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Maleimide cycloadditions by sulfinyldienes: is the sulfur configuration the only controller of the diastereofacial selectivity?

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Abstract—Cyclohexylsulfinyl-3-methyl-1,3-butadienes **5**, **6**, and 1-[1-(cyclohexylsulfinyl)ethenyl]cyclohexene (**7**), easily prepared from cyclohexanethiol (**1**) via transient cyclohexanesulfenic acid (**4**), were reacted with *N*-phenylmaleimide under different conditions, at normal and high pressure. The stereochemical outcome of these cycloadditions contributes a better understanding of the relationships among different factors controlling facial diastereoselection.

1. Introduction

In the last 20 years a number of articles have dealt with the synthetic scope and limitations of the sulfinyl group acting as stereodifferentiating element in Diels–Alder (DA) cycloadditions.[1] The electronic and structural features of the chiral sulfur atom, bearing the strongly electron-withdrawing sulfinyl oxygen, the sterically undemanding lone pair, and the alkyl or aryl group, assure, in almost all cases, very good stereoselection results. In particular, the stereochemical behaviour of sulfinyl dienes, in which the sulfoxide sulfur is directly linked to the diene skeleton, depends upon the position of the sulfoxide moiety within the diene, the electronic and steric nature of dienophile, and eventually the involvement of a catalyst in the cycloaddition. It has been frequently observed that dienophiles such as maleimides approach 2-sulfinyl dienes from their less hindered and more nucleophilic face (the one bearing the electronic lone pair) with the sulfinyl group adopting a conformation along the C(diene)–S bond in which the electrostatic repulsions between the sulfinyl oxygen and the heteroatoms of the dienophile are minimised (**A** in Fig. 1).[2]

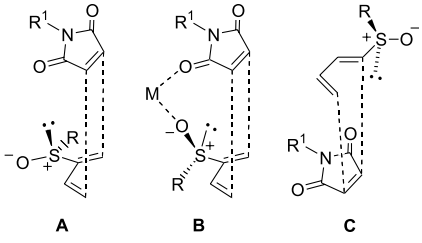

Figure 1. Favoured *endo*-approaches of maleimides in Diels–Alder reactions with sulfinyl dienes.

The presence of a catalyst, able to link the basic centres of the two reagents, changes the conformational preference of the diene to allow this association (**B** in Fig. 1). In the less reactive 1-sulfinyl dienes the favoured approach of maleimide takes place again from the less hindered face of the diene that adopts a conformation exhibiting the greatest distance between the oxygen atoms of diene and dienophile (**C** in Fig. 1).[3]

Table 1 illustrates the preferred diene face for dienophile *endo*-approach in uncatalyzed cycloadditions of several 2-sulfinyl dienes with maleimides. We have chosen to tabulate all the literature data corroborated by X-ray analysis of the major (or unique) cycloadduct. In order to facilitate the reading of the paper, the sulfur CIP descriptors have been converted into sulfur *pseudo*-descriptors (*pR* or *pS*, column 6 in Table 1) obtained by assigning arbitrarily

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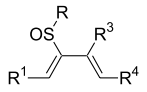
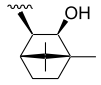
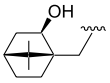
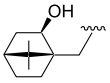
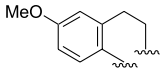
Table 1. Literature data concerning Diels–Alder *endo*-diastereoselective cycloadditions of maleimides with



Entry	R	R^1	R^3/R^4	Diene config.	Sulfur *pseudo*-config.	Dienophile	Preferred diene face for dienophile *endo*-approach	Ref.
1	*p*MeC$_6$H$_4$	H	H/Me	(R_S,*E*)	(*pS*)	Maleimide	(*Re*)	2a
2		H	H/H	(R_S)	(*pR*)	NPM	(*Si*)	2b
3		H	H/OMe	(R_S,*E*)	(*pR*)	NPM	(*Si*)	2c
4		H	H/OMe	(S_S,*E*)	(*pS*)	NPM	(*Re*)	2d
5		H	–(CH$_2$)$_4$–	(R_S)	(*pR*)	NPM	(*Si*)	2e
6		H		(S_S)	(*pS*)	NPM	(*Si*)	4
7	C_6H_5	Me	H/H	(R_S,*Z*)	(*pS*)	NPM	(*Re*)	2f

the priority to the sulfinyl oxygen, followed by the diene system, and finally by alkyl or aryl substituent at sulfur atom. Furthermore, the face descriptor is assigned by referring to the diene carbon directly linked to the sulfur atom (column 8 in Table 1). Apart from the example shown in entry 6, the reported cases are consistent with sulfur configuration controlling the diastereofacial selectivity: maleimides prefer the approach to (*pS*)-2-sulfinyl dienes from their less hindered (*Re*) face (entries 1, 4, and 7), and vice-versa the (*Si*) face of approach is chosen by dienophile when (*pR*) is the configuration at the sulfinyl sulfur of the diene (entries 2, 3, and 5).

In the addition of *N*-phenylmaleimide (NPM) to the enantiopure 2-sulfinyldiene reported in entry 6 of Table 1, low *endo*/*exo*-diastereoselectivity and complete but reversed diastereofacial selectivity in the *endo*-approach were observed. A tentative rationalisation of these results was based on the high steric requirements of both diene and dienophile,[4] such that the less sterically congested *exo*-approaches occurred in high percentage but without significant facial discrimination, while the more sterically demanding *endo*-approach happened with complete facial selection. NPM cycloadded to the diene from a face opposite to the one normally observed for analogous sulfinyl dienes (Table 1, entries 1–5, and 7) and this unexpected result was explained by proposing a preferred diene **D** conformation (Fig. 2) in which the electrostatic repulsion between the sulfinyl oxygen and the π-system of the fused benzene ring is avoided in the transition state of the cycloaddition. In other occasions, we could observe how the diene steric requirements dramatically affected the stereochemical results of DA cycloadditions involving 2-sulfinyl dienes,[5] and we wondered if the sulfur configuration could be regarded as the only controller of the diastereofacial selectivity.

