Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
This journal is © The Royal Society of Chemistry 2022

Supporting Information

Mechanistic understanding and the rational design of SiO_2@CD catalyst for selective protection of L-lysine

Pinyi Li,[a,b] Xue Fu,[a,c] Qiang Zhou, [a] Xuewen Fu,[a] An Wang,[c] Guolin Zhang, [a] Wei Jiao [a] and Chun Wang*[a]

[a] *Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China*

[b] *University of Chinese Academy of Sciences, Beijing 100049, China*

[c] *College of Architecture and Environment, Sichuan university, Chengdu 610065, China*

Email: wangchun@cib.ac.cn

Table of contents

1.General remark

L-Lysine (L-lys), β-Cyclodextrin (β-CD), 9-fluorenemethyl-*N*-succinylimidecarbonate (Fmoc-OSu), Benzyl bromide (BnBr) were purchased from Sun Chemical Technology (Shanghai) Co., Ltd. Tetraethyl orthosilicate (TEOS), Benzyl chloroformate (Cbz-Cl) were purchased from Macklin Biochemical (Shanghai) Co., Ltd. 3-isocyanatopropyltriethoxysilane (IPTES) was purchased from Aladdin Bio-Chem Technology (Shanghai) Co., Ltd. Ethylene Diamine Tetraacetic Acid (EDTA), Sodium carbonate (Na_2CO_3) and Copper sulfate pentahydrate ($CuSO_4.5H_2O$) were purchased from Kelong Chemicals (Chengdu) Co., Ltd. All other chemicals used were of analytical grade. All commercially available chemicals and reagents were used without any further purification unless mentioned otherwise. All solvents and reagents were used without further purification except THF (dried). Chromatographic purification was performed on silica gel (200−300 mesh). Analytical thin-layer chromatography was performed on silica gel 60-F254 (Qingdao, China), which was detected by fluorescence. ^{1}H NMR spectra were recorded on 400, MHz. ^{13}C NMR spectra were recorded at 100 MHz. Assignments of ^{1}H NMR and ^{13}C NMR signals were made. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. The spectra were recorded with $CDCl_3$ or D_2O as the solvent. The peaks around δ 7.26 (^{1}H NMR) and 77.16 (^{13}C NMR) correspond to $CDCl_3$. The peaks around δ 4.79 (^{1}H NMR)) correspond to D_2O. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), and so forth. Coupling constants (*J*) are given in hertz. Chemical shifts (δ) are reported in parts per million relatives to tetramethylsilane as an internal standard. The ESI-HRMS was carried out on a Bruker Bio TOF IIIQ (quadrupole time of flight) mass spectrometer. Transmission electron microscopy (TEM) images were obtained on a Tecnai-G2-F20 electron microscope operating at 200 kV. All chemical shifts were referenced to tetramethylsilane (TMS).

2.Reactions of 1a and 2 with β-CD catalysis.

To a stirred solution of carbonate buffer was added β-CD (20 mol%) (12 mL, pH = 9). Then L-lys **1a** (1 mmol, 1 equiv) was added into the solution, and the mixture was stirred at 25 °C (oil bath) for 30 min, followed by dropwise addition of **2** (1.1 mmol, 1.1 equiv). The mixture was continuously stirred for 1-2 h; After that, H_2O (12 mL) and EA (6 mL) were added to the solution. The mixture was ultrasonicate for 2 min, then transferred into a separatory funnel. The white solids floated on the surface of the aqueous mixture were collected and washed successively with water (5×10.0 mL) and EA (5×10.0 mL). The residue was purified by flash chromatography on silica gel to give the desired products (DCM/MeOH = 10:1, 0.1% TFA was used).

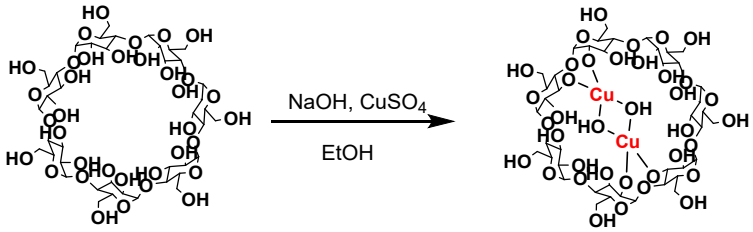
For the mechanism investigation, the reversed addition sequence of **1** and **2** was performed as following: To a stirred solution of carbonate buffer (12 mL, pH = 9) was added β-CD (20 mol%). **2** (1.1 mmol, 1.1 equiv) was added and the mixture was stirred

at 25 °C (oil bath) for 1 h, followed by addition of L-lys **1a** (1 mmol, 1 equiv). The rest of the operation was the same with above standard reaction procedure.

3.Reactions of 1(a or b) and 2a with Cu^{2+}@β-CD catalysis.

Preparation of Cu^{2+}@β-CD: Cu^{2+}@β-CD was synthesized according to reported method. To a 50 mL round-bottom flask was added 0.2 N NaOH (12 mL) and 0.02 M $CuSO_4$ (12 mL) aqueous solution, and the solution was stirred for 10 min at room temperature. Then β-CD was added into the above solution. The mixture was continuously stirred for 1 h, and then ethanol (12 mL) was added. The mixture was allowed to stand at 25 °C (oil bath) for 12 h, the blue solids were collected by filtration to afford Cu^{2+}@β-CD and to be used as the catalyst for investigation of the reactions of **1** (**a** or **b**) with **2a** respectively.

Scheme S1. Synthesis of Cu^{2+}@β-CD

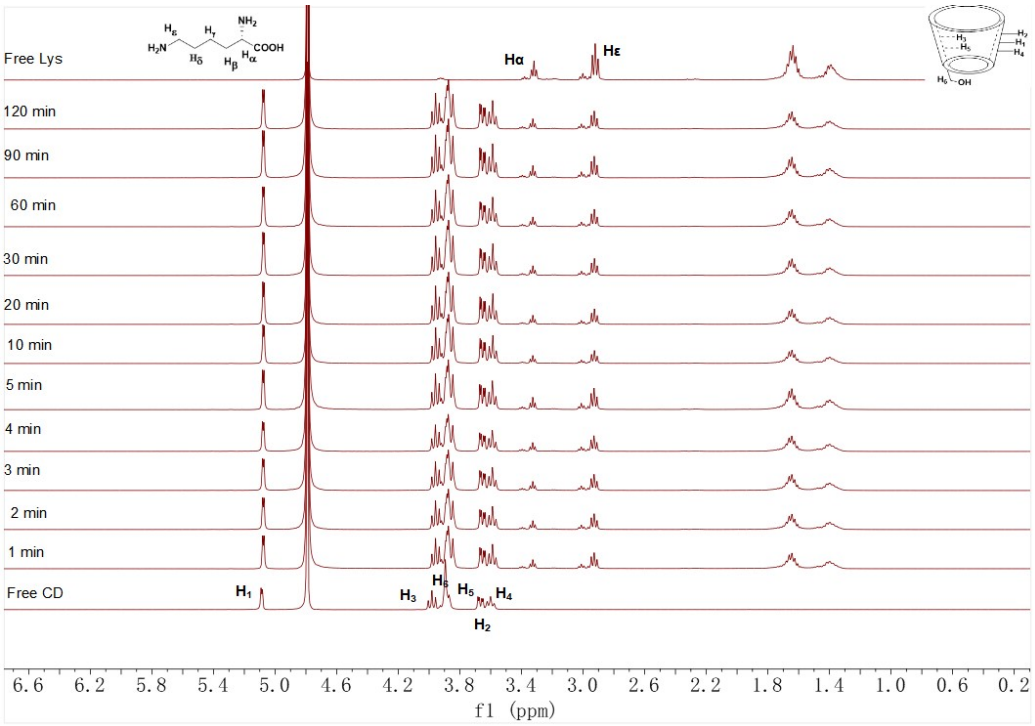


4. Time evolution of ^{1}H NMR investigation for the binary complex and ternary complex formation

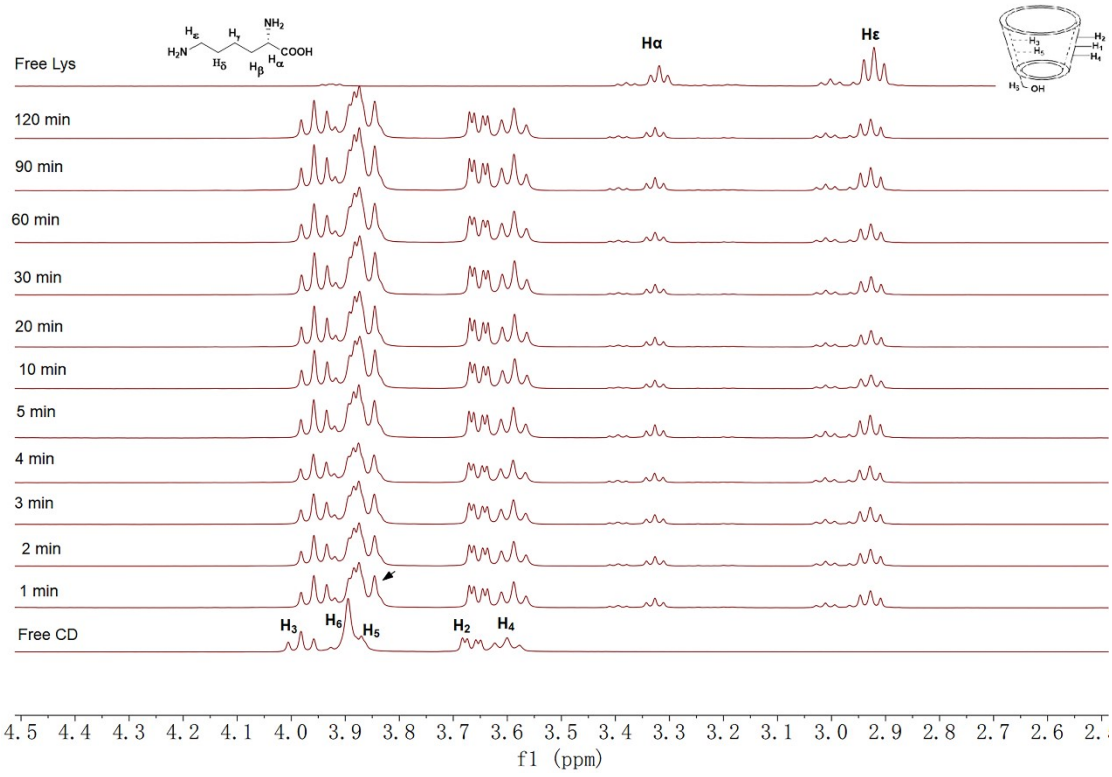
Preparation of sample (1a.CD): To a solution of Na_2CO_3 (5.3 mg, 0.05 mmol) in D_2O (500 ul) in a 10 mL round bottom flask was added β-CD (56.7 mg, 100 mol%). L-lys **1a** (7.3 mg, 0.05 mmol) was added into the above solution. The mixture was transferred into NMR tube recorded using a Bruker-400 M at 25 °C. The time evolution of the ^{1}H NMR spectra is shown in Figure S1a and S1b

Preparation of sample (1a.CD.2a): To a solution of Na_2CO_3 (5.3 mg, 0.05 mmol) in D_2O (500 ul) in a 10 mL round bottom flask was added β-CD (11.3 mg, 20 mol%). L-lys **1a** (7.3 mg, 0.05 mmol) was added into the above solution. The mixture was stirred at 25 °C (oil bath) for 0.5 h, followed by the addition of Cbz-Cl (7.0 ul, 0.05 mmol) (**1a**: β-CD: Cbz-Cl = 1:0.2:1, molar ratio). The mixture was transferred into NMR tube recorded using a Bruker-400 M at 25 °C. The time evolution of the ^{1}H NMR spectra is shown in Figure S1c and S1d.

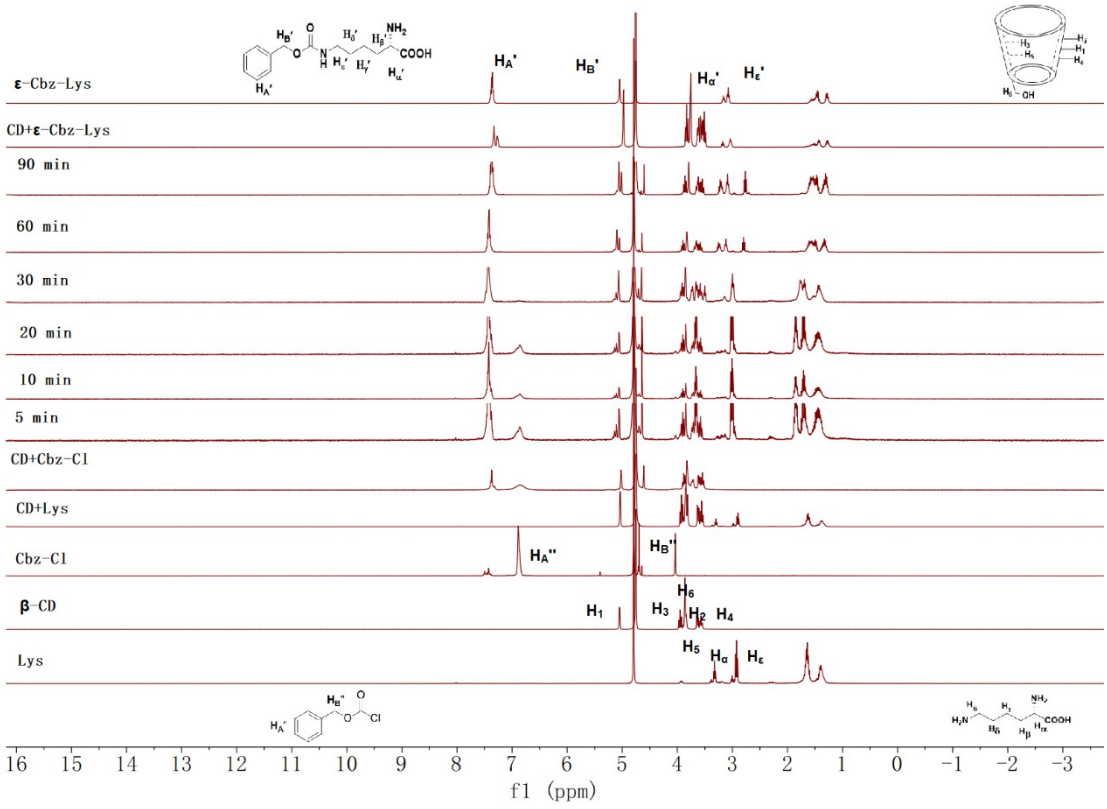
(a)


Free Lys
120 min
90 min
60 min
30 min
20 min
10 min
5 min
4 min
3 min
2 min
1 min
Free CD
Hα
Hε
H1
H3
H6
H5
H4
H2
6.6 6.2 5.8 5.4 5.0 4.6 4.2 3.8 3.4 3.0 2.6 2.2 1.8 1.4 1.0 0.6 0.2
f1 (ppm)

(b)


Free Lys
120 min
90 min
60 min
30 min
20 min
10 min
5 min
4 min
3 min
2 min
1 min
Free CD
Hα
Hε
H3
H6
H5
H2
H4
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6
f1 (ppm)

(c)



(d)

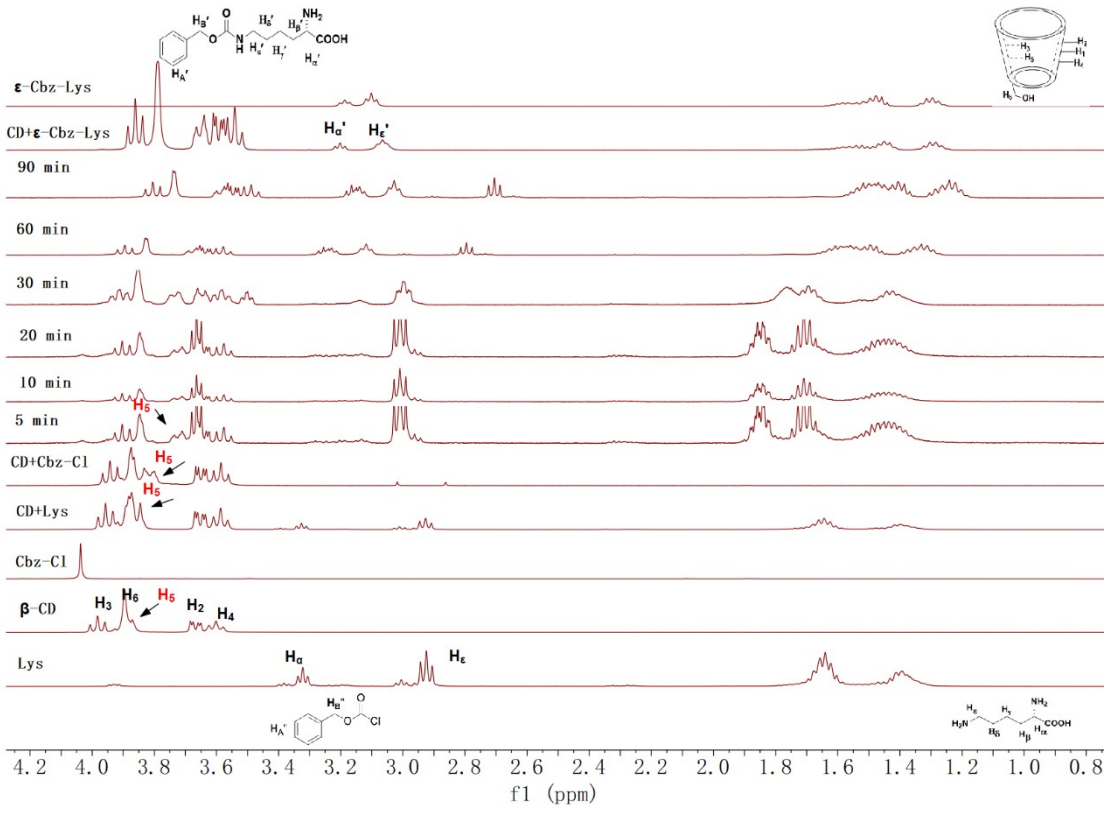


Figure S1. (a) ^{1}H NMR spectra for the mixture of [CD]= 0.1 mmol/mL and [Lys]= 0.1 mmol/mL in D_2O at different times; (b) Enlarged view of ^{1}H NMR spectra; (c) Kinetic study of the reaction

by *in-situ* three components ^{1}H NMR experiment ([CD]= 0.02 mmol/mL, [Lys]= 0.1 mmol/mL and [Cbz-Cl] = 0.1 mmol/mL) (d) Enlarged view of ^{1}H NMR spectra.

