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Selective Colorimetric Sensing of Geometrical Isomers of Dicarboxylates in Water by Using Functionalized Gold Nanoparticles

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Abstract: A colorimetric sensing system based on gold nanoparticles functionalized with a water-soluble anion-recognition motif, an *o*-(carboxamido)trifluoroacetophenone analogue, has been developed. The nanoparticle system selectively senses specific isomers of dicarboxylates that are geometrically favorable for the binding-induced aggregation process; thus, it discriminates a *trans*-dicarboxylate fumarate from its *cis*-isomer maleate, and benzene-1,4-dicarboxylate from its isomeric benzene-1,2-and benzene-1,3-dicarboxylates in water, exhibiting a color change from red to blue.

Keywords: dicarboxylates · geometrical isomers · gold · nanoparticles · sensors

Introduction

In recent years, surface functionalization of gold nanoparticles (AuNPs) has attracted growing attention owing to their tunable photophysical properties and various potential applications, including in colorimetric nanosensors in the chemical and biological sciences.[1] The visual-sensing ability of AuNPs relies on changes in the surface plasmon resonance (SPR), which is dependent on the aggregation state, surface morphology, and so on.[1a,2] Generally, the aggregation of AuNPs in solution through analyte-triggered interparticle cross-linking leads to a change in color from red to blue or purple, which is useful for observing molecular-recognition events.[1a,3] This fundamental optical property of AuNPs has been intensively used for the development of nanoparticle probes for biological macromolecules.[1b,3] Also, AuNPs have been successfully used for the development of molecular probes for small molecules of organic and inorganic analytes.

We have focused on the unique signaling mechanism of AuNPs; that is, their aggregation through the binding-induced interparticle cross-linking leads to changes in SPR. The interparticle cross-linking requires a "three-body" molecular-recognition event between a ditopic analyte and two nanoparticles. Such molecular interactions can be dependent on the directionality of two interacting end groups of the analyte, and thus may be used for specific sensing purposes such as the selective sensing of geometrical isomers of organic compounds, for example, the selective recognition and sensing of geometrical isomers such as that between *trans* and *cis* isomers or between 1,2-, 1,3-, and 1,4-disubstituted benzene derivatives. Only a limited number of examples of the selective sensing of such geometrical isomers are known so far.[4] To recognize and sense geometrical isomers, we need recognition and sensing systems that discriminate both the geometry and the functionality of the analytes. The synthesis of such systems is rather difficult to realize in the case of organic receptor systems.

The importance of anions in a wide range of biological and chemical processes[5] encourages the development of various recognition and sensing systems for specific anions.[6] Accordingly, AuNP-based optical sensors for biologically important small-molecule anions have also been developed.[1a,6a,g,7] Most of the sensing systems were examined in organic solvents; thus, there is still a need to develop AuNP-based colorimetric sensors that probe anions, particularly in aqueous media.

Recent efforts have been made in the development of selective sensing methods for carboxylates owing to their presence in a variety of biologically important molecules.[6,8] Over the last few years, we have developed several molecular receptors and sensors based on a novel recognition motif, *o*-(carboxamido)trifluoroacetophenone (CATFA),[9] which efficiently recognizes anions such as carboxylates.[9b]

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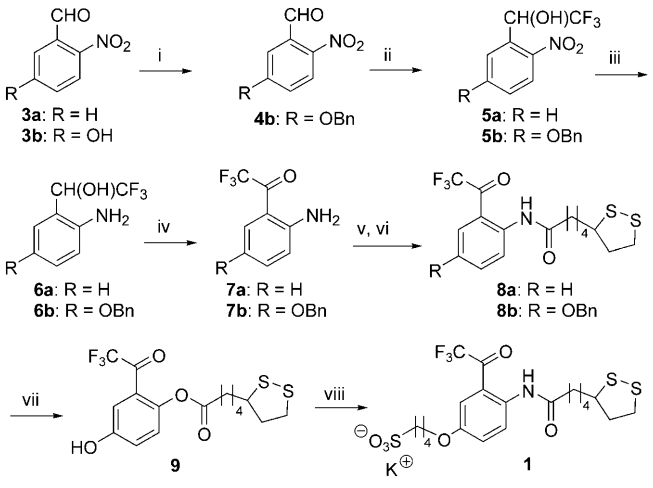
This binding motif is neutral and recognizes anions through the reversible formation of a covalent bond at the trifluoroacetyl carbon atom, which seems to be a promising property for its application to nanoparticle-based sensing systems for geometrical isomers. Thus, we synthesized gold nanoparticles functionalized with the CATFA derivative **8a** (Scheme 1) as a colorimetric sensing system for isomeric dicarboxylates, which required post-treatment with poly(vinyl alcohol) to improve its stability in water.[10] Although the CATFA-functionalized AuNP system showed the unique recognition property of discriminating a *trans* dicarboxylate, fumarate, from its *cis* isomer, maleate, the corresponding change in SPR was less pronounced probably because the polymer layer sterically hindered the molecular-recognition event required for the interparticle cross-linking. Furthermore, the polymer-modified sensing system has to be optimized against several experimental variables such as the concentrations of the ligand, polymer, and analyte. To overcome these undesirable properties and to secure the stability of the nanoparticles in water, we devised a new sensing system in which AuNPs are functionalized with a water-soluble CATFA analogue. The CATFA ionophores readily form hydrated species at the trifluoroacetyl carbonyl group in the presence of water molecules, which limits their applications for sensing weak-binding anions in aqueous media. One way to overcome this limitation may be found in integrated recognition systems such as the functionalized nanoparticles. As the nanoparticle-based recognition systems involve not a single recognition event but multiple molecular interactions, the weaker binding affinity of CATFA ionophores in water may be overcome. This is our rationale for investigating



