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A Biomimetic Principle for the Chemical Modification of Metal Surfaces: Synthesis of Tripodal Catecholates as Analogues of Siderophores and Mussel Adhesion Proteins

Elisa Franzmann,[a] Faiza Khalil,[a] Christoph Weidmann,[b] Michael Schröder,[b] Marcus Rohnke,[b] Jürgen Janek,[b] Bernd M. Smarsly,[b] and Wolfgang Maison*[a]

Abstract: By following a biomimetic design principle, tetravalent scaffolds based on an adamantyl and trisalkylmethyl core structure have been synthesized. These scaffolds have been coupled to three catecholamines, thus resembling the characteristic tripodal recognition motif of many natural metal binders, such as mussel adhesion proteins and siderophores, for example, enterobactin. Besides this tripodal recognition element, our scaffolds provide a fourth position for the conjugation of effector molecules. These effectors can be conjugated through biocompatible conjugation techniques to the scaffold and can be used to tailor the properties of different metal surfaces for a range of applications, for example, in implant engineering. Herein, we describe the synthesis of several tripodal metal binders and their immobilization on TiO_2 surfaces by using a simple dip-coating procedure. Furthermore, we demonstrate the conjugation of our surface binders to the dye eosin Y as an effector molecule by peptide coupling. The resulting surfaces have been analyzed by using ellipsometry, time-of-flight secondary ion mass spectrometry, IR spectroscopy, and contact-angle measurements to confirm the specific loading on TiO_2 films and nanoparticles with our trivalent surface binders. As a proof of concept, we have demonstrated the functionalization of TiO_2 nanoparticles with the eosin Y dye.

Keywords: biomimetic synthesis · catecholates · siderophores · surface chemistry · synthetic methods

Introduction

The chemical modification of material surfaces by the molecular self-assembly of functionalized anchor molecules is an attractive concept for various applications in fields such as marine technology,[1] medicine,[2] hygiene technology,[3] and microelectronics.[4] The major advantages of this principle for the generation of functional surfaces are 1) the availability of efficient and scalable coating techniques (compatible with large surface areas and 3D objects), 2) the generation of chemically well-defined surfaces, and 3) the need for relatively low amounts of anchor molecules. Methods for the covalent immobilization of molecular monolayers rely on the use of appropriately functionalized anchor molecules, including thioles for gold and silver surfaces,[5] silanols for glass surfaces,[6] and phosphates or phosphonates for various metal surfaces.[7] All of these immobilization techniques have drawbacks, such as limited stability or a limited range of substrate materials. Recently, catecholates have received considerable interest as reagents for the mild modification of metal and metal oxide surfaces by using convenient dip-and-rinse protocols.[8] This approach may be considered biomimetic because catecholate moieties are key components of natural metal binders such as mussel adhesion proteins.[8c,9] In the *Mytilus edulis* foot protein 5 (Mefp-5), derived from marine mussels, the catecholate derivative 3,4-dihydrophenylalanine (DOPA) is the key constituent for adhesion and makes up about 27% of all amino acids.[10] In addition, catecholates are abundant motifs in many siderophores, such as enterobactin (Figure 1).[11]

The use of mussel adhesion proteins and catecholates derived thereof for surface immobilization was pioneered by Waite[9] and Grätzel and co-workers[12] and later established by Messersmith and co-workers.[8a–c,e,13] Many different catecholates, which range from synthetic derivatives to natural products in monomeric and also polymeric forms, have been used for the modification of various metal and metal oxide surfaces.[10d,14] Particularly interesting for surface engineering is the use of small bifunctional catecholate derivatives, such as dopamine as an anchor group, and a small selection of

[a] Dipl.-Chem. E. Franzmann, Dipl.-Chem. F. Khalil, Prof. Dr. W. Maison
Justus-Liebig-University Giessen
Institute of Organic Chemistry
Heinrich-Buff-Ring 58, 35392 Giessen (Germany)
Tel: (+49) 641-99-34330
E-mail: wolfgang.maison@org.chemie.uni-giessen.de

[b] Dipl.-Chem. C. Weidmann, Dipl.-Chem. M. Schröder, M. Rohnke, Prof. Dr. J. Janek, Prof. Dr. B. M. Smarsly
Justus-Liebig-University Giessen
Institute of Physical Chemistry
Heinrich-Buff-Ring 58, 35392 Giessen (Germany)

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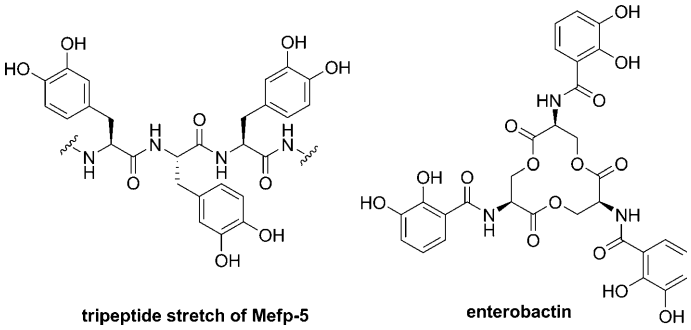


Figure 1. Natural catecholate derivatives. A) A fragment of the mussel adhesion protein Mefp-5 of *Mytilus edulis* with its characteristic trimeric repeats of L-DOPA and B) the siderophore enterobactin (enterochelin).

suitable compounds is presented in Figure 2. These anchors may be conjugated to effector molecules such as poly(ethylene glycol), biopolymers, drugs, and dyes for the specific

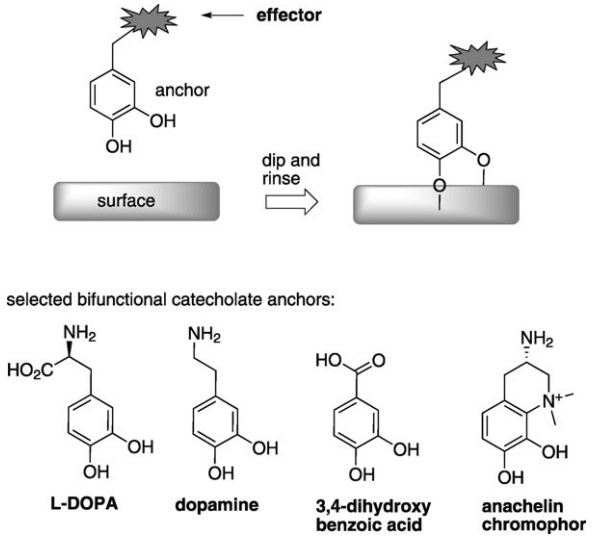


Figure 2. Surface modification by the self-assembly of bifunctional catecholate derivatives with dip-and-rinse protocols.

