On conformational and configurational aspects of molecular motors
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Chapter 7:

Making of a molecular motor by chemical stimuli

Herein a strategy is reported to decelerate the rotation of light-driven molecular motors. The rotary speed of a molecular motor functionalized with a biphenol moiety could be reduced in situ by covalent functionalization as well as non-covalent substrate binding, as was concluded on the basis of $^1$H NMR and UV/vis spectroscopy. These findings constitute an important step in the development of responsive and tunable molecular machinery.

Chapter 7

7.1 Introduction

One of the main characteristics of biological motors, which stands out compared to artificial motors, is their ability to regulate activity in response to multiple stimuli.\(^1\) Although in principle synthetic molecular switches and motors are responsive to a certain stimulus, examples in which an additional orthogonal stimulus can be used to exert an increased level of control, are limited. In order to approach the level of complexity found in biological machines, it is crucial to be able to control the behavior of synthetic motors with diverse stimuli.

In chapter 1 several approaches have been described to make light-driven molecular motors responsive to chemical stimuli. For a motor functionalized with a pseudo-rotaxane, it has been shown that the rotation can be blocked and unblocked by the addition of acid and base.\(^2\) Also, the direction of rotation of a specific molecular motor could be inverted by using base as stimulus.\(^3\) Most recently, it was shown that the rotational speed of light-driven molecular motors can be increased by transition metal complexation, which induces conformational changes.\(^4\)

In a recent study it was shown that a biaryl functionalized light-driven motor 1 show remarkable behavior.\(^5\) Compound 1 consisted of a fluorene lower half and an indanone upper half coupled to a naphthalene moiety via a biaryl single bond (Figure 1). Based on \(^1\)H NMR, UV/Vis and CD spectroscopy, supported by DFT calculations, it was demonstrated that the rotations around the biaryl single bond and the double bond are locked and show synchronous motion. In other words, rotation around the biaryl single bond only occurred, when there is rotation around the double bond.

![Figure 1: (a) Molecular motor exhibiting locked synchronous rotor motion. (b) DFT optimized structure of the motor.\(^5\)](image)

In scheme 1 the mechanism for the locked rotation is shown. During the photochemical isomerization step, the biaryl moiety slides along the fluorene half and remains parallel to it. In the course of the thermal helix inversion (THI) on the other hand, the biaryl transitions from a nearly parallel orientation relative to the fluorene moiety, to orthogonal relative to the lower half. This specific behavior is the consequence of the system’s tendency to reduce steric hindrance between these two moieties.
Scheme 1: The rotational cycle of a molecular motor with a biaryl rotor moiety. (a) front view. (b) top view.
In view of the specific behavior of the biaryl moiety in the transition state (TS), it is
reasoned that restraining the biaryl moiety and thereby limiting the rotation around
single bond could result in an increase in steric hindrance during the THI. In this way,
the rotational speed of the light-driven molecular motor may be influenced, for example
by chemical stimuli. The biaryl moiety thus forms a handle to alter the rotary behavior
of the motor. In this respect biphenol as the biaryl unit is an especially interesting option
as the straightforward covalent functionalization or the supramolecular binding of a
guest is known to influence the conformational freedom, i.e. biaryl rotation. (Scheme 2).

\[ \text{Scheme 2: Proposed way of decelerating the rotational speed of the motor via covalent}
\text{functionalization or non-covalent binding.} \]

In this chapter the synthesis and study the biphenol functionalized molecular motor 2 is
described. It is investigated whether the covalent functionalization or non-covalent
binding of hosts results in a decrease in rotational speed.

### 7.2 Results and Discussion

Motor 2 was synthesized in seven steps starting from the commercially available ketone
3 (Scheme 3). Compound 3 was brominated using N-Bromosuccinimide (NBS) to
obtain bromoketone 4. Suzuki coupling with (2-methoxyphenyl)boronic acid using
conditions developed by Buchwald et al\(^6\) gave compound 5. Deprotonation with
lithium diisopropylamide (LDA), followed by the addition of CH\(_3\)I afforded a
diastereomeric mixture of ketone 6 (dr. 45:55). Note that compound 6 possesses an
axially chiral biaryl moiety as well as a stereogenic center. Conversion of the ketone
group into the hydrazone was accomplished with hydrazine monohydrate in boiling
ethanol. The corresponding diazo compound of hydrazone 7 was synthesized by the
oxidation with phenyliodine bis(trifluoroacetate) (PIFA), which was subsequently
coupled to freshly prepared thiofluorenone to give episulfide 8. Desulfurization with
hexamethylphosphotriamine (HMPT) provided the overcrowded alkene 9 (dr. 45:55).
Motor 2 was obtained by the removal of the methoxy groups using CH$_3$MgI under neat conditions.$^7$