Scheme 1. Synthesis of CATFA derivative **1**. i) $PhCH_2Br$, K_2CO_3, acetone, reflux, 3 h, 94%; ii) $TMSCF_3$ (1.2 equiv), CsF (10 mol%), DME, 95%; iii) Fe (5 equiv), NH_4Cl (1.2 equiv), EtOH/H_2O (1:1), 2 h, 80°C, 89%; iv) CuCl (5 mol%), $DEADH_2$ (5 mol%), 1,10-phenanthroline (5 mol%), K_2CO_3 (10 mol%), 4-Å molecular sieves, toluene, 85°C, 1.5 h, 68%; v) thioctic acid, oxalyl chloride (1.2 equiv), DMF (cat. amount), CH_2Cl_2, 3 h, 0–25°C; vi) K_2CO_3 (1.2 equiv), THF, 1 day, 25°C, 31%; vii) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, 1 day, 25°C, 84%; viii) K_2CO_3, 1,4-butane sultone, acetone, reflux, 2 h, 40%. Bn = benzyl, DEAD = diethyl azodicarboxylate, DME = 1,2-dimethoxyethane, DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl.

nanoparticle-based sensing systems functionalized with water-soluble CATFAs. Although the new nanoparticle sensing system does not require the polymer-stabilization step, it shows much improved stability in water. More importantly, the water-soluble sensing system exhibits higher sensitivity toward specific dicarboxylate anions. This is the first example in which selective sensing of carboxylates is realized by using a water-soluble trifluoroacetophenone ionophore. The AuNP sensor neatly discriminates fumarate, a key component of the Krebs cycle[11] with other important biological activities,[12] from maleate. Moreover, the present system can also discriminate benzene-1,4-dicarboxylate, the anionic form of industrially important terephthalic acid,[13] with high sensitivity from its geometrical 1,2- and 1,3-isomers.

Results and Discussion

The CATFA derivative of thioctic acid **1**, which has a sulfonate functionality, was readily synthesized by following the route in Scheme 1. The functionalized AuNPs **2** (Figure 1) were prepared by the treatment of citrate-stabilized gold hydrosols ((13 ± 1) nm, 9.0 nM; adjusted to pH 11)[14] with a methanolic solution of **1** and were isolated from the excess ligand material by centrifugation. A solution of AuNPs **2** was stable for several months under refrigeration (0–5°C) without showing any decomposition.

The solution of AuNPs was characterized by UV/Vis and FTIR spectroscopy, TEM, energy-dispersive X-ray spectroscopy (EDX), and X-ray photoelectron spectroscopy (XPS). The final concentration of the solution of functionalized AuNPs was estimated to be 6.8 nM from the UV/Vis spectrum of the solution of nanoparticles.[3a] The average diameter of the gold core was (13 ± 1) nm as determined by TEM (Figure 1), which is similar to that of the original citrate-stabilized particles. The FTIR spectrum of the solution of nanoparticles showed the required amide N–H and sulfonate O=S=O (1076 and 1163 cm^{-1}) stretching vibrations (see the Supporting Information, Figure S1b).[16]

EDX analysis gave the atom percentage values of the functionalized AuNPs **2** (Au: 17.53; S: 3.17; K: 0.89; F: 3.06%). In the high-resolution XPS analysis (Figure 2), the appearance of a peak at around 162 eV ($S(2p_{3/2})$) proves that the sulfur atom is bound to the AuNP surface (S–Au),[17] and the small band near 169 eV is an indication of the presence of sulfonate (SO_3^-) species.[17b] The N(1s) peak at around 401 eV and the C(1s) signal at around 285 eV also confirm the presence of amide N–H[18] and C–S bonds, respectively.[17a] The number of capping ligands present per nanoparticle is about 4200 as estimated from EDX analysis, with the assumption that the average nucleation number is about 68000 gold atoms per particle (the atom density of bulk gold is about 58.01 atoms nm^{-3}).[17a,19]