modulation of surface properties.[8a,b,11b,15] Inspired by the intriguing molecular symmetry of siderophores, such as enterobactin,[16] we have designed triscatecholates **3**, **4**, **6**, **8**, **10**, and **12–14** with a tripodal binding motif based on adamantane and trisalkylmethyl scaffolds. Many enterobactin mimetics are known.[17] However, to the best of our knowledge, none of these mimetics have been applied to surface modification. By using trimeric catecholates **3**, **4**, **6**, **8**, **10**, and **12–14** instead of monomeric derivatives, such as dopamine, we assume to achieve binding to metal surfaces characterized by high thermal, mechanical and pH stability. In addition, our scaffolds permit the conjugation of effector molecules by using standard peptide chemistry or other bioorthogonal techniques. We have used these scaffolds before as modular components for targeted chemotherapy and molecular imaging.[18] Thus, they are a valuable molecular platform to which many different anchor molecules and effectors might be conjugated. With an exchange of a catecholate for another adhesive, for example, it would be easy to tune the surface specificity of our devices.

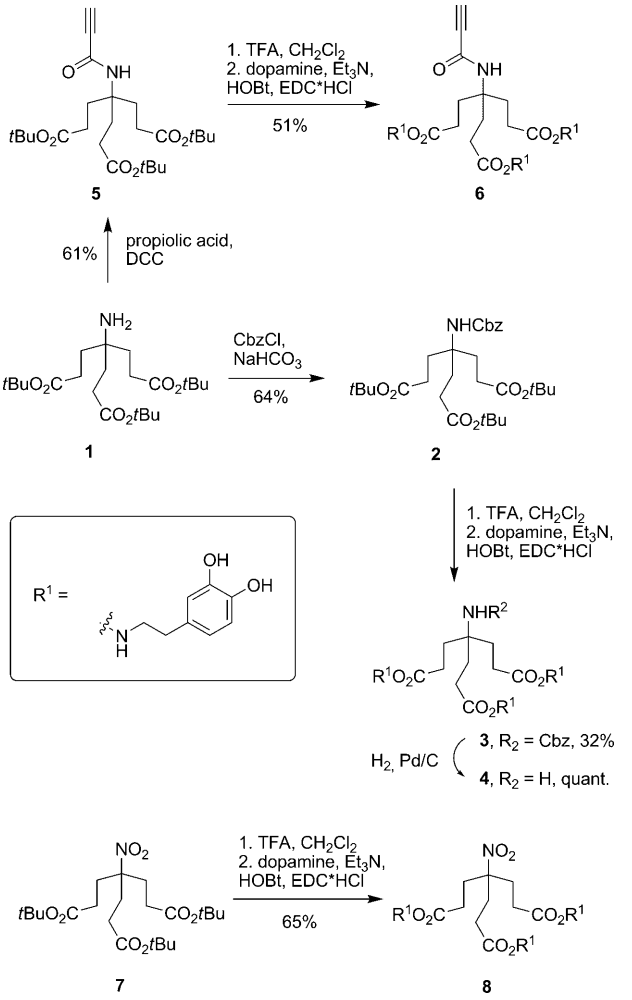
Herein, we describe the synthesis of triscatecholates **3**, **4**, **6**, **8**, **10**, and **12–14** and their application to the functionalization of TiO_2 films and nanoparticles. The resulting surfaces were analyzed by using IR spectroscopy, contact-angle measurements, time-of-flight secondary ion mass spectrometry (TOF-SIMS), and ellipsometry.

Results and Discussion

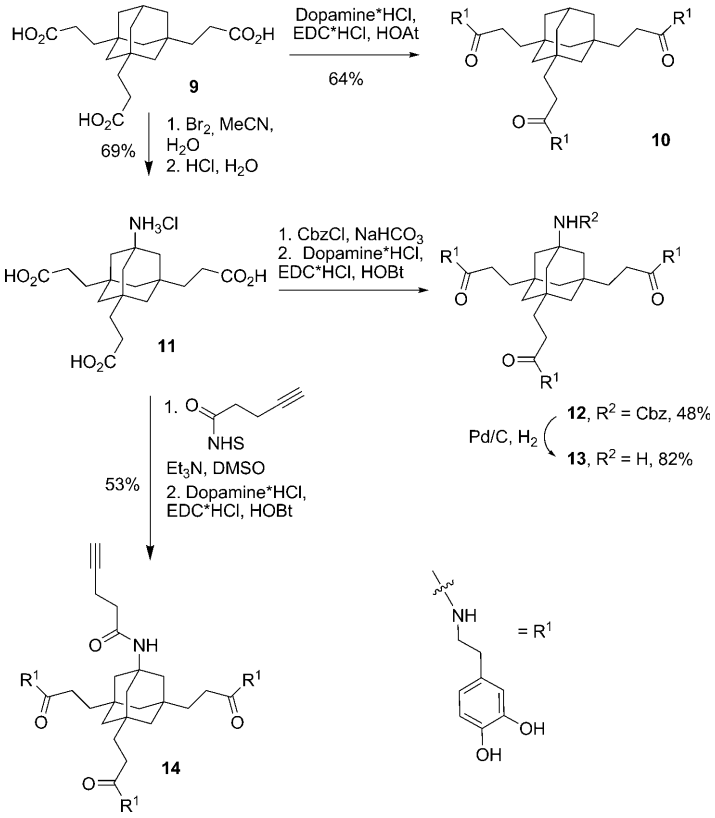
The compounds central to our concept are modular scaffolds **3**, **4**, **6**, **8**, **10**, and **12–14**. These scaffolds have several desirable properties: they permit the assembly of three catecholates to a tripodal motif, they can be easily coupled to effector molecules either before or after surface immobilization, and they are relatively easy to synthesize.[19]

