DOI: 10.1002/chem.201002671

Synthesis and Isomerization Studies of Cyclotrisazobiphenyl

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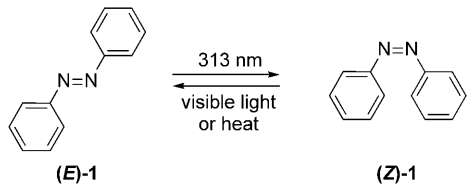
Abstract: We report an efficient synthesis of cyclotris[(*E*)-3′-(biphenyl-3-yldiazenyl)] compounds (CTBs). An unsubstituted CTB molecule is accessible in four steps in 10% yield overall, whereas a hexa(methoxymethyl ether) CTB analogue was prepared in nine steps (26% yield). The final macrocyclization step was accomplished in up to 80% yield by using a metal-template effect. Furthermore, the photochromic properties were investigated, and all four isomers were detected and characterized by NMR spectroscopy. A strong influence from the solvent and the irradiation wavelength on the switching process was observed. Irradiation in pyridine yielded the highest amount of the all-*Z* isomer in the photostationary state. For a full conversion to the all-*E* isomer, the reaction has to be heated to 45°C. The isomerization to the all-*E* isomer is slow at room temperature, with a half-life time of the all-*Z* isomer of more than nine days in dimethyl sulfoxide (DMSO). Conditions were established to access each possible isomer as the major component in the photostationary state.

Keywords: azobenzene · macrocycles · molecular devices · photochromism · template synthesis

Introduction

Molecular switches offer the unique opportunity to control the spatial arrangement of compounds on the molecular level.[1] Out of the many photochromic structures known, the azobenzene scaffold offers many advantages.[2] On switching by UV irradiation from the *E* to *Z* isomer, the molecule undergoes a drastic reduction in length by approximately 7 Å (Scheme 1). Switching is reversible with heat or light, mostly without degradation of the system; both the isomers are fairly stable under ambient conditions; and the switching properties are adjustable by the attachment of suitable substituents. Therefore, the azobenzene switch has been used for a variety of applications, thus showing its enormous potential.[3] This structural theme has been incorporated in photoresponsive host–guest systems,[4] such as azobenzene-containing cages[5a] and catenanes.[5b] In addition, the activity of catalysts containing an azobenzene moiety was switched on and off.[6] Furthermore, azobenzene compounds are a common tool in biochemistry to control the orientation of peptides and influence their folding.[7] Even further, an azobenzene switch was used to direct neuronal activity.[8] Recently, the azobenzene unit has been heavily used in the area of materials chemistry;[3b,c] applications range from the incorporation of azobenzene compounds into polymers[9] to immobilization on surfaces.[10] As an example for the latter case, surfaces with controllable wettability were produced.[11]



Scheme 1. Isomerization of the azobenzene switch.

However, most of the azobenzene compounds that are used for specific applications, are based on one single azobenzene entity. Although oligomers of conjugated azobenzene compounds were already prepared over 60 years ago by Ruggli et al.,[12] there is only one report of the photochemical properties of a *para*-bis(azobenzene) and a *meta*-bis(azobenzene) derivative.[13] Considerable influence of the second azobenzene unit has been observed: although in the case of the *para* derivative the $E \rightarrow Z$ quantum yield is only approximately 0.02 with 13% of isomerization detected, for the *meta* derivative the quantum yield per azobenzene unit is actually higher than in the parent azobenzene ($\Phi = 0.12$) in which 79% of the *E*,*E* isomer was converted into the *Z*,*Z* isomer. At present, the *ortho* derivative has not been examined.

Recently, the preparation of different macrocycles[14] containing multiple azobenzene units has been presented (Scheme 2).[15] Contrary to the linear analogues, in some cases the *Z* isomer constitutes the more stable form. Tamaoki and co-workers beautifully characterized all three possible isomers of cyclobisazobiphenyl **3** by X-ray analysis.[16] The high stability of the *Z* isomer is often ascribed to the

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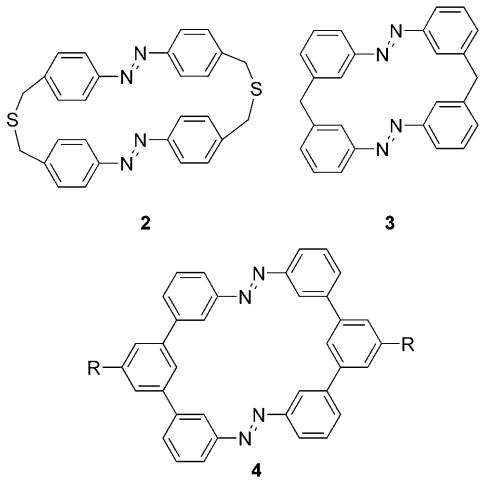
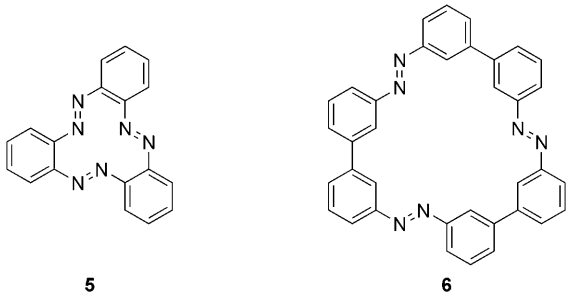
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem201002671.



Scheme 2. Examples of azobenzene-containing macrocycles by Rau,[15a] Tamaoki,[16] and Mayor[15c] **2**–**4**, respectively.

macrocyclic ring strain. The same group also reported the preparation of macrocycles containing more than two azo moieties through an unselective reductive cyclization of dinitro aryl compounds.[17] They also investigated the photoisomerization of a [2$_3$](4,4′)azobenzophane by HPLC and identified four relatively stable isomers.[17c] Their studies also showed that the photoisomerization proceeds consecutively, namely, *E*,*E*,*E*→*E*,*E*,*Z*→*E*,*Z*,*Z*→*Z*,*Z*,*Z*.

