Molecular and biomolecular switches

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Chapter 3

3,4-Dithienylfurans – coupling of molecular switching to reversible cycloaddition

This chapter focuses on the study of the interplay between photochemical switching and cycloadditions reactions. Both processes, the switching as well as the cycloaddition reaction, are reversible, resulting in three stable states of the switching system. In the first state, the dithienylfuran molecule is not photoactive and it has to undergo a cycloaddition reaction to give the cycloadduct that is photochromic. This cycloaddition reaction is reversible and the retro-cycloaddition reaction can restore the dithienylfuran moiety. This is an example of the control of photoreactivity by a second chemical transformation (reaction gated switching). The cycloadduct obtained after the reaction of dithienylfuran with the dienophile shows behaviour typical for photochromic diarylethenes, resulting in the ring-closed isomer after UV irradiation and restoring the ring-open isomer after irradiation with visible light. However, until the system is in the state of ring-closed isomer no retro-cycloaddition can occur (switching gated reaction). While the ring opened cycloadduct can undergo the photoreaction as well as the retro-cycloaddition reaction, the other two states have only one possibility. The dithienylfuran allows only the cycloaddition reaction to proceed and its photoreactivity is blocked, while the closed form of the cycloadduct can undergo the photochromic reaction while its reactivity with respect to retro-cycloaddition reaction is hindered.

3.1 Diels-Alder / retro Diels-Alder reaction couple

The Diels-Alder reaction is widely used in organic chemistry due to its excellent ability to create a six membered ring with up to four stereogenic centers in a regio- and stereoselective manner[1]. It is a very versatile procedure, used to make not only carbon-carbon bonds but also carbon-heteroatom and heteroatom-heteroatom bonds. The structural complexity of the products that can be achieved in a single step is the reason for its frequent use in the construction of complex molecules and natural products[2].

Heating the product of the Diels-Alder reaction often results in the decomposition of the compound and regeneration of the original diene and the dienophile. This reverse process, called retro-Diels-Alder reaction[3], was observed by Diels and Alder in 1929[4]. Although not of such high synthetic value as the Diels-Alder reaction, the retro-Diels-Alder reaction also found its applications in chemistry. Due to the requirement of high temperature, it is quite common and well known in mass spectrometry[5]. Synthetic applications started to appear in larger numbers with the advancement of the pyrolytic methods, particularly flash vacuum pyrolysis[6]. Several monographs and review articles were devoted to the application of this reaction in synthetic organic chemistry[3,7].

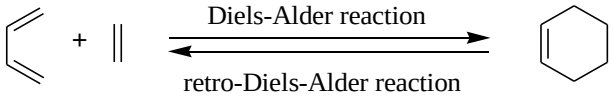


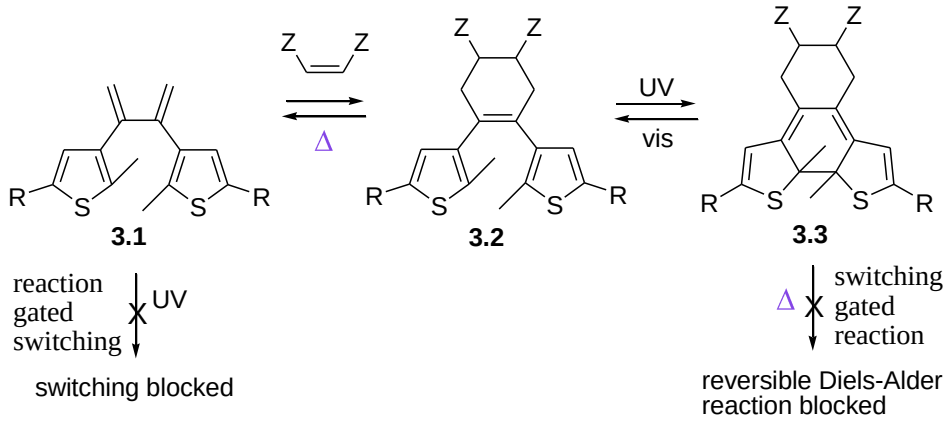
Figure 3.1 Diels-Alder/retro-Diels-Alder reactions.

The most important feature of the Diels-Alder / retro Diels-Alder reactions is the reversibility controlled by thermal conditions only. No additional reagents are needed to drive either of the two reactions and no other products are released in the course of the reactions, which makes this reaction couple a perfect tool for the reversible attachment of two molecules. As such it has been applied to prepare reversible polymers[8], in which the cross-linking, or even the polymerization itself is based on this principle. Other examples in the field of supramolecular chemistry, are thermally responsive dendrimers[9] and the reversible attachment of fullerenes[10].

Our goal is to combine reversible photochemical switching with a reversible chemical reaction, such that they will mutually affect each other. The principle of resulting gating mechanism is shown in Scheme 3.1 The switch will be locked in one of its states until it undergoes the Diels-Alder cycloaddition and the retro Diels-Alder reaction will be restrained after switching. This system can be interpreted as a photoswitchable device with a chemical lock (reaction gated switching) or a molecular connector with an optical lock (switching gated reaction) (Scheme 3.1).

The common structural feature essential for those two mechanisms is the central olefin double bond of the dithienylethene photochromic switch that connects the two thiophenes. The switch precursor **3.1** (Scheme 3.1), based on dithienyl substituted diene, is photochemically inert because it lacks this double bond. However, under appropriate conditions, it can react reversibly with the dienophile to give cycloadduct **3.2**. During the Diels-Alder reaction, the bonding pattern is changed, resulting in the double bond positioned between the thiophene rings. This change creates a hexatriene system typical for the diarylethene switches and thus compound **3.2** becomes photochromic and can undergo a

light-induced ring-closing reaction resulting in **3.3**. In the closed-ring isomer **3.3** the bonding pattern has changed again making the retro-Diels–Alder reaction impossible. Since the photochemical reaction is reversible, irradiation with visible light will induce the ring-opening reaction and convert the molecule **3.3** back to the **3.2**, which is now able to undergo the retro-Diels–Alder reaction thereby transforming the cycloadduct to its components.



Scheme 3.1 The principle of switching coupled to a reversible Diels-Alder reaction.

To develop an effective system based on the Diels-Alder/retro-Diels-Alder reaction couple, it would be desirable to avoid extremely high temperatures. This can be achieved through decreasing the Gibbs energy of activation of the process by the catalysis[11] and via an appropriate choice of the diene and dienophile components. Diels –Alder reactions are known to be accelerated by catalysis in different ways. Besides catalysis by chemical species, usually Bronsted or Lewis acids[12], Diels-Alder reactions are sensitive to pressure[13], ultrasound[14] and solvent effects[15].