Analysis of a solution of 2 in CDCl$_3$ with $^1$H NMR spectroscopy showed that 2 exists as two conformational isomers in a ratio of about 10:1 (Figure 2a). The two conformers were identified as the isomers having a synclinal and anticlinal orientation of the hydroxyl functionalities. Based on the chemical shift of the phenolic protons (H$_e$), it was concluded that the major conformer has a synclinal conformation (Figure 2a). The internal hydrogen bonding in the synclinal conformer is reflected in the downfield shift of the hydroxyl signals in the $^1$H NMR spectrum (Figure 2a). The minor conformer has two peaks in the $^1$H NMR spectrum at 5.6 and 4.9 ppm belonging to hydrogens H$_e$, similar to the chemical shift of the phenolic proton of hydroxybenzene.

The barrier of biaryl single bond rotation, or atropisomerization, is low for 2,2’-biphenols, probably due to internal hydrogen bonding lowering the TS for this process.$^8$ A structurally similar motor as 2 (with a six-membered carbon ring upper half fused to the alkene instead of a five-membered ring) has a low barrier for biaryl rotation ($\Delta^4G = 78.2 \pm 1.1$ kJ mol$^{-1}$)$^9$. The barrier for atropisomerization for 2 also has to be low as the addition of an equal amount of CD$_3$OD to a solution of 2 in CD$_3$Cl led to the re-equilibration to a different conformational ratio (>95:5) in less than several minutes at room temperature. It is therefore safe to say that the barrier for biaryl rotation has to be below 85 kJ mol$^{-1}$.

Scheme 3: Synthesis of motor 2.
With motor 2 in hand, a series of UV/Vis and $^1$H NMR experiments were conducted to study the behavior of the compound upon irradiation. $^1$H NMR spectroscopy showed that irradiation of 2 with 365 nm light at $-50^\circ$ C, led to the formation of the metastable isomer in a photostationary state ratio (PSS) of 43:57 (metastable:stable) (Figure 2b). It was observed that the phenolic protons (He) shift from around 7.5 ppm to around 5 ppm. Based on this observation, it is proposed that the photogenerated isomer has an anticlinal conformation. This is in accordance with the photochemical isomerization behavior of biaryl motor 1. Heating the sample to room temperature resulted in the conversion of the metastable isomer to the stable isomer, in line with the expected behavior for these compounds (Figure 2c).

Figure 2: $^1$H NMR spectrum of 2 in CD$_2$Cl$_2$ upon irradiation with 365 nm light at $-50^\circ$ C. (a) Initial state (b) Spectrum after irradiation. PSS 43:57 (metastable:stable) (c) Spectrum of sample after heating (recorded at $-50^\circ$ C). *Peaks originating from solvent.
In the UV/Vis spectrum a bathochromic shift with isosbestic points was observed upon the formation of the metastable isomer by irradiation of a solution 2 with 365 nm light at $-53^\circ$C (Figure 3). The thermal isomerization of the metastable isomer was followed in time at seven different temperatures ($-53^\circ$C to $-38^\circ$C with 2.5 °C intervals) using UV/vis spectroscopy. Eyring analysis was used to determine $\Delta^\ddagger G$ (20 °C) for the THI which was found to be 69.9 kJ mol$^{-1}$. This barrier is comparable to the barrier for the THI of motor 1, which is 76.6 ± 0.8 kJ mol$^{-1}$.5

![Figure 3](image)

**Figure 3:** (Left) UV/vis absorption spectra of 2 in CH$_2$Cl$_2$ and at $-53^\circ$C and spectral changes upon irradiation with 365 nm light. (Right) Eyring plot of the THI of 2.

As the THI of light-driven molecular motors is the rate-determining step of the rotary cycle,10 the barrier of the THI is a direct measure of the rotational speed of the molecular motors. The found $\Delta^\ddagger G$ (20 °C) for the THI of 69.9 ± 1 kJ mol$^{-1}$ for 2 corresponds to a rotational frequency of 1.1 Hz at room temperature.