Even though some approaches by N=N bond formation as the final cyclization were developed for the synthesis of such macrocycles, this step usually poses a problem in the preparation. Macrocyclization reactions are typically performed under high dilution conditions and produce only low yields most of the time. Due to these preparative drawbacks, most of the known azobenzenophanes possess only two azobenzene bridges, which are connected by alkyl linkers.[17] The introduction of additional azo units further increases the complexity of the synthesis and the photochemistry. The smallest possible macrocycle containing more than two azobonds, that is, cyclotrisazobenzene **5**, was first reported by Dreiding and co-workers (Scheme 3).[18] However, the authors did not comment on the photochemical properties. We have recently shown that cyclotrisazobenzene compounds are accessible in good yields through a different route.[19] As

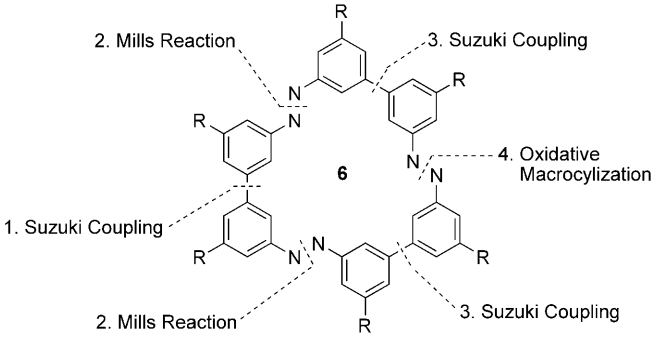


Scheme 3. Cyclotrisazobenzene **5** and CTB **6**.

expected, these molecules do not isomerize, probably due to the ring strain induced in the isomerization process. Hence, we designed a larger member of the macrocyclic trisazoaromatic family, namely, cyclotris[(*E*)-3′-(biphenyl-3-yldiazenyl)] (CTB) **6**. In this case, the strain during isomerization is greatly minimized due to the larger diameter of the structure and the flexibility around the biphenyl bond. Such a system should undergo a dramatic three-dimensional change in an isomerization reaction. The all-*E* isomer will adopt a flat arrangement while isomerization will force the molecule to deviate from planarity and span a three-dimensional cavity. Additionally, the influence of the cyclic design on the photochemical properties of each azobenzene unit will be highly interesting and will further contribute to the understanding of the nature of multi-azobenzene switches.

Results and Discussion

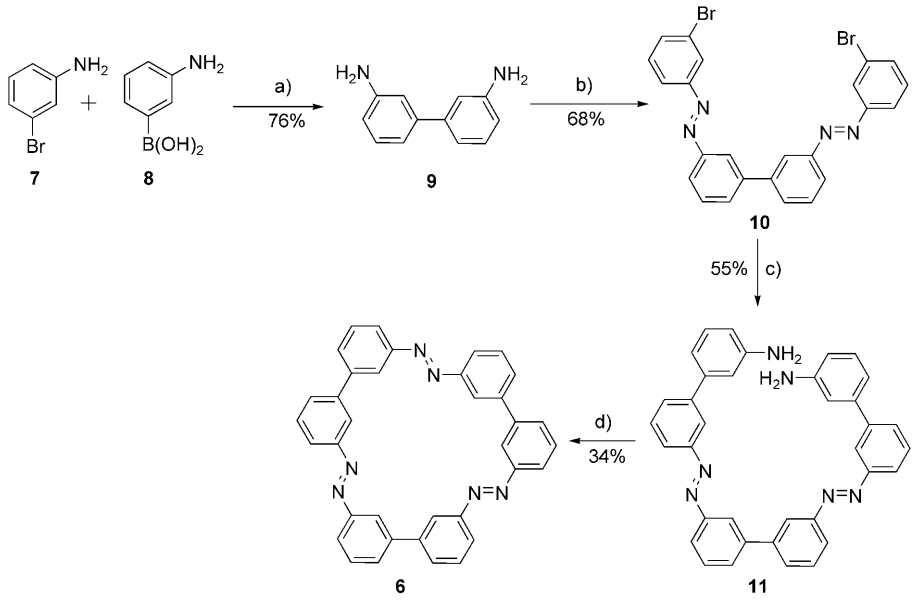
Synthesis: The target structure consists of three biphenyl units connected at the 3-position by an azo bridge. In our prior synthesis of cyclotrisazobenzene, an aromatic diamine core was elongated by a modified Mills reaction developed in our laboratory. The strategy for the preparation of CTBs was adapted for the larger target molecule (Scheme 4). It



Scheme 4. Retrosysnthesis of CTB.

was decided to build up a biphenyl core and elongate it on both sides by one benzene unit by using the Mills reaction. A Suzuki reaction was envisioned to prepare a trisbiphenyl–bisazo chain that bears two neighbouring amino groups. This linear precursor would be closed by an oxidative macrocyclization reaction.

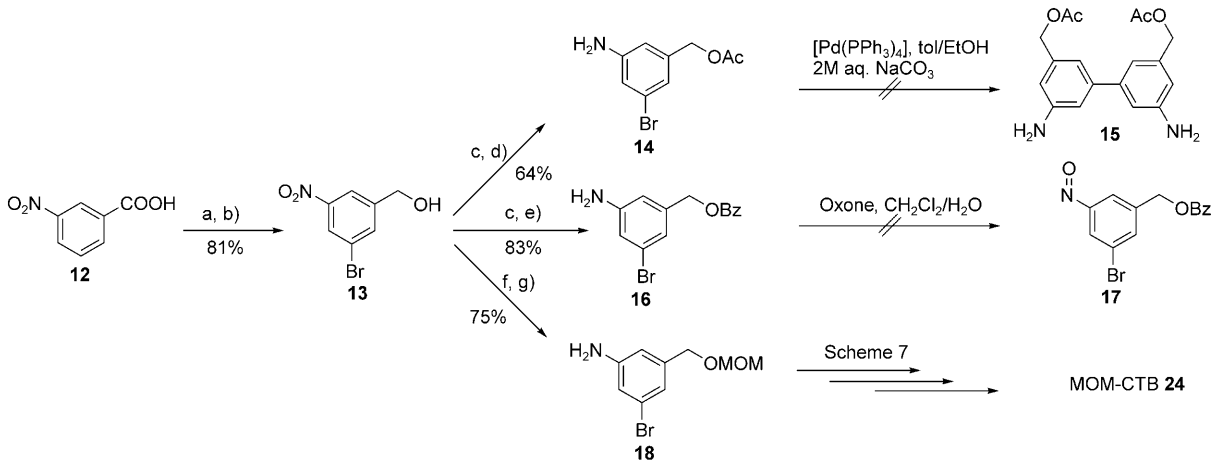
The synthesis of the parent unsubstituted CTB started with 3-bromoaniline (**7**) and the corresponding 3-aminophenyl boronic acid (**8**; Scheme 5). Although, the latter is also commercially available, it can also be conveniently prepared from the corresponding bromo compound **7** by a Miyaura borylation reaction.[20] Suzuki coupling of **7** and **8** provided 3,3′-bisaminobiphenyl (**9**),[21] which had now been elongated under our modified Mills conditions. The required nitroso coupling partner can be easily obtained by using a method reported by Priewisch and Rück-Braun (oxone in a



Scheme 5. Synthesis of the unfunctionlized parent CTB **6**. Reagents and conditions: a) $[Pd(PPh_3)_4]$, Na_2CO_3, toluene/EtOH/H_2O (65:5:2.5; 76%); b) 3-bromonitrosobenzene, AcOH (68%); c) **8**, $[Pd(PPh_3)_4]$, Na_2CO_3, toluene/EtOH/H_2O 65:5:2.5; 3 h (55%); d) $Pb(OAc)_4$, NEt_3, THF (34%).