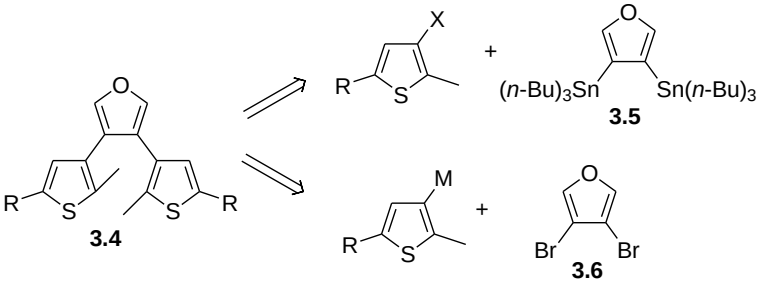
Reversibility of the Diels-Alder reaction has been described for anthracenes[16], fulvenes[17], cyclopentadienes[18] and furans[19]. The most suitable diene for the construction of a reversible system is furan. The cycloadditions using furan were one of the first studied Diels-Alder reactions and addition of maleic anhydride to furan is a typical textbook example of this cycloaddition reaction. Due to the aromaticity of the furane ring, the cycloadditions product of the reaction is not substantially energetically favored and the Gibbs energy of the reaction is quite low, making the reverse-Diels-Alder reaction more feasible. On the other hand, it also causes more difficulties in the cycloaddition reaction itself.

During our work, a related system, based on the fulvene instead of the furan central part was developed by the group of Branda[20].

3.2 Synthesis of the 3,4-dithienyl substituted furan

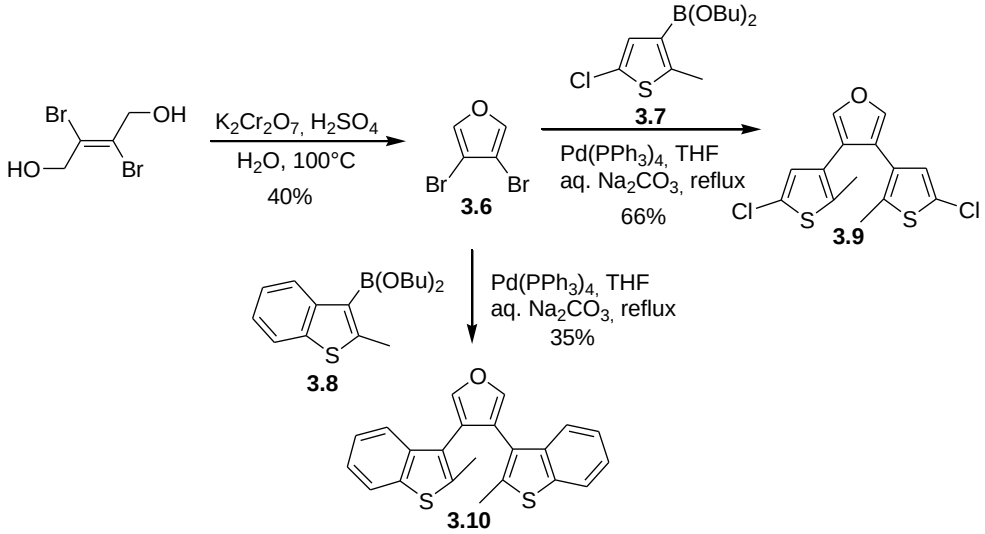
The most convenient synthesis we envisioned for the desired switch precursor, the 3,4-disubstituted furan **3.4**, involves a double diaryl cross-coupling reaction between the appropriately substituted thiophene and furan derivative (Scheme 3.2). Two suitably substituted furan derivatives have been described in the literature[21,22]. Although the

synthesis using 3,4-bis(tri-*n*-butylstannyl)furan **3.5** would be more straightforward, since it can be coupled directly to any halogen substituted thiophene derivative, its preparation is quite costly and tedious[21]. 3,4-Dibromofuran **3.6** can be prepared in one step from cheap starting materials[22], but requires the thiophene derivative to be converted to a suitable reaction partner. Furthermore, in the case of problems during the synthesis, it allows to use various coupling reactions[23] depending on which thiophene precursor will be used.



Scheme 3.2 Short retrosynthetic analysis of the switch precursor.

3,4-Dibromofuran **3.6** was synthesized through oxidation of commercial (*E*)-2,3-dibromo-2-butane-1,4-diol using chromosulfuric acid. The product **3.6** decomposes under the reaction conditions and has to be continuously removed from the reaction mixture by steam distillation. Due to its instability it can be stored at -20°C for a maximum of one to two months.

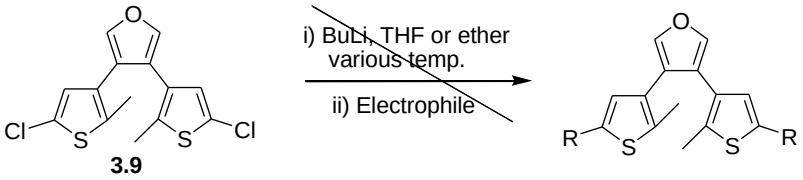


Scheme 3.3 Synthesis of the switch precursors.

This dibromide **3.6** was coupled with 2.5 equivalents of the boronic acid esters **3.7** and **3.8** prepared from the corresponding 3-bromo-5-chloro-2-methyl-thiophene and 3-bromo-2-methyl-benzo[b]thiophene, respectively. A one pot procedure for the preparation of esters and subsequent coupling was used[24]. The desired products **3.9** and **3.10** were obtained in moderate yields of 66% and 35%, respectively. The use of the boronic acids,

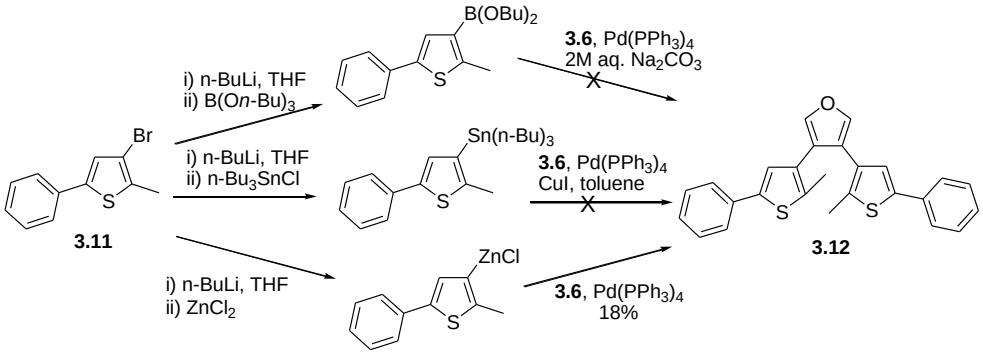
isolated after the hydrolysis of the esters **3.7** and **3.8**, in the coupling reaction gave much lower yields due to extensive deboronation. The identity of the products **3.9** and **3.10** was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopy (see experimental part).

Compound **3.9** was expected to be a convenient synthon suitable for the synthesis of a group of related compounds resulting from substitution on the C5 of the thiophenes (Scheme 3.4). A wide range of the dithienyl perfluoro- and perhydro-cyclopentenes can be synthesized from analogous synthons [24] by halogen lithium exchange and subsequent reaction with electrophiles. However, we did not succeed in replacing the chlorine atoms for other functional groups. Despite many attempts using n-BuLi or t-BuLi in ether or THF solvents and a range of electrophiles (DMF, diethyl carbamate, B(O*n*-Bu)$_3$, H$^+$) the reaction did not yield the desired product. The problem is the metal-halogen exchange step in which the hydrogens at C2 and C5 of the furan probably interfere.



Scheme 3.4 The unsuccessful attempts to derivatize the synthon **3.9**.