After it was established that motor 2 functions as anticipated, it was investigated whether the rotary speed of the motor could be influenced by restraining the biaryl moiety. To this end, motor 10 was studied (Scheme 4). This compound was obtained from precursor 2 by alkylation with CH$_2$I$_2$ using K$_2$CO$_3$ as base. Compound 10 was obtained as a single isomer, as was concluded on the basis of $^1$H NMR spectroscopy (Figure 4a).

![Scheme 4](image)

**Scheme 4:** Synthesis of compound 10.

The behavior of this motor was also examined with $^1$H NMR and UV/Vis spectroscopy. Characteristic shifts in the NMR spectra were observed upon irradiation of 10 at 365 nm
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at −30 °C, confirming the formation of the metastable isomer (PSS ratio: 91:9 metastable:stable) (Figure 4).

\[\text{C(Ha)3} \quad \text{O} \quad \text{O} \quad (\text{He})2\text{C} \quad \text{O} \quad \text{O} \quad \text{CH2} \quad \text{Hb} \quad \text{Hc} \quad \text{Hd} \quad \text{He} \quad \text{Ha}^{*} \quad \text{Hb} \quad \text{Hc} \quad \text{Hd} \quad \text{Ha}^{*}\]

(a)

(b)

Figure 4: $^1$H NMR of 10 in CD$_2$Cl$_2$ upon irradiation with 365 nm light−50 °C. (a) Initial state (b) PSS.

A bathochromic shift in the UV/Vis spectrum was observed upon irradiation of 10 with 365 light at 20 °C, indicating the formation of the metastable isomer. The subsequent THI was followed in time at various temperatures (30 °C to 42.5 °C) using UV/Vis spectroscopy, and the $\Delta^{\ddagger}G$ (20 °C) for this process was found to be 93.4 ± 1 kJ mol$^{-1}$ (Figure 5).

\[\Delta^{\ddagger}G (20 °C) = 93.4 \text{ kJ mol}^{-1}\]
\[\Delta^{\ddagger}H^* = 81.6 \text{ kJ mol}^{-1}\]
\[\Delta^{\ddagger}S^* = -40.0 \text{ J mol}^{-1} K^{-1}\]

Figure 5: (Left) UV/vis absorption spectra of 10 in CH$_2$Cl$_2$ and at 20 °C and spectral changes upon irradiation with 365 nm light. (Right) Eyring plot of the THI of 10.

The increase of 23.5 kJ mol$^{-1}$ in Gibbs free energy for the THI as compared to the diol precursor signifies a large decrease in the rotational speed. While motor 2 rotates approximately 1 time per second, tethering the biphenol with a methylene spacer, results in a decrease of the rotational speed by a factor $1.6 \times 10^4$, effectively braking the rotary
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motion. Importantly, the methylene spacer can be removed again using HCl (aq.) in refluxing ethanol. Braking of the rotary motion can thus be achieved in a reversible manner.

This approach however does not allow for in situ control of the behavior of the molecular motor, as it requires two reaction steps with various reagents and purification steps. These issues can be addressed by inducing conformational changes using non-covalent interactions. Hence, we explored ways to influence the biphenol moiety and thereby alter the rotary motion of the motor by non-covalent binding of diamines. It is known that 2,2’-biphenol and their derivatives can bind strongly to amines, diamines and aminoalcohols via hydrogen bonding.11

1H NMR spectroscopy revealed that trans-(±)-N,N'-dimethyl-1,2-cyclohexanediamine (11) binds to motor 2 in CD₂Cl₂. In the UV/Vis spectrum a bathochromic shift with clear isosbestic points was observed upon successive addition of 11 to 2. The binding constant of 11 to 2 was determined by a titration experiment with UV/Vis spectroscopy and was found to be \( K_a = 6.3 \times 10^3 \pm 3 \times 10^2 \text{ M}^{-1} \) in CH₂Cl₂ (Figure 6).

