Chapter IV:

Third generation molecular motors: Achiral unidirectional molecular motors

Achiral molecular motors in which the presence of a pseudo-asymmetric carbon atom proved to be sufficient for exclusive autonomous disrotary motion of two appended rotor moieties are described. Isomerization around the two double bonds enables both rotors to move in the same direction with respect to their surroundings—like wheels on an axle—demonstrating that autonomous unidirectional rotary motion can be achieved in a symmetric system.

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Introduction

Artificial molecular motors enable a wide variety of functions such as movement at nanoscale\textsuperscript{1-7}, allow molecular system to operate far from equilibrium\textsuperscript{8,9} and dynamic control of mechanical, electronic and transport properties.\textsuperscript{10-15} Due to the ability to mimic dynamic and mechanical functions of complex biological systems, yet maintaining simplicity of design and robustness towards broad range of operating conditions, autonomous molecular devices are highly desirable. Many impressive applications of such machinery have been demonstrated including molecular electronics\textsuperscript{16,17}, molecular logic devices\textsuperscript{18,19}, artificial muscles\textsuperscript{20,21}, delivery systems\textsuperscript{22-24}, responsive surfaces\textsuperscript{25,26}, and switchable catalysis\textsuperscript{27-29}.

While the majority of these applications might not require directionality as a property embedded within the devices, the control over the directionality of rotary motion is essential to performing certain mechanical tasks, as is seen with ATPase-mediated transport\textsuperscript{30}, flagella-based bacterial swimming\textsuperscript{31} and the rotation of microscopic objects at the liquid crystal air interface by directional rotation of a chiral nematic phase\textsuperscript{32}.

Chirality embedded in a molecule is not a prerequisite for directionality in a motor system as shown for a stimuli-induced movement of mechanically interlocked motor by Leigh and co-workers (Scheme 1).\textsuperscript{33,34} In this case, a specific sequence of chemical steps is used to induce the rotary motion of the smaller macrocycle between three different binding sites in a [2]catenane by changing the binding affinity ($K_a$) of the three stations for the smaller macrocycle. It should be noted though, that autonomous directionality is not inherent in this system, but it is introduced by the researcher performing the specific sequence of chemical transformations.
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Scheme 1. The concept of unidirectional rotation in a mechanically interlocked motor proposed and realized by the group of Leigh. (reproduced from ref. 33)

Despite the use of an achiral molecule in a surface-mounted motor with appending redox-active ferrocene units published by Vives et al., the directionality in this motor is in fact governed by the entire system being non-symmetric due to presence of the two electrodes (Figure 1). 35

Figure 1. Chemical structure of the electrochemically driven molecular motor embedded between two electrodes by Vives et al. (reproduced from ref. 35)

In order to enable autonomous directional movement and avoid an equal probability of clockwise and anticlockwise rotation around a single rotary axle connecting rotor and stator, our synthetic rotary motors rely on the chirality of the system. In biological motors, transfer of point chirality to helical chirality and chiral macromolecular assemblies determine the rotational direction, and in the overcrowded alkene-based rotary motors the direction of rotation is dictated by point chirality, due to creating an energetic difference between the two available helical chiral structures.
In the first and second generation light-driven molecular motors, the presence of stereocenters is an essential for unidirectional movement; one of the basic requirements of a rotary motor besides energy consumption, rotary motion and a repetitive process. However, is chirality a requirement for autonomous directional rotary motion in these light-driven motors or can rotary function be achieved with an achiral molecule? Symmetry considerations of rotary motion dictate that from the submolecular level e.g. disrotatory motions in electrocyclic reactions, to macroscopic length scales e.g. the rotation of two (car) wheels on an axle, the directionality of rotary motion from an observer at the symmetry plane is opposite. Despite the entire system being symmetric (Cs plane of symmetry) the rotatory motion of the two wheels on an axle with respect to the surrounding is identical (e.g. both forward rotation for an external observer33) allowing concerted rotary motion to induce directional translational motion. Translating these symmetry considerations to a stereochemical design featuring two integrated rotor moieties in a meso compound we demonstrate here that a symmetric (achiral) light-driven molecular motor is feasible (Figure 2).

**Design and synthesis of p-xylene based third generation motors**

The design of the achiral molecular motor system (Figure 2) is based on second generation rotary motors37,39 featuring a helical structure (P or M helicity) and a single stereocenter (R or S chirality). The direction of light-powered rotary motion is governed by the central chirality (R or S) of the molecular motor and the enantiomer with P helicity induces counterclockwise rotation upon repetitive photochemical and thermal isomerization steps, while clockwise rotary motion is observed for the M-helical structure. We envisioned that upon merging two enantiomers of such a motor 4.1 (Figure 2) the resulting molecule will lose its chirality (symmetric meso structure 4.2) but it will maintain a pseudo-asymmetric carbon40-42 at C2 with the potential to control directionality of rotation. This pseudo-asymmetric center allows each rotor part to retain its helicity and undergo unidirectional rotation, provided it is still able to undergo a photochemical E-Z isomerization (PEZ) followed by a subsequent thermal helix inversion (THI). If alternatively the PEZ isomerization were to be followed by a thermal E-Z isomerization no net rotation would be achieved and it would function as a switch. It should be emphasized that the symmetric meso structure 4.2 accommodates two helical moieties with distinct P and M configuration. Although molecular chirality is not a prerequisite to achieve unidirectional rotary motion (*vide infra*), i.e. permanent point chirality is not required, there is
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still a need for some chiral information in the form of pseudo-asymmetry. *Meso-(r)-4.2*, featuring a methyl and hydrogen at C2, was inaccessible due to insurmountable problems in each of the synthetic steps which is attributed to the acidity of the hydrogen at the pseudo-asymmetric carbon (C2, double allylic position) in 4.2.

Figure 2. Schematic design of achiral motors; merging of two enantiomers of motor 4.1 (opposite helicities (P,M) and central chirality (R,S) indicated) give rise to symmetric double overcrowded alkene 4.2 (pseudo-asymmetric carbon atom indicated with its stereo descriptor (r)), substitution of hydrogen at C2 for fluorine gives meso-4.3.

Introduction of an additional methyl group at C2 as in *meso-4.2* would afford a quaternary center and eliminate these problems, but such a molecule would lose its pseudo-asymmetric center (two methyl substituents at C2) and therefore its potential unidirectionality of rotation. In the second generation molecular motors such as 4.1 (Figure 2) the stereocenter has two substituents of which one is pseudo-equatorially oriented towards the fluorene moiety which creates steric hindrance while the other substituent is in a pseudo-axial orientation away from the fluorene. The difference in size of these substituents allows for the existence of a stable state with the small substituent in the pseudo-equatorial orientation and a metastable state when the larger substituent is oriented pseudo-equatorially. Analogously in this symmetric ‘third’ generation of molecular motors (4.2) the two substituents (Me and R1) at the pseudo-asymmetric center C2 in the core part should have a distinct difference in size to provide a difference in energy between the two possible meso isomers. This energy difference should always thermodynamically drive the rotor units forward through sequential photochemical and thermal helix isomerization steps in the
same direction to the global minimum energy configuration and therefore control the directionality of rotor movement relative to the core part. We anticipated that a quaternary center at C2 bearing a methyl group and a fluorine atom, as present in *meso-(s)-4.3* (Figure 2), would provide a sufficient difference in size. Furthermore, the introduction of a substituent at the rotor units induces dissymmetry in the rotors allowing each individual step in the 360° rotary cycle to be analyzed (*vide infra*).