5.Preparation of binary and ternary complexes for 2D Roesy spectra.

Binary complex of 1a.β-CD. To a solution of Na_2CO_3 (5.3 mg, 0.05 mmol) in D_2O (500 ul) (pH = 9.6) in a 10 mL round bottom flask was added β-CD (11.3 mg, 20 mol%). L-lys **1a** (7.3 mg, 0.05 mmol) was added into the above solution under stirring. The mixture was stirred at 25 °C (oil bath) for 0.5 h and transferred into NMR tube (**1a**: β-CD = 1:0.2, molar ratio). The Roesy spectrum of the prepared sample was recorded using an INVOA-600 M at 25 °C.

Ternary complex of 1a. β-CD. Ben-ac. To a solution of Na_2CO_3 (5.3 mg, 0.05 mmol) in D_2O (500 ul) (pH = 9.6) in a 10 mL round bottom flask was added β-CD (11.3 mg, 20 mol%). L-lys **1a** (7.3 mg, 0.05 mmol) was added into the above solution. The mixture was stirred at 25 °C (oil bath) for 0.5 h, followed by the addition of Ben-ac (7.2 ul, 0.05 mmol) (**1a**: β-CD: Ben-ac = 1:0.2:1, molar ratio). The mixture was continuously stirred for 0.5 h and transferred into NMR tube. The Roesy spectrum of the prepared sample was recorded using an INVOA-600 M at 25 °C.

Preparation of final products (ε-3aa) with β-CD for 2D Roesy spectra. To a solution of Na_2CO_3 in D_2O (1.0 mL, pH = 12) in a 10 mL round bottom flask were added β-CD (22.7 mg, 0.02 mmol) and ε-**3aa** (5.6 mg, 0.02 mmol). The mixture was stirred at 50 °C (oil bath) for 0.5 h and transferred into NMR tube. The Roesy spectrum of the prepared sample was recorded using an INVOA-600 M at 25 °C.

6. Determination of the binding constants for substrate (1a) to β-CD and product (ε-3aa) to β-CD

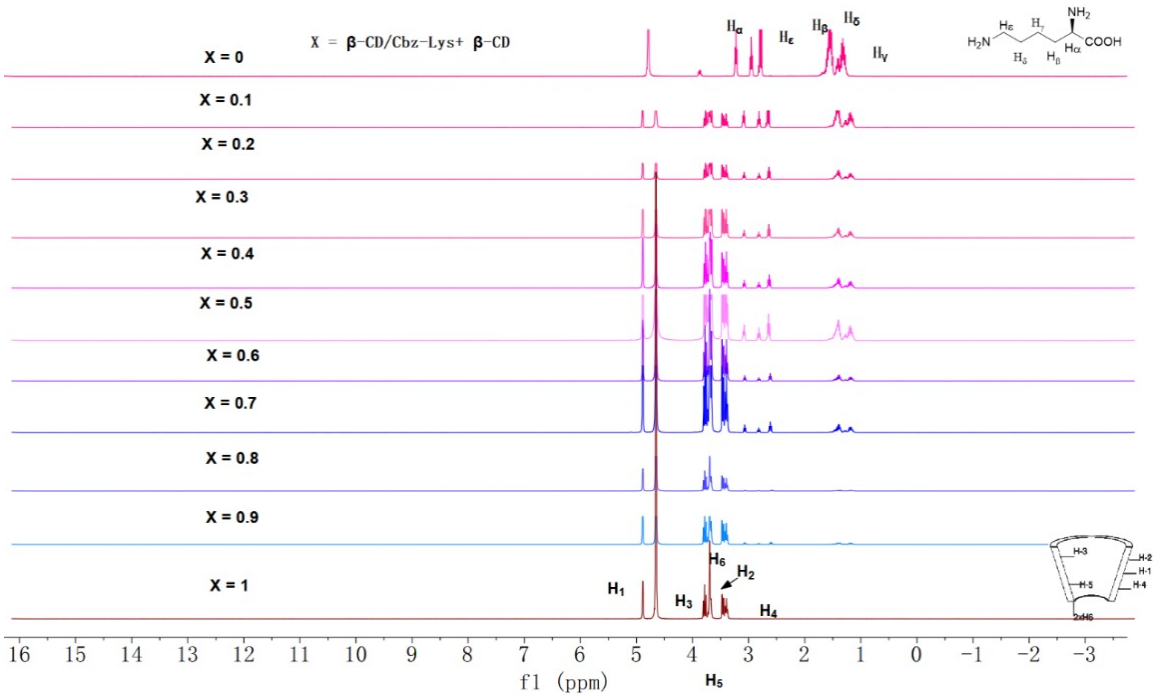
6.1 Binding stoichiometries of 1a to CD and ε-3aa to CD

^{1}H NMR titration：The samples of different molar ratio of β-CD (H) to **1a** (G) with a consistent total concentration of (H+G)/mL = 0.08 mmol/mL, were prepared for the ^{1}H NMR titration. To the solutions of β-CD (H mmol, H = 0, 0.004, 0.008, 0.012, 0.016, 0.02, 0.024, 0.028, 0.032, 0.036, 0.04) in D_2O (0.5 mL, pH = 11-12) were added **1a** (G mmol, G = 0.04, 0.036, 0.032, 0.028, 0.024, 0.02, 0.016, 0.012, 0.008, 0.04, 0), respectively. The solutions were stirred at 50 °C for 0.5 h and transferred into NMR tubes. The ^{1}H NMR spectra of the prepared samples were recorded using an INVOA-600 M instrument at 25 °C (Figure S2).

The samples of ε-**3aa** and CD were prepared similarly with above described for **1a** and β-CD. The results of ^{1}H NMR titration were presented in Figure S3.

^{1}H NMR titration：

(a)



(b)

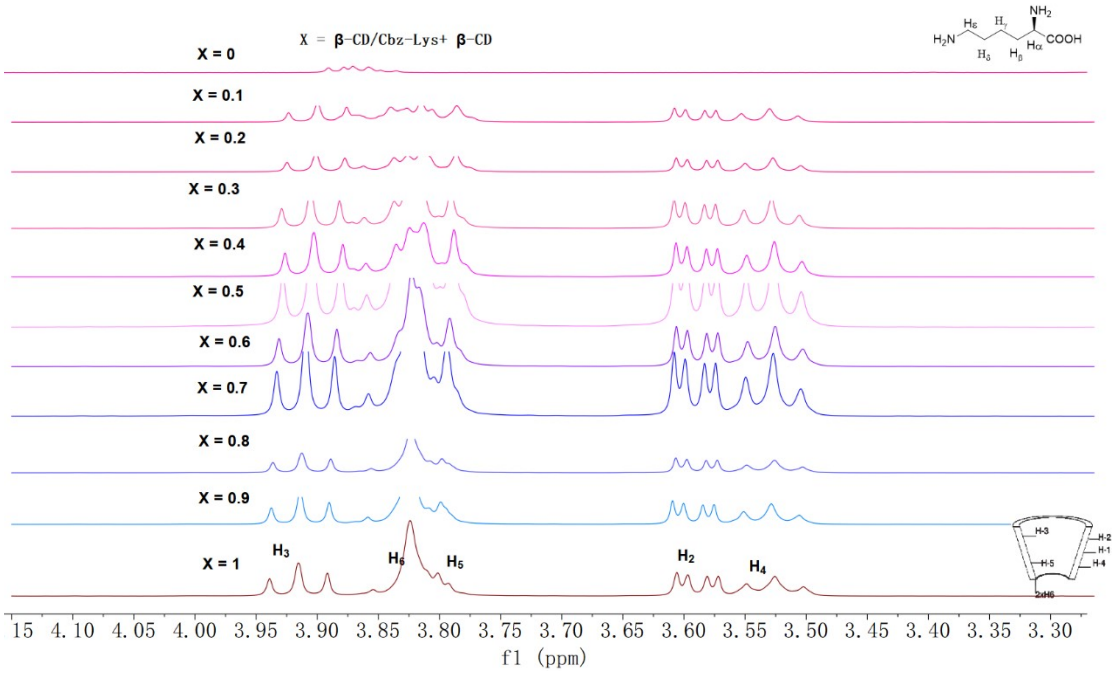
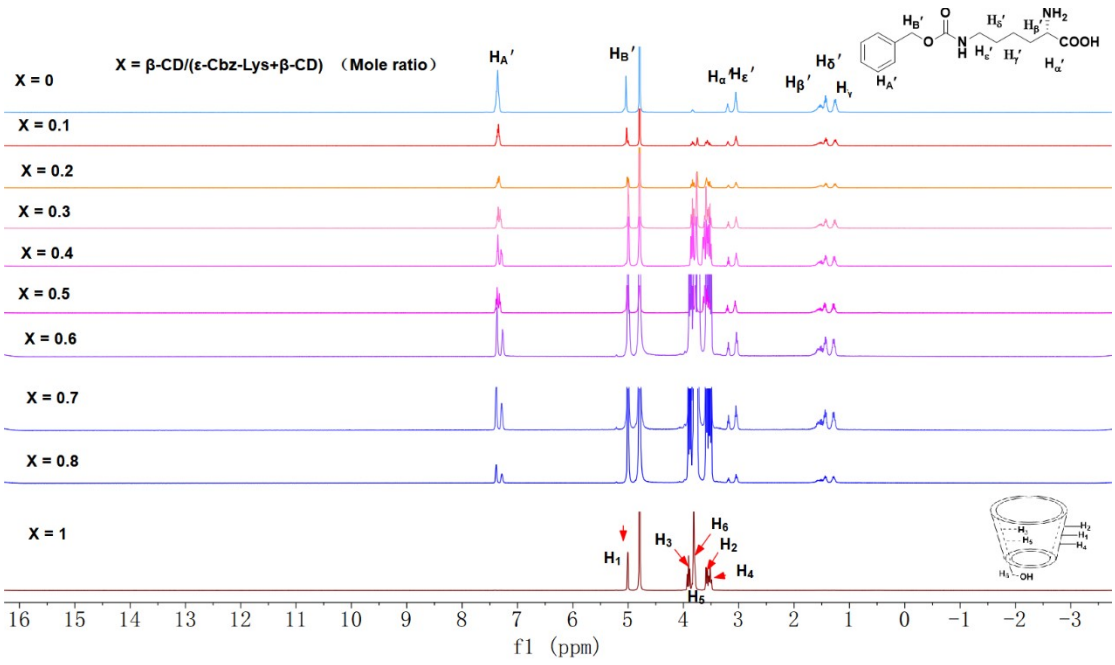


Figure S2. (a) ^{1}H NMR spectra (600 MHz, 298 K, D_2O) of different molar ratio of **1a** and β-CD. **(b)** Enlarged view for the ^{1}H NMR spectra of H_3, H_5 and H_6.

(a)



(b)

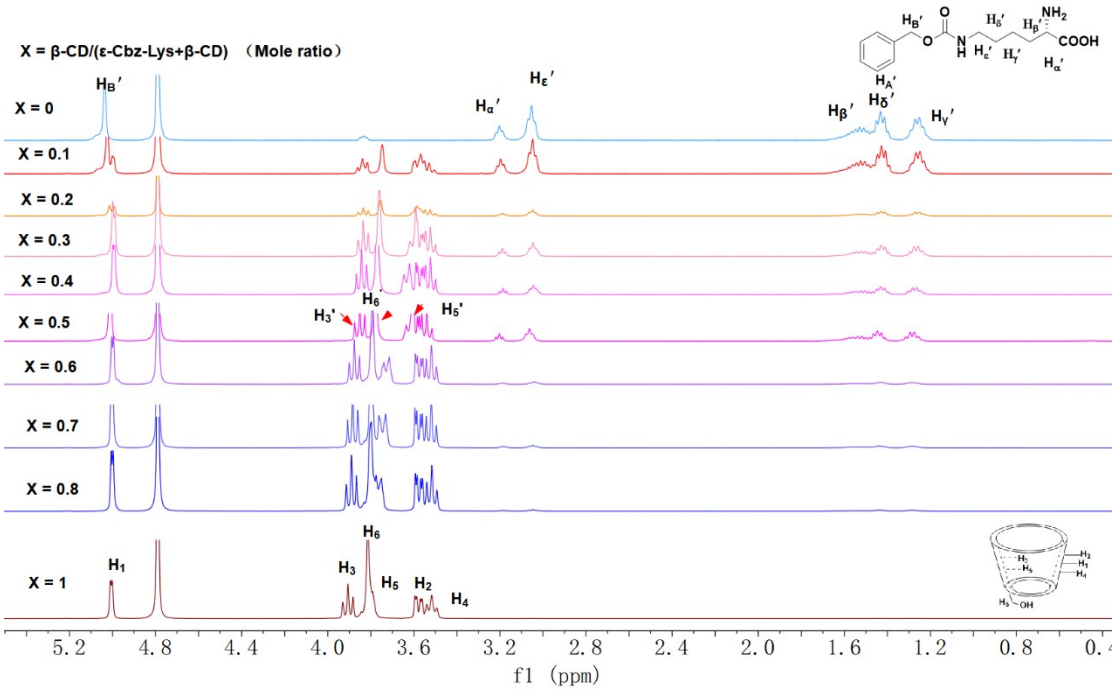


Figure S3 (a) ^{1}H NMR spectra (600 MHz, 298 K, D_2O) of ε-**3aa** in the presence of the β-CD at different concentrations. (b) Enlarged view for the ^{1}H NMR spectra of high-field signal (H_3, H_5, H_6).

6.2 Job's plot

The Job's plot was obtained by plotting the chemical shift changes ($\Delta\delta_{H3} = \delta_{free}-\delta_{obs}$) of the H_3-proton of β-CD between the chemical shift in the absence of **1a** (δ_{free}) and that in the presence of **1a** (δ_{obs}) multiplied by the mole fraction of β-CD (χ) against the mole

fraction of β-CD (Figure S4a). The maximum host/guest ratio of 0.5 founded on the graph revealing a 1:1 complex of **1a** and β-CD.

The chemical shift changes ($\Delta\delta_{H6} = \delta_{free}-\delta_{obs}$) of the H_6-protons of β-CD between the values in the absence of ε-**3aa** (δ_{free}) and those in the presence of ε-**3aa** (δ_{obs}) multiplied by the mole fraction of β-CD (χ) was plotted against the mole fraction of β-CD (Figure S3b). The maximum host/guest ratio was also founded at 0.5 on the Job's plot, which indicated a 1:1 complex of ε-**3aa** and β-CD.

Job's plot:

(a) **(b)**

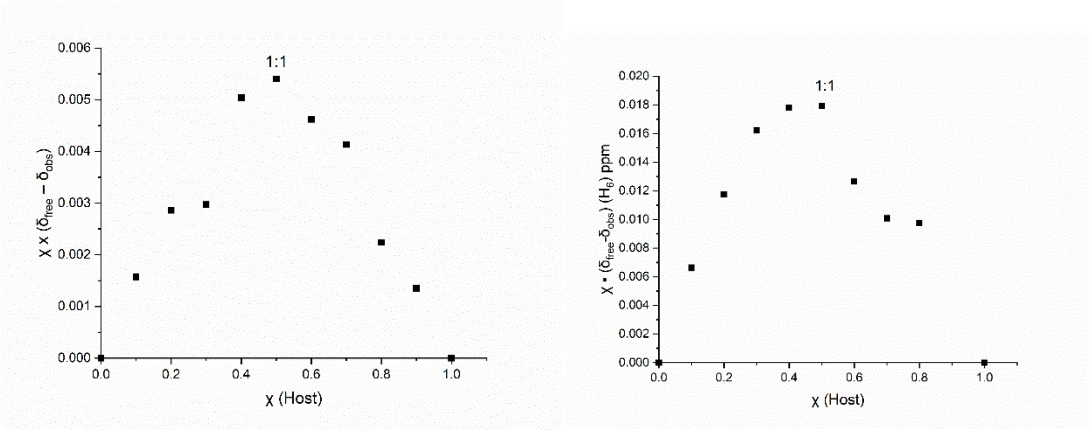


Figure S4. (a) Job's plot between β-CD and **1a** obtained by plotting the chemical shift changes of the protons (H_3 of β-CD, $\Delta\delta_{H3} = \delta_{free}-\delta_{obs}$) against CD's mole fraction (χ); **(b)** Job's plot between β-CD and ε-**3aa** obtained by plotting the chemical shift changes of the protons (H_6 of β-CD, $\Delta\delta_{H6} = \delta_{free}-\delta_{obs}$) against CD's mole fraction (χ).