![Figure 6](image)

**Figure 6:** (Left) Changes in UV/Vis spectrum of 2 in CH₂Cl₂ (5.57 x 10⁻⁴ M) (200 μl in a 1 mm cuvette) upon sequential addition of a solution of 11 (5.25 x 10⁻³ M) and 2 (5.57 x 10⁻⁴ M) in CH₂Cl₂. (Right) Changes in absorptivity at 415 nm as a function of 11 added. The data was fitted using BindFit to a 1:1 binding model to give \( K_a = 6.3 \times 10^3 \text{ M}^{-1} \).12

The found binding constant is in the range of previously reported binding constants of 2,2’-biphenol derivatives with similar diamines (Figure 7). Closer examination of the values show that especially biphenols with electron withdrawing groups display high affinity for diamine guests. For these complexes, it is theorized that charge-assisted hydrogen bonds are responsible for the high binding constants.13
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Figure 7: Selected complexes of 2,2’-biphenols with diamines and their binding constants.\textsuperscript{9a,f}

After it was established that 11 binds to 2, the effect of the binding on the behavior of motor 2 was investigated. To this end, the same experiments were conducted as for motors 2 and 10. A sample of 2 (2.5 mM) with 11 (4 equiv) in CD\textsubscript{2}Cl\textsubscript{2} was irradiated with 365 nm light at −30 °C. The binding of 11 did not inhibit the photoisomerization of 2 from the stable to metastable isomer. A PSS ratio of 80:20 (metastable:stable) was obtained. Upon heating to room temperature the metastable isomer reverted to the stable isomer (Figure 8).

Figure 8: \textsuperscript{1}H NMR of 2 (1 mg/mL) and 11 (4 equiv) in CD\textsubscript{2}Cl\textsubscript{2} upon irradiation with 365 nm light. (a) \textsuperscript{1}H NMR of 2·11. (b) PSS mixture 80:20 (metastable:stable). (c) The spectrum obtained after heating of the PSS mixture showed some decomposition.

In the UV/Vis absorption spectrum of complex 2·11, a bathochromic shift was observed with clear isosbestic points upon irradiation with 365 nm. The thermal relaxation of the metastable to the stable isomer of 2 complexed with 11 was followed in time at various temperatures (−10 to 0 °C) (Figure 9). Eyring analysis of this process gave a $\Delta^\ddagger G$ (20 °C) of 80.9 ± 1 kJ mol\textsuperscript{−1} for the THI. The addition of 11 to 2 thus leads to an
increase in $\Delta^{2}G$ (20 °C) of the THI of 11 kJ mol$^{-1}$ and hence a decrease of the rotary frequency of motor 2 from 1.1 Hz to 0.012 Hz.

**Figure 9:** (Left) UV/vis absorption spectra of 2·11 in CH$_2$Cl$_2$ and at −10 °C and spectral changes upon irradiation with 365 nm light. (Right) Eyring plot of the THI of 2·11.

In order to show that the non-covalent binding of 10 to motor 2 is reversible, ways to accomplish decomplexation were explored. In figure 10 the spectral changes in the absorption spectra upon addition of either acetic acid or methanol to a solution of 2·11 are shown. In both cases it can be observed that after addition, the spectrum of 2 is obtained (Figure 6 and 10). (The spectral changes caused by the addition of 11 are reverted). From this observation it can be concluded that the dissociation of the complex 2·11 can be achieved by addition of methanol or acetic acid. The use of non-covalent substrate binding via hydrogen bonding thus enables the dynamic control of the rotary speed of a molecular motor.

**Figure 10:** (Left) UV/vis spectrum of a solution of 2·11 in CH$_2$Cl$_2$ ($\approx$2.4 x 10$^{-4}$ M, 250 μl) and spectral change upon addition of acetic acid (1 drop). (Right) UV/vis spectrum of a solution of 2·11 in CH$_2$Cl$_2$ ($\approx$1.2 x 10$^{-4}$ M, 250 μl) and spectral change upon addition of methanol (20 μl).
In table 1 the data on motors 2 and 10 and the complex 2·11 are summarized.

<table>
<thead>
<tr>
<th>Compound</th>
<th>PSS (365 nm)$^a$</th>
<th>$\Delta^G$</th>
<th>$t_{1/2}$ (s)$^c$</th>
<th>$\omega$ (Hz)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>43:57</td>
<td>69.9</td>
<td>0.32</td>
<td>1.1</td>
</tr>
<tr>
<td>10</td>
<td>91:9</td>
<td>93.4</td>
<td>5.0 x 10$^3$</td>
<td>7.0 x 10$^{-5}$</td>
</tr>
<tr>
<td>2·11</td>
<td>80:20</td>
<td>80.9</td>
<td>30</td>
<td>1.2 x 10$^{-2}$</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of motors 2, 10 and complex 2·11. $^a$metastable:stable, $^b$kJ mol$^{-1}$, $^c$ $t_{1/2} = \ln(2)/k$, $^d$ $\omega = \frac{1}{2} k$.

Scheme 5: Covalent and non-covalent regulation of the speed of molecular motor 2.

### 7.3 Conclusions

In conclusion, we have shown how the behavior of a biphenol functionalized molecular motor can be controlled via reversible covalent and non-covalent modifications. UV/Vis and $^1$H NMR spectroscopy revealed that motor 2 functions as anticipated. The tethering of the biphenol moiety with a methylene spacer resulted in a decrease of the rotational speed by a factor of 1.6 x 10$^4$, thereby effectively braking the rotary motion. Furthermore, it was found that the motor has the ability to bind diamine 11, which did increase the barrier of the THI by 11 kJ mol$^{-1}$. As the diamine can be released again by either addition of methanol or acetic acid, the behavior of the molecular motor can be reversibly modulated. This approach represents a new way of controlling the molecular motor via chemical triggers and is a key step in the development of light-driven molecular motors which display responsiveness to changes in the environment.

### 7.4 Experimental Section

**General Remarks**

For general comments, see chapter 2. Compound 3 was purchased from Fluorochem. Prof. dr. Wesley R. Browne is acknowledged for technical assistance with low-temperature UV/Vis measurements.
7-bromo-6-methoxy-2,3-dihydro-1H-inden-1-one (4)

N-Bromosuccinimide (7.30 g, 41.0 mmol) was added to a solution of 6-methoxy-2,3-dihydro-1H-inden-1-one (6.00 g, 37.0 mmol) in acetonitrile (200 mL). The reaction mixture was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo, redissolved in EtOAc (200 mL), washed with H2O (200 mL) and brine (200 mL), dried over Na2SO4 and subsequently concentrated in vacuo. The crude product was recrystallized from toluene to afford 4 as a white solid (4.20 g, 17.4 mmol, 47% yield). M.p. 171-172 °C. 1H NMR (400 MHz, CDCl3) δ 7.35 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 3.92 (s, 3H), 3.13 – 2.90 (m, 2H), 2.84 – 2.64 (m, 2H). 13C NMR (100 MHz, CDCl3) δ 204.1, 155.6, 149.2, 135.2, 125.9, 118.2, 108.3, 57.0, 37.8, 23.9. HRMS (ESI+) calcd for C10H10BrO2 [M+H]+ 240.9859, found: 240.9496.

6-methoxy-7-(2-methoxyphenyl)-2,3-dihydro-1H-inden-1-one (5)

A Schlenk flask was charged with bromoketone 4 (4.00 g, 16.6 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 208 mg, 0.51 mmol), Pd2dba3 (114 mg, 0.12 mmol), K3PO4 (10.60 g, 49.94 mmol), and 2-methoxyphenylboronic acid (5.20 g, 34.2 mmol). Three vacuum/N2 cycles were performed before toluene (30 mL) was added via syringe and the reaction mixture was heated at 100 °C for 16 h. EtOAc (30 mL) was added and the organic phase was washed with H2O (60 mL) and brine (60 mL), and subsequently dried over Na2SO4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO2, pentane/EtOAc) to afford 5 as a white solid (3.62 g, 13.5 mmol, 81% yield). M.p. 142-143 °C, 1H NMR (400 MHz, CDCl3) δ 7.44 – 7.39 (m, 1H), 7.37 (ddd, J = 8.4, 7.4, 1.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.13 (dd, J = 7.4, 1.8 Hz, 1H), 7.04 – 6.95 (m, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 3.06 (t, J = 6.1 Hz, 2H), 2.62 (ddd, J = 6.4, 4.8, 3.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 205.4, 157.2, 156.3, 147.2, 135.5, 131.0, 129.0, 126.2, 125.1, 123.0, 120.1, 118.3, 110.8, 56.8, 55.7, 37.5, 24.4. HRMS (ESI+) calced for C17H16O3Na [M+Na]⁺ 291.0989, found: 291.0992.

6-methoxy-7-(2-methoxyphenyl)-2-methyl-2,3-dihydro-1H-inden-1-one (6)

A solution of n-BuLi in hexanes (1.6 M, 1.54 mL, 2.46 mmol) was added to a solution of NH(i-Pr)2 (345 μl, 249 mg, 2.46 mmol) in THF (20 mL) at 0 °C and the solution was stirred for 0.5 h. The solution was cooled to −78 °C and a solution of ketone 5 (600 mg, 2.24 mmol) in THF (10 mL) was added dropwise via syringe. The solution was stirred for 0.5 h. CH3I (0.69 mL, 1.57 g, 11 mmol) was added to the reaction mixture, after which the cooling bath was removed. The reaction mixture was stirred for 16 h and treated with a saturated solution of NH4Cl (aq.) (20 mL). EtOAc (50 mL) was added and the organic phase was washed with brine (50 mL), and dried over Na2SO4 and concentrated in vacuo. The crude product was purified by column chromatography

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(SiO₂, pentane/EtOAc) to afford ketone 6 as a white solid in a diastereomeric ratio of dr: 45:55 (520 mg, 1.94 mmol, 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.37 (m, 2H), 7.32 – 7.25 (m, 1H), 7.26 – 7.14 (m, 1H), 7.11 – 6.97 (m, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H) (major), 3.74 (s, 3H) (minor), 3.43 – 3.27 (m, 1H), 2.79 – 2.61 (m, 2H), 1.284 (d, J = 7.1 Hz, 3H) (major), 1.276 (d, J = 6.9 Hz, 3H) (minor). ¹³C NMR (100 MHz, CDCl₃) δ 207.7 (minor), 207.6 (major), 157.1 (major), 156.9 (minor), 156.3 (major), 156.2 (minor), 145.3 (major), 145.1 (minor), 134.9 (minor), 134.7 (major), 131.0 (minor), 130.7 (major), 128.8, 126.0 (major), 125.9 (minor), 125.2 (major), 124.9 (minor), 123.1 (major), 122.9 (minor), 120.0, 118.2 (minor), 118.1 (major), 110.7 (major), 110.6 (minor), 56.6, 55.5 (major), 55.4 (minor), 43.0 (major), 42.9 (minor), 33.5, 33.5, 16.2 (major), 15.9 (minor). HRMS (ESI+) calcd for C₁₈H₁₉O₃ [M+H]+ 283.1329, found: 283.1330.

(6-methoxy-7-(2-methoxyphenyl)-2-methyl-2,3-dihydro-1H-inden-1-ylidene)hydrazine (7)

Hydrazine monohydrate (200 μl) was added to a solution of ketone 6 (194 mg, 0.69 mmol) and Sc(OTf)₃ (17 mg, 0.03 mmol) in ethanol (10 mL). The reaction mixture was heated at reflux for 16 h. The reaction mixture was poured into water and extracted with CH₂Cl₂ (2 x 50 mL). The organic phase was washed with H₂O (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography (SiO₂, pentane/EtOAc) to yield hydrazone 7 as a slightly yellow solid (149 mg, 0.50 mmol, 73%) ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.28 (m, 1H), 7.28 – 7.07 (m, 2H), 7.05 – 6.91 (m, 3H), 4.96 (br, 2H), 3.75 (s, 3H) (minor diastereoisomer), 3.72 (s, 6H), 3.70 (s, 3H) (major diastereoisomer), 3.31 – 3.14 (m, 2H), 2.54 (d, J = 14.9 Hz, 1H), 1.21 (app t, J = 6.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 159.6, 159.0, 157.8, 157.1, 156.7, 156.3, 137.7, 137.3, 137.0, 136.6, 131.6, 130.8, 128.0, 127.9, 126.1, 125.4, 125.0, 125.0, 123.4, 122.5, 120.2, 119.9, 112.7, 112.5, 111.0, 110.9, 56.5, 56.4, 56.0, 55.7, 37.2, 37.0, 32.5, 32.5, 17.1, 16.7.

9-(6-methoxy-7-(2-methoxyphenyl)-2-methyl-2,3-dihydro-1H-inden-1-ylidene)-9H-fluorene (9)

Bis(trifluoroacetoxy)iodo)benzene (921 mg, 2.14 mmol) was added to a solution of hydrazone 7 (604 mg, 2.04 mmol) in DMF (15 mL) at –40 °C. The reaction mixture was stirred for 2 min, after which a solution of freshly prepared thiofluorenone (800 mg, 4.08 mmol) in DMF (5 mL) was added via syringe. Stirring was continued for 16 h, allowing the reaction mixture to warm up to rt. EtOAc (100 mL) was added and the organic phase was extracted with brine (4 x 100 mL) and dried over Na₂SO₄. The crude product was purified by column chromatography (SiO₂, pentane/CH₂Cl₂) to yield episulfide 8 as a diastereomeric mixture (421 mg, 0.91 mmol, 45%) Diastereoisomer A:
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$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69 (d, $J$ = 7.3 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.47 – 7.38 (m, 2H), 7.35 (t, $J$ = 7.4 Hz, 1H), 7.28 (t, $J$ = 7.4 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.13 – 7.01 (m, 3H), 6.90 (d, $J$ = 8.3 Hz, 1H), 6.68 (d, $J$ = 8.1 Hz, 1H), 4.03 (s, 3H), 3.70 (s, 3H), 3.13 – 2.93 (m, 1H), 2.44 (dd, $J$ = 14.6, 5.5 Hz, 1H), 2.14 (d, $J$ = 14.5 Hz, 1H), 1.31 (d, $J$ = 6.9 Hz, 3H). Diastereoisomer B: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 – 7.60 (m, 2H), 7.63 (d, $J$ = 7.6 Hz, 1H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.41 – 7.29 (m, 3H) 7.24 – 6.98 (m, 4H), 6.98 – 6.91 (m, 2H), 6.77 (d, $J$ = 8.1 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.06 – 2.91 (m, 1H), 2.36 (dd, $J$ = 14.6, 5.6 Hz, 1H), 2.12 (d, $J$ = 14.5 Hz, 1H), 1.28 (d, $J$ = 7.1 Hz, 3H). HRMS (ESI+) calcd for C$_{31}$H$_{26}$O$_2$Na$^+ [M+Na]^+$ 485.1546, found: 485.1536. HMPT (423 mg, 471 $\mu$L, 2.59 mmol) was added to a solution of episulfide 8 (mixture of diastereoisomers, 400 mg, 0.86 mmol) dissolved in THF 5 mL). The reaction mixture was stirred for 36 h, and was concentrated in vacuo. The obtained crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$) to afford alkene 9 (320 mg, 0.74 mmol, 86%) as a yellow solid as a diastereomeric mixture (dr. 45:55). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 – 7.81 (m, 2H), 7.67 – 7.60 (m, 3H), 7.52 (d, $J$ = 7.5 Hz, 1H), 7.44 (d, $J$ = 7.5 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.33 – 7.27 (m, 4H), 7.10 – 7.04 (m, 3H), 7.02 (d, $J$ = 8.2 Hz, 1H), 6.98 – 6.85 (m, 4H), 6.82 (t, $J$ = 7.8 Hz, 1H), 6.68 – 6.60 (m, 2H), 6.46 (t, $J$ = 7.4 Hz, 1H), 6.40 (d, $J$ = 8.3 Hz, 1H), 4.17 (dp, $J$ = 20.0, 6.5 Hz, 2H), 3.94 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.35 (s, 3H), 3.37 – 3.29 (m, 2H), 2.65 (d, $J$ = 8.0 Hz, 1H), 2.61 (d, $J$ = 8.0 Hz, 1H), 1.53 (d, $J$ = 7.0 Hz, 3H), 1.48 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.6, 156.4, 155.8, 155.3, 152.1, 150.2, 142.0, 140.8, 140.1, 140.0, 139.7, 139.0, 138.4, 138.2, 137.2, 136.8, 134.9, 131.3, 131.0, 128.4, 128.2, 128.0, 126.7, 126.6, 126.4, 126.4, 126.3, 125.8, 125.7, 125.3, 125.2, 125.0, 124.9, 124.5, 124.2, 123.9, 123.4, 119.8, 119.5, 119.4, 119.4, 117.9, 117.9, 112.6, 112.5, 110.5, 110.3, 56.3, 56.1, 55.0, 54.7, 45.8, 45.3, 41.0, 40.6, 18.8, 18.6. HRMS (ESI+) calcd for C$_{31}$H$_{27}$O$_2$ [M+H]$^+$ 431.2006, found: 431.2000.

3-(9H-fluoren-9-ylidene)-4-(2-hydroxyphenyl)-2-methyl-2,3-dihydro-1H-inden-5-ol (2)

A solution of CH$_3$MgI (1.2 mL, 3 M in Et$_2$O, 3.6 mmol) was added to a Schlenk flask charged with alkene 9 (260 mg, 0.60 mmol) and the suspension was heated at 70 °C, allowing the evaporation of Et$_2$O. The obtained solid was heated at 160 °C for 16 h to yield a yellow foam. The reaction was cooled with an ice bath and ice was carefully added. CH$_2$Cl$_2$ and an aqueous HCl (1 M) solution was added and the biphasic system was stirred to ensure complete dissolution of any solid particles. The organic phase was washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated in vacuo. The product was purified by column chromatography (SiO$_2$, pentane/EtOAc) to afford biphenol 2 as a yellow solid (216 mg, 0.54 mmol, 89%). $^1$H NMR (400 MHz, CD$_2$OD/CDCl$_3$ 1:1) $\delta$ 7.81 (d, $J$ = 7.0 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.51 (d, $J$ = 7.8 Hz, 1H), 7.37 (d, $J$ = 7.4 Hz, 1H), 7.30 – 7.17 (m, 3H), 7.03 – 6.98 (m, 2H), 6.97 – 6.91 (m, 2H), 6.70 (t, $J$ = 7.7
Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 6.31 (t, J = 7.5 Hz, 1H), 4.15 (p, J = 8.6, 7.7 Hz, 1H), 3.27 (dd, J = 14.4, 6.0 Hz, 1H), 2.61 (d, J = 14.4 Hz, 1H), 1.50 (d, J = 6.7 Hz, 3H). $^1$H NMR (100 MHz, CD$_3$OD/CDCl$_3$ 1/1) δ 153.5, 153.0, 151.2, 141.2, 141.2, 140.7, 140.0, 139.0, 137.6, 133.2, 130.9, 129.3, 127.5, 127.2, 127.2, 127.0, 126.3, 126.1, 125.4, 125.0, 124.5, 120.3, 119.8, 119.1, 118.3, 116.8, 45.0, 41.0, 18.9. HRMS (ESI+) calcd for C$_{29}$H$_{22}$O$_2$Na [M+Na]$^+$ 425.1512, found: 425.1508.

12-(9H-fluoren-9-ylidene)-11-methyl-11,12-dihydro-10H-benzo[d]indeno[4,5-f][1,3]dioxepine (10)

Diiodomethane (46 mg, 14 μl, 0.17 mmol) and K$_2$CO$_3$ (70 mg, 0.51 mmol) were added to a solution of biphenol 2 (23 mg, 57 μmol) in acetone (10 mL). The reaction mixture was heated at reflux for 16 h, after which the mixture was reduced in vacuo. The crude product was redissolved in EtOAc and the organic phase was washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by column chromatography (SiO$_2$, pentane/EtOAc) yielded acetal 10 (7 mg, 17 μmol, 30%) as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.93 – 7.87 (m, 1H), 7.67 – 7.63 (m, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.40 – 7.28 (m, 4H), 7.21 (d, J = 7.9 Hz, 1H), 7.16 (dd, J = 7.7, 1.6 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.97 – 6.88 (m, 1H), 6.84 (td, J = 7.6, 1.2 Hz, 1H), 6.62 (td, J = 7.5, 1.4 Hz, 1H), 5.77 (d, J = 3.3 Hz, 1H), 5.70 (d, J = 3.3 Hz, 1H), 4.26 (p, J = 6.6 Hz, 1H), 3.37 (dd, J = 14.6, 6.2 Hz, 1H), 2.70 (d, J = 14.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.3, 151.8, 148.8, 144.9, 144.7, 140.4, 139.2, 139.1, 138.5, 136.8, 132.9, 132.0, 130.9, 129.1, 128.8, 127.0, 126.9, 126.6, 125.9, 125.8, 124.3, 124.2, 121.9, 121.2, 119.5, 118.0, 102.4, 44.1, 40.6, 18.6. HRMS (ESI+) calcd for C$_{30}$H$_{23}$O$_2$ [M+H]$^+$ 415.1693, found: 415.1692.

7.5 References

9. S. F. Pizzolato, Personal communication.