Functionalization of molecules in confined space
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Chapter 4

Towards Utilizing Unidirectional Molecular Motion for Controlling Microscopic Particle Movement
Part I: Design, synthesis and fabrication

Brownian motion rules at the micro- and nano- scale and the control of motion by introducing directional movement has always been a great challenge. Even though notable advance has been made in the field of self-propulsion, the necessity of designing systems with easy and precise control over directionality is highly desired. Molecular motors based on overcrowded alkenes can undergo continuous 360° unidirectional rotation which is non-reciprocal mimicking rotary motion of natural flagella. In addition, the incorporation of molecular motors into larger architectures enables the development of various photoresponsive materials, i.e., artificial muscle. Here, we report microsized motor-functionalized particles that are designed to propel towards a light source due to the collective action of a single layer of molecular motor. The aim is that upon irradiation with UV light, the motor-functionalized microparticles are separated with a bright and a dark face because of the limited light penetration depth. The molecular motors on the bright face are triggered by UV light and start to rotate, enhancing the diffusion of the surrounding molecules (water or surfactant) via momentum transfer. As the molecular motors on the dark side remains inactivated, a slip flow may emerge which can drive the microparticle moving according to the light source. In this chapter, we will focus on the design, synthesis, surface modification and characterization.
Chapter 4

4.1 Introduction

In nature, continuous unidirectional rotation is ubiquitous, such as in the ATPase and flagellum (motor) propulsion systems. Based on their rotary behavior, various sophisticated functions are derived. Among these functions, propulsive (e.g., translational) motion is of major importance because motility is vital for the survival of many organisms. As in bacteria, the rotation of flagella relative to the cell body produces a ‘corkscrew’ movement (Figure 4.1A), leading to efficient propulsion. According to Purcell’s theory, only geometrically non-reciprocal movement can produce net displacement at low Reynolds numbers in a non-Newtonian fluid where the objects experience viscous force of several orders of magnitude higher than the inertial forces. On the other hand, reciprocal movement, e.g. scallop motion, would only produce displacement forward and backward in the same environment (Figure 4.1B).

Figure 4.1 Two modes of propulsive motion. (A) ‘Corkscrew’ swimming motion of bacteria flagella. When the flagella rotate counter-clockwise, the bacteria will move forward. (B) The propulsion of a scallop. A scallop opens its shells slowly and closes them quickly, thus it produces a thrust which can propel itself forward. Reproduced with permission from Ref. 7. Copyright 2014 Springer Nature.
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So far, scientists have developed many systems operating at low Reynolds number. Most of these systems are based on ‘jet’ propulsion by ejecting bubbles or backward flows. Nevertheless, the stimuli for these ‘jet’ swimmers are usually ‘fuel’ chemicals which lacks spatial control, leading to the propulsion in all directions. Even though non-reciprocal rotary movement is known to be efficient for self-propulsion at low Reynolds number, there are few examples utilizing rotary motion, which are, however, based on top-down nanofabrication and require large setup (e.g., devices for magnetic field generation) to achieve rotary function. Hence, the challenge still remains since the control over directionality and ease of operation are so far difficult to achieve simultaneously for propulsive systems. Nevertheless, the study whether propulsive systems can be achieved based on artificial rotor smaller than the micrometer-sized magnetic rotor, i.e., at molecular scale, is also intriguing.

The alkene-based molecular motor developed in our group is a good candidate to take up this challenge since it uses light as the energy input which can be controlled spatially via the incident direction. In addition, comparing to other photoswitches the light-driven motors can undergo continuous 360° unidirectional rotation which is non-reciprocal. As aforementioned, only the geometrically non-reciprocal movement can produce net displacement at low Reynolds number. Recent studies also revealed that active enzymes could propel upwards a gradient of substrate concentration via interacting with their immediate surroundings and causing enhanced diffusive transport of molecules or particles during catalytic reaction. Hypothesis has been made that this enhanced diffusion may be caused by non-reciprocal conformational changes of active enzymes during substrate turnover, generating force and transfer ‘momentum’ to the surrounding. Molecular motors, as distinct from natural enzymes (based on catalytic reactions), use light as the energy source and undergo well-defined continuous conformational changes. By combining the collective motion of molecular motors being part of a microscopic object, cooperative effects may be generated to direct a microscopic motion.

Here, we design a novel propulsive system in water which aims to exhibit controlled directional propulsion at low Reynolds number. By grafting molecular motors onto the surface of a silica microparticle, a separation of a distinct active irradiated side and an inert non-irradiated side will be present and due to limited light penetration depth, endowing the particle with Janus properties. We hypothesize that the locomotion of surrounding molecules (solvents or surfactants) can be enhanced via momentum transfer from rotary motors on the irradiated side, creating a gradient (i.e., of fluid pressure, osmotic pressure) near the particle
surface. Consequently, this gradient is expected to induce a slip flow near the surface, thus direct the movement of the microparticle. This design is an attempt to achieve photoresponsive directional propulsion via non-reciprocal rotation at the molecular level. In this chapter, we will focus on the design, synthesis, surface grafting method and corresponding characterization.

### 4.2 Design of the propulsive particle

The design of our photoresponsive propulsive particle was based on the notion that symmetry breaking of a particle occurs by the separation of irradiated and non-irradiated faces even though the particle is uniformly modified. As illustrated in Figure 4.2, similarly with the Earth’s terminator, a particle can be divided by light, forming a Janus particle with bright and dark faces. Because only motors on the bright side could be triggered by light, we expected to achieve a cooperative effect by the collective molecular rotation and its asymmetric distribution. We hypothesized that the rotation of motor would disturb the surrounding solvent near the irradiated surface, generating enhanced diffusion on this side which could further create a slip flow to propel the particle. For example, due to rotation the solvent diffusion is enhanced near the irradiated side via momentum transfer, a simultaneous gradient of diffusion rate of the solvent will occur. Thus, similar to the case of active enzymes, the particles will propel to the direction of the irradiated side (towards the light source) which is assumed to have higher rate of diffusion of the surrounding molecules.

![Illustrative images of the propulsive particle](image)

**Figure 4.2** Illustrative images of the propulsive particle. (A) The light source divides a spherical object into two faces, namely, a bright and a dark one. With molecular motors attached on the whole surface, only the bright face is active by irradiation. (B) A cartoon demonstrates the separation of two faces on a particle, showing Janus property.
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We employed commercially available silica particles (from Sigma-Aldrich) with a diameter of 5 µm as the substrate. The advantages of silica include that it has widely been applied in surface modification which avoids undesired surface plasmon effects compared to gold substrates. The size of the particle is in micron range for the benefit of visualization with an optical microscope. In addition, when \( d \gg \lambda \), Rayleigh scattering by which the whole particle surface is evenly irradiated can be avoided, thus it facilitates the asymmetric distribution of irradiation on the particle surface. To functionalize silicon-based substrates with photoswitches, interfacial reactions are increasingly used. Among these approaches, copper (I)-catalyzed azide-alkyne click reactions are the most widely employed due to its advantageous properties such as mild reaction conditions (i.e. room temperature), stable products, high yield, and easy detection (i.e. the characteristic signals of azido groups in X-ray photoelectron spectroscopy). Furthermore, our earlier studies have demonstrated that molecular motors were still able to function on the silicon-based substrates after being covalently bound to the surface via click reactions. Thus, in this study, we also tethered molecular motors onto silica particles via click reactions and in order to conduct this method, the surface was modified with azido groups.

For the molecular design, the structure consists of four parts: a rotary motor core, a rigid handle, a poly ethylene glycol (PEG) chain, and bipodal legs (Figure 4.3). Regarding the rotary core, we chose two second-generation motors with fast half-lives of THI due to natural flagella have rotary frequencies within \( 10^{-6} \) Hz. As depicted in figure 4.3, motor 4.1 has a motor core which usually shows a half-life of THI in \( 10^{-7} \) s scale, while that of motor 4.2 is usually in the range of \( 10^{-3} \) s. It is noteworthy to point out that motor 4.1 has a sulfur atom, which facilitates the characterization of the motor using element analysis. The rotor was elongated with a phenylacetylene handle because a previous study revealed that a long and rigid rotor would enhance the interaction between molecular motor and surrounding solvent. We employed a PEG chain tethered at the end of the rigid handle, aiming to increase the interaction with the medium, i.e., water. Finally, the legs were attached to the motor moiety via an ether linker. They contain a C8 spacer in order to prevent undesired effects from the particle surface, e.g., interference with the surface and avoiding steric hindrance, and a terminal alkyne which is ready for surface attachment. It is also noteworthy to mention that the two-leg design was aimed to prevent the molecule from undergoing uncontrolled motion around a single bond.
4.3 Results and Discussion

4.3.1 Synthesis

The approaches towards the synthesis of motor 4.1 and 4.2, which comprise the synthesis of PEG chain, the leg, the rigid linker and the motor cores are described in this section.

For the PEG chain, commercially available monomethyl ether 4.3 with an average molecular weight of 400 was used. The derivalization of its terminal hydroxyl group via tosylation was achieved under basic condition, \(^{50}\) which allows product 4.4 to be used in the attachment to the rigid linker via ether bond formation (Scheme 4.1).

Scheme 4.1 Tosylation of PEG400 monomethyl ether.
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As illustrated in Scheme 4.2, the synthesis of the leg started from 1,8-octanediol, which was treated with sodium hydride and then propargyl bromide to yield a monopropargyl ether \textbf{4.6}. The hydroxyl group at the other end was further modified with a tosyl group to give \textbf{4.7}. In addition, the terminal alkyne was protected with a triisopropylsilyl (TIPS) group to avoid undesired byproducts during the synthesis of compound \textbf{4.27} via a Sonogashira coupling.

\begin{equation}
\text{HO} \quad \text{OH} \\
1) \text{Natr, DMF, 0 °C, 1 h} \\
2) \text{Br, } 0^\circ \text{C} \rightarrow \text{rt, 24 h, 61%} \\
\text{HO} \quad \text{O} \\
\text{TcCl, (C}_3\text{H}_5\text{N, DCM, rt, 16 h, 51%} \\
\text{HO} \\
\text{TIPS, } \text{TIPS} \\
\text{TIPS, TIPS}
\end{equation}

Scheme 4.2 Synthesis of the leg \textbf{4.8}.