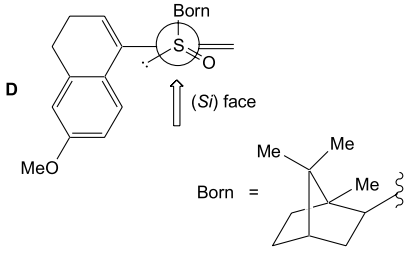
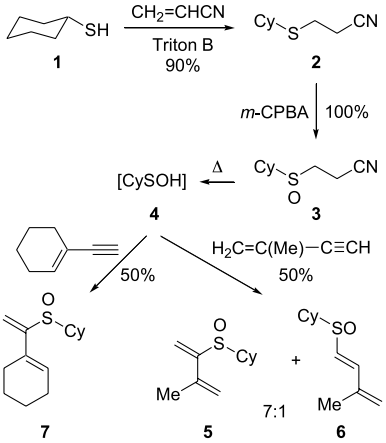


Figure 2. Preferred conformation **D** of (S_S)-4-{1-[(1*S*)-*exo*-2-bornylsulfinyl]ethenyl}-1,2-dihydro-7-methoxynaphthalene in its Diels–Alder *endo*-approach with NPM (entry 6 in Table 1).

For a deeper understanding of this matter, we accomplished the synthesis of 1- and 2-sulfinyl dienes with a cyclohexyl moiety directly linked to the sulfinyl sulfur atom, and substituents in 3 or 3,4-positions of the diene skeleton. In



Scheme 1.

Table 2. Reaction conditions of the Diels–Alder cycloadditions of dienes **5–7** with *N*-phenylmaleimide (NPM)

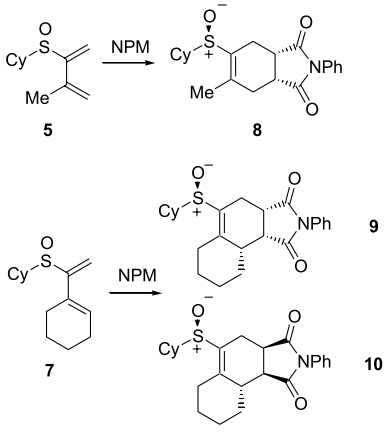
Entry	Reactants (equiv ratio)[a]	Solvent	Conditions	Products (ratio)	Yield[b] (%)
1	**5**/NPM (1:5)	$CH_2Cl_2/CHCl_3$ (3:1)	40 °C, 60 h, 1 bar	**8**	55
2	**5**/NPM (1:5)	$CH_2Cl_2/CHCl_3$ (3:1)	25 °C, 20 h, 8 kbar	**8**	53
3	**5**/NPM (1:5)	PhMe	70 °C, 20 h, 1 bar	**8**	48
4	**5**/NPM (1:5)	CH_2Cl_2	50 °C, 18 h, 8 kbar	**8**	46
5	**7**/NPM (1:6)	PhMe	70 °C, 21 h, 1 bar	**9/10** (5.3:1)	47
6	**7**/NPM (1:5.7)	CH_2Cl_2	25 °C, 24 h, 8 kbar	**9**	69
7	**7**/NPM (1:5.4)	CH_2Cl_2	50 °C, 19 h, 8 kbar	**9**	45
8	**6**/NPM (1:5)	PhMe	70 °C, 24 h, 1 bar	—	—
9	**6**/NPM (1:5)	CH_2Cl_2	25 °C, 24 h, 8 kbar	**11/12** (3.6:1)	60

[a] Diene concentration 0.1 M.
[b] The yields refer to isolated cycloadducts.

this paper, we report the results of the DA reactions of these dienes with NPM under thermal conditions, at normal and high pressure. It is well known that high pressure can accelerate DA reactions, therefore allowing cycloadditions of poorly reactive and/or heat sensitive substrates to be carried out under mild conditions.[6] We have chosen NPM as dienophile mainly for its intrinsic ability to produce crystalline cycloadducts that could be subjected to X-ray analysis and give us unassailable stereochemical responses.

2. Results and discussion

Cyclohexanethiol (**1**) was reacted with acrylonitrile in the presence of trimethylbenzylammonium hydroxide (Triton B) to give the thioether **2** in 90% yield (Scheme 1).[7] Oxidation of **2** with 3-chloroperbenzoic acid (*m*-CPBA) gave cyclohexyl sulfoxide **3**, that constitutes suitable precursor of transient sulfenic acid **4**.[8] Acid **4**, thermally generated in the presence of the enyne acceptor, *syn*-added to the triple bond of 2-methyl-1-buten-3-yne leading to the formation of dienes **5** and **6** in 7:1 ratio and 50% overall yield. Cyclohexylsulfinyl dienes **5** and **6** were easily separated by column chromatography and fully characterised. 1-[1-(Cyclohexylsulfinyl)ethenyl]cyclohexene (**7**) was obtained in useful yield (50%) as the product of the completely regioselective addition of sulfenic acid **4** to the triple bond of 1-ethynylcyclohexene.



Scheme 2.