Synthesis of triscatecholates: The preparation of trisalkylmethyl scaffold **1** is scalable and has been reported by Newkome et al. previously.[19a] Therefore, scaffold **1** was an ideal starting material for the synthesis of a first set of flexible triscatecholates. The free amine was protected with CbzCl to give **2**, and the obtained *tert*-butyl esters were cleaved under acidic conditions to give the corresponding tricarboxylic acid, which was subsequently coupled to three equivalents of dopamine with EDC/HOBt to give triscatecholate **3** (Scheme 1). Final deprotection of the Cbz group gave triscatecholate **4** with a free primary amine group for effector conjugation. A second derivative **6** was obtained following a similar reaction sequence. In this case, amine **1** was acylated with propiolic acid to give *tert*-butyl ester **5**. Acidic cleavage of the ester and subsequent conjugation to dopamine gave triscatecholate **6**. The propiolate moiety in **6** may be used for the conjugation of effectors through the Huisgen cycloaddition. A third triscatecholate **8** was synthesized from nitro derivative **7**. In a first step, the *tert*-butyl esters were cleaved under acidic conditions and the resulting tricarboxylic acid was coupled to three equivalents of dopamine using EDC/HOBt to give triscatecholate **8**.

The corresponding adamantyl derivatives **10** and **12–14** were prepared according to Scheme 2 from the known precursor **9**, which is available in two high-yielding steps from commercial precursors.[19b] The coupling of tricarboxylic acid **9** to dopamine gave triscatecholate **10** without an additional functional group at the remaining fourth bridgehead position of the adamantane unit. Alternatively, amino derivative **11** was synthesized as a hydrochloride salt by following a two step-procedure reported previously by us.[18d] The resulting amine **11** was protected with a Cbz group and coupled to dopamine to give the Cbz-protected triscatecholate **12**. Subsequent deprotection gave free amine **13**. Alternatively, amino tricarboxylic acid **11** was first acylated with the *N*-hydroxysuccinimide (NHS) ester of 4-pentynoic acid and then



Scheme 1. Synthesis of triscatecholates **3**, **4**, **6**, and **8** with trisalkylmethyl scaffolds and different conjugation sites for effector moieties. CbzCl = benzyl chloroformate, EDC·Cl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = hydroxybenzotriazole TFA = trifluoroacetic acid.



Scheme 2. Synthesis of triscatecholates **10** and **12**–**14** with adamantyl scaffolds and different conjugation sites for effector moieties. DMSO = dimethyl sulfoxide.

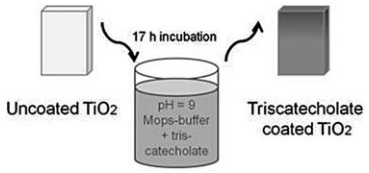


Figure 3. Schematic illustration of the dip-coating procedure of catecholates and TiO_2 in aqueous solution of MOPS buffer.

coupled to dopamine by using the standard procedure to give triscatecholate **14**.

Overall, four scaffolds **10** and **12**–**14** with either amino or alkynyl groups for effector conjugation were synthesized in gram quantities.

Evaluation of surface-binding properties: We focused on TiO_2 surfaces for our first binding studies because many surface-modified titanium-based materials are used as nanoelectronics, sensors, energy-storage devices, photovoltaics, and biomaterials, such as implants.[15c,20] In addition, TiO_2 surfaces are readily available in the form of nanoparticles and films.

The immobilization of triscatecholates **6**, **8**, **10**, **12**, and **13** by self-assembly on TiO_2 films (prepared on silicon wafer) was performed by aqueous dip-coating in MOPS buffer under standard conditions (Figure 3).[15a,b]

TiO_2 films (layer thickness of 100 nm on a silicon wafer of 2.5×2.5 cm) were cleaned with water and methanol and dipped into solutions of triscatecholates **6**, **8**, **10**, **12**, and **13** (1.25 mg/15 mL) in concentrated salt buffer (0.1 M MOPS/0.6 M NaCl/0.6 M K_2SO_4) for 13 hours at room temperature. After this incubation, the coated surfaces were carefully and repeatedly rinsed with purified water and methanol to wash away residual buffer and unbound catecholate derivatives.

The resulting modified surfaces were submitted to different analytical techniques to verify the binding of our triscatecholates to the TiO_2 films.

Surface analysis: First, we examined the polarity of the surfaces by measuring the water contact angles. In each case, the initial water contact angle for the uncoated TiO_2 surface was between 25 and 30° (Table 1). After storage of the TiO_2 films in the pure MOPS buffer solution for 13 hours, the water contact angle decreased to about 5°, thus reflecting a change of surface polarity as a result of the alkaline buffer

Table 1. Results of the water contact-angle (Θ) measurements of catecholate derivatives **6**, **8**, **10**, **12**, and **13**.

Catecholate	Θ (TiO_2) [°][a]	Θ (TiO_2+MOPS) [°][a]	Θ (TiO_2+MOPS+catecholate) [°][a]
6	27.9	8.2	18.5
8	32.3	5.8	22.9
10	28.0	5.0	38.5
12	25.6	8.2	22.9
13	29.1	5.0	11.7
dopamine	30.9	7.6	10.7

[a] Average values for 3–4 measurements are given.

solution. After incubation with the triscatecholate derivatives, a substantial increase in the water contact angle Θ was observed, thus reflecting a decrease in surface polarity upon immobilization of the organic molecules. As expected, the largest effect was observed for triscatecholate **10** with an unsubstituted adamantyl scaffold ($\Theta = 38.5°$; Figure 4).

Figure 4. A) Pure TiO_2 surface: contact angle $\Theta = 24°$; B) TiO_2 surface treated with MOPS buffer: contact angle $\Theta = 5°$; C) TiO_2 surface treated with **10** in MOPS buffer: contact angle $\Theta = 38.5°$.

Analysis by TOF-SIMS was used to verify the nature of the bound organic material on the TiO_2 films.

For the detection of the bound organic molecules, the surface was analyzed with Bi_3^+ primary ions. Each sample was measured in the positive and negative modes of operation, that is, by detecting positive and negative secondary ions. For the elimination of the sample background in each case, a reference area without immobilized molecules was measured and afterward the difference spectrum was calculated.

Secondary molecular ions were detectable for monomeric dopamine only and the characteristic signals for $C_8H_9NO_2^+$, $TiC_8H_9NO_2^+$, and $Ti_2C_8H_9NO_2^+$ were clearly identified in the positive-mode mass spectra. As a result of the high fragmentation rate of the triscatecholate derivatives, it was impossible to detect the molecular ions of these larger compounds in most cases. However, characteristic fragments were observed in each case. Compound **8**, for example, was identified unambiguously by a characteristic NO_2^- signal in the negative mode (Figure 5).

