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The influence of reaction conditions on the Diels–Alder cycloadditions of 2-thio-3-chloroacrylamides; investigation of thermal, catalytic and microwave conditions†

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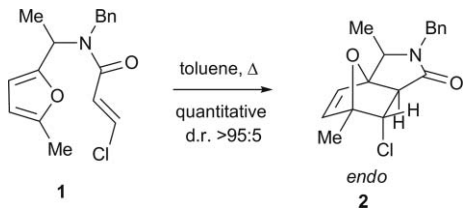
The Diels–Alder cycloadditions of cyclopentadiene and 2,3-dimethyl-1,3-butadiene to a range of 2-thio-3-chloroacrylamides under thermal, catalytic and microwave conditions is described. The influence of reaction conditions on the outcome of the cycloadditions, in particular the stereoselectivity and reaction efficiency, is discussed. While the cycloadditions have been attempted at the sulfide, sulfoxide and sulfone levels of oxidation, use of the sulfoxide derivatives is clearly beneficial for stereoselective construction of Diels–Alder cycloadducts.

Introduction

The Diels–Alder cycloaddition is one of the most frequently used carbon–carbon bond forming reactions in organic synthesis.[1–8] The use of highly functionalized adducts in the preparation of natural products and biologically active compounds is continuing to grow,[5,6] especially with the advent of enantioselective catalysts for the reaction.[9–11] The popularity of the Diels–Alder reaction as a synthetic tool is partly due to the high degree of stereo- and regioselectivity which accompanies the reaction.[1,2] The presence of directing groups leads to further control of the reaction with the result that a desired adduct diastereomer can be formed almost exclusively. The use of directing groups has been widely exploited by Garcia Ruano and co-workers in their use of enantiopure sulfoxides to control the formation of stereogenic centres in the Diels–Alder reaction.[8,12,13]

We have recently reported the highly efficient and stereoselective transformation of α-thioamides to the corresponding α-thio-β-chloroacrylamide derivatives on treatment with NCS.[14] The chemoselective and stereoselective oxidation of the β-chloroacrylamides to the sulfoxide and sulfone levels of oxidation has extended the scope of this methodology.[15] The employment of β-chloroacrylamides as dipolarophiles in 1,3-dipolar cycloadditions has also been reported recently.[16,17] The β-chloroacrylamides are a highly functionalized group of unsaturated compounds, and the range of substituents which can be incorporated on the basic acrylamide framework is substantial.[14,18] These derivatives are potential dienophiles leading to novel cycloadducts in reactions with dienes. We have described asymmetric and diastereoselective sulfur oxidation in these series, leading to enantioenriched sulfinyl derivatives of the β-chloroacrylamides.[15,19] Based on earlier work by Garcia Ruano, excellent asymmetric induction is envisaged in cycloadditions due to the chiral sulfoxide moiety.[8,12,13]

The intramolecular Diels–Alder cycloaddition of the β-chloroacrylamide derivative **1** was reported by Jung and Street in 1984.[20] To the best of our knowledge, this is the only example of the employment of a β-chloroacrylamide as a dienophile in the Diels–Alder reaction. A high degree of diastereoselectivity was achieved (>95 : 5 *endo*:*exo*) when **1** was heated in toluene at reflux for 1 h (Scheme 1).



1 **2**

Scheme 1

Herein, we report the Diels–Alder cycloadditions of a range of β-chloroacrylamides to cyclopentadiene and 2,3-dimethyl-1,3-butadiene under thermal, catalytic and microwave conditions.

Results and discussion

Cyclopentadiene

Initial investigations focused on the highly reactive cyclopentadiene, which is fixed in the s-*cis* geometry required for Diels–Alder cycloaddition. Preliminary experiments involved heating a solution of the sulfide **5a** in dichloromethane with an excess of cyclopentadiene at reflux for 16 h; these simple thermal processes proved unsuccessful, with no reaction observed. Elevating the temperature by conducting the reaction in toluene also failed to provide the cycloadduct, with the sulfide **5a** again recovered unchanged (Scheme 2).

At this stage it was decided to activate the β-chloroacrylamides towards Diels–Alder cycloaddition by oxidising the sulfide to the more electron withdrawing sulfoxide.[15] Indeed, reaction of the sulfoxide **3a** in dichloromethane with an excess of cyclopentadiene at reflux for 16 h successfully afforded two diastereomeric

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Table 1 Reaction of the α-sulfinyl-β-chloroacrylamides with cyclopentadiene

Entry	β-Cl	R^1	R^2	Method[a] (*endo* : *exo*,[b] % yield[c]) A	B	C	D	E[d]	F	Adduct
1	**3a**	Ph	Tol	1.3 : 1[e] (93)	1.7 : 1	1.8 : 1	8.8 : 1	4.2 : 1	—	**4a**
2	**3b**	Ph	Et	1.2 : 1 (74)	1.4 : 1[i]	2.1 : 1	5.5 : 1	5.2 : 1	—	**4b**
3	**3c**	Ph	Bn	1.3 : 1[f] (84)	1.3 : 1[j]	—	—	6.2 : 1	—	**4c**
4	**3d**	Ph	*i*Pr	1.2 : 1 (89)	1.4 : 1[k]	2.0 : 1	5.4 : 1	5.3 : 1	—	**4d**
5	**3e**	Ph	*n*Bu	1.2 : 1 (76)	1.4 : 1[l]	—	—	4.8 : 1	—	**4e**
6	**3f**	Ph	Allyl	1.3 : 1 (79)	1.5 : 1[m]	—	—	4.5 : 1	—	**4f**
7	**3g**	Ph	H	1.6 : 1 (74)	2.3 : 1	2.4 : 1	2.4 : 1	—	—	**4g**
8	**3h**	Ph	4-F-C_6H_4	1.7 : 1 (96)	—	—	—	—	—	**4h**
9	**3i**	4-MeO-C_6H_4	Tol	1.3 : 1 (98)[g]	—	—	—	3.5 : 1	—	**4i**
10	**3j**	4-MeO-C_6H_4	Bn	1.1 : 1 (89)[g]	—	—	—	5.7 : 1	—	**4j**
11	**3k**	4-MeO-C_6H_4	Et	1.2 : 1 (74)	—	—	—	5.2 : 1	—	**4k**
12	**3l**	4-NO_2-C_6H_4	Tol	1.3 : 1[h] (79)	—	—	—	—	—	**4l**
13	**3m**	*n*Bu	Tol	1 : 1 (87)	—	—	—	—	—	**4m**
14	**3n**	*n*Bu	Bn	1 : 1.1 (84)	—	—	—	—	—	**4n**
15	(±)**3o**	*n*Bu	4-F-C_6H_4	1.1 : 1 (95)	—	—	—	—	—	**4o**
16	(−)-**3o**[n]	*n*Bu	4-F-C_6H_4	1.1 : 1 (79)	—	—	—	—	—	**4o**
17	(+)-**3o**[o]	*n*Bu	4-F-C_6H_4	1.1 : 1 (75)	—	—	—	—	—	**4o**
18	**3p**	Bn	Bn	1 : 1.4 (88)	—	—	—	—	—	**4p**
19	**3q**	Bn	4-F-C_6H_4	1 : 1.2 (90)	—	—	—	—	1.1 : 1 (69)	**4q**
20	**3r**	Bn	(*R*)-(+)-CH(CH_3)Ph	1 : 1.3 (94)	—	—	—	—	—	**4r**
21	**3s**	Me	4-F-C_6H_4	1 : 1 (93)	1 : 1	1 : 1	1 : 1	1 : 1	1 : 1 (97)	**4s**
22	**3t**	*i*Pr	4-F-C_6H_4	1.4 : 1 (87)	—	—	—	—	—	**4t**

