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Synthesis of an azobenzene-linker-conjugate with tetrahedrical shape

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Abstract

The synthesis of a tripodal linker system with an adamantane core unit and an azobenzene headgroup is reported for the preparation of photochromic SAMs on gold surfaces. For the final Sonogashira-coupling of the ethynylene-linker precursor **4** with the *p*-iodo substituted azobenzene **6** model studies were required to optimize the coupling step in the presence of a diazene functionality. The photochromic properties of the photoswitch-linker-conjugate **1** were investigated in solution, and compared to the behavior of the precursor **6**.
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Keywords: Azobenzene; Photoswitch; Tripod; Linker-conjugate; cis/trans-Isomerisation

Photochromic compounds have been widely investigated as promising candidates for optical data storage, microelectronics, non-linear optics and on/off-switching of functional molecules in biology[1–5] Especially azobenzene derivatives have gained enormous interest in these research fields. This class of photoactive compounds isomerizes from the trans- to the cis-state by activation with light in the UV/vis region or by electron transfer. The reverse reaction can be achieved by illumination with UV/vis light of a different wavelength or appears by thermal relaxation.[1] The shift in structure causes a significant change in physical properties, for example, absorption spectra or dipole moment. During the past years there has been a tremendous and consistent research effort for the development of switchable azobenzene-modified surfaces by using Langmuir–Blodget-films or self-assembly.[1,6] The investigation and characterization of chromophore containing self assembled monolayers (SAMs), which are formed by covalent binding of sulfides or disulfides to a solid surface, for example, gold or silver, are seen as an auspicious approach toward the development of materials with novel optical and electronical properties.[6] Generally, one-dimensional linkers like alkanethiols are used for the preparation of SAMs on gold.

In most cases the alkyl chains are tilted in order to maximize the interchain van der Waals interactions. However, the final orientation of a chromophore headgroup is not always easy to predict.[6–8]

Moreover, π-aggregation of the attached chromophores is a known problem that changes or even suppresses the chromophore properties.[6,9] Recently, Galoppini,[9,12] Tour,[10,11] and others.[13–17] have developed three-dimensional linkers with a tetrahedrical core unit for sufficient control of the perpendicular shape and the headgroup to surface distance. Additionally, it has been shown that tripods are feasible linkers that prevent π-stacking or dimerization of azobenzenes when adsorbed on gold or applied as AFM-tip.[18,19]

Herein, we report the synthesis of a tripodal linkersystem with an adamantane core and an azobenzene headgroup containing an additional nitrile functionality in *p*-position. The nitrile acts as a reporter group for spectroscopy on surfaces, for example, SFG (sum frequency generation) or HREELS (high resolution electron energy loss spectroscopy). For immobilization on metal surfaces the system provides three protected thiol groups (Fig. 1). The classical thiol protection groups are thioethers or thioesters. Due to the fact that the cleavage of thioethers requires

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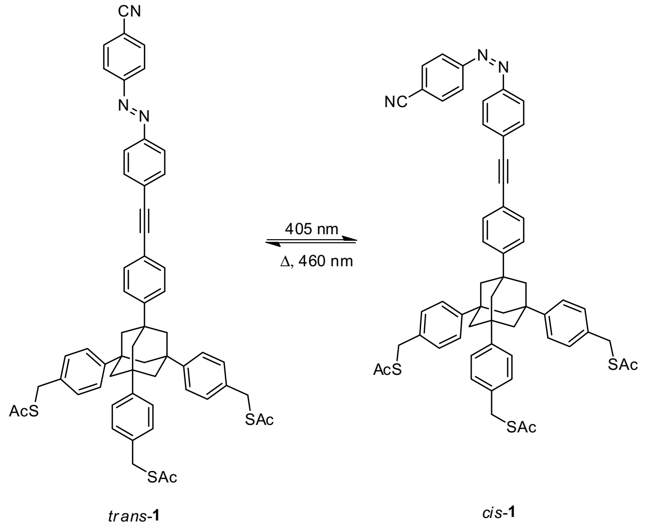