6.3 ESI-MS spectra of 1a.CD and ε-3aa.CD

Preparation of substrate (1a) with β-CD for ESI-MS analysis: To a solution of Na_2CO_3 (5.3 mg, 0.05 mmol) in H_2O (500 ul) (pH = 9.6) in a 10 mL round bottom flask was added β-CD (56.7 mg, 0.05 mmol). L-lys **1a** (7.3 mg, 0.05 mmol) was added into the above solution under stirring. The mixture was stirred at 25 °C (oil bath) for 0.5 h. The ESI-MS spectra of the prepared sample was recorded using Bruker Bio TOF IIIQ (quadrupole time of flight) mass spectrometer.

Preparation of final products (ε-3aa) with β-CD for ESI-MS analysis: To a solution of Na_2CO_3 in H_2O (1.0 mL, pH = 12) in a 10 mL round bottom flask was added β-CD (22.7 mg, 0.02 mmol) and ε-**3aa** (5.6 mg, 0.02 mmol). The mixture was stirred at 50 °C (oil bath) for 0.5 h. The ESI-MS spectra of the prepared sample was recorded using Bruker Bio TOF IIIQ (quadrupole time of flight) mass spectrometer.

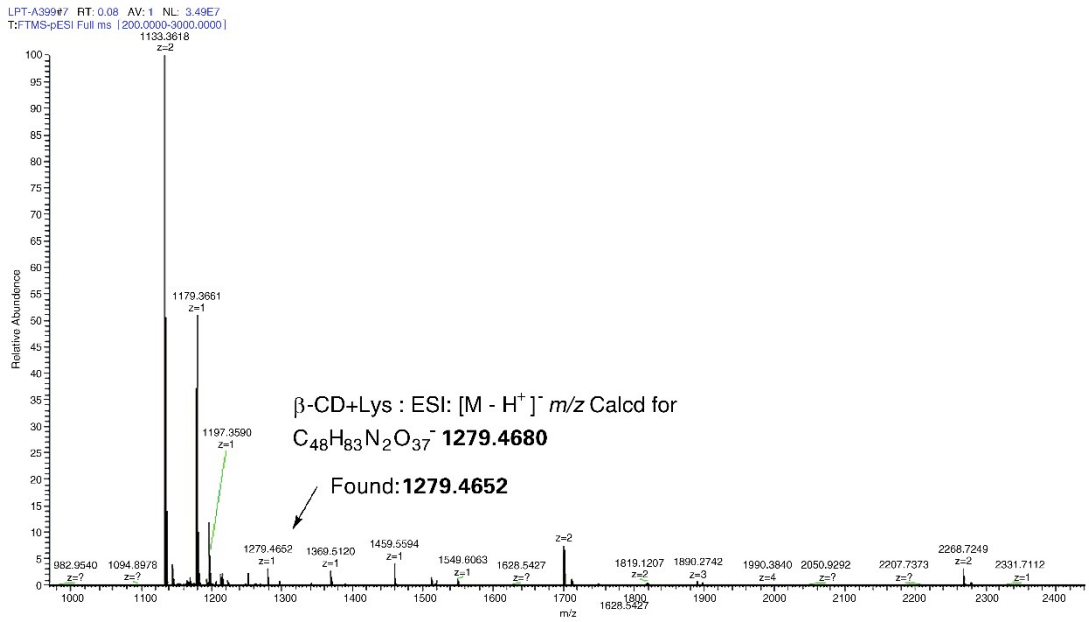


Figure S5. ESI-MS spectra of 1:1 solution of **1a** and β-CD.

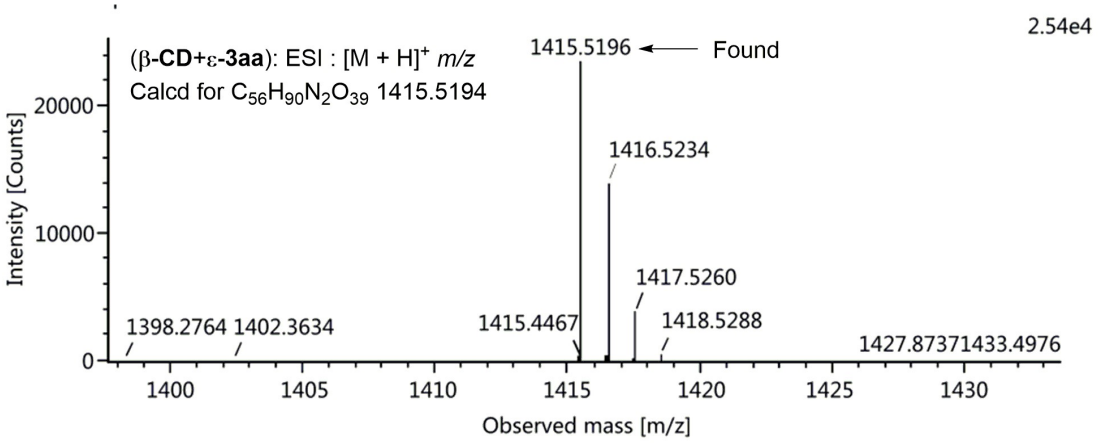


Figure S6. ESI-MS spectra of 1:1 solution of ε-**3aa** and β-CD.

6.4 Determination of the binding constants of 1a to β-CD and ε-3aa to CD

Determination of the binding constants of 1a to β-CD: In order to determine the binding constant of the 1:1 complex formed between the **1a** (ε-**3aa**) and β-CD, the experimental ^{1}H NMR data acquired from the Job's plot (continuous variation method) was used. The binding constant of **1a** with β-CD was calculated by the equation (1) reported by M. Bogdan [1].

$\Delta\delta_c$ is separate variable and denoted as the chemical shift of the protons in the pure inclusion complex. The value of $\Delta\delta_c$ is that produce the best fit of calculated to observed data $\Delta\delta_{H3}$ (Table S1). The curves were obtained by plotting the chemical shift changes ($\Delta\delta_{H3} = \delta_{free}-\delta_{obs}$) of the H_3-protons of β-CD between the values in the absence of **1a** (δ_{free}) and those in the presence of **1a** (δ_{obs}) against the mole fraction of β-CD in aqueous solution. We can obtain the value of $\Delta\delta_c$ *(χ = 0.5, $\Delta\delta_c$-H_3* = 0.0962 ppm*)* from

the curve (Figure S7). The binding constants for the 1:1 complex (Lys+β-CD, $K_{1a.CD}$=1595.3 M^{-1}) were evaluated by a nonlinear least-squares curve-fitting regression analysis according to Equation (1).

Determination the binding constant of ε-3aa to β-CD: The procedures were the similar with above described for the calculation of $\Delta\delta_c$, excepting that the value of $\Delta\delta_{H6}$ was used to determine the binding constant of ε-**3aa** to β-CD. The chemical shift changes ($\Delta\delta_{H6} = \delta_{free}-\delta_{obs}$) of the H_6-protons of β-CD between the values in the absence of ε-**3aa** (δ_{free}) and those in the presence of ε-**3aa** (δ_{obs}) was plotted against the mole fraction of β-CD (Figure S8). We can obtain the value of $\Delta\delta_c$ *(χ = 0.5, $\Delta\delta_c$-H_6* = 0.03295 ppm*)* from the curve (Figure S8). The binding constants for the 1:1 complex (ε-Cbz-Lys+β-CD, $K_{3aa.CD}$=2359 M^{-1}) were evaluated by a nonlinear least-squares curve-fitting regression analysis according to Equation (1).

Table S1. The change of ^{1}H Chemical shifts ($\Delta\delta_{H3}$) of **1a.CD**.

Assignment	Mole fraction χ (Host) / δ_0 (ppm)	$\Delta\delta_{H3}$ (ppm)								
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
H_3 (β-CD)	**3.9064**	**0.0157**	**0.0143**	**0.0099**	**0.0126**	**0.0108**	**0.0077**	**0.0059**	**0.0028**	**0.0015**

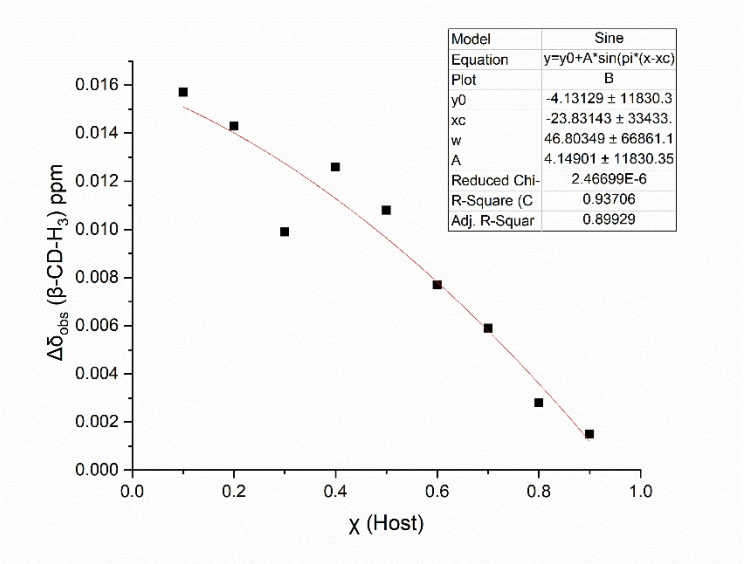


Figure S7. The graph was plotted by the chemical shift changes of protons ($\Delta\delta_{H3}$) in β-CD VS the mole fraction of Host (χ)

Table S2. The change of ^{1}H Chemical shifts ($\Delta\delta_{H6}$) of ε-**3aa.CD**.

Assignment	Mole fraction χ (Host) / δ_0 (ppm)	$\Delta\delta_{H6}$ (ppm)							
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8
H_6 (β-CD)	**3.8138**	**0.0663**	**0.0588**	**0.0540**	**0.0451**	**0.0358**	**0.0211**	**0.0144**	**0.0153**

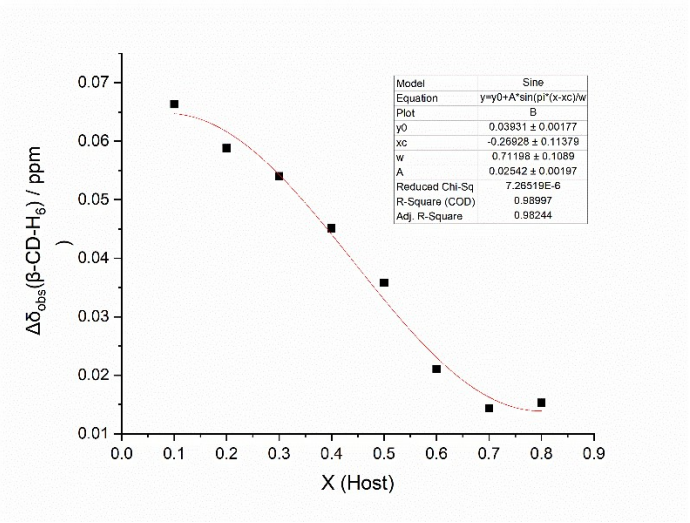


Figure S8. The graph was plotted by the chemical shift changes of protons ($\Delta\delta_{H6}$) in β-CD VS the mole fraction of Host (χ)

6.5 Reactions of 1a and 2a with β-CD catalysis in the presence of products (ε-3aa)

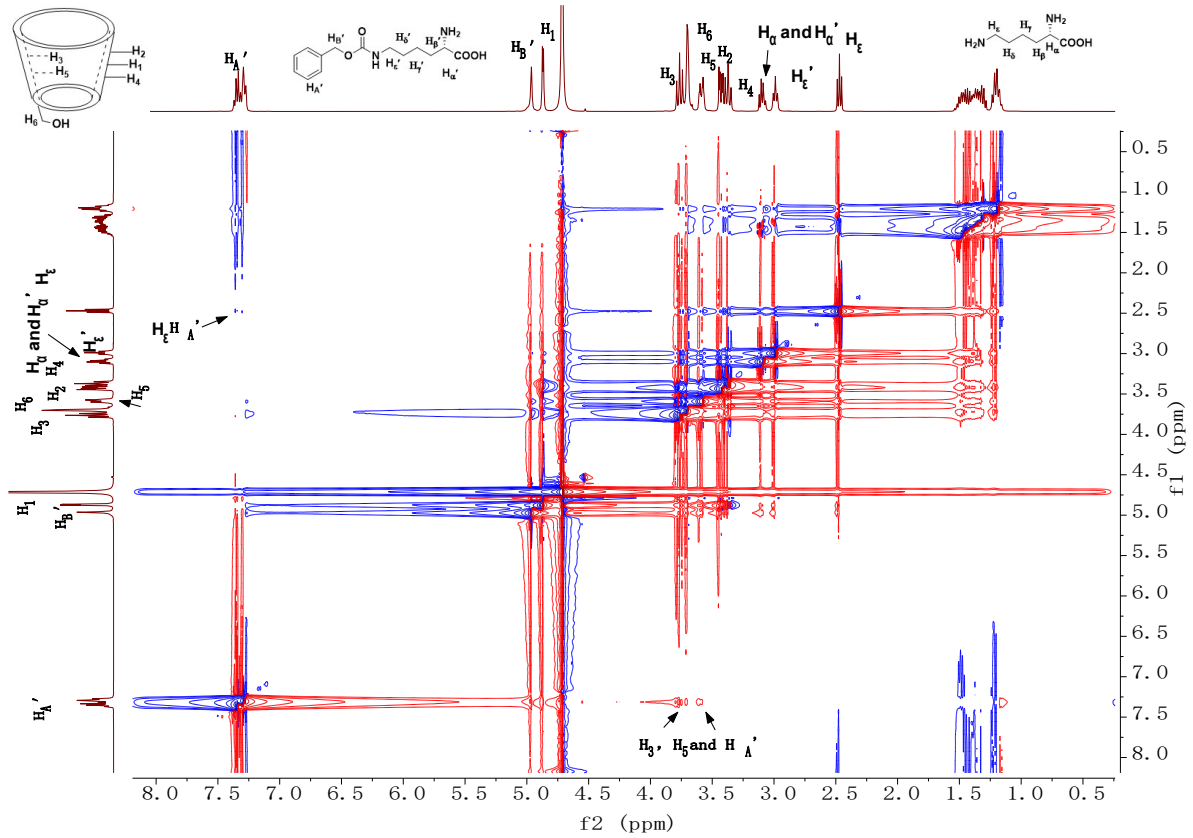
Addition sequence of 1a-3aa-2a: To a stirred solution of carbonate buffer was added β-CD (22.7 mg, 20 mol%) (12 mL, pH = 9). Then **1a** (0.5 mmol, 0.5 equiv) was added into the solution, and the mixture was stirred at 25 °C for 0.5 h, followed by the addition of ε-**3aa** (0.5 mmol, 0.5 equiv). The mixture was continuously stirred for 0.5 h. Then, **2a** (0.5 mmol, 1 equiv) was added into the mixture. The mixture was stirred for 1.5 h at 25 °C (Oil bath). After that, H_2O (12 mL) and EA (6 mL) were added to the solution. The mixture was ultrasonicate for 2 min, then transferred into a separator funnel. The white solids floated on the surface of the aqueous mixture were collected and washed successively with water (5×10.0 mL) and EA (5×10.0 mL), and was subjected for HPLC analysis.

The reversed addition sequence of 3aa-1a-2a: To a stirred solution of carbonate buffer was added β-CD (22.7 mg, 20 mol%) (12 mL, pH = 9). Then product ε-**3aa** (0.5 mmol, 0.5 equiv) was added into the solution, and the mixture was stirred at 25 °C for 0.5 h, followed by the addition of **1a** (0.5 mmol, 0.5 equiv). The mixture was continuously stirred for 0.5 h. Then, **2a** (0.5 mmol, 0.5 equiv) was added into the mixture. The mixture was stirred for 1.5 h at 25 °C (Oil bath). After that, H_2O (12 mL) and EA (6 mL) were added to the solution. The mixture was ultrasonicate for 2 min, then transferred into a separator funnel. The white solids floated on the surface of the aqueous mixture were collected and washed successively with water (5×10.0 mL) and EA (5×10.0 mL), and was subjected for HPLC analysis.