[a] Method A: 10 equivalents cyclopentadiene, CH_2Cl_2, reflux, 16 h; Method B: 10 equivalents cyclopentadiene, 1% $CuCl_2$, CH_2Cl_2, rt, 10 h to 2 d; Method C: 7 equivalents cyclopentadiene, 1% $CuCl_2$, CH_2Cl_2, reflux, 16 h; Method D: 7 equivalents cyclopentadiene, 1% $Cu(OTf)_2$, CH_2Cl_2, rt, 16 h; Method E: 10 equivalents cyclopentadiene, 1% $Cu(OTf)_2$, CH_2Cl_2, reflux, 1–2 h; Method F: 10 equivalents cyclopentadiene, CH_2Cl_2, MW, 100 °C, 5 min. [b] Determined by integration of the ^{1}H NMR spectra of the crude products for Method A, and purified products for Methods B–F. [c] Unless otherwise stated, isolated yield following chromatographic purification. [d] For the $Cu(OTf)_2$ catalysed reactions at reflux, a blue-black substance formed after heating for ~30 min, believed to be a polymer of cyclopentadiene. Garcia Ruano and Honeychuck have reported a similar phenomenon.[12,21] [e] Ratio after chromatography was 1.40 : 1. [f] Ratio after chromatography was 3 : 1. [g] Yield of crude product; no further purification was conducted. [h] Purified by trituration in ether/hexane. [i] Reaction time 2 days. [j] Reaction conversion was 50%. [k] Reaction conversion was 50% after 16 h. Reaction conversion was 100% after 2 days. [l] Reaction conversion was 63%. [m] Reaction conversion was 55%. [n] % ee of Sulfoxide (+)-**3o** 53%. [o] % ee of Sulfoxide (−)-**3o** 53%.

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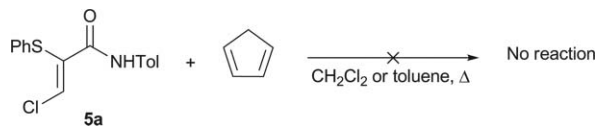

Scheme 2

cycloadducts **4a**-*endo* and **4a**-*exo*, isolated as an inseparable mixture in a 1.3 : 1 crude ratio, and a 1.4 : 1 ratio following chromatographic purification (entry 1, Table 1), confirming that the sulfoxide group was sufficiently activating to enable cycloaddition under relatively mild conditions. The major diastereomer was subsequently shown to have the amide *endo*, while the minor diastereomer had the amide *exo*. Conducting the reaction in toluene did not lead to a significant increase in the reaction rate, and thus all further thermal cycloadditions with cyclopentadiene were routinely carried out in dichloromethane. The optimum reaction time was determined by monitoring the progress of the cycloaddition of **3a** with cyclopentadiene over a period of 16 h; after heating at reflux for 10 h, substantial amounts of **3a** remained by TLC analysis. When heating was continued for a further 6 h, complete conversion of **3a** to the cycloadduct **4a** was evident by TLC analysis, and all subsequent cycloadditions were thus heated at reflux in dichloromethane for 16–18 h.

The scope of the Diels–Alder cycloaddition was investigated by varying the amide group and the sulfoxide substituent (entries 2–22, Table 1, Method A). In all instances, complete conversion was observed and a mixture of *endo* and *exo* cycloadducts were isolated. The *endo* adduct was the major adduct obtained in most instances, however the degree of *endo*/*exo* selectivity was low, with the highest diastereomeric ratio (1.7 : 1) achieved for the *N*-4-fluorophenyl sulfoxide **3h** (entry 8, Table 1). Cycloaddition of the enantioenriched sulfoxides (+)-**3o** and (−)-**3o** afforded similar diastereomeric ratios as those obtained using racemic **3o** as expected (entries 15–17, Table 1, Method A).

In an attempt to increase the reaction selectivity and the rate of the cycloaddition, the reaction of the sulfoxides with cyclopentadiene was next conducted in the presence of two copper catalysts, $CuCl_2$ and $Cu(OTf)_2$, at both room temperature and at reflux in dichloromethane (entries 1–7, entries 9–11 and entry 21, Table 1, Methods B–E).

