated and the catalyst was washed with diethyl ether (3× 5 mL). The catalyst could be used directly after removing the residue volatile under vacuum. The organic portions were combined and concentrated. The residue was purified by column chromatography on silica gel to afford the desired product (58 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.26 (1H, m), 1.16–1.74 (4H, m), 2.13–2.16 (1H, m), 2.37–2.47 (2H, m), 2.68–2.70 (1H, m), 3.72–3.79 (1H, m), 4.59–4.66 (1H, dd), 4.91–4.96 (1H, dd), 7.15–7.35 (5H, m) ppm; the enantiomeric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol/hexane 10:90), 25 °C, 0.5 mL min^{-1}; t_R = 20.86 (minor), t_R = 25.47 (major).

All the Michael adducts are known products.[17,21]

Typical procedure for the reactivation of catalysts 1e/2i: The deactivated catalyst (0.025 mmol) was treated with 1 M HCl/dioxane (1 mL). The result mixture was stirred for 5 min at room temperature. The solid catalyst was separated and washed sequentially with methanol and ethyl ether (3×5 mL). The obtained solid was resuspended in CH_2Cl_2 (0.5 mL) and **2i** (4.0 mg, 0.028 mmol) was added. The reaction mixture was then stirred for 1 h. The solid was separated and washed with CH_2Cl_2 and diethyl ether. After removing the residue solvent under vacuum, the solid was used directly in the catalytic reactions.

Acknowledgements

This study was supported by the Natural Science Foundation of China (NSFC 20421202, 20632060, and 20542007), the Ministry of Science and Technology (MoST), and the Chinese Academy of Sciences.

[1] For selected reviews of organocatalysis, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) A. Berkessel, H. Groger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; c) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; d) B. List, J. W. Yang, *Science* **2006**, *313*, 1584–1585.

[2] For comprehensive reviews, see: a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429; b) M. Benaglia, *New J. Chem.* **2006**, *30*, 1525–1533; c) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367–1390.

[3] For a monograph on supported asymmetric catalysts, see: a) *Chiral Catalyst Immobilization and Recycling* (Eds.: D. E. De Vos, I. F. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; for recent reviews on supported asymmetric catalysts, see: b) C. E. Song, S. Lee, *Chem. Rev.* **2002**, *102*, 3495–3524; c) Q. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385 –3466; d) D. E. De Vos, M. Dams, B. F. Sels, P. A. Jacobs, *Chem. Rev.* **2002**, *102*, 3615 –3640; e) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217–3274; f) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; g) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850–4881; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732–4762.

[4] For recent examples, see: a) R. Annunziata, M. Benaglia, F. Cozzi, G. Tocco, *Org. Lett.* **2000**, *2*, 1737–1739; b) M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171–173; c) M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149–152; d) M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2002**, *344*, 533–542; e) M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *J. Mol. Catal. A* **2003**, *204*, 157–163; f) G. Pozzi, M. Cavazzini, S. Quici, M. Benaglia, G. Dell′Anna, *Org. Lett.* **2004**, *6*, 441–443; g) A. Puglisi, M. Benaglia, M. Cinquini, F. Cozzi, G. Celentano, *Eur. J. Org. Chem.* **2004**, 567–573; h) S. A. Selkala, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941–945; i) C. Ogawa, M. Sugiura, S. Kobayashi, *Chem. Commun.* **2003**, 192–193; j) H. S. Kim, Y. M. Song, J. S. Choi, J. W. Yang, H. Han, *Tetrahedron* **2004**, *60*, 12051–12057; k) M. R. M. Andreae, A. P. Davis, *Tetrahedron: Asymmetry* **2005**, *16*, 2487–2492; l) K. Akagawa, S. Sakamoto, K. Kudo, *Tetrahedron Lett.* **2005**, *46*, 8185–8187; m) J. D. Revell, D. Gantenbein, P. Krattiger, H. Wennemers, *Biopolymers* **2006**, *84*, 105–113; n) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655; o) Y. Zhang, L. Zhao, S. S. Lee, J. Y. Ying, *Adv. Synth. Catal.* **2006**, *348*, 2027–2032; p) F. Giacalone, M. Gruttadauria, A. M. Marculescu, R. Noto, *Tetrahedron Lett.* **2007**, *48*, 255–259; q) L. Gu, Y. Wu, Y. Zhang, G. Zhao, *J. Mol. Catal. A* **2007**, *263*, 186–194; r) Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417–4420; s) X. Liu, Y. Li, G. Wang, Z. Chai, Y. Wu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 750–755; t) Y. Li, X. Liu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 2034–2039.

[5] For an excellent review on noncovalent immobilization, see: a) J. Horn, F. Michalek, C. C. Tzschucke, W. Bannwarth, *Top. Curr. Chem.* **2004**, *242*, 43–75; for excellent new advances, see: b) K.

Ding, Z. Wang, X. Wang, Y. Liang, X. Wang, *Chem. Eur. J.* **2006**, *12*, 5188–5197.

[6] For recent examples, see: a) M. Gruttadauria, S. Riela, C. Aprile, P. Lo Meo, F. D′Anna, R. Noto, *Adv. Synth. Catal.* **2006**, *348*, 82–92; b) Z. An, W. H. Zhang, H. M. Shi, J. He, *J. Catal.* **2006**, *241*, 319–327; c) M. Gruttadauria, S. Riela, P. L. Meo, F. D′Anna, R. Noto, *Tetrahedron Lett.* **2004**, *45*, 6113.