The motor core of \textbf{4.1} contains a six-membered lower part and a five-membered upper half structure. For the synthesis of the lower ketone \textbf{4.14}, a literature procedure was followed. As depicted in Scheme 4.3, disulfide \textbf{4.10} was prepared from the oxidation of thiophenol \textbf{4.9}. Meanwhile, an amide \textbf{4.12} was synthesized from an acid \textbf{4.11} which was treated with oxalyl chloride, followed by the addition of diethylamine. Subsequent \textit{ortho}-lithiation of \textbf{4.12} and addition of disulfide \textbf{4.10} generated compound \textbf{4.13}, which was treated with diisopropylamine (LDA) to yield ketone \textbf{4.14} via a cyclization.

\begin{equation}
\text{O} \quad \text{OH} \\
\text{O} \quad \text{OH} \\
\text{KmBrO}_3 \\
\text{CuSO}_4, \text{H}_2\text{O, (C}_3\text{H}_7\text{H}_2\text{N)Br, DCM, rt, 1 h, 77%}} \\
\text{O} \quad \text{O} \\
\text{4.10} \\
\text{O} \quad \text{O} \\
1) \text{oxalyl chloride, DME/DCM/THF, rt, 1 h} \\
2) \text{Et}_3\text{NH, Et}_3\text{N, DCM, rt, 18 h, 78%} \\
\text{O} \quad \text{O} \\
\text{4.12} \\
\text{O} \quad \text{O} \\
1) \text{BuLi, TMEDA, THF, -80 °C, 1 h} \\
2) \text{- 80 °C to rt, 20 h, 69%} \\
\text{O} \quad \text{O} \\
\text{4.13} \\
\text{LDA, THF, rt, 1 h, 90%} \\
\text{O} \quad \text{O}
\end{equation}

Scheme 4.3 Synthesis of the ketone \textbf{4.14}.
Regarding the upper rotor, the synthesis started with a one-pot Friedel-Crafts acylation/ Nazarov cyclization by mixing 1-bromonaphthalene and methacrylic acid in polyphosphoric acid (115% H₃PO₄ basis) at elevated temperature (Scheme 4.4). The generated cyclic ketone 4.16 was heated at reflux together with Lawesson’s reagent (LR) in toluene, providing the thioketone 4.17.

Scheme 4.4 Synthesis of the upper thioketone 4.17.

Next, cyclic ketone 4.14 was treated with LR in toluene at reflux, followed by quenching with hydrazine monohydrate to produce hydrazone 4.19, which was further oxidized using MnO₂ to diazo compound 4.20 (Scheme 4.5). Thioketone 4.17 was then reacted in a Barton-Kellogg cross-coupling together with the diazo 4.20 to yield episulfide 4.21. After desulphurization of episulfide 4.21 by heating at 60 °C with tris(dimethylamino)phosphine (HMPT) in toluene, 4.21 was converted to overcrowded alkene 4.22. Regarding the elongation of the rotor part, a

Scheme 4.5 Synthesis of the motor core 4.25 before coupling with legs and PEG chain.
Sonogashira coupling was conducted to substitute the original bromo group with a trimethylsilylacetylene to form 4.23, followed by removal of the trimethylsilyl group using tetra-n-butylammonium fluoride (TBAF) solution. Subsequently, a demethylation of 4.24 was performed using MeMgI under neat condition.\textsuperscript{54} By carefully controlling the reaction time and temperature, compound 4.25 with two free hydroxyl groups was obtained in modest yield.

Using the two hydroxyl groups in compound 4.25, two legs were installed by alkylation of 4.25 with 4.8 in CH\textsubscript{3}CN under basic condition, giving compound 4.26 as a yellow oil with 80\% yield. (Scheme 4.6). Then, the rotor was further elongated by coupling a phenol group onto the terminal acetylene of 4.26 via another Sonogashira reaction, yielding compound 4.27 with a terminal hydroxyl group for connection with the PEG chain. Finally, 4.27 was alkylated with the tosylated PEG chain 4.4 under basic condition and the generated 4.28 was subsequently treated.

Scheme 4.6 Final steps in the synthesis of the goal motor 4.1 by installation with legs and PEG chain (n=9).
with a TBAF solution for the deprotection of TIPS group. The relatively low yield of the last two steps might result from the loss during chromatography due to the high affinity between PEG and silica gel. NMR analysis and high-resolution mass spectrum (HRMS) demonstrated that the ultimate motor 4.1 was successfully synthesized in 22 steps with an overall yield of 0.4%.

Comparing to motor 4.1, for the synthesis of 4.2 a similar route was followed except for its seven-membered stator. For the seven-membered stator part, a cyclic ketone 4.31 was first synthesized via a Parham cyclization of a carboxylic acid 4.30, which was prepared via lithiation of 4.29 and subsequent addition of CO$_2$ using a literature procedure$^{55}$ (Scheme 4.7).

Scheme 4.7 Synthesis of seven-membered ketone 4.31.

With the ketone 4.31 in hand, the remaining of the synthesis of 4.2 was similar with that of 4.1, except for the last two steps where we deprotected the TIPS group before attaching the PEG chain (Scheme 4.8 and 4.9). This change in order of reactions was attempted to decrease the loss of PEG-containing compounds during column chromatography. Motor 4.2 was, as in the case of motor 4.1, characterized

Scheme 4.8 Synthesis of the motor core 4.39 bearing seven-membered lower stator part before coupling with legs and PEG chain.
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Scheme 4.9 Final steps in the synthesis of the target motor 4.2 by installation with legs and PEG chain (n=9).

using NMR spectroscopy and HRMS, with an overall yield of 0.2% in a 20-step synthesis route.

Finally, we synthesized a control compound which only bears the lower stator part of the motor 4.1. This control compound will undergo thermal relaxation after absorbing 365 nm light instead of unidirectional rotation. The synthesis of control compound 4.44 is shown in Scheme 4.10. It started with the demethylation of compound 4.14, which was achieved by treatment with BBr₃ in DCM. 52 After thioxanthone coupling with 4.7, thioxanthone 4.44 was obtained in 60% yield which was ready for surface attachment.
Motor 4.1 and 4.2 are derivatives of ultrafast molecular motors with half-life time of THI in $10^{-7}$s and $10^{-3}$s range, respectively. Our earlier studies indicated that alkylation of motor via an ether bond formation did not significantly affect its rotary speed. Even though the modification of molecular motor with a rigid phenyl-ethynylene group on the rotor part would increase the solvent displacement which would lead to a longer half-life time of THI, this elongation of half-life is less than twice in a non-viscous solvent (THF) and six-times in a viscous solvent (THF/glycerol mixture) according to our previous study. Therefore, we assume our motor 4.1 and 4.2 possess half-life time similar to their parent motors, namely, in the $10^{-7}$s and $10^{-3}$s range, respectively. For more accurate measurements of the rotary behavior, transient spectroscopy will be employed.

4.3.2 Enantiomers assignment

The biological flagella differentiate their moving behavior by opposite rotary directions, namely, clockwise and counter-clockwise, and the bacteria can move forward only when flagella rotate counter-clockwise. Even though this behavior is assumed to be correlated to the built-in helicity in the filament protein, the necessity to obtain enantiopure motor which rotates merely clockwise/counter-clockwise will afford comprehensive understanding of our system. Therefore, enantiomers of compound 4.27 were separated using preparative chiral stationary phase HPLC (see Experimental Section 4.6.3) and assigned to the absolute R- or S- configuration according to density functional theory (DFT) calculations (see Experimental Section 4.6.4). In brief, the obtained enantiomers of 4.27 were characterized with circular dichroism (CD) spectroscopy whereby the measured CD spectra were compared with the calculated ones. As depicted in Figure 4.4B, the calculated CD spectrum of a clockwise rotary motor (from a top view) has a redshift comparing to the measured spectrum of one.
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enantiomer (black line in Figure 4.4C), however, their major bands (for calculated spectrum: 420 nm, 380 nm, and 330 nm; for measured spectrum: 394 nm, 345 nm, and 305 nm) share similar sign of Cotton effect, indicating that the measured CD spectrum (black line in Figure 4.4C) is in accordance with a clockwise rotating isomer (S)-4.27. The remaining part of the synthesis towards enantiopure 4.1 was conducted following the same method as for the racemic material shown in Scheme 4.6, and the products were characterized by NMR analysis and their optical rotations.

**Figure 4.4** Enantiomers of molecular motor. (A) The structures of two enantiomers of motor 4.27; (B) the calculated CD spectrum of the clockwise rotating isomer 4.27 (right one in (A)) using TD-DFT at B3LYP/6-31G(d, p) level; (C) Measured CD spectra of two enantiomers of 4.27 separated using preparative chiral HPLC (solvent: DCM).

### 4.3.3 Surface attachment and characterization

Immobilization of the molecular motors 4.1 and 4.2 and the control compound 4.44 onto the silica microparticles (d= 5 µm, from Sigma-Aldrich) is depicted in Scheme 4.11. Before the attachment, the particle surface was pre-functionalized with a monolayer of azidosilanes. Driven by *in situ* formation of polysiloxane connecting to the original Si-OH groups on surface, a monolayer of azido-terminated silanes was formed by treating the microparticles with 3-(azidopropyl)triethoxysilane in DMF at 80 °C. Finally, compounds with terminal alkyne groups (4.1, 4.2, or 4.44) were grafted onto the azido-functionalized surface via a Cu(I)-catalyzed azide-alkyne click reaction. The detailed fabrication method is given in Experimental Section 4.6.5.
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Scheme 4.11 Attachment of alkyne-terminated compounds onto azido-functionalized silica microparticles (n=9).

To verify the successful modification of these silica microparticles, X-ray photoelectron spectroscopy (XPS) analysis was performed on three types of particles: bare silica microparticles (S1), azido-functionalized ones (S2) and microparticles immobilized with motor 4.1 (S3). Figure 4.5 displays the C 1s, N 1s, Si 2p, and S 2p spectra among which the N 1s and S 2p regions are most characteristic. Figure 4.5A shows the N 1s spectral region which is fitted with three components assigned to N-H/N-R (399.0 eV), N (400.9 eV), and N+ (404.4 eV). As demonstrated in the N 1s spectrum of S2 (the lower spectrum in Figure 4.5A), a well-separated N+ component represents the central nitrogen atom in the azido group, which is very characteristic and coexists in two mesomeric forms, indicating the successful connection of azido groups on SiO2 support. On the other hand, the disappearance of N+ component in S3 (the upper spectrum in Figure 4.5A), together with appearance of the broad feature at 398-403 eV (characteristic of N-H, N-R, and N=N), suggesting that the azido group is transformed into a triazole moiety after the click reaction. To further verify the incorporation of the motor 4.1 on the surface, we also analyzed the S 2p region of the XPS spectrum of S3 (Figure 4.5D). A typical doublet signal (S 2p3/2 and S 2p1/2) of sulfur atom is observed, demonstrating the presence of sulfur-containing species (motor 4.1) on the particle surface.
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Figure 4.5 XPS spectra of (A) N 1s; (B) Si 2p; (C) C 1s; and (D) S 2p. Samples: bare silica microparticles (S1), particles functionalized with azido groups (S2), and particles after the click reaction with motor 4.1 (S3).