Employment of 1% $CuCl_2$ by weight at room temperature led to modest increases in the *endo*/*exo* selectivity, with diastereomeric ratios of up to 2.3 : 1 achieved with β-chloroacrylamide **3g** *cf.* 1.6 : 1

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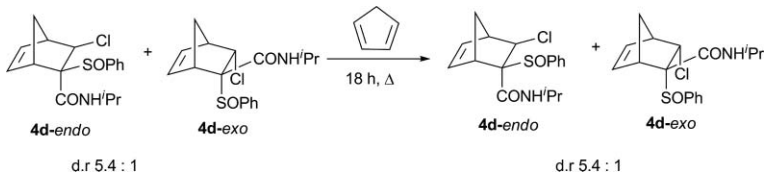


Scheme 3

with this substrate under thermal conditions, and a highest d.r. of 1.7 : 1 under thermal conditions. Significantly, the cycloaddition proceeds at room temperature in the presence of $CuCl_2$, albeit more slowly than the thermal reactions at reflux in the absence of catalyst. Increasing the temperature of the $CuCl_2$ catalysed reaction led to similar rates to the non-catalysed process, with complete conversion in all instances after heating at reflux for 16 h. A slight increase in the diastereoselectivity of the cycloaddition was observed, with diastereomeric ratios of up to 2.4 : 1 achieved (entry 7, Table 1, Method C).

Moving from $CuCl_2$ to $Cu(OTf)_2$ resulted in a significant increase in the reaction efficiency and diastereoselectivity. The use of 1% $Cu(OTf)_2$ by weight led to an enhancement of diastereoselection, with the *endo* isomer formed in synthetically useful ratios (d.r. of up to 8.8 : 1). There was also a significant increase in the reaction rate observed when the cycloaddition was performed under reflux conditions, with the starting material completely consumed after 1–2 h, although the diastereoselectivity was optimum when the cycloadditions were conducted at room temperature.

Finally, the microwave assisted Diels–Alder cycloadditions of the sulfoxides **3q** and **3s** with cyclopentadiene were attempted (entries 19 and 21, Table 1, Method F). Although the *endo* : *exo* selectivities were similar to those achieved under thermal conditions in the absence of Lewis acid catalysis, a large decrease in the reaction time from 16 h to just 5 min was observed.

In general, the *N*-aryl substituted β-chloroacrylamides led to the greatest diastereoselectivity, with the *N*-tolyl substituted β-chloroacrylamide **3a** resulting in the greatest diastereomeric ratios (up to 8.8 : 1) for the copper catalysed processes (entry 1, Table 1), while the *N*-4-fluorophenyl derived β-chloroacrylamide **3h** gave the greatest diastereoselectivity (1.7 : 1) under thermal conditions (entry 8, Table 1). Interestingly, cycloaddition of the *S*-methyl sulfoxide **3s** with cyclopentadiene led to an equimolar mixture of diastereomers under thermal, copper catalysed and microwave conditions (entry 21, Table 1).

To determine if the cycloaddition was under kinetic or thermodynamic control, the adduct **4d** (d.r. 5.4 : 1) was re-exposed to the thermal cycloaddition conditions. After heating at reflux for 18 h, the diastereomeric ratio was unchanged suggesting that the formation of the adducts is irreversible, and therefore the diastereomeric ratio is under kinetic control (Scheme 3).

While the cycloadditions produced a mixture of just two diastereomeric cycloadducts, it was necessary to determine which two of the potential four cycloadducts were formed. Thus, *endo* and *exo* isomers with opposite stereochemistry at the sulfoxide could potentially form in the cycloaddition process as illustrated in Fig. 1.

To determine if the adducts were diastereotopic at sulfur, the adduct **4a** (as a 1.3 : 1 mixture of diastereomers) was oxidized with

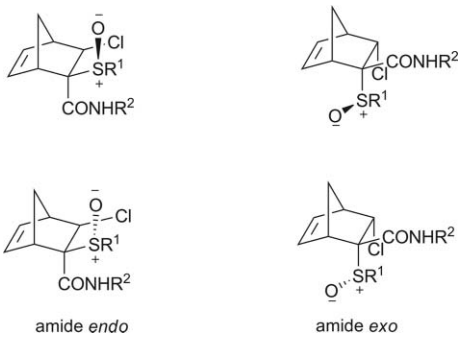
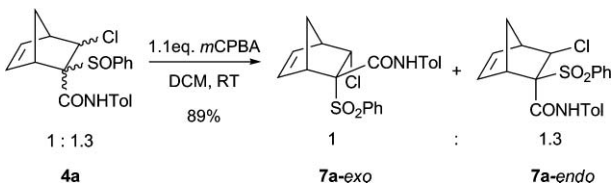


Fig. 1

1.4 equivalents of *m*CPBA; a 1.3 : 1 mixture of diastereomers was obtained. The presence of two sulfone adduct diastereomers in the same ratio following oxidation confirmed that the adducts were diastereomeric at carbon, and did not just differ in relative configuration at sulfur (Scheme 4).



Scheme 4

Though the majority of the adducts (**4a**, **4c–4t**) were isolated as a chromatographically inseparable mixture of diastereomers, the two adduct diastereomers of the *N*-ethyl adduct **4b** were separable by chromatography on silica gel. The relative stereochemistry in the adducts **4b**-*endo* and **4b**-*exo* was unequivocally determined by X-ray crystallographic and NOE studies.

Analysis of the crystal structures revealed that the major adduct diastereomer had the amide moiety *endo* (Fig. 2), while in the minor adduct the amide moiety was *exo* (Fig. 3). In both cases, the *cis* relationship of the sulfoxide and the chlorine was retained as expected. The crystal structures provided firm evidence of the relative stereochemistry at the sulfoxide in each case.

The stereochemical assignment was confirmed by NOE studies; for the major adduct **4b**-*endo*, irradiating at H-3 showed the expected enhancement of H-4 and H-5, as the proton on C-3 is spatially close to that at C-4. The enhancement observed at H-5 was less than that at H-4. The minor adduct **4b**-*exo* was also irradiated at H-3, with enhancement of H-4 and H-7a observed. The enhancement at H-7a is very significant as it is not present in the experiment employing **4b**-*endo* (Fig. 4).

The assignment of the stereochemistry of each of the other cycloadducts was by analogy, and in particular the coupling

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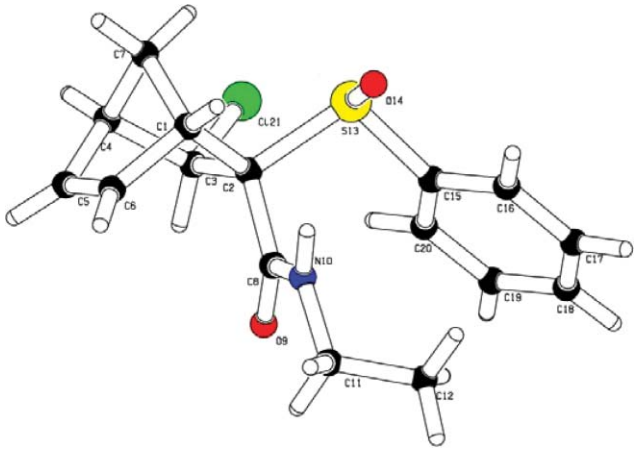

Fig. 2 Crystal structure of **4b**-*endo*.