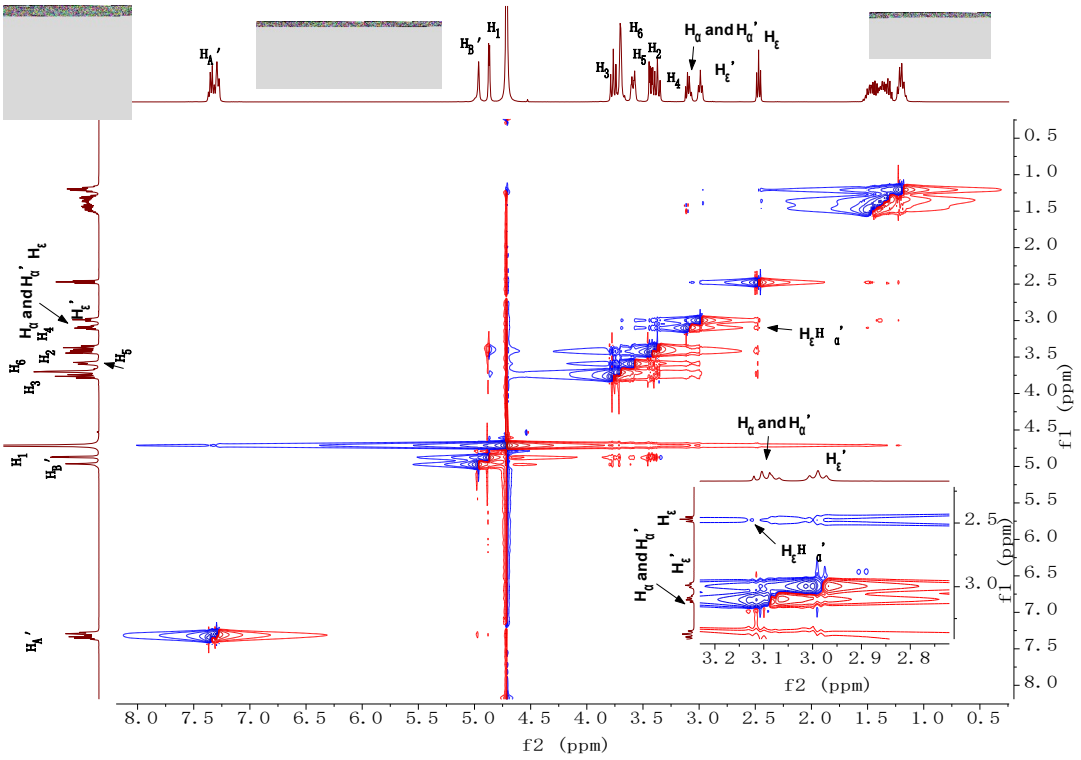
Preparation of ternary complex of 1a.β-CD. ε-3aa for 2D ROESY spectra.

To a solution of Na_2CO_3 (10.6 mg, 0.1 mmol) in D_2O (600 ul) (pH = 11) in a 10 mL round bottom flask was added β-CD (22.7 mg, 20 mol%). L-lys **1a** (7.3 mg, 0.05 mmol) was added into the above solution under stirring. The mixture was stirred at 50 °C (oil bath) for 0.5 h. After that, the ε-**3aa** (14.0 mg, 0.05 mmol) was added. The mixture was continuously stirred for 0.5 h at 25 °C, and transferred into NMR tube (**1a**+ε-**3aa**):β-CD = 1:0.2, molar ratio). The Roesy spectrum of the prepared sample was recorded using an INVOA-600 M at 25 °C (Figure S9).

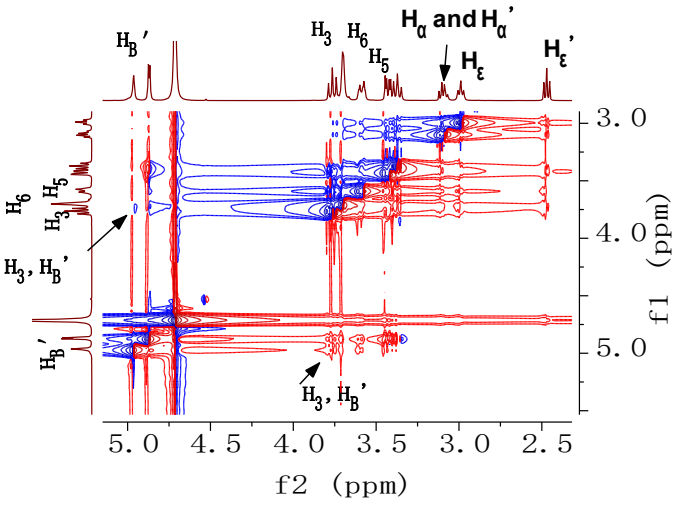
(a)



(b)


f2 (ppm)
f1 (ppm)
H_α and H_α'
H_ε'
H_ε H_α'

(c)


H_B'
H_3 H_6 H_5
H_α and H_α'
H_ε
H_ε'
H_3, H_B'
f2 (ppm)
f1 (ppm)

(d)

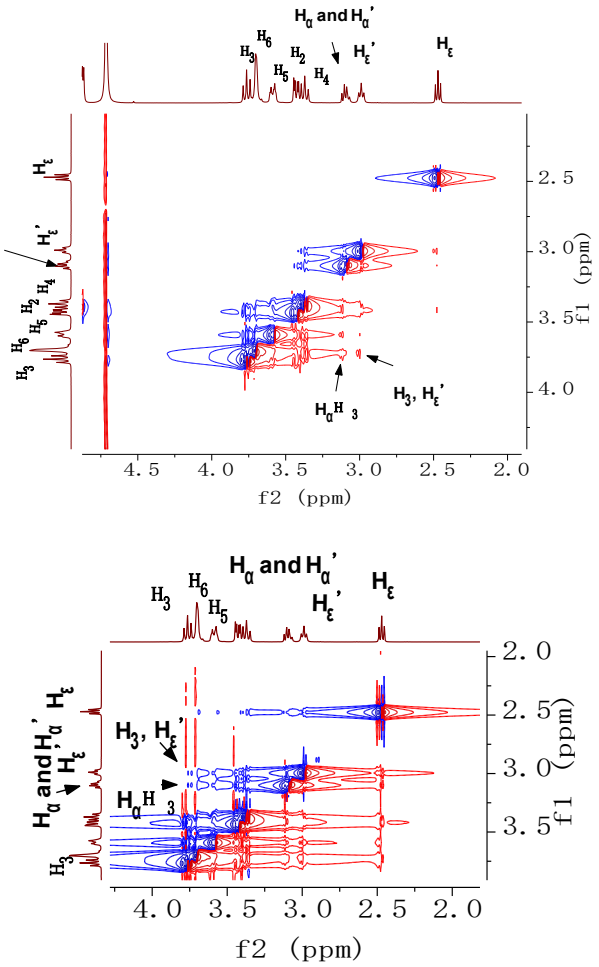


Figure S9. (a) 2D ROESY spectrum of ternary complex between **1a**, ε-**3aa** and β-CD (addition sequence: (**1a**+**CD**)-**3aa**). (b) Enlarged view for H_{α}' and H_{ε} (c) Enlarged view for H_B' and H_3 (d) Enlarged view for Hα and H_3, H_{ε}' and H_3.

7. Preparation and characterization of SiO_2@CD

7.1 Preparation of SiO_2@CD

Preparation of SiO_2 Nanoparticles (SiO_2NPs). The synthesis of SiO_2 Nanoparticles (SiO_2NPs) was achieved referring to the method reported by Stöber. [2] Ethanol (44 mL), water (11 mL), and ammonia solution (1.1 mL) were mixed in a round bottom flask and vigorously stirred at 40˚C (oil bath). Then a mixed solution of TEOS (4.4 mL, 20 mmol) and ethanol (20 mL) was quickly added to the above solution and the mixture was stirred for 15 h. The final suspension was centrifuged and rinsed with acetone. Finally, the obtained SiO_2NPs were vacuum dried at 120˚C (oil bath) for 24 h.

Preparation of β-CD-silane. To a solution of β-CD (1.135 g, 1 mmol) in anhydrous DMF (10 mL) was added 3-Isocyanatopropyltriethoxysilane (IPTES, 272.4 ul, 1.1 mmol) dropwise. The reaction mixture was stirred at 80 ˚C (oil bath) for 6 h under Nitrogen atmosphere. After cooling down to room temperature, acetone (20 mL) was added and the precipitates was collected by filtration. The white solids were washed

with acetone (3×10.0 mL) and purified by recrystallization (EtOH). Finally, the obtained β-CD-silane was vacuum dried at 60˚C for 24 h.

Preparation of SiO_2@CD-X (X = 5, 10, 20, 30). To a solution of β-CD-silane (x mmol, x = 0.05, 0.1, 0.2, 0.3) in anhydrous DMF (20 mL) was added SiO_2NPs (500 mg). The mixture was heated to 110 ˚C (oil bath) and stirred vigorously for 24 h under Nitrogen atmosphere. Finally, the solids were collected by filtration and washed with water, vacuum dried for 12 h to afford SiO_2@CD-X (X = 5, 10, 20, 30).

7.2 Characterization of SiO_2@CD

7.2.1 ^{1}H and ^{13}C NMR spectra of β-CD-silane

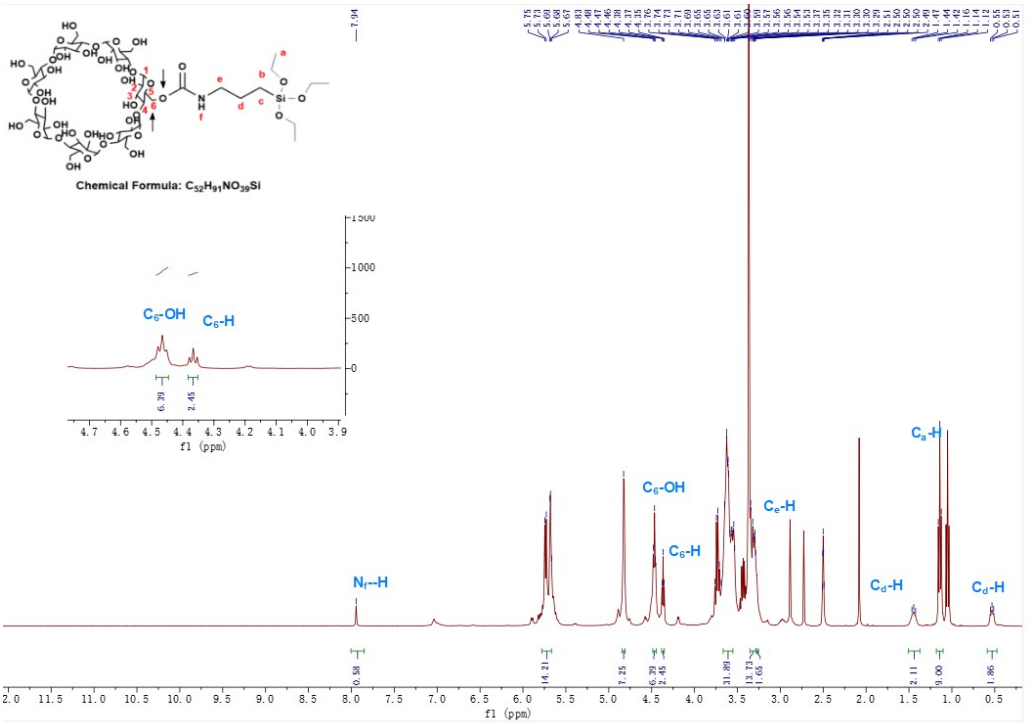


Figure S10. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum for β-CD-silane

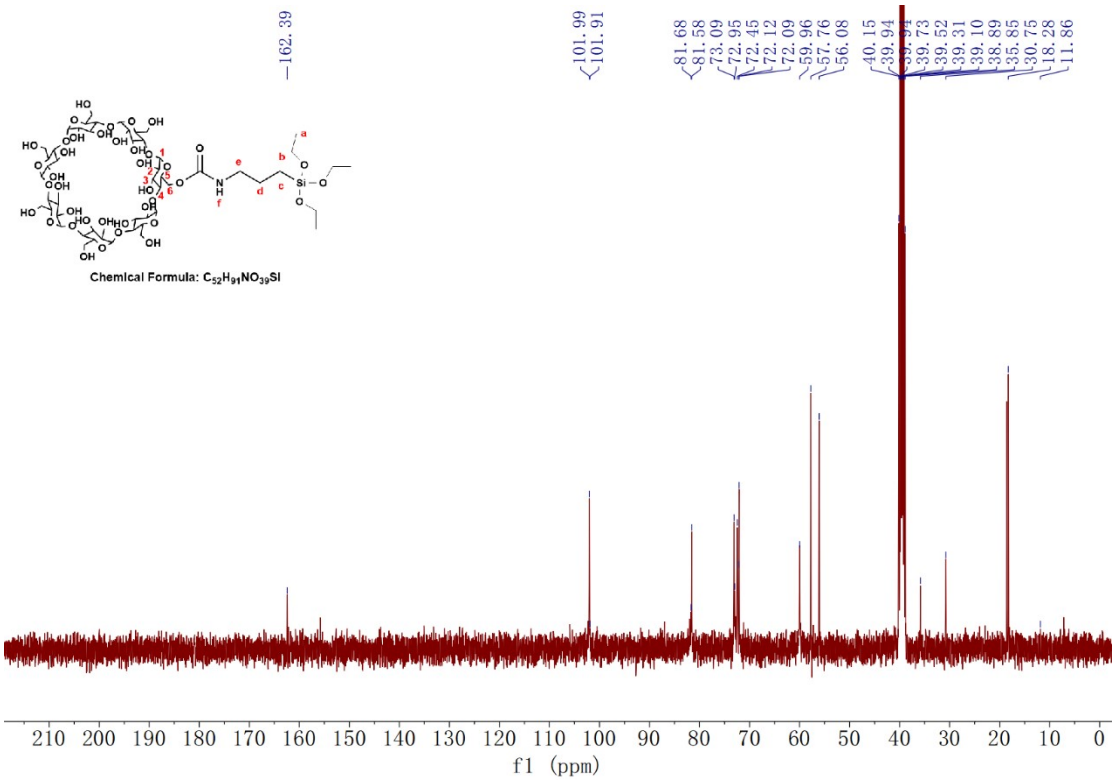


Figure S11. ^{13}C NMR (101 MHz, DMSO-d_6) spectrum for β-CD-silane

7.2.2 SEM image of SiO_2NPs

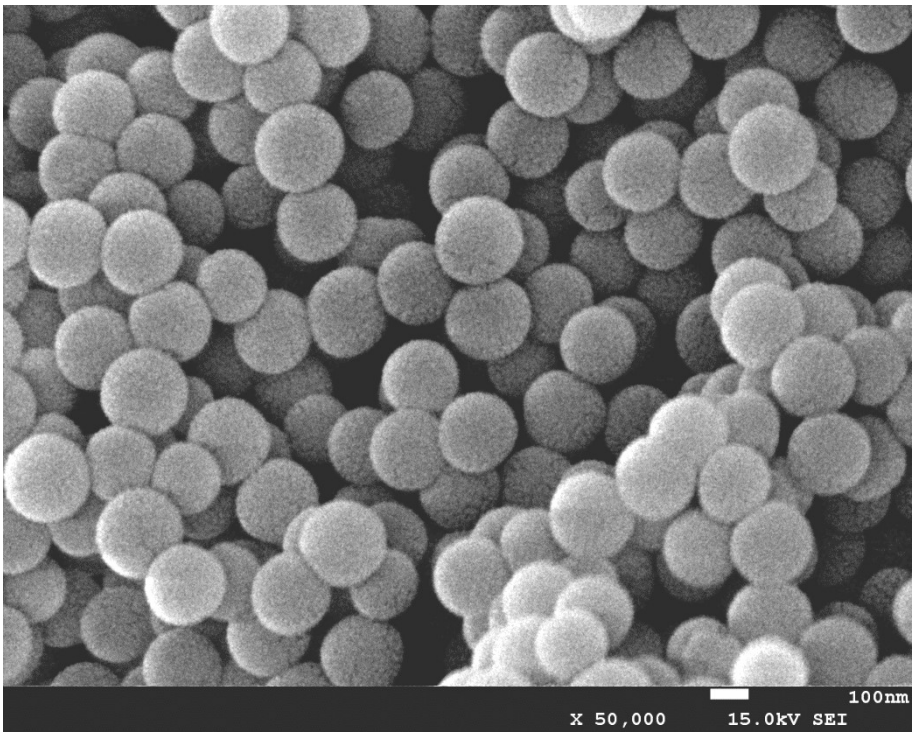


Figure S12. SEM image of SiO_2NPs

7.2.3 Determination of β-CD content on the surface of SiO_2@CD by Ultraviolet-visible spectrophotometry (UV-vis).

The experimental procedure was referred to Cravotto's method. [3] The buffer solution

(pH 10.5) was prepared by dissolving Na_2CO_3 (13.2 g) and $NaHCO_3$ (2.1 g) in ultrapure water (250 mL). Phenolphthalein (Php) stock solution (5 mmol/L) was prepared from Php powder (159.2 mg, 0.5 mmol) dissolved in ethanol (100 mL). The Php stock solution (160 uL) was diluted with the buffer solution (250 mL, pH 10.5) to achieve a Php standard solution (0.008 mmol/L). β-CD stock solution (650 mg/L) was prepared by dissolving β-CD powder (650 mg) in ultrapure water (1 L), and a series volume of β-CD stock solution (0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.8 mL, 1 mL) was added into 10 mL Volumetric flask and diluted with Php standard solution to tick mark to achieve a series concentration of CD-Php solution (6.5 mg/L, 13 mg/L, 19.5 mg/L, 26 mg/L, 52 mg/L, 65 mg/L). The concentrations of the Php-CD solution were measured by UV-visible absorbance spectra at the wavelength of 553 nm at room temperature. The calibration graph of β-CD concentrations (x) versus Php-CD absorbance (y) were plotted (Figure S12).