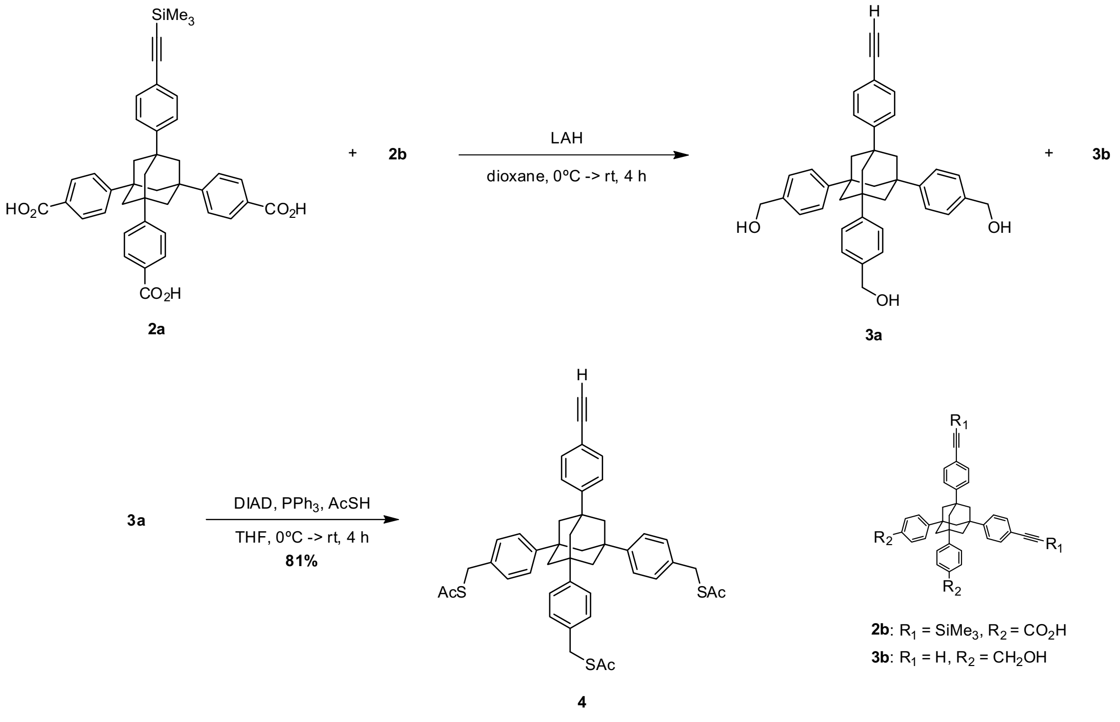
Fig. 1. Photoisomerization and thermal relaxation of the azobenzene-linker-conjugate **1**.

harsh conditions we decided to use the latter protection approach. The three anchoring groups of the linker generate a triangle footprint with a side length about 12–15 Å. However, it has been shown that the anchoring of all the three thiols in systems with tetrahedral shape is elusive.[11,14] Hence, for a better flexibility we inserted a methylene unit between the anchoring moiety and the phenyl ring of the adamantane core.

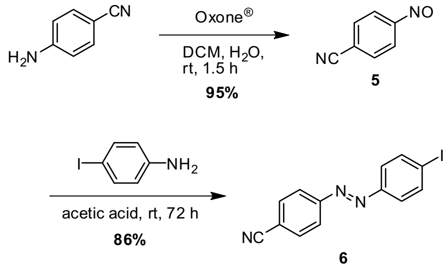
The synthesis of the linker building block **4** was accomplished in six steps, starting with the literature known conversion of 1-bromoadamantane to 1,3,5,7-(4-tetraiodophenyl)adamantane in 39% yield over two steps.[20,21] The following Sonogashira-coupling with trimethylsilylacetylene and the carboxylation with *t*-BuLi and CO_2 gave precursor **2a** as previously reported.[12] By following the literature protocol, compound **2a** is obtained as a mixture of the tri- and dicarboxylic acid (**2a**,**b**, see Scheme 1) which was used in the next step to avoid the difficult separation by column chromatography.[12] Alcohol **3a** was synthesized by the reduction of acid **2a** with LAH. 1,4-Dioxane as a more polar solvent was used to avoid problems observed when dissolving the lipophobic acid mixture **2a,b** in Et_2O. Under these conditions the reduction of the acid functionalities is accompanied by a cleavage of the silyl protection group furnishing the free acetylene. Similar Si–C bond cleavage reactions have been previously reported for alkylsilanes using LAH in THF.[22]