![Scheme 2. Schematic representation of the conceived rotation of appending rotor units, one at a time.](image)

The synthesis of fluorinated third generation motors started with preparation of the central core 4.5. The synthetic procedure for this molecule reported in the literature featured many steps and it was therefore desirable to develop a shorter route. Eventually, the indandione 4.4 was synthesized by a double Friedel-Crafts acylation of *p*-xylene with 2-methylmalonyl dichloride in 38% yield (Scheme 3). The choice of solvent (CS₂ or CH₂Cl₂) did not have a significant influence on the yield of the reaction. Electrophilic fluorination in the α-position of the diketone 4.4 proceeded smoothly to give the indandione 4.5 in excellent yield. It was later established that the use of K₂CO₃ to facilitate formation of the corresponding enolate greatly increases rate of the reaction, completing the conversion in 1 h instead of 16 hours.
Scheme 3. Synthesis of the central core 4.5 from p-xylene.

The diketone 4.5 was converted into the corresponding dithioketone 4.6 using a mixture of P₂S₅ and Lawesson’s reagent in refluxing toluene for 16 hours (Scheme 4). Remarkably, the fluorine substituent was capable of withstanding these conditions. The conversion to the double thioketone could be conveniently monitored using ¹⁹F NMR spectroscopy. The signal of the fluorine atom shifted downfield to -134.5 ppm (dithioketone). The isolated dithioketone 4.6 was used immediately in the double Barton-Kellogg coupling with 9-diazofluorenone. Subsequently, the mixture was treated with HMPT to desulphurize the episulfide and provide the final third generation motor 4.3 in 33% yield over the three steps.

Scheme 4. Synthesis of the motor 4.3 via double Barton-Kellogg coupling.

In analogous fashion, the desymmetrized motor 4.7 was synthesized for the purpose of investigating unidirectionality of these motors based on this unprecedented scaffold (Scheme 5). The motor 4.7 was formed as a mixture of four isomers due to different configurations (E/Z) around the double bonds. The separation of isomers was performed by SFC.
Scheme 5. Synthesis of the desymmetrized motor 4.7 as a mixture of the four possible geometric isomers.

Photochemical and thermal isomerization studies of \( p \)-xylene based motors in solution

The photochemical and thermal isomerization processes of 4.3 were followed by UV-vis spectroscopy (Figure 3a). Irradiation of \( \text{meso-}(s)\)-4.3 by UV-light (365 nm in CH\(_2\)Cl\(_2\), Figure 3c) at -80 °C was accompanied by a bathochromic shift in the UV-Vis absorption spectrum in accordance with second generation motors and indicative of an increase in alkene strain as expected for \( (P)\)-4.3/\( (M)\)-4.3. After reaching the photostationary state (PSS), the sample was allowed to warm to room temperature and full reversal to the original UV-vis spectrum was observed in accordance with the anticipated helix inversion to \( \text{meso-}(s)\)-4.3' (Figure 3). No sign of decomposition was observed over two photochemical-thermal isomerization cycles. During both the thermal and photochemical processes an isosbestic point was observed at the same wavelength (412 nm), establishing the absence of formation of \( \text{meso-}(r)\)-4.3 (Figure 3b) during the photochemical or thermal isomerizations. The calculated barriers for thermal interconversion of \( \text{meso-}(r)\)-4.3 to \( \text{meso-}(s)\)-4.3 is \( \Delta T^G^\circ = 106 \) kJ.mol\(^{-1}\), and for \( (P)\)-4.3 /\( (M)\)-4.3 to \( \text{meso-}(s)\)-4.3 \( \Delta T^G^\circ = 73.5 \) kJ.mol\(^{-1}\). This means that at room temperature \( (P)\)-4.3/\( (M)\)-4.3 will quickly isomerize (\( t_\frac{1}{2} \) at room temperature = 1 s) while \( \text{meso-}(r)\)-4.3 would be slow to isomerize (\( t_\frac{1}{2} \) at room temperature = 4 d) and therefore result in a lasting change in the absorption spectra of 4.3.
Independent NMR spectroscopy experiments confirmed that the starting isomer is the expected meso-(s)-4.3 with a C₅ symmetrical configuration (Figure 3d, ¹H NMR spectrum i) with the fluorine in a pseudo-equatorial configuration indicated by the strong through-space coupling of the fluorine and the proximal aromatic protons (¹⁹F NMR (470 MHz, CD₂Cl₂) δ = -133.94 (qt, ³J₈₉(9,F) = 17.2 Hz, ⁶J₉₈(F,H1) = 5.6 Hz), vide infra). Irradiation at -56 °C produces a metastable state in which the isochronosity of the absorptions of the two rotors is lost, indicative of the expected C₁ symmetry of (P)-4.3/(M)-4.3 and the sample was irradiated until a photostationary state of 7.5 : 92.5 (meso-(s)-4.3 : (P)-4.3/(M)-4.3) was reached (Figure 3d, ¹H NMR spectrum ii). No trace of meso-(r)-4.3 was observed during irradiation nor when the sample was allowed...
to warm as indicated by the emergence and disappearance of only one additional $^{19}\text{F}$ absorption assigned to $(P)$-$\text{4.3}$/$(M)$-$\text{4.3}$ (Figure 4a). In theory, it is possible that meso-$(r)$-$\text{4.3}$ could be formed by two $E$-$Z$ photoisomerizations at both carbon-carbon double bonds, in which the first forms metastable $(P)$-$\text{4.3}$/$(M)$-$\text{4.3}$ and the second forms meso-$(r)$-$\text{4.3}$. Photo-excitation of meso-$(s)$-$\text{4.3}$ or $(P)$-$\text{4.3}$/$(M)$-$\text{4.3}$ has never been observed to lead to the formation of meso-$(r)$-$\text{4.3}$. This might be explained by an asymmetric excited state surface of $(P)$-$\text{4.3}$/$(M)$-$\text{4.3}$ which is to be expected of molecules with a $C_1$ symmetry; such an asymmetry could lead to the exclusive $E$-$Z$ photoisomerization of the carbon-carbon double bond that forms meso-$(s)$-$\text{4.3}$.