Another good marker is the adamantyl cation $C_{10}H_{11}^+$, which was clearly detected for triscatecholates **10**, **12**, and **13**. A small section of the mass spectrum in the positive mode for **10** is depicted in Figure 6.

The adlayer thickness of the functionalized TiO_2 surfaces was measured by ellipsometry for immobilized triscatecholate **13** and dopamine (Figure 7). A clear trend was observed for dopamine: an increase in the concentration of dopamine in the buffer solutions led to a significant increase in the adlayer thickness. This outcome reflects the tendency of

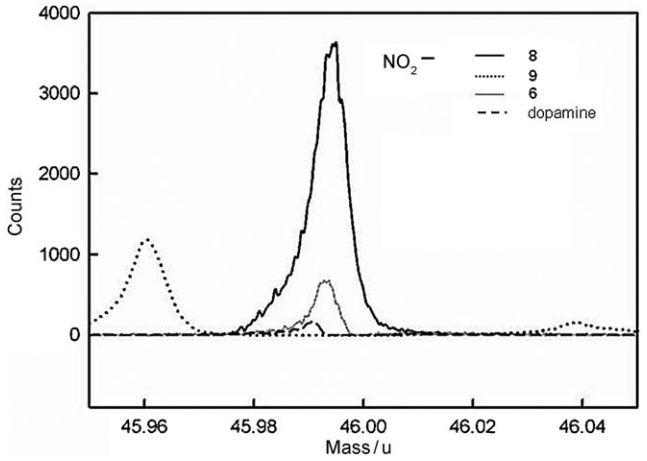


Figure 5. TOF-SI mass spectrum of **8** immobilized on TiO_2. The negative-mode spectrum of the functionalized surfaces shows the characteristic mass signal at m/z 45.99 u for NO_2^-.

dopamine to form polydopamine on TiO_2.[21] In contrast, triscatecholate **13** showed no tendency to polymerize and the adlayer thickness stayed constant.

In a last set of experiments, we immobilized triscatecholate **12** and the eosin Y-loaded derivative **15** on TiO_2 nanoparticles (P25). The conjugation of eosin Y to triscatecholate **13** was done under standard peptide-coupling conditions to give the triscatecholate/dye conjugate **15** as a red powder, which was characterized by means of MS (ESI) and used without further purification for surface immobilization. The loading of TiO_2 nanoparticles (P25) was performed with triscatecholates **12** and **15** under sonication conditions in MOPS buffer for 12 hours. The binding of triscatecholates

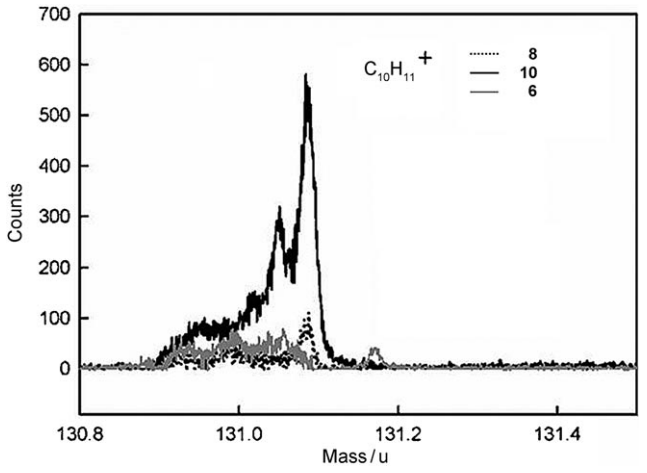


Figure 6. TOF-SI mass spectrum of **10**. The positive-mode spectrum of the functionalized surfaces shows the characteristic mass signal at m/z 131 u for the adamantyl cation.

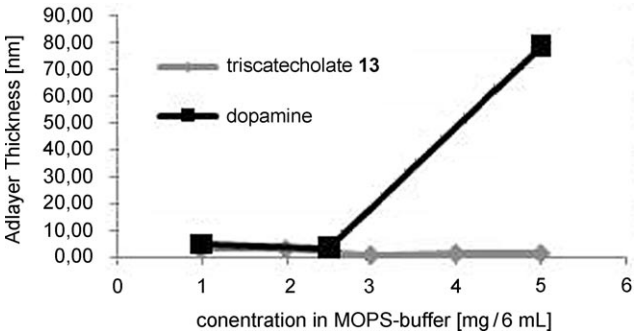


Figure 7. Changes of the adlayer thickness of different concentrations of triscatecholate **13** and dopamine.

to the nanoparticles after thorough washing was clearly confirmed by characteristic signals in the IR spectra (as depicted for triscatecholate **12** on TiO_2 in Figure 8).

In addition, the successful immobilization of the eosin Y-labeled triscatecholate **15** on TiO_2 nanoparticles (P25) was clearly visible by the deep-red color after washing (Figure 9 and Scheme 3). Eosin Y itself is bright red and does not bind to the TiO_2 surface (Figure 9, tube 2).

Conclusion

Bifunctional catecholate derivatives are versatile tools to tailor surface properties by using reliable and convenient dip-and-rinse procedures. This approach is biomimetic and has been derived from mussel adhesion proteins and siderophores containing catecholates. With the synthesis of bifunctional triscatecholates **3**, **4**, **6**, **8**, **12**–**15**, we have extended this biomimetic principle that imitates tripodal catecholate assemblies in nature. These triscatecholates bind to TiO_2 films and nanoparticles, which was confirmed by using contact-angle measurements, ellipsometry, IR spectroscopy, and TOF-SIMS, and allow surface functionalization with effector molecules. These effectors may be introduced before surface immobilization as demonstrated with the dye conjugate **15**. Alternatively, alkyne-substituted catecholates, such as **6** and **14**, allow the generation of 'clickable' materials that may be modified by effector coupling to the surface.

By using multivalent catecholate derivatives, we expect high thermal, mechanical, and pH stability of triscatecholate-functionalized surfaces while conserving a molecularly well-defined immobilization pattern. It should be noted that our surface binders have a modular character and their surface specificity may therefore be tailored by the use of other adhesives than catecholates.