Diene **5** cycloadded to NPM under different reaction conditions, as reported in Table 2, at atmospheric and high pressure (Scheme 2). The reaction occurred with complete facial diastereoselection leading to the unique cycloadduct **8**. Results listed in Table 2 show that the increased pressure accelerates DA process (compare entries 1 and 2) but does not affect either stereochemical results or yields. Crystallisation from ethyl acetate of compound **8** afforded crystals suitable for X-ray analysis whose result, shown in Figure 3, confirmed the structural determination conducted by extensive NMR investigation. Since the chemical shifts of H_2-4 and H_2-7 were very close in ^1H spectra, distinction between them was made by the observed NOE involving the methyl protons and nearest H-7. Furthermore, H-3a and H-7a were assigned by selective decoupling of H_2-4 and H_2-7, and by ^1H–^{13}C hetero-correlated experiments. Finally, the 9.0 Hz value of $J_{3a,7a}$ confirmed the *cis*-arrangement of H-3a and H-7a, while the extended boat conformation of the cyclohexene ring, observed also in the solid state (Fig. 3), followed from the coupling constant values $J_{3a,4}$ (7.1, 2.4 Hz) and $J_{7,7a}$ (6.0, 2.9 Hz). X-ray analysis of adduct **8** allowed the

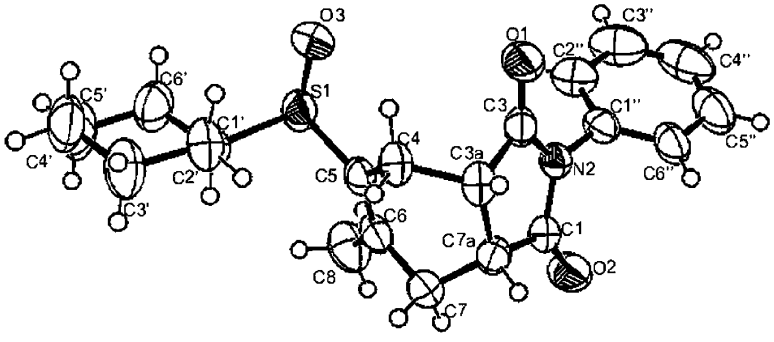


Figure 3. Perspective view of the structure of **8** with probability displacements ellipsoids representing all non-H atoms. The atom-numbering scheme is consistent with the systematic nomenclature numbering.

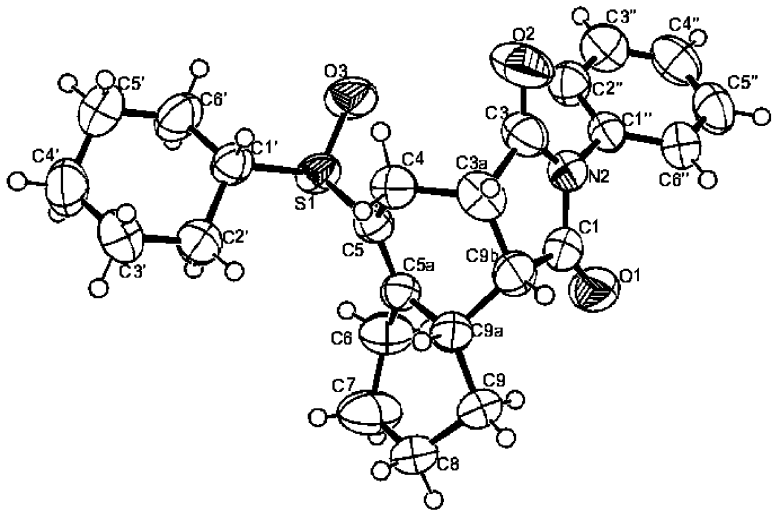


Figure 4. Perspective view of the structure of **9** with probability displacements ellipsoids representing all non-H atoms. The atom-numbering scheme is consistent with the systematic nomenclature numbering.

unambiguous assignment of the configuration to the newly formed stereocentres 3a and 7a, in relation to the configuration of the sulfinyl sulfur atom, as (3a*S**,7a*R**,R_S*). This stereochemical outcome is consistent with NPM *endo*-approach to the (*Re*) face of diene (R_S)-**5** (analogously to entry 6 in Table 1).

Entries 5–7 in Table 2 concern the results of DA reaction of NPM with inner-outer diene **7**. When cycloaddition was performed in toluene, at 70 °C, a complete π-facial selectivity was observed and two cycloadducts **9** (*endo*) and **10** (*exo*) were obtained in 5:1 ratio, 47% total yield (Scheme 2). High pressure (entries 6 and 7 in Table 2) led to complete *endo*/*exo*-diastereoselectivity, and *endo*-cycloadduct **9** was isolated as unique and crystalline product of reaction. The best yield (69%, entry 6 in Table 2) was obtained when cycloaddition was performed under the pressure of 8 kbar, at 25 °C in dichloromethane. Cycloadduct **9** was recrystallised from ethyl acetate and its X-ray structure is shown in Figure 4. The *cis*-arrangement of H-3a, H-9a, and H-9b is a consequence of the *endo*-approach of NPM that occurs on the (*Re*) face of (R_S)-sulfinyldiene **7**, as demonstrated by the (3a*S**,9a*S**,9b*R**,R_S*) configuration of **9**. An extensive NMR investigation was performed on both cycloadducts **9** and **10**, the structure determination of the latest being based on these measurements. All the experiments were performed in $CDCl_3/C_6D_6$ mixtures of different ratios to allow a significant scattering of proton signals that overlap in neat $CDCl_3$.

The separation of the cyclohexyl protons H_2-2′–H_2-6′ from all the other methylene protons and the consequent ^1H and ^{13}C assignments were performed by TOCSY experiments. The rather different chemical shifts of the cyclohexyl protons in the two adducts **9** and **10** is an interesting consequence of the different configuration of the moiety C(3a)–C(9b)–C(9a), and then of the different anisotropy effect of C(5)–C(5a) double bond. The *cis*-arrangement of H-3a and H-9b in both cycloadducts **9** and **10** follows from the NOE observed between them, together with $J_{3a,9b}$ values (8.7, 9.4 Hz for **9** and **10**, respectively). Comparison of $J_{9a,9b}$ of **9** (5.9 Hz) with the corresponding coupling in **10** (7.3 Hz) confirms the *cis*-arrangement (*pseudo*-axial/equatorial) of H-9a and H-9b in **9**, and thus a *trans* stereochemical relationship (*pseudo*-diaxial) of the same protons in **10**. Further support to this stereochemical assignment is given by the NOE observed between H-9a and H-9b: while for cycloadduct **9** a large NOE was observed between these protons, also NOE between them, although very small, was observed in the case of adduct **10**, coming from the *exo*-approach of NPM to the (*Re*) face of (R_S)-**7**.