The final coupling of an azobenzene precursor to the linker-conjugate was planned via a palladium-mediated Sonogashira-coupling. Because of the strong affinity of sulfur containing groups, especially free thiols, for transition metals like palladium, the protection of the sulfur atoms is mandatory. Again thioesters are superior to thioethers, since cleavage of the latter can also be initiated by palladium catalysts. Also, the reduction of the azobenzene moiety to the hydrazine with simultaneous formation of disulfide dimers or polymers could be a problem without protection.[23] In the past, the coupling of alkynes with palladium in the presence of thioacetate functionalities was successfully achieved by several groups.[10,14,15]

Hence the introduction of the thioacetate groups was carried out starting from **3a**. An elegant method is the



Scheme 1. Synthesis of the ethynylene-linker containing thioacetate anchoring groups.



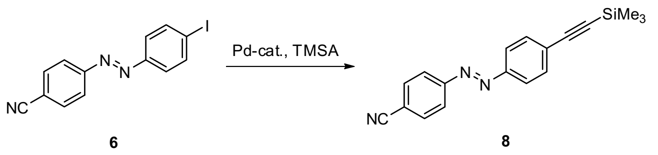
Scheme 2. Synthesis of azobenzene **6**.

activation of the alcohol functionality with triphenylphosphine and azodicarboxylate followed by a nucleophilic substitution with acids furnishing the corresponding esters.[24] Alcohol **3a** was treated with diisopropylazodicarboxylate, acetyl mercaptan and an excess of triphenylphosphine,[10] to give acetate **4** in 81% yield.

The azobenzene coupling partner **6** was prepared by a two-step synthesis (Scheme 2). The iodo-substituted compound was chosen due to the better reactivity towards the oxidative addition by the active palladium catalyst thereby compensating the higher costs. Firstly, *p*-aminobenzonitrile was oxidized with Oxone® in a two-phase reaction with water/DCM to give 4-nitrosobenzonitrile **5** in 95% yield (Scheme 2) as previously described by us.[25] Subsequent condensation of the latter with *p*-iodoaniline in acetic acid afforded azobenzene **6** as an orange solid in 86% isolated yield.

For the Sonogashira-coupling reaction the optimal conditions were screened by a model reaction using azobenzene **6** and trimethylsilylacetylene.[26]

Table 1
Model Sonogashira-reactions with azobenzene **6** and TMSA



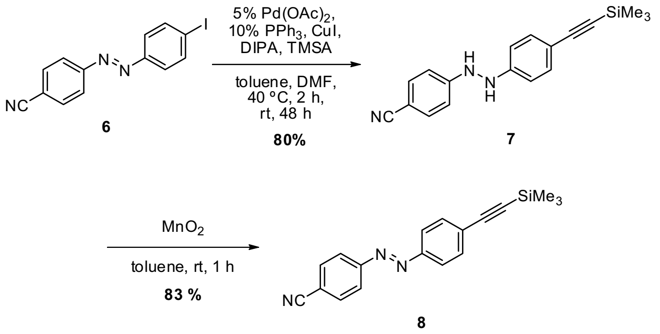
Entry	Cat./ligand	Conditions	(%)[a]
1	3% $Pd(PhCN)_2Cl_2$, 6% $[(t\text{-}Bu)_3PH]BF_4$	2% CuI, DIPA, dioxane, 8 h at 40 °C, 12 h at rt	60
2	3% $Pd(PPh_3)_2Cl_2$, 10% PPh_3	5% CuI, NEt_3, THF, 18 h at 45 °C	24
3	3% $Pd(PPh_3)_4$	5% CuI, NEt_3, THF, 18 h at 45 °C	42
4	5% $Pd(PPh_3)_2Cl_2$, 10% PPh_3	10% CuI, NEt_3, toluene, DMF, 18 h at 50 °C	76
5	5% $Pd(OAc)_2$, 10% PPh_3	10% CuI, NEt_3, toluene, DMF, 18 h at 50 °C	68[b]
6	10% $Pd(PPh_3)_4$	10% CuI, NEt_3, toluene, DMF, 18 h at 50 °C	87
7	5% $Pd(OAc)_2$, 10% PPh_3	5% CuI, DIPA, toluene, DMF, 2 h at 40 °C, 48 h at rt	80[c]