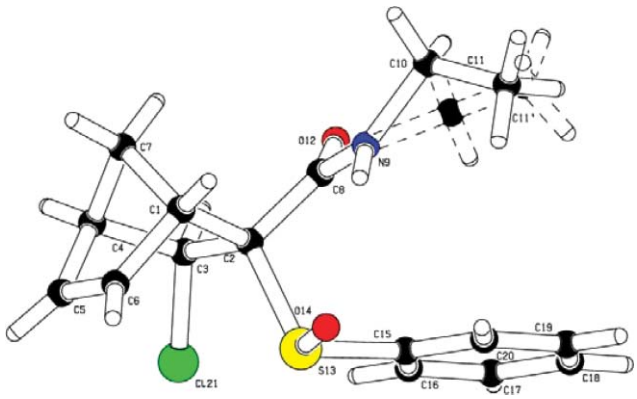

Fig. 3 Crystal structure of **4b**-*exo*.

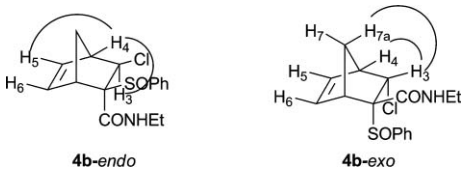

Fig. 4

constants $J_{3,4}$ are very characteristic; 4 Hz for the *exo* adducts and 2 Hz for the *endo* adducts (see for example Fig. 5).[22]

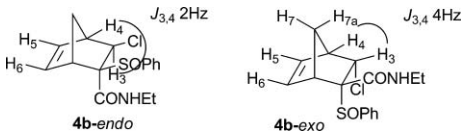

Fig. 5

The α-sulfinyl-β-chloroacrylamides are conformationally constrained due to an intramolecular hydrogen bond between the amide proton and the sulfoxide, adopting the s-*cis* conformation.[14] In each of the cycloadditions, just two diastereomers of each of the cycloadducts are obtained. Complete diastereofacial control by the sulfoxide is observed, with the preferred approach of cyclopentadiene to the β-chloroacrylamides avoiding steric interactions with the R^1 group which blocks the approach of the diene from above (as illustrated in Fig. 6). When approaching

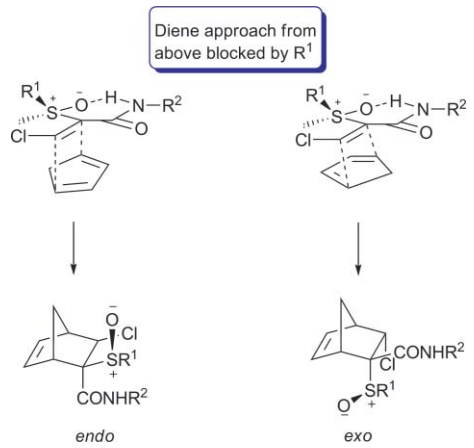

Fig. 6

the β-chloroacrylamide from the lower face, cyclopentadiene can add from two directions as depicted in Fig. 6, leading to the diastereomers with the amide in the *endo* and *exo* positions.

Employment of the enantiopure (*R*)-(+)-α-methylbenzylamine derived β-chloroacrylamide (*R*,*S*s)-**3r** yielded a diastereomeric ratio of 1 : 1.3 (*endo*:*exo*) of the inseparable cycloadducts, both of which are enantiopure, in 94% yield (entry 20, Table 1, Method A) as illustrated in Fig. 7. The cycloadducts are not readily separated at this stage, but can be separated through further functionalisation. The relative stereochemistry of the precursor sulfoxide was determined by X-ray crystallographic analysis of the diastereomeric (*R*,*R*s)-**3r**.[19] Thus, asymmetric induction from the sulfoxide chiral auxiliary is very effective in the cycloaddition process, with complete diastereofacial control, albeit yielding *endo* and *exo* isomers.

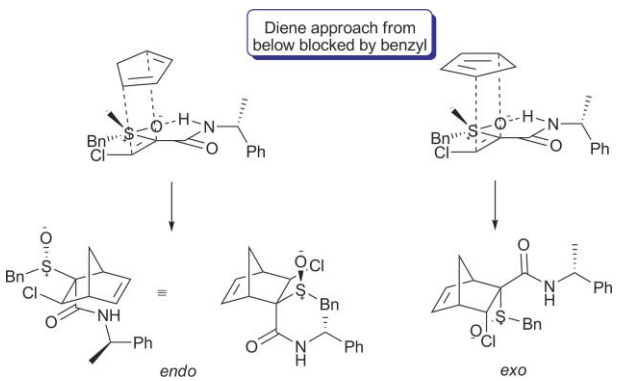

Fig. 7

Similarly, reaction of each of the enantioenriched sulfoxides (–)-**3o** and (+)-**3o** with cyclopentadiene led to the enantioenriched adducts (–)-**4o** and (+)-**4o**, which were isolated in 79% and 75% yield respectively, again as a mixture of *endo* and *exo* diastereomers, but with excellent transfer of chirality from sulfur to carbon in the cycloaddition process (entries 16 and 17, Table 1, Method A).

Employment of the Lewis acid catalysts $CuCl_2$ and $Cu(OTf)_2$ led to an increase in the diastereoselectivity of the cycloaddition, with approach of the diene favouring the formation of the *endo* diastereomer. Clearly, the change in the diastereomeric ratio is due to coordination of the metal to the sulfoxide.