Noteworthy, in both cycloadditions of NPM to 2-cyclohexylsulfinyl dienes **5** and **7** the diene face of dienophile approach was opposite to the one normally observed in the literature but in accordance with the result reported in entry 6 of Table 1. The experimental data can be rationalised by suggesting that, when a tertiary carbon is directly linked to the sulfinyl group of the diene, the dienophile approaches the diene face opposite to the one including the sterically demanding alkyl substituent that arranges itself at about 90° with respect to the diene reactive plane. If the diene skeleton is unsubstituted at C(3) (R^3 = H in Fig. 5), **E** conformation is a reliable alternative to **A** (Figs. 1 and 5), maintaining transoid sulfur oxygen to C(1)–C(2) double bond, and directing NPM onto the same (*Si*) face of the (pR_S)-2-sulfinyl diene. However, if a substituent is

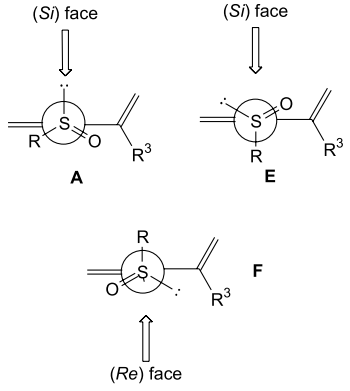
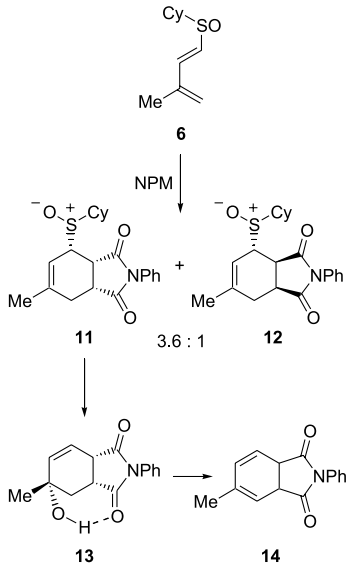


Figure 5. Conformational preferences in Diels–Alder transition states of (pR_S)-2-sulfinyl dienes.



Scheme 3.

present at C(3), as occurs in dienes **5** and **7**, the steric hindrance between sulfinyl oxygen and unsaturated moiety including R^3 affords the dienophile approach from the opposite (*Re*) face, (pR_S)-sulfinyl diene adopting in the transition state the **F** conformation (Fig. 5) that corresponds to **D** in Figure 2.

It has been demonstrated that 1-sulfinyl dienes are much less reactive than 2-sulfinyl dienes, and the reactivity dependence on the position of the sulfinyl group in the diene skeleton has been explained on the basis of the electronic characteristics of the sulfoxide moiety.[9] It was not a surprise when (*E*)-1-cyclohexylsulfinyl-3-methyl-1,3-butadiene (**6**) did not give any significant result in its reaction with NPM at atmospheric pressure: complex mixtures, but no cycloadducts, were detected (Table 2, entry 8). When NPM reacted with **6** under high pressure (entry 9) a 3.6:1 mixture of cycloadducts **11** and **12** was obtained in 60% yield (Scheme 3). The major product of the reaction comes from the *endo*-approach of NPM to the (*Re*) face of (R_S)-sulfinyl diene **6** (**C** in Fig. 1) as commonly accepted,[3] while the minor cycloadduct was obtained by the *exo*-approach of dienophile to the same face of (R_S)-sulfinyl diene **6**. The ^{1}H NMR data are in good agreement with these structure assignments if we consider conformational preferences of the cyclohexene ring as half-boat **G** in the *endo*-cycloadduct **11** and half-chair **H** in the *exo*-cycloadduct **12** (Fig. 6). On this basis the chemical shift difference of H-4, geminal to the sulfinyl group, appears diagnostic in the attribution of stereochemistry to diastereoisomers **11** and **12**. H-4 resonates at lower field in **12** (4.00 ppm) with respect to **11** (3.71 ppm) since in **12** H-4 falls into the deshielding cone of NPM carbonyl function. Furthermore, in both cycloadducts **11** and **12**, H-3a resonates at lower field (3.52 and 3.59 ppm in **11** and **12**, respectively), with respect to H-7a (3.36 and 3.38 ppm in **11** and **12**, respectively), this suggests that the sulfinyl group adopts a rigid disposition with the H-3a in the deshielding zone of the sulfinyl oxygen atom.[3c] When cycloadduct **11** was left standing for 15 days at room temperature in chloroform solution, it evolved into compound **13** as a consequence of the well-known sulfoxide–sulfenate rearrangement of allyl sulfoxides. Spontaneous dehydration of **13** led to known *N*-phenyl-4-methyl-1,2-dihydrophthalimide (**14**) (Scheme 3).[10] The occurrence of these conversions is supported by mass spectrometry and NMR experiments.[†]

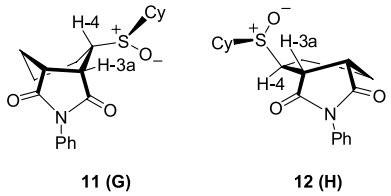


Figure 6. Partial stereostructures of (4*S**,R_S*)-4-cyclohexylsulfinyl-3a,4,7,7a-tetrahydro-6-methyl-2-phenyl-1*H*-isoindole-1,3(2*H*)-diones **11** and **12**.