To determine the contents of β-CD grafted on the surface of SiO_2NPs, SiO_2@CD-X (10 mg) were dispersed in Php standard solution (100 mL) respectively, and vigorously stirred for 1 h. The suspension was subjected for UV-visible spectrum analysis. The content of β-CD on SiO_2@CD (mmol%/500 mg) was calculated by formula. The formula was as follow:

The content of β-CD on SiO_2@CD (mmol%/500 mg) = [(0.1981-A)/0.0015]•V•50/1134.99

(A was the absorbance of Php-CD solution measured by UV-vis; V is the volume of Php standard solution. "1134.99" is the Molecular Wight of β-CD.)

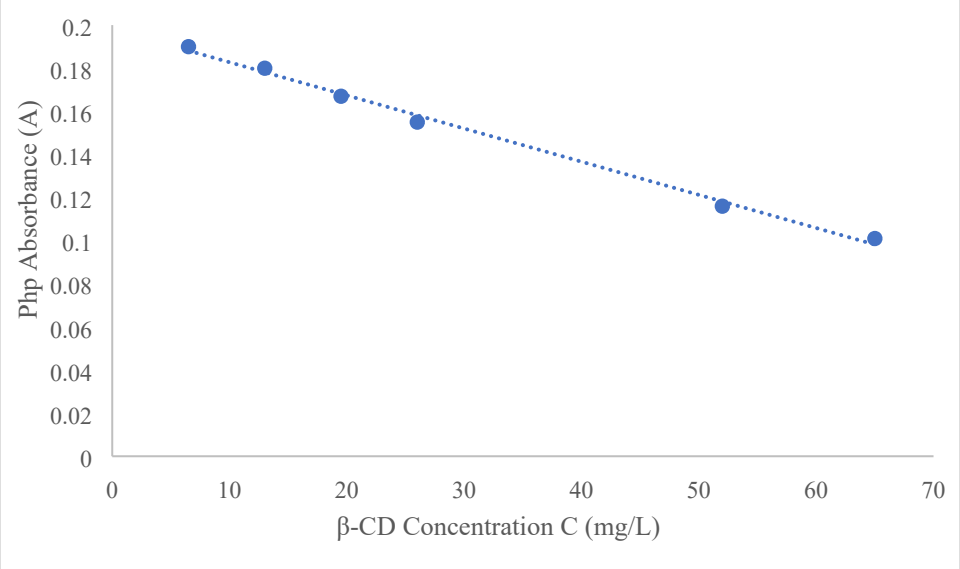


Figure S13. UV-visible absorbance of Php vs β-CD concentration

7.2.4 Thermogravimetry analysis (TGA) for SiO_2@CD-10

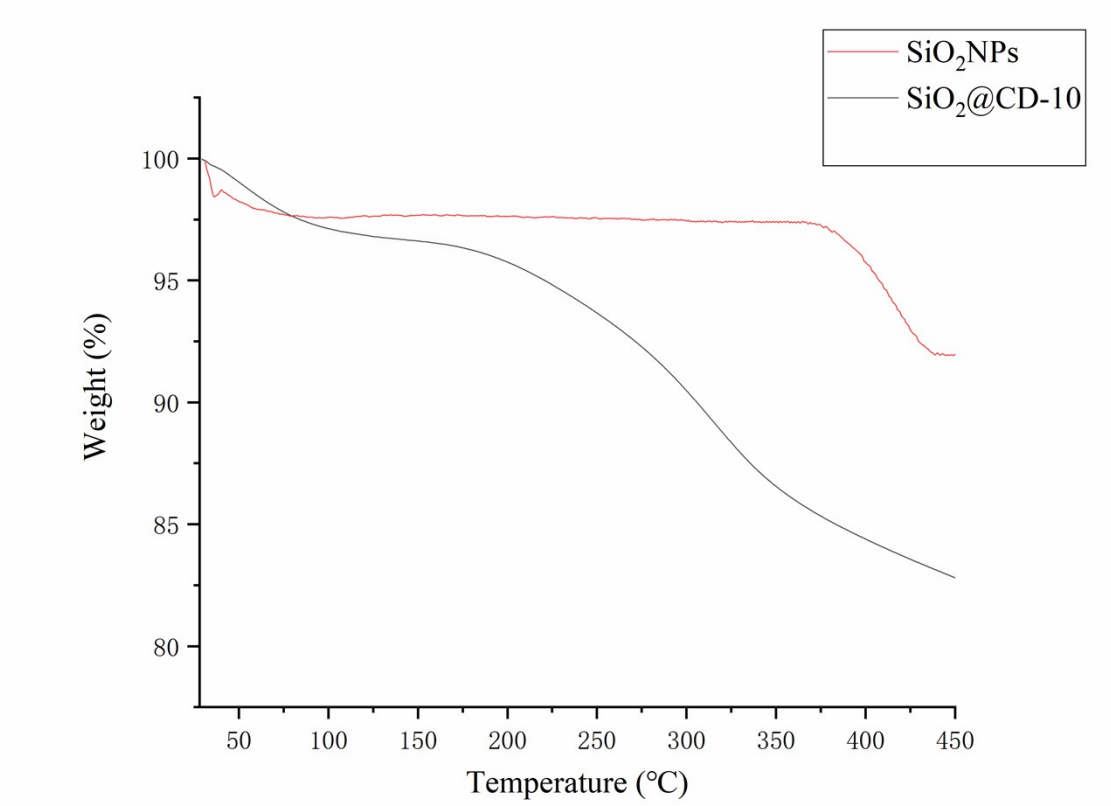


Figure S14. TGA graphs of SiO_2NPs and SiO_2@CD-10

7.3 Reactions of 1a and 2 with SiO_2@CD catalysis.

To a stirred solution of carbonate buffer was added SiO_2@CD-10 (23.0 mg, about 4 mol% β-CD) (4 mL, pH = 9). Then L-lys **1a** (0.1 mmol, 1 equiv) was added into the solution and the mixture was vigorously stirred at 25 °C (oil bath) for 1 h, followed by dropwise addition of **2** (0.11 mmol, 0.11 equiv). The reaction mixture was continuously stirred for 5 h. Once the reaction was done, the products and catalysts were automatically separated with the products floating on the surface of the aqueous mixture and the catalysts remained on the bottom of the flask. And the products were easily isolated by a separatory funnel and purified by washing with H_2O (5×10.0 mL) and EA (5×10.0 mL).

Gram-Scale experiments. To a stirred solution of carbonate buffer (40 mL) was added SiO_2@CD-10 (2.3 g, about 4 mol% β-CD to **1a**) (pH = 9). Then L-lys **1a** (1.462 g, 10 mmol) was added into the solution and the mixture was vigorously stirred at 25 °C (oil bath) for 1 h, followed by dropwise addition of **2a** (1.548 mL, 11 mmol). The reaction mixture was continuously stirred for 5 h. Once the reaction was done, the products and catalysts were automatically separated with the products floating on the surface of the aqueous mixture and the catalysts remained on the bottom of the flask. And the products

were easily isolated by a separatory funnel and purified by washing with H_2O (5×10.0 mL) and EA (5×10.0 mL). The obtained product was vacuum dried at 60 ˚C for 24 h to get white solid (1.81 g, yield 65%).

7.4. Reusability of SiO_2@CD-10

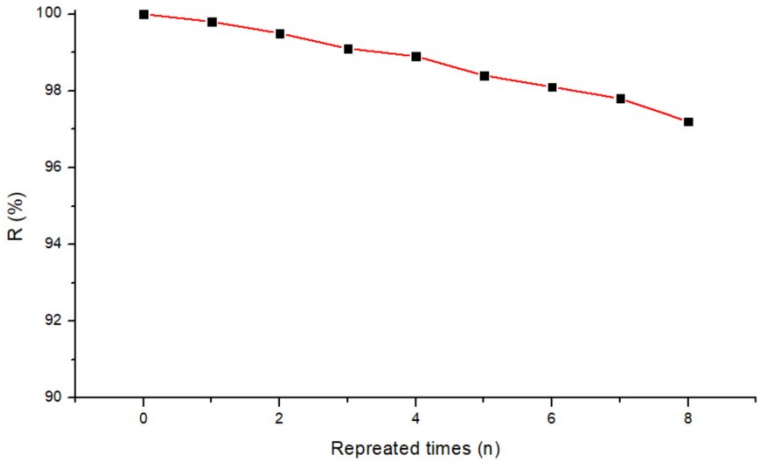
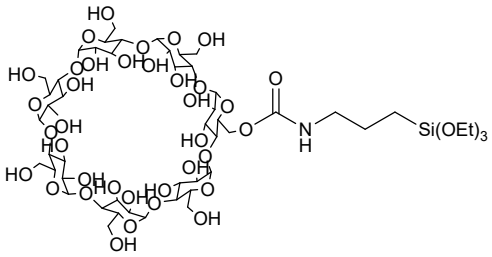


Figure S15. The graph of repeated times (n) vs catalytic efficiency (R) of SiO_2@CD-10

Reference:

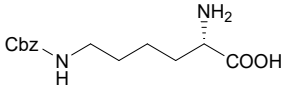
1) V. J. Smith, D. Bogdan, M. R. Caira, M. Bogdan, S. A. Bourne, S. I. Fărcaş, *Supramolecular Chemistry* **2009**, *22*, 172-177.
2) W. Stöber, A. Fink, E. Bohn, *J. Colloid Interface Sci.* **1968**, *26*, 62-69.
3) K. Martina, F. Baricco, G. Berlier, M. Caporaso, G. Cravotto, *ACS Sustain. Chem. Eng.* **2014**, *2*, 2595-2603.

8. ^{1}H and ^{13}C NMR data for all compounds



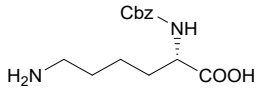
β-CD-silane

β-CD-silane. White solid, mp >300 ºC; 735.4 mg, Yield 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 5.87-5.57 (m, 14H), 4.88-4.78 (m, 7H), 4.47 (t, J = 5.6 Hz, 6H), 4.12 (t, J = 12.5 Hz, 2H), 3.76-3.51 (m, 32H), 3.36-3.26 (m, 14H), 3.17 (d, J = 5.2 Hz, 2H), 1.81-0.94 (m, 9H), 0.91- 0.52 (m, 2H), 0.47 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 102.0, 101.9, 81.7, 81.6, 73.1, 73.0, 72.5, 72.1, 72.1, 60.0, 57.8, 56.1, 40.2, 35.9, 30.8, 18.3, 11.9; HRMS (ESI) *m/z* calcd for $C_{52}H_{92}NO_{39}Si[M+H]^+$ 1382.5010 , found 1382.5014.



ε–3aa

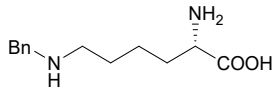
N_ε-((benzyloxy)carbonyl)-L-lysine (ε-**3aa**). The compound was purified by filtration and washed with water (3x10 mL) and ethyl acetate (3x10 mL). White solid, mp 250-251 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.91-6.96 (m, 5H), 5.08 (s, 2H), 3.19 (t, *J* = 6.4 Hz, 1H), 3.10 (t, *J* = 6.8 Hz, 2H), 1.67-1.38 (m, 4H), 1.37-1.19 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 183.6, 158.4, 136.6, 128.8, 128.3, 127.6, 66.7, 55.9, 40.3, 34.4, 28.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}N_2O_4$ $[M+H]^+$ 281.1496, found 281.1496.



α**–3aa**

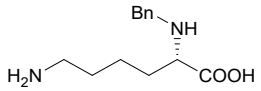
N_α-((benzyloxy)carbonyl)-L-lysine (α-**3aa**). (R_f = 0.2; dichloromethane/methanol = 10:1, 0.1% TFA). White solid, mp 226-227 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.77-7.03 (m, 5H), 5.08 (s, 2H), 3.19 (t, *J* = 6.4 Hz, 1H), 3.10 (t, *J* = 6.8 Hz, 2H), 1.79-1.41 (m, 4H), 1.36-1.17 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 179.6, 157.8, 136.6, 128.8, 128.3, 127.7, 66.9, 56.1, 39.2, 31.2, 26.3, 22.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}N_2O_4$ $[M+H]^+$ 281.1496, found 281.1491.

(Heterogeneous condition (ε-**3aa**+α-**3aa**): 22.2 mg, yield 79%; Homogeneous condition (ε-**3aa**+α-**3aa**): 236.6 mg, yield 84%).



ε**–3ab**

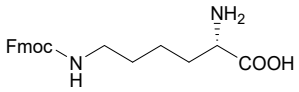
N_ε-benzyl-L-lysine (ε-**3ab**). (R_f=0.2; dichloromethane/ methanol = 5:1, 0.1% TFA). Colorless oil, ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56-7.35 (m, 5H), 4.20 (s, 2H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.14-2.99 (m, 2H), 2.07-1.85 (m, 2H), 1.78 (p, *J* = 7.7 Hz, 2H), 1.68-1.45 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ 174.7, 130.8, 129.7, 129.6, 129.2, 54.5, 51.0, 46.6, 29.9, 25.2, 21.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ 237.1598, found 237.1553.



α**–3ab**

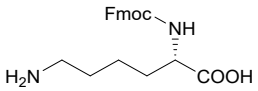
N_α-benzyl-L-lysine (α-**3ab**). (R_f=0.25; dichloromethane/ methanol = 5:1, 0.1% TFA). Colorless oil. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71-7.19 (m, 5H), 4.20 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 1H), 3.12-2.96 (m, 2H), 2.09-1.84 (m, 2H), 1.84-1.70 (m, 2H), 1.64-1.44 (m, 2H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 162.4, 123.1, 121.5, 121.1, 120.7, 44.2, 42.8, 38.5, 21.5, 17.0, 13.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ 237.1598, found 237.1597.

(Heterogeneous condition (ε-**3ab**+α-**3ab**): 11.0 mg, yield 47%; Homogeneous condition (ε-**3ab**+α-**3ab**): 142.7 mg, yield 60%).



ε–**3ac**

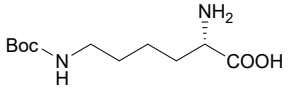
N_{ε}-(((9H-fluoren-9-yl) methoxy) carbonyl)-L-lysine (ε-**3ac**). (R_f=0.25; dichloromethane/ methanol = 5:1, 0.1% TFA). White solid, mp 208-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 7.5 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.46-7.38 (m, 2H), 7.37-7.28 (m, 2H), 4.40-4.25 (m, 2H), 4.24-4.11 (m, 1H), 3.28 (t, J = 6.0 Hz, 2H), 2.96 (q, J = 6.4 Hz, 2H), 1.90-1.50 (m, 2H), 1.44-1.22 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.3, 156.1, 143.9, 140.7, 127.6, 127.1, 125.2, 120.1, 65.2, 53.7, 46.8, 30.6, 29.1, 22.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ 369.1809, found 369.1818.



α–**3ac**

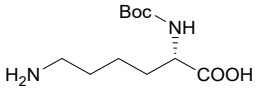
N_{α}-(((9H-fluoren-9-yl) methoxy) carbonyl)-L-lysine (α-**3ac**). (R_f=0.33; dichloromethane/ methanol = 5:1, 0.1% TFA). White solid, mp 27-28 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.4 Hz, 1H), 7.37-7.24 (m, 2H), 4.31-4.24 (m, 2H), 4.20 (t, J = 6.9 Hz, 1H), 3.23-3.11 (m, 2H), 3.06-2.84 (m, 2H), 1.79-1.67 (m, 1H), 1.66-1.48 (m, 1H), 1.46-1.15 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 182.4, 171.8, 144.7, 141.6, 128.7, 128.1, 126.1, 121.1, 66.2, 52.8, 47.6, 30.4, 29.7, 22.5, 22.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ 369.1809, found 369.1861.

(Heterogeneous condition (ε-**3ac**+α-**3ac**): 6.7 mg, yield 18%; Homogeneous condition (ε-**3ac**+α-**3ac**): 87.3 mg, yield 24%).



ε–**3ad**

N_{ε}-(tert-butoxycarbonyl)-L-lysine (ε-**3ad**). (R_f=0.33; dichloromethane/ methanol = 10:1, 0.1% TFA). White solid, mp 225-227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (s, 1H), 3.09-3.03 (m, 1H), 2.91-2.84 (m, 2H), 1.75-1.62 (m, 2H), 1.58-1.47 (m, 2H), 1.40-1.23 (m, 11H); ^{13}C NMR (101 MHz, D_2O) δ172.6, 156.2, 78.7, 52.5, 37.4, 27.9, 26.4, 25.5, 19.5; HRMS (ESI) *m/z* calcd for $C_{11}H_{23}N_2O_4$ $[M+H]^+$247.1652, found 247.1651.