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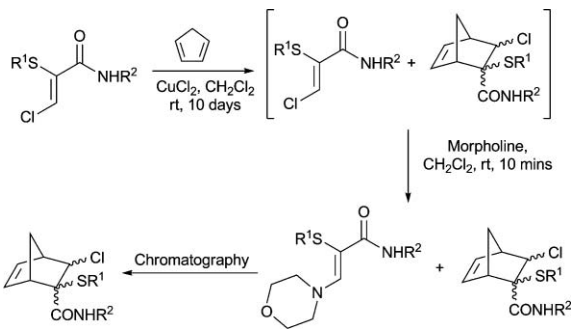
Table 2 Reaction of sulfide derivatives with cyclopentadiene

Entry	Sulfide	R^1	R^2	Method[a]	% conv.[b]	Adduct	*endo* : *exo*[b]	% yield[c]
1	**5a**	Ph	Tol	A	0	—	—	—
2	**5a**	Ph	Tol	G	77	**6a**	4.0 : 1	65
3	**5b**	Ph	Et	G	27	**6b**	1.3 : 1	17+9
4	**5c**	Ph	Bn	G	43	**6c**	1.7 : 1	39
5	**5d**	Ph	*i*Pr	G	22	**6d**	1.5 : 1	17+8
6	**5e**	Ph	*n*Bu	G	34	**6e**	1.9 : 1	25
7	**5f**	Ph	allyl	G	46	**6f**	2.0 : 1	31
8	**5g**	4-NO_2-C_6H_4	Tol	G	—[d]	**6g**	2.7 : 1	54
9	**5h**	*n*Bu	Tol	G	—[e]	**6h**	4.0 : 1[f]	33
10	**5i**	*n*Bu	Bn	G	—[e]	**6i**	2.7 : 1[f]	46
11	**5j**	Bn	4-F-C_6H_4	H	95	**6j**	3.1 : 1[g]	88

[a] Method A: 10 equivalents cyclopentadiene, CH_2Cl_2, reflux; Method G: 1. 1.2 equivalents $CuCl_2$, CH_2Cl_2, rt, 10 days, 2. morpholine, 3. chromatography; Method H: MW, 300 W, 150 °C, 10 min. [b] Unless otherwise stated, as determined by ^{1}H NMR spectroscopy of the crude product mixture after removal of the copper catalyst by chromatography on silica gel. [c] Isolated yield following chromatographic purification. [d] The % conversion could not be accurately estimated due to the adduct aromatic proton signals obscuring the β-chloroacrylamide β-proton signal on the ^{1}H NMR spectrum of the crude product mixture. [e] The % conversion could not be accurately estimated due to broadening of the signals in the ^{1}H NMR spectra. [f] Ratio after reaction of the crude product with morpholine followed by purification by chromatography. [g] Ratio after purification by chromatography.

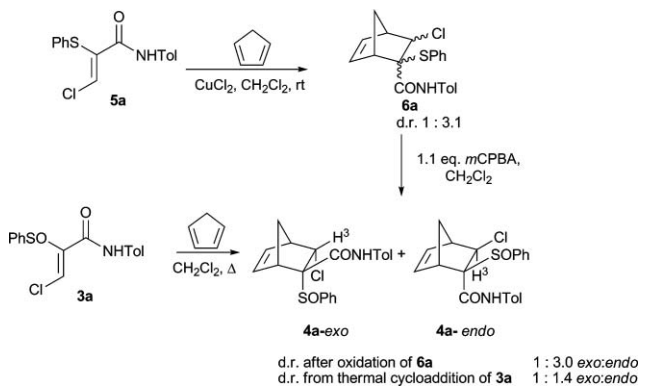
Following the success of the copper catalysed and microwave enhanced cycloadditions of the sulfoxides, the dienophilic behaviour of the less reactive sulfide derivatives with cyclopentadiene was re-examined. The Diels–Alder cycloaddition of the sulfide **5a** with cyclopentadiene was attempted in the presence of a range of Lewis acid catalysts, with $CuCl_2$ proving to be the most expedient catalyst. However, stoichiometric amounts of the catalyst (1.2 equivalents) and long reaction times (typically 10 days) were required, and it was necessary to add fresh portions of cyclopentadiene to the reaction mixture every 48 h. The cycloaddition was then conducted for a range of sulfides (entries 2–10, Table 2). Even with prolonged reaction times, the highest conversion of sulfide to cycloadduct observed was 77% (entry 2, Table 2). Attempts to separate the cycloadduct from the unreacted starting material in each instance by chromatography were unsuccessful. It was previously shown that the sulfides undergo nucleophilic substitutions readily with morpholine to yield very polar substances.[15] As the cycloadducts cannot readily undergo reaction with morpholine, the substitution of the sulfides with morpholine was exploited in separating the unreacted sulfides from the cycloadducts. Thus, following removal of the copper catalyst, the product mixture containing the unreacted sulfide and cycloadduct was dissolved in dichloromethane and, based on the estimated amount of unreacted starting material as determined by ^{1}H NMR spectroscopy of the crude reaction mixture, 2.5 equivalents of morpholine was added (Scheme 5). Purification by chromatography then provided the sulfide cycloadducts free of starting material.

As with the sulfoxide adducts, only two sets of signals were seen on both the ^{1}H and ^{13}C NMR spectra; therefore it was envisaged that the sulfide adducts directly analogous to the sulfoxide adducts isolated earlier were formed with the amide moiety *endo* and *exo*. Oxidation of the sulfide adduct **6a** with *m*CPBA to the corresponding sulfoxide adduct **4a** and comparison of the shifts and the coupling constants in the ^{1}H NMR spectra confirmed that



Scheme 5

the relative stereochemistry was the same in the sulfide adducts as in the sulfoxide adducts (Scheme 6), with the same diastereomer (amide *endo*) predominating. Interestingly, oxidation of the sulfide cycloadducts produced the same sulfoxides as had been isolated from the cycloaddition with the α-sulfinyl-β-chloroacrylamides. No evidence for formation of diastereomers at sulfur was observed.