To carry out the titrations, each specific solution of analyte (5.0 mM; stock solution) was added incrementally to an aqueous solution of **2** (300 μL of the initial solution was diluted to 1.0 mL to give a 2.0 nM solution of AuNPs), and

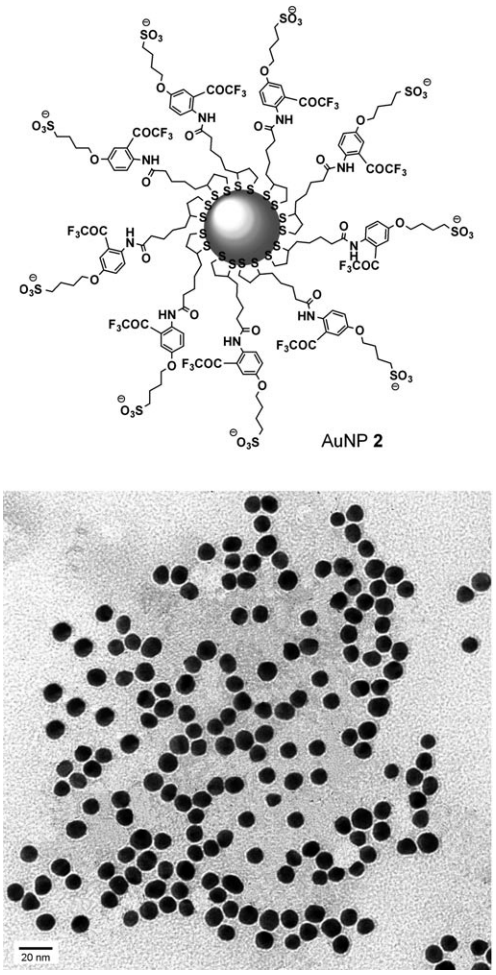


Figure 1. Schematic representation of the functionalized AuNP **2** (top) and TEM image taken from an ensemble of **2** (bottom).

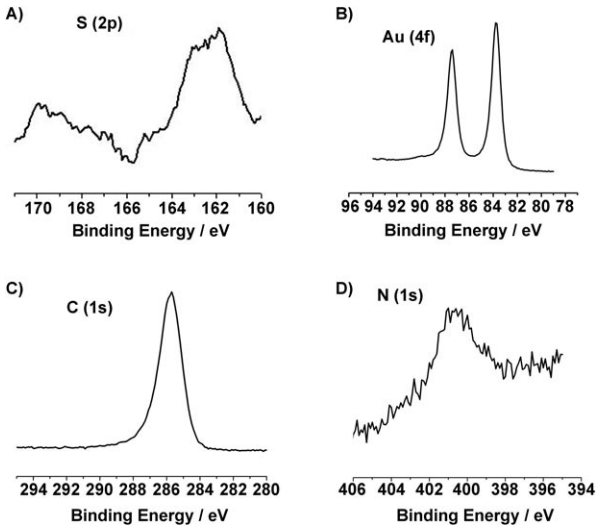


Figure 2. XPS spectra in the regions of A) S(2p), B) Au(4f), C) C(1s), and D) N(1s) in the AuNPs **2** deposited onto a silicon substrate.

UV/Vis spectra were recorded at 10-min intervals after each addition. In this AuNP-based system, both the geometrical disposition and the conformational flexibility of the carboxylate groups affected the aggregation as well as the color change. In the case of fumarate, the SPR band (λ_{max} = 524 nm) initially decreased in intensity with little change in wavelength upon addition of analyte, but after addition of 100 μL (5.0 mM) of analyte, the band broadened and shifted to longer wavelength, which resulted in a large red shift of (59 ± 5) nm (Figure 3A).[20] The color of the solution also changed accordingly from red to purple, which indicates nanoparticle aggregation. This aggregation was further confirmed by TEM (Figure 3B).