Furthermore, we analyzed the Si 2p and C 1s spectra (Figure 4.5B and C), which also support the successful modification of azido groups and motor 4.1 of S2 and S3, respectively. Specifically, in Si 2p region, modification of the bare SiO$_2$ particles (103.1 ± 0.1 eV) with 3-(azidopropyl)triethoxysilane results in formation of an additional doublet in Si 2p spectra (see S2 and S3 in Figure 4.5B) which can be attributed to functionalized Si-OR groups (101.7 ± 0.1 eV), where R is azidopropyl group (S2 and S3 in Figure 4.5B). Meanwhile, regarding C 1s spectra, all samples contain typical components of adventitious carbon: 284.8 eV (C–C, C–H), 286.3 eV (C-OC, C-OH, C-NC, C-NH), 287.8 eV (C=O) and 288.8 eV (O=C–OR, O=C–OC). They can also originate from organic molecules present in the samples. However, C 1s spectrum of S3 reveals a mere increase of the component
with the BE of 286.3 eV, which may be attributed to C-NR and C-OR bonds of the attached motors, where R = C or H.

Having proved the successful modification of motor 4.1 on silica microparticles, we next studied their corresponding surface coverage. Thermogravimetric analysis (TGA) and UV/vis spectroscopy are widely used methods to characterize surface coverage of modified surfaces. However, the former method is usually utilized for mesoporous or small particles with a high surface-to-volume ratio, while the latter one is for transparent quartz substrate. Since there is, to the best of our knowledge, no characterization method to study the surface coverage of these compounds on microsized silica particles, the surface grafting density $\delta$ was measured on two other analogous materials, namely, 4.1-functionalized silica nanoparticles (which have high surface-to-volume ratio) and quartz surface (for both of the fabrication methods, see Experimental Section 4.6.5). Regarding 4.1-functionalized silica nanoparticles (d= 10-20 nm), the TGA study was carried out by heating the nanoparticles under a nitrogen atmosphere from room temperature to 800 °C at a rate of 10 °C per minute. The results are shown in Figure 4.6 where $\delta$ can be calculated using the equation below:

$$
\delta = \frac{\left( \frac{W_{\text{Org}}}{W_{\text{Inorg}}} \right) \rho V_{\text{Particle}} N_A}{M_{\text{Org}} S_{\text{Particle}}}
$$

Typically, the weight loss below 200 °C is associated with the volatilization of adsorbed water and residual organic solvent. Therefore, the weight loss for organic components on azido-functionalized and motor-functionalized nanoparticles are estimated to be 8.2% and 21.8%, respectively. With the size (d= 10-20 nm) and density (2.4 g/cm³), $\delta$ (azido) and $\delta$ (motor) were calculated to be about 3.0-6.0 groups/nm² and 0.3-0.6 motor/nm², respectively. Even though these results indicated that only 20% of azido groups were converted after the click reaction, it should be noted that the $\delta$ values and azido conversion of our system are quite comparable with reported click-functionalized silica materials (mesoporous silica particles, silica nanoparticles).
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Figure 4.6 TGA data of azido-functionalized (black line) and motor 4.1-functionalized (red line) silica nanoparticles.

An alternative method to obtain the δ value is by measuring the absorption spectrum on a large and flat surface. By grafting motor 4.1 onto a quartz substrate, the absorption of the interfacial single molecule layer was characterized using UV/vis spectroscopy. By comparing the absorbance of the motor-attached quartz with that of a solution of motor 4.1 whose concentration was known (Figure 4.7), surface coverage was calculated via an equation deduced from Beer-Lambert law:

\[
\frac{A_1}{A_2} = \frac{\delta_1}{c_2L_2}
\]

where \(A_1\) and \(A_2\) are the absorbance of the quartz slide and the solution, respectively, and \(c_2\) is the concentration of solution while \(L_2\) is the optical path length. Thus, δ (motor) was found to be approximately 0.7 motor/nm² on quartz, which is in the same range as the aforementioned value of motor-functionalized nanoparticles characterized via TGA.

Figure 4.7 UV/vis absorption spectra of (A) a quartz slide with motor 4.1 modified on both sides and (B) solution of motor 4.1 in THF with a concentration of 8 X 10⁻⁶ M.
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The series of characterization using XPS, TGA, and UV/vis spectroscopy demonstrated motor 4.1 was successfully grafted onto azido-functionalized silica surface with moderate surface coverage. It is noteworthy to point out that the surface coverage of motor 4.1 is beneficial for the next stage of study considering the size of individual motor (roughly 1 nm in diameter from Figure 4.4A), indicating neither extremely tight packing nor sparse grafting of the motor. Using similar methods (Experimental Section 4.6.5), motor 4.2 and control compound 4.4 were tethered onto silica microparticles and quartz substrates, and the UV/vis studies revealed that the δ values (for motor 4.2: δ = 0.6 motor/nm²; for compound 4.44: δ = 0.7 motor/nm²) were in similar range with motor 4.1 on quartz (Figure 4.8).

Figure 4.8 UV/vis absorption spectra of quartz slides functionalized with (A) motor 4.2 and (C) compound 4.44 on both sides, and the solution of (B) motor 4.2 and (D) compound 4.44 in THF with a concentration of 8 X 10⁻⁶ M.
4.4 Conclusions

Molecular motors which were designed for the fabrication of light-driven microswimmers, were successfully synthesized. Furthermore, the enantiomers of motor 4.1 were separated and the configuration was assigned based on experimental and calculated CD spectra. Via Cu(I)-catalyzed azide-alkyne click reaction, motor 4.1 was grafted onto silica microparticles as verified by XPS analysis. TGA and UV/vis measurements on analogous motor-functionalized silica surfaces reveal a moderate surface coverage. The studies in this chapter demonstrate successful fabrication of the desired system, which help us obtain a better understanding of surface properties and lay the foundation for the next step of propulsive studies as described in Chapter 5.

4.5 Acknowledgement

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4.6 Experimental Section

4.6.1 General remarks

For general comments, see chapter 2.

4.6.2 Synthesis

**Compound 4.4**

To a solution of PEG400 monomethyl ether (1.2 g, ~3 mmol) in THF (10 mL) and 1 M aq. NaOH (10 mL), TsCl (855 mg, 4.5 mmol) was added at 0 °C. After stirring at r.t. for 24 h, the reaction mixture was quenched with water (100 mL), following by extraction with ethyl acetate (2 X 50 mL). The organic phase was further washed with water (3 x 100 mL), brine (100 mL) and dried over Na₂SO₄. Being
concentrated \textit{in vacuo}, the crude product was purified using column chromatography (DCM: MeOH= 95: 5) to give 4.4 (859 mg, 1.5 mmol, 49 \%) as a colorless oil. \textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \(\delta\) 7.74 (d, \(J = 7.9\) Hz, 2H), 7.31 (d, \(J = 7.9\) Hz, 2H), 4.10 (t, \(J = 4.7\) Hz, 2H), 3.66 – 3.48 (m, 34H), 3.32 (s, 3H), 2.40 (s, 3H). This \textsuperscript{1}H NMR data is in accordance with Ref. 50.

\textbf{Compound 4.6} \textsuperscript{51}

To a suspension of NaH (480 mg, 20.0 mmol) in anhydrous DMF (40 mL) was added dropwise a solution of 1,8-octanediol (2.92 g, 20.0 mmol) in anhydrous DMF (10 mL) at 0 °C. After stirring for 1 h, propargyl bromide (2.8 mL, 80 wt\% in toluene, 16.0 mmol) was added dropwise. The resulting mixture was stirred at r.t. for another 24 h. After quenching with water (100 mL), the reaction mixture was extracted with ethyl acetate (2 \times 30 mL). The combined organic layers were washed with brine (100 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. After removing the solvents \textit{in vacuo}, the residue was purified using column chromatography (pentane: ethyl acetate = 3: 1) to afford compound 4.6 (2.25g, 12.2 mmol, 61 \%) as a clear liquid. \textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \(\delta\) 4.08 (s, 2H), 3.57 (t, \(J = 6.6\) Hz, 2H), 3.46 (t, \(J = 6.7\) Hz, 2H), 2.39 (s, 1H), 1.96 (s, 1H), 1.63 – 1.43 (m, 4H), 1.40 – 1.16 (m, 8H). This \textsuperscript{1}H NMR data is in accordance with Ref. 51.

\textbf{Compound 4.7} \textsuperscript{51}

To a solution of compound 4.6 (1.78 g, 9.7 mmol) in DCM (30 mL) was added Et\textsubscript{3}N (5 mL, 35.9 mmol). After being stirred for 30 min, TsCl (2.75 g, 14.4 mmol) was added and the resulting mixture was allowed to stir for another 16 h at r.t. After quenching with water (100 mL), the mixture was extracted with DCM (30 mL). The organic layer was extensively washed with water (4 \times 100 mL), brine (100 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. After removal of the solvent, the residue was purified using column chromatography (pentane: ethyl acetate = 5: 1) to give compound 4.7 (1.84 g, 5.4 mmol, 56\%) as a clear oil. \textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \(\delta\) 7.77 (d, \(J = 8.3\) Hz, 2H), 7.33 (d, \(J = 8.2\) Hz, 2H), 4.11 (d, \(J = 2.4\) Hz, 2H), 4.00 (t, \(J = 6.5\) Hz, 2H), 3.47 (t, \(J = 6.5\) Hz, 2H), 2.43 (s, 3H), 2.40 (t, \(J = 2.4\) Hz, 1H), 1.70 – 1.49 (m, 4H), 1.34 – 1.17 (m, 8H). This \textsuperscript{1}H NMR data is in accordance with Ref. 51.
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**Compound 4.8**

To a solution of compound 4.7 (1.5g, 4.4 mmol) in anhydrous THF (20 mL) was added n-BuLi (1.6 M in hexane, 2.75 mL, 4.4 mmol) and the resulting mixture was allowed to stir at -78 °C for 1 h. Then triisopropylsilyl chloride (TIPSCl, 1.03 mL, 4.8 mmol) was added and the reaction mixture was warmed slowly to r.t. and stirred for another 16 h. After quenching with NH₄Cl (aq., 100 mL) solution, the mixture was extracted with ethyl acetate (2 × 30 mL), followed by washing with brine (100 mL) and drying over Na₂SO₄. After evaporating the solvents, the crude product was further purified using column chromatography (pentane: DCM = 9: 1) to give compound 4.8 (1.56 g, 3.2 mmol, 72%) as a clear oil. 

\[ ^1H \text{NMR (400 MHz, Chloroform-}d) \delta 7.78 (d, J = 8.1 \text{ Hz}, 2H), 7.34 (d, J = 8.1 \text{ Hz}, 2H), 4.16 (s, 2H), 4.01 (t, J = 6.5 \text{ Hz}, 2H), 3.52 (t, J = 6.5 \text{ Hz}, 2H), 2.44 (s, 3H), 1.67 – 1.49 (m, 4H), 1.34 – 1.18 (m, 8H), 1.07 – 1.05 (m, 21H). \]

\[ ^13C \text{NMR (101 MHz, Chloroform-}d) \delta 144.74, 133.40, 129.92, 128.02, 103.85, 87.27, 70.76, 69.75, 58.87, 29.59, 29.29, 28.99, 28.94, 26.18, 25.40, 21.76, 18.70, 17.83, 12.42, 11.30. \]

HRMS (ESI+, m/z) calculated for C₂₇H₄₇O₄Si [M + H]⁺ 495.2959, found 495.2951.