**Figure 4.** (a) i) $^{19}\text{F}$ NMR spectrum of meso-$(s)$-$\text{4.3}$ (CD$_2$Cl$_2$, 564 MHz, rt); ii) $^{19}\text{F}$ NMR spectrum of the sample irradiated to PSS in NMR (CD$_2$Cl$_2$, 564 MHz, $-20^\circ\text{C}$); iii) $^{19}\text{F}$ NMR spectrum at $t = 30$ min (CD$_2$Cl$_2$, 564 MHz, $-20^\circ\text{C}$). (b) Expansion of the $^{19}\text{F}$ NMR spectrum of meso-$(s)$-$\text{4.3}$ (CD$_2$Cl$_2$, 564 MHz, rt) depicting splitting of the signal.

The $^{19}\text{F}$ NMR spectroscopy shows quadruple triplet with coupling constants of 17.2 and 5.6 Hz, respectively (Figure 4b). The same splitting ($J_{AM}(H_9,F) = 17.2$ Hz) can be observed in the $^1\text{H}$ NMR spectrum of $\text{4.3}$, in which the signal for the methyl group on the pseudoasymmetric carbon is split to a doublet with a coupling constant of 17.2 Hz. While the coupling of $J_{AM}(F,H_1) = 5.6$ Hz is not as clearly visible, this is due to additional through-space spin-spin coupling of H$_1$ and the fluorine atom at the pseudoasymmetric atom, as evidenced by the broadening of signal of H$_1$ compared to that of H$_4$. Upon irradiation, an upfield shift of the $^{19}\text{F}$ signal is observed, and the initial spectrum is completely recovered upon standing or warming to room temperature (Figure 4a).

Upon increasing the temperature of the sample to $-38^\circ\text{C}$ the $^1\text{H}$ NMR spectrum of meso-$(s)$-$\text{4.3}'$ was obtained after 12 h (Figure 3d, $^1\text{H}$ NMR spectrum iv which is identical to the $^1\text{H}$ NMR spectrum i of meso-$(s)$-$\text{4.3}$ due to the symmetry of the
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roto
dors). This sequence is in accordance with a photoequilibrium between meso-(s)-4.3 and metastable states (P)-4.3/(M)-4.3, followed by a thermal isomerization of (P)-4.3/(M)-4.3 to afford meso-(s)-4.3’. Following this thermal process over time using NMR, the energies of activation were derived (Δ‡H° 78.3±1.6 kJ.mol⁻¹, Δ‡S° 10.0±6.5 J.K⁻¹.mol⁻¹, Δ‡G° 75.3±0.3 kJ.mol⁻¹, t½=1 h at T=-31.8±0.1 °C, see Figure 5) in good agreement with the calculated barrier (Δ‡G°calc 73.5 kJmol⁻¹).

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Figure 5. (a) Thermodynamic data for the thermal helix inversion of (P)-4.3/(M)-4.3 to meso-(s)-4.3. (b) Eyring plot for the thermal process.

To prove unequivocally the unidirectionality in the rotor motion, asymmetric substitution of the rotors is required in order to identify a single PEZ-THI sequence for each of the isomers involved in the rotary cycle. To this end, a methoxy substituent was introduced in each of the rotors units providing compounds 4.7 (Scheme 5). The four isomers of 4.7 were separated using preparative supercritical fluid chromatography on a chiral stationary phase (SFC, isomers 1-4).

The rotational behavior of isomer 1, (R,(Z,M),(E,P))-4.7, was studied (Figure 6) in CD₂Cl₂ by irradiation using 365 nm light at -90 °C for no more than three hours to prevent any thermal isomerization and subsequent warming to room temperature in the dark allowing for a thermal isomerization to take place. The products were identified by SFC and ¹H NMR as the expected (s,E,E)-4.7 and (s,Z,Z)-4.7 isomers (Figure 6b). These data provide unequivocal evidence for a sequence of two steps; first a single photochemical E-Z isomerization of either rotor (step 1) yielding a mixture of the starting material and two helical metastable isomers ((M,Z,Z)-4.7 and (P,E,E)-4.7), followed by a thermal helix inversion of the rotating unit to (s,Z,Z)-4.7 and (s,E,E)-4.7 (step 2), completing a half turn rotation of either rotor unit. These experiments were repeated for each of the individual isomers 2-4 ((s,(Z,P),(E,M))-4.7, (s,E,E)-4.7 and (s,Z,Z)-4.7) and
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they show identical behavior. Each of the four isomers produces the anticipated products of a PEZ-THI sequence with a single rotor unit undergoing a 180° rotation, providing the evidence for unidirectionality of rotary motion in these double overcrowded alkenes. In all cases the rotor unit that undergoes the initial photochemical isomerization continues rotary motion in the same forward direction through a subsequent thermal helix inversion in accordance with the process shown in Figure 2.45

Figure 6. Unidirectional rotation of (R,(Z,M),(E,P))-4.7 followed by SFC and ¹H NMR. (a) Photochemical E-Z isomerization of (R,(Z,M),(E,P))-4.7 yields metastable helical intermediates which undergo thermal helix inversions to produce a mixture of (s,Z,Z)-4.7 and (s,E,E)-4.7. (b) Left: SFC chromatograms (Chiralpak® IA, 32% 2-propanol in CO₂, 340 nm, 3.5 mL min⁻¹, T = 40 °C, 180 bar). Right: ¹H NMR spectra (CD₂Cl₂, 500 MHz, rt) of the methoxy absorptions. i) isolated isomer 1, R,(Z,M),(E,P))-4.7, in red; ii) mixture after irradiation of R,(Z,M),(E,P))-4.7 with 365 nm light for 3 h at -90 °C in CD₂Cl₂ directly followed by a thermal isomerization in the dark for 1 h at room temperature; iii) SFC chromatograms and ¹H NMR spectra of all isolated isomers of 4.7 superimposed for reference with individual isomers color coded as follows: 1 red R,(Z,M),(E,P))-4.7; 2 green (S,(Z,P),(E,M))-4.7; 3 blue (s,E,E)-4.7; 4 purple (s,Z,Z)-4.7 (note that the ¹H NMR spectra of isomers 1 and 2 overlap on account of their enantiomeric relationship).
In conclusion, it has been shown that in third generation molecular motors presented herein, the presence of a pseudo-asymmetric center is sufficient to induce unidirectional rotary motion. Although the molecule is achiral and possesses a plane of symmetry, the pseudo-asymmetric carbon atom with two substituents of distinct size imposes the necessary bias that results in unidirectional rotation of the two rotor moieties powered by light. Thereby, the intrinsic directionality in autonomous rotary motion at the molecular level can be obtained in a genuine achiral molecular motor providing important insight in the control of nanoscale movement facing the challenge to design future molecular machines.

**Synthesis of other third generation motors**

**Third generation motors with a benzene-based core**

Being inspired by the functioning design of the achiral molecular motors, we have envisioned that tuning the rotational speed would prove to be beneficial for application as nanomachines. As a first step, reduction of the steric hindrance between the stator and the rotors was conceived, thus achieving much shorter half-life of the metastable state which is an important property when considering directional movement of the molecules on a surface (Figure 7).