[7] For recent examples, see: a) P. Kotrusz, I. Kmentova, B. Gotov, Š. Toma, E. Solèániová, *Chem. Coummn.* **2002**, 2510–2511; b) T.-P. Loh, L.-C. Feng, H.-Y. Yang, J.-Y. Yang, *Tetrahedron Lett.* **2002**, *43*, 8741–8743; c) N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Synlett* **2003**, 1906–1909; d) P. Kotrusz, S. Toma, H.-G. Schmalz, A. Adler, *Eur. J. Org. Chem.* **2004**, 1577–1583; e) H. M. Guo, L. F. Cun, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, *Chem. Commun.* **2005**, 1450–1452; f) P. Kotrusz, S. Alemayehu, T. Toma, H. G. Schmalz, A. Adler, *Eur. J. Org. Chem.* **2005**, 4904–4911; g) A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 3949–3952; h) M. S. Rasalkar, M. K. Potdar, S. S. Mohile, M. M. Salunkhe, *J. Mol. Catal. A: Chem.* **2005**, *235*, 267–270; i) R. T. Dere, R. R. Pal, P. S. Patil, M. M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351–5353; j) H. M. Guo, H. Y. Niu, M. X. Xue, Q. X. Guo, L. F. Cun, A. Q. Mi, Y. Z. Jiang, J. J. Wang, *Green Chem.* **2006**, *8*, 682–684; k) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079; l) L. Zu, H. Li, J. Wang, X. Yu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 5131–5134.

[8] For examples, see ref. [2c] and a) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165–3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097; b) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Tetrahedron* **2007**, *63*, 1923–1930; c) W. S. Miao, T. H. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1711–1718.

[9] For a concept article, see: P. Barbaro, *Chem. Eur. J.* **2006**, *12*, 5666–5675.

[10] A. Michrowsak, K. Mennecke, U. Kunz, A. Kirschning, K. Grela, *J. Am. Chem. Soc.* **2006**, *128*, 13261–13267.

[11] a) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; b) B. List, *Chem. Commun.* **2006**, 819–824.

[12] For a review, see: S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579.

[13] For examples, see: a) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177; b) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; c) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; d) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735; e) S. V. Pansare, K. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625; f) D. Gryko, M. Zimnicka, R. Lipiñski, *J. Org. Chem.* **2007**, *72*, 964–970; g) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075.

[14] For excellent reviews, see: a) R. Haag, S. Roller, *Top. Curr. Chem.* **2004**, *242*, 1–42; b) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275–3300; for recent examples on PS-supported nonchiral organocatalysts, see: c) L. J. Zhao, H. S. He, M. Shi, P. H. Toy, *J. Comb. Chem.* **2004**, *6*, 680–683; d) L. J. Zhao, C. K.-W. Kwong, M. Shi, P. H. Toy, *Tetrahedron* **2005**, *61*, 12026–12032; e) C. K.-W. Kwong, R. Huang, M. J. Zhang, M. Shi, P. H. Toy, *Chem. Eur. J.* **2007**, *13*, 2369–2376; f) P. H. Toy, M. Shi, *Tetrahedron* **2005**, *61*, 12025–12025.

[15] For reviews on direct aldol reactions, see: a) *Modern Aldol Additions* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**; b) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36–44; c) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406–1430; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374.

[16] Strong solid acids, such as heteropoly acids, were applied in the present strategy and improved stereoselectivity was obtained; however, the reaction only worked under homogeneous conditions and lower activity or inert catalysis was observed under heterogeneous conditions; see: S. Luo, J. Li, H. Xu, L. Zhang, J.-P. Cheng, *Org. Lett.* **2007**, *9*, 3675–3678.

[17] For a review, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; for recent examples, see: b) B. List, P. Pojarliew, J. H. Maritn, *Org. Lett.* **2001**, *3*, 2423–2425; c) D. Enders, A. Seki, *Synlett* **2002**, 26–28; d) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740; e) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530; f) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; g) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; h) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611–3614; i) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559–2561; j) S. Mosse, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559–2562; k) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 5991–5996; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; l) J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321–4332; m) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079; n) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; o) Y. Xu, A. Cordova, *Chem. Commun.* **2006**, 1451–1453; p) Y. Xu, W. Zou, H. Sunden, I. Ibrahem, A. Cordova, *Adv. Synth. Catal.* **2006**, *348*, 418–424; q) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451–1453; r) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; s) M.-L. Zhu, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Tetrahedron: Asymmetry* **2006**, *17*, 491–493; t) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; u) D. Terakado, M. Takano, T. Oriyama, *Chem. Lett.* **2005**, *34*, 962–963; v) D. Enders, M. R. M. Huttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; w) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 3170–3175; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; x) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; y) C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, 611–614; z) J. M. Betancort, K. Sakthivel, R. Thayumanava, F. Tanaka, ; C. F. Barbas III, *Synthesis* **2004**, 1509–1521.

[18] L. Gu, Y. Wu, Y. Zhang, G. Zhao, *J. Mol. Catal. A* **2007**, *263*, 186–194.

[19] Commercial sulfonated polystyrenes were systematically examined in this study; on the basis of the present results, it is highly possible that some commercial sulfonated polystyrenes may serve as good solid-acid supports in a manner similar to the acid supports used in this study by judicious selection of suitable loading amounts of the acid unit, proper cross-linking, and favorable particle size.

[20] K. Manabe, S. Kobayshi, *Adv. Synth. Catal.* **2002**, *344*, 270–273.

[21] a) S. Z. Luo, X. L. Mi, S. Liu, H. Xu, J.-P. Cheng, *Chem. Commun.* **2006**, 3687–3689; b) S. Z. Luo, H. Xu, X. L. Mi, J. Y. Li, X. X. Zheng, J.-P. Cheng, *J. Org. Chem.* **2006**, *71*, 9244–9247.

Received: July 23, 2007
Published online: November 15, 2007