3. Conclusions

The stereochemical results observed in uncatalyzed cycloadditions of NPM with chiral 2-cyclohexylsulfinyl-1,3-dienes **5** and **7** allowed a deeper insight into the comprehension of the factors that affect the facial diastereoselection in these DA reactions. We have demonstrated the exiguousness of the generally accepted assumption that the sulfur configuration is the only controller of the diastereofacial selectivity in DA reactions involving 2-sulfinyl dienes, since (i) the feature of the non-diene group linked to the sulfoxide sulfur, (ii) the steric requirements of the dienophile, (iii) the presence of a 3-substituent on the 2-sulfinyl-1,3-diene skeleton all contribute to the identification of the preferred face of approach by the dienophile. All these factors, together with sulfur configuration, have to be taken into consideration for an accurate foresight of the facial discrimination. In particular, the relevance of the structural characteristics of the non-diene group linked to the sulfoxide sulfur become evident if we compare the reactivity of diene **7** and the one quoted in Table 1, entry 5: these dienes differ only for cyclohexyl or isoborneol substituent at sulfur, and this difference alone exchanges the preferred face of NPM approach. The use of high pressure improved the stereochemical outcome of NPM cycloaddition by 1-[1-(cyclohexylsulfinyl)ethenyl]cyclohexene (**7**), and allowed DA reaction of the poorly reactive (*E*)-1-cyclohexylsulfinyl-3-methyl-1,3-butadiene (**6**).

[†] (3a*R**,5*S**,7a*S**)-3a,4,5,7a-Tetrahydro-5-hydroxy-5-methyl-2-phenyl-1*H*-isoindole-1,3(2*H*)-dione (**13**). ^{1}H NMR (400 MHz) δ 7.5–7.2 (m, 5H, H-2″,3″,4″,5″,6″), 6.00 (m, 2H, H-6,7), 3.61 (m, 1H, H-7a), 3.08 (m, 1H, H-3a), 2.40 (m, 1H, H_A-4), 1.86 (m, 1H, H_B-4), 1.37 (s, 3H, Me). ^{13}C NMR (100 MHz) δ 179.0 and 175.8 (C-1,3), 137.1 and 123.7 (C-6,7), 132.1 (C-1″), 129.1 (C-3″,5″), 128.6 (C-4″), 126.5 (C-2″,6″), 67.0 (C-5), 40.6 (C-7a), 37.1 (C-3a), 36.2 (C-4), 29.4 (Me); MS *m*/*z* (rel. intensity) 257 (M^+, 23), 242 (6), 214 (3), 138 (21), 93 (base), 77 (14). *N*-Phenyl-4-methyl-1,2-dihydrophthalimide (**14**): MS *m*/*z* (rel. intensity) 239 (M^+, 24), 193 (3), 120 (41), 105 (base), 91 (40), 77 (1).

4. Experimental

4.1. General

Solvents were purified according to standard procedures. Petrol refers to light petroleum, bp 30–40 °C. All reactions were monitored by TLC on commercially available precoated plates (Aldrich silica gel 60 F 254) and the products were visualised with vanillin [1 g dissolved in MeOH (60 mL) and conc. H_2SO_4 (0.6 mL)] and/or I_2. Column chromatographies were performed on Aldrich 60 and/or Riedel de Haën silica gel (32–63 μm; 230–400 mesh ASTM). Melting points were determined on a Büchi microscopic apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ solution on a Perkin-Elmer Paragon 500 FT-IR. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions (unless otherwise stated) with $SiMe_4$ as internal standard on Varian Mercury 300 and VXR-400 spectrometers. The NMR attributions are supported by APT, homodecoupling, COSY, ^1H–{^1H} NOE, HETCOR, and TOCSY experiments. Quaternary carbons were assigned by 2D long-range hetero-correlated experiments. Proton and carbon nuclei, marked with ($'$), pertain to the cyclohexyl moiety, while ($''$) marks vinyl protons in compound **7** and phenyl nuclei in compounds **8–13**. Mass spectra were measured by a Hewlett Packard 5970 GC–MS instrument. All chiral compounds are racemic mixtures. Cycloadditions under pressure were realised using an UNIPRESS-EQUIPMENT liquid piston vessel LV 30/16.

X-ray crystallography. All measurements were carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at room temperature. Graphite-monochromated Cu Kα radiation (40 mA/−40 kV) and a KM4 CCD/SAPPHIRE detector were used for cell parameter determination and data collection. The integrated intensities, measured using the ω scan mode, were corrected for Lorentz and polarisation effects.[11] The substantial redundancy in data allows empirical absorption corrections (SADABS[12]) to be applied using multiple measurements of symmetry-equivalent reflections. The structures were solved by direct methods of SIR97[13] and refined using the full-matrix least squares on F^2 provided by SHELXL97.[14] The non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms were refined as isotropic. Aromatic and cyclohexyl hydrogens were assigned in calculated positions, the others were found in the Fourier difference synthesis.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 264418 (adduct **8**) and 264419 (adduct **9**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. 3-Cyclohexylthiopropanenitrile (2).[7] Acrylonitrile (0.79 mL, 12.0 mmol) was added slowly to a solution (anhydrous THF, 45 mL) of cyclohexanethiol (1.22 mL, 10.0 mmol) and Triton B (0.54 mL, 40 wt% solution in MeOH, 1.2 mmol) at −78 °C. The reaction mixture was allowed to reach spontaneously the room temperature, and water (80 mL) was added. The crude product was extracted with Et_2O (4×80 mL). The combined organic layers were washed with saturated NaCl solution (3×50 mL) and dried (Na_2SO_4). Evaporation of the solvent gave an oily residue that was purified by column chromatography eluting with petrol/EtOAc 4:1. Sulfide **2** (1.52 g, 9.0 mmol, 90% yield) was isolated as an oil. ^1H NMR (300 MHz) δ 2.81 (split t, 2H, J_{vic}=7.3 Hz, H_2-3), 2.73 (m, 1H, H-1$'$), 2.62 (split t, 2H, H_2-2), 2.0–1.2 (m, 10H, H_2-2$'$,3$'$,4$'$,5$'$,6$'$). Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93. Found: C, 63.93; H, 9.06.