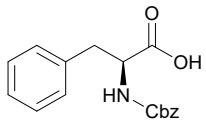


α–**3ad**

N_{α}-(tert-butoxycarbonyl)-L-lysine (α-**3ad**). (R_f=0.33; dichloromethane/ methanol = 10:1, 0.1% TFA). White solid, mp. 200-201°C. ^{1}H NMR (400 MHz, D_2O) δ 3.91-3.87 (m, 1H), 3.00 (t, J = 7.5 Hz, 2H), 1.89-1.54 (m, 4H), 1.53-1.34 (m, 11H); ^{13}C NMR

(101 MHz, D_2O) δ 179.9, 157.6, 81.0, 55.8, 39.3, 31.3, 27.7, 26.4, 22.1. HRMS (ESI) *m/z* calcd for $C_{11}H_{23}N_2O_4$ $[M+H]^+$ 247.1652, found 247.1652.

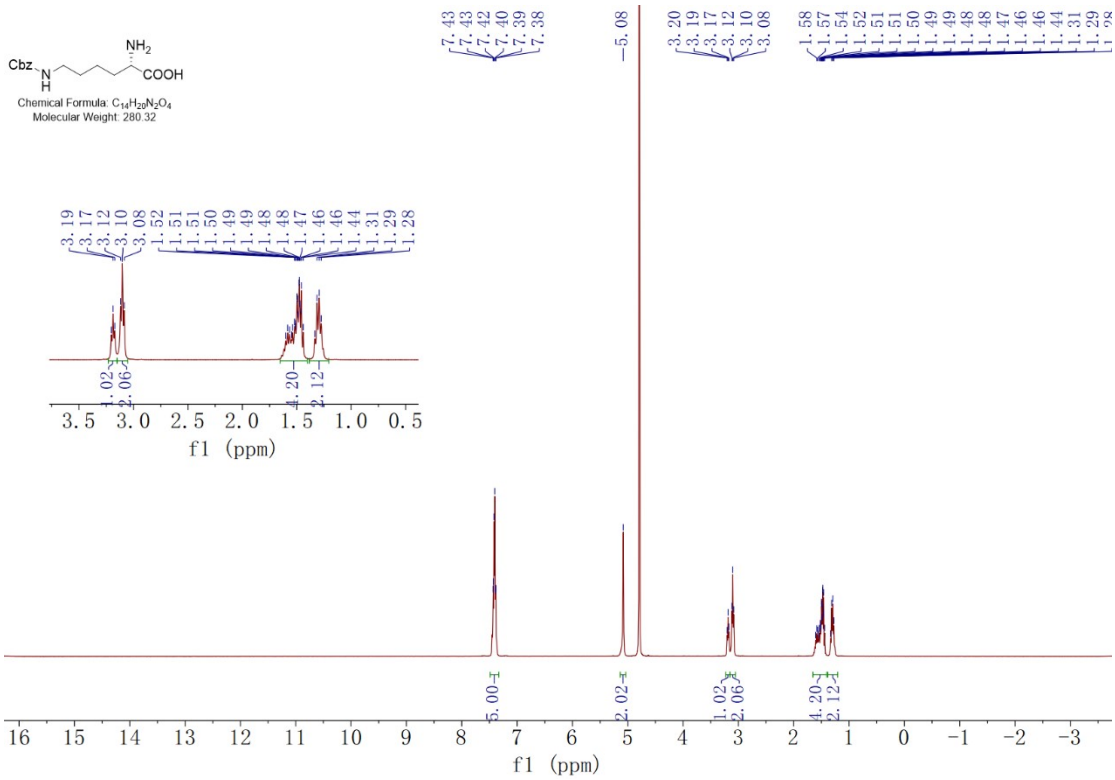
(Heterogeneous condition (ε-**3ad**+α-**3ad**): 2.6 mg, yield 10%; Homogeneous condition (ε-**3ad**+α-**3ad**): 43.6 mg, yield 18%).



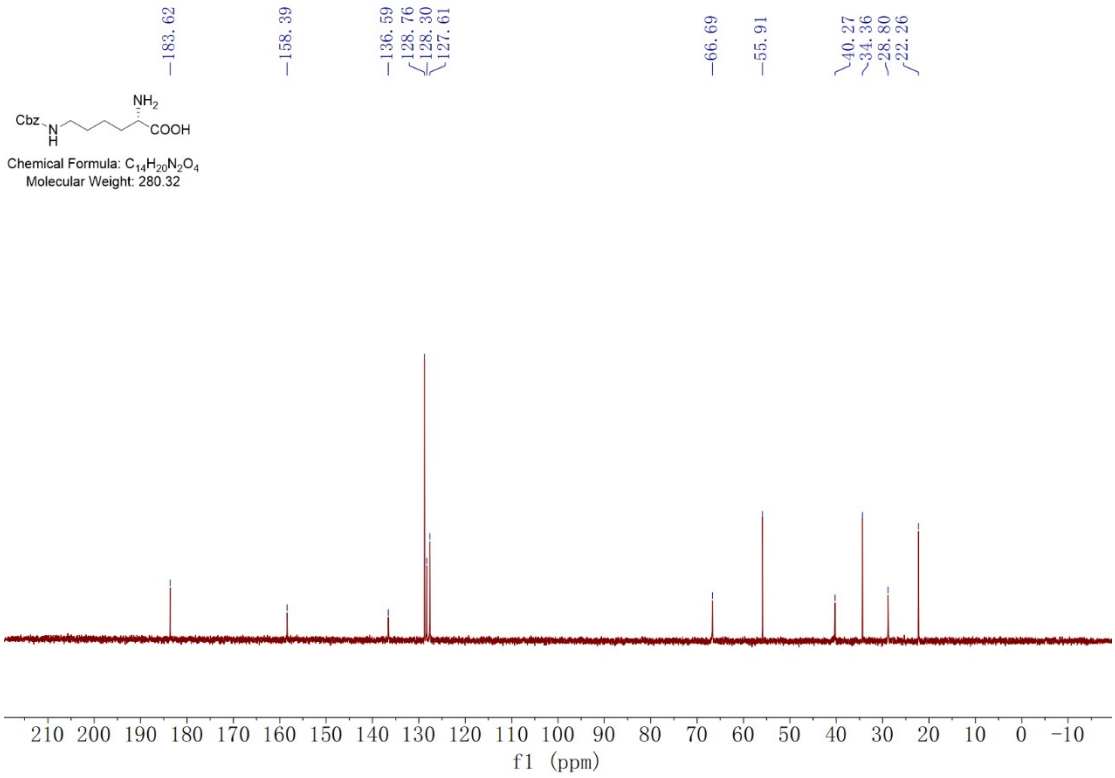
α–**3ba**

((benzyloxy)carbonyl-L-phenylalanine (α-**3ba**). (R_f=0.41; dichloromethane/ methanol = 10:1, 0.1% TFA). White solid, mp 85-87 °C; (140.1 mg, yield 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 8.4 Hz, 1H), 7.42-7.04 (m, 9H), 4.97 (s, 2H), 4.28-4.04 (m, 1H), 3.07 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.84 (dd, *J* = 13.8, 10.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 156.0, 137.9, 137.0, 129.1, 128.3, 128.2, 127.7, 127.5, 126.4, 65.2, 55.6, 36.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$ 300.1230, found 300.1230.

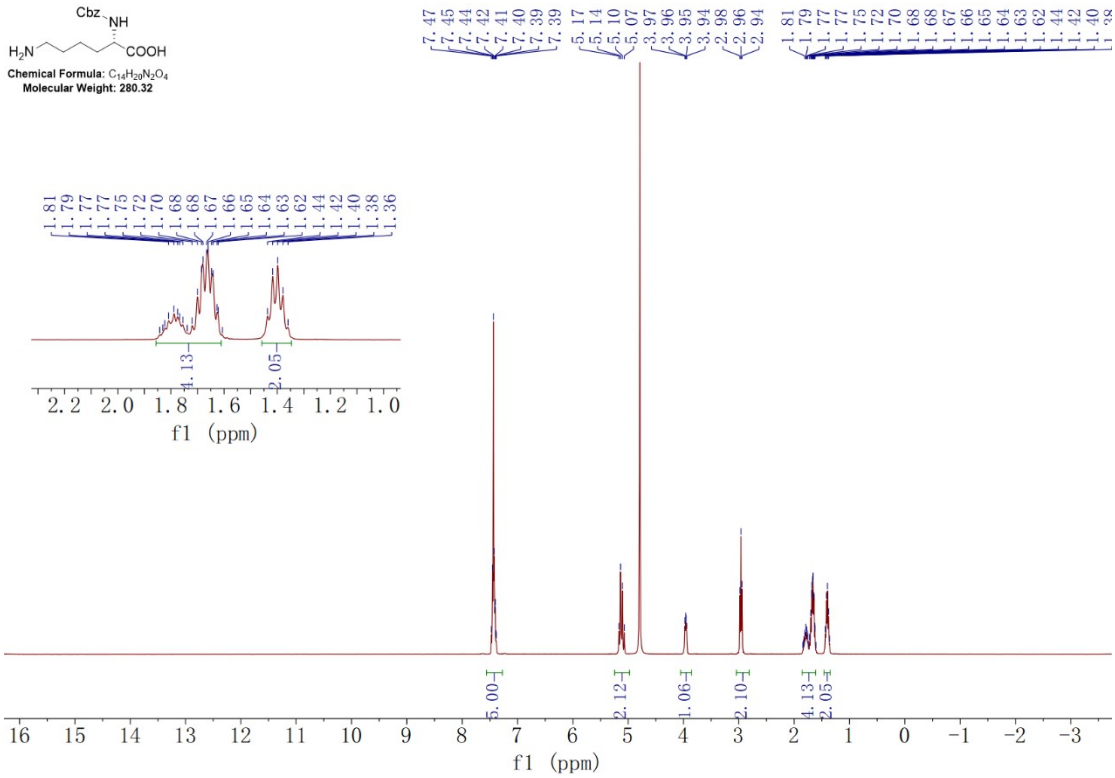
9. Copies of ^{1}H and ^{13}C NMR for all compounds



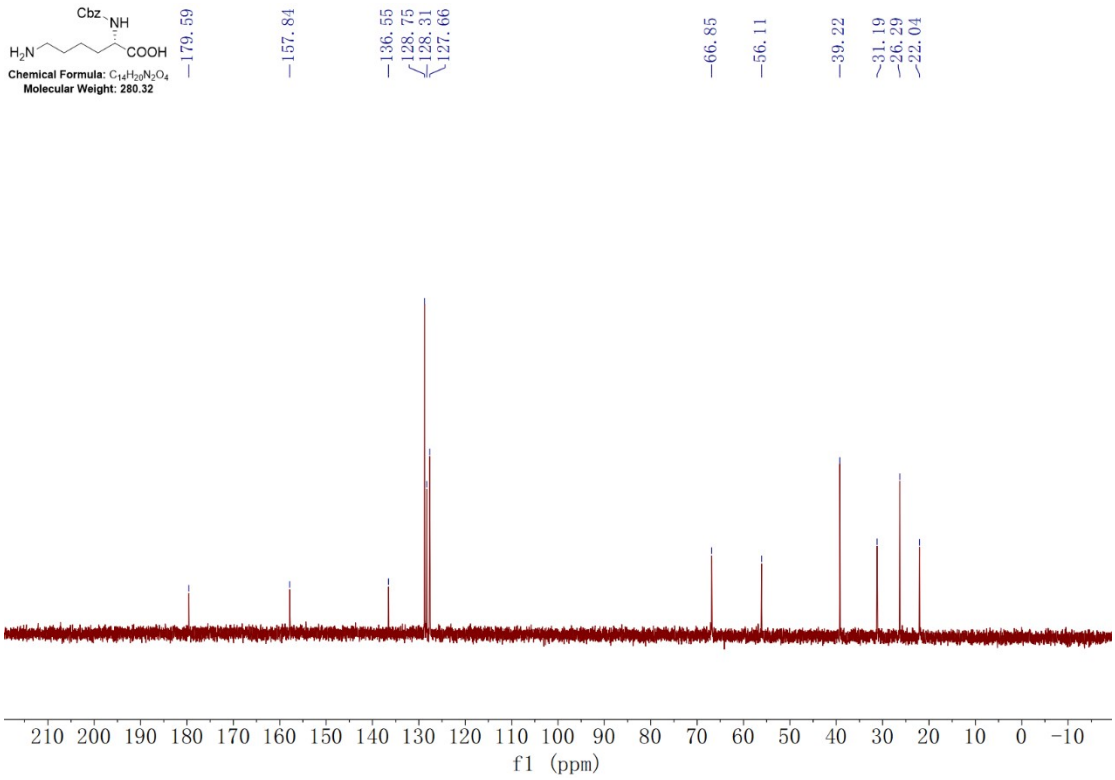
^{1}H NMR (400 MHz, D_2O) spectrum of ε-**3aa**



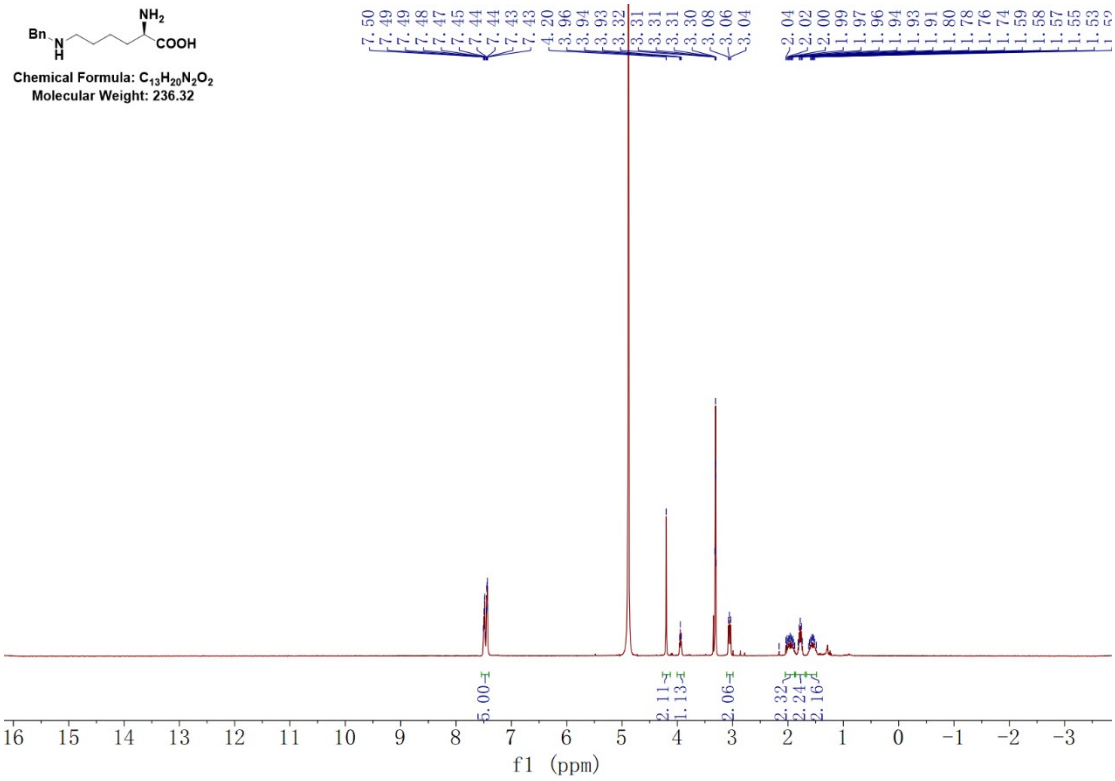
^{13}C NMR (101 MHz, D_2O) spectrum of ε-**3aa**



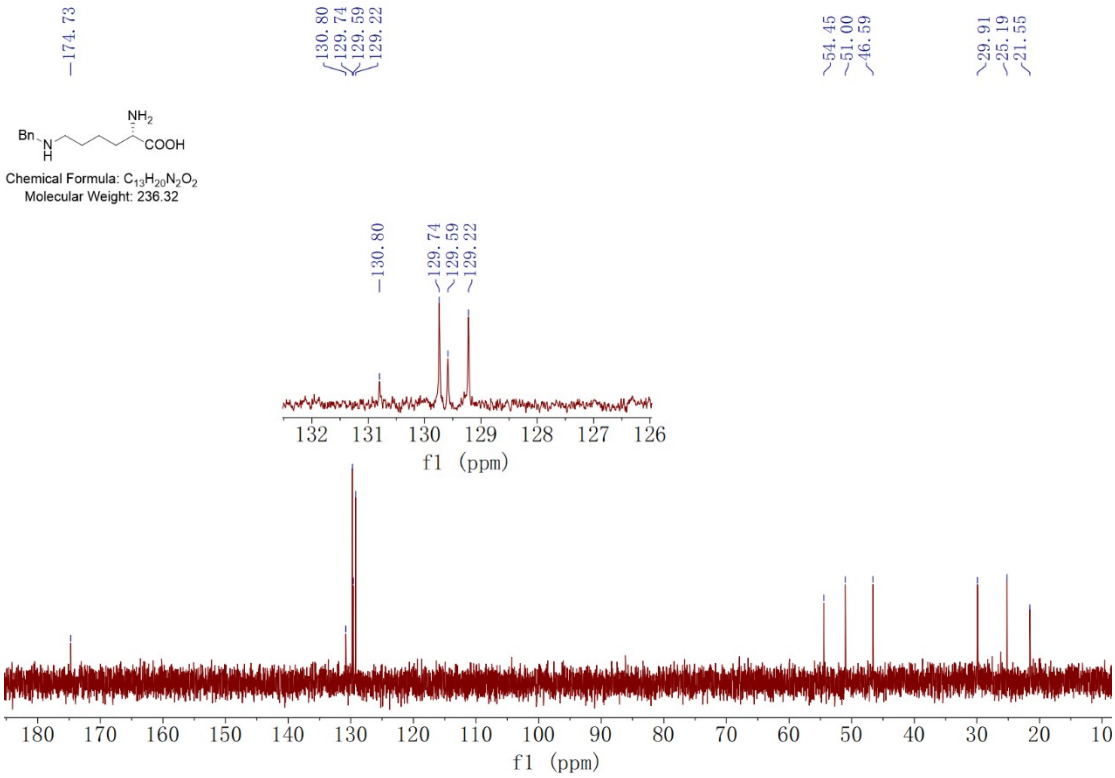
^{1}H NMR (400 MHz, D_2O) spectrum of α-**3aa**