Since the photochromic performance of the switch obtained after the Diels-Alder reaction of **3.10** was not ideal for our purpose (*vide infra*), we had to go one step back and use again cross-coupling with 3,4-dibromofuran **3.6** in order to prepare different dithienyl substituted furans. To our surprise, although the synthesis of **3.9** and **3.10** was well reproducible, our attempts to use the same conditions to couple differently substituted thiophenes failed. Therefore, other coupling methodologies were applied and besides the Suzuki coupling also Stille and Negishi cross-coupling reactions were tried using 3-bromo-2-methyl-5-phenyl-thiophene **3.11** as a source for the organometallic intermediate (Scheme 3.5). The coupling reaction using the Negishi procedure was successful but the product **3.12** was obtained in a low yield of only 18%. A possible reason for these synthetic difficulties is that the 3.4-dibromofuran **3.6,** which is quite unstable, might decompose at higher temperatures required for the coupling reactions. This is supported by the observation that no 3,4-dibromofuran and only small amounts of the monosubstituted furan derivative are present in the mixture at the end of the reaction.

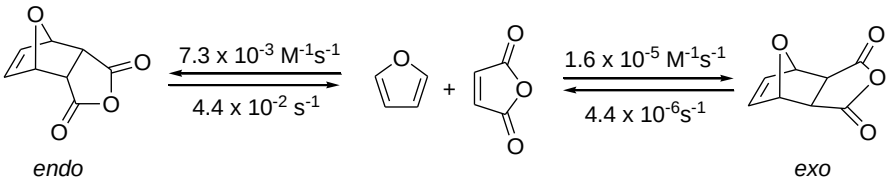


Scheme 3.5 The various cross-coupling reactions examined in the synthesis of **3.12**.

3.3 Synthesis of switches through a Diels-Alder reaction

In general, furan can undergo Diels-Alder reactions as a diene component with a variety of dienophiles such as activated alkenes or alkynes[3,19]. The yield and stereoselectivity of the reaction depends strongly on the substituents present on the furan ring and on the dienophile, wheras it is also sensitive to solvent, temperature and concentration.

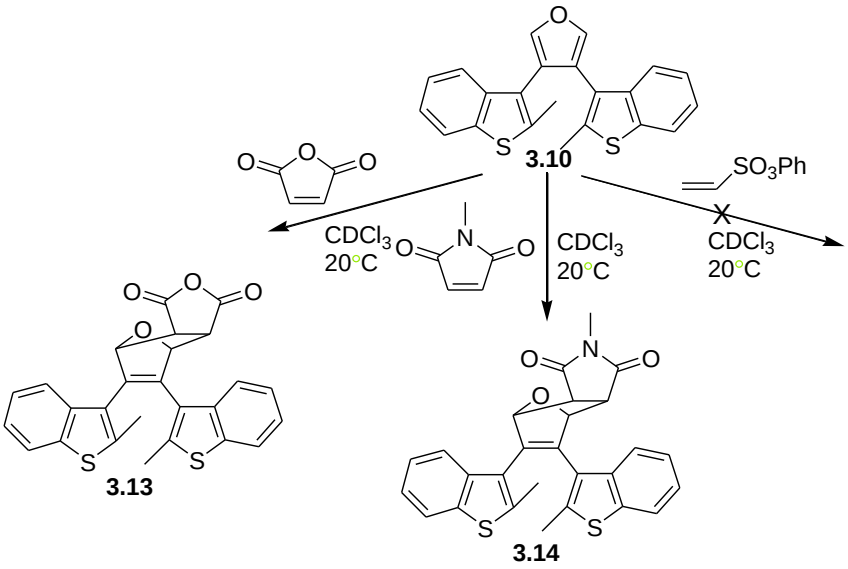
Probably the best studied systems that have provided deep insight into the mechanism of the Diels-Alder and the retro-Diels-Alder reaction are the furan-maleic anhydride and furan-maleimide systems[19, 25] (Scheme 3.6). Based on these studies the suggestion that the intramolecular pathway is responsible for isomerization of the *endo* adduct to the *exo* adduct was ruled out. It has been shown that the cycloaddition is in fact reversible and while the *endo* isomer is obtained at low temperatures, the *exo* isomer is favored at equilibrium[19d]. The complete kinetic characterization supported those observations. The *endo* isomer is created almost 500 times faster than *exo*, which makes it the kinetically favoured product. However, the rate of a reverse reaction is also very high. On the other hand the *exo* product, although more difficult to create, has a reverse reaction 10 000 times slower than the *endo* product, being thus the thermodynamically favored product.



Scheme 3.6 The kinetic parameters for the Diels-Alder reaction of furan with maleic anhydride at 40°C in acetonitrile.

The Diels-Alder reaction of **3.10** was performed using various dienophiles (Scheme 3.7). Besides the thoroughly studied and well described maleic anhydride cycloaddition we applied the N-methylmaleimide dienophile, which shows very similar reactivity[26]. Phenyl vinylsulfonate is also very reactive dienophile, which is known to add to electron poor dienes, such as furan, even at room temperature[27].

Both maleic anhydride and N-methylmaleimide added to the switch precursor **3.10**, even at room temperature. In order to follow the reactions in real time by ^{1}H NMR spectroscopy, the additions were performed in $CDCl_3$ in NMR tubes. Using five equivalents of the dienophile and concentration of diene of ca. 0.1 mol dm^{-3}, the reaction takes more than a week to go to completion at room temperature. To our surprise, the phenyl vinylsulfonate that should have been the most reactive dienophile gave no reaction at all at room temperature.



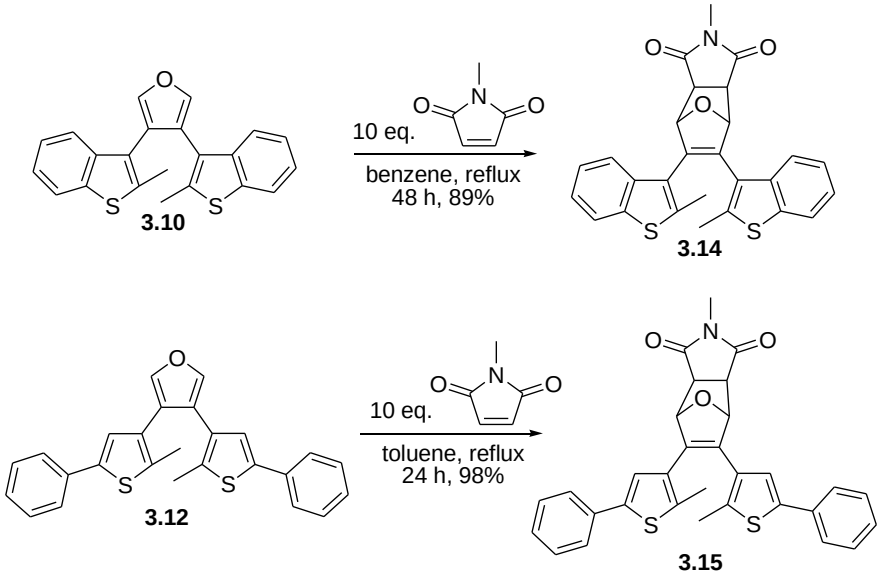
Scheme 3.7 Reaction of the switch precursor **3.10** with different dienophiles (see text).