![Figure 7](image.png)

**Figure 7.** Reduction of the p-xylene core to a benzene core.

In the first step of the synthesis, a double condensation of dimethyl phthalate and pentan-3-one with the aid of sodium hydride affords the mono-substituted indandione 4.8 (Scheme 6). In an analogous fashion as for the p-xylene based
molecular motors, the indandione was fluorinated using Selectfluor® in acetonitrile in excellent yield. The resulting indandione 4.9 was then converted into the corresponding dithioketone 4.10 using Lawesson’s reagent. Interestingly, this dithioketone was found to be much less stable than the analogue 4.6 and decomposed during the reaction unless a fresh batch of Lawesson’s reagent in dry toluene was used. Reacting 4.10 with 9-diazofluorenone in toluene, followed by desulphurization using HMPT, the motor 4.11 was isolated in 14 % yield over the 3 steps. Unlike the motor 4.3, the analogue 4.11 was found to be substantially less stable and decompose in CDCl₃. Slow evaporation of a CH₂Cl₂ solution provided a single crystal suitable for X-ray analysis (Figure 8). The structure shows that the fluorene units are sandwiching the fluorine atom as expected based on the through-space coupling described for the previous motor 4.3 in Figure 4b.

Scheme 6. Synthesis of the analogue 4.11 featuring a benzene central core.
Figure 8. X-ray structure of the molecular motor 4.11. The fluorine atom is depicted in yellow. Hydrogen atoms have been omitted for clarity. (a) front view, with the benzene core in the x-y plane. (b) side view, with the benzene core in the x-y plane.

In order to prove that these fast third generation are capable of undergoing unidirectional rotation of the fluorene rotors upon irradiation, asymmetry had to be introduced in the rotating units (Scheme 7). Performing the double Barton-Kellogg using 2-methoxy-9-diazofluorenone, the desymmetrized motor 4.12 was synthesized as a statistical mixture of the four possible geometric isomers. As in the previous case, these were found to be inseparable by flash column chromatography. Therefore, supercritical fluid chromatography (SFC) was employed to isolate the individual isomers.44

Scheme 7. Synthesis of the desymmetrized derivative 4.12.
Other third generation motors

Further modifications in the scaffold of the third generation motors were explored, primarily to eliminate the instability of the fluorine atom on the pseudoasymmetric carbon, and to allow for a possibility of derivatization for applications such as attachment on surfaces. For this purpose, motors bearing two alkyl substituents (4.13-14) or alkyl/aryl (4.15) substituents were proposed (Figure 9). Eventually, the terminal alkene of 4.14 might be functionalized by hydroboration or radical addition of thioacetic acid, while the methoxy group of 4.15 could be deprotected to provide a handle for derivatization.

Figure 9. Envisioned more sterically hindered molecular motors, featuring isopropyl group at the pseudoasymmetric carbon.

The indenedione 4.15 was prepared by double Friedel-Crafts acylation of \( p \)-xylene using 2-isopropylmalonyl dichloride and \( \text{AlCl}_3 \) in a moderate yield. The mono-substituted indenedione 4.16 was then alkylated using methyl iodide in acetonitrile to access 4.17. It has been observed that a competing O-alkylation is taking place along with C-alkylation, with the two products being difficult to separate. However, the use of 50% KF on Celite together with Aliquat 336 substantially suppress formation of the O-alkylated product.\(^{47}\) The reason for this selectivity still remains unclear.

The indenedione 4.17 was subsequently transformed into the corresponding thioketone 4.18 using a mixture of \( \text{P}_2\text{S}_5 \) and Lawesson’s reagent. The thioketone 4.18 did not undergo the following Barton-Kellogg coupling as anticipated. Instead, it has been observed that only side of the central core reacts, while the other thioketone remains unreacted. This has been circumvented before by transforming the remaining thioketone into a hydrazone and performing second Barton-Kellogg coupling, considerably lengthening the synthesis.\(^{48}\) To prevent this, it was decided to explore the possibility of inverted Barton-Kellogg
coupling involving conversion of the indenedione 4.18 to bisdiazo-derivatives. Unfortunately, reaction of 4.18 with hydrazine hydrate resulted in a complex mixture and did not provide the desired bishydrazone 4.19. The reaction was, however, successful for a less hindered, dimethyl substituted, indanedione before. This suggests the steric hindrance introduced by the presence of isopropyl substituent prevents this transformation.

Scheme 8. Synthesis and functionalization of indenedione core 4.17.

The α-aryl substituted indenedione 4.20 was synthesized in one step by a condensation of phthalide with p-methoxybenzaldehyde in presence of sodium methoxide (Scheme 9).\textsuperscript{46} Remarkably, alkylation with 2-iodopropane in DMF provided an inseparable mixture of C-alkylated 4.21 and O-alkylated products (20:1) in excellent yield.\textsuperscript{49} Unfortunately all further attempts to derivatize the indenedione 4.21 to the corresponding dithioketone or bishydrazone were unsuccessful and only the starting material was isolated.


From these two examples, it can be concluded that more sterically hindered systems either cannot be transformed to the required intermediates using status
*quo* methods or the Barton-Kellogg coupling itself does not proceed as expected due to poor reactivity of the intermediates. Further investigation is necessary to establish a functional synthesis for these hindered and more advanced systems.

**Photochemical and thermal isomerization studies of other third generation motors in solution**

**Third generation motors with benzene-based core**

The behavior of motor 4.11 under irradiation was investigated using $^1$H NMR and UV-vis spectroscopy. As expected, no changes were observed in the $^1$H or $^{19}$F NMR spectrum at high or low temperature, or after irradiation at room or low temperature, which is in agreement with the very low barrier for THI predicted by quantum chemical calculations. Therefore, in order to prove these fast third generation molecular motors are capable of undergoing rotation of the fluorene units under UV irradiation in a unidirectional fashion, asymmetry was introduced in the rotor units and the desymmetrized motor 4.12 was synthesized (*vide supra*).

Scheme 10. Rotational cycle of 4.12 depicting the anticipated photochemical/THI relationship of the individual isomers.
The individual isomers were separated using SFC (45% 2-propanol in CO₂, Chiralpak ID® at 3.5 ml/min, 40 °C, 160 bar). The four isomers are indistinguishable by UV-vis specroscopy, however, $^{19}$F and $^1$H NMR spectroscopy allowed for assignment of the individual isomers where the enantiomers 1-4.12 and 3-4.12 displayed identical NMR spectra and were assigned based on their retention time in analogy to 4.7. Irradiation of an isolated isomer of 4.12 is expected to allow it to undergo a photochemical E-Z isomerization to be directly followed by a thermal helix inversion. This produces the two connected isomers in a 50:50 ratio (Scheme 10), which subsequently produce both the starting isomer as well as the last isomer connected to those isomers again in a 50:50 ratio. Finally, this last isomer is formed but at the same time undergoes isomerization producing the two intermediate isomers again. Based on these processes, the reactions are expected to be described by the following integrated rate laws in which ‘A’ is taken to be the starting isomer, ‘B’ and ‘C’ as the connected isomers and ‘D’ the final isomer according to the reaction equation D$\rightleftharpoons$C$\rightleftharpoons$A$\rightleftharpoons$B$\rightleftharpoons$D:

\[
\begin{align*}
[A] &= y_A + z_A \cdot e^{-t/k_1} + 2 \cdot z_A \cdot e^{-t/(2k_1)} \\
[B] &= y_B + z_B \cdot e^{-t/k_1} \\
[C] &= y_C + z_C \cdot e^{-t/k_1} \\
[D] &= y_D + z_D \cdot \frac{(1+k_2^{-1}e^{-t/k_1}-k_1^{-1}e^{-t/k_1})}{k_1^{-1}-k_2^{-1}}
\end{align*}
\]