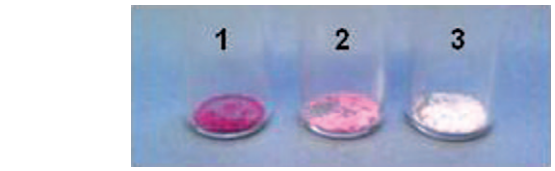
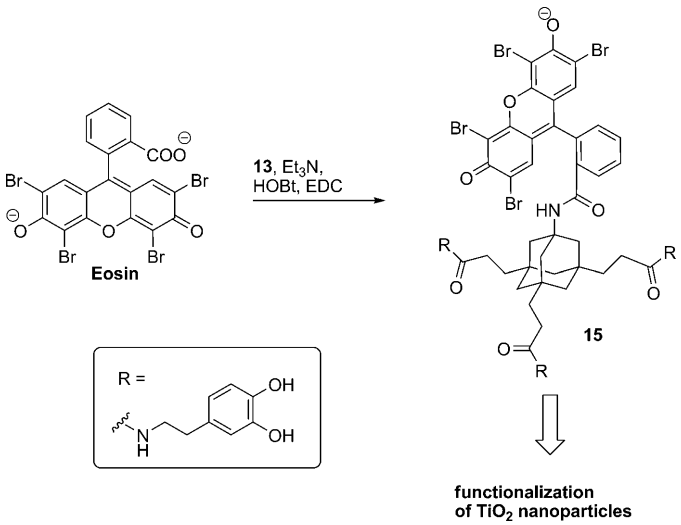


Figure 9. 1) Eosin Y-labeled triscatecholate **15** immobilized on TiO_2 nanoparticles after thorough washing with water and methanol; 2) TiO_2 nanoparticles after incubation with pure eosin Y and thorough washing with water and methanol; 3) pure TiO_2 (P25).



Scheme 3. Synthesis of the eosin Y-labeled triscatecholate **15** for immobilization on TiO_2 nanoparticles.

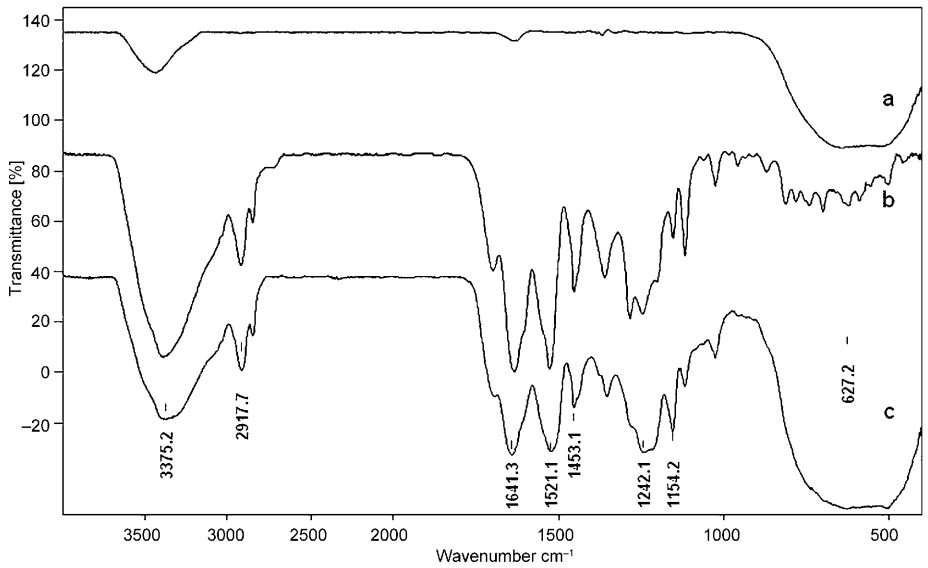


Figure 8. The characteristic FTIR spectrum for a) pure TiO_2 nanoparticles (P25), b) pure triscatecholate **12**, and c) triscatecholate **12** immobilized on TiO_2 nanoparticles.

Experimental Section

Synthetic precursors: The following educts were prepared according to literature procedures: **1**,[19a] **2**,[22] **7**,[19a] **9**,[19b] and **11**.[18d]

Immobilization on TiO_2 surfaces: Silicon wafers ((100)-oriented Si single crystal (surface area: 2.5×2.5 cm)) were coated with TiO_2 films of 100 nm thickness by hydrolysis of $TiCl_4$ in water and ethanol. The surfaces were cleaned twice with water and methanol and were dried in a compressed air steam.

The appropriate catecholate (5 mg) was dissolved in MeOH (5 mL) and H_2O (15 mL). An aliquot of this stock solution (5 mL) was added to 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (10 mL; 0.1 M MOPS/0.6 M NaCl/0.6 M K_2SO_4). TiO_2 surfaces were dipped into the solution of catecholate in buffer and left for 13 h. The plates were rinsed excessively with water and methanol.

Immobilization of catecholates on TiO_2 nanoparticles: The TiO_2 nanoparticles are commercially available from Degussa (TiO_2, P25). These nanoparticles have a specific surface area of $50\pm15\ m^2g^{-1}$, an average particle size of 21 nm, and a purity of 99.5%.

TiO_2 nanoparticles (1 equiv by mass) and the appropriate catecholate (4 equiv) were stirred for 12 h in MOPS buffer with sonication, separated by centrifugation, washed with excessively H_2O and MeOH, and dried in vacuo.

Preparation of triester 2: Compound **1** (3.0 g, 7.2 mmol) was dissolved in dioxane/water (100 mL; 1:1) and cooled to 0 °C. Na_2CO_3 (0.7 g, 8.3 mmol) and CBzCl (1.4 g, 1.2.0 mL, 8.3 mmol) were added, and the solution was stirred at 0 °C for 2 h and at room temperature for 2 h. The reaction mixture was extracted three times with CH_2Cl_2, the combined organic layers were washed three times with 1 M HCl, dried over Na_2SO_4, filtered, and concentrated. The resulting crude product was purified by flash chromatography on silica gel (petrol ether/EtOAc) to give triester **2** as a colorless solid (2.5 g, 4.6 mmol, 64%). R_f=0.42 (petroleum ether/EtOAc 8.5:1.5); cerium ammonium nitrate; m.p. 100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.32 (m, 5H), 5.04 (s, 2H), 4.83 (s, 1H), 2.20 (t, ^3J=7.5, ^3J=8.3 Hz, 6H), 1.91 (t, ^3J=8.2, ^3J=7.4 Hz, 6H), 1.43 ppm (s, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.7, 154.3, 136.7, 128.6, 128.2, 128.1, 80.7, 66.3, 56.7, 30.2, 29.8, 28.2 ppm; IR (KBr): $\tilde{\nu}$=3348, 1726, 757 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{30}H_{47}NO_8$: 572.3199 [M+Na$^+$]; found: 572.3195; elemental analysis calcd (%) for C 65.63, H 8.65, N 2.55; found: C 65.55, H 8.62, N 2.55.