4.1.2. 3-Cyclohexylsulfinylpropanenitrile (3). *m*-CPBA (3.82 g 80%, 17.7 mmol) was dissolved in CH_2Cl_2 (50 mL) freshly distilled and added dropwise to a solution of sulfide **2** (3.00 g, 17.7 mmol) in CH_2Cl_2 (50 mL) at −40 °C. When the reaction appeared complete by TLC (30 min) a 10% solution of $Na_2S_2O_3$ was added (50 mL) and the organic layer was extracted and washed with a saturated solution of $NaHCO_3$ (3×60 mL, until the neutrality was reached) and water (2×80 mL). Evaporation of the solvent under reduced pressure gave sulfoxide **3** as an oil not needing of purification (quantitative yield). ^1H NMR (300 MHz) δ 3.0–2.8 (m, 4H, H_2-2,3), 2.67 (tt, 1H, J_{vic}=11.2, 3.5 Hz, H-1$'$), 2.2–1.2 (m, 10H, H_2-2$'$,3$'$,4$'$,5$'$,6$'$). Anal. Calcd for $C_9H_{15}NOS$: C, 58.34; H, 8.16. Found: C, 58.22; H, 8.40.

4.1.3. Cyclohexylsulfinyl-3-methyl-1,3-butadienes 5 and 6. A solution of sulfoxide **3** (3.00 g, 16.2 mmol) and 2-methyl-1-buten-3-yne (15.4 mL, 162.0 mmol) in toluene (25 mL) was maintained at 95 °C. When the reaction appeared complete by TLC (7 h) the solvent was removed under reduced pressure. Column chromatography (petrol/EtOAc 9:1) of the crude product mixture afforded 2-cyclohexylsulfinyl-3-methyl-1,3-butadiene (**5**) as first eluted oil (1.41 g, 7.1 mmol, 44% yield). ^1H NMR (300 MHz) δ 5.88 (s, 1H, H_A-1), 5.87 (s, 1H, H_B-1), 5.16 (s, 1H, H_A-4), 5.14 (s, 1H, H_B-4), 2.56 (tt, 1H, J_{vic}=12.0, 3.7 Hz, H-1$'$), 2.00 (s, 3H, Me), 1.9–1.1 (m, 10H, H_2-2$'$,3$'$,4$'$,5$'$,6$'$). Anal. Calcd for $C_{11}H_{18}OS$: C, 66.62; H, 9.15. Found: C, 66.61; H, 9.18. Then the minor product (*E*)-1-cyclohexylsulfinyl-3-methyl-1,3-butadiene (**6**) (0.20 g, 1.0 mmol, 6% yield) was eluted as an oil. ^1H NMR (300 MHz) δ 6.92 (AB d, 1H, $J_{1,2}$=15.4 Hz, H-2), 6.27 (AB d, 1H, H-1), 5.28 (br s, 2H, H_2-4), 2.64 (tt, 1H, J_{vic}=11.4, 3.5 Hz, H-1$'$), 2.2–1.1 (m, 10H, H_2-2$'$,3$'$,4$'$,5$'$,6$'$), 1.92 (s, 3H, Me). Anal. Calcd for $C_{11}H_{18}OS$: C, 66.62; H, 9.15. Found: C, 66.50; H, 8.99.

4.1.4. 1-[1-(Cyclohexylsulfinyl)ethenyl]cyclohexene (7). A solution of sulfoxide **3** (2.00 g, 10.8 mmol) in neat 1-ethynylcyclohexene (8 mL, 67.4 mmol) was maintained at 130 °C. When the reaction appeared complete by TLC (30 min) the crude mixture was purified by column chromatography eluting with petrol/EtOAc 9:1. Diene **7** was isolated as an oil (1.29 g, 5.4 mmol, 50% yield). ^1H NMR (300 MHz) δ 5.95 (br t, 1H, $J_{2,3}$=4.0 Hz, H-2), 5.73 (s, 1H, H_A-2$''$), 5.72 (s, 1H, H_B-2$''$), 2.51 (tt, 1H, J_{vic}=12.0, 3.7 Hz, H-1$'$), 2.4–1.1 (m, 18H, H_2-2$'$,3,3$'$,4,4$'$,5,5$'$,6,6$'$). Anal. Calcd for $C_{14}H_{22}OS$: C, 70.54; H, 9.30. Found: C, 70.69; H, 9.47.

4.2. General procedure for the Diels–Alder reactions of sulfinyl dienes 5–7 with NPM

As reported in Table 2, the cycloadditions were accomplished at atmospheric pressure (entries 1, 3, 5, and 8) and under high pressure conditions (entries 2, 4, 6, 7, and 9). For the experiments performed at atmospheric pressure, a solution of the diene (1.5 mmol) in the quoted solvent (5 mL) was added to NPM dissolved in the same solvent (10 mL). The resulting solution was maintained at the indicated temperature, then cooled and the solvent evaporated under vacuum. For the experiments performed at high pressure, a solution of diene (1.5 mmol) and dienophile in the quoted solvent (12 mL) was placed into a 15 mL Teflon vial and solvent was added until the vial was completely filled. The vial was closed and kept at 8 kbar at the indicated temperature. After depressurising, the solvent was removed in vacuo. Each crude mixture obtained (all entries in Table 2) was purified by column chromatography on silica gel eluting with EtOAc/hexane 4:1.