[a] Conversion to azobenzene **8** determined by ^1H NMR.
[b] 1:1 mixture of azobenzene **8** and hydrazine **7**.
[c] Isolated yield of hydrazine **7**.

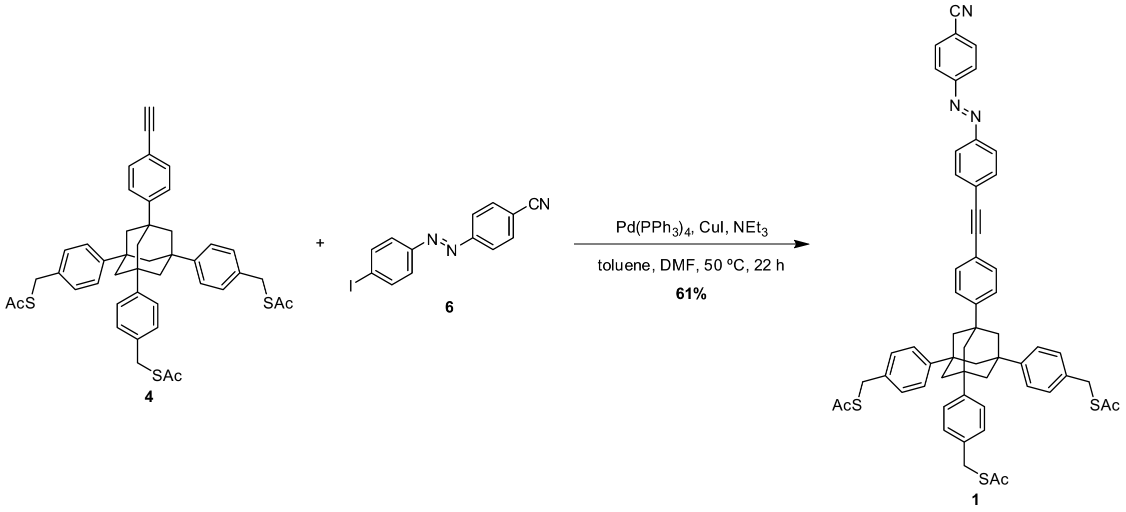
By using standard Sonogashira-conditions in THF only a low conversion of azobenzene **6** could be monitored (Table 1, entries 1 and 2).[26] Even with bulky electron-rich phosphine ligands, successfully applied by Fu[27] for the coupling of arylhalides, only a moderate conversion of the starting material was detected. Interestingly, with $Pd(OAc)_2$ and triphenylphosphine as ligand coupling and the reduction of the azo-functionality gave hydrazine **7** in 80% isolated yield (Table 1, entry 7). While the reduction of stabilized azo-compounds with electron-withdrawing groups (DEAD, DIAD) is easily induced by triphenylphosphine, there are only few and less detailed publications about the reduction of azoarenes under Sonogashira-coupling conditions.[28] However, for entry 7 (Table 1) triphenylphosphine was used in catalytic amounts only. Thus, a catalytic activation of the azo-functionality by the palladium center is another reasonable suggestion.[29] A comparable transformation of azoarenes to hydrazines published by Muniz occurs with a (bathocuproine)palladium complex and acetic acid in DCM. Apparently, in the coupling and reduction of **6** furnishing **7**, trimethylsilylacetylene can act as a proton donor. It must be noted that the reduction of the N=N double bond also easily occurs in the presence of free thiols and moisture,[23] or in the presence of a variety of transition metals.[30] Anyhow, under the Sonogashira conditions employed, the reducing reagent is not clearly identified yet and thus more detailed examinations are necessary. However, the hydrazine was easy transferred to the azobenzene by oxidization with manganese dioxide in 83% yield (Scheme 3). Fortunately, azobenzene **8** was obtained with 10 mol % $Pd(PPh_3)_4$ in a toluene/DMF mixture at 50 °C (Table 1, entry 6) with 87% conversion by avoiding the use of $Pd(OAc)_2/PPh_3$. Analogously, the tripodal linker **4** was reacted with azobenzene **6** in 22 h to yield the final photoswitch-linker-conjugate **1** in 61% after work-up and purification by flash chromatography (Scheme 4).[33]