Preparation of triscatecholate 3: A solution of triester **2** (2.0 g, 3.6 mmol) in CH_2Cl_2 and TFA (45 mL, 1:1) was stirred at room temperature for 3 h. The reaction mixture was concentrated and coevaporated twice with CH_2Cl_2 to give the corresponding triacid (1.3 g, 3.3 mmol, 92%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.34–7.33 (m, 5H), 4.98 (s, 2H), 2.12 (t, 6H, ^3J=7.8, ^3J=7.8 Hz), 1.79 ppm (t, 6H, ^3J=8.4, ^3J=7.8 Hz); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=174.5, 154.3, 137.5, 128.4, 127.7, 127.5, 64.7, 55.8, 29.2, 28.1 ppm; IR (KBr): $\tilde{\nu}$=3433, 1712, 697 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{23}NO_8$: 404.1321[M−Na$^+$]; found: 404.1326; elemental analysis calcd (%) for C 52.46, H 6.17, N 3.34; found: C 52.69, H 6.08, N 3.37. The tricarboxylic acid (200 mg, 0.52 mmol) and Et_3N (1.44 mL; 10.4 mmol) were dissolved in anhydrous DMF (10 mL) and cooled to 0 °C. EDC·Cl (330 mg, 1.72 mmol), HOBt (230 mg, 1.72 mmol), and dopamine hydrochloride (260 mg, 1.72 mmol) were added, and the resulting solution was stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (20 mL) and washed three times with 1 M HCl and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. This crude product was suspended in Et_2O (100 mL) and stirred for 2 h. Filtration gave triscatecholate **3** (140 mg, 0.18 mmol, 34%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.35–7.30 (m, 5H), 6.62 (d, 3H, ^3J=7.87 Hz), 6.57 (s, 3H), 6.42 (d, 3H, ^3J=7.87 Hz), 5.00 (s, 2H), 3.41–3.36 (m, 6H), 3.15–3.14 (m, 6H), 2.00 (s, 6H), 1.78 ppm (s, 6H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=172.0, 145.1, 143.5, 137.4, 130.3, 128.4, 127.7, 127.5, 64.9, 56.2, 40.7, 34.8, 30.4, 29.7 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{42}H_{50}N_4O_{11}$: 809.3374 [M−Na$^+$]; found: 809.3374.

Preparation of triscatecholate 4: Triscatecholate **3** (35 mg, 0.044 mmol) was dissolved in anhydrous MeOH (10 mL) and a catalytic amount of Pd/C was added. The resulting suspension was stirred at room temperature for 12 h under H_2 (balloon). Filtration over celite and concentration of the filtrate gave compound **4** (287 mg, 0.044 mmol, quant.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=6.76 (d, 3H, ^3J=8.0 Hz), 6.70 (s, 3H), 6.56 (d, 3H, ^3J=8.0 Hz), 3.50–3.48 (m, 12H), 2.21–2.19 (m, 6H), 1.67–1.65 ppm (m, 6H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=172.1, 145.0, 143.5, 130.2, 119.1, 115.9, 115.5, 48.6, 40.6, 34.6, 29.7 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{34}H_{44}N_4O_9$: 653.3187 [M−H$^+$]; found: 653.3186.

Preparation of triester 5: Compound **1** (3.6 g, 8.7 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Propiolic acid (0.73 g, 10.4 mmol) and *N*,*N*-dicyclohexylcarbodiimide (DCC; 2.2 g, 10.4 mmol) were added and the solution was stirred at room temperature for 12 h. CH_2Cl_2 was removed in vacuo and the residue was dissolved in EtOAc, washed three times with 1 M HCl, three times with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The resulting crude product was purified by flash chromatography on silica gel (petrol ether/EtOAc) to give triester **5** as a colorless solid (2.5 g 5.3 mmol, 61%). R_f=0.47 (petroleum ether/EtOAc, 2:1, molybdophosphoric acid); m.p. 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.38 (s, 1H), 2.69 (s, 1H), 2.23 (t, 6H, ^3J=7.6, ^3J=8.1 Hz), 1.98 (t, 6H, ^3J=8.1, ^3J=7.6 Hz), 1.43 ppm (s, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.7, 151.3, 81.0, 78.0, 71.8, 59.0, 30.0, 29.8, 28.2 ppm; IR (KBr): $\tilde{\nu}$=3260, 1724, 1539, 1154 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{25}H_{41}NO_7$: 490.2781 [M−Na$^+$]; found: 490.2781; elemental analysis calcd (%) for C 64.22, H 8.84, N 3.00; found: C 64.22, H 8.84, N 3.01.

Preparation of triscatecholate 6: A solution of triester **5** (500 mg, 1.67 mmol) in CH_2Cl_2 and TFA (45 mL, 1:1) was stirred at room temperature for 3 h. The mixture was concentrated in vacuo and the resulting oil was coevaporated with CH_2Cl_2 three times to give the corresponding triacid (410 mg) as an intermediate. This crude product (320 mg, 1.10 mmol) and Et_3N (1.44 mL; 10.4 mmol) were dissolved in anhydrous DMF (10 mL) and cooled to 0 °C. EDC·Cl (600 mg, 4.3 mmol), HOBt (580 mg, 4.3 mmol), dopamine hydrochloride (650 mg, 4.3 mmol), and Et_3N (0.91 mL, 6.6 mmol) were added, and the resulting solution was stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (20 mL) and washed three times with 1 M HCl and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. This crude product was suspended in Et_2O (100 mL) and stirred for 2 h. Filtration gave compound **6** (600 mg, 0.85 mmol, 51%). ^{1}H NMR (400 MHz, [D$_4$]CH_3OD): δ=6.68 (d, 3H, ^3J=7.9 Hz), 6.64 (s, 3H), 6.52 (d, 3H, ^3J=7.9 Hz), 3.51 (s, 1H), 3.39–3.34 (m, 6H), 2.63 (t, 6H, ^3J=7.1 Hz), 2.12 (s, 6H), 2.13–2.09 (m, 6H), 1.94–1.92 ppm (m, 6H); ^{13}C NMR (100 MHz, [D$_4$]CH_3OD): δ=175.5, 146.2, 144.8, 132.0, 121.1, 117.0, 116.4, 74.6, 60.3, 42.4, 35.8, 31.5, 31.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{37}H_{44}N_4O_{10}$: 727.2955 [M+Na$^+$]; found: 727.2961.