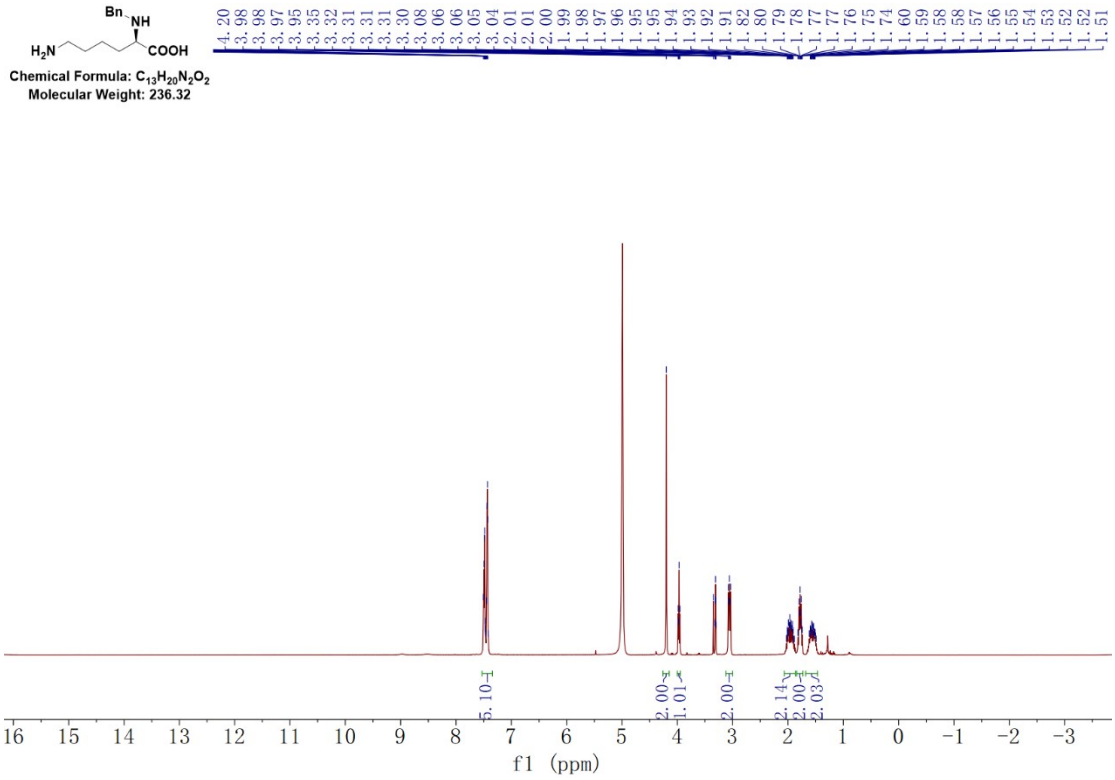
^{13}C NMR (101 MHz, D_2O) spectrum of α-**3aa**



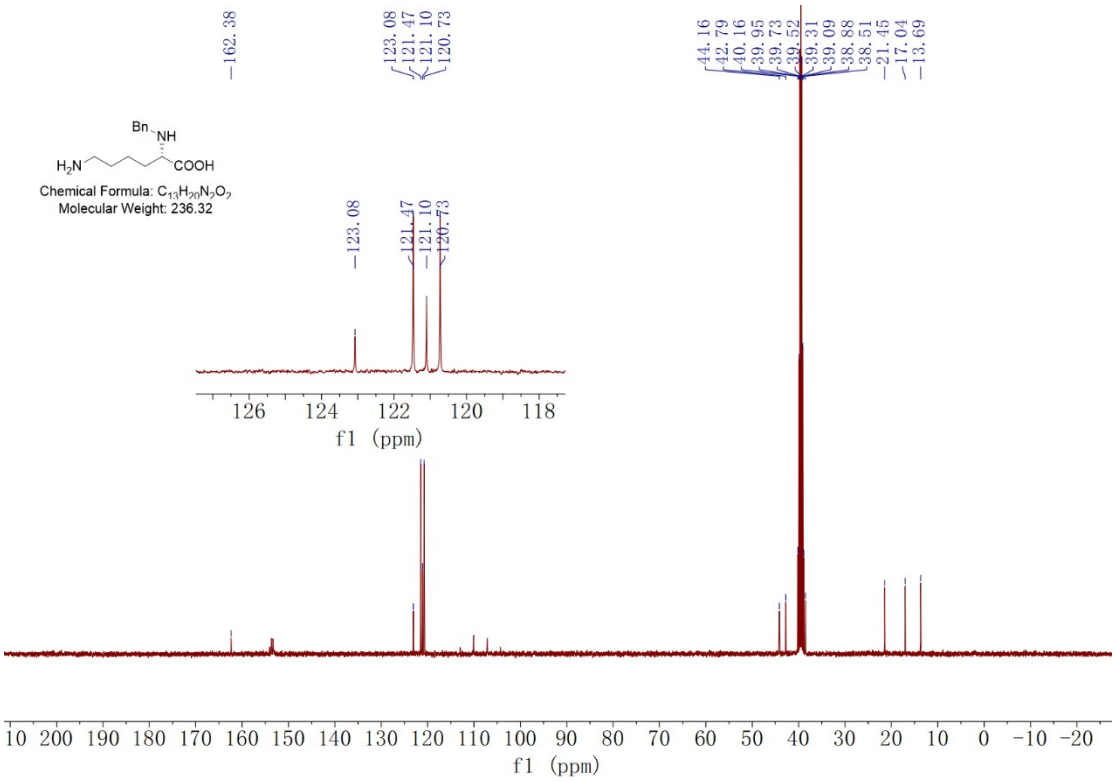
^{1}H NMR (400 MHz, Methanol-d_4) spectrum of ε-**3ab**



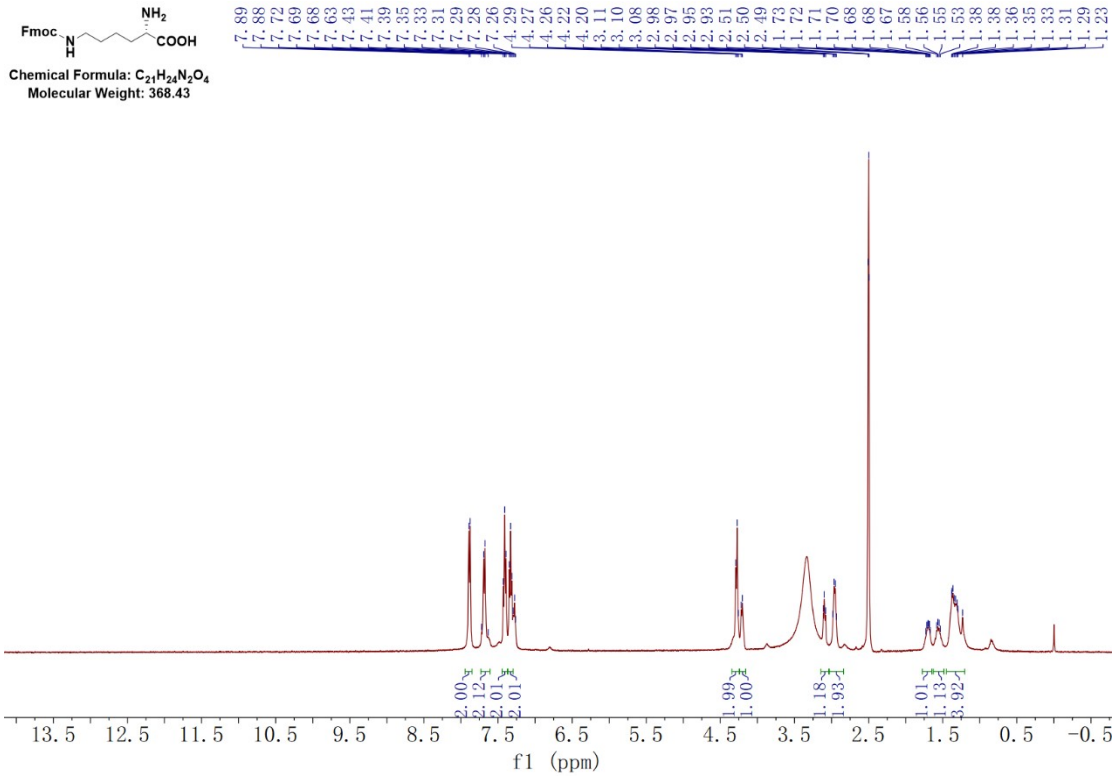
^{13}C NMR (101 MHz, D_2O) spectrum of ε-**3ab**



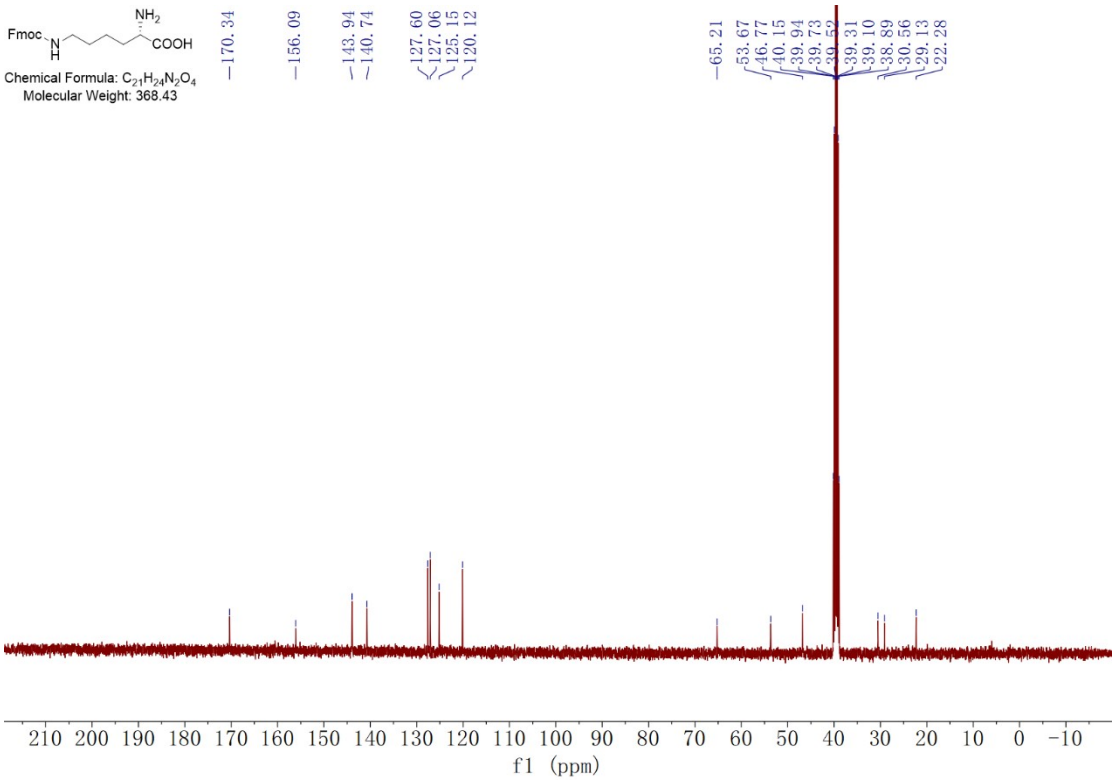
^{1}H NMR (400 MHz, Methanol-d_4) spectrum of α-**3ab**



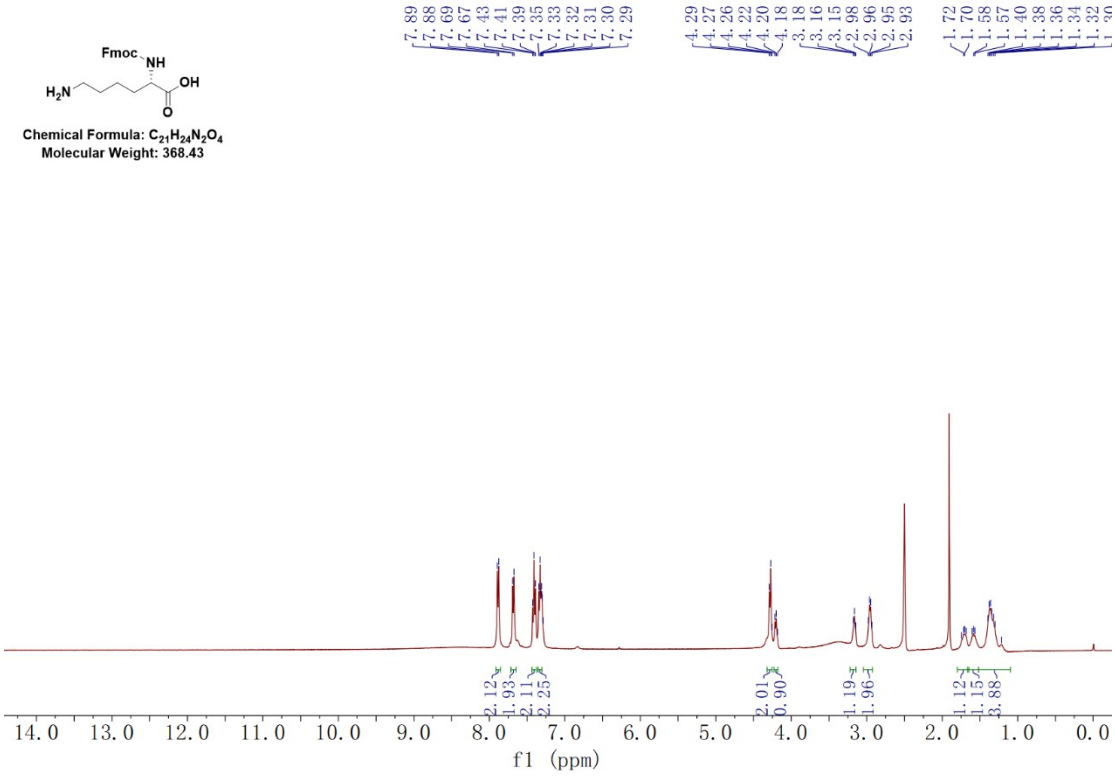
^{13}C NMR (101 MHz, Methanol-d_4) spectrum of α-**3ab**



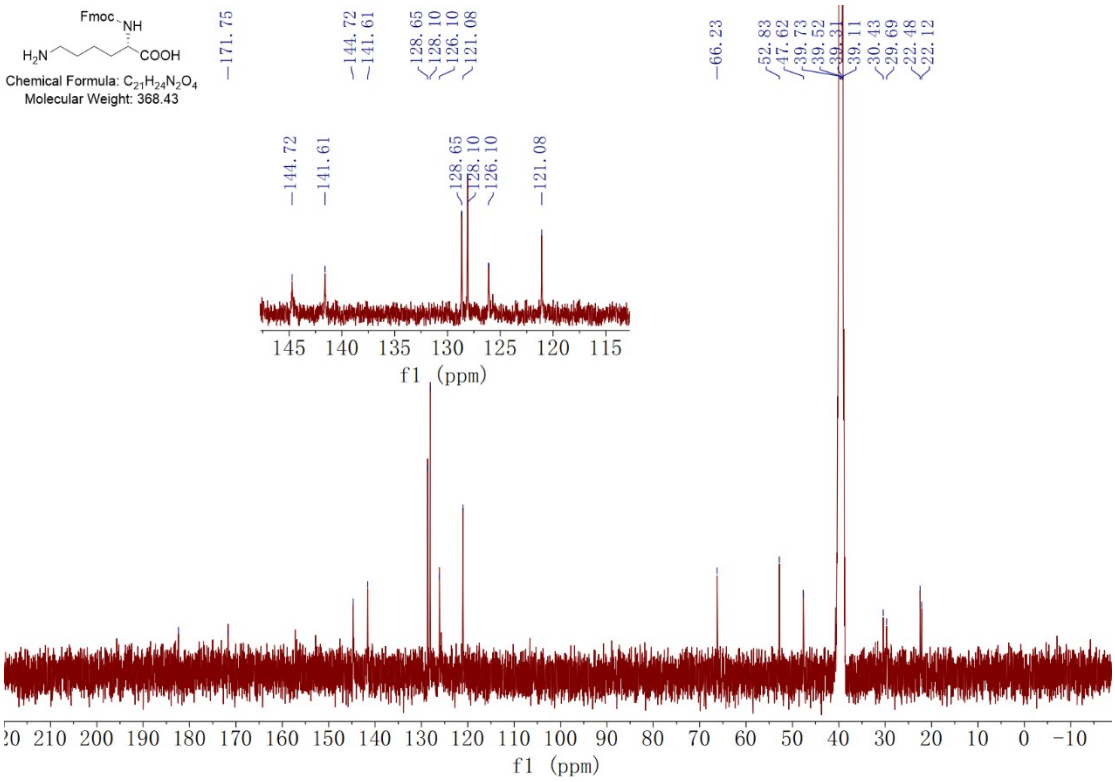
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ε-**3ac**