Photoisomerization of azobenzenes **6** and **1** can be achieved by illumination with light and was investigated by UV/vis spectroscopy.[34]

The UV/vis spectra of the azobenzene-linker-conjugate **1** in the trans-state and of the cis-/trans-mixture in the photo-stationary state (pss) were compared to the



Scheme 3. Formation of hydrazine **7** and subsequent oxidation to azobenzene **8**.



Scheme 4. Synthesis of the azobenzene-linker-conjugate **1** by Sonogashira-coupling.

corresponding spectra of azobenzene **6** (Fig. 2). The spectra of *trans*-azobenzene **1** in DCM ($c = 2.63 \times 10^{-5}$ mol/L) shows an intense absorption maximum at $\lambda_{max} = 376$ nm that corresponds to the π–π* transition band, which is red shifted by 31 nm with respect to the iodo-substituted compound **6**, due to the more extended π conjugation (see Table 2 for the data of both the compounds). The n–π* transition band of **1** is overlapped by the π–π* band in contrast to the two separated bands observed for compound **6**. The considerable increase of absorption below $\lambda = 270$ nm and the shoulder at about $\lambda = 288$ nm can be assigned to the ethynylene–phenylene backbone.

The quotient-functions of azobenzene **6** and azobenzene **1** attain their maxima at $\lambda = 364$ nm and $\lambda = 395$ nm, respectively. Irradiation of azobenzene **1** with vis light (405 nm used instead of 395 nm) causes an appreciable decrease and hypsochromic shift of the π–π* transition band and a simultaneous increase of the shoulder at around $\lambda = 288$ nm. The corresponding pss was reached within minutes. Isomerisation of *trans*-**6** to *cis*-**6** occurs via the irradiation of 365 nm light on a similar timescale with a blue-shift of the transition band from $\lambda = 345$ to $\lambda = 302$ nm. Due to the clear separation of the n–π* and π–π* bands also an increasing absorption at $\lambda = 440$ nm was observed.

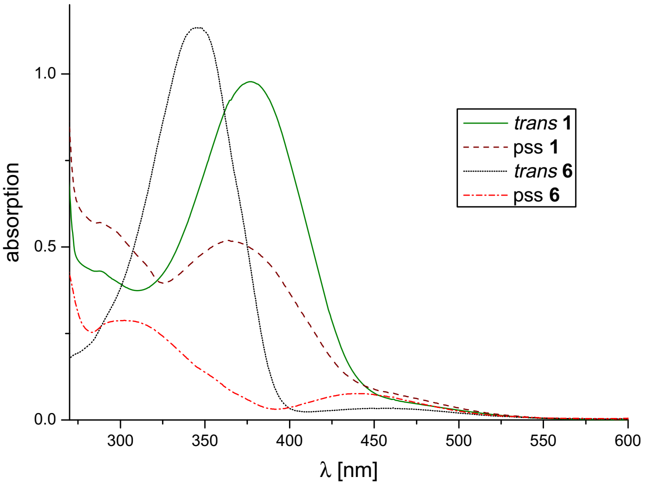


Fig. 2. UV/vis absorption spectra of azobenzenes **6** (trans = dotted line, pss = dashed-dotted line, $c = 3.88 \times 10^{-5}$ mol/L) and **1** (trans = solid line, pss = dashed line, $c = 2.63 \times 10^{-5}$ mol/L) in DCM.