In the case of other aliphatic dicarboxylates (i.e., maleate, succinate, glutarate), a decrease in the intensity of the SPR band was observed along with small wavelength shifts (Figure 2A), and accordingly no color change was observed even at higher analyte concentrations. When 200 μL (5.0 mM) of each of the aliphatic dicarboxylates was added

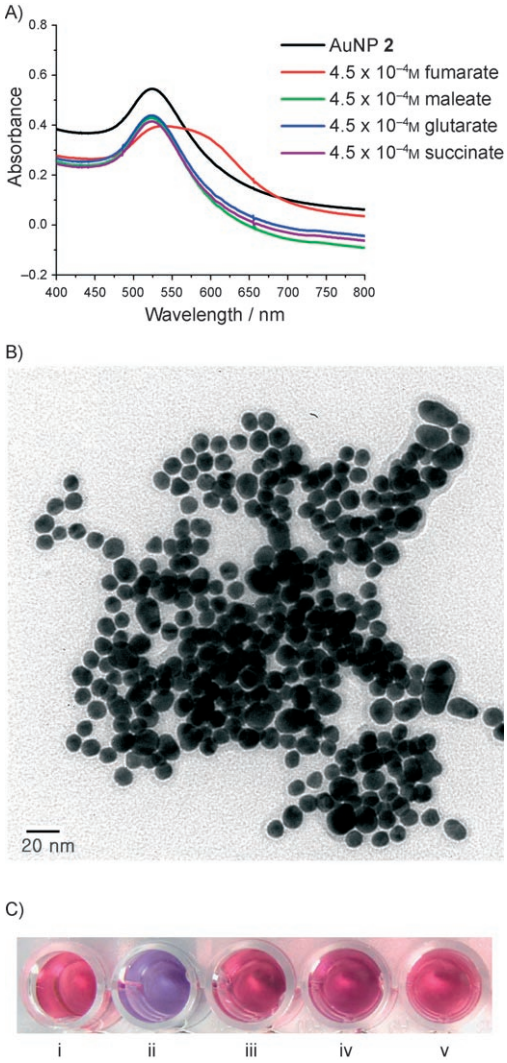


Figure 3. A) Changes in the UV/Vis spectrum of an aqueous solution of **2** (2.0 nM, 1.0 mL) upon addition of fumarate, maleate, succinate, and glutarate (100 μL, 4.5×10^{-4} M). B) TEM image of **2** after addition of fumarate. C) Colorimetric assay with an aqueous solution of **2** (2.0 nM) i) without analyte and with 200 μL (5.0 mM) of ii) fumarate, iii) maleate, iv) succinate, and v) glutarate as sodium salt.

to the solution of AuNPs (300 μL, 2.0 nM; Figure 3C), only fumarate turned the color of the solution from red to blue; the other anions caused little color change. Also, the color remained unchanged even at higher concentrations of the other dicarboxylates.

These results can be explained by assuming the selective aggregation of AuNPs through interparticle cross-linking. The *trans* geometry of fumarate favors interparticle cross-linking with the nanoparticles, which is not possible in the case of maleate owing to its unfavorable geometry. In the case of the other aliphatic dicarboxylates, the cross-linking seems to be unfavorable due to their conformational flexibility. In these cases, intraparticle cross-linking, that is, molecular interactions between two carboxylate groups of the analyte and the trifluoroacetyl binding sites in the same nanoparticle, rather than interparticle cross-linking, seems to be dominant.

To verify the geometrical and conformational factors further, we also carried out the sensing experiments for a series of di- and tricarboxylates of benzene. The nanoparticle probe **2** showed remarkably high sensitivity towards benzene-1,4-dicarboxylate (terephthalate) among other geometrical isomers and analogues: the SPR band broadened and shifted rapidly toward longer wavelength upon addition of 3.0 μL (5.0 mM) of the analyte, which resulted in a large red shift of (69 ± 5) nm. Thus, benzene-1,4-dicarboxylate is a more favorable analyte for the interparticle cross-linking of AuNP **2** compared to fumarate.

The color of the solution changed from red to blue through extensive nanoparticle aggregation, which was further confirmed by TEM analysis (Figure 4B). Other carboxylates such as benzene-1,3-dicarboxylate, benzene-1,3,5-tricarboxylate, and benzene-1,4-diacetate exhibited small decreases in the intensity of the SPR band with little wavelength shifts (Figure 4A), and accordingly no color change was observed (Figure 4C, set I) at lower concentrations (up to 16 μM). The TEM images of these samples, for example, benzene-1,3-dicarboxylate and benzene-1,3,5-tricarboxylate (see the Supporting Information, Figures S6 and S7, respectively), showed little aggregation in accordance with the UV/Vis spectral and color changes. However, these anions behaved differently at higher analyte concentrations ($\geq 10^{-4}$ M; Figure 4C, set II). Benzene-1,4-diacetate showed a distinct color change from red to blue, whereas benzene-1,3-dicarboxylate and benzene-1,3,5-tricarboxylate, both of which provide two carboxylate groups with the same geometrical disposition, showed "half-way" color changes to purple. The two substrates seem to induce some degree, though not extensive, of nanoparticle aggregation. These results clearly indicate that the disposition of the carboxylate groups is an important factor for inducing the effective interparticle cross-linking of probe **2** by the molecular-recognition process. In the case of benzene-1,2-dicarboxylate, the vicinal carboxylate groups are not suitably disposed to induce the interparticle cross-linking; instead, an intraparticle linkage seems to be more favorable, and no visible color change results.