two-phase system of CH_2Cl_2/water).[22] After installing two of the three azo units, the chain was further extended by using a Suzuki coupling reaction with building block **10**. Although it is known that Pd can interact with the azo functionality,[23] bisaminoazobiphenyl **11** can be obtained in good yield. With all the carbon atoms in place, the most difficult step, that is, the macrocyclization reaction, was attempted. Surprisingly, the azomacrocycle was obtained under our optimized conditions in 34% yield. The $Pb(OAc)_4$ complex seems not only to act as an oxidant, but also facilitates the macrocyclization as a template by coordinating to the nitrogen atoms. Analysis of the crude reaction mixture by MALDI-MS clearly showed that the macrocycle contained Pb. Therefore, the workup was modified by treating the reaction mixture with a solution of ethylenediaminetetraacetic acid (EDTA). Unfortunately, macrocycle **6** is insoluble in most common solvents, except CS_2, thus prohibiting proper purification and making it difficult to work with.

Hence, a second-generation synthesis was planned, which included solubilizing chains on the core macrocycle. The general strategy was in accordance with the one developed for the parent system **6**. We learned from our studies on cyclotrisazobenzene that direct alkoxy substitution on the aromatic portions causes difficulties in the final oxidative macrocyclization. Consequently, a benzylic alcohol was chosen as the functionality attached; that way, the alcohol offers a multitude of possibilities for further functionalization without interfering with the synthesis. A well-reasoned protection strategy must be used to decrease the polarity of the macrocycle and aid purification compatible with the reaction conditions. Based on the success in our synthesis of cylotrisazobenzene, the acetate protecting group was used first (Scheme 6). The preparation of the bromo and boronic acid building blocks proceeded in good yield overall. However, this acetyl ester was cleaved during the Suzuki reaction to install the biphenyl unit, probably by the carbonate base. In

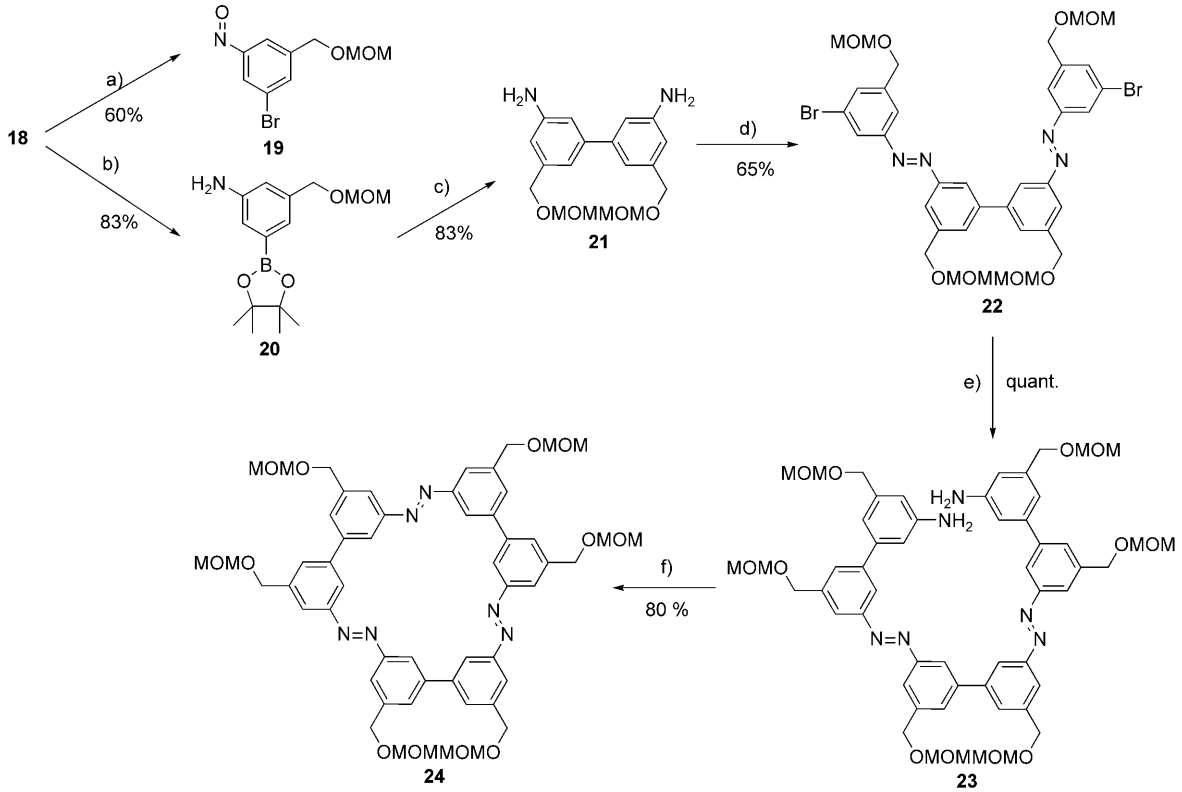


Scheme 6. Screening of different protecting groups. Reagents and conditions: a) NBS, H_2SO_4, 60°C, 20 h (83%); b) $BH_3{\cdot}SMe_2$, THF, 60°C, 3 h (99%); c) $SnCl_2{\cdot}2H_2O$, EtOH, 60°C, 1 h (99%); d) Ac_2O, DMAP, Et_3N, CH_2Cl_2 (64%); e) benzoic acid anhydride, DMAP, Et_3N, CH_2Cl_2 (83%); f) methyl chloromethyl ether, $N(iPr)_2Et$, CH_2Cl_2, room temperature, 3 h (90%); g) Fe, AcOH, 100°C, 1 h (83%). DMAP = *N*,*N*-dimethylaminopyridine, NBS = *N*-bromosuccinamide.

a second attempt, a benzoate compound was chosen that exhibits an increased base stability.[24] Although the Suzuki reaction smoothly gave the desired biphenyl moiety, the oxidation to nitroso compound **17** was very slow and unselective. A similar result was obtained by employing a triisopropylsilyl ether as a protecting group. It turned out that the preparation of the nitroso compound, a crucial step in the synthesis, was highly dependent on the choice of the protecting group.

Finally, the methoxymethyl (MOM) ether group was chosen, thus requiring the protected 3-amino-5-bromobenzylic alcohol **18** as the basic building block for our synthesis. This compound was prepared in four steps by bromination of 3-nitrobenzoic acid (**12**),[25] reduction of the carboxylic acid,[26] protection of the resulting alcohol as a MOM ether,[27] and a Bechamp reduction of the nitro group (Scheme 6).[28] The overall yield was 61% over four steps. Building block **18** was converted into boronic ester **20** by a Miyaura reaction (Scheme 7).[20] The nitroso compound **19** was also prepared from the same starting material by using the protocol of Priewisch and Rück-Braun.[22] The modified Mills reaction quantitatively introduced the next two aryl units with the required bromine functions for the upcoming cross-coupling reaction. A Suzuki coupling with boronic ester **20** gave the desired diamine **23** in excellent yield. Yet despite extensive efforts toward purification by using different chromatographic methods, we could not obtain **23** in a pure form suitable for elementary analysis. The ^{1}H NMR spectroscopy showed, among other things, solvent impurities, which were not removable.[29] However, the impurities did not affect the final macrocyclization reaction, as a high yield of 80% of **24** was obtained in this step. The cyclization was again performed with $Pb(OAc)_4$ as the oxidant for the parent unsubstituted case. As before, Pb seems to act as a template to pre-coordinate the linear precursor and facilitate macrocyclization. The lower yield for the parent macrocycle **6** might be attributed to the low solubility. Substituted macrocycle **24** was easily purified by simple column chromatography. In general, this method constitutes a powerful protocol for the oxidative cyclization of diamines to azobenzenophanes.

Isomerization studies: The absorbtion spectra of macrocycles **6** and **24** show the typical characteristics of an azobenzene compound. The π–π* transition encounters a slight bathochromic shift relative to azobenzene itself, thus resulting in an absorption maximum at $\lambda_{max}=313$ and 317 nm for **6** and **24**, respectively. Upon irradiation of both macrocycles at $\lambda=365$ nm, the maximum absorption at $\lambda_{max}=320$ nm decreased and a second maximum absorption at around $\lambda_{max}=430$ nm increased in intensity (Figure 1). Additionally, the maximum absorption at $\lambda_{max}=251$ nm shifts to $\lambda_{max}=243$ nm



Scheme 7. Synthesis of MOM-CTB **24**. Reagents and conditions: a) oxone, CH_2Cl_2/H_2O, room temperature, 5 h (60%); b) bis(pinacolato)diboron, [Pd(dppf)Cl_2·CH_2Cl_2, KOAc, DMF 100 °C, 2 h (83%); c) **18**, [Pd(PPh_3)$_4$], K_2CO_3, THF/H_2O, 80 °C, 19 h (83%); d) **19**, AcOH, room temperature, 20 h (65%); e) **20**, [Pd(PPh_3)$_4$], K_2CO_3, THF/H_2O, 100 °C, 20 h (quant.); f) $Pb(OAc)_4$, NEt_3, THF, room temperature, 3 h (80%). dppf = 1,1′-bis(diphenylphosphino)ferrocene.

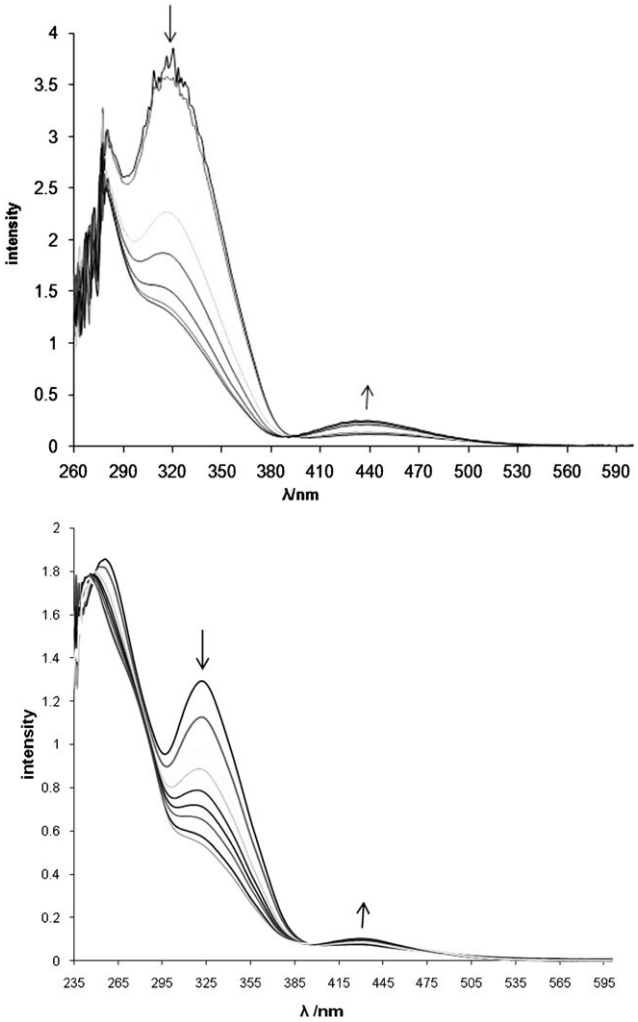


Figure 1. UV/Vis spectrum and isomerization of the parent macrocycle CTB **6** (2×10^{-5} mol L^{-1}) in benzene (top) and MOM-CTB **24** (1×10^{-5} mol L^{-1}) in chloroform (bottom).

in the process for macrocycle **24**. On the contrary to the cyclotrisazobenzene compounds, the CTBs underwent isomerization smoothly, as predicted by our rationalization. However, as there are three azo bonds, the UV spectrum does not give any information about which azo bond is isomerized and to which degree. Due to the low solubility of the parent macrocyle **6** all the following studies were only performed on the MOM-protected CTB **24**.

A more detailed picture of the isomerization reaction can be obtained by ^{1}H NMR spectroscopic measurements. Macrocycle **24** undergoes stepwise isomerization and, ultimately, four different isomers are present in the photostationary state (PSS) (Figure 2). The all-*E* and all-*Z* isomers exhibit a higher grade of symmetry (C_3) than the mixed isomers. In these isomers, all the protons of the different benzene rings have the same chemical environment; therefore, only three different signals were observed. On the other hand, the mixed isomers possess only one symmetry plane and as a

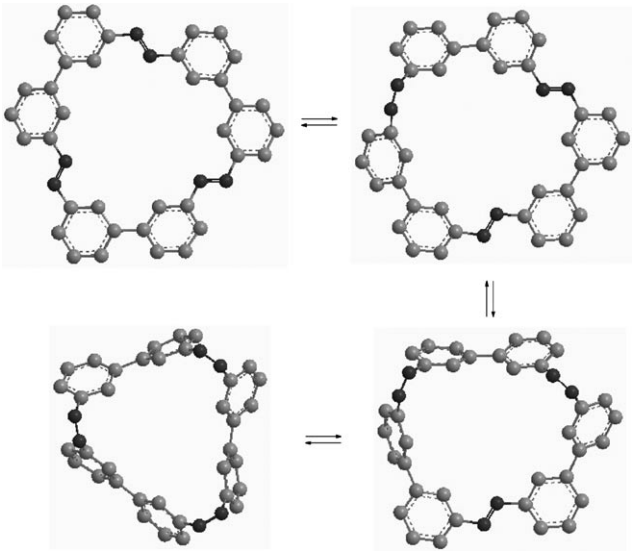


Figure 2. MM2 simulation of all four different isomers of CTB **6**.

result nine different signals were detectable by ^{1}H NMR spectroscopic analysis. It was possible to assign all the different isomers in the mixture (Figure 3). After heating at 45 °C overnight, the macrocycle undergoes complete thermal *Z*→*E* isomerization, thus proving the reversibility of the process.

The PSS was measured after irradiation at $\lambda = 365$ nm for 20 hours in different solvents. The results showed a significant influence of the solvent on the ratio of the isomers in the PSS (Figure 4). Irradiation in chloroform, as a rather apolar solvent, was shown to be less efficient because less than half of the macrocycle was converted into the all-*Z* isomer.

Experiments carried out in more polar solvents, such as acetonitrile or dimethyl sulfoxide (DMSO), showed an enrichment of the all-*Z* isomer, and an even higher percentage of the fully isomerized species was detected in benzene. Because the all-*E* isomer should have the lowest polarity as the sum of dipole moments should cancel out, isomerization should be favored in polar solvents. However, polarity can not explain the high ratio of the all-*Z* isomer/all-*E* isomer in benzene. Another stabilizing effect might be a host–guest interaction in the all-*Z* isomer. In this case, a solvent molecule could be enclosed by the all-*Z* macrocycles, which might exist in a bowl-shaped geometry. To prove such an effect, other aromatic solvents such as toluene and pyridine were screened. If a host–guest interaction were responsible for the stabilization of the all-*Z* isomer, the sterically more-hindered toluene should yield a smaller amount of the all-*Z* isomer. The degree of isomerization in toluene is slightly lower, thus supporting the proposed effect as at least one possible explanation. A solvation effect that has been similarly observed for calix[6]arenes can also be postulated as a reason for the stabilization.[30] Pyridine, as a polar aromatic solvent, yielded, in accordance with these results, the highest amount of the all-*Z* isomer.

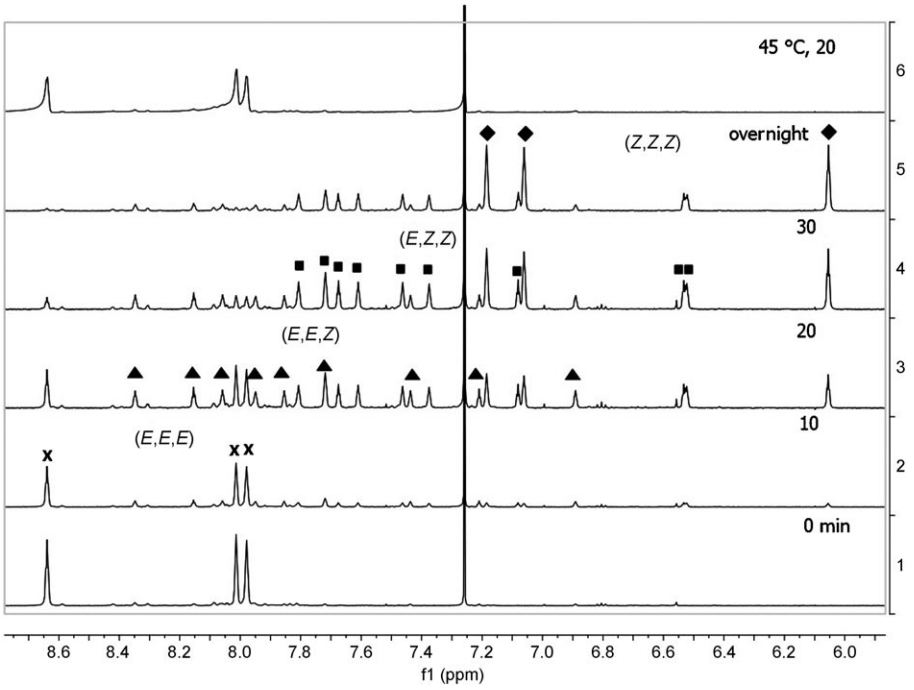


Figure 3. Isomerization of MOM-CTB **24** in $CDCl_3$ by irradiation at $\lambda = 365$ nm.

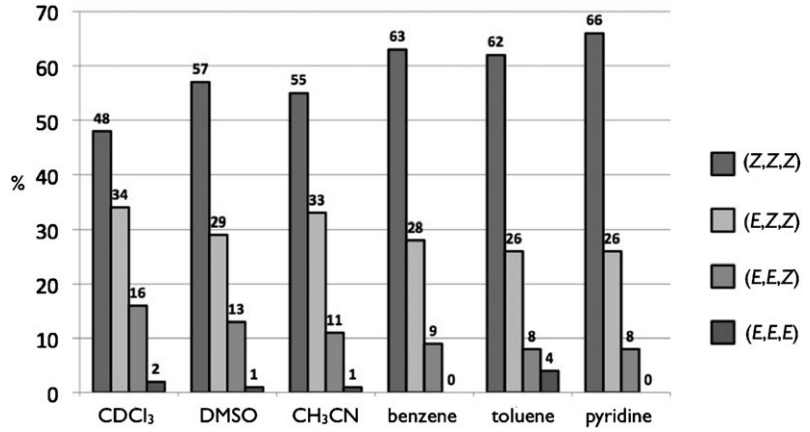


Figure 4. PSS of MOM-CTB **24** in different solvents.

The solvent effect could also be seen in the thermal $Z \rightarrow E$ back-isomerization reaction. The half-life time in chloroform of 4.7 days for the all-*Z* isomer was twice as much than in dimethyl sulfoxide (DMSO; $t_{1/2} = 9.4$ days).[31] The results are noteworthy because they show that the choice of solvent influences the isomerization behavior of macrocycle **24**. Azobenzene itself shows only a very slight solvent dependence of the reaction rate of the thermal $Z \rightarrow E$ isomerization.[32] However, the quantum yield for the $E \rightarrow Z$ photochemical isomerization reaction increases with increasing polarity of the solvent, whereas an opposite effect was observed for the $Z \rightarrow E$ isomerization reaction.[33]

Another set of experiments carried out was the irradiation of macrocycle **24** at different wavelengths. It is known that visible light and UV light of low wavelength facilitates photochemical $Z \rightarrow E$ isomerization. Usually, light with a wavelength of $\lambda = 450$ nm is used for this purpose. When a sample of the macrocycle, which was irradiated at $\lambda = 365$ nm until the PSS was reached, was irradiated with visible light (400 W halogen flood light), a fast and almost complete disappearance of the all-*Z* isomer accompanied by an increase in the all-*E* isomer was observed. However, the predominant isomer after prolonged isomerization was the *E*,*E*,*Z* isomer.

Irradiation at $\lambda = 254$ nm resulted in a similar picture (Figure 5). Yet, the all-*E* isomer was the most-abundant species under these conditions. Furthermore, the isomerization behavior at $\lambda = 306$ nm was investigated. At this wavelength, the PSS consists mainly of the *E*,*Z*,*Z* and *E*,*E*,*Z* isomers, with an overall majority of the azobenzene in the *E*,*Z*,*Z* conformation. With this knowledge, isomerization of the macrocycle can be controlled by choosing the appropriate solvent and wavelength for irradiation. Depending on the parameter, each of the four different isomers can be addressed separately and obtained as the major species in the mixture.

Conclusion

In summary, we have presented the first highly efficient synthesis of conjugated photochromic CTBs. The parent unsubstituted analogue **6** can be obtained in four steps in 10% overall yield, whereas the MOM-protected CTB **24** is accessible in nine linear steps with an overall yield of over 26%. It is especially of note that in the final macrocyclization reaction the oxidant $Pb(OAc)_4$ also acts as a template for the ring formation. Under the irradiation conditions, both macrocycles underwent isomerization smoothly. For the MOM-protected CTB **24**, all four different isomers were assigned by NMR spectroscopy. It was also shown that by changing crucial parameters, such as solvent or irradiation wave-

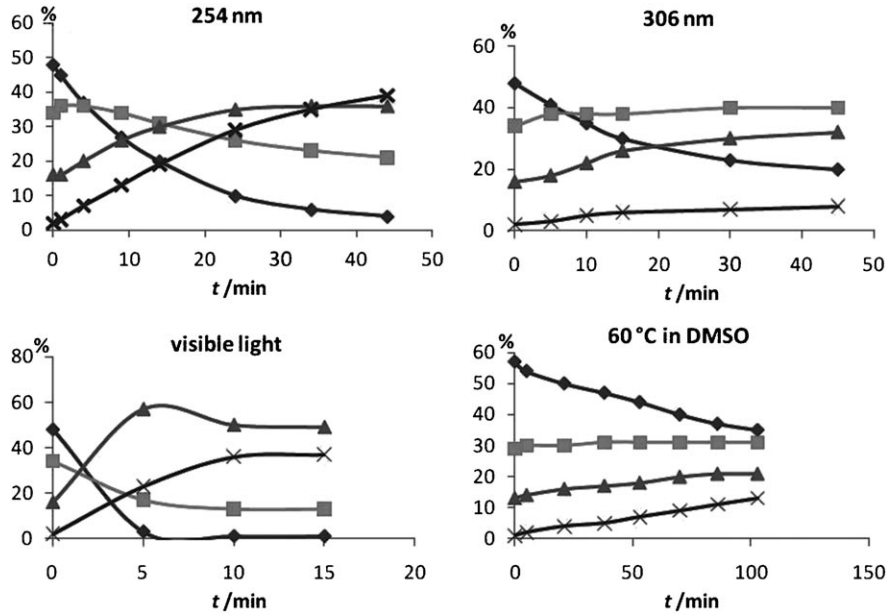


Figure 5. Proportions of different MOM-CTB isomers after irradiation with different light sources: ×=*E,E,E* isomer; ▲=*E,E,Z* isomer; ■=*E,Z,Z* isomer; ◆=*Z,Z,Z* isomer.

length, the ratio of the different isomers in the PSS could be controlled. Future work will focus on exploitation of this phenomenon in the design of molecular grippers and multi-photochromic storage devices.

Experimental Section

Bisazodiamine 11: 3-Bromonitrosobenzene (1.63 g, 8.76 mmol, 2.50 equiv) was added to a solution of 3,3′-diaminobiphenyl (**9**; 646 mg, 3.50 mmol, 1.00 equiv) in acetic acid (50 mL). The suspension was stirred overnight and a precipitate formed, which was collected by filtration and taken up in CH_2Cl_2. After drying over $MgSO_4$ and removal of the solvent, the residue was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2 1:1) to yield dibromide **10** as an orange solid (1.24 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.25 (s; 2H), 8.10 (s; 2H), 7.94 (t, ^3J=8.7 Hz, 4H), 7.83 (d, ^3J=7.7 Hz; 2H), 7.64 (t, ^3J=7.9 Hz; 2H), 7.62 (d, ^3J=7.7 Hz; 2H), 7.43 ppm (t, ^3J=7.9 Hz; 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=153.9, 153.2, 141.8, 134.2, 130.9, 130.5, 130.2, 125.1, 123.6, 123.5, 122.8, 122.2 ppm.

A three-necked flask was charged with **10** (937 mg, 2.11 mmol, 1.00 equiv), 3-aminophenylboronic acid (**8**; 867 mg, 6.33 mmol, 3.00 equiv), [$Pd(PPh_3)_4$] (148 mg, 127 μmol, 6 mol%), and a solvent mixture of toluene/ethanol/2 M Na_2CO_3 (65:5:2.5, 72.5 mL). The reaction mixture was degassed with a stream of argon for 20 min before it was heated to 100 °C under argon for 20 h. The reaction mixture was cooled down and diluted with EtOAc and H_2O (3:1, 400 mL). The organic phase was washed with brine (100 mL) and dried over $MgSO_4$. After removal of the solvent, the residual brown oil was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to yield **11** as an orange solid (636 mg, 55%). M.p. 167–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s; 2H), 8.19 (s; 2H), 7.98 (d, ^3J=7.9 Hz; 4H), 7.93 (d, ^3J=7.9 Hz; 2H), 7.83 (d, ^3J=7.6 Hz; 2H), 7.71 (d, ^3J=7.6 Hz; 2H), 7.65 (t, ^3J=7.8 Hz; 2H), 7.58 (t, ^3J=7.8 Hz; 2H), 7.27 (t, ^3J=7.8 Hz; 2H), 7.10 (d, ^3J=7.6 Hz; 2H), 7.02 (s; 2H), 6.72 ppm (d, ^3J=7.7 Hz; 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=153.6, 153.4, 147.3, 142.8, 142.0, 141.8, 130.2, 130.14, 130.09, 130.07, 129.8, 122.5, 122.2, 122.13, 122.06, 118.1, 114.9, 114.3 ppm; MS (EI, 70 EV): *m/z* (%): 544 (61) $[M]^+$, 168 (100).

CTB 6: Freshly crystallized $Pb(OAc)_4$ (809 mg, 1.82 mmol, 2.30 equiv) dissolved in dry THF (12 mL) was added dropwise to a solution of 3,3′-diaminobisazobiphenyl (**11**; 432 mg, 739 mmol, 1.00 equiv) dissolved in dry THF (90 mL). After stirring overnight, (1.16 g), water (80 mL), and CH_2Cl_2 (80 mL) were added. The reaction mixture was stirred for 30 min, extracted with CS_2, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residual solid was washed with CH_2Cl_2 and acetone to obtain an orange powder (120 mg, 34%). M.p. >245 °C; ^{1}H NMR (400 MHz, CS_2/$CDCl_3$ 1:1): δ=8.68 (s; 6H), 8.00 (d, ^3J=7.9 Hz; 6H), 7.93 (d, ^3J=7.4 Hz; 6H), 7.65 ppm (d, ^3J=7.8 Hz; 6H); MS (EI, 70 EV): *m/z* (%): 540 (52) $[M]^+$, 481 (100); further characterization was not possible due to the insolubility of **6**.

1-Bromo-3-[(methoxymethoxy)-methyl]-5-nitrobenzene: A solution of 3-bromo-5-nitrobenzylic alcohol (**13**; 9.17 g, 39.5 mmol, 1.00 equiv) in CH_2Cl_2 (115 mL) was treated with diisopropylethylamine (20.6 mL, 119 mmol, 3.00 equiv) and with chloromethyl methyl ether (9.00 mL, 119 mmol, 3.00 equiv). After stirring for 3 h at room temperature, a nitrogen stream was bubbled through the reaction mixture for 15 min. The reaction was quenched by the addition of aqueous saturated NH_4Cl (50 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (hexane/EtOAc 5:1) of the residue yielded a pale-orange oil (9.82 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.29 (s; 1H), 8.17 (s; 1H), 7.84 (s; 1H), 4.75 (s, CH_2; 2H) 4.67 (s, CH_2; 2H), 3.42 ppm (s, CH_3; 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=149.2, 142.6, 136.5, 126.1, 123.2, 121.2, 96.6 (CH_2), 67.7 (CH_2), 56.1 ppm (CH_3); MS (FAB): *m/z* (%): 276 (5) $[M+2]^+$, 274 (4) $[M]^+$, 45 (100); elemental analysis calcd (%) for $C_9H_{10}BrNO_4$: C 39.15, H 3.65, N 5.07; found: C 39.27, H 3.78, N 5.13.

1-Bromo-3-[(methoxymethoxy)methyl]-5-aminobenzene (18): A solution of 1-bromo-3-[(methoxymethoxy)methyl]-5-nitrobenzene (9.50 g, 34.4 mmol, 1.00 equiv) in acetic acid (70 mL) was heated to 80 °C. Iron powder (10.5 g, 186 mmol, 5.40 equiv) was added slowly over 90 min with the temperature kept below 90 °C. After the addition was complete, the reaction was stirred for additional 30 min, diluted with water (200 mL), and extracted with *tert*-BuOMe (2×150 mL). The combined organic phases were washed with water (100 mL), dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Flash column chromatography of the residue on silica gel (hexane/EtOAc, 1:1) yielded **18** as a yellow oil (7.03 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.87 (s; 1H), 6.75 (s; 1H), 6.58 (s; 1H), 4.68 (s, CH_2; 2H), 4.46 (s, CH_2; 2H), 3.73 (bs, NH_2; 2H) 3.40 ppm (s, CH_3; 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=148.2, 141.4, 123.4, 120.9, 117.4, 113.2, 96.1 (CH_2), 68.7 (CH_2), 55.8 ppm (CH_3); MS (EI, 70 EV): *m/z* (%): 247 (21) $[M+2]^+$, 245 (22) $[M]^+$, 185 (100); elemental analysis calcd (%) for $C_9H_{12}BrNO_2$: C 43.92, H 4.91, N 5.69; found: C 43.80, H 5.03, N 5.67.

1-Bromo-3-[(methoxymethoxy)methyl]-5-nitrosobenzene (19): A solution of 1-bromo-3-[(methoxy)methyl]-5-aminobenzene (**18**; 2.53 g, 10.3 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) was treated with oxone (12.7 g, 20.6 mmol, 2.00 equiv) dissolved in water (200 mL). The reaction mixture was stirred at room temperature for 3 h, the organic layer was separated and washed with saturated aqueous NH_4Cl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and water (100 mL). After drying over $MgSO_4$ and removal of

the solvent, a dark-green oil was obtained, which was purified by column chromatography on silica gel (hexane/EtOAc 5:1) to yield **19** as a green oil, which crystallized in the freezer to form a brown solid (1.61 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s; 1H), 7.87 (s; 1H), 7.74 (s; 1H), 4.78 (s, CH_2; 2H), 4.74 (s, CH_2; 2H), 3.44 ppm (s, CH_3; 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4, 142.6, 136.7, 124.2, 121.6, 120.7, 96.6 (CH_2), 67.9 (CH_2), 56.1 ppm (CH_3); MS (EI, 70 EV): *m/z* (%): 259 (12) $[M]^+$, 45 (100); elemental analysis calcd (%) for $C_9H_{10}BrNO_3$: C 41.56, H 3.88, N 5.39; found: C 41.65, H 4.07, N 5.41.

Boronic ester 20: A three-necked flask was charged with 1-bromo-3-[(methoxymethoxy)methyl]-5-aminobenzene (**18**; 3.00 g, 12.2 mmol, 1.00 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (797 mg, 0.98 mmol, 8 mol%), bis(pinacolato)diboron (3.41 g, 13.4 mmol, 1.1 equiv), and potassium acetate (4.18 g, 36.6 mmol, 3.00 equiv). The flask was flushed with argon for 5 min and dry DMF (90 mL) was added with a syringe. After degassing the mixture with an argon stream for 20 min, the reaction mixture was stirred at 100°C for 1 h. After the reaction mixture had cooled, it was diluted with diethyl ether (150 mL) and washed with brine (50 mL) and water (50 mL). After drying over $MgSO_4$, removal of the solvent, and flash column chromatography on a short column of silica gel (hexane/EtOAc 1:1), **20** was obtained as a pale-brown oil (2.95 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s; 1H), 7.07 (s; 1H), 6.82 (s; 1H), 4.69 (s, CH_2; 2H) 4.52 (s, CH_2; 2H), 3.66 (bs, NH_2; 2H), 3.41 (s, CH_3; 3H), 1.33 ppm (s, CH_3; 12H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.1, 138.4, 124.4, 120.6, 117.4.6, 95.7 (CH_2), 83.7 [$C(CH_3)_2$] 69.1 (CH_2), 55.3 (CH_3), 24.9 ppm [$C(CH_3)_2$]; MS (FAB): *m/z* (%): 293 (66) $[M]^+$, 45 (100); elemental analysis calcd (%) for $C_{15}H_{24}BNO_4$: C 61.45, H 8.25, N 4.78; found: C 61.03, H 8.66, N 4.58.

5,5′-Bis[(methoxymethoxy)methyl]biphenyl-3,3′-diamine (21): A three-necked flask was charged with boronic ester **20** (1.34 g, 4.55 mmol, 1.10 equiv), 1-bromo-3-[(methoxymethoxy)methyl]-5-aminobenzene (**18**; 1.02 g, 4.14 mmol, 1.00 equiv), and $[Pd(PPh_3)_4]$ (145 mg, 0.12 mmol, 3 mol%) and flushed with argon. THF (200 mL) and aqueous K_2CO_3 (2M, 50 mL) were added to the reaction mixture, which was degassed with an argon stream for 20 min and stirred at 80°C overnight. The reaction was allowed to cool, and the organic layer was separated and washed with water and brine (100 mL). After drying over $MgSO_4$ and removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (EtOAc/hexane 3:1→5:1) to yield **21** as a yellow oil, which still contained residual EtOAc even after extensive drying under high vacuum (1.15 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s; 2H), 6.80 (s; 2H), 6.67 (s; 2H), 4.72 (s, CH_2; 4H) 4.55 (s, CH_2; 4H), 3.74 (bs, NH_2; 4H) 3.42 ppm (s, CH_3; 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.2, 143.0, 139.8, 117.6, 113.9, 113.7, 96.0 (CH_2), 69.5 (CH_2), 55.8 ppm (CH_3); MS (EI, 70EV): *m/z* (%): 332 (44) $[M]^+$, 272 (100).

Bisazodibromide 22: A solution of 5,5′-bis[(methoxymethoxy)methyl]biphenyl-3,3′-diamine (**21**; 967 mg, 2.91 mmol, 1.00 equiv) and 1-bromo-3-[(methoxymethoxy)methyl]-5-nitrosobenzene (**19**; 1.59 g, 6.11 mmol, 2.10 equiv) in acetic acid (70 mL) was stirred for 19 h at room temperature. The solvent was removed under reduced pressure and the black residue was purified by flash column chromatography on silica gel (hexane/EtOAc 3:1→3:2) to yield **22** as a red oil, which crystallized upon standing at room temperature (1.54 g, 65%). M.p. 86°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s; 2H), 8.03 (s; 2H), 7.96 (s; 2H), 7.92 (s; 2H), 7.84 (s; 2H), 7.65 (s; 2H), 4.81 (s, CH_2; 4H), 4.79 (s, CH_2; 4H), 4.77 (s, CH_2; 4H), 4.69 (s, CH_2; 4H), 3.48 (s, CH_3; 6H) 3.45 ppm (s, CH_3; 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.8, 153.4, 141.8, 141.7, 140.5, 133.1, 129.7, 124.5, 123.6, 122.3, 122.0, 121.6, 96.41 (CH_2), 96.39 (CH_2), 69.1 (CH_2), 68.4 (CH_2), 56.0 ppm (CH_3); MS (FAB): *m/z* (%): 817 (18) $[M+H]^+$, 45 (100); elemental analysis calcd (%) for $C_{36}H_{40}Br_2N_4O_8$: C 52.95, H 4.94, N 6.86; found: C 52.98, H 5.03, N 6.83.

Bisazodiamine 23: A three-necked flask was charged with boronic ester **20** (1.19 g, 4.07 mmol, 2.20 equiv), bisazodibromide **22** (1.51 g, 1.85 mmol, 1.00 equiv), and $[Pd(PPh_3)_4]$ (130 mg, 0.11 mmol, 6 mol%) and flushed with argon. THF (90 mL) and aqueous K_2CO_3 (2M, 23 mL) was added to the reaction mixture, which was degassed with an argon stream for 20 min and stirred at 80°C overnight. The reaction mixture was allowed to cool down and the organic layer was separated and washed with water and brine (50 mL). After drying over $MgSO_4$ and removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 100:3) to yield a red oil, still containing impurities, which did not influence the next step (1.61 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s; 2H), 8.12 (s; 2H), 7.98 (s; 2H), 7.94 (s; 2H), 7.84 (s; 2H), 7.72 (s; 2H), 7.08 (s; 2H), 6.95 (s; 2H), 6.73 (s; 2H), 4.82 (s, 4H, CH_2), 4.80 (s, CH_2; 4H), 4.79 (s, CH_2; 4H), 4.76 (s, CH_2; 4H), 4.74 (s, CH_2; 4H), 4.60 (s, CH_2; 4H), 3.81 (s, NH_2; 4H), 3.48 (s, CH_3; 6H), 3.46 (s, CH_3; 6H), 3.44 ppm (s, CH_3; 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.7, 153.5, 147.5, 142.9, 142.0, 140.3, 140.2, 140.0, 132.5, 129.42, 129.35, 122.0, 121.8, 121.4, 121.1, 117.5, 114.3, 113.7, 96.4 (CH_2), 96.3 (CH_2), 96.1 (CH_2), 69.5 (CH_2), 69.2 (4C, CH_2), 56.0 (CH_3), 55.9 (CH_3) 55.8 ppm (CH_3); MS (FAB): *m/z* (%): 989 (9) $[M+H]^+$, 45 (100).

MOM-CTB 24: A suspension of $Pb(OAc)_4$ (4.86 g, 11 mmol, 6.90 equiv) in THF (250 mL) was added dropwise to a solution of bisazodiamine **23** (1.57 g, 1.59 mmol, 1.00 equiv) in THF (150 mL) and triethylamine (2.21 mL, 15.9 mmol, 10.0 equiv) over 20 min. After stirring for an additional 3 h, ethylenediaminetetraacetate (EDTA; 4.65 g, 15.9 mmol, 10.0 equiv) and water/CH_2Cl_2 (1:1, 200 mL) was added. After the mixture had been stirred for 20 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on neutral alox (hexane/toluene/EtOAc 1:1:2) to yield an orange-red solid (1.26 g, 80%). M.p. 162–165°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s; 6H), 8.01 (s; 6H), 7.98 (s; 6H), 4.83 (s, CH_2; 12H), 4.82 (s, CH_2; 12H), 3.49 ppm (s, CH_3; 18H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.6, 140.4, 140.3, 128.2, 121.8, 121.7, 96.4 (CH_2), 69.3 (CH_2), 56.0 ppm (CH_3); MS (FAB): *m/z* (%): 985 (7) $[M+H]^+$, 45 (100); elemental analysis calcd (%) for $C_{54}H_{60}N_6O_{12}$: C 52.95, H 4.94, N 6.86; found: C 52.98, H 5.03, N 6.83.

Acknowledgements

We thank the Swiss National Science foundation (SNSF) for financial support. H.A.W. is indebted to the Fonds der Chemischen Industrie for a Liebig fellowship.

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Received: September 17, 2010
Published online: February 3, 2011

