Electronic Supplementary Material (ESI) for Analyst.

Supplementary Information

Improved Discrimination of Phenylalanine Enantiomers by Surface Enhanced Raman Scattering Assay: Molecular Insight into Chiral Interaction

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Experimental section

1. Reagents and chemicals

Silver nitrate (>98%) was purchased from Sinopharm Chemical Reagent Co., Ltd. Ascorbic acid, sodium borohydride and sertraline hydrochloride (Sert, >98%, HPLC) were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. Chloroauric acid hydrate, D-/L-phenylalanine, cetyltrimethylammonium bromide (CTAB, 99%), cetyltrimethylammonium chloride (CTAC, 99%) were purchased from Adamas Reagent Co., Ltd. The reagents above were used as-received, and deionized water (18.25 MΩ□cm) was used for the following experiments.

2. Instruments and characterizations

TEM images and EDS spectra were collected on a JEM-2100F transmission electron microscopy (200 kV accelerating voltage) incorporated with an energy dispersive spectrometer. UV-Vis absorption spectra were obtained on a dual-beam UV-Vis spectrophotometer (Shimadzu UV-1800) using a cuvette with an optical path length of 10 millimeters. XPS spectra were collected on an X-Ray Photoelectron Spectrometer (Shimadzu Axi165). Circular Dichroism (CD) spectra were recorded on a JASCO-1500 spectrophotometer using a cuvette with an optical path length of 10 millimeters.

Raman and SERS spectra were acquired on a DXR2xi Raman Imaging Microscope (Thermo Scientific™) using a 785 nm laser focused by a ×10 objective lens (the spot size is about 7 microns). The acquisition parameters for Raman spectra were set as follows: a 785 nm laser with a power of 1.8 mW, 0.3 s exposure time, 500 scans. The acquisition parameters for SERS spectra were as follows: a 785 nm laser with a power of 1.3 mW, 0.04 s exposure time, 500 scans. A glass slide coated with a flat aluminium foil was used to load samples. The powder samples were spread on the aluminium foil. For the samples dispersed or dissolved in aqueous solutions, they were firstly dropped onto the aluminium foil and then dried in air at room temperature. Spectra were pre-corrected using medium baseline correction of the DXR2xi Raman Imaging Microscope. For a given sample, several replicate Raman or SERS spectra were collected from different spots to evaluate the reproducibility (based on RSD values), and then one typical single spectrum is selected and shown in this manuscript.

3. Synthesis of gold nanorods (Au NRs)

The glass beakers were cleaned with aqua regia and then sufficiently washed with deionized water. Au NRs were prepared using a seed-mediated growth method. [1-2]

Preparation of seed solution: CTAB (0.2733 g) was dissolved in 7.50 mL of H_2O by ultrasonic treatment at room temperature, to which 0.25 mL of $HAuCl_4$ solution (0.01 mol/L) and 0.60 mL of fresh sodium borohydride solution (0.01 mol/L) were added in progress under stirring. After a fast stirring for 2 minutes, the above solution was placed in an incubator at 30 ^oC for 2 hours to obtain the seed solution.

Preparation of growth solution: 1.70 ml of $HAuCl_4$ solution (0.01 mol/L) was added into mL of CTAB solution (0.10 mol/L). After a stirring of 2 minutes, $AgNO_3$ (0.25 ml, 0.01 mol/L) was added and then a stirring of 2 minutes was followed. Finally, 0.27ml of fresh ascorbic acid solution (0.10 mol/L) was added under stirring. With the

solution color changing from bright yellow to colorless and transparent, the seed solution was formed.

Synthesis of Au NRs: 0.40 mL of seed solution was mixed with the as-prepared growth solution by ultrasonic treatment for 2 minutes. The solution above was left to stand for 24 hours at room temperature, and Au NRs were finally collected by three centrifugation (10000 rpm, 15 min)-washing (using water) cycles.

4. **Synthesis of Ag coated Au NRs (Au@Ag NRs)** [3]

3 mL of Au NRs dispersion was mixed with a CTAC solution (9.00 mL, 20 mmol/L) with stirring. Then, 5 μL of $AgNO_3$ (0.10 mol/L) was added with a stirring of 2 minutes, followed by the addition 5 μL of ascorbic acid solution (0.10 mol/L). After a further stirring of 2 minutes, the solution above was left to stand in a water-bath at 70^{o}C for 3 hours. After cooling down to room temperature, Au@Ag NRs were acquired by four centrifugation (9000 rpm, 15 min)-washing cycles.