The reactions were then scaled up and performed at higher temperature, using boiling benzene as a solvent and 10 equivalents of the dienophile (Scheme 3.8). The adduct **3.14** was formed almost quantitatively after 48 h and was isolated in 89 % yield. The use of maleic anhydride, which is prone to hydrolysis, however, gave a mixture of products, containing besides the desired **3.13** also products resulting from anhydride ring opening. Since further measurements and photochemical experiments require the pure adduct, we decided to continue only with **3.14** which has the added value of variation of possible substituents on the imide nitrogen. The dithienyl-ethene **3.15** was obtained in a similar manner from the dithienyl-furane derivative **3.12** and 10 equivalents of N-methylmaleimide. To our surprise after 48 h in boiling benzene only a trace of the product was observed. The reaction was repeated in boiling toluene, resulting in a 98% yield of the cycloadduct **3.15** after 24 h. The ^{1}H NMR ^{13}C NMR and mass spectra showed that the cycloaddition reaction was successful and the desired products **3.14** and **3.15** were obtained.

As expected, in both cases only the thermodynamically more stable *exo* isomer was isolated. Small amounts of the kinetic *endo* isomer were observed only when the reaction was followed in real time by ^{1}H NMR spectroscopy and the conversion of reactants to the adduct was still low. NMR evidence for the *exo* isomer is the presence of new singlet peaks at 5.74 and 5.50 ppm for **3.13** and **3.14,** respectively, corresponding to the protons at C2 of the furan ring. It is known that the torsional angle between the protons at C2 of the furan ring and those of the maleimide moiety in the *exo* isomer is close to 90° resulting, according to the Karplus equation[28], in a coupling constant close to zero and a singlet signal. For the *endo* isomer, with a torsional angle around 35°, the corresponding proton appears as a multiplet[19d].

To perform the Diels-Alder reaction under more convenient conditions and in a shorter time we tried to use Lewis acids ($ZnCl_2$, ZnI_2, $BF_3.OEt_2$, $HfCl_4$) as a catalyst. Our ultimate goal was to be able to perform the Diels-Alder reaction and subsequent photochemical ring closure in one pot and at ambient temperature as would be desirable if

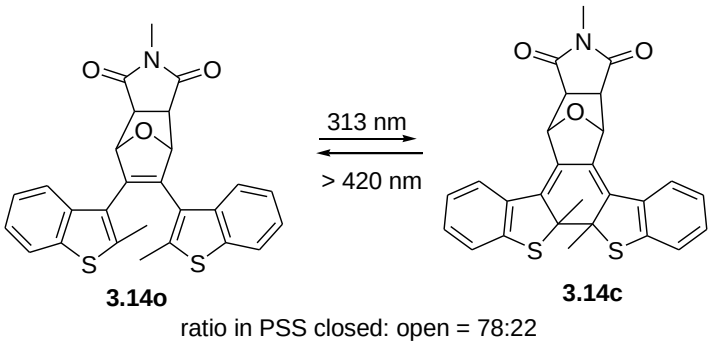
the system should work as a molecular device. The most effective catalyst was $BF_3.OEt_2$, however, as we found later, its presence interfered with the photochemistry. The addition of $BF_3.OEt_2$ (0.2 eq) to the mixture of **3.12** and N-methylmaleimide resulted in formation of the product **3.15** within 24h at 40°C, compared to 48h at 80°C without the catalyst. The ring-closing reaction of the diarylethene **3.15o** in the presence of $BF_3.OEt_2$ proceeded as expected to give the closed form **3.15c**, as observed by UV-vis spectroscopy. However, it was followed by a rapid thermochromic ring-opening back to **3.15o** within 1h, accompanied by partial decomposition of the diarylethene molecule (see Scheme 3.10, vide infra). Since **3.15c** in pure solvents (dichloromethane, benzene, toluene) shows no thermochromism, even when heated to 80°C for 48h, this effect must be a result of the presence of the catalyst. The closed form of the switch in the presence of the catalyst becomes unstable, leading partly back to the open form and partly decomposition of the material.



Scheme 3.8 Synthesis of the new diarylethenes **3.14** and **3.15** through the Diels-Alder reaction.

3.4 Photochemistry of the dithienylethene cycloadducts

The Diels –Alder reaction results in a change of the bonding pattern of the product. Two of the four electrons of the furan π-bonds take part in the creation of the two new single bonds connecting the furan to the dienophile, and the remaining two electrons are involved in a new π- bond between the C2 and C3 carbons of the furan ring (Scheme 3.8). This double bond completes the photoactive hexatriene system and the product thus becomes photochromic (Scheme 3.9).



Scheme 3.9 Photochromic behavior of the diarylethene **3.14**.

As expected, irradiation of a dichloromethane solution of the switch precursor **3.10** (UV-vis spectrum of **3.10** is shown in Figure 3.2a) with 254 nm UV light did not cause any change in its UV spectra (**3.10** does not absorb at 313 nm, which is the standard wavelength of light used to induce the ring closing reaction, see Figure 3.2a). This proves that the **3.10** is not photochromic and its switching is gated by the cycloaddition reaction. Irradiation of the solution of the cycloadduct with N-methylmaleimide **3.14o** (Scheme 3.9 and Figure 3.2a) with 313 nm UV light resulted in a different UV spectrum together with a visual colour change from colourless to red (Figure 3.2a). This indicates the presence of the closed isomer **3.14c** with a longer conjugated system. While the open form **3.14o** absorbs light only in the UV region with absorption maximum at 236 nm and two lower absorption bands at 294 and 302 nm, the closed form absorbs also in the visible region at 440 nm, which results in the red colour of the solution. The ratio of the open and closed form in the photostationary state was **3.14c** : **3.14o** / 78 : 22 as determined by ^{1}H NMR spectroscopy, which means that about three quarters of the molecules are in the closed form while one quarter still remain in the open form.