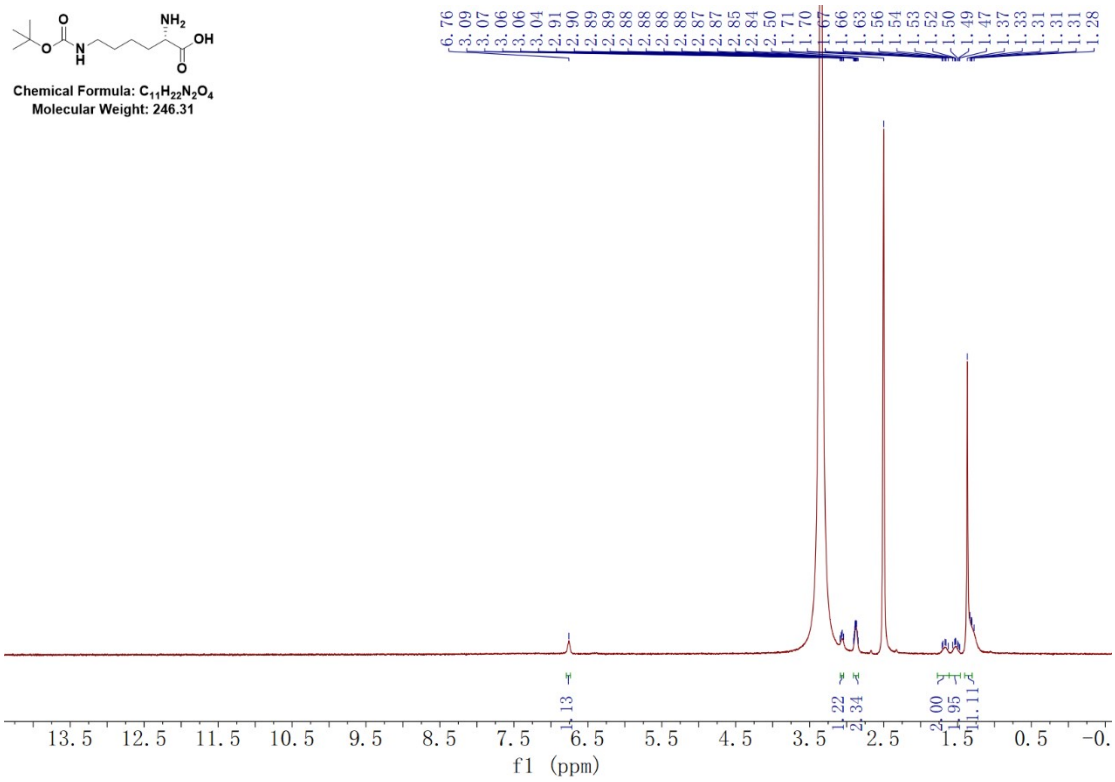
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of ε-**3ac**



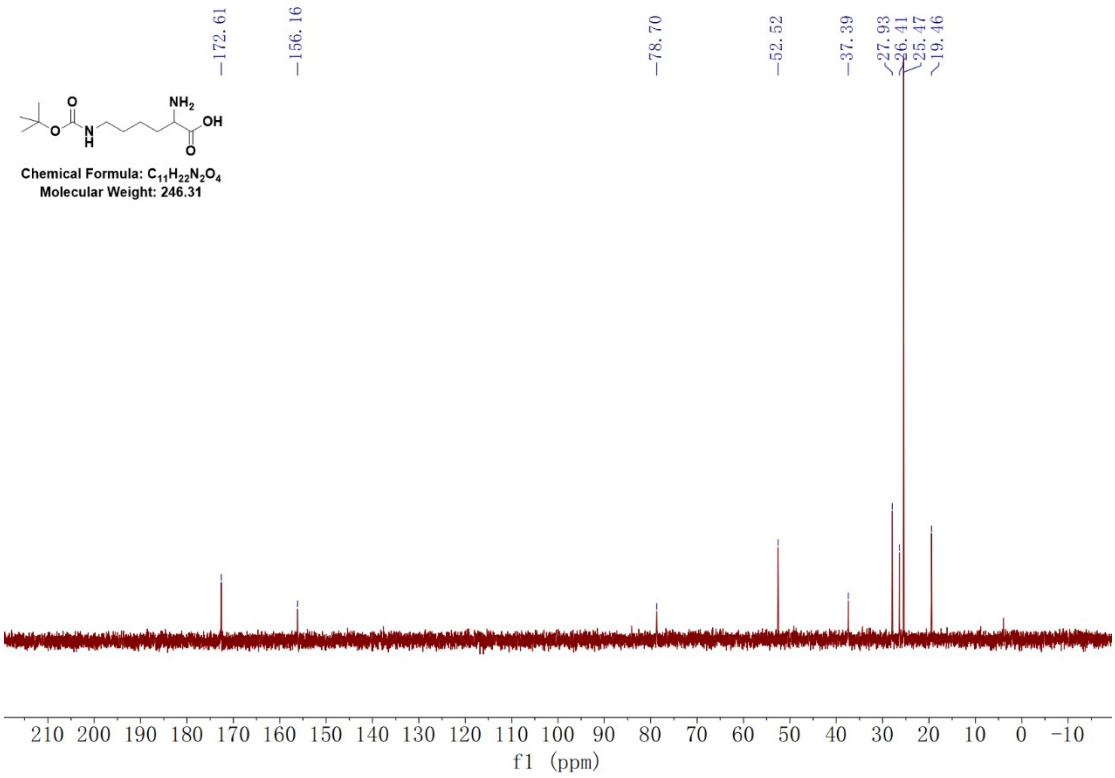
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of α-**3ac**



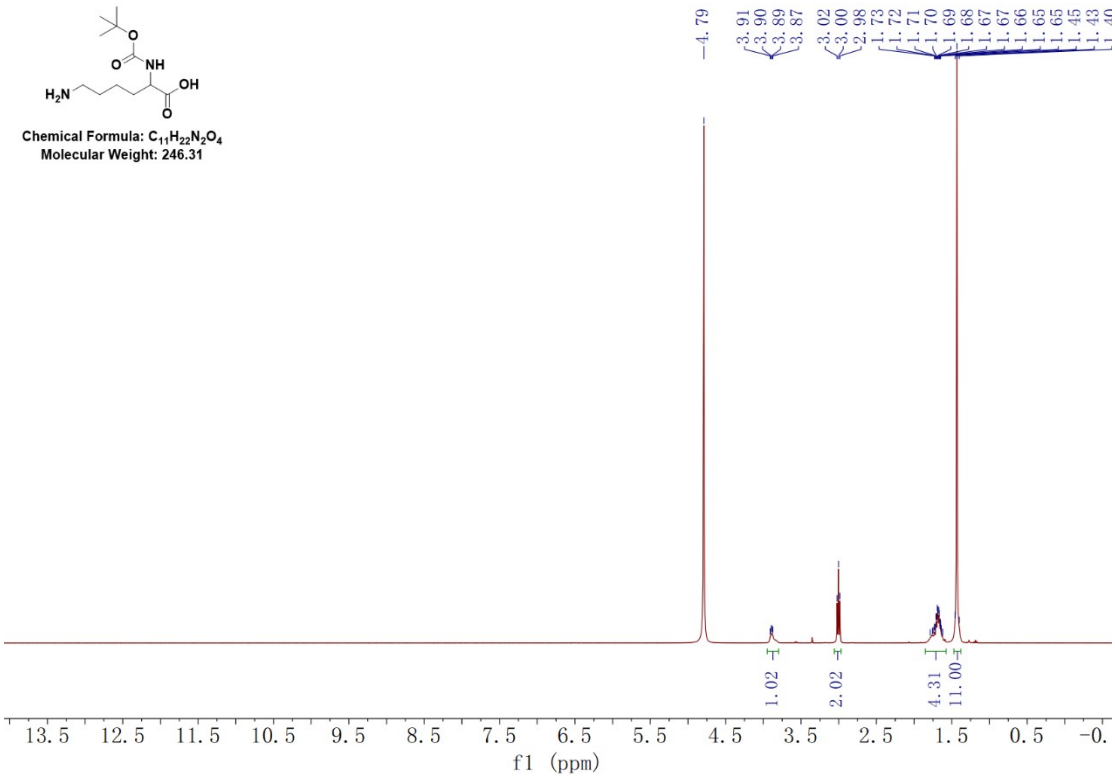
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of α-**3ac**



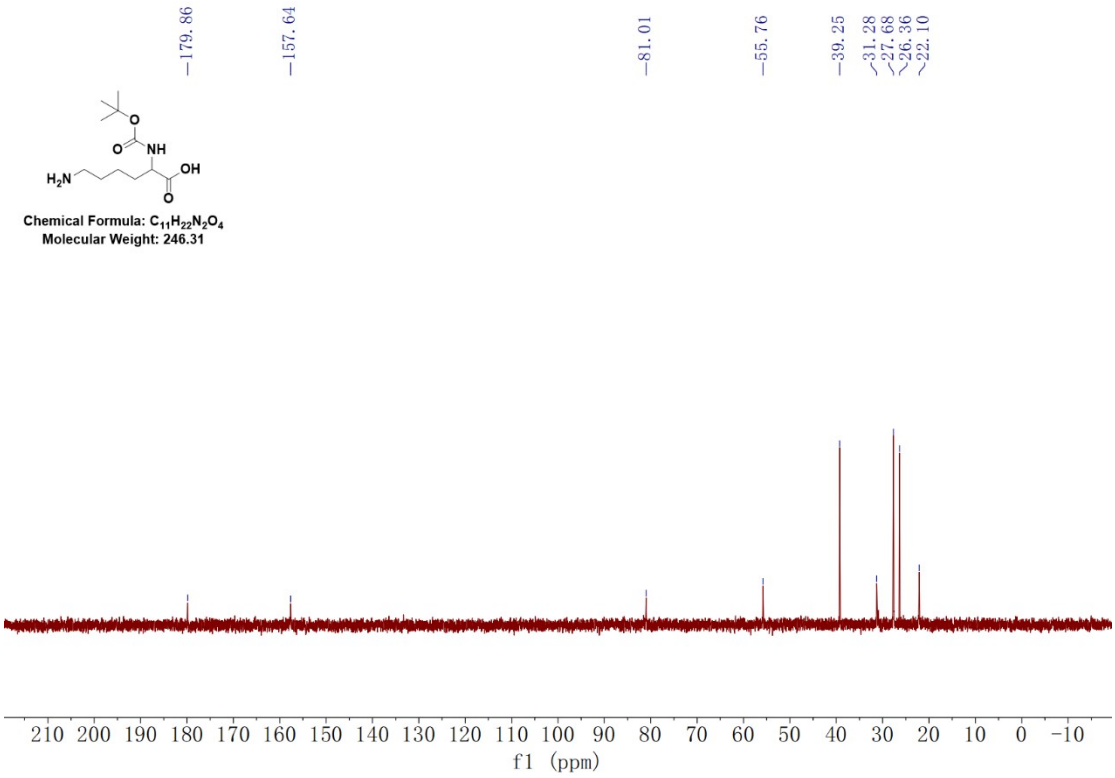
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ε-**3ad**



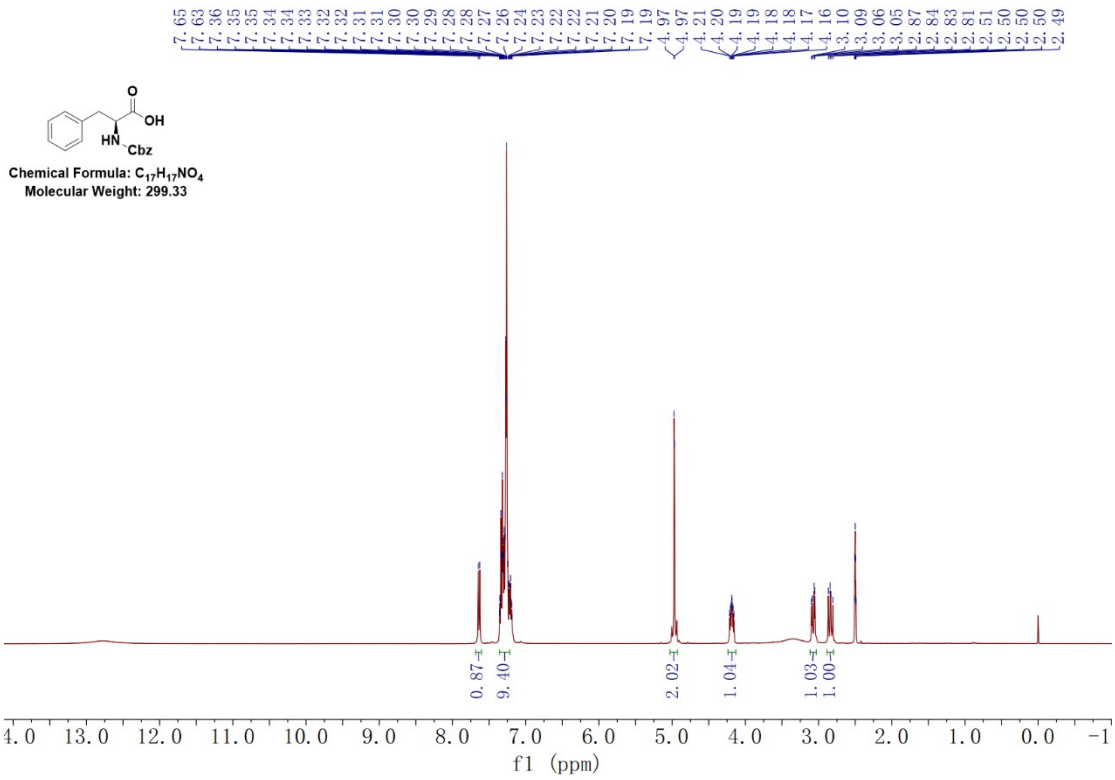
^{13}C NMR (101 MHz, D_2O) spectrum of ε-**3ad**



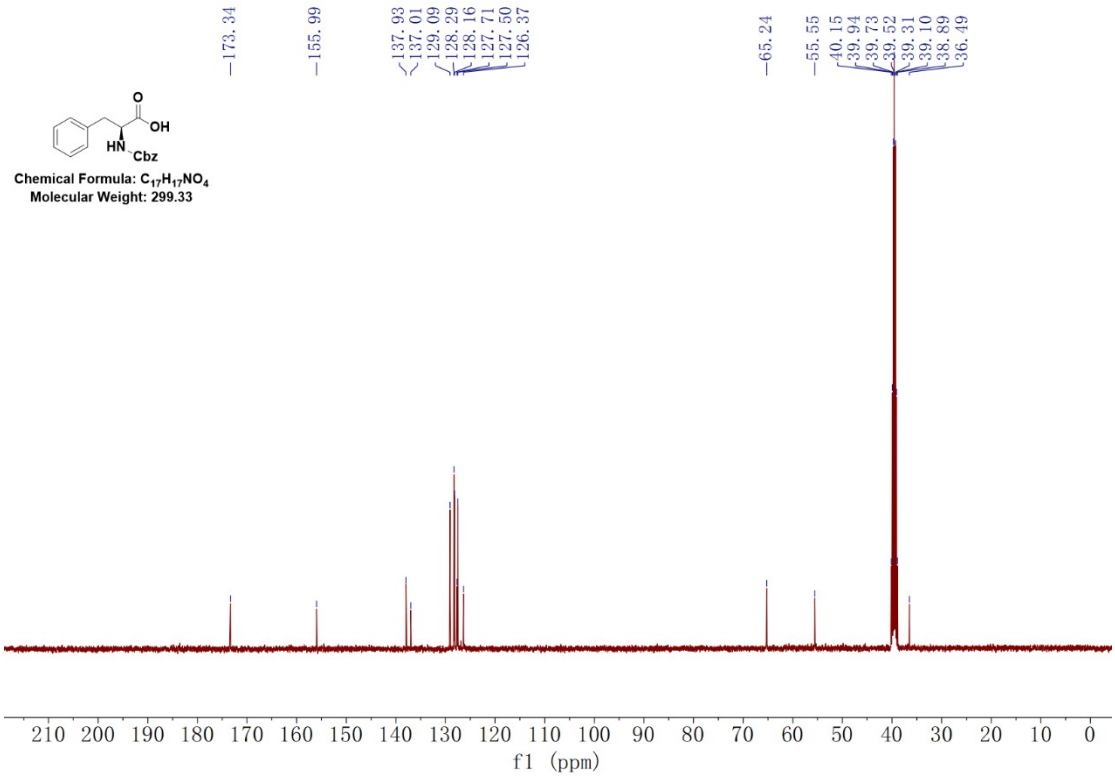
^{1}H NMR (400 MHz, D_2O) spectrum of α-**3ad**



^{13}C NMR (101 MHz, D_2O) spectrum of α-**3ad**



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of α-**3ba**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of α-**3ba**