**Compound 4.10**

To a suspension of CuSO₄·5H₂O (12.5 g, 50.0 mmol), KMnO₄ (12.5 g, 80.0 mmol), and tetraoctylammonium bromide (2.5 g, 4.5 mmol) in DCM (300 mL) was added 2-methoxybenzenethiol 4.9 (5 g, 35.0 mmol) and the resulting mixture was allowed to stir for 3 h at r.t. The reaction mixture was filtered over celite and the filtrate was purified using column chromatography (pentane: ethyl acetate = 5: 1) to yield compound 4.10 (3.76 g, 13.5 mmol) as a white solid. 

\[ ^1H \text{NMR (400 MHz, Chloroform-}d) \delta 7.52 (dd, J = 7.8, 1.6 \text{ Hz}, 2H), 7.22 – 7.15 (m, 2H), 6.94 – 6.88 (m, 2H), 6.86 (d, J = 8.1 \text{ Hz}, 2H), 3.90 (s, 6H). \]

This \(^1H\) NMR data is in accordance with Ref. 52.

**Compound 4.12**

To a solution of 3-methoxybenzoic acid (9.5 g, 63.0 mmol) in DCM (50 mL) and THF (50 mL), a drop of DMF and oxalyl chloride (16 g, 126.0 mmol) were added and the mixture was allowed to stir at r.t. for 1 h. After being placed in vacuum, the residue was dissolved again in DCM (50 mL). The solution was kept at 0°C, followed by the addition of diethylamine (6.8 mL, 65.0 mmol) and trimethylamine (9.0 mL, 65.0 mmol). After being stirred at r.t. for 18 h, the reaction mixture was
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quenched with water (100 mL), followed by extraction with ethyl acetate (2 × 30 mL). The combined organic layers were washed with 10% aq. HCl (2 × 100 mL) and 1M aq. NaOH (2 × 100 mL) solutions. After removal of the solvents, the crude product was purified by column chromatography (DCM: MeOH = 10: 1) to give 4.12 (10.1 g, 49.1 mmol, 78%) as a yellow oil. 1H NMR (400 MHz, Chloroform-d) δ 7.21 – 7.10 (m, 1H), 6.83 – 6.70 (m, 3H), 3.67 (s, 3H), 3.47 – 3.00 (m, 4H), 1.24 – 0.84 (m, 6H). 1H NMR data is in accordance with Ref. 52.

Compound 4.13 52

To a solution of TMEDA (0.96 mL, 6.6 mmol) in THF (50 mL) was added s-BuLi (1.4 M in cyclohexane, 4.7 mL, 6.6 mmol) at -80 °C. After stirring for 30 min, a solution of compound 4.12 (1.24 g, 6.0 mmol) in THF (2 mL) was added slowly at -80 °C and the resulting mixture was allowed to stir for another 1 h. Compound 4.10 (2.5 g, 9.0 mmol) was dissolved in THF (10 mL) and added to the yellow suspension while keeping the temperature at -80 °C. After slowly warming to r.t., the resulting mixture was stirred for 20 h. The reaction mixture was then quenched with water (100 mL), followed by extraction with ethyl acetate (2 × 30 mL). The combined organic phase was then washed with water (2 × 100 mL), brine (100 mL), and dried over Na2SO4. After removal of the solvents, the residue was purified using column chromatography (pentane: ethyl acetate = 2: 1) to give 4.13 (1.43 g, 4.1 mmol, 69%) as a white solid. 1H NMR (400 MHz, Chloroform-d) δ 7.43 (d, J = 7.8 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.95 – 6.90 (m, 2H), 6.79 (d, J = 8.2 Hz, 1H), 6.75 – 6.69 (m, 1H), 6.68 – 6.65 (m, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.72 – 3.59 (m, 1H), 3.39 – 3.26 (m, 1H), 3.16 – 3.05 (m, 1H), 3.04 – 2.92 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H) 0.97 (t, J = 7.1 Hz, 3H). 1H NMR data is in accordance with Ref. 52.

Compound 4.14 52

To a solution of 4.13 (518 mg, 1.5 mmol) in THF (20 mL) was slowly added LDA solution (2M in THF/heptane/ethylbenzene, 3.8 mL, 7.5 mmol) and the mixture was stirred for 1 h at r.t. The dark solution was quenched with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). After washing with brine (50 mL) and drying of the organic solution over Na2SO4, the resulting solution was concentrated in vacuo and crystallized from ethyl acetate to give 4.14 (367 mg, 1.4 mmol, 90%) as yellow needle-shaped crystals. 1H NMR (400 MHz, Chloroform-d) δ 8.25 (dd, J = 8.1, 1.1 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 4.06 (s, 6H). 1H NMR data is in accordance with Ref. 52.
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**Compound 4.16**

To mechanically stirred polyphosphoric acid (200 g) was added 1-bromonaphthalene (20.4 mL, 146 mmol) at 80 °C. After 10 min, methacrylic acid (37 mL, 650 mmol) was added and stirred at 100 °C for 10 h. Upon completion, the mixture was cooled to r.t. and poured onto ice, the viscous mixture was further dissolved by extensive water. The aqueous phase was extracted with ethyl acetate (2 × 300 mL). The resulting organic phase was further washed with aq. NaOH (1M, 200 mL), brine (100 mL) and then filtered over celite. After concentrating *in vacuo*, the crude product was purified using column chromatography (pentane: ethyl acetate = 10: 1) to give ketone 4.16 (1.4 g, 5.2 mmol, 4%) as a white solid. 1H NMR (400 MHz, Chloroform-d) δ 9.19 (d, J = 8.2 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.75 – 7.59 (m, 2H), 3.46 (dd, J = 18.1, 8.0 Hz, 1H), 2.86 – 2.74 (m, 2H), 1.38 (d, J = 7.3 Hz, 3H). 1H NMR data is in accordance with Ref. 53.

**Compound 4.17**

Ketone 4.16 (602 mg, 2.2 mmol), Lawesson’s reagent (1.8 g, 4.4 mmol) were dissolved together in toluene (60 mL) and the mixture was heated at reflux for 4 h. After cooling to r.t., the solids were filtered and washed with DCM. The filtrate was concentrated *in vacuo* and purified using column chromatography (pentane: ethyl acetate = 95: 5) to give dark purple oil which was immediately used in the next step.

**Compound 4.19**

To a solution of ketone 4.14 (1.5 g, 5.5 mmol) in toluene (50 mL), Lawesson’s reagent (5.6 g, 13.8 mmol) was added. The resulting mixture was heated at reflux for 1 h. After cooling to r.t., the precipitates were filtered and washed with DCM. The filtrate was concentrated *in vacuo*, and the residue was dissolved in THF (10 mL). To the green solution was added 4 mL of hydrazine monohydrate and the resulting mixture was stirred for 1 h until the color completely disappeared. After concentrating *in vacuo*, the crude product was purified using column chromatography (DCM: MeOH = 95: 5) to give hydrazone 4.19 (1.4 g, 4.9 mmol, 89%) as a pale yellow solid. 1H NMR (400 MHz, Chloroform-d) δ 7.65 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.36 – 7.26 (m, 2H), 6.90 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.86 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H).
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**Compound 4.20**

To a solution of 4.19 (572 mg, 2 mmol) in THF (20 mL) was added MnO$_2$ (1.7 g, 20 mmol). After stirring at 0 °C for 1 h, the mixture was filtered over celite and the filtrate was immediately used in the next step without further purification.

**Compound 4.21**

The aforementioned 4.17 and 4.20 were mixed together in THF (30 mL) and stirred at r.t. for 16 h. Upon completion, the mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (pentane: ethyl acetate = 3: 1) to give 4.21 (325 mg, 0.6 mmol, 30%) as a white solid.

$^1$H NMR (400 MHz, Methylene Chloride-d$_2$) δ 9.07 (d, $J = 8.0$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 – 7.24 (m, 4H), 6.92 (t, $J = 8.0$ Hz, 1H), 6.88 (dd, $J = 7.6$, 1.7 Hz, 1H), 6.42 (dd, $J = 8.2$, 1.1 Hz, 1H), 3.94 (s, 3H), 3.65 (s, 3H), 3.46 (dd, $J = 15.4$, 6.5 Hz, 1H), 2.38 (d, $J = 15.4$ Hz, 1H), 1.54 – 1.47 (m, 1H), 1.04 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (101 MHz, Methylene Chloride-d$_2$) δ 155.91, 155.53, 143.94, 140.39, 136.20, 132.68, 132.53, 130.94, 128.37, 127.39, 127.03, 126.70, 126.03, 125.86, 125.25, 125.08, 124.48, 123.74, 123.54, 122.84, 121.42, 119.01, 109.29, 108.92, 71.82, 62.53, 56.48, 56.27, 41.39, 38.30, 21.58. HRMS (ESI+, m/z) calculated for C$_{29}$H$_{24}$BrO$_2$S$_2$ [M + H]$^+$ 547.0219, found 547.0212.