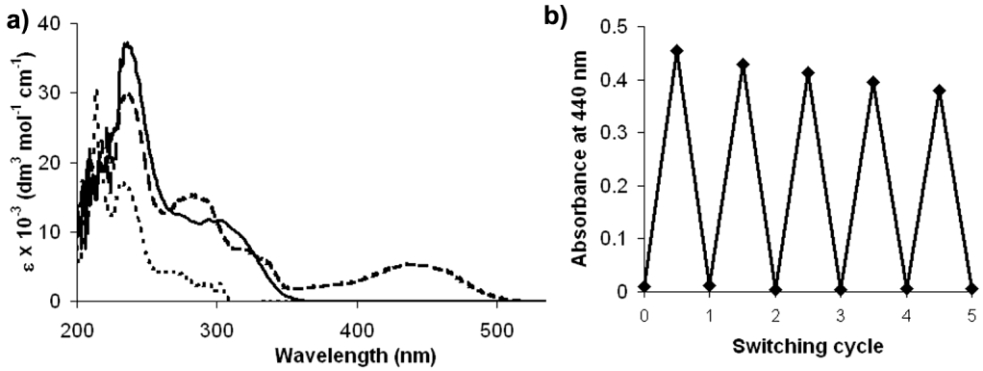


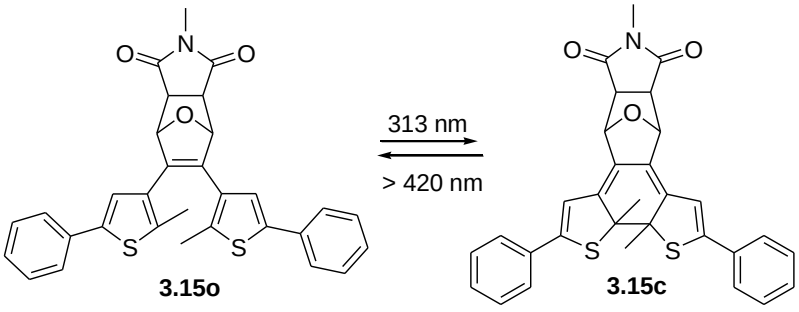
Figure 3.2 UV-vis spectra of cycloadduct **3.14**. a) open form **3.14o** (——) and mixture at the photostationary state after irradiation with 313 nm light (-----) in dichloromethane, together with **3.10** (·····); b) absorbance monitored at 440 nm during alternate irradiation with 313 nm UV light and >420 nm visible light.

The closed form **3.14c** is thermally stable and no thermochromic ring-opening was observed upon heating to 80°C for 48h in toluene. Since 48h and 80°C are the conditions necessary for the establishment of the equilibrium between the dithienylfuran **3.10**, N-methylmaleimide and the product of their cycloadditions **3.14o** (Scheme 3.8), this means that the retro-cycloaddition reaction can be blocked by the ring-closing reaction, since the ring-closed product **3.14c** can withstand such temperatures, i.e. the retro-cycloaddition can be effectively gated by switching.

Irradiation of the solution containing the closed ring isomer **3.14c** with visible light with a wavelength longer than 420 nm, results in the restoration of the original UV-vis spectrum of the open form **3.14o**. Alternate irradiations with 313 nm UV light and >420 nm visible light were followed by UV-vis spectroscopy to asses the fatigue resistance of the switch (Figure 3.2b). The switching cycle can be repeated several times, however some decomposition occurs already after a few cycles. The decrease in the absorbance at 440 nm was about 15% after 5 cycles (Figure 3.2b).

Although the diarylethene switch **3.14** shows efficient photochromic behaviour, it is not an ideal candidate for the study of the mutual influence of photochromism and the cycloadditions reaction. The major drawback is the relatively high content of the open form in the photostationary state (Scheme 3.9), which upon heating partially undergoes the retro-Diels-Alder addition giving the original components **3.10** and N-methylmaleimide. Furthermore the fatigue resistance of **3.14** is not excellent. Diarylethene **3.15**, however, does not posses any of those drawbacks.

Irradiation with 313 nm UV light converted **3.15o** to **3.15c** (Scheme 3.10), as can be seen from the UV-vis spectra before and after the irradiation (Figure 3.3a). A new absorption, typical for the closed form of the switch, appeared at 518 nm and the solution changed colour to blue. ^{1}H NMR spectroscopy of the irradiated solution shows the presence of only the closed form **3.15c**, which means that complete conversion is achieved in the photostationary state.



Scheme 3.10 Photochromic behavior of the diarylethene **3.15**.

As in the case of **3.14c,** the ring-closed form **3.15c** is also thermally stable and showed no change in the UV-vis spectrum after heating to 100°C for 48h in toluene. The irradiation of the solution of **3.15c** with visible light with a wavelength > 420 nm resulted in the ring-opening reaction and the original UV-vis spectrum of the open form **3.15o** was restored (Figure 3.3a). The fatigue resistance of this diarylethene was also studied by performing several ring-closing and ring-opening cycles while following the absorption at 518 nm (the maximum of the absorption band in the visible region for the closed form

3.15c) (Figure 3.3b). The decrease in absorbance was only about 1% after five switching cycles and a clear isosbestic point at 332 nm was observed during the whole process, which means that this switch has an excellent fatigue resistance.

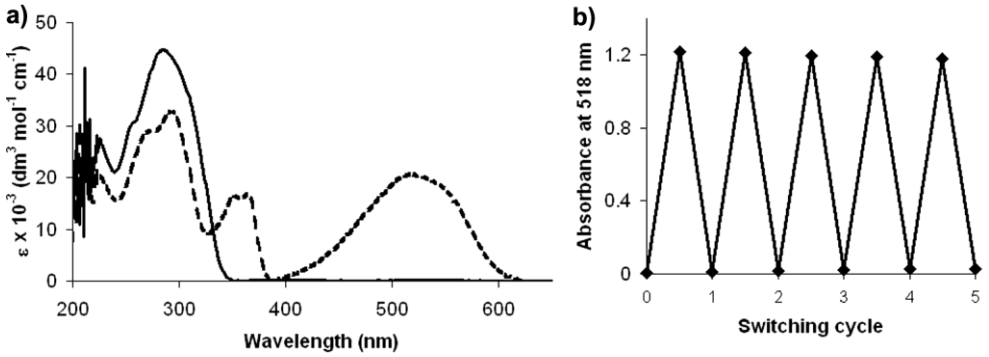
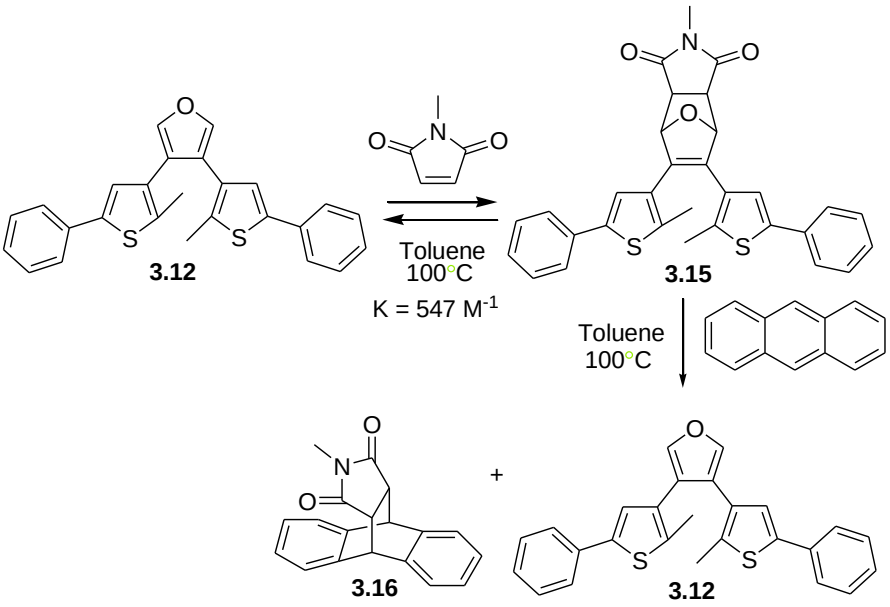


Figure 3.3 UV-vis spectra of cycloadduct **3.15**. a) open form **3.15o** (——) and at the photostationary state after irradiation with 313 nm light (-----) in toluene; b) absorbance monitored at 440 nm during alternate irradiation with 313 nm UV light and >420 nm visible light.