4.2.1. (3a*S,7a*R**,*R*$_S$*)-5-Cyclohexylsulfinyl-3a,4,7,7a-tetrahydro-6-methyl-2-phenyl-1*H*-isoindole-1,3(2*H*)-dione (8).** Pale yellow crystals, mp 162–163 °C (EtOAc), IR ν_{max} 1713 (C=O) cm^{-1}. ^{1}H NMR (400 MHz) δ 7.42 (m, 2H, H-3″,5″), 7.34 (m, 1H, H-4″), 7.28 (m, 2H, H-2″,6″), 3.37 (ddd, 1H, $J_{3a,4A}$=2.4 Hz, $J_{3a,4B}$=7.1 Hz, $J_{3a,7a}$=9.0 Hz, H-3a), 3.34 (ddd, 1H, $J_{7a,7A}$=2.9 Hz, $J_{7a,7B}$=6.0 Hz, H-7a), 3.26 (dd, 1H, $J_{4A,4B}$=15.2 Hz, H$_A$-4) 2.82 (dd, 1H, $J_{7A,7B}$=15.2 Hz, H$_A$-7), 2.61 (tt, 1H, J_{vic}=10.8, 3.8 Hz, H-1′), 2.47 (dd, H$_B$-7), 2.36 (dd, 1H, H$_B$-4), 2.16 (m, 1H, H$_A$-6′), 2.04 (br s, 3H, Me), 1.89 (m, 1H, H$_A$-3′), 1.79 (m, 1H, H$_A$-2′), 1.68 (m, 1H, H$_A$-5′), 1.57 (m, 1H, H$_A$-4′), 1.47 (m, 1H, H$_B$-6′), 1.28 (m, 2H, H$_B$-2′,4′), 1.25 (m, 1H, H$_B$-3′), 1.22 (m, 1H, H$_B$-5′). ^{13}C NMR (100 MHz) δ 177.9 and 177.3 (C-1,3), 145.2 (C-6), 133.7 (C-5), 132.0 (C-1″), 129.3 (C-3″,5″), 128.8 (C-4″), 126.7 (C-2″,6″), 59.1 (C-1′), 39.9 (C-7a), 39.8 (C-3a), 31.9 (C-7), 26.6 (C-6′), 26.2 (C-2′), 25.8, 25.5, and 25.2 (C-3′,4′,5′), 20.8 (Me), 20.5 (C-4). Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.89; H, 6.78. Found: C, 67.80; H, 6.81.

X-ray structural analysis of **8**: formula $C_{21}H_{25}NO_3S$, M=371.48, monoclinic, space group $P2_1/c$, a=11.399(7) Å, b=10.761(8) Å, c=16.815(10) Å, β=107.43(5)°, V=1968(2) Å^3, Z=4, D_c=1.254, μ=1.618 mm^{-1}, $F(000)$=792. 5223 Reflections were collected in a $13.28<\theta<58.93$ range with a completeness to θ 92.7%; 2616 were independent, the parameters were 264, and the final R index was 0.0506 for reflections having $I>2\sigma I$, and 0.0549 for all data.

4.2.2. (3a*S,9a*S**,9b*R**,*R*$_S$*)-5-Cyclohexylsulfinyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (9).** Pale yellow crystals, mp 202–203 °C (EtOAc), IR ν_{max} 1713 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3/C_6D_6$ 1:1) δ 7.37 (m, 2H, H-3″,5″), 7.27 (m, 1H, H-4″), 7.26 (m, 2H, H-2″,6″), 3.28 (dd, 1H, $J_{3a,4A}$=2.4 Hz, $J_{4A,4B}$=15.8 Hz, H$_A$-4), 3.17 (ddd, 1H, $J_{3a,4B}$=8.1 Hz, $J_{3a,9b}$=8.7 Hz, H-3a), 3.07 (dd, 1H, $J_{9a,9b}$=5.9 Hz, H-9b), 2.54 (tt, 1H, J_{vic}=10.8, 3.7 Hz, H-1′), 2.50 (m, 1H, H$_A$-6), 2.39 (ddd, 1H, $J_{8,9a}$=11.0, 6.2 Hz, H-9a), 2.30 (m, 1H, H$_B$-6), 2.24 (m, 1H, H$_A$-9), 2.18 (dd, H$_B$-4), 2.17 (m, 1H, H$_A$-2′), 1.85 (m, 1H, H$_A$-5′), 1.84 (m, 1H, H$_A$-7), 1.83 (m, 1H, H$_B$-9), 1.70 (m, 1H, H$_A$-3′), 1.62 (m, 1H, H$_A$-4′), 1.60 (m, 1H, H$_A$-8), 1.51 (m, 1H, H$_A$-6′), 1.46 (m, 1H, H$_B$-7), 1.45 (m, 1H, H$_B$-2′), 1.29 (m, 1H, H$_B$-8), 1.23 (m, 1H, H$_B$-4′), 1.21 (m, 1H, H$_B$-5′), 1.19 (m, 1H, H$_B$-3′), 1.17 (m, 1H, H$_B$-6′). ^{13}C NMR (100 MHz, $CDCl_3/C_6D_6$ 1:1) δ 177.0 (C-3), 176.6 (C-1), 150.9 (C-5a), 132.0 (C-1″), 130.8 (C-5), 128.9 (C-3″,5″), 128.5 (C-4″), 126.0 (C-2″,6″), 58.7 (C-1′), 43.3 (C-9b), 39.8 (C-3a), 39.2 (C-9a), 27.2 (C-6), 26.5 (C-2′), 26.0, 25.7, 25.4, and 25.1 (C-3′,4′,5′,6′), 25.2 (C-9), 22.6 (C-8), 22.2 (C-7), 20.0 (C-4). Anal. Calcd for $C_{24}H_{29}NO_3S$: C, 70.04; H, 7.10. Found: C, 70.12; H, 6.98.

X-ray structural analysis of **9**: formula $C_{24}H_{29}NO_3S$, M=411.54, orthorhombic, space group P cab, a=12.427(1) Å, b=16.259(1) Å, c=21.454(1) Å, V=4334.8(5) Å^3, Z=8, D_c=1.261, μ=1.519 mm^{-1}, $F(000)$=1760. 10429 reflections were collected in a $4.93<\theta<59.05$ range with a completeness to θ 95.8%; 2985 were independent, the parameters were 274, and the final R index was 0.0505 for reflections having $I>2\sigma I$, and 0.0632 for all data.