**Compound 4.22**

Episulfide 4.21 (300 mg, 0.55 mmol) and HMPT (0.3 mL, 1.65 mmol) were dissolved in toluene (5 mL) in a sealed schlenk tube. After being stirred at 60 °C for 18 h, the reaction mixture was cooled and concentrated *in vacuo*. The crude product was purified using column chromatography (pentane: DCM = 3: 1) to give 4.22 (246 mg, 0.48 mmol, 87%) as a slightly yellow solid.

$^1$H NMR (400 MHz, Chloroform-d) δ 8.10 (d, $J = 8.5$ Hz, 1H), 7.75 (s, 1H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.33 – 7.23 (m, 2H), 6.94 (d, $J = 8.5$ Hz, 1H), 6.86 (t, $J = 7.5$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 6.61 – 6.53 (m, 2H), 6.34 – 6.28 (m, 1H), 4.37 – 4.19 (m, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.61 (dd, $J = 15.6$, 6.2 Hz, 1H), 2.57 (d, $J = 15.5$ Hz, 1H), 0.75 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 156.69, 156.36, 145.93, 145.10, 140.61, 138.28, 136.05, 130.95, 130.21, 129.08, 128.10, 126.93, 126.91, 126.85, 126.77, 125.62, 125.42, 124.14, 123.97, 123.53, 121.36, 120.19, 108.16, 107.76, 56.29, 56.15, 39.60, 38.03, 19.50. HRMS (ESI+, m/z) calculated for C$_{29}$H$_{24}$BrO$_2$S [M + H]$^+$ 515.0498, found 515.0491.
Compound 4.23

Compound 4.22 (220 mg, 0.43 mmol), CuI (4 mg, 5 mol%), Pd(PPh₃)₂Cl₂ (8 mg, 2.5 mol%), and (i-Pr)₂NH (1 mL) were dissolved in degassed and anhydrous DMF (5 mL) and the mixture was stirred at 60 °C for 10 min. Ethynyltrimethylsilane (0.19 mL, 1.36 mmol) was then added and the resulting mixture was allowed to stir at 90 °C for 18 h. The reaction mixture was quenched with aq. NH₄Cl solution (1M, 30 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (3 × 30 mL), brine (30 mL), and dried over Na₂SO₄. After removal of the solvents in vacuo, the residue was purified with column chromatography (pentane: ethyl acetate = 9: 1) to give 4.23 (127 mg, 0.24 mmol, 56%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.21 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.28 – 7.26 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.87 – 6.81 (m, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 – 6.49 (m, 2H), 6.29 (dd, J = 7.3, 1.5 Hz, 1H), 4.34 – 4.24 (m, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.58 (dd, J = 15.4, 6.1 Hz, 1H), 2.56 (d, J = 15.5 Hz, 1H), 0.74 (d, J = 6.8 Hz, 3H), 0.33 (s, 9H). ¹³C NMR (101 MHz, Chloroform-d) δ 156.64, 156.36, 145.44, 144.58, 140.64, 138.29, 137.22, 132.93, 129.32, 129.02, 128.70, 126.88, 126.79, 126.64, 125.98, 125.16, 125.12, 124.01, 123.51, 121.79, 121.49, 120.19, 108.18, 107.75, 103.86, 100.30, 56.29, 56.15, 39.51, 37.83, 19.56, 0.26. HRMS (ESI+, m/z) calculated for C₃₄H₃₃O₂SSi [M + H]⁺ 533.1964, found 533.1947.

Compound 4.24

To a solution of compound 4.23 (40 mg, 0.08 mmol) in THF (5 mL) was added TBAF (1 M in THF, 0.2 mL) and the resulting mixture was allowed to stir at 0 °C for 1 h. After quenching with aq. NH₄Cl solution (1M, 20 mL), the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic phase was further washed with water (2 × 20 mL), brine (20 mL) and dried over Na₂SO₄. After removal of the solvent in vacuo, the residue was purified by column chromatography (pentane: ethyl acetate = 9: 1) to give 4.24 (33 mg, 0.07 mmol, 96%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.23 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.29 – 7.26 (m, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.62 – 6.53 (m, 2H), 6.34 – 6.29 (m, 1H), 4.37 – 4.24 (m, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.60 (dd, J = 15.4, 6.2 Hz, 1H), 3.51 (s, 1H), 2.58 (d, J = 15.5 Hz, 1H), 0.75 (d, J = 6.8 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 156.66, 156.36, 145.44, 144.58, 140.59, 138.25, 137.50, 133.02, 129.49, 129.11, 129.01, 126.89, 126.84,
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126.68, 125.86, 125.24, 124.18, 123.52, 121.46, 120.85, 120.19, 108.20, 107.77, 82.61, 82.53, 56.29, 56.15, 39.52, 37.85, 19.54. HRMS (ESI+, m/z) calculated for C$_{31}$H$_{25}$O$_2$S [M + H]$^+$ 461.1570, found 461.1563.

Compound 4.25

To a powder of compound 4.24 (100 mg, 0.22 mmol) in a Schlenk tube under nitrogen were added 3 drops of THF, followed by addition of MeMgI (3M in Et$_2$O, 0.36 mL, 1.10 mmol). The temperature was raised to 160 °C until all the solvents were removed in vacuo and the temperature was maintained for another 1 h. After cooling, the reaction mixture was quenched using cooled aq. NH$_4$Cl solution (1M, 10 mL) and the resulting suspension was extracted with ethyl acetate (2 × 10 mL), followed by washing with water (20 mL), brine (20 mL) and drying over Na$_2$SO$_4$. The solvents were evaporated in vacuo and the residue was purified using column chromatography (DCM: Methanol = 9:1) to give 4.25 (65 mg, 0.15 mmol, 69%) as a yellow solid. $^1$H NMR (400 MHz, Chloroform-d) δ 8.25 (d, $J$ = 8.4 Hz, 1H), 7.71 (s, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.03 (d, $J$ = 8.3 Hz, 1H), 6.95 – 6.90 (m, 1H), 6.88 (dd, $J$ = 8.0, 1.1 Hz, 1H), 6.67 (dd, $J$ = 8.0, 1.2 Hz, 1H), 6.58 (t, $J$ = 7.8 Hz, 1H), 6.31 (dd, $J$ = 7.5, 1.2 Hz, 1H), 4.40 – 4.23 (m, 1H), 3.62 (dd, $J$ = 15.6, 6.3 Hz, 1H), 3.51 (s, 1H), 2.62 (d, $J$ = 15.6 Hz, 1H), 0.83 (d, $J$ = 6.8 Hz, 3H). HRMS (ESI-, m/z) calculated for C$_{29}$H$_{19}$O$_2$S [M - H]$^-$ 431.1100, found 431.1113.

Compound 4.26

Compound 4.25 (75 mg, 0.17 mmol), 4.8 (257 mg, 0.51 mmol), and K$_2$CO$_3$ (234 mg, 1.70 mmol) were mixed in 3 mL CH$_3$CN and the mixture was allowed to stir at 80 °C for 16 h. Upon completion, the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na$_2$SO$_4$. After removal of the solvents in vacuo, the desired product 4.26 was obtained using column chromatography (pentane: DCM = 3:1) as a yellow oil (146 mg, 0.14 mmol, 80%). $^1$H NMR (400 MHz, Chloroform-d) δ 8.24 (d, $J$ = 8.4 Hz, 1H), 7.68 (s, 1H), 7.38 (d, $J$ = 7.8 Hz, 1H), 7.30 – 7.22 (m, 2H), 6.97 (d, $J$ = 8.5 Hz, 1H), 6.89 – 6.81 (m, 1H), 6.78 (d, $J$ = 8.0 Hz, 1H), 6.60 – 6.49 (m, 2H), 6.30 (dd, $J$ = 7.4, 1.4 Hz, 1H), 4.36 – 4.27 (m, 1H), 4.23 – 4.11 (m, 6H), 4.09 – 3.98 (m, 2H), 3.65 – 3.54 (m, 5H), 3.51 (s, 1H), 2.57 (d, $J$ = 15.4 Hz, 1H), 1.99 – 1.87 (m, 4H), 1.68 – 1.55 (m, 8H), 1.48 – 1.36 (m, 12H), 1.21 – 1.02 (m, 42H), 0.75 (d, $J$ = 6.7 Hz, 3H).
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$^{13}$C NMR (101 MHz, Chloroform-d) δ 156.02, 155.77, 145.06, 144.46, 144.09, 140.22, 137.84, 137.61, 132.95, 129.67, 129.05, 128.96, 126.69, 126.56, 126.52, 125.78, 125.15, 125.07, 124.69, 124.37, 121.34, 120.67, 119.92, 109.65, 108.87, 103.87, 87.16, 82.58, 69.82, 69.25, 69.02, 58.84, 39.49, 37.78, 29.67, 29.57, 29.54, 29.50, 29.34, 29.27, 26.33, 26.31, 26.13, 26.09, 19.48, 18.70, 11.25. HRMS (ESI+, m/z) calculated for C$_{69}$H$_{100}$O$_4$S$i_2$N [M + NH$_4$]$^+$ 1094.6906, found 1094.6918.

**Compound 4.27**

Compound 4.26 (98 mg, 0.09 mmol), 4-iodophenol (40 mg, 0.18 mmol), CuI (2 mg, 10 mol%), Pd(PPh$_3$)$_2$Cl$_2$ (3 mg, 5 mol%), and (i-Pr)$_2$NH (1 mL) were dissolved in degassed and anhydrous DMF (3 mL) and the mixture was allowed to stir at 40 °C for 24 h. The reaction mixture was quenched with aq. NH$_4$Cl solution (1M, 30 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (3 × 30 mL), brine (30 mL), and dried over Na$_2$SO$_4$. After removal of the solvents in vacuo, the residue was purified with column chromatography (pentane: ethyl acetate = 3:1) to give 4.27 (40 mg, 0.03 mmol, 38%) as a yellow solid. $^1$H NMR (400 MHz, Chloroform-d) δ 8.29 (d, $J = 8.4$ Hz, 1H), 7.68 (s, 1H), 7.52 (d, $J = 8.6$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.28 (s, 2H), 6.96 (d, $J = 8.5$ Hz, 1H), 6.89 – 6.81 (m, 3H), 6.80 – 6.74 (m, 1H), 6.59 – 6.47 (m, 2H), 6.32 (dd, $J = 7.5$, 1.4 Hz, 1H), 5.11 (s, 1H), 4.35 – 4.29 (m, 1H), 4.21 – 4.11 (m, 6H), 4.09 – 4.00 (m, 2H), 3.64 – 3.52 (m, 5H), 2.58 (d, $J = 15.5$ Hz, 1H), 1.98 – 1.87 (m, 4H), 1.65 – 1.57 (m, 8H), 1.44 – 1.37 (m, 12H), 1.09 – 1.05 (m, 42H), 0.76 (d, $J = 6.8$ Hz, 3H). HRMS (ESI+, m/z) calculated for C$_{69}$H$_{100}$O$_4$S$i_2$N [M + NH$_4$]$^+$ 1094.6906, found 1094.6918.