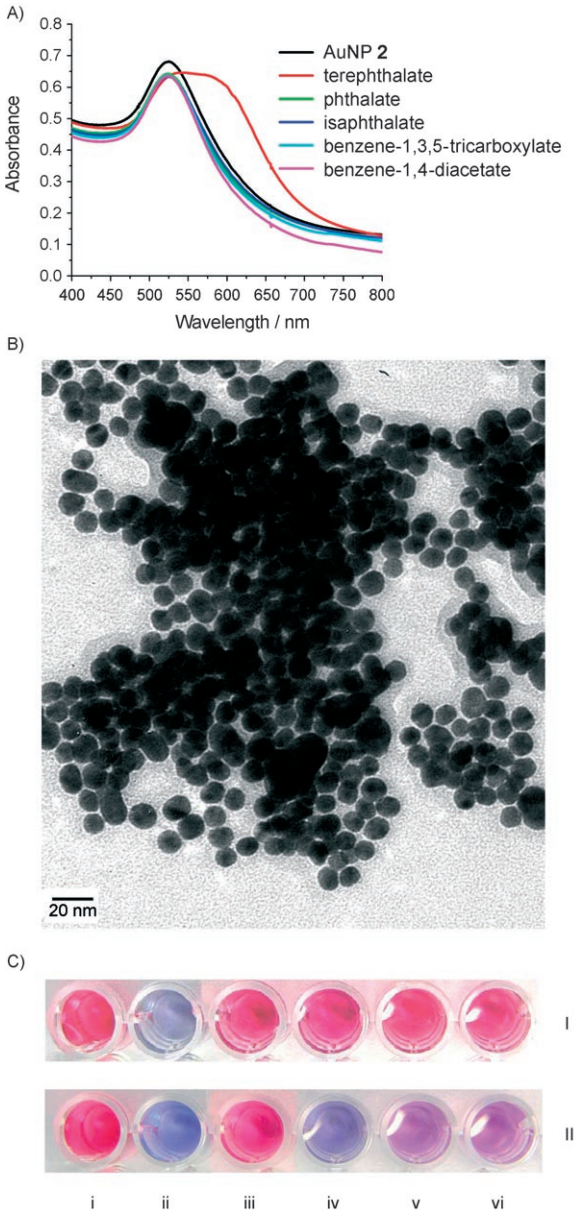


Figure 4. A) Changes in the UV/Vis spectrum of an aqueous solution of **2** (2.0 nM, 1.0 mL) upon addition of terephthalate, phthalate, isophthalate, benzene-1,3,5-tricarboxylate, and benzene-1,4-diacetate (16 μM each). B) TEM image of **2** after addition of terephthalate. C) Colorimetric assays with an aqueous solution of **2** (2.0 nM): i) without analyte and with ii) terephthalate, iii) phthalate, iv) benzene-1,4-diacetate, v) isophthalate, and vi) benzene-1,3,5-tricarboxylate as sodium salt. I: with 10 μL of analyte; II: with 50 μL of analyte.

Conclusions

We have demonstrated that gold nanoparticles functionalized with a water-soluble trifluoroacetophenone derivative constitute a stable and efficient sensing system that discriminates isomeric dicarboxylate anions in water. The nanoparticle system selectively senses specific isomers of dicarboxylates that are geometrically favorable for the binding-induced aggregation process; thus, it discriminates the *trans*

dicarboxylate fumarate from its *cis* isomer maleate, and benzene-1,4-dicarboxylate from its isomers benzene-1,2- and benzene-1,3-dicarboxylate in water, by exhibiting a color change from red to blue. The results presented herein clearly demonstrate that the sensing approach with a receptor-functionalized gold nanoparticle system is promising for the selective sensing of geometrical isomers, a rather demanding task by the conventional "molecular-sensor" approach. Current efforts are directed towards the development of nanoparticle-based probes for the selective detection of other biologically important anions in aqueous media.