Table 2
UV/vis data of the azobenzenes and rates of thermal back reaction in DCM at 25 °C

	$\lambda_{max,trans}$ (nm) (ε)[a]	$\lambda_{max,pss}$ (nm) (ε)[a]	λ_{iso} (nm)	k_{rev} (min^{-1})	$t_{1/2}$ (h)
6	345 (29219)	302 (7407), 440 (197)	288, 400	6.01×10^{-4}	19.2
1	376 (37167)	288 (21670), 364 (19726)	320, 444	2.70×10^{-3}	4.28

[a] [$dm^3mol^{-1}cm^{-1}$].

Without light cis-isomers of azobenzenes slowly revert back to the thermodynamic more favorable trans-isomers (shown in Fig. 3). Both spectra show two isosbestic points at $\lambda = 288$ nm and $\lambda = 400$ nm for azobenzene **6** and at $\lambda = 320$ nm and $\lambda = 444$ nm for azobenzene **1**, indicating a clear conversion of the isomers into each other without the formation of side products. By monitoring the change of absorption at the optimal irradiation wavelength during the relaxation, the kinetic of the process was determined.

Thereby first-order characteristics were found for the thermal backreactions. The obtained time constants are shown in Table 2 for each azo-compound, indicating that the half-life time of the conjugated azobenzene **1** is by a factor of 5 smaller than the half-life time of azobenzene **6**. The results are in agreement with the data published for systems with analogous π-conjugation.[31]

In conclusion, an azobenzene-linker-conjugate with acetate protected thiol anchoring groups to address gold surfaces has been synthesized from the corresponding iodo-substituted azobenzene **6** and the ethynylene-linker

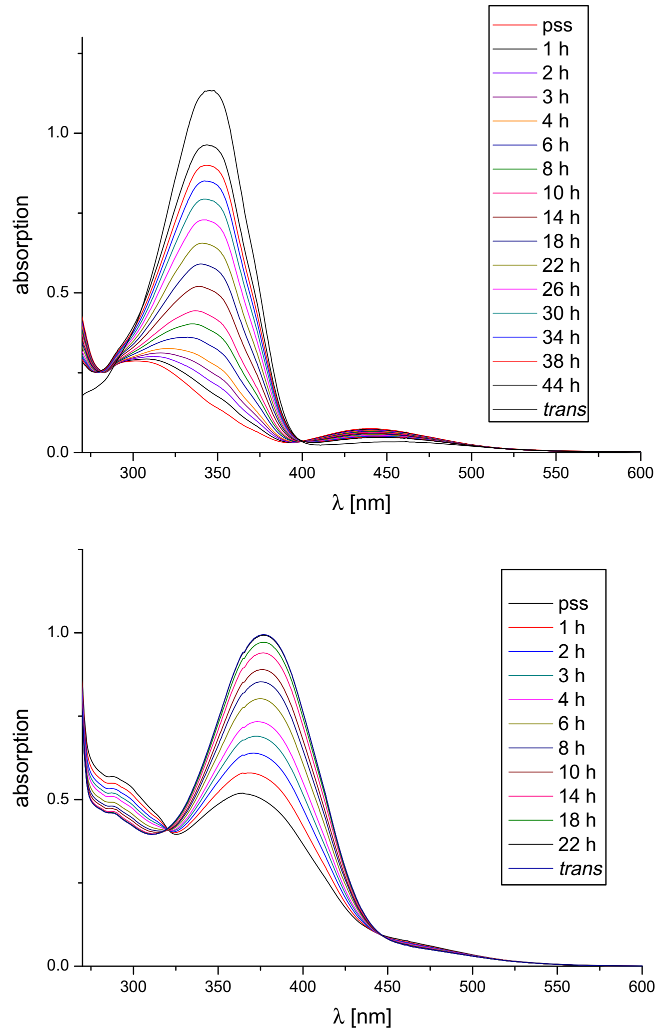


Fig. 3. Thermal relaxation of azobenzenes **6** (top, $c = 3.88 \times 10^{-5}$ mol/L) and **1** (bottom, $c = 2.63 \times 10^{-5}$ mol/L) measured in DCM at 25 °C.

precursor **4** by Sonogashira-cross-coupling. The UV/vis data and the photochromic properties of the synthesized azobenzene **1** in solution have been determined and discussed in comparison to precursor **6**.