4.2.3. (3a*R,9a*S**,9b*S**,*R*$_S$*)-5-Cyclohexylsulfinyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (10).** Pale yellow crystals, mp 182–183 °C (EtOAc), IR ν_{max} 1712 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3/C_6D_6$ 1:1) δ 7.35 (m, 2H, H-3″,5″), 7.24 (m, 1H, H-4″), 7.22 (m, 2H, H-2″,6″), 3.22 (dd, 1H, $J_{3a,4A}$=1.9 Hz, $J_{4A,4B}$=16.4 Hz, H-4), 3.07 (ddd, 1H, $J_{3a,4B}$=7.3 Hz, $J_{3a,9b}$=9.4 Hz, H-3a), 2.92 (dd, 1H, $J_{9a,9b}$=7.3 Hz, H-9b), 2.63 (tt, 1H, J_{vic}=10.8, 3.6 Hz, H-1′), 2.58 (ddd, 1H, $J_{6A,6B}$=15.4 Hz, $J_{6A,7}$=4.4, 3.5 Hz, H$_A$-6), 2.32 (ddd, 1H, $J_{9,9a}$=13.4, 4.6 Hz, H-9a), 2.30 (dd, 1H, H$_B$-4), 2.20 (m, 1H, H$_A$-2′), 2.14 (m, 1H, H$_B$-6), 2.02 (m, 1H, H$_A$-9), 1.80 (m, 1H, H$_B$-9), 1.78 (m, 1H, H$_A$-8), 1.74 (m, 1H, H$_A$-3′), 1.6–1.5 (m, 2H, H$_2$-7), 1.38 (m, 1H, H$_A$-4′), 1.34 (m, 1H, H$_B$-2′), 1.30 (m, 1H, H$_B$-8), 1.20 (m, 1H, H$_B$-3′), 1.17 (m, 1H, H$_A$-5′), 1.03 (m, 2H, H$_B$-4′, H$_A$-6′), 0.88 (m, 1H, H$_B$-6′), 0.77 (m, 1H, H$_B$-5′). ^{13}C NMR (100 MHz, $CDCl_3/C_6D_6$ 1:1) δ 177.5 (C-3), 175.9 (C-1), 150.4 (C-5a), 132.1 (C-1″), 131.9 (C-5), 128.9 (C-3″,5″), 128.2 (C-4″), 126.0 (C-2″,6″), 57.3 (C-1′), 43.1 (C-9b), 39.8 (C-3a), 39.5 (C-9a), 26.7 (C-2′), 26.3 (C-6), 25.9 (C-6′), 25.5 (C-4′), 24.8 (C-3′), 24.5 (C-5′,9), 21.7 (C-8), 21.2 (C-7), 20.5 (C-4). Anal. Calcd for $C_{24}H_{29}NO_3S$: C, 70.04; H, 7.10. Found: C, 69.98; H, 7.15.

4.2.4. (3a*S,4*S**,7a*R**,*R*$_S$*)-4-Cyclohexylsulfinyl-3a,4,7,7a-tetrahydro-6-methyl-2-phenyl-1*H*-isoindole-1,3(2*H*)-dione (11).** Low melting solid, IR ν_{max} 1712 (C=O) cm^{-1}. ^{1}H NMR (400 MHz) δ 7.5–7.3 (m, 5H, H-2″,3″,4″,5″,6″), 5.69 (m, 1H, H-5), 3.71 (dd, 1H, $J_{3a,4}$=7.0 Hz, $J_{4,5}$=6.4 Hz, H-4), 3.52 (dd, 1H, $J_{3a,7a}$=9.6 Hz, H-3a), 3.36 (dt, 1H, $J_{3a,7a}=J_{7a,7B}$=9.6 Hz, $J_{7a,7A}$=5.7 Hz, H-7a), 2.9–2.8 (m, 2H, H-1′, H$_A$-7), 2.38 (dd, 1H, $J_{7A,7B}$=16.8 Hz, H$_B$-7), 2.0–1.2 (m, 10H, H$_2$-2′,3′,4′,5′,6′), 1.96 (s, 3H, Me). ^{13}C NMR (100 MHz) δ 177.6 and 175.8 (C-1,3), 144.3 (C-6), 131.7 (C-1″), 129.1 (C-3″,5″), 128.5 (C-4″), 126.6 (C-2″,6″), 112.6 (C-5), 56.5 (C-1′), 52.4 (C-4), 41.4 (C-3a), 38.4 (C-7a), 28.5 (C-7), 26.4, 25.5, 25.2, 25.0, and 24.6 (C-2′,3′,4′,5′,6′), 24.2 (Me). Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.89; H, 6.78. Found: C, 67.77; H, 6.84.

4.2.5. (3a*R,4*S**,7a*S**,R_S*)-4-Cyclohexylsulfinyl-3a,4,7,7a-tetrahydro-6-methyl-2-phenyl-1*H*-isoindole-1,3(2*H*)-dione (12).** Low melting solid, IR ν_{max} 1712 (C=O) cm^{-1}. ^1H NMR (400 MHz) δ 7.5–7.4 (m, 5H, H-2″,3″,4″,5″,6″), 5.53 (m, 1H, H-5), 4.00 (dd, 1H, $J_{3a,4}$= 5.4 Hz, $J_{4,5}$=5.5 Hz, H-4), 3.59 (dd, 1H, $J_{3a,7a}$=9.5 Hz, H-3a), 3.38 (ddd, 1H, $J_{7a,7A}$=6.2 Hz, $J_{7a,7B}$=9.3 Hz, H-7a), 2.8–2.7 (m, 2H, H-1′, H_A-7), 2.54 (dd, 1H, $J_{7A,7B}$=16.5 Hz, H_B-7), 2.0–1.2 (m, 10H, H_2-2′,3′,4′, 5′,6′), 1.90 (s, 3H, Me). ^{13}C NMR (100 MHz) δ 178.8 and 175.8 (C-1,3), 143.4 (C-6), 132.9 (C-1″), 129.9 (C-3″,5″), 129.3 (C-4″), 127.5 (C-2″,6″), 117.0 (C-5), 58.0 (C-1′), 55.9 (C-4), 42.4 (C-3a), 39.8 (C-7a), 29.5 (C-7), 28.6, 26.7, 26.3, 26.1, and 23.2 (C-2′,3′,4′,5′,6′), 24.6 (Me). Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.89; H, 6.78. Found: C, 67.95; H, 6.80.

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