Experimental Section

Materials and Methods

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DPX-300 spectrometer. Coupling constants (J) are reported in hertz. Chemical shifts are shown in ppm. An external CF_3COOH standard ($\delta = 0.00$ ppm) was used for ^{19}F NMR spectral measurements. UV/Vis spectra were recorded on an HP 8453 spectrophotometer. FTIR spectra were recorded at a spectral resolution of 4 cm^{-1} with a Bomem DA8 FTIR spectrometer equipped with a liquid-nitrogen-cooled mercury–cadmium–telluride (MCT) detector. Diffuse reflectance infrared Fourier transform (DRIFT) spectra of 1% samples in KBr (Sigma-Aldrich, spectroscopy-grade) were recorded by using a DRIFT attachment (Praying Mantis Model, Harrick Scientific Corp.). TEM images were recorded on a JEOL 2100 microscope operating at 100 keV. Samples for TEM were prepared by spreading a drop of aqueous solution of nanoparticles onto standard carbon-coated copper grids (400 mesh). EDX analysis was carried out in a Philips XL series (XL 30S FEG) unit. High-resolution soft XPS was performed at the 8A1 beam line of a Pohang light source. The base pressure of the chamber was 2×10^{-10} Torr. The incident photon energy was about 630 eV. The photoelectrons emitted from the sample by the incident photons were analyzed with an electron analyzer (Physical electronics: Model PHI 3057 with an Omega lens and a 16-channel detector). At this photon energy, the energy resolution of the technique was >200 meV. The binding energy was calibrated by measuring the Au(4f) peak from Au-deposited Si substrate. High-resolution mass spectra were recorded on a JEOL JMS-700 spectrometer.

Syntheses

4b: 5-Hydroxy-2-nitrobenzaldehyde (**3b**; 2.5 g, 0.015 M) and K_2CO_3 (3.1 g, 1.5 equiv) were placed in a 250-mL two-necked flask equipped with a reflux condenser. Acetone (100 mL) was added, and the mixture was heated under reflux for 30 min. Benzyl bromide (2.6 mL, 0.023 M) was then added, and the mixture was heated under reflux for another 3 h. The mixture was then cooled to room temperature and filtered, and the filtrate was evaporated in vacuo. The residue obtained was dissolved in EtOAc (60 mL) and washed successively with water (2×20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated in vacuo. The resulting residue was purified by column chromatography (silica gel; 5% EtOAc in hexanes) to give 5-(benzyloxy)-2-nitrobenzaldehyde (**4b**; 3.45 g, 94%) as a yellowish solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.17$ (s, 2H), 7.18 (dd, $J = 9.1$, 2.9 Hz, 1H), 7.31–7.43 (m, 5H), 8.10 (d, $J = 9.1$ Hz, 1H), 10.42 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 69.9$, 113.1, 118.0, 126.1, 126.4, 127.5, 127.7, 133.1, 133.8, 141.1, 161.9, 187.3 ppm.

5b: Compound **4b** (3.0 g, 0.012 mol) and anhydrous CsF (0.185 g, 10 mol%) were placed in a 250-mL two-necked flask. DME (60 mL) was added, and the mixture was cooled to 0°C. $TMSCF_3$ (2.0 M in THF, 0.014 mol, 0.72 mL) was added, and the mixture was stirred for 5 h at room temperature. HCl (10%, 30 mL) was then added, and the resulting mixture was stirred for 30 min. The mixture was extracted with EtOAc, washed successively with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel; 10% EtOAc in hexanes) to afford pure 1-[5-(benzyloxy)-2-nitrophenyl]-2,2,2-trifluoroethanol (**5b**; 3.72 g, 95%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.95$ (s, 1H), 5.18 (s, 2H), 6.30–6.38 (m, 1H) 7.06 (dd, $J = 9.1$, 2.8 Hz, 1H), 7.35–7.45 (m, 5H), 7.50–7.61 (m, 1H), 8.12 ppm (d, $J = 9.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 65.2$, 65.6, 66.0, 66.4 (q, $J = 32$ Hz, $CH(OH)CF_3$), 69.8, 114.3, 114.5, 117.2, 120.9, 124.6, 128.3 (q, $J = 281$ Hz, CF_3), 126.6, 127.0, 127.6, 127.8, 131.1, 134.2, 140.2, 161.7 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -1.4$ ppm.

6b: Fe powder (1.4 g, 25 mmole) and NH_4Cl (0.321 g, 6.0 mmol) were placed in a 100-mL two-necked flask equipped with a reflux condenser and a dropping funnel. Aqueous EtOH (50%, 20 mL) was added, and the mixture was heated under reflux for 10 min. A solution of **5b** (1.63 g, 5 mM) in EtOH (20 mL) was added dropwise through a dropping funnel, and heating was maintained at 80°C for 2 h. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. The concentrated solution was extracted with EtOAc (2×15 mL), washed with brine (20 mL), dried over Na_2SO_4, and evaporated in vacuo. The solid residue was purified by column chromatography (silica gel; 10% EtOAc in dichloromethane) to give 1-[2-amino-5-(benzyloxy)phenyl]-2,2,2-trifluoroethanol (**6b**; 1.33 g, 89%) as a brownish-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.95$–5.01 (m, 3H), 6.78–6.90 (m, 3H), 7.30–7.60 ppm (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz): $\delta = 62.4$, [69.8, 70.2, 70.6, 71.0] (q, $J = 32$ Hz, $CH(OH)CF_3$), 71.4, 112.4, 116.1, 119.8, 123.5 (q, $J = 278$ Hz, CF_3), 117.6, 122.6, 128.2, 128.4, 129.0, 137.9, 139.6, 152.6, 158.5 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -2.26$ ppm.

