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ARTICLE TYPE

Heterogeneous Asymmetric Henry-Michael One-pot Reaction Synergically Catalyzed by the Grafted Chiral Bases and Inherent Achiral Hydroxyls on Mesoporous Silica Surface[†]

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Highly efficient and enantioselective asymmetric Henry-Michael one-pot reaction has been achieved on the bifunctional heterogeneous catalysts with inherent achiral ¹⁰ hydroxyls as acidic sites and immobilized chiral amines as basic sites. The final product was afforded in a yield of up to 85 % and ee of 99 %.

Natural biological systems effectively produce elaborate molecules in continuous ways, avoiding time-consuming and ¹⁵ costly operations and thus more environmentally-benign. To simulate the efficient natural processes, the concept of one-pot catalysis has been proposed by catalytic chemists¹ using enzymes², metal complexes³, and small organic molecules⁴ as effective catalysts. Small organic molecules have attracted ²⁰ persistent attention as organocatalysts in the last decade because of, for example, their higher chemical stability than enzymes, better resistance to moisture and oxygen than metal complexes, lower cost, and absence of metal residue and

toxicity. Acidic-basic bi-functionalized organocatalysts are ²⁵ especially interesting⁵ because they could act via acid-base synergy in one-pot catalysis.

Despite the successful application of homogeneous acidbase bifunctional organocatalysts in asymmetric one-pot reactions, how to avoid the mutual deactivation of acidic and ³⁰ basic sites has always been a great issue.⁶ Heterogenization of

- ³⁰ basic sites has always been a great issue. Heterogenization of homogeneous catalytic sites provides the opportunity to figure out this issue. Early research focused on the immobilization of acidic and basic functionalities separately on independent supports.⁷ Later, researchers began to pay more attention on the immobilization of acidic aci
- ³⁵ the immobilization of acidic and basic functionalities coinstantaneously on one support.^{8,9} To our best knowledge, however, no heterogeneous chiral bifunctional catalysts for asymmetric one-pot reaction have been reported. The asymmetric one-pot catalysis using the surface achiral sites as

⁵⁰ one catalytic centre of the bifunctional catalysts is especially challenging. Here, we report the one-pot asymmetric catalysis of heterogeneous bifunctional catalysts with the inherent achiral hydroxyls of mesoporous silica (SBA-15 materials) as acidic sites and immobilized chiral amines as basic sites. The ⁵⁵ synergetic catalysis of surface-inherent acids and immobilized

bases demonstrated enhanced activity while afforded excellent enantioselectivity in asymmetric Henry-Michael one-pot reaction (Scheme 1), a synthon for montanine-like amaryllidaceae alkaloids¹⁰ produced in 99% ee. Montanine-60 like amaryllidaceae alkaloids are recognized to have potential applications as antiviral and antineoplastic drugs, insect antifeedants, and acetylcholinesterase inhibitors.¹¹



Scheme 1 Asymmetric Henry-Michael One-pot Reaction.

- 65 (S)-2-(((allyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine, (S)-2-(((allyldimethylsilyl)oxy)methyl)pyrrolidine, S-(2aminophenyl)-4-(allyloxy)pyrrolidine-2-carbothioate, and S-(1-methyl-1H-imidazol-2-yl)-4-(allyloxy)pyrrolidine-2-
- carbothioate, all with pyrrolidine struture, are selected as the 70 precursors of grafted amines in this work. To graft the amines, thiol-functionalized SBA-15 (SBA-15-SH) was synthesized following a reported procedure.¹² By the deconvolution of ²⁹Si MAS NMR signals (Fig. S1), the silanol content on SBA-15-SH surface is determined to be 6.73 mmol/g according to the 75 reported method.^{13,14} Based on the specific surface area (900 m^2/g), the silanol density is calculated as 7.48 μ mol/m². The immobilization of the chiral amines on SBA-15-SH was achieved by the reaction between -SH and -C=C-, with (S)diphenylprolinol silyl ether (SBA-py-si-diph), (S)-prolinol 80 silyl ether (SBA-py-si), S-(2-aminophenyl) pyrrolidine-2carbothioate (SBA-py-pri), and S-(1-methyl-1H-imidazol-2yl)pyrrolidine-2-carbothioate (SBA-py-ter) as grafted amine moieties (Scheme 2). The resonances at 31, 33 (Si-(CH₂)₃-S-CH₂-CH₂-), 26, 45, 55, 65 (pyrrolidine), 121, 131, 143, 160 85 (aromatic carbon in SBA-py-si-diph and SBA-py-pri), and 5
- ppm (-Si(CH₃)₂ in SBA-py-si-diph and SBA-py-si) in the 13 C CP/MAS NMR spectra (Fig. S2) clearly confirm the grafted