**Compound 4.28**

Compound 4.27 (20 mg, 0.02 mmol), 4.4 (18 mg, 0.04 mmol), and K$_2$CO$_3$ (25 mg, 0.18 mmol) were mixed in 3 mL DMF and the mixture was allowed to stir at 80 °C for 18 h. The reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (3 × 30 mL), brine (30 mL), and dried over Na$_2$SO$_4$. After removal of the solvents, the crude product was purified using column chromatography (ethyl acetate: MeOH = 95:5) to give 4.28 (10 mg, 0.007 mmol, 39%) as a yellow oil. $^1$H NMR (400 MHz, Chloroform-d) δ 8.29 (d, $J = 8.2$ Hz, 1H), 7.68 (s, 1H), 7.55 (d, $J = 8.7$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.29 – 7.26 (m, 2H), 6.97 – 6.90 (m, 3H), 6.84 (t, $J = 7.2$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.59 – 6.48 (m, 2H), 6.32 (dd, $J = 7.4$, 1.3 Hz, 1H), 4.36 – 4.27 (m, 1H), 4.19 – 4.12 (m, 8H), 4.07 – 4.01 (m, 2H), 3.88 (t, $J = 4.8$ Hz, 2H).
Hz, 2H), 3.77 – 3.51 (m, 49H), 3.38 (d, J = 2.7 Hz, 5H), 2.58 (d, J = 15.5 Hz, 1H),
1.97 – 1.84 (m, 4H), 1.64 – 1.58 (m, 8H), 1.43 – 1.37 (m, 12H), 1.08 (d, J = 2.5 Hz,
42H), 0.76 (d, J = 6.8 Hz, 3H). HRMS (ESI+, m/z) calculated for C₉₄H₁₄₂NO₁₄SSi₂
[M + NH₄⁺]⁺ 1597.9723, found 1597.9731.

**Compound 4.1**

To a solution of compound **4.28** (10 mg, 0.007 mmol) in THF (3 mL) was added
TBAF (1 M in THF, 0.1 mL) and the resulting mixture was allowed to stir at 0 °C
for 1 h. After quenching with aq. NH₄Cl solution (1M, 20 mL), the reaction
mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic phase
was further washed with water (3 × 20 mL), brine (20 mL) and dried over Na₂SO₄.
After removal of the solvent *in vacuo*, the residue was purified by column
chromatography (ethyl acetate: MeOH = 95: 5) to give **4.24** (6 mg, 0.005 mmol,
76%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 8.29 (d, J = 8.3 Hz,
1H), 7.68 (s, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.29 – 7.26 (m,
2H), 6.97 – 6.91 (m, 3H), 6.84 (d, J = 8.0 Hz, 1H), 6.59 – 6.49 (m, 2H), 6.32 (dd,
J = 7.4, 1.4 Hz, 1H), 4.37 – 4.27 (m, 1H), 4.20 – 4.11 (m, 8H), 4.09 – 4.00 (m,
1H), 3.88 (t, J = 4.8 Hz, 2H), 3.78 – 3.47 (m, 28H), 3.37 (s, 2H), 2.58 (d, J = 15.5 Hz,
1H), 2.42 (t, J = 2.4 Hz, 2H), 1.97 – 1.84 (m, 4H), 1.65 – 1.59 (m, 8H), 1.43 – 1.37 (m,
12H), 0.76 (d, J = 6.8 Hz, 3H). ¹³C NMR (151 MHz, Chloroform-d) δ 159.09, 156.10, 155.84, 145.35, 144.81, 140.48, 138.08, 136.80, 133.19, 132.74, 129.35, 129.16, 127.89, 126.75, 126.57, 126.55, 126.03, 125.04, 124.95, 124.87, 124.53, 122.28, 121.51, 120.05, 115.98, 114.92, 109.80, 109.00, 95.17, 87.18, 80.23, 74.20, 72.08, 71.03, 70.79, 70.73, 70.71, 70.65, 70.41, 69.81, 69.39, 69.15, 67.68, 67.66, 61.92, 59.16, 58.15, 39.60, 37.83, 29.67, 29.56, 29.53, 29.51, 29.39, 29.33, 26.24, 26.22, 26.17, 26.13, 19.58. HRMS (ESI+, m/z) calculated for C₇₆H₁₀₂NO₁₄S [M + NH₄⁺]⁺ 1284.7016, found 1284.7038.

For (S)-**4.1**, [α]_<sub>D</sub>²⁰ = +23.3 (c 0.5, CH₂Cl₂); for (R)-**4.1**, [α]_<sub>D</sub>²⁰ = -23.1 (c 0.5, CH₂Cl₂).

**Compound 4.3**<sup>55</sup>

To a solution of compound **4.29** (11 g, 40 mmol) in anhydrous THF (100 mL) at -
100 °C was slowly added n-BuLi (2.5M in hexane, 16 mL). After 1 h of stirring at -
100 °C, dry ice (roughly 5 g) was added and the reaction mixture was allowed to
warm to r.t. over 2 h. The excess amount of CO₂ was removed by three times of
free-pump-thaw. The reaction mixture was cooled to -100 °C again and n-BuLi
(10.4 mL, 26 mmol) was added. After slowly warming to r.t., the mixture was
stirred for another 16 h. Upon completion, the reaction mixture was quenched with
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water (200 mL) and extract with DCM (2 × 50 mL). The combined organic layers were washed with aq. 10% HCl (2 × 100 mL), aq. 1M NaOH (2 × 100 mL) solution, brine (100 mL) and dried over Na₂SO₄. After evaporating the solvents in vacuo, the crude product was purified using column chromatography (pentane: ethyl acetate = 3: 1) to yield 4.31 (820 mg, 3 mmol, 15%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.16 (d, J = 8.8 Hz, 2H), 6.84 (dd, J = 8.8, 2.6 Hz, 2H), 6.69 (d, J = 2.7 Hz, 2H), 3.85 (s, 6H), 3.13 (s, 4H). ¹H NMR data is in accordance with Ref. 55.

**Compound 4.33**

To a solution of ketone 4.31 (220 mg, 0.8 mmol) in toluene (5 mL), Lawesson’s reagent (1 g, 2.5 mmol) was added. The resulting mixture was heated at reflux for 1 h. After cooling to r.t., the solids were filtered and washed with DCM. The filtrate was concentrated in vacuo, followed by adding THF (10 mL). To the blue solution was added 1 mL of hydrazine monohydrate and the resulting mixture was stirred for 1 h until the color completely disappeared. After concentrating in vacuo, the crude product was purified using column chromatography (DCM: MeOH = 95: 5) to give hydrazone 4.33 (210 mg, 0.7 mmol, 91%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.58 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.77 (ddd, J = 11.5, 8.5, 2.6 Hz, 2H), 6.58 (d, J = 2.6 Hz, 1H), 5.46 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H).

**Compound 4.34**

To a solution of 4.33 (210 mg, 0.7 mmol) in THF (10 mL) was added MnO₂ (600 mg, 7.0 mmol). After stirring at 0 °C for 1 h, the mixture was filtered over celite and the filtrate was immediately used in the next step without further purification.

**Compound 4.35**

Compound 4.17 (prepared from 204 mg of 4.16) and 4.34 (prepare from 210 mg 4.33) were mixed together in THF (30 mL) and the solution was stirred at r.t. for 16 h. Upon completion, the mixture was concentrated in vacuo, followed by column chromatography (pentane: ethyl acetate = 3: 1) to give 4.25 (265 mg, 0.5 mmol, 66%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.50 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.68 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.04 – 6.98 (m, 1H), 6.69 (dd, J = 8.7, 2.8 Hz, 1H), 6.60 (dd, J = 8.5, 2.7 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 6.11 (d, J = 2.6 Hz,
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1H), 3.75 (s, 3H), 3.57 (s, 3H), 3.35 (dd, J = 16.0, 7.1 Hz, 1H), 3.27 – 3.16 (m, 1H), 2.95 – 2.82 (m, 1H), 2.75 – 2.59 (m, 2H), 2.04 – 1.95 (m, 2H), 1.16 (d, J = 7.1 Hz, 3H). HRMS (ESI+, m/z) calculated for C₃₁H₂₈BrO₂S [M + H]+ 542.0988, found 542.0962.

Compound 4.36

Episulfide 4.35 (265 mg, 0.49 mmol) and HMPT (0.27 mL, 1.5 mmol) were dissolved in toluene (5 mL) in a sealed Schlenk tube. After being stirred at 60 °C for 18 h, the reaction mixture was cooled and concentrated in vacuo. The crude product was purified using column chromatography (pentane: DCM = 3: 1) to give 4.36 (240 mg, 0.48 mmol, 96%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.12 (d, J = 8.7 Hz, 1H), 7.75 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.97 – 6.89 (m, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.76 (dd, J = 8.3, 2.6 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 6.47 (d, J = 8.5 Hz, 1H), 6.06 (dd, J = 8.5, 2.7 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, J = 13.6, 4.4 Hz, 1H), 3.68 – 3.60 (m, 4H), 3.58 – 3.47 (m, 2H), 3.15 – 3.00 (m, 1H), 2.82 (dt, J = 13.5, 4.1 Hz, 1H), 2.50 (d, J = 15.7 Hz, 1H), 0.75 (d, J = 6.9 Hz, 3H). ¹³C NMR (151 MHz, Chloroform-d) δ 158.75, 158.56, 145.60, 143.85, 140.27, 137.67, 137.37, 135.80, 134.41, 133.76, 131.18, 130.65, 130.03, 128.35, 128.32, 127.13, 127.11, 125.59, 125.24, 123.57, 116.36, 113.30, 111.35, 111.25, 55.41, 55.28, 39.52, 39.36, 34.31, 31.81, 19.00. HRMS (ESI+, m/z) calculated for C₃₁H₂₈BrO₂ [M + H]+ 511.1267, found 511.1166.