Concentrated solutions in CH$_2$Cl$_2$ of the individual isomers 1–4 of 4.12 purged with argon were placed in the autosampler of the SFC machine, in front of which a UV-lamp (365 nm) was positioned. High concentration was used to allow minimal injection volume, in order to keep the change in total volume as small as possible, simultaneously ensuring the process lasts long enough for the collection of sufficient data. While the samples were being irradiated, SFC samples were taken in regular intervals and the chromatograms were integrated and the normalized integrals plotted against time.
Figure 10. SFC integrals normalized over time of the four isolated isomers of 4.12 under 365 nm irradiation at rt.

The black lines (Figure 10) are equations 1–4 fitted against the experimental data points by least squares analysis providing high coefficients of determination ($R^2 > 0.997$). Each starting isomer is fitted against equation 1, taking the place of A in the proposed reaction equation. The expected isomers connected to the starting isomers are fitted against equation 2 and 3 taking the place of B and C and the final isomer is fitted against equation 4 as D. For example, starting from isomer 1 of 4.12 as A, the reaction equation becomes $3 \iff 2 \iff 1 \iff 4 \iff 3$, and isomer 1 exhibits exponential decay to its equilibrium concentration, isomer 1 and 4 exhibit exponential formation to their equilibrium concentration and isomer 3 exhibits an S shaped curve signifying its delayed formation. The observed behavior proves the connectivity of the isomers as in the proposed rotational cycle (Scheme 10) and was observed likewise starting from the other isomers (2–4) of 4.12 (Figure 10). Inferring from the fitted lines (Figure 10), it is clear that in each instance, isomers ‘B’ and ‘C’ reach their equilibrium concentration faster than ‘A’ and ‘D’ do, though it should be noted that that does not mean they stop participating in the rotary cycle, however, in a steady state they in fact keep rotating being the intermediates between ‘A’ and ‘D’.

Conclusions

We have demonstrated the thermal and rotational behavior of a series of third generation light-driven molecular motors (4.3, 4.7, 4.11 and 4.12). The steric
motive of the core proved to be decisive in the tuning of the potential speed of double overcrowded alkenes. The benzene-based motor 4.11 is potentially the fastest unidirectional motor based on overcrowded alkenes reported to date and its desymmetrization into motor 4.12 allowed for the visualization of the equal rotation of the two rotor units, perfectly following the predicted kinetic model for their rotational behavior. Transient absorption spectroscopy is required to allow further investigation of its behavior and properties.

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Jos C. M. Kistemaker is greatly acknowledged for performing the irradiation experiments described in this chapter and collaboration on all projects concerning the third generation motors.

**Experimental section**

**General remarks**

For general remarks regarding synthesis, characterization and experimental details see Chapter 2. All photochemical experiments were carried out using a Spectroline model ENB-280C/FE lamp at $\lambda = 365 \pm 30$ nm or an LED (5 W, 365 nm, 10 nm width at half-height), mounted in a modified Nalorac Z-Spec probe in the Varian Innova-600 NMR. Samples irradiated for $^1$H NMR spectroscopy were placed 3-5 cm from the lamp. Irradiations at low temperatures were performed in standard EtOH/N$_2$ bath. Photostationary states were determined by monitoring changes in UV-vis spectra or $^1$H NMR spectra until no further changes were observed. Irradiations of the ultrafast motors were performed as follows – concentrated solutions in CH$_2$Cl$_2$ pruged with argon were placed in the autosampler of the SFC machine, in front of which a ENB-280C/FE lamp was positioned. Kinetic analysis of the thermal isomerization steps was performed by UV-vis spectroscopy. Changes in UV-vis absorptions were monitored at different temperatures. The array of the UV-vis spectra was processed using multivariate analysis (from 200 to 800 nm) to obtain the corresponding rate constants from which an Eyring plot was constructed. $\Delta^\ddagger G^\circ$, $\Delta^\ddagger H^\circ$, $\Delta^\ddagger S^\circ$ and $t_{1/2}$ (20 °C) were extracted from this plot.
Synthesis of the compounds

2,4,7-Trimethyl-1H-indene-1,3(2H)-dione (4.4).
Oxalyl chloride (25.0 mL, 286 mmol) was added to a stirred solution of 2-methylmalonic acid (10.0 g, 85.0 mmol) and few drops of DMF in dry CH₂Cl₂ (150 mL) at room temperature. After stirring for 16 h, the volatiles were removed under reduced pressure. The residue was redissolved in dry CH₂Cl₂ (150 mL) and p-xylene (7.3 mL, 59.3 mmol) was added. The solution was heated to reflux and solid AlCl₃ (23.7 g, 178 mmol) was added portionwise over 2 h. The reaction was quenched by pouring onto ice (~300 mL). The organic layer was separated and the water layer was washed with CH₂Cl₂ (2 × 80 mL). The combined organic layers were washed with brine (100 mL) and dried over MgSO₄. The solvents were evaporated at reduced pressure. The residue was purified by column chromatography on silica gel (pentane : ethyl acetate – 30 : 1) followed by recrystallization from hetpane (10 mL) to give 4.4. Yield: 4.21 g (38%). White needles. Mp 89.3–90.5 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.43 (s, 2H), 2.98 (q, 1H, J = 7.6 Hz), 2.69 (s, 6H), 1.37 (d, 3H, J = 7.6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 202.4, 139.4, 137.2, 135.9, 49.4, 18.4, 10.4.

2-Fluoro-2,4,7-trimethyl-1H-indene-1,3(2H)-dione (4.5).
A solution of 4.4 (1.08 g, 5.7 mmol) and Selectfluor® (2.64 g, 7.5 mmol) in acetonitrile (50 mL) was heated to 70 °C for 16 h. The solvent was evaporated under reduced pressure and the residue was partitioned between diethyl ether (50 mL) and water (40 mL). The organic layer was separated, washed with water (3 × 30 mL), brine (30 mL) and dried over MgSO₄. The volatiles were evaporated at reduced pressure to give the pure product 4.5. Yield: 4.21 g (38%). White solid. Mp 91.3-93.2 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.54 (s, 2H), 2.72 (s, 6H), 1.63 (d, 3H, J = 23.1 Hz). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 196.2 (d, J = 17.3 Hz), 138.7, 137.4 (d, J = 2.8 Hz), 137.3 (d, J = 2.8 Hz), 89.3 (d, J = 194.6 Hz), 18.5, 18.2 (d, J = 26.8 Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -166.4 (q, J = 23.1 Hz). HRMS (APCI⁺): calcd for C₁₂H₁₂FO₂⁺ (M + H⁺) 207.0816 found 207.0815.
9,9’-(2-Fluoro-2,4,7-trimethyl-1H-indene-1,3(2H)-diylidene)bis(9H-fluorene) (4.3).