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[†] Electronic Supplementary Information (ESI) available: general information, experimental details, ¹H NMR data for organic amine, ¹³C NMR for heterogeneous catalyst, and ¹H NMR, ¹³C NMR and chiral HPLC results for product analysis. See DOI: 10.1039/b000000x/

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amines on support surface. As determined from the elemental analysis results, the loading of pyrrolidine ranges from 0.28 to 0.40 mmol/g for amine-grafted samples (Table 1). Based on the specific surface areas, the density of grafted pyrrolidine s was calculated to range from 0.30 to 0.44 μ mol/m². The molar ratio of surface hydroxyl to grafted pyrrolidine is around 20:1 (Table 1) for each heterogeneous catalyst, meaning there are enough hydroxyl groups around amine sites.



Scheme 2 The structure of designed heterogeneous catalysts

The heterogeneous catalysts are then used to catalyze the Henry-Michael one-pot reaction between benzaldehyde, nitromethane, and cyclohexanone. The results (Table 1) show that, each heterogeneous catalyst designed here exhibits good 15 activity and excellent enantioselectivity in the Henry-Michael one-pot reaction. (S)-diphenylprolinol silyl ether (py-si-diph) has been reported to be efficient catalyst for homogeneous Michael reactions,¹⁵ but never for Henry reactions in either homogeneous or heterogeneous system. The heterogeneous 20 catalyst SBA-py-si-diph designed here, however, surprisingly catalyzed not only the Michael reaction but also the Henry and Henry-Michael one-pot reactions, giving 47% conversion of 1 in the Henry reaction, 90% conversion of 3 in the Michael reaction, and 40 % yield of 5 in the Henry-Michael 25 one-pot reaction (Table 1, entry 1). This work investigated the homogeneous Henry reaction using py-si-diph as catalyst and observed no catalytic activity. The catalysis of SBA-py-sidiph in either Henry or Henry-Michael one-pot reaction is thus supposed to result from the synergies of surface hydroxyl 30 group as acidic site with the grafted pyrrolidine as basic site.

The acidic-basic synergies rousted the reactions. Without the steric hidrance of the two phenyl groups as in SBA-py-si-diph, SBA-py-si afforded 99% conversion of 1 in the heterogeneous Henry reaction and 66% yield of 5 in the heterogeneous 35 Henry-Michael one-pot reaction (Table 1, entry 2). SBA-py-

pri afforded a yield of 5 similar to SBA-py-si, with 74% conversion of 1 in the Henry reaction and 85% conversion of 3 in the Michael reaction (Table 1, entry 3). SBA-py-ter catalyzed the Michael reaction similarly to SBA-py-pri while 40 the Henry reaction more effectively than SBA-py-pri. A yield of up to 85% for 5 is afforded on SBA-py-ter (Table 1, entry 4). Especially amazing and encouraging, an ee of 98% for anti-isomers and an ee of 71% for syn-isomers are afforded on SBA-py-si-diph (Table 1, entry 1), and more than 95% ee was 45 observed for both syn- and anti- configured product on SBApy-si, SBA-py-pri, and SBA-py-ter (Table 1, entries 2-4). It is worthy to note that this work is the first report of heterogeneous asymmetric one-pot reaction. Owing to the expected synergies, the asymmetric Henry-Michael one-pot 50 reaction, which is difficult to achieve with homogeneous counterpart, has been achieved on the heterogeneous catalyst designed here with satisfactory yields afforded. The ee observed here are even comparable to other homogeneous systems reported previously¹⁶ which also provided 5 as 55 product. Even more, the breakthrough is the asymmetric catalysis involving achiral hydroxyls as one of the synergistic catalytic sites.