3.5 Retro-Diels-Alder reaction

The last process to be investigated for this system is the possibility of blocking the photochromic switching using the retro-cycloaddition reaction. Heating of **3.15** at 100°C for 48h in toluene is sufficient to establish the equilibrium between the diene **3.12**, N-methylmaleimide as a dienophile and the cycloadditions product **3.15** (Scheme 3.11). However, the equilibrium is strongly shifted to the side of the product with an equilibrium constant of 547 M^{-1}. The reaction equilibrium constant was determined by observing the ratio of reactants and product at equilibrium using ^{1}H NMR spectroscopy at three different concentrations. The solution of pure cycloadduct **3.15** (concentrations of 10 mg/ml, 1 mg/ml and 0.1 mg/ml in deuterated toluene) was heated to 100°C for 48h to reach equilibrium. Even for the lowest concentration (0.1 mg/ml) the solution still contained 9% of the cycloadduct **3.15**. The high temperature required for the retro-cycloaddition and the equilibrium strongly favouring the cycloadduct present two major drawbacks of this system.

The retro-cycloaddition proceeded as expected but the switching behaviour could not be completely blocked, since even at low concentrations the photoactive cycloadduct **3.15** is still present. To solve this problem, the equilibrium that establishes during heating should be shifted to the side of the diene and dienophile. Such a shift in the equilibrium occurs when one of the components is removed from the mixture effectively decreasing its concentration to zero. Since the goal is to liberate the dithienylfuran **3.12** from its cycloadduct, the component that should be removed is the N-methylmaleimide dienophile. This is most readily achieved by allowing the N-methylmaleimide to react with a diene more reactive than furan, anthracene being a good candidate (Scheme 3.11).



Scheme 3.11 The reversibility of the cycloadditions reaction and shifting of its equilibrium by trapping the dienophile.

The retro-Diels-Alder reaction was then performed in the presence of one equivalent of anthracene (Scheme 3.11) under the same conditions. As can be seen from the experiment where the reaction was followed by ^{1}H NMR spectroscopy (Figure 3.4), the reaction was complete after 48h at 100°C, when signals corresponding to the cycloadduct **3.15** or the free N-methylmaleimide ceased to be observed (Figure 3.4d). The ^{1}H NMR spectrum after the reaction showed the presence of only two components; the dithienylfuran **3.12** was identified through comparison with the ^{1}H NMR spectrum of the pure compound and presence of N-methyl-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboximide **3.16** was confirmed through comparison with the ^{1}H NMR spectra reported in literature[29]. The ^{1}H NMR spectrum measured during the reaction (24h at 100°C) shows the mixture of the reactants and the products. Signals for **3.15** along with signals for the free N-methylmaleimide and its cycloadduct with anthracene, are clearly visible (Figure 3.4c). The method of scavenging the dienophile by the concurrent cycloaddition reaction with anthracene was indeed successful, resulting in the complete retro-Diels-Alder reaction of **3.15** and liberation of the photochemically inactive dithienylfuran **3.12**.

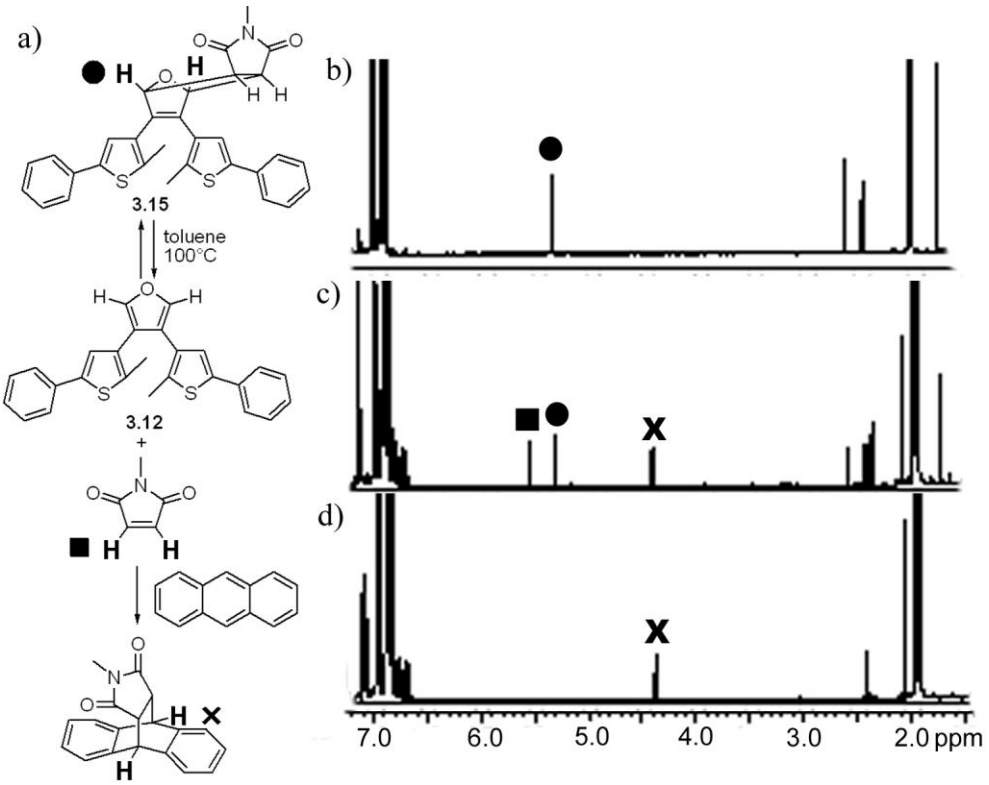
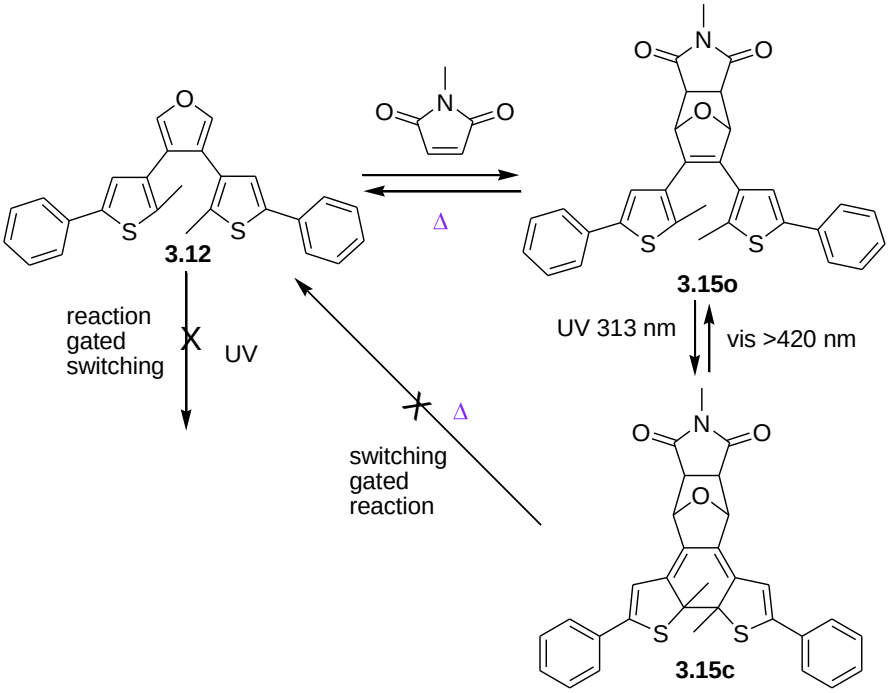


Figure 3.4 Reaction scheme and partial ^{1}H NMR spectra (region 2-7 ppm) of the reaction mixture during retro-Diels –Alder reaction of **3.15** in toluene-d8 using anthracene as a dienophile scavenger a) reaction scheme, b) **3.15** + anthracene before reaction, c) reaction mixture after 24 h at 100°C d) reaction mixture after 48 h at 100°C.