5. Preparation of Au@Ag-D-Phe (or Au@Ag-L-Phe)

3 mL of Au@Ag NRs-containing solution was mixed with 10 uL of D-Phe (or L-Phe) solution ($2.0x10^{-3}$ mol/L), and then this mixture (the final concentration of D-Phe (or L-Phe) is $6.7x10^{-6}$ mol/L) was placed in a water bath at 70 ^{o}C for 30 minutes. After cooling down to room temperature, Au@Ag-Phe (or Au@Ag-L-Phe) solution was prepared.

6. Preparation of Au@Ag-D-Phe-Sert (or Au@Ag-L-Phe-Sert)

Sert was firstly dissolved in ethanol-water solvents (the volume ratio between ethanol and water is 5 : 95). Then, 10 μL of Sert solution (0.02 mol/L) was mixed with 10 μL of Au@Ag-D-Phe (or Au@Ag-D-Phe) solution to result in Au@Ag-D-Phe-Sert (or Au@Ag-D-Phe-Sert).

Computational Details

All DFT calculations were performed with Gaussian 16 software package[4] at M06[5]/6-31G(d) level in gas-phase. Different conformations for ionic form of L-phenylalanine, sertraline hydrochloride salt, and hydrogen-bonded complex of the ionic L-phenylalanine and sertraline hydrochloride salt (The initial structure was built according to single-crystal structure of sertraline hydrochloride and acetic acid reported by Almarsson and co-workers[6]) were optimized, with only the most stable ones presented in this report. The total energies (Electronic energies, Gibbs free energies, Unit: Hartree), charge, multiplicity, and geometrical coordinates for D-Phe-Sert and L-Phe-Sert are summarized in Table S2 and Table S3, respectively.

References:

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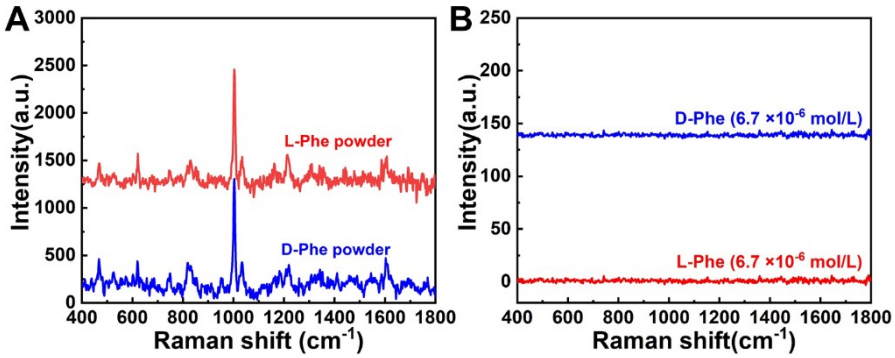

Figure S1. Raman spectra of A) D-Phe and L-Phe powders; B) D-Phe and L-Phe with a concentration of 6.7×10^{-6} mol/L.