Preparation of triscatecholate 8: Compound **7** (100 mg, 0.36 mmol) and Et_3N (0.47 mL; 3.40 mmol) were dissolved in absolute DMF (10 mL) and cooled to 0 °C. EDC·Cl (0.25 g, 1.62 mmol), HOBt (0.22 g, 1.62 mmol), dopamine hydrochloride (0.25 g, 1.62 mmol), and Et_3N (0.47 mL, 3.40 mmol) were added sequentially and stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc (20 mL) and washed three times with 1 M HCl and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. This crude product was suspended in Et_2O (100 mL) and stirred for 30 min in a water bath at 30 °C. The resulting slurry was filtered and the procedure was repeated five times to give triscatecholate **8** (160 mg, 0.23 mmol, 65%).^{1}H NMR (400 MHz, [D$_4$]CH_3OH): δ=6.68 (d, 3H, ^3J=8.0 Hz), 6.63 (d, 3H, ^4J=2.0 Hz), 6.50 (dd, 3H, ^3J=8.1, ^4J=2.0 Hz), 3.34–3.30 (m, 6H), 2.63 (t, 6H, ^3J=7.4 Hz), 2.16–2.09 ppm (m, 12H); ^{13}C NMR (100 MHz, [D$_4$]CH_3OH): δ=174.1, 146.2, 144.7, 132.0, 121.1, 117.0, 116.4, 94.1, 42.2, 35.8, 32.3, 31.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{34}H_{42}N_4O_{11}$: 681.2798 [M−H$^+$]; found: 681.2797.

Preparation triscatecholate 10: Tris(2-carboxyethyl)adamantane (**9**; 500 mg, 1.42 mmol) was dissolved in anhydrous DMF (60 mL) and cooled to 0 °C (ice bath). Et_3N (2.54 mL, 18.32 mmol) was added to the reaction mixture, which was stirred for 5 min. EDC·Cl (900 mg,

4.69 mmol) and HOAt (9.38 mg, 4.69 mmol) were added to the reaction mixture, which was stirred for 30 min. Dopamine hydrochloride (890 mg, 4.69 mmol) was added to the reaction mixture, which was stirred for 72 h at room temperature. The reaction mixture was concentrated and the residue was dissolved in EtOAc (30 mL) and 1 M HCl (5 mL) and then washed with saturated aqueous $KHSO_4$ solution three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Freeze drying gave a light-brown solid, which was suspended in Et_2O (100 mL) and stirred for 30 min in a water bath at 30 °C. The resulting slurry was filtered and the procedure was repeated five times to give triscatecholate **10** (687 mg, 0.906 mmol, 64 %). ^{1}H NMR (400 MHz, [D$_4$]MeOH): δ = 6.62 (d, 3H, ^2J(H,H) = 8.0 Hz), 6.49–6.47 (m, 3H), 6.47 (d, 3H, ^2J(H,H) = 8.0 Hz), 3.33–3.30 (m, 6H), 2.55 (t, 6H, ^3J(H,H) = 8.0 Hz), 2.10 (t, 6H, ^3J(H,H) = 8.0 Hz), 1.42–1.35 (m, 12H), 1.13–1.05 ppm (m, 6H); ^{13}C NMR (100 MHz, [D$_4$]MeOH): δ = 177.2, 164.9, 146.3, 144.8, 142.7, 132.0, 129.6, 121.1, 116.9, 116.4, 47.3, 42.3, 42.0, 40.9, 37.0, 34.6, 31.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{43}H_{55}N_3O_9$: 756.3866 [$M-H^+$]; found: 756.3862.

Preparation of triscatecholate 12: Tris(2-carboxyethyl)aminoadamantane (**11**; 500 mg, 1.20 mmol) was dissolved in dioxane (30 mL) and added to $NaHCO_3$ (300 mg, 4.09 mmol) dissolved in water (30 mL). NaOH (2 M) was added to the reaction mixture to achieve a pH of 9, and the solution was cooled to 0 °C (ice bath). Benzyl chloroformate (CbzCl; 0.24 mL, 1.74 mmol) was added to the reaction mixture, which was stirred for 12 h at room temperature. The reaction mixture was washed three times with CH_2Cl_2 (30 mL) and three times with EtOAc (30 mL), acidified to pH 1, and extracted six times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the intermediate Cbz-protected triacid (524 mg, 1.05 mmol, 84 %). M.p. 221 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.06 (br, 3H), 7.43–7.39 (m, 5H), 7.07 (s, 1H), 5.01 (s, 2H), 2.20 (t, 6H, ^3J(H,H) = 7.9 Hz), 1.42 (s, 6H), 1.37 (t, 6H, ^3J(H,H) = 8.2 Hz), 1.08 (d, 3H, ^2J(H,H) = 13.2 Hz), 1.00 ppm (d, 3H, ^2J(H,H) = 13.2 Hz); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 175.0, 154.1, 137.3, 128.3, 127.7, 127.7, 64.5, 51.9, 44.5, 44.5, 37.4, 34.3, 27.9 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{35}N_1O_8$: 524.2255 [$M+Na^+$]; found: 524.2260. The Cbz-protected triacid (50 mg, 0.099 mmol) was dissolved in anhydrous DMF (30 mL) and the solution was cooled to 0 °C (ice bath). *N*,*N*-diisopropylethylamine (DIPEA; 0.22 mL, 0.127 mmol) was added to the reaction mixture, which was stirred for 10 min. EDC·Cl (63 mg, 0.327 mmol) and HOBt (44 mg, 0.327 mmol) were added to the reaction mixture, which was stirred for 20 min. Dopamine hydrochloride (62 mg, 0.327 mmol) was then added, and the solution was stirred for 72 h at room temperature. The reaction mixture was concentrated and the residue dissolved in EtOAc (30 mL) and 1 M HCl (5 mL). This solution was washed with saturated aqueous $KHSO_4$ solution three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Freeze drying gave a light-white solid, which was suspended in Et_2O (10 mL) and stirred for 30 min in a water bath at 30 °C. The resulting slurry was filtered and the procedure was repeated five times to give triscatecholate **12** (43 mg, 0.047 mmol, 48 %). ^{1}H NMR (400 MHz, [D$_4$]MeOH): δ = 7.17–7.11 (m, 5H), 6.54 (d, 3H, ^2J(H,H) = 8.0 Hz), 6.53–6.51 (m, 3H), 6.38 (d, 3H, ^2J(H,H) = 8.0 Hz), 4.84 (s, 2H), 3.19–3.17 (m, 6H), 2.49 (t, 6H, ^3J(H,H) = 7.2 Hz), 1.97 (t, 6H, ^3J(H,H) = 7.6 Hz), 1.40 (s, 6H), 1.28 (t, 6H, ^3J = 7.6 Hz), 0.96 (d, 3H, ^2J(H,H) = 12.0 Hz), 0.88 ppm (d, 3H, ^2J = (H,H) 12.0 Hz); ^{13}C NMR (100 MHz, [D$_4$]MeOH): δ = 176.8, 156.8, 146.2, 144.7, 138.5, 132.0, 128.9, 128.8, 129.4, 121.1, 116.9, 116.4, 66.7, 53.7, 46.3, 45.9, 42.3, 40.1, 36.1, 35.8, 31.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{52}H_{64}N_4O_{10}$: 929.4307 [$M+Na^+$]; found: 929.4314.