Compound 4.37

Compound 4.36 (120 mg, 0.24 mmol), CuI (2 mg, 5 mol%), Pd(PPh₃)₂Cl₂ (4 mg, 2.5 mol%), and (i-Pr)₂NH (1 mL) were dissolved in degassed and anhydrous DMF (3 mL) and stirred at 60 °C for 10 min. Ethynyltrimethylsilane (0.07 mL, 0.48 mmol) was then added and the resulting mixture was allowed to stir at 90 °C for 18 h. The reaction mixture was quenched with aq. NH₄Cl solution (1M, 30 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (3 × 30 mL), brine (30 mL), and dried over Na₂SO₄. After removal of the solvents in vacuo, the residue was purified with column chromatography (pentane: ethyl acetate = 9: 1) to give 4.37 (96 mg, 0.18 mmol, 76%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.23 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.92 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.76 (dd, J = 8.3, 2.7 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.57 (s, 3H), 3.35 (dd, J = 16.0, 7.1 Hz, 1H), 3.27 – 3.16 (m, 1H), 2.95 – 2.82 (m, 1H), 2.75 – 2.59 (m, 2H), 2.04 – 1.95 (m, 2H), 1.16 (d, J = 7.1 Hz, 3H). HRMS (ESI+, m/z) calculated for C₃₁H₂₈BrO₂S [M + H]+ 542.0988, found 542.0962.
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2.7 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 6.45 (d, J = 8.5 Hz, 1H), 6.03 (dd, J = 8.6, 2.7 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, J = 13.6, 4.4 Hz, 1H), 3.67 – 3.59 (m, 4H), 3.58 – 3.51 (m, 1H), 3.46 (dd, J = 17.9, 14.1, 4.4 Hz, 1H), 2.81 (dt, J = 13.5, 4.1 Hz, 1H), 0.73 (d, J = 6.8 Hz, 3H), 0.33 (s, 9H). HRMS (ESI+, m/z) calculated for C$_{36}$H$_{37}$O$_2$Si [M + H]$^+$ 529.2558, found 529.2461.

Compound 4.38

To a solution of compound 4.37 (400 mg, 0.76 mmol) in THF (20 mL) was added TBAF (1 M in THF, 2 mL) and the resulting mixture was allowed to stir at 0 °C for 1 h. After quenching with aq. NH$_4$Cl solution (1M, 20 mL), the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic phase was further washed with water (2 × 20 mL), brine (20 mL) and dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography (pentane: ethyl acetate = 9: 1) to give 4.38 (345 mg, 0.76 mmol, 99%) as a yellow solid. $^1$H NMR (400 MHz, Chloroform-d) δ 8.25 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.97 – 6.90 (m, 1H), 6.76 (dd, J = 8.3, 2.6 Hz, 1H), 6.66 (d, J = 2.6 Hz, 1H), 6.47 (d, J = 8.5 Hz, 1H), 6.05 (dd, J = 8.6, 2.7 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, J = 13.7, 4.4 Hz, 1H), 3.70 – 3.60 (m, 4H), 3.58 – 3.44 (m, 3H), 3.15 – 3.01 (m, 1H), 2.82 (dt, J = 13.6, 4.1 Hz, 1H), 2.50 (d, J = 15.6 Hz, 1H), 0.74 (d, J = 6.9 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 158.73, 158.56, 144.22, 140.27, 137.68, 137.37, 137.22, 134.97, 133.75, 133.29, 130.73, 129.39, 128.76, 128.29, 127.02, 126.05, 125.20, 125.00, 120.42, 116.31, 113.27, 111.33, 111.22, 82.63, 82.39, 55.39, 55.26, 39.34, 39.24, 34.32, 31.79, 19.03. HRMS (ESI+, m/z) calculated for C$_{33}$H$_{29}$O$_2$ [M + H]$^+$ 457.2162, found 457.2066.

Compound 4.39

To a powder of compound 4.38 (100 mg, 0.22 mmol) in a schlenk tube under nitrogen were added 3 drops of THF, followed by addition of MeMgI (3M in Et$_2$O, 0.36 mL, 1.10 mmol). The temperature was raised to 160 °C until all the solvents were removed in vacuo and the temperature was maintained for another 1 h. After cooling, the reaction mixture was quenched using cooled aq. NH$_4$Cl solution (1M, 10 mL) and the resulting suspension was extracted with ethyl acetate (2 × 10 mL), followed by washing with water (20 mL), brine (20 mL) and drying over Na$_2$SO$_4$. The solvents were evaporated in vacuo and the residue was purified using column
chromatography (DCM: Methanol = 9: 1) to give 4.39 (78 mg, 0.18 mmol, 83%) as a yellow solid. \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta 8.23 (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.68 (s, 1\text{H}), 7.42 (d, J = 8.3 \text{ Hz}, 1\text{H}), 7.30 – 7.26 (m, 1\text{H}), 7.14 (d, J = 8.2 \text{ Hz}, 1\text{H}), 6.99 – 6.92 (m, 1\text{H}), 6.79 (d, J = 2.5 \text{ Hz}, 1\text{H}), 6.69 (dd, J = 8.1, 2.5 Hz, 1\text{H}), 6.60 (d, J = 2.7 \text{ Hz}, 1\text{H}), 6.41 (d, J = 8.3 \text{ Hz}, 1\text{H}), 5.96 (dd, J = 8.3, 2.7 Hz, 1\text{H}), 3.85 – 3.68 (m, 1\text{H}), 3.68 – 3.58 (m, 1\text{H}), 3.49 – 3.39 (m, 3\text{H}), 3.12 – 2.95 (m, 1\text{H}), 2.81 – 2.71 (m, 1\text{H}), 2.49 (d, J = 15.8 \text{ Hz}, 1\text{H}), 0.76 (d, J = 6.9 \text{ Hz}, 3\text{H}). HRMS (ESI-, m/z) calculated for C\(_{31}\)H\(_{23}\)O\(_2\) [M - H] \(^{-}\) 427.1703, found 427.1614.

**Compound 4.40**

Compound 4.39 (78 mg, 0.18 mmol), 4.8 (225 mg, 0.46 mmol), and K\(_2\)CO\(_3\) (248 mg, 1.80 mmol) were mixed in 3 mL CH\(_3\)CN and the mixture was allowed to stir at 80 \(^\circ\)C for 16 h. Upon completion, the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (2 \(\times\) 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na\(_2\)SO\(_4\). After removal of the solvents \textit{in vacuo}, the desired product 4.40 was obtained using column chromatography (pentane: DCM = 3: 1) as a yellow oil (138 mg, 0.12 mmol, 69%). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta 8.25 (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.68 (s, 1\text{H}), 7.43 (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.29 – 7.26 (m, 1\text{H}), 7.18 (d, J = 8.4 \text{ Hz}, 1\text{H}), 6.96 – 6.90 (m, 1\text{H}), 6.85 (d, J = 2.5 \text{ Hz}, 1\text{H}), 6.74 (dd, J = 8.3, 2.6 \text{ Hz}, 1\text{H}), 6.65 (d, J = 2.6 \text{ Hz}, 1\text{H}), 6.45 (d, J = 8.5 \text{ Hz}, 1\text{H}), 6.03 (dd, J = 8.5, 2.7 \text{ Hz}, 1\text{H}), 4.19 – 4.16 (m, 4\text{H}), 3.96 (t, J = 6.6 \text{ Hz}, 2\text{H}), 3.80 – 3.63 (m, 4\text{H}), 3.55 – 3.43 (m, 7\text{H}), 3.12 – 2.99 (m, 1\text{H}), 2.83 – 2.74 (m, 1\text{H}), 2.49 (d, J = 15.6 \text{ Hz}, 1\text{H}), 1.82 – 1.75 (m, 2\text{H}), 1.64 – 1.53 (m, 10\text{H}), 1.36 – 1.29 (m, 12\text{H}), 1.07 (d, J = 4.1 \text{ Hz}, 42\text{H}), 0.74 (d, J = 6.8 \text{ Hz}, 3\text{H}). HRMS (ESI+, m/z) calculated for C\(_{71}\)H\(_{104}\)O\(_4\)Si\(_2\)N [M + NH\(_4\)] \(^{+}\) 1090.7498, found 1090.7291.

**Compound 4.41**

Compound 4.40 (138 mg, 0.12 mmol), 4-iodophenol (138 mg, 0.63 mmol), Cul (2 mg, 10 mol%), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (3 mg, 5 mol%), and (i-Pr\(_2\))NH (1 mL) were dissolved in degassed and anhydrous DMF (3 mL) and the mixture was allowed to stir at 40 \(^\circ\)C for 24 h. The reaction mixture was quenched with aq. NH\(_4\)Cl solution (1M, 30 mL) and extracted with ethyl acetate (2 \(\times\) 10 mL). The combined organic layers were washed with water (3 \(\times\) 30 mL), brine (30 mL), and dried over Na\(_2\)SO\(_4\). After removal of the solvents \textit{in vacuo}, the residue was purified with column chromatography (pentane: ethyl acetate = 3: 1) to give 4.41 (52 mg, 0.04 mmol,
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35%) as a yellow oil. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.33 (d, $J = 8.4$ Hz, 1H), 7.68 (s, 1H), 7.56 – 7.50 (m, 2H), 7.44 (d, $J = 8.6$ Hz, 1H), 7.30 – 7.26 (m, 1H), 7.20 (d, $J = 8.3$ Hz, 1H), 6.97 – 6.90 (m, 1H), 6.88 – 6.83 (m, 3H), 6.75 (dd, $J = 8.3$, 2.5 Hz, 1H), 6.66 (d, $J = 2.6$ Hz, 1H), 6.48 (d, $J = 8.5$ Hz, 1H), 6.04 (dd, $J = 8.5$, 2.6 Hz, 1H), 5.32 (s, 1H), 4.18 (d, $J = 7.1$ Hz, 4H), 3.96 (t, $J = 6.6$ Hz, 2H), 3.82 – 3.63 (m, 4H), 3.58 – 3.46 (m, 6H), 3.13 – 3.00 (m, 1H), 2.80 (dt, $J = 13.4$, 4.1 Hz, 1H), 2.51 (d, $J = 15.6$ Hz, 1H), 1.84 – 1.71 (m, 2H), 1.70 – 1.47 (m, 10H), 1.38 – 1.30 (m, 12H), 1.08 (dd, $J = 5.6$, 2.5 Hz, 42H), 0.75 (d, $J = 6.8$ Hz, 3H).

HRMS (ESI+, m/z) calculated for $C_{77}H_{108}O_5Si_2N$ [M + NH$_4$]$^+$ 1282.7760, found 1282.7554.