Acknowledgements

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Supplementary data

The synthesis and complete characterisation (^{1}H NMR, ^{13}C NMR, mp, R_f, MS, HRMS, IR, copies of ^{1}H, ^{13}C); UV/vis absorption spectra and graphical determination of the half-life time of **1** and **6** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.086.

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32. *4-(((E)-4-(4-(3,5,7-Tris(4-(acetylthiomethyl)phenyl)adamantane-1-yl)-phenylethynyl)phenyl)diazenyl)benzonitrile* (**1**): In a flask, azobenzene **6** (99.6 mg, 299 μmol), tetrakistriphenylphosphine palladium(0) (28.8 mg, 24.9 μmol) and copper(I) iodide (2.72 mg, 24.9 μmol) were dissolved in a degassed mixture of toluene and DMF (2:1, 4 mL) under nitrogen atmosphere. Then tripod **4** (182 mg, 249 μmol) dissolved in the same solvent mixture (4 mL), and triethylamine (0.5 mL) was added via a syringe and the reaction mixture was stirred at 50 °C for 12 h. Then the same amount of palladium-catalyst was added, and stirring at 50 °C was continued until no further conversion could be detected (TLC monitoring, 10 h). The mixture was poured into water (20 mL) and the aqueous layer was separated and extracted with ethyl acetate (30 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by flash chromatography

on silica gel (DCM/hexane 3:1) to give the trans-isomer of azobenzene **1** (142 mg, 152 μmol, 61%) as a red solid. Mp 144 °C; R_f: 0.57 (DCM/hexane/acetonitrile 4:1:0.01); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, $J = 8.7$ Hz, 2H), 7.94 (d, $J = 8.6$ Hz, 2H), 7.82 (d, $J = 8.9$ Hz, 2H), 7.68 (d, $J = 8.7$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 6H), 7.28 (d, $J = 8.3$ Hz, 6H), 4.11 (s, 6H), 2.35 (s, 9H), 2.12 (s, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 195.3, 154.6, 151.5, 150.3, 148.3, 135.6, 133.4, 132.6, 131.9, 129.0, 127.6, 125.4, 125.4, 125.3 123.6, 120.7, 118.6, 114.2, 93.0, 89.0, 47.2, 39.6, 39.2, 33.1, 30.5; IR (ATR): 3090 (w), 3052 (w), 3027 (w), 2998 (w), 2920 (m), 2897 (w), 2849 (w), 2226 (w), 2212 (w), 1912 (w), 1688 (vs), 1595 (m), 1511 (m), 1448 (w), 1410 (m), 1354 (s), 1132 (s), 1102 (m), 1018 (w), 957 (m), 852 (m), 838 (m); MS (FAB) *m*/*z* (%): 934 (<1, M^+), 391 (17), 149 (100). MS calcd for $C_{58}H_{51}N_3O_3S_3$ 934.2, found 934; Anal. Calcd for $C_{58}H_{51}N_3O_3S_3$: C, 74.57; H, 5.50; N, 4.50. Found: C, 74.09; H, 5.44; N, 4.59.

34. Due to the fact that both isomers show an absorption over the whole spectral bandwidth, continuous illumination always leads to mixtures. Hence, it is not possible to convert either isomer quantitatively into the other by activation with light. However, the composition of the isomers in the pss can be varied by changing the irradiation wavelength.[1] The highest ratio of either isomer in the corresponding pss is obtained at a wavelength at which the quotient of the corresponding extinction coefficients is maximized. The best wavelength can be evaluated, for example, by dividing the UV/vis spectra of the trans-isomer by the spectra of the cis-/trans-mixture in the pss. The maximum of the resulting function indicates the optimal irradiation wavelength for the trans- to cis-photoisomerisation.