Preparation of triscatecholate 13: Triscatecholate **12** (43 mg, 0.047 mmol) was dissolved in anhydrous MeOH and a catalytic amount of Pd/C was added. The resulting mixture was stirred under N_2 for 72 h, filtered, and concentrated to give free amine **13** (30 mg, 0.039 mmol, 82 %). ^{1}H NMR (400 MHz, [D$_4$]MeOD): δ = 6.64 (d, 3H, ^2J = 8.0 Hz), 6.62–6.60 (m, 3H), 6.48 (d, 3H, ^2J(H,H) = 8.0 Hz), 3.27 (t, 6H, ^3J(H,H) = 7.0 Hz), 2.60 (t, 6H, ^3J(H,H) = 7.7 Hz), 2.08 (t, 6H, ^3J = 7.7 Hz), 1.44–1.42 (m, 12H), 1.11–1.08 ppm (m, 6H); ^{13}C NMR (100 MHz, [D$_4$]MeOD): δ = 176.4, 146.2, 144.8, 132.0, 121.1, 117.1, 116.4, 54.9, 45.3, 45.0, 42.2, 39.6, 36.4, 35.8, 31.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{43}H_{56}N_4O_9$: 773.4120 [$M-H^+$]; found: 773.4120.

Preparation of triscatecholate 14: Compound **11** (250 mg, 0.62 mmol) was dissolved in dimethyl sulfoxide (DMSO; 20 mL) and Et_3N (0.35 mL, 2.50 mmol) and succinimidyl-4-pentiolate (181 mg, 0.93 mmol) were added. The reaction mixture was stirred for 12 h at room temperature and concentrated. The residue was dissolved in EtOAc (20 mL) and washed with saturated aqueous $KHSO_4$ solution. The organic layer was concentrated and the residue dissolved in 1 M NaOH (20 mL), washed with EtOAc, and concentrated to give the crude product. This crude product was dissolved in DMF (60 mL) and the solution was cooled to 0 °C (ice bath). Et_3N (0.90 mL, 8.002 mmol) was added and the solution was stirred for 5 min. EDC·Cl (405 mg, 2.05 mmol) and HOBt (277 mg, 2.05 mmol) were added and the solution was stirred for 5 min. Dopamine hydrochloride (389 mg, 2.05 mmol) was added and the solution was stirred for 72 h at room temperature. The reaction mixture was concentrated, dissolved in EtOAc (30 mL) and 1 M HCl (5 mL), and washed with saturated aqueous $KHSO_4$ solution three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Freeze drying gave a colorless solid, which was suspended in Et_2O (100 mL) and stirred for 30 min in a water bath at 30 °C. The resulting slurry was filtered and the procedure was repeated five times to give triscatecholate **14** (282 mg, 0.331 mmol, 53 %, a small impurity of residual HOBt). ^{1}H NMR (400 MHz, [D$_4$]MeOH): δ = 6.65 (d, 3H, ^2J(H,H) = 8.0 Hz), 6.61–6.60 (m, 3H), 6.50 (d, 3H, ^2J(H,H) = 8.0 Hz), 3.32–3.27 (m, 6H), 2.60 (t, 6H, ^2J-(H,H) = 8.0 Hz), 2.39–2.35 (m, 2H), 2.29–2.23 (m, 2H), 2.11–2.07 (m, 7H), 1.59–1.57 (m, 6H), 1.43–1.39 (m, 6H), 1.04 (dd, 3H, ^2J(H,H) = 12.0 Hz), 1.03 ppm (dd, 3H, ^2J(H,H) = 12.0 Hz); ^{13}C NMR (100 MHz, [D$_4$]MeOD): δ = 176.8, 173.3, 146.3, 144.8, 132.0, 121.1, 116.9, 116.4, 79.3, 67.2, 49.9, 46.3, 45.6, 42.3, 40.2, 36.8, 36.1, 35.8, 31.2, 19.7, 15.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{48}H_{60}N_4O_{10}$: 851.4237 [$M-H^+$]; found: 851.4232.

Preparation of triscatecholate 15: Triscatecholate **12** (6.2 mg, 0.008 mmol) was dissolved in anhydrous DMF (10 mL) and the solution was cooled to 0 °C (ice bath). Et_3N (0.004 mL, 0.032 mmol) was added and the solution was stirred for 5 min. EDC·Cl (1.9 mg, 0.010 mmol) and HOBt (1.4 mg, 0.010 mmol) were added and the solution was stirred for 5 min. Eosin Y disodium salt (7.2 mg, 0.010 mmol) was added and the solution was stirred for 24 h at room temperature. The reaction mixture was concentrated, characterized by using MS (ESI), and used without further purification.

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