7b: CuCl (9.8 mg, 0.1 mmol), 1,10-phenanthroline (18 mg, 0.1 mmol), and 4-Å molecular sieves were placed in a 100-mL two-necked flask equipped with a reflux condenser. Toluene (30 mL) and K_2CO_3 (28 mg, 0.2 mmol) were added, and the mixture was stirred for 30 min at room temperature. $DEADH_2$ (18 mg, 0.1 mmol) and **6b** (0.59 g, 2.0 mmol) were added successively, and the mixture was heated for 1.5 h in an oil bath at 80–90°C under oxygen atmosphere. Upon cooling to room temperature, the mixture was diluted by addition of diethyl ether (20 mL) and filtered through a pad of celite. The solution was washed successively with water (20 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated in vacuo. The resulting residue was purified by column chromatography (silica gel; 10% EtOAc in hexanes) to give 1-[2-amino-5-(benzyloxy)phenyl]-2,2,2-trifluoroethanone (**7b**; 0.40 g, 68%) as an orange solid. M.p.: 81.3°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.99$ (s, 2H), 6.23 (br s, 2H), 6.66 (d, $J = 9.1$ Hz, 1H), 7.14 (dd, $J = 2.7$, 9.1 Hz, 1H), 7.22 (t, $J = 1.8$ Hz, 1H), 7.32–7.43 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 71.1$, 110.4, 111.5, 115.3, 119.2, 123.0 (q, $J = 289$ Hz, CF_3), 113.3, 113.4, 113.4, 113.5, 119.1 127.8, 128.3, 128.4, 128.8, 136.8, 149.0, 179.6, 180.0, 180.4, 180.9 ppm (q, $J = 33$ Hz, $COCF_3$); ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = 5.98$ ppm; HRMS: m/z calcd for $C_{15}H_{12}F_3NO_2$: 295.0820 $[M]^+$; found: 295.0807.

8b: Thioctic acid (0.206 g, 1.0 mmol) and dichloromethane (3 mL) were placed in a 25-mL round-bottomed flask, and the mixture was cooled to 0°C. Oxalyl chloride (0.152 g, 1.2 mmol) was added, and the mixture was stirred for 10 min at 0°C. DMF (1 drop) was added, and the reaction mixture was stirred for 3 h at room temperature. The solution was evaporated in vacuo. The thioctyl chloride obtained was used directly in the next step, but was dissolved in THF (1.5 mL) prior to use. A solution of **7b** (0.189 g, 1.0 mmol) and K_2CO_3 (0.165 g, 1.2 mmol) in THF (1.5 mL) were placed in a sealed tube, the solution of thioctyl chloride in THF was added, and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated, ethyl acetate (10 mL) was added, and the mixture was washed with aqueous HCl (10%, 5 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The resulting residue was purified by column chromatography (silica gel; 15% EtOAc in hexane) to give *N*-[4-(benzyloxy)-2-(2,2,2-trifluoroacetyl)phenyl]-5-(1,2-dithiolan-3-yl)pentanamide (**8b**; 0.145 g, 31%) as a yellow solid. M.p.: 94°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.44$–1.61 (m, 2H), 1.69–1.83 (m, 4H) 1.87–1.98 (m, 1H), 2.42–2.52 (m, 3H), 3.07–3.23 (m, 2H), 3.54–3.63 (m, 1H), 5.10 (s, 2H), 7.30–7.47 (m, 7H), 8.70–8.76 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.9$, 28.6, 34.5, 38.1, 38.3, 40.1, 56.2, 70.5, 110.5, 114.4, 118.2, 122.1 (q, $J = 289.8$ Hz, CF_3), 116.3, 122.8, 125.0, 127.4, 128.2, 128.6, 135.8, 137.0, 153.2, 171.7, 181.7,

182.2, 182.7, 183.1 ppm (q, $J=34.5$ Hz, $COCF_3$); ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta=6.28$ ppm; HRMS: m/z calcd for $C_{23}H_{24}O_3NF_3S_2$: 483.1150 $[M]^+$; found: 483.1148.