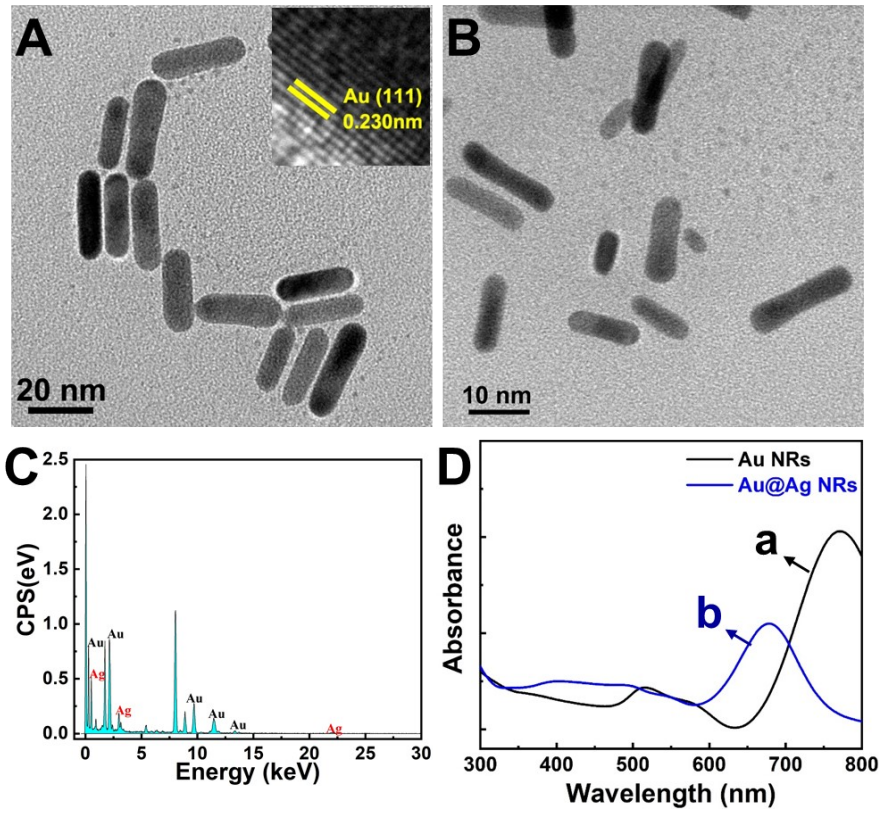

Figure S2. TEM image (inset, HRTEM image) of A) Au NRs and B) Au@Ag NRs; C) EDS spectrum of Au@Ag NRs; D) UV-Vis absorption spectra of (a) Au NRs and (b) Au@Ag NRs.

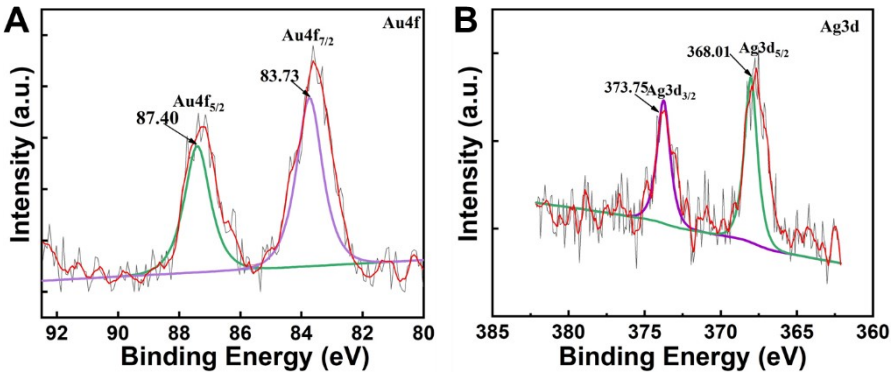

Figure S3. XPS patterns of A) Au 4f and B) of Ag 3d in Au@Ag NRs.

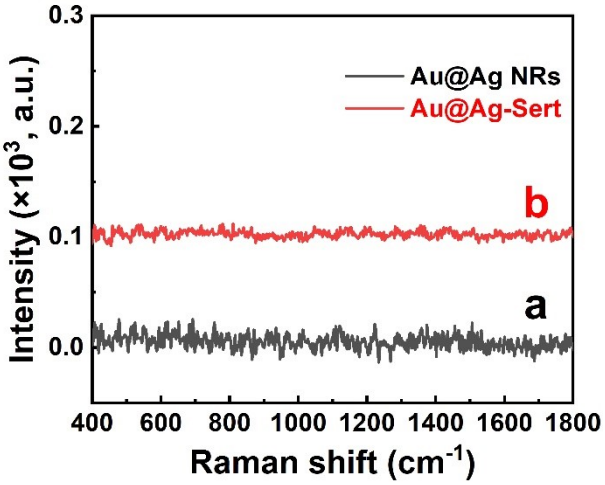

Figure S4. SERS spectra of (a) Au@Ag NRs and (b) Au@Ag-Sert.

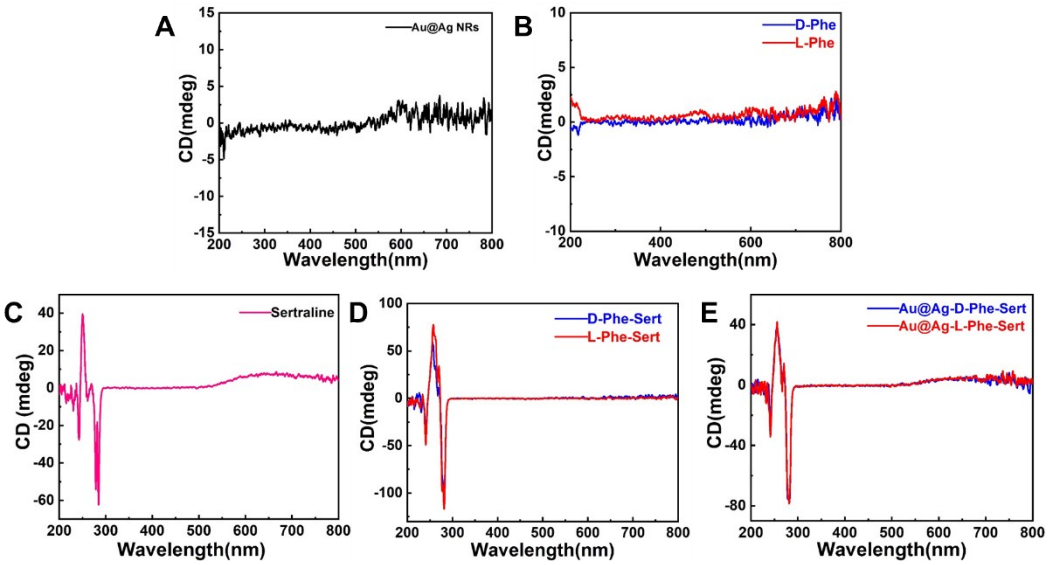

Figure S5. CD spectra of A) Au@Ag NRs; B) D-Phe (blue) and L-Phe (red) solutions (6.7×10^{-6} mol/L); C) Sert solution (0.02 mol/L); D) D-Phe-Sert (blue) and L-Phe-Sert (red); E) Au@Ag-D-Phe-Sert (blue) and Au@Ag-L-Phe-Sert (red).

Table S1. RSD values for the signals intensities of five bands on the 30 replicate SERS spectra of Au@Ag-D-Phe-Sert (or Au@Ag-D-Phe-Sert).

Bands	RSD values	
	Au@Ag-D-Phe-Sert	Au@Ag-L-Phe-Sert
1080 cm^{-1}	5.2%	3.2%
1143 cm^{-1}	10.0%	10.7%
1393 cm^{-1}	11.3%	7.6%
1434 cm^{-1}	8.8%	5.7%
1585 cm^{-1}	11.9%	6.0%

Table S2. Total energies (Electronic energies, Gibbs free energies, Unit: Hartree), charge, multiplicity, and geometrical coordinates for D-Phe-Sert.

Sum of electronic and zero-point Energies		-2647.296331	
Sum of electronic and thermal Free Energies		-2647.358372	
Charge		0	
Multiplicity		1	
Geometrical coordinates			
	x	y	z
Cl	3.942646058	0.567267573	8.466966494
Cl	5.630147978	3.127241551	7.539291253
N	1.699619005	-3.10905458	3.827121195
C	3.998775212	-3.973955402	4.113264094
C	3.988970035	-5.274555677	4.62600532
C	4.927952199	-5.688551819	5.559572868
C	5.907379885	-4.793893042	5.980349453
C	5.938942891	-3.508381	5.459008356
C	4.993417001	-3.071969965	4.526431082
C	2.948625215	-3.564626892	3.109492822
C	3.438648892	-2.445411708	2.205910964
C	3.948015937	-1.28800007	3.045944948
C	5.144186049	-1.688876086	3.920337613
C	0.752018524	-4.16883959	4.22811723
C	5.387797057	-0.571894991	4.913723835
C	4.766643946	-0.5596277	6.160949621
C	4.83301767	0.567688949	6.971683333
C	5.545973078	1.694468393	6.557861885
C	6.193914022	1.676796667	5.32661595
C	6.1085422	0.554648339	4.514241848
Cl	0.232438827	-0.73875586	2.344021223
N	-0.649689778	0.691708274	4.915931862
C	1.761659824	1.286324219	4.976576615
C	1.572389554	2.776107506	4.956405771
C	0.974636004	3.408901648	3.863272618
C	1.959387324	3.549588241	6.054449806
C	0.763369507	4.785513245	3.869685883
C	1.753714971	4.92425282	6.060364856

C	1.151512715	5.545403185	4.96854696
O	1.986054233	-1.390657141	5.878331388
O	-0.25965557	-1.614655345	5.877304459
C	0.804639556	-0.968167589	5.843075977
C	0.630537053	0.564674146	5.68763257
H	1.952540574	-2.574137797	4.703159828
H	1.184471475	-2.397752588	3.243369337
H	3.236432074	-5.978305534	4.266358016
H	4.902556347	-6.704786384	5.948064433
H	6.655681087	-5.102608817	6.70826632
H	6.717201979	-2.814334924	5.77810341
H	2.643295063	-4.435907194	2.51097517
H	2.628302004	-2.109164915	1.544556297
H	4.244272561	-2.84964908	1.573508307
H	3.143444022	-0.91998308	3.699237234
H	4.228556906	-0.438188043	2.408935696
H	6.031701085	-1.741478402	3.261530591
H	0.353618379	-4.659637239	3.334567954
H	-0.044299165	-3.68275446	4.801328445
H	1.270498617	-4.893809086	4.862858492
H	4.156344429	-1.399031054	6.484105985
H	6.751243573	2.55625062	5.011913549
H	6.598021359	0.561343142	3.539444799
H	-1.272282192	-0.025088497	5.330048022
H	-1.043227907	1.635027001	4.909970779
H	2.686053763	1.014581624	5.502118942
H	1.839615786	0.886203537	3.95360769
H	0.699232483	2.81458438	2.988622608
H	2.440573185	3.063051201	6.90695835
H	0.305219354	5.266618381	3.006667948
H	2.072189006	5.515333018	6.91771137
H	0.993085224	6.622596782	4.971387059
H	0.454526688	1.007906408	6.680216456
H	-0.463094834	0.345410704	3.925916766

Table S3. Total energies (Electronic energies, Gibbs free energies, Unit: Hartree), charge, multiplicity, and geometrical coordinates for L-Phe-Sert.

Sum of electronic and zero-point Energies		-2647.296907	
Sum of electronic and thermal Free Energies		-2647.356403	
Charge		0	
multiplicity		1	
Geometrical coordinates			
	x	y	z
Cl	-0.291428218	2.533101537	2.593759582
Cl	1.543751213	5.121060881	2.141153372
N	1.644693318	-3.233208734	3.808157515
C	3.440024271	-1.925720004	4.857964295
C	3.291145765	-2.162230561	6.230324919
C	3.657434477	-1.205450294	7.163467465
C	4.200351861	0.001449659	6.725247734
C	4.318297194	0.253355722	5.366549422
C	3.920114005	-0.689167195	4.410474284
C	3.130223188	-3.049544635	3.898335605
C	3.766303436	-2.825080222	2.535543251
C	3.471641091	-1.427782442	2.012414989
C	4.041449271	-0.341455199	2.931861706
C	1.175891005	-4.521541701	3.259228403
C	3.414109704	1.013378244	2.66264483
C	2.026460902	1.160932115	2.683175585
C	1.44036088	2.408362981	2.515571089
C	2.237600656	3.537704823	2.313497545
C	3.620686956	3.39662295	2.273755407
C	4.200597128	2.145489267	2.449209497
Cl	-0.259231287	-1.547804479	2.10228573
N	-1.505540701	-0.340742141	4.622628681
C	-0.263168478	-0.03030408	6.746886259
C	-0.033168495	1.431411625	6.479662695
C	1.187844586	1.859122725	5.954127231
C	-1.037378019	2.377557967	6.695558069
C	1.412424949	3.199908528	5.672956856
C	-0.821551841	3.722418379	6.400612085
C	0.40398425	4.136762485	5.8896507
O	0.172186578	-3.10894897	6.019737248
O	-2.008149797	-2.503363182	5.899162803

C	-0.785096848	-2.317895886	5.818904285
C	-0.390270893	-0.852644294	5.469846505
H	1.196068131	-3.129331718	4.771330041
H	1.178762901	-2.487488331	3.225041898
H	2.873651281	-3.1133889	6.562565706
H	3.538607398	-1.406056381	8.226454708
H	4.510527586	0.756697177	7.445491689
H	4.704778224	1.216798282	5.029987343
H	3.500223605	-3.991056146	4.333991417
H	3.429778924	-3.587978291	1.820225054
H	4.851973471	-2.96736653	2.652627952
H	2.384687063	-1.303782735	1.888890708
H	3.893038682	-1.300450575	1.006728052
H	5.122036725	-0.249776168	2.718455629
H	1.423380311	-4.592703518	2.196192748
H	0.088752594	-4.549529921	3.375261912
H	1.631373508	-5.343347292	3.820380668
H	1.364903198	0.299720636	2.804067192
H	4.235309473	4.278479381	2.106154842
H	5.286750192	2.050847485	2.420595024
H	-2.327374511	-0.87537063	4.982908824
H	-1.621519736	0.677220301	4.671233602
H	-1.173350487	-0.181639335	7.348287413
H	0.574140119	-0.46754541	7.312069522
H	1.969408508	1.122705606	5.762777124
H	-1.993029342	2.057549184	7.116235983
H	2.377617773	3.510673561	5.270264614
H	-1.613914699	4.448803782	6.573794609
H	0.573271505	5.185668616	5.652028288
H	0.530891522	-0.796871149	4.874882126
H	-1.310336026	-0.641236854	3.628719671