3.6 Conclusion

A system that combines photochemical switching with chemical reactivity which mutually affect each other was developed. This system can exist in each of the three basic states (Scheme 3.12). Dithienylfuran **3.12** it is photochemically inert (reaction gated switching), but with a suitable dienophile (N-methylmaleimide) at elevated temperature can undergo the Diels-Alder cycloaddition reaction to give the diarylethene **3.15o**. The cycloadditions reaction is reversible and upon heating **3.15o** in very diluted solution, or in the presence of dienophile scavenger compound **3.12** is restored. The second state, diarylethene **3.15o** manifests behaviour typical for the photochromic molecular switch. Upon irradiation with UV light the ring-closing reaction takes place resulting in the third state, the closed form **3.15c**, quantitatively. This photochemical process is reversible, and after irradiation of **3.15c** with visible light, **3.15o** is restored. Heating of **3.15c**, unlike **3.15o**, does not results in the retro-Diels-Alder reaction. To obtain again the dithienylfuran **3.12**, compound **3.15c** has to be first switched back to **3.15o** (switching gated reaction). This

molecular design comprises a three stage coupled system in which both photoswitching and reversible cycloadditions are gated and mutually depend on each other.



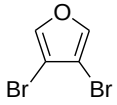
Scheme 3.12 Overview of the interplay between chemical reactivity and photochemical switching.

3.7 Experimental section

General information:

For general information on synthesis, characterization and photochemical studies, see Chapter 2.

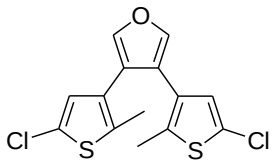
3,4-Dibromofuran (3.6)[22]



(*E*)-2,3-dibromo-2-butene-1,4-diol (24.6 g, 0.1 mol) was dissolved in sulfuric acid (60 ml of a 7.5% aqueous solution) at 80°C in a three necked flask. The flask was equipped with a distillation condenser, addition funnel and a steam generator was attached to it. When the steam distillation started, the chromosulfuric acid prepared from potassium dichromate (28 g), concentrated sulfuric acid (20 ml, 36 g) and water (100 ml), was added dropwise from the addition funnel over 2 h. The distillation was continued for 1 h. The collected distillate was extracted with petroleum ether (3 x 100 ml), the organic extracts were washed with Na_2CO_3 (50 ml of sat. aq. solution) and dried over Na_2SO_4. Evaporation of the solvent gave the product (9 g, 40%) as a colourless liquid that is pure enough for the next step.

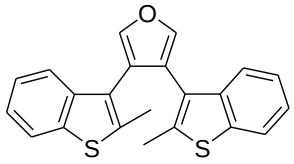
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (s, 2H).
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 104.02 (s), 141.58 (d).
MS (EI): 224 [M^+]; HRMS calcd. for C_4H_2O 223.8472 found 223.8486.

3,4-Bis-(5-chloro-2-methyl-thiophen-3-yl)-furan (3.9)



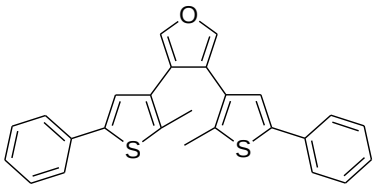
3-Bromo-5-chloro-2-methyl-thiophene (1.06 g, 5 mmol) dissolved in anhydrous Et_2O (10 ml) under nitrogen, and n-BuLi (3.5 ml of 1.6 M solution in *n*-hexane, 5.5 mmol) was slowly added at -78°C. This mixture was stirred for 1 h at the same temperature and then $B(OBu)_3$ (1.6 ml, 1.38 g, 6 mmol) was added at once. After stirring for 30 min at -78°C the reaction mixture was allowed to warm and stirred for 30 min at r.t. Next 3,4-dibromo-furan (450 mg, 2 mmol), $Pd(PPh_3)_4$ (138 mg, 0.12 mmol) and aq. Na_2CO_3 (10 ml of a 2M aq. solution) together with THF (10 ml) were added and the reaction mixture was heated at reflux overnight. After cooling to r.t. Et_2O (50 ml) and water (50 ml) were added, the organic layer separated and the aqueous layer extracted with Et_2O (2x50 ml). The combined organic extracts were then dried over Na_2SO_4 and the solvents evaporated. Purification by chromatography (silica gel, *n*-hexane) yielded 432 mg (66%) of the product.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 6H), 6.52 (s, 2H), 7.46 (s, 2H).
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.96 (q), 120.36 (s), 125.74 (s), 127.84 (d), 127.99 (s), 134.41 (s), 141.05 (d).
MS (EI): 328 [M^+]; HRMS calcd. for $C_{14}H_{10}Cl_2OS_2$ 327.9550 found 327.9553.

3,4-Bis-(2-methyl-benzo[b]thiophen-3-yl)-furan (3.10)



3-Bromo-2-methyl-benzo[b]thiophene (1.13 g, 5 mmol) was dissolved in anhydrous THF (10 ml) under nitrogen and n-BuLi (3.5 ml of 1.6 M solution in *n*-hexane, 5.5 mmol) was slowly added at -78°C. This mixture was stirred for 1 h at the same temperature and then $B(OBu)_3$ (1.6 ml, 1.38 g, 6 mmol) was added all at once. After stirring for 30 min at -78°C the reaction mixture was allowed to warm up and stirred for 30 min at r.t. Next 3,4-dibromo-furan (450 mg, 2 mmol), $Pd(PPh_3)_4$ (138 mg, 0.12 mmol) and Na_2CO_3 (10 ml of a 2M aq. solution) together with THF (10 ml) were added and reaction mixture was heated at reflux overnight. After cooling to r.t. Et_2O (50 ml) and water (50 ml) were added, the organic layer separated and the water layer extracted with Et_2O (2x50 ml). The combined organic extracts were then dried over Na_2SO_4 and the solvents evaporated. Purification by chromatography (silica gel, *n*-hexane:toluene / 3:1) yielded 275 mg (38%) of the product as a white solid m.p. 156-157°C .
^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 6H), 7.16-7.22 (m, 4H), 7.48-7.53 (m, 2H), 7.63-7.68 (m, 2H) 7.71 (s, 2H).
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.59 (q), 120.15 (s), 121.93 (d), 122.11 (d), 123.79 (d), 123.83 (s), 124.15 (d), 138.00 (s), 138.26 (s) 140.19 (s), 142.21 (d).
MS (EI): 360 [M^+]; HRMS calcd. for $C_{22}H_{16}OS_2$ 360.0643 found 360.0641.