Scheme 6

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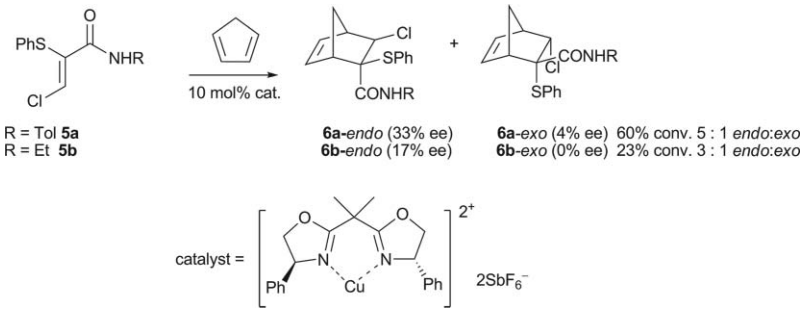


Scheme 7

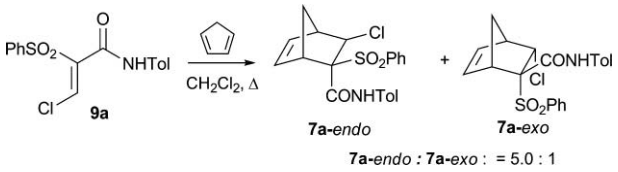
The relative stereochemistry of the sulfide adducts was also confirmed by examination of the coupling constants of H-3 in the major and the minor adducts, which were identical in the sulfide adducts to those of the sulfoxide adducts. Most of the cycloadducts were isolated as an inseparable mixture of diastereomers following chromatographic purification, however, it was possible to separate the *N*-ethyl adducts **6b**-*endo* and **6b**-*exo* (entry 3, Table 2) and the *N*-isopropyl adducts **6d**-*endo* and **6d**-*exo* (entry 5, Table 2).

In general the cycloadditions were most efficient with *N*-aryl amides, and equally, diastereoselectivities tended to be highest with these derivatives (entries 2 and 9, Table 2), as seen in cycloadditions with the analogous sulfoxides. Interestingly, similar diastereoselectivities were observed with the *n*-butylthio and phenylthio derivatives (entries 2 and 4, Table 2 *cf.* entries 9 and 10, Table 2).

The microwave assisted Diels–Alder cycloaddition of the β-chloroacrylamides with cyclopentadiene was also attempted at the sulfide level (entry 11, Table 2). Following heating of the sulfide **5j** in an excess of cyclopentadiene at 150 °C for 10 min under solvent-free conditions, there was 95% conversion to the resulting cycloadduct **6j**, the highest conversion achieved to date for the cycloadditions with the sulfides. Significantly, this was also the first time that the sulfide cycloadducts were formed in the absence of a Lewis acid catalyst. Following purification by chromatography, the cycloadduct **6j** was isolated in 88% yield in an *endo*:*exo* ratio of 3.1 : 1.

Preliminary investigation into the use of chiral Lewis acid catalysts was also undertaken as illustrated in Scheme 7. The Cu(II) bisoxazoline catalyst developed by the Evans group was employed,[23] and initial attempts to effect the cycloaddition of the *N*-tolyl sulfide **5a** using 10 mol% of the chiral catalyst in dichloromethane at room temperature resulted in very low conversion (30% in 6 days). A range of solvents were screened, including water, methanol, ethanol, hexane and ether, with most efficient cycloadditions observed using ether as solvent. The enantioselectivities achieved were low, with the highest enantiopurity (33% ee) achieved for **6a**-*endo*.

The Diels–Alder cycloadducts have also been synthesised at the sulfone level of oxidation. However, due to the difficulty in forming the sulfone derivatives of the β-chloroacrylamides,[15] the majority of the sulfone adducts synthesised were formed by oxidation of the corresponding sulfoxide adducts using *m*CPBA in dichloromethane (see later). The sulfone derivative of the *N*-tolyl β-chloroacrylamide **9a** was prepared, however, by refluxing the sulfoxide with a large excess of *m*CPBA in dichloromethane for 18 h. After work-up, this material was used without further purification in the Diels–Alder cycloaddition with cyclopentadiene at reflux in dichloromethane to give the cycloadduct **7a**, with an *endo* : *exo* ratio of 5.0 : 1 (Scheme 8). The increase in diastereoselectivity of the cycloaddition on oxidizing the sulfoxide (*endo*:*exo* 1.3: 1) to the sulfone (*endo* : *exo* 5.0 : 1) may be due to the electronic impact of the sulfonyl group, or may reflect catalysis of the cycloaddition by residual 3-chlorobenzoic acid. Further work is required to clarify this.



Scheme 8

Oxidation of adducts

In order to compare the adducts at the sulfide, sulfoxide and sulfone levels of oxidation, a series of oxidation experiments were undertaken where the separated diastereomers of the *N*-ethyl adduct **6b**-*endo* and **6b**-*exo* and the *N*-tolyl adduct **6a** were converted from the sulfide adducts to the sulfoxide adducts and then on to the sulfone adducts to correlate the diastereomers at each level of sulfur oxidation (Scheme 9).

The oxidations were conducted by sequential addition of *m*CPBA with monitoring by ^{1}H NMR spectroscopy. With the separated *N*-ethyl cycloadducts **6b**-*exo* and **6b**-*endo*, it was possible to observe the oxidation sequence from sulfide to sulfoxide to sulfone, therefore correlating the cycloadduct diastereomers at each level of sulfide oxidation. Oxidation of the *exo* diastereomer appeared to proceed more rapidly than oxidation of the corresponding *endo* diastereomer, and indeed, further oxidation of the *exo* diastereomer to the epoxide **8b**-*exo* was observed in the presence of excess *m*CPBA, while the corresponding process was not seen with the diastereomeric *endo* sulfone.

Similarly, a mixture of the *N*-tolyl cycloadducts **6a**-*endo* and **6a**-*exo* was oxidised through the sequence sulfide to sulfoxide to sulfone, again enabling correlation of the diastereomeric cycloadducts. In this instance, both diastereomers appeared to oxidise at approximately the same rate, however, there was some evidence for over oxidation of **7a**-*exo* to the epoxide **8a**-*exo* on addition of a third portion of *m*CPBA.