9: A solution of **8b** (0.12 g, 0.25 mmol) in dichloromethane (2 mL) was placed in a two-necked flask, and Me_2S (2 mL) was added under nitrogen atmosphere. $BF_3{\cdot}Et_2O$ (177 μL) was then added, and the reaction mixture was stirred for 10 h at 30 °C. The solvent was evaporated in vacuo, and ethyl acetate (10 mL) and water (5 mL) were added to the residue. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue obtained was purified by column chromatography (silica gel; 25% EtOAc in hexane) to give *N*-[4-(hydroxy)-2-(2,2,2-trifluoroacetyl)phenyl]-5-(1,2-dithiolan-3-yl)pentanamide (**5**; 0.083 g, 84%) as a yellow solid. M.p.: 115 °C; ^1H NMR (CD_3OD, 300 MHz): $\delta=1.44$–1.53 (m, 2H), 1.57–1.73 (m, 4H) 1.83–1.92 (m, 1H), 2.32 (t, $J=7.3$ Hz, 2H), 2.40–2.47 (m, 1H), 2.77 (br s, 1H), 3.02–3.16 (m, 2H), 3.53–3.58 (m, 1H), 6.77–6.81 (m, 1H), 6.95–7.0 (m, 1H), 7.92–7.96 ppm (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz): $\delta=26.4$, 29.98, 35.9, 37.7, 38.8, 39.5, 41.4, 57.6, 98.8, 99.0, 99.4, 99.8 (q, $J=31.0$ Hz), 117.5, 118.1, 118.8, 122.6, 126.4, 130.3 (q, $J=286.0$ Hz, CF_3), 125.4, 126.0,131.1, 155.1, 173.3 ppm; ^{19}F NMR (CD_3OD, 282 MHz): $\delta=-8.95$ ppm; HRMS: m/z calcd for $C_{16}H_{18}O_3NF_3S_2$: 393.0680 $[M]^+$; found: 393.0674.

1: Compound **9** (0.040 g, 0.10 mmol) and K_2CO_3 (0.016 g, 0.12 mmol) were placed in a two-necked flask. Acetone (5 mL) was added, and the mixture was heated under reflux for 10 min. 1,4-Butane sultone (12.2 μL, 0.12 mmol) was added, and the reaction mixture was heated under reflux for 2 h. Upon cooling to room temperature, the mixture was filtered, and the filtrate was evaporated. The crude residue was triturated sequentially with diethyl ether (2×1 mL), dichloromethane (2×1 mL), ethyl acetate (2×1 mL), and water (1 mL). The sticky liquid obtained was dried in vacuo to give the desired potassium *N*-[4-(4′-butoxysulfonate)-2-(2,2,2-trifluoroacetyl)phenyl]-5-(1,2-dithiolan-3-yl)pentanamide (**1**; 0.023 g, 40%) as a yellow liquid. ^1H NMR (CD_3OD, 300 MHz): $\delta=1.45$–1.52 (m, 2H), 1.587–1.74 (m, 4H) 1.85–1.92 (m, 1H), 2.1–2.26 (m, 1H), 2.34–2.42 (m, 3H), 3.09–3.20 (m, 3H), 3.49–3.75 (m, 2H), 6.67–6.77 (m, 2H), 8.13–8.17 ppm (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz): $\delta=26.6$, 26.7 30.0, 35.9, 38.8, 39.1, 39.5, 41.4, 57.6, 64.5, 73.7 116.8, 117.3, 117.5, 117.8, 121.5, 124.5, 127.4, 130.4 (q, $J=221$ Hz, CF_3), 128.6, 155.1, 157.0 173.6 ppm; ^{19}F NMR (CD_3OD, 282 MHz): $\delta=-2.88$ ppm; MS (ESI): $m/z=538$.

Preparation of solution of CATFA-functionalized AuNPs: A solution of sodium citrate dihydrate (130 mg, 0.44 mmol) in deionized water (5 mL, purified by using a Milli-Q™ water-purification system) was added quickly to a light-yellow solution of $HAuCl_4{\cdot}3H_2O$ (57 mg, 0.144 mmol) in deionized water (100 mL) under reflux. The resulting solution became deep-red within minutes, was stirred for 30 min under reflux, and was allowed to cool to room temperature. The reaction mixture was filtered through a cellulose nitrate membrane filter (pore size: 0.2 μm) to give a gold colloidal solution, which was diluted with deionized water (135 mL) and used in the following CATFA functionalization. For the functionalization, the pH of the diluted gold colloidal solution (20 mL, 9.0 nM) was adjusted to 11 with 0.5 M aqueous NaOH. A methanolic solution of **1** (2.0 mM, 2.0 mL) was added dropwise to this solution, and the resulting mixture was stirred at room temperature for 2 days. The CATFA-functionalized nanoparticles were then centrifuged twice (at 10000 rpm) for 20 min followed by decantation of supernatants to remove the excess CATFA. The purified CATFA-functionalized AuNPs were redissolved in deionized water. The pH of the resulting solution was around 7, and the concentration of the resulting solution of AuNPs, as calculated from UV/Vis spectral data, was 6.8 nM.

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