3,4-Bis-(2-methyl-5-phenyl-thiophen-3-yl)-furan (3.12)



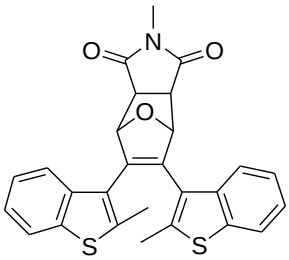
3-Bromo-2-methyl-5-phenyl-thiophene (0.9 g, 3.5 mmol) was dissolved in anhydrous THF (10 ml) under nitrogen and n-BuLi (2.2 ml of 1.6 M solution in *n*-hexane, 3.5 mmol) was slowly added at -78°C. This mixture was stirred for 1 h at the same temperature and then $ZnCl_2$ (4.8 ml of 10% solution in THF, 3.5 mmol) was added. After stirring for 10 min at -78°C the reaction mixture was allowed to warm up and stirred for 1 h at r.t. Next 3,4-dibromo-furan (337 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (86 mg, 0.075 mmol) were added and the reaction mixture was heated at reflux overnight. After cooling to r.t. NH_4Cl (20 ml of sat. aq. solution) was added, and the mixture extracted with Et_2O (3x30 ml). The combined organic extracts were then dried over Na_2SO_4 and the solvents evaporated. Purification by chromatography (silica gel, *n*-hexane:toluene / 9:1) yielded 114 mg (18%) of the product as a colourless oil that solidifies upon standing.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 6H), 7.03 (s, 2H), 7.26 (t, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 4H), 7.52 (d, *J* = 7.3 Hz, 4H), 7.60 (s, 2H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.28 (q), 121.20 (s), 125.25 (d), 125.50 (d), 127.21 (d), 128.92 (d), 129.77 (s), 134.43 (s), 135.46 (s), 140.02 (s), 140.75 (d).

MS (EI): 412 [M^+]; HRMS calcd. for $C_{26}H_{20}OS_2$ 412.0956 found 412.0941.

4-Methyl-8,9-bis-(2-methyl-benzo[*b*]thiophen-3-yl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (3.14)



3,4-Bis-(2-methyl-benzo[b]thiophen-3-yl)-furan (36 mg, 0.1 mmol) and N-methylmaleimide (111 mg, 1 mmol) were dissolved in benzene (1 ml) and refluxed for 48 h. Then the solvent was evaporated and the residue purified by column chromatography (silica gel, *n*-hexane:ethyl acetate / 3:1) to give 42 mg (89%) of product as a white solid that decomposes upon heating.

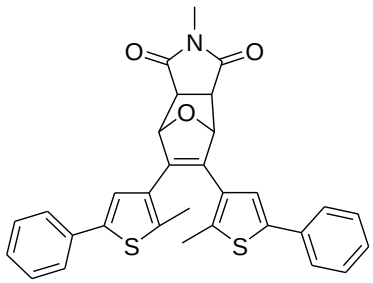
^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 6H), 3.05 (s, 3H), 3.46 (s, 2H), 5.74 (s, 2H) 7.25-7.35 (m, 4H) 7.60-7.65 (m, 2H), 7.7-7.75 (m, 2H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.87 (q), 25.23 (q), 48.82 (d), 85.38 (d), 122.40 (d), 125.63 (d), 127.77 (d), 129.08 (d), 130.53 (s), 133.80 (s), 137.24 (s), 138.47 (s), 141.71 (s), 176.19 (s).

MS (EI): 471 [M+]; HRMS calcd. for $C_{27}H_{21}NO_3S_2$: 471.0963. Found: 471.0951.

Anal. calcd. for $C_{27}H_{21}NO_3S_2$: C, 68.76; H, 4.49; N, 2.97; S, 13.60. Found: C, 68.49; H, 4.62; N, 3.12; S, 13.31.

4-Methyl-8,9-bis-(2-methyl-5-phenyl-thiophen-3-yl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (3.15)



3,4-Bis-(2-methyl-5-phenyl-thiophen-3-yl)-furan (41 mg, 0.1 mmol) and N-methyl-maleimide (111 mg, 1 mmol) were dissolved in toluene (1 ml) and refluxed for 48 h. Then the solvent was evaporated and the residue purified by column chromatography (silica gel, *n*-hexane:ethyl acetate / 3:1) to give 51 mg (98%) of the product as a white solid that decomposes upon heating.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 6H), 3.04 (s, 3H), 3.21 (s, 2H), 5.50 (s, 2H), 7.09 (s, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 4H), 7.54 (d, *J* = 7.3 Hz, 4H)

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.87 (q), 25.23 (q), 48.82 (d), 85.38 (d), 122.40 (d), 125.63 (d), 127.77 (d), 129.08 (d), 130.53 (s), 133.80 (s), 137.24 (s), 138.47 (s), 141.71 (s), 176.19 (s).

MS (EI): 523 [M+]; HRMS calcd. for $C_{31}H_{25}NO_3S_2$: 523.1276. Found: 523.1263.

Anal. calcd. for $C_{31}H_{25}NO_3S_2$: C, 71.10; H, 4.81; N, 2.67; S, 12.25. Found: C, 70.79; H, 4.91; N, 2.82; S, 12.07.

Typical UV-vis spectroscopy measurement

A solution of **3.14o** (3 ml of $8.5x10^{-4}$ solution in dichloromethane) together with a small stirring bar was placed in a quartz cell with 1 cm path length and a teflon stopper. The cell was placed in a cell holder with built in magnetic stirring and four openings, allowing irradiation with high-pressure Hg lamp in perpendicular direction to the measuring beam of the Hewlet-Packard HP 8453 FT diode array spectrometer. After acquisition of the spectrum, the sample was irradiated with the light from the Hg lamp, equipped with 313 nm bandpass filter, for 1 min. The spectrum of the irradiated solution was measured, and the sample was irradiated for another 1 min. Irradiation in 1 min intervals combined with spectrum acquisition after each interval was repeated untill the photostationary state was achieved, i.e. no difference was observed between spectrum before and after irradiation. For this particular sample, irradiation time of 3 min with 313 nm UV light was sufficient to achieve the photostationary state between the open form **3.14o** and the closed form **3.14c**. Then the filter in the lamp was changed for > 420 nm fluorescence filter, and the irradiation and measuring procedure was repeated until the spectrum of the pure open form **3.14o** was obtained again. For this particular sample, irradiation time of 1 min with >420 nm visible light was sufficient to isomerize all the closed form **3.14c** back to the open form **3.14o**.

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[21] Compound **3.5** can be prepared in 19% yield by heating bis(tributylstannyl)acetylene (cost of 5g package in Aldrich catalogue is 240 €) with 4-phenyloxazole at 185°C for 7 d followed by chromatography, fractional distillation and again chromatography. See: (a) Yang, Y.; Wong, H. N. C. *J. Chem. Soc., Chem. Commun.* **1992**, 656-658. (b) Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583-9608. Quite recently a new more effective synthesis was described in: Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Synth. Commun.* **2003**, *33*, 3205-3209.

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