**Compound 4.42**

To a solution of compound 4.41 (20 mg, 0.017 mmol) in THF (3 mL) was added TBAF (1 M in THF, 0.1 mL) and the resulting mixture was allowed to stir at 0 °C for 1 h. After quenching with aq. NH$_4$Cl solution (1M, 20 mL), the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic phase was further washed with water (3 × 20 mL), brine (20 mL) and dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography (pentane: ethyl acetate = 3: 1) to give 4.42 (15 mg, 0.017 mmol, 96%) as a yellow oil. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.32 (d, $J = 8.4$ Hz, 1H), 7.68 (s, 1H), 7.55 – 7.50 (m, 2H), 7.44 (d, $J = 8.6$ Hz, 1H), 7.30 – 7.26 (m, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 6.97 – 6.91 (m, 1H), 6.88 – 6.82 (m, 3H), 6.75 (dd, $J = 8.3$, 2.6 Hz, 1H), 6.66 (d, $J = 2.6$ Hz, 1H), 6.48 (d, $J = 8.5$ Hz, 1H), 6.04 (dd, $J = 8.5$, 2.6 Hz, 1H), 4.14 (d, $J = 2.4$ Hz, 2H), 4.13 (d, $J = 2.4$ Hz, 2H), 3.96 (t, $J = 6.7$ Hz, 2H), 3.80 – 3.63 (m, 4H), 3.56 – 3.44 (m, 6H), 3.13 – 2.99 (m, 1H), 2.84 – 2.75 (m, 1H), 2.51 (d, $J = 15.6$ Hz, 1H), 2.42 (t, $J = 2.4$ Hz, 1H), 2.40 (t, $J = 2.4$ Hz, 1H), 1.84 – 1.75 (m, 2H), 1.71 – 1.47 (m, 10H), 1.37 – 1.29 (m, 12H), 0.75 (d, $J = 6.8$ Hz, 3H). HRMS (ESI+, m/z) calculated for $C_{59}H_{68}O_5N$ [M + NH$_4$]$^+$ 870.5092, found 870.4890.

**Compound 4.2**

Compound 4.42 (15 mg, 0.017 mmol), 4.4 (19 mg, 0.034 mmol), and K$_2$CO$_3$ (23 mg, 0.17 mmol) were mixed in 3 mL DMF and the mixture was allowed to stir at 80 °C for 18 h. The reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na$_2$SO$_4$. After removal of the solvents,
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the crude product was purified using column chromatography (ethyl acetate: MeOH = 95: 5) to give 4.28 (16 mg, 0.012 mmol, 73%) as a yellow oil. \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.34 (d, \(J = 8.3\) Hz, 1H), 7.68 (s, 1H), 7.55 (d, \(J = 9.0\) Hz, 2H), 7.44 (d, \(J = 8.4\) Hz, 1H), 7.30 – 7.26 (m, 1H), 7.19 (d, \(J = 8.3\) Hz, 1H), 6.97 – 6.90 (m, 3H), 6.85 (d, \(J = 2.5\) Hz, 1H), 6.74 (dd, \(J = 8.3, 2.6\) Hz, 1H), 6.65 (d, \(J = 2.6\) Hz, 1H), 6.48 (d, \(J = 8.5\) Hz, 1H), 6.04 (dd, \(J = 8.6, 2.6\) Hz, 1H), 4.14 (d, \(J = 2.4\) Hz, 2H), 4.12 (d, \(J = 2.4\) Hz, 2H), 3.96 (t, \(J = 6.6\) Hz, 2H), 3.88 (t, \(J = 4.9\) Hz, 2H), 3.79 – 3.60 (m, 47H), 3.57 – 3.45 (m, 11H), 3.41 – 3.37 (m, 5H), 3.11 – 3.01 (m, 1H), 2.83 – 2.75 (m, 1H), 2.51 (d, \(J = 15.6\) Hz, 1H), 2.41 (t, \(J = 2.4\) Hz, 1H), 2.40 (t, \(J = 2.4\) Hz, 1H), 1.84 – 1.73 (m, 2H), 1.66 – 1.58 (m, 10H), 1.46 – 1.32 (m, 12H), 0.75 (d, \(J = 6.8\) Hz, 3H). HRMS (ESI+, m/z) calculated for \(C_{78}H_{106}O_{14}N\) [M + NH\(_4\)]\(^+\) 1280.7608, found 1280.7395.

Compound 4.43

To a solution of compound 4.14 (200 mg, 0.74 mmol) in anhydrous DCM (50 mL) was slowly added BBr\(_3\) (0.3 mL, 3.7 mmol) at 0 \(^\circ\)C. After warming up to r.t., the reaction mixture was allowed to stir for another 18 h, followed by quenching it with ice water (100 mL). The aqueous phase was extracted with ethyl acetate (3 \(\times\) 50 mL) and the combined organic phase was washed with brine (100 mL) and dried over Na\(_2\)SO\(_4\). After removal of the solvents, the crude product was purified using column chromatography to give 4.43 (152 mg, 0.62 mmol, 83%) as a green solid. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.95 (d, \(J = 8.0\) Hz, 2H), 7.40 (t, \(J = 8.0\) Hz, 2H), 7.22 (d, \(J = 7.8\) Hz, 2H).

Compound 4.44

Compound 4.43 (20 mg, 0.082 mmol), 4.8 (121 mg, 0.246 mmol), and K\(_2\)CO\(_3\) (113 mg, 0.82 mmol) were mixed in 3 mL DMF and the mixture was allowed to stir at 90 \(^\circ\)C for 24 h. Upon completion, the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (2 \(\times\) 10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na\(_2\)SO\(_4\). After removal of the solvents \textit{in vacuo}, the pure product 4.40 was obtained using column chromatography (pentane: ethyl acetate = 3: 1) as a pale yellow solid (28 mg, 0.049 mmol, 60%). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.23 (d, \(J = 8.2\) Hz, 2H), 7.42 (t, \(J = 8.0\) Hz, 2H), 7.12 (d, \(J = 7.9\) Hz, 2H), 4.19 (t, \(J = 6.5\) Hz, 4H), 4.15 – 4.10 (m, 4H), 3.51 (t, \(J = 6.6\) Hz, 4H), 2.40 (t, \(J = 2.4\) Hz, 1H), 2.00 – 1.87 (m, 4H), 1.67 – 1.56 (m, 8H), 1.48 – 1.35 (m, 12H). \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 180.59,
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154.54, 130.18, 128.55, 126.00, 121.46, 113.26, 80.19, 74.20, 70.37, 69.59, 58.16, 29.65, 29.53, 29.38, 29.15, 26.21, 26.10. HRMS (ESI+, m/z) calculated for C_{35}H_{45}O_{5}S [M + H]^+ 577.2982, found 577.2991.

4.6.3 Enantiomers separation

The separation of enantiomers of compound 4.27 was performed on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector and FRC-10A Fraction Collector, using Chiracel AD-H column (n-heptane : i-PrOH = 96 : 4), 1.0 mL/min, 40 °C, injection volume: 10 µL, detection at 402 nm.

Figure 4.9 Chiral HPLC chromatogram of compound 4.27.

4.6.4 DFT calculations

Density functional theory (DFT) (DFT at B3LYP/6-31G(d, p)) was used to optimize the structure, followed by a time-dependent DFT (TD-DFT) calculation to obtain the CD spectrum of clockwise rotating (S)-4.27 (the long alkyl legs was replaced with shorter methyl groups for easier calculation process). A CH₂Cl₂ solvation model was chosen.
4.6.5 Surface modification

Azido-functionalized silica microparticles

The azido-functionalized silica microparticles were prepared following literature procedures. 63 20 mg silica microparticles (d= 5 µm, from Sigma-Aldrich) were pretreated with 5% aq. HCl (3 mL) by heating together at 90 °C for 4h. The resulting mixture was centrifuged and redispersed into water (2 × 3 mL), and the solids were isolated and dried in oven at 90 °C for 10 min. To a suspension of the abovementioned microparticles in DMF (3 mL) was added 3-(azidopropyl)triethoxysilane (50 µL) and the resulting mixture was heated at 80 °C for 16 h. After cooling to r.t., the solids were centrifuged out and washed with DMF (3 × 3 mL), water (2 × 3 mL), and MeOH (2 × 3 mL), followed by drying in oven at 90 °C for 10 min.

Motor-functionalized silica microparticles

10 mg azido-functionalized microparticles and 5 mg of compounds 4.1, 4.2 or 4.44, respectively, were mixed together in DMF (3 mL) and the resulting mixture was added with a suspension of CuSO₄·5H₂O (0.06 mg) and sodium ascorbate (0.10 mg) in DMF (10 µL). After stirring at 40 °C for 24 h, the solids were isolated by centrifugation, followed by extensive washing with DMF (2 × 3 mL), water (2 × 3 mL), Na₂EDTA (1 M, 2 × 3 mL), water (2 × 3 mL), and MeOH (2 × 3 mL). The obtained particles were dried in a glass vial in vacuo at r.t.

Azido- and motor- functionalized silica nanoparticles

Started with 20 mg silica nanoparticles (d= 10-20 nm, from Sigma-Aldrich), the rest of the preparation was the same with microsized particles.

Motor-functionalized quartz

Quartz slides (Micro to Nano) were cut into pieces to fit into the reactor. The quartz substrates were initially heated in piranha solution (aq. 98 % H₂SO₄ and aq. 30% H₂O₂ with a volume ratio of 7: 3) at 90 °C for 2 h. These samples were then washed with water, MeOH, and dried with N₂. Similar with the abovementioned procedures of silica microparticles, these samples were treated with HCl, 3-(azidopropyl)triethoxysilane, and motor, to obtain the motor-attached quartz.
4.6.6 XPS measurements

X-ray photoelectron spectroscopy (XPS) measurements were carried out on a K-Alpha XP spectrometer (Thermo Scientific), equipped with a monochromatic small-spot (400 μm) X-ray source (Al $K\alpha = 1486.6$ eV). The measurements were conducted at background pressure of $\sim 8 \times 10^{-8}$ mbar reaching maximum of $3 \times 10^{-7}$ mbar during the measurements due to the flow of low energy $\text{Ar}^+$ ions involved in the charge neutralization process. High-resolution spectra of core levels were recorded with a pass energy of 50 eV and wide-range survey spectra were recorded with a pass energy of 200 eV. Powder samples were dispersed on conductive carbon tape. Charge correction was done by referencing the binding energy of C-C, C-H component in C 1s spectral region to 284.8 eV. For each sample, N 1s spectra were collected at first in order to avoid possible degradation of the azido groups upon prolonged exposure to X-rays.63

4.7 References

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