A solution of the diketone 4.5 (251 mg, 1.2 mmol), P₂S₅ (808 mg, 3.6 mmol) and Lawesson’s reagent (1.47 g, 3.6 mmol) in toluene (20 mL) was heated at reflux under nitrogen atmosphere until full conversion to the bisthioketone 4.6 as monitored by ¹⁹F NMR (~16 h; ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -134.5 (q, J = 20.6 Hz)). The mixture was left to cool down and passed directly over a short column of silica gel. The column was washed (pentane : ethyl acetate – 10 : 1) until no more thioketone was eluted as indicated by TLC. The solvents were removed under reduced pressure. The resulting red colored oil (4.6) was redissolved in toluene (20 mL) and solid 9-diazo-9H-fluorenone⁵¹ (484 mg, 2.5 mmol) was added portionwise to the stirred solution. After stirring at room temperature for 3 h, HMPT (460 μl, 2.5 mmol) was added and the stirring continued overnight. The volatiles were evaporated at reduced pressure. The residue was adsorbed on silica gel and purified by column chromatography on silica gel (pentane : CH₂Cl₂ – 5 : 1). The resulting pale orange solid was further purified by washing with ethanol (2 × 3 mL) and pentane (2 × 2 mL) to give the pure product 4.3. Yield: 174 mg (33%). Bright yellow solid. Mp 240.9-241.2 °C (dec.). ¹H NMR (500 MHz, CD₂Cl₂): δ (ppm) 8.10 (m, 2H), 7.69–7.73 (m, 4H), 7.43 (d, 2H, J = 7.9 Hz), 7.28–7.35 (m, 4H), 7.26–7.29 (m, 4H), 7.12 (dd, 2H, J₁ = 7.5 Hz, J₂ = 7.5 Hz), 2.19 (d, 3H, J = 17.2 Hz), 2.14 (s, 6H). ¹³C NMR (126 MHz, CD₂Cl₂): δ (ppm) 145.8, 145.6, 141.1, 141.1, 139.8, 139.4, 138.2, 136.8, 134.5, 132.6, 131.0, 127.8, 127.5, 127.2, 127.1, 126.6, 126.4, 123.4, 119.2, 119.0, 109.4 (d, J = 206.2 Hz), 21.9 (d, J = 24.2 Hz), 21.2. ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -133.2 (qt, J₁ = 16.7 Hz, J₂ = 5.4 Hz). HRMS (APCI⁺): calcd for C₃₈H₂₈F⁺ (M + H⁺) 503.2170 found 503.2155.

9,9’-(2-Fluoro-2,4,7-trimethyl-1H-indene-1,3(2H)-diylidene)bis(2-methoxy-9H-fluorene) (4.7).

A solution of the diketone 4.5 (402 mg, 1.9 mmol), P₂S₅ (2.16 g, 9.7 mmol) and Lawesson’s reagent (3.14 g, 7.76 mmol) in toluene 25 mL was heated at reflux under nitrogen atmosphere until full conversion to the bisthioketone 4.6 as monitored by ¹⁹F NMR (~16 h; ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -134.5 (q, J = 20.6 Hz)). The mixture was left to cool down and passed directly over a short column of silica gel. The column was washed (pentane : ethyl acetate – 10 :
1) until no more thioketone was eluted as indicated by TLC. The solvents were removed under reduced pressure. The resulting red colored oil (4.6) was redissolved in toluene (10 mL) and slowly added into a stirred solution of freshly prepared 9-diazoo-2-methoxy-9H-fluorene51 (559 mg, 2.5 mmol) in THF (40 mL). After stirring at room temperature for 3 h, HMPT (460 µl, 2.5 mmol) was added and the stirring continued overnight. The volatiles were evaporated at reduced pressure. Absolute ethanol (30 mL) was added to the residue and the mixture was stirred for 30 min. The yellow precipitate was filtered off and washed with ethanol (3 × 10 mL) give the product 4.7 as a mixture of isomers (1:1:2) inseparable by column chromatography. Yield: 322 mg (34%). Bright yellow solid. Mp 240.5–241.4 °C (dec.). 1H NMR (400 MHz, CDCl3): δ (ppm) 8.06 (dd, 2H, J1 = 6.5 Hz, J2 = 6.5 Hz), 7.66 (m, 2H), 7.60 (dd, 8H, J1 = 8.6 Hz, J2 = 8.6 Hz), 7.44 (d, 2H, J = 7.9 Hz), 7.24–7.32 (m, 10H), 7.03–7.08 (m, 4H), 6.92 (dd, 2H, J1 = 8.4 Hz, J2 = 1.1 Hz), 6.87 (dd, 2H, J1 = 8.2 Hz, J2 = 2.0 Hz), 3.93 (s, 6H), 3.69 (s, 3H), 3.67 (s, 3H), 2.17–2.25 (m, 18H). 13C NMR (100 MHz, CDCl3): δ (ppm) 159.99, 159.60, 159.58, 146.39, 146.37, 146.3, 146.19, 146.18, 146.1, 142.3, 142.21, 142.19, 142.15, 142.13, 142.07, 141.14, 141.12, 141.00, 140.95, 140.67, 140.64, 139.42, 139.36, 139.33, 139.30, 137.74, 135.52, 135.50, 135.43, 135.41, 135.34, 135.32, 135.22, 135.20, 134.32, 134.30, 133.95, 133.54, 133.40, 133.26, 132.35, 132.32, 132.30, 132.27, 128.75, 128.31, 127.85, 127.81, 127.71, 127.67, 126.34, 126.29, 126.20, 126.18, 126.13, 126.11, 124.09, 124.06, 120.39, 120.36, 119.13, 119.01, 114.49, 114.35, 114.07, 114.00, 113.92, 113.86, 113.43, 111.07, 111.00, 110.24, 109.88, 109.01, 108.94, 56.14, 56.01, 55.90, 55.79, 22.58, 22.34, 21.65, 21.62. 19F NMR (376 MHz, CDCl3): δ (ppm) -132.7 (qt, J1 = 16.9 Hz, J2 = 4.8 Hz), -133.1 (qt, J1 = 16.9 Hz, J2 = 5.2 Hz), -133.3 (qt, J1 = 16.8 Hz, J2 = 5.4 Hz). HRMS (APCI+): calcd for C40H32FO2+ (M + H+) 563.2381 found 563.2364.

2-Fluoro-2-methyl-1H-indene-1,3(2H)-dione (4.9).
A solution of 4.816 (1.10 g, 6.84 mmol), K2CO3 (1.23 g, 8.89 mmol) and Selectfluor® (3.15 g, 8.89 mmol) in acetonitrile (50 mL) was heated at reflux for 16 h. The solvent was evaporated under reduced pressure and the residue was partitioned between diethyl ether (50 mL) and water (40 mL). The organic layer was separated, washed with water (3 × 30 mL), brine (30 mL) and dried with MgSO4. The volatiles were evaporated at reduced pressure to give the pure product 4.9. Yield: 1.17 g (96%). White solid. Mp 63.2–64.5 °C. 1H NMR (400 MHz, CDCl3): δ (ppm) 8.06 (dd, 2H, J1 = 5.8 Hz, J2 = 3.0 Hz), 7.97 (dd, 2H, J1 = 5.8 Hz, J2 = 3.0 Hz), 1.67 (d, 3H, J = 23.2 Hz). 13C NMR
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(100 MHz, CDCl₃): δ (ppm) 195.0 (d, J = 17.6 Hz), 140.0, 137.4, 124.7, 89.6 (d, J = 196.6 Hz), 18.1 (d, J = 26.8 Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -167.2 (q, J = 23.2 Hz). HRMS (ESI): calcd for C₁₀H₄F₂⁺ (M + H⁺) 179.0503 found 179.0495.

9,9’-(2-Fluoro-2-methyl-1H-indene-1,3(2H)-diylidene)bis(9H-fluorene) (4.11).
A solution of the diketone 4.9 (272 mg, 1.5 mmol) and Lawesson’s reagent (3.71 g, 9.2 mmol) in toluene (20 mL) was refluxed under nitrogen atmosphere for 16 h. (¹⁹F NMR (~16 h; ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -136.4 (q, J = 21.3 Hz)). The mixture was left to cool down and passed directly over a short column of silica gel. The column was washed (pentane : ethyl acetate – 10 : 1) until no more thioketone 4.10 was eluted as indicated by TLC. The solvents were removed under reduced pressure. The resulting blue oil (4.10, 70 mg) was redissolved in toluene (20 mL) and solid 9-diazo-9H-fluorenone (166 mg, 0.9 mmol) was added portionwise to the stirred solution. After stirring at room temperature for 3 h, HMPT (160 µl, 0.9 mmol) was added and stirring was continued overnight. The volatiles were evaporated at reduced pressure. Ethanol (10 mL) was added to the residue and the solid was filtered off. The resulting yellow solid was further purified by washing with ethanol (2 x 2 mL) and pentane (2 x 2 mL) to give the pure product 4.11. Yield: 99 mg (14%). Bright yellow solid. Mp >187 °C (dec.). ¹H NMR (400 MHz, CD₂Cl₂): δ (ppm) 8.43 (d, 2H, J = 8.0 Hz), 7.34–7.36 (m, 2H), 8.18 (dd, 2H, J₁ = 5.9 Hz, J₂ = 3.2 Hz), 7.74–7.89 (m, 4H), 7.33–7.41 (m, 8H), 7.17 (dd, 2H, J₁ = 7.7 Hz, J₂ = 7.7 Hz), 2.21 (d, 3H, J = 15.7 Hz). ¹³C NMR (100 MHz, CD₂Cl₂): δ (ppm) 146.0, 145.8, 142.0 (d, J = 5.7 Hz), 141.1 (d, J = 8.2 Hz), 138.1, 137.6, 131.5, 130.0, 129.0, 128.9 (d, J = 2.0 Hz), 128.4, 127.7, 127.6, 127.4 (d, J = 2.4 Hz), 126.7, 124.5, 119.8 (d, J = 3.8 Hz), 106.7 (d, J = 200.9 Hz), 20.3 (d, J = 23.2 Hz). ¹⁹F NMR (376 MHz, CD₂Cl₂): δ (ppm) -140.4 (q, J = 15.8 Hz). HRMS (ESI): calcd for C₃₆H₂₃⁺ (M – F⁻) 455.1794 found 455.1769.

9,9’-(2-Fluoro-2,4,7-trimethyl-1H-indene-1,3(2H)-diylidene)bis(2-methoxy-9H-fluorene) (4.12).
A solution of the diketone 4.9 (300 mg, 1.7 mmol) and Lawesson’s reagent (4.09 g, 10.1 mmol) in toluene (25 mL) was heated at reflux under nitrogen atmosphere for 16 h. (¹⁹F NMR (~16 h; ¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -136.4 (q, J = 21.3 Hz)). The mixture was left to cool down and passed directly over a short column of silica gel. The column was washed (pentane : ethyl acetate – 10 : 1) until no more thioketone 4.10 was
eluted as indicated by TLC. The solvents were removed under reduced pressure. The resulting blue colored oil (4.10, 117 mg) was redissolved in toluene (10 mL) and solid 9-diazo-2-methoxy-9H-fluorene\textsuperscript{51} (300 mg, 1.3 mmol) was added portionwise to the stirred solution. After stirring at room temperature for 3 h, HMPT (245 \( \mu \)L, 1.3 mmol) was added and stirring was continued overnight. The volatiles were evaporated at reduced pressure. Ethanol (10 mL) was added to the residue and the solid was filtered off. The resulting yellow solid was further purified by washing with ethanol (2 \( \times \) 2 mL) and pentane (2 \( \times \) 2 mL) to give the pure product 4.12 as a statistical mixture of isomers. Yield: 188 mg (21%). Bright yellow solid. \( \text{Mp} \geq 180 ^\circ \text{C} \) (dec.). \textsuperscript{1}H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \( \delta \) (ppm) 8.39 (dd, 1H, \( J_1 = 7.2 \text{ Hz}, J_2 = 7.2 \text{ Hz} \)), 8.24–8.30 (m, 2H), 8.18–8.20 (m, 1H), 8.03 (dd, 1H, \( J_1 = 8.8 \text{ Hz}, J_2 = 2.2 \text{ Hz} \)), 7.91 (1H, m), 7.62–7.68 (m, 4H), 7.30–7.36 (m, 5H), 7.10 (dd, 2H, \( J_1 = 8.3 \text{ Hz}, J_2 = 2.2 \text{ Hz} \)), 6.98 (dd, 2H, \( J_1 = 8.3 \text{ Hz}, J_2 = 2.2 \text{ Hz} \)), 6.93 (m, 1H), 3.96–3.97 (s, 3H), 3.79 (m, 3H), 2.17–2.25 (m, 3H). \textsuperscript{13}C NMR: could not be recorded due to extremely low solubility. \textsuperscript{19}F NMR (376 MHz, CD\(_2\)Cl\(_2\)): \( \delta \) (ppm) -139.5 (q, \( J = 15.7 \text{ Hz} \)), -134.0 (q, \( J = 16.0 \text{ Hz} \)), -140.3 (q, \( J = 15.8 \text{ Hz} \)). HRMS (ESI): calcd for C\(_{38}\)H\(_{27}\)O\(_2\)^{+} (M – F) 515.2006 found 515.1987.

**2-Isopropyl-4,7-dimethyl-1H-indene-1,3(2H)-dione (4.16).** Oxalyl chloride (7.4 mL, 86.3 mmol) was added to a stirred solution of 2-isopropylmalonic acid (4.00 g, 27.4 mmol) and few drops of DMF in dry CH\(_2\)Cl\(_2\) (120 mL) at room temperature. After stirring for 16 h, the volatiles were removed under reduced pressure. The residue was redissolved in dry CH\(_2\)Cl\(_2\) (150 mL) and \( p \) -xylene (2.28 g, 21.5 mmol) was added. The solution was brought to reflux under nitrogen atmosphere and solid AlCl\(_3\) (7.59 g, 56.9 mmol) was added portionwise over 2 h. The reaction was quenched by pouring onto ice (~ 300 mL). The organic layer was separated and the water layer was washed with CH\(_2\)Cl\(_2\) (3 \( \times \) 50 mL). The combined organic layers were washed with brine (100 mL) and dried with MgSO\(_4\). The solvents were evaporated at reduced pressure. The residue was purified by column chromatography on silica gel (pentane to pentane : ethyl acetate = 5 : 1) to give 4.16 as yellow oil (3.74 g, 17.3 mmol, 81%). \textsuperscript{1}H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.40 (s, 2H), 2.81 (d, \( J = 3.7 \text{ Hz} \), 1H), 2.69 (s, 6H), 2.60–2.44 (m, 1H), 1.06 (d, \( J = 6.8 \text{ Hz} \), 6H). \textsuperscript{13}C NMR (75 MHz, CDCl\(_3\)) \( \delta \) (ppm) 202.7, 140.3, 137.1, 135.7, 59.0, 29.2, 19.5, 18.5.
2-Isopropyl-2,4,7-trimethyl-1H-indene-1,3(2H)-dione (4.17).
A mixture of 4.16 (1.27 g, 5.9 mmol), KF on celite (50%, 0.19 g, 1.6 mmol), Aliquat 336 (0.230 g, 0.57 mmol) and K₂CO₃ (0.92 g, 6.6 mmol) were added to acetonitrile (60 mL). The mixture was heated to reflux and iodomethane (1.07g, 7.5 mmol) was added. The mixture was heated to reflux for 3 more hours. The mixture was divided between diethyl ether (100 mL) and water (500 mL) and the organic phase was extracted with aq. NaOH (2 × 300 mL, 1 M), aq. HCl (30 mL, 1 M), sat. aq. NaHCO₃ (30 mL), water (30 mL) and brine (30 mL). The combined organic layers were dried with MgSO₄ and the solvents were removed under reduced pressure. The crude product was purified by column chromatography (pentane : ethyl acetate – 50 : 1) to give indenedione 4.17 as a yellow oil (0.846 g, 3.91 mmol, 67%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.41 (s, 2H), 2.69 (s, 6H), 2.12 (hept, J = 6.9 Hz, 1H), 1.24 (s, 3H), 0.92 (d, J = 7.0 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 206.6, 139.0, 137.2, 135.7, 56.3, 34.2, 18.5, 18.1, 17.5.

2-Isopropyl-2,4,7-trimethyl-1H-indene-1,3(2H)-dithione (4.18).
The indenedione 4.17 (0.30 g, 1.3 mmol) was dissolved in p-xylene (45 mL). Lawesson's reagent (2.08 g, 5.2 mmol) and P₂S₅ (1.16 g, 5.2 mmol) were added and the mixture was heated to reflux under nitrogen atmosphere. After 30 h and 100 h, more P₂S₅ (2 × 1.2 g, 2 × 5.2 mmol) was added. The mixture was cooled down to rt after a week, pentane (45 mL) was added and the mixture was filtered through a pad of celite (2 × 1 cm). The pad was washed with pentane (2 × 20 mL) The solvent was removed under vacuum and the product was purified by column chromatography (pentane) to give 4.18 as purple oil (0.21 g, 0.79 mmol, 61%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.46 (s, 2H), 2.82 (s, 6H), 2.41– 2.31 (m, 1H), 1.54 (s, 3H), 0.82 (d, J = 6.5 Hz, 73H). ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 147.6, 140.0, 139.3, 43.5, 27.8, 25.1, 20.5.

2-(4-Methoxyphenyl)-1H-indene-1,3(2H)-dione (4.20).
A mixture of isobenzofuran-1(3H)-one (5.00 g, 37.3 mmol), 4-methoxybenzaldehyde (5.07 g, 37.3 mmol) and MeONa (6.00 g, 112 mmol) was dissolved in a mixture of EtOAc (25 mL) and MeOH (40 mL) and heated to reflux under nitrogen atmosphere. After stirring for 2 h, the color changed to dark red. Water (70 mL) was added to the reaction mixture at this point and the reflux was resumed for additional 30 min. Upon cooling down to rt, the reaction mixture was poured into water (150
mL). The mixture was acidified to pH 2 with conc. HCl and filtered. The filter cake was washed with water (2 × 50 mL) and the solid was triturated at 70 °C with EtOH (90 mL) acidified with 5 drops of conc. HCl. The mixture was left to cool down in freezer overnight, filtered and washed with EtOH (40 mL) to give 4.20 as white solid (5.3 g, 21.0 mmol, 57%). Mp. 153.1–154.2 °C. 1H NMR (300 MHz, CDCl3) δ (ppm) 8.02 (dd, J = 12.6, 5.6 Hz, 2H), 7.86 (dd, J = 12.2, 2.9 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 9.1 Hz, 2H), 4.21 (1H, s), 3.75 (3H, s). 13C NMR (75 MHz, CDCl3) δ (ppm) 198.7, 159.8, 142.6, 136.0, 129.9, 125.2, 123.7, 114.5, 59.1, 55.3.

2-Isopropyl-2-(4-methoxyphenyl)-1H-indene-1,3(2H)-dione (4.21). A mixture of 4.20 (2.00 g, 7.9 mmol), 2-iodopropane (2.69 g, 1.6 mL, 15.8 mmol) and K2CO3 (3.30 g, 23.7 mmol) in dry DMF (40 mL) was heated to 115 °C under nitrogen atmosphere. After stirring for 3 h, the reaction mixture was cooled to rt and water (70 mL) was added. The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with water (2 × 30 mL), brine (30 mL) and dried with MgSO4. The solvents were removed under reduced pressure and the residue was evaporated with heptane (2 × 30 mL). The crude product was purified by column chromatography (pentane : ethyl acetate – 30 :1) to give 4.21 as yellow oil (1.82 g, 6.2 mmol, 78%) contaminated with a small amount of the O-alkylated product (~5%). 1H NMR (300 MHz, CDCl3) δ (ppm) 7.97 (m, 2H), 7.81 (m, 2H), 7.41 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 3.75 (3H, s), 2.75 (septet, J = 6.8 Hz, 1H), 0.93 (d, J = 6.9 Hz, 6H).

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