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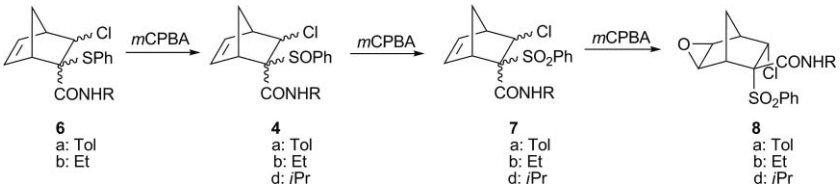


6
a: Tol
b: Et

4
a: Tol
b: Et
d: *i*Pr

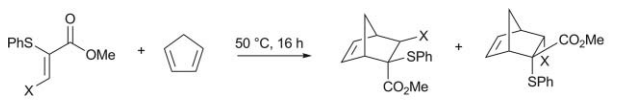
7
a: Tol
b: Et
d: *i*Pr

8
a: Tol
b: Et
d: *i*Pr

Scheme 9

A mixture of the *N*-isopropyl sulfoxide adducts **4d**-*endo* and **4d**-*exo* was also exposed to the *m*CPBA oxidation conditions (Scheme 9), and again the reaction was monitored by ^{1}H NMR spectroscopy. While both the *endo* and *exo* diastereomers were oxidized effectively to the sulfones, partial over-oxidation of **7d**-*exo* to the corresponding epoxide **8d**-*exo* (up to 30%) was observed, similar to results with the *N*-tolyl and *N*-ethyl adducts.

Cycloadditions of β-chloroacrylates 10a and 10b with cyclopentadiene. We have demonstrated that the synthesis of the β-chloroacrylamides can be effectively extended to the corresponding acrylates.[18] The effect of replacing the amide moiety of the β-chloroacrylamides with the ester functionality on the Diels–Alder cycloadditions with cyclopentadiene was therefore investigated. The cycloaddition of the β-chloroacrylate **10a** at the sulfide level of oxidation with cyclopentadiene was initially attempted using Method A (10 eq. of cyclopentadiene, dichloromethane, reflux, 16 h); approximately 15% conversion to the adduct **11a** was evident by ^{1}H NMR spectroscopy. This was the first time that an adduct of a β-chloro compound at the sulfide level of oxidation had formed without the use of Lewis acid catalysis, high pressure or microwaves. In order to drive the reaction to completion, the β-chloroacrylate **10a** was reacted with a large excess of cyclopentadiene (approximately 20 equivalents) under solvent-free conditions at 50 °C for 16 h. Following purification by chromatography, the cycloadducts **11a**-*endo* and **11a**-*exo* were obtained free of starting material in an 86% yield and a diastereomeric ratio of 4.1 : 1 respectively (Scheme 10). The stereochemistry of the two diastereomers was assigned by comparison of the NMR spectra of **11a** with those of the amide derivatives. The Diels–Alder cycloaddition of the bromo derivative **10b** with cyclopentadiene was also conducted using the solvent-free conditions described above; the cycloadduct **11b** was obtained in an 85% yield and a diastereomeric ratio of 4.3 : 1 (*endo*:*exo*) (Scheme 10).



X = Cl, **10a**
X = Br, **10b**

11a-*endo*
11b-*endo*

11a-*exo* (d.r 4.1 : 1)
11b-*exo* (d.r 4.3 : 1)

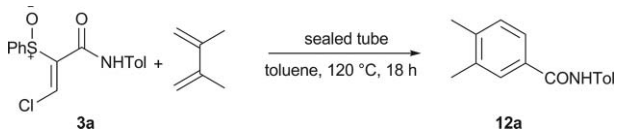
Scheme 10

Thus, an increase in reactivity and selectivity is observed on substituting the β-chloroacrylamides with the β-chloroacrylates in Diels–Alder cycloadditions with cyclopentadiene.

2,3-Dimethyl-1,3-butadiene

The reactivity of the β-chloroacrylamides in cycloadditions with the acyclic diene 2,3-dimethyl-1,3-butadiene was next explored. Unlike cyclopentadiene, which is fixed in the s-*cis* geometry required for Diels–Alder cycloadditions, rotation around the C(2)–C(3) bond is possible in 2,3-dimethyl-1,3-butadiene, leading to both the s-*cis* and s-*trans* conformers. The barrier to this rotation has been calculated experimentally as 4.3 kcal mol^{-1},[24] and as a result of this rotation the reactivity of 2,3-dimethyl-1,3-butadiene in cycloadditions with β-chloroacrylamides is expected to be much lower than cyclopentadiene.[25,26]

Preliminary investigations were conducted using the sulfoxide **3a** as dienophile. The cycloaddition with 2,3-dimethyl-1,3-butadiene was attempted in dichloromethane at reflux in the absence and presence of Cu(OTf)$_2$; the unreacted precursor **3a** was isolated in both instances. The use of elevated pressure, achieved by heating the solution in a sealed tube, to promote this Diels–Alder cycloaddition was then investigated. On heating a solution of the diene with the β-chloroacrylamide **3a** in toluene in a sealed tube for 18 h, the trisubstituted aromatic product **12a** was isolated in 87% yield (Scheme 11).

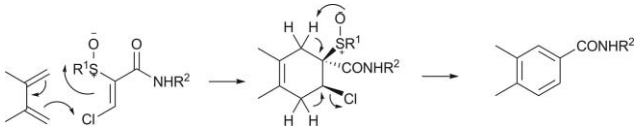


3a **12a**

Scheme 11

The use of microwave technology to promote the Diels–Alder cycloaddition between the acyclic diene 2,3-dimethyl-1,3-butadiene and the β-chloroacrylamides was next explored to avoid the use of sealed tubes. The microwave assisted cycloadditions of the sulfoxides with 2,3-dimethyl-1,3-butadiene proved to be very successful, with complete conversion to the trisubstituted aromatic adducts following microwave heating for 30 min at 150 °C using 10 equivalents of 2,3-dimethyl-1,3-butadiene under solvent-free conditions (Table 3).

The Diels–Alder cycloaddition proceeds *via* the cyclohexene adduct, but this easily eliminates both the sulfoxide and chloride groups, either spontaneously or on silica gel, to yield the trisubstituted aromatic as the final product (Scheme 12).



Scheme 12

The cyclohexene intermediate was evident in the ^{1}H NMR spectra of the crude products from each of the benzylsulfinyl cycloadditions (entries 3–7, Table 3), although the substituted aromatic products account for the major sets of signals present. These cyclohexene adducts do not survive the purification conditions of

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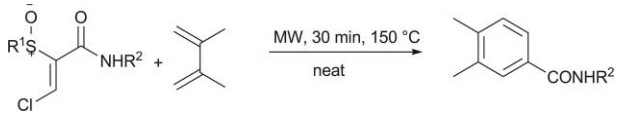
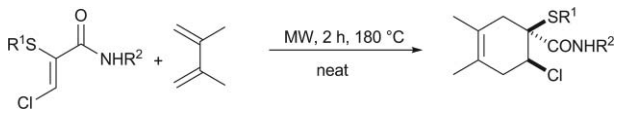
Table 3 Microwave assisted cycloaddition of sulfoxides with 2,3-dimethyl-1,3-butadiene



Entry	Sulfoxide	R^1	R^2	Product	% yield[a]
1	**3a**	Ph	Tol	**12a**	59
2	**3n**	*n*-Bu	Bn	**12b**	39
3	**3p**	Bn	Bn	**12b**	53
4	**3q**	Bn	4-F-C_6H_4	**12c**	83
5	**3u**	Bn	Tol	**12a**	95
6	**3v**	Bn	Me	**12d**	42
7	**3w**	Bn	Ph	**12e**	53

[a] Isolated yield after chromatography on silica gel.

Table 4 Microwave assisted cycloaddition of sulfides and 2,3-dimethyl-1,3-butadiene



Sulfide	R^1	R^2	Product	% yield[a]
5a	Ph	Tol	**13a**	91
5j	Bn	4-F-C_6H_4	**13b**	98
5k	Bn	Bn	**13c**	98
5l	Bn	Me	**13d**	58

[a] Isolated yield after chromatography on silica gel.

chromatography on silica gel, and elimination of the sulfoxide and chloride substituents affords the substituted aromatic products, with no evidence of the cyclohexene adducts in the ^{1}H NMR spectra of the purified products. In contrast, the cyclohexene adducts were not evident in the ^{1}H NMR spectra of the crude products from the cycloaddition of the benzenesulfinyl derivative **3a** (entry 1, Table 3) and the *n*-butylsulfinyl derivative **3n** (entry 2, Table 3) with the 2,3-dimethyl-1,3-butadiene, indicating that the benzenesulfinyl and *n*-butylsulfinyl groups are more easily eliminated than the benzylsulfinyl group. A similar effect was seen in earlier studies on 1,3-dipolar cycloadditions with the β-chloroacrylamides.[16] Interestingly, the isolated yields of **12a** and **12b** were lower from the cycloaddition of **3a** and **3n** than from the cycloaddition of the corresponding benzylsulfinyl derivatives **3u** and **3p** (entries 1 and 2, Table 3 *vs.* entries 3 and 5, Table 3), presumably associated with the more facile elimination during the cycloaddition.

The microwave assisted Diels–Alder cycloaddition of 2,3-dimethyl-1,3-butadiene with the sulfide derivatives, which are inherently weaker dienophiles, was also investigated. Following heating of the sulfides with 2,3-dimethyl-1,3-butadiene at 180 °C for 2 h, the cyclohexene adducts were isolated (Table 4).

The ^{1}H NMR spectra of the crude products were very clean and on purification by chromatography on silica gel, the cyclohexene adducts **13a–13d** were isolated, with no evidence of sulfide or chloride elimination. The potential to isolate the cyclohexene adducts or the aromatic products from the cycloaddition processes based on the level of sulfide oxidation is potentially synthetically useful.

Conclusion

Diels–Alder cycloadditions of cyclopentadiene to α-sulfinyl-β-chloroacrylamides can be effected under thermal, copper catalysed and microwave conditions to afford a range of novel cycloadducts. In all instances, excellent diastereofacial control from the sulfoxides is observed, although leading to a mixture of *endo* and *exo* diastereomers. An increase in the reactivity and selectivity is observed on employment of copper catalysts, while a significant increase in the reaction rate is observed under microwave irradiation. While the Diels–Alder cycloadditions of cyclopentadiene to α-thio-β-chloroacrylamides could not be achieved under thermal conditions, successful cycloaddition was observed either through use of copper catalysis or microwave irradiation.

Cycloaddition of the β-chloroacrylamides at both the sulfide and sulfoxide levels of oxidation with the acyclic diene 2,3-dimethyl-1,3-butadiene can be effected thermally using microwave heating. This is particularly significant, as copper catalysed cycloaddition with the acyclic diene was unsuccessful. In the case of the sulfoxides, only the aromatised products are isolated after purification, while with the more robust sulfides, the cyclohexenes are readily isolated and characterised.

Experimental

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide and ethyl acetate was distilled from potassium carbonate. Hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. Cyclopentadiene was freshly prepared by cracking cyclopentadiene dimer at 180 °C and distilling the monomer into an ice-cooled flask and then stored at −18 °C. While this material was typically used within 2 h of preparation, samples of cyclopentadiene stored at −18 °C were found to dimerise so slowly that the reagent did not need to be redistilled for up to 5 days.

Infrared spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids on a Perkin Elmer Paragon 1000 FT-IR spectrometer.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. ^{1}H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a JEOL PMX-60SI spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in hertz (Hz).

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionization (ESI) mode using 50% water–acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionization (ESI) mode using 50% water–acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

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Elemental analyses were performed by the Microanalysis Laboratory, National University of Ireland, Cork, using Perkin–Elmer 240 and Exeter Analytical CE440 elemental analysers. Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

Flash chromatography was performed using Kieselgel silica gel 60, 0.040–0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV (254 nm) light detection, iodine staining, vanillin staining and ceric sulfate staining.

Microwave assisted synthesis was achieved using the CEM Discover Labmate Synthesiser in conjunction with ChemDriver software (Version 3.5.0) and the CEM Discover S-Class Synthesiser in conjunction with Synergy software.

The synthesis of **3a–3w**, **5a–5l** and **10a** and **10b** has already been described.[14,15,18] Selected experimental data, including representatives of each of the synthetic methods, are given below–full experimental procedures and spectroscopic data for all compounds described in the paper are given in the supporting information.

Preparation of sulfoxide adducts

2-*exo*-Benzenesulfinyl-3-*exo*-chlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid ethylamide 4b-*endo* and 2-*endo*-benzenesulfinyl-3-*endo*-chlorobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid ethylamide 4b-*exo*. Freshly distilled cyclopentadiene (1.3 g, 1.6 mL, 19.4 mmol) was added to a solution of **3b** (1.0 g, 3.9 mmol) in dichloromethane (20 mL). The reaction solution was then heