Supporting information

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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General

Powder X-ray diffraction (PXRD) patterns were obtained on a Bruker D8 focus X-ray diffractometer with Cu K_{α} radiation operated at 30 mA and 45 kV. Nitrogen adsorption/desorption experiments were performed at 77 K on a Quantackrome Autosorb-1 system. The specific surface area was calculated using the adsorption branch by the standard BET method and the mesopore size distribution was calculated from the adsorption branch using the Barret-Joyner-Halenda (BJH) method. Elemental analysis of C, H, N, and S was performed using a VarioEL (Elmentar Analysensysteme Gmbh) elemental analyzer. ¹H NMR spectra were recorded on Bruker Avance 400 MHz NMR spectrometer (Bruker, Bremen, Germany). The spectra were recorded in CDCl₃ as solvent at ambient temperature. The solid state NMR experiments were carried out on a Bruker Avance 300 MHz solid-state spectrometer. HPLC analysis was carried out using Varian Prostar 210 HPLC with Prostar 325 UV-Vis detector.



Fig. S1. ²⁹Si MAS NMR spectrum of SBA-15-SH. The molar fractions of Qⁱ and Tⁱ species were determined from the areas of the signals after the decomposition fitting. The Q⁴, Q³, T³ and T² species were considered as molecules $Si(O_{0.5})_4$, $Si(O_{0.5})_3$ OH, R-Si($O_{0.5})_3$ and R-Si($O_{0.5})_2$ OH.



Fig. S2. ¹³C CP/MAS NMR spectra of a) SBA-15-SH, b) SBA-py-si-diph, c) SBA-py-si, d) SBA-py, e) SBA-py-pri, and f) SBA-py-ter.



Fig. S3. The reaction mechanism for the asymmetric Henry-Michael one-pot reaction on SBA-py-si.



Fig. S4. A proposed mechanism for the enantioselective formation of major product.

Experimental details

1. Synthesis

SBA-15-SH: The synthesis of SBA-15-SH material was performed according to the following procedure with a molar ratio of TEOS : Surfactant : HCl : H₂O of 1 : 0.017 : 5.854 : 162.681. Triblock copolymer poly(ethylene glycol)-B-poly(propylene glycol)-B-poly(ethylene glycol), referred to as P123 (Aldrich, average Mn~5800), was used as the template. Organosilane 3-mercaptopropyltrimethoxysilane (Aldrich, 95%), as the source of thiol groups, was introduced into the mixture with a MPTMS/(MPTMS+TEOS) molar ratio of 20%. A certain amount of P123 was dissolved in a mixture of water and 2 M hydrochloric acid (36-38%) aqueous solution with strong stirring at 40 °C and then TEOS was added dropwise into the mixture, followed by the addition of MPTMS 45 min later. After stirring for another 24 h, the mixture was moved into Teflon-lined autoclaves and aged for 24 h at 140 °C. The solid was filtered and air-dried, followed by extraction with anhydrous ethanol at 55 °C for 24 h to remove the template. The final material was obtained after drying overnight at 40 °C in atmosphere.

(S)-2-(((allyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine: A solution of (S)-diphenylprolinol (1.265 g, 5 mmol) in CH₂Cl₂ (20 mL) was treated with triethylamine (767 μL, 5.5 mmol). Allylchlorodimethylsilane (803 μL, 5.5 mmol) was added dropwise to the solution. The mixture was stirred at 25 °C for 20 h. The reaction mixture was directly purified by silica gel chromatography (hexane/EtOAc=10/1) to afford the desired product. ¹HNMR (400 MHz, CDCl₃): δ = 7.38-7.48 (m, 10H, -C₆H₅-), 5.70 (m, 1H, -CH₂CH=CH₂), 5.02-5.07 (m, 2H, -CH=CH₂), 3.59 (m, 1H, α-CH Pro), 2.70-2.80 (m, 2H, δ-CH₂ Pro), 2.0 (s, -NH Pro), 1.90 (s, 2H, -SiCH₂CH-), 1.43-1.68 (m, 4 H, β-CH₂ Pro, γ-CH₂ Pro), 0.21 (s, 6 H, 2x -Si-CH₃).

(S)-2-(((allyldimethylsilyl)oxy)methyl)pyrrolidine: A solution of (S)-prolinol (0.506 g, 5 mmol) in CH₂Cl₂ (20 mL) was treated with triethylamine (767 μL, 5.5 mmol). Allylchlorodimethylsilane (803 μL, 5.5 mmol) was added dropwise to the solution. The mixture was stirred at 25 °C for 20 h. The reaction mixture was directly purified by silica gel chromatography (hexane/EtOAc=10/1) to afford the desired product. ¹HNMR (400 MHz, CDCl₃): δ = 5.70 (m, 1H, -CH₂CH=CH₂), 5.02-5.07 (m, 2H, -CH=CH₂), 3.75-4.00 (m, 2H, -OCH₂CH-), 2.83 (m, 1H, α-CH₂ Pro), 2.70-2.80 (m, 2H, δ-CH₂ Pro), 2.0 (s, -NH Pro), 1.90 (s, 2H, -SiCH₂CH-), 1.43-1.68 (m, 4 H, β-CH₂ Pro, γ-CH₂ Pro), 0.21 (s, 6 H, 2x -Si-CH₃).

N-*tert*-**Butoxycarbonyl**-(**S**)-**prolinol:** A solution of di-*tert*-butyldicarbonate (1.102 g, 5.05 mmol) in ethanol (1.5 mL) was added dropwise at room temperature and under vigorous stirring into a solution containing (**S**)-prolinol (0.506 g, 5 mmol) in ethanol (3.75 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 3 h; then, the solvent was evaporated at 40 °C under reduced pressure. The crude product was directly purified by silica gel chromatography (petroleum ether/EtOAc=3/1). ¹H NMR (400 MHz, CDCl₃): δ =3.56 (s, 1H, -OH), 3.50 and 3.25 (m, 2H, -CH₂OH), 3.43 (m, 1H, α-CH Pro), 3.30 and 3.40 (m, 2H, δ-CH₂ Pro), 1.43-1.68 (m, 4H, β-CH₂ Pro, γ-CH₂ Pro), 1.38 (s, 9H, C(CH₃)₃).

(S)-*tert*-butyl-2-((allyloxy)methyl)pyrrolidine-1-carboxylate: A solution of N-*tert*-Butoxycarbonyl-(S)-prolinol (1.741 g, 8.65 mmol) in anhydrous THF (30 mL) was added dropwise under nitrogen atmosphere to a suspension of NaH (60% mineral oil, 751 mg, 18.77 mmol) in anhydrous THF (20 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h, and 18-crown-6 (228 mg, 0.86 mmol) and allyl bromide (1.403 g, 11.6 mmol) were then added. The mixture was stirred for 1 h at ambient temperature, and then at 50 °C overnight. After cooling to ambient temperature, water (100 mL) was added. The aqueous phase was extracted with hexane in order to remove

the unreacted allyl bromide. The aqueous phase was acidified to pH 2-3 by adding a solution of NaHSO₄ (2 M), and was then extracted with ethyl acetate. The organic phase was dried using MgSO₄ and concentrated under reduced pressure to give the desired product as a viscous oil. ¹H NMR (400 MHz, CDCl₃): $\delta = 6.06$ (m, 1H, -CH=CH₂), 5.42 and 5.28 (m, 2H, -CH=CH₂), 4.04 (m, 2H, -OCH₂CH=), 3.71 and 3.46 (m, 2H, -OCH₂CH-), 3.67 (m, 1H, α -CH Pro), 3.30 and 3.40 (m, 2H, δ -CH₂ Pro), 1.43-1.68 (m, 4H, β -CH₂ Pro, γ -CH₂ Pro), 1.38 (s, 9H, C(CH₃)₃).

N-*tert*-**Butoxycarbonyl-trans-4-hydroxy-L-proline:** A mixture of trans-4-hydroxy-L-proline (1.5 g, 0.038 mol) in a 2:1 mixture of THF/H₂O (75 mL) was treated first with 10% aqueous NaOH (15 mL) and then with di-*tert*-butyldicarbonate (12 g, 0.056 mol). The reaction mixture was stirred at room temperature overnight and then the THF was removed by vacuum. The residue was adjusted to pH 2-3 by the addition of 10% aqueous NaHSO₄. The acidic solution was extracted with ethyl acetate for several times. The combined organic extracts were washed with H₂O, and then dried over anhydrous Na₂SO₄. Removal of the desiccant and evaporation of the solvent in vacuum gave N-tert-Butoxycarbonyl-trans-4-hydroxy-L-proline, which was used without further purification. ¹H NMR (400 MHz, CDCl₃): δ =4.30-4.43 (m, 2H, α-CH Pro, γ-CH Pro), 3.36-3.58 (m, 2H, δ-CH₂ Pro), 2.06-2.35 (m, 2H, β-CH₂ Pro), 1.35 (s, 9H, C(CH₃)₃).

4-(allyloxy)-1-(*tert***-butoxycarbonyl)pyrrolidine-2-carboxylic acid:** A solution of N-*tert*-Butoxycarbonyl-trans-4-hydroxy-L-proline (2 g, 8.65 mmol) in anhydrous THF (30 mL) was added dropwise under nitrogen atmosphere to a suspension of NaH (60 % mineral oil, 751 mg, 18.77 mmol) in anhydrous THF (20 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h, and 18-crown-6 (228 mg, 0.86 mmol) and allyl bromide (1.403 g, 11.6 mmol) were then added. The mixture was stirred for 1 h at ambient temperature, and then at 50 °C overnight. After cooling to ambient temperature, water (100 mL) was added. The aqueous phase was extracted with hexane in order to remove the unreacted allyl bromide. The aqueous phase was acidified to pH 2-3 by adding a solution of NaHSO₄ (2 M), and was then extracted with ethyl acetate. The organic phase was dried using MgSO₄ and concentrated under reduced pressure to give the desired product as a viscous oil. ¹H NMR (400 MHz, CDCl₃): δ = 6.06 (m, 1H, -CH=CH₂), 5.42 and 5.28 (m, 2H, -CH=CH₂), 4.22 (m, 1H, α-CH Pro), 4.04 (m, 2H, -OCH₂CH=), 3.61 and 3.36 (m, 2H, δ-CH₂ Pro), 2.94 (m, 1H, γ-CH₂ Pro), 2.08 and 1.83 (m, 2H, β-CH₂ Pro), 1.38 (s, 9H, C(CH₃)₃).

tert-butyl-(2-mercaptophenyl)carbamate: A solution of di-*tert*-butyldicarbonate (1.102 g, 5.05 mmol) in ethanol (1.5 mL) was added dropwise at room temperature and under vigorous stirring into a solution containing 2-aminobenzenethiol (0.626 g, 5 mmol) in ethanol (3.75 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 4 h; then, the solvent was evaporated at 40 °C under reduced pressure. The crude product was directly purified by silica gel chromatography (hexane/EtOAc=10/1). ¹H NMR (400 MHz, CDCl₃): $\delta = 9.15$ (s, 1H, -NH-), 6.94-7.37 (m, 4H, -C₆H₄-), 3.40 (s, 1H, -SH), 1.38 (s, 9H, C(CH₃)₃).

tert-butyl-4-(allyloxy)-2-(((2-((tert-butoxycarbonyl)amino)phenyl)thio)carbonyl)pyrrolidine-1-carboxylate:

Dicyclohexylcarbodiimide (DCC) (3.54 g, 17.1 mmol) was added to a mixture of CH_2Cl_2 (10 mL) containing 4-(allyloxy)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (4.5 g, 16.6mmol) and *tert*-butyl-(2-mercapto-phenyl)carbamate (3.852 g, 17.1 mmol) at 0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 16 h under a nitrogen atmosphere. Then diethyl ether (25 mL) was added to the reaction mixture, and the formed white precipitate (N,N-dicyclohexylurea (DCU)) was removed by filtration. The solvent was evaporated, and then dried in vacuum. The crude product was directly purified by silica gel chromatography (hexane/EtOAc=5/1). ¹H NMR (400 MHz, CDCl₃): δ = 9.15 (s, 1H, -NH-), 6.94-8.05 (m, 4H, -C₆H₄-), 6.06 (m, 1H,

-CH=CH₂), 5.42 and 5.28 (m, 2H, -CH=CH₂), 4.21 (m, 1H, α-CH Pro), 4.04 (m, 2H, -OCH₂CH=), 3.61 and 3.36 (m, 2H, δ-CH₂ Pro), 2.13 and 1.88 (m, 2H, β-CH₂ Pro), 2.94 (m, 1H, γ-CH₂ Pro), 1.38 (s, 18H, C(CH₃)₃).

tert-butyl-4-(allyloxy)-2-(((1-methyl-1H-imidazol-2-yl)thio)carbonyl)pyrrolidine-1-carboxylate:

Dicyclohexylcarbodiimide (DCC) (3.54 g, 17.1 mmol) was added to a mixture of CH_2Cl_2 (10 mL) containing 4-(allyloxy)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (4.5 g, 16.6mmol) and 1-methyl-1H-imidazole-2-thiol (1.952 g, 17.1 mmol) at 0 °C under a nitrogen atmosphere. The reaction was stirred at room temperature for 16 h under a nitrogen atmosphere. Then diethyl ether (25 mL) was added to the reaction mixture, and the formed white precipitate (N,N-dicyclohexylurea(DCU)) was removed by filtration. The solvent was evaporated, and then dried in vacuum. The crude product was directly purified by silica gel chromatography (hexane/EtOAc=5/1). ¹H NMR (400 MHz, CDCl_3): δ = 7.13 (m, 1H, =CHN-), 6.89 (m, 1H, =CHN=), 6.06 (m, 1H, -CH=CH_2), 5.42 and 5.28 (m, 2H, -CH=CH_2), 4.21 (m, 1H, α -CH Pro), 4.04 (m, 2H, -OCH₂CH=), 3.61 and 3.36 (m, 2H, δ -CH₂ Pro), 3.61 (s, 3H, -NCH₃-), 2.94 (m, 1H, γ -CH₂ Pro), 2.13 and 1.88 (m, 2H, β -CH₂ Pro), 1.38 (s, 9H, C(CH₃)₃).

2. Preparation

Grafting of chiral amines: The thiol-functionalized mesoporous silicas SBA-15-SH (1 g) was added to a degassed solution of each chiral amine (1.5 mmol) and AIBN (0.024 g, 0.145 mmol) in 50 ml of anhydrous toluene. The mixture was stirred at 110 °C for 24 h under N₂ atmosphere. After cooling to ambient temperature, the solid was filtered and washed with toluene and CH_2Cl_2 . Finally, the Boc group was removed by suspended the grafted solid in 12 mL of CH_2Cl_2/TFA (v/v=3) for 3 h. The solid was filtered and washed with CH_2Cl_2 , ethanol, and water. The light yellow powder was dried at 40 °C in vacuum for 24 h.

3. Typical procedure for the Henry-Michael one-pot reaction

Typically, benzaldehyde (5.5 μ L, 0.05 mmol) was added to heterogeneous catalyst (0.015 mmol, 30 mol%) in a micro reaction flask. Then, nitromethane (1 mL) and 1,1,2,2-tetrachloroethane (5.25 μ L, 0.05 mmol) was added. The reaction mixture was stirred at 90 °C for 72 h. After the cyclhexanone (2 mL) was added, the mixture was stirred for 48 h at 25 °C. After removal of the catalyst by filtration, the diastereoselectivity, conversion and yield were determined by ¹H NMR analysis. The mixture was dissolved in the flow phase (isopropanol/n-hexane: v/v=10/90) to determine the enantiomeric excess (ee) of product by chiral-phase HPLC analysis (column: Chiralpak-AD-H, flow phase: isopropanol/n-hexane (v/v=10/90), flow rate: 0.5 mL/min, detection wavelength: 254 nm). The crude product purified by flash column chromatography (silica gel, hexane/EtOAc), and then evaporated the solvent to give the pure product as a white solid.

Product analysis

2-(2-nitro-1-phenylethyl)cyclohexanone:



¹H NMR (400 MHz, CDCl₃): $\delta = 7.34-7.16$ (m, 5H, C₆H₅-), 4.95 and 4.63 (m, 2H, -NCH₂-), 3.76 (m, 1H, C₆H₅CH-), 2.68 (m, 1H, O=CCH-), 2.49-2.33 (m, 2H, O=CCH₂-), 2.10-1.19 (m, 6H, -CH₂-). ¹³C NMR (400 MHz, CDCl₃): 211.9, 137.8, 128.9, 128.8, 127.9, 77.0, 52.5, 44.0, 42.8, 33.2, 28.5, 25.0.

¹H NMR of Product:



¹³C NMR of Product:



HPLC:

Column: Chiralpak-AD-H Flow Phase: isopropanol/n-hexane (v/v=10/90) Flow Rate: 0.5 mL/min Detection Wavelength: 254 nm

Racemic product:

syn-diastereomer:

(2S, 1'R): t=7.96 min, 49%; (2R, 1'S): t=11.65 min, 51%

anti-diastereomer:



(2R, 1'R): t=8.94 min, 49%; (2S, 1'S): t=19.79 min, 51%

Product catalyzed by SBA-py-si-diph:

syn-diastereomer: (2S,1'R): t=8.09 min, 14%; (2R,1'S): t=11.26 min, 86%; *ee*: 73% *anti*-diastereomer: (2R,1'R): t=9.55 min, 99%; (2S,1'S): t=19.81 min, 1%; *ee*: 98%



Product catalyzed by SBA-py-si:

syn-diastereomer: (2S,1'R): t=7.79 min, 1%; (2R,1'S): t=10.91 min, 99%, *ee*: 99% *anti*-diastereomer: (2R,1'R): t=8.86 min, 98%; (2S,1'S): t=20.59 min, 2%, *ee*: 96%



Product catalyzed by SBA-py-pri:

syn-diastereomer: (2S,1'R): t=8.09 min, 2%; (2R,1'S): t=10.96 min, 98%, *ee*: 97% *anti*-diastereomer: (2R,1'R): t=8.86 min, 98%; (2S,1'S): t=20.59 min, 2%, *ee*: 96%



Product catalyzed by SBA-py-ter:

syn-diastereomer: (2S,1'R): t=8.07 min, 1%; (2R,1'S): t=10.91 min, 99%, *ee*: 98% *anti*-diastereomer: (2R,1'R): t=9.12 min, 97%; (2S,1'S): t=19.80 min, 3%, *ee*: 95%



Product catalyzed by py-ter:

syn-diastereomer: (2S,1'R): t=8.95 min, 11%; (2R,1'S): t=10.97 min, 89%, *ee*: 78% *anti*-diastereomer: (2R,1'R): t=9.19 min, 76%; (2S,1'S): t=21.09 min, 24%, *ee*: 52%



Product catalyzed by SBA+py-ter:

syn-diastereomer: (2S,1'R): t=7.88 min, 7%; (2R,1'S): t=11.06 min, 93%, *ee*: 86% *anti*-diastereomer: (2R,1'R): t=9.34 min, 12%; (2S,1'S): t=19.30 min, 88%, *ee*: 77%



4-(allyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid





tert-butyl-4-(allyloxy)-2-(((1-methyl-1H-imidazol-2-yl)thio)carbonyl)pyrrolidine-1-carboxylate



tert-butyl-4-(allyloxy)-2-(((2-((tert-butoxycarbonyl)amino)phenyl)thio)carbonyl)pyrrolidine-1-carboxylate











S19