To further confirm the acidic-basic synergies, the surface hydroxyls of SBA-py-ter was capped by post-silvlation with -60 Si(CH₃)₃. Not only the conversion of **1** in the Henry reaction reduced markedly from 99% to 50%, but the conversion of 3 in the Michael reaction also from 88% to 73%. As a result, the yield of 5 reduced from 85% to 37% with the ee preserved. Many researches¹⁷ reported the addition of acids as co-catalyst 65 to improve the activity and enantioselectivity of Michael reaction. The control experiment showed that homogeneous py-ter afforded only 40% yield, and 78% ee for syn-isomer and 52% ee for anti-isomer in the Michael reaction, proving that the -OH groups on the heterogeneous catalysts designed 70 here could facilitate the Michael reaction as co-catalytic acid. On the physical mixture of SBA-15-SH and py-ter, only 9% yield of 5 was achieved. The ee was 86% for syn-isomer and 77% for anti-isomer, also lower than on SBA-py-ter. This suggests the covalent grafting of chiral amines to the support 75 surface favors the acid-base synergic catalysis probably due to avoiding undesired acid-base neutralization.

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Table 1 Henry-Michael one-pot reaction on designed catalysts.^a

syn-is	omer:	(2R,1'S) (2R,1'S) (2R,1'R) (2R,1'S) (2R		somer: $\bigvee_{n=1}^{n} \bigvee_{n=1}^{n} \bigvee_{n=1}^{$						
		Pyrrolidine	Density of grafted	Molar ratio of	Conversion	Conversion	Vield of 5		ee (%) ^d	
Entry	Catalyst	(mmol/g)	(µmol/m ²)	grafted pyrrolidine ^b	of $1 (\%)^c$	of 3 (%) ^c	$(\%)^{c}$	syn : anti ^c	(2R,1'S)	(2R,1'R)
1	SBA-py-si-diph	0.36	0.40	18:1	47 (45)	90 (90)	40 (38)	74:26 (75:25)	71 (73)	98 (97)
2	SBA-py-si	0.40	0.44	17:1	99 (97)	70 (72)	66 (67)	56:44 (54:46)	99 (99)	97 (96)
3	SBA-py-pri	0.28	0.31	24:1	74 (76)	85 (86)	61 (60)	72:28 (75:25)	97 (97)	96 (95)
4	SBA-py-ter	0.36	0.40	19:1	99 (97)	88 (88)	85 (84)	79:21 (79:21)	99 (98)	95 (93)

^a Reaction conditions: benzaldehyde (0.05 mmol), catalyst (30 mol%), nitromethane (1 mL), and cyclohexanone (2 mL); Henry reaction: 90 °C, 72 h; 80 Michael reaction: 25 °C, 48 h. ^b The ratio of the silanol density of SBA-15-SH to the density of grafted pyrrolidine. ^c Determined by ¹H NMR. Determined by ¹H NMR and HPLC. The figures in the parentheses are reproduced results.

In light of the one-pot Henry-Michael reaction between benzaldehyde and nitromethane on the catalyst with combined tertiary and primary amine on silica-alumina9, the mechanism 85 of the asymmetric Henry-Michael one-pot reaction in this work could be proposed (Fig. S3). In the Henry reaction, the carbonyl oxygen and carbonyl carbon of benzaldehyde are

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respectively activated by surface hydroxyls and the secondary amine of pyrrolidine to form an imine intermediate. The α proton of nitromethane is abstracted by the primary amine (SBA-py-pri), secondary amine (SBA-py-si-diph and SBA-pys si), or tertiary amine (SBA-py-ter) with the assistance of surface hydroxyl sites. The deprotonated nitromethane nucleophilically attacks the imine intermediate to result in the nitrostyrene which directly participates in Michael reaction. In the Michael reaction, the cyclohexanone is activated by the

- 10 secondary amine of pyrrolidine to form an enamine intermediate. The surface silanols would orientate the nitro group of nitrostyrene through hydrogen bonds so that the enamine acts as a necleophile and attacked the nitrostyrene from different faces. Because of the hinderance effect of the 15 mesoporous channel on the re attack on anti-enamine and the
- interaction between surface silanols and nitrostyrene, the (2R, 1'S) isomer is afforded as major product (Fig. S4).

The reusability of the heterogeneous catalyst designed here was also investigated using SBA-py-ter as an example. SBA-20 py-ter was recycled by simple filtration and re-used for catalytic runs (Fig. 1). 73% yield, and 93% ee for syn-isomer and 89% ee for anti-isomer are preserved in three recycle runs.



Fig.1 The recycle of SBA-py-ter in asymmetric Henry-Michael one-pot reaction. 25

In summary, this work has demonstrated the asymmetric Henry-Michael one-pot reaction on designed heterogeneous catalysts with inherent achiral hydroxyls of support surface as acid sites and grafted chiral amines as base sites. The final 30 product are afforded in up to 85% yield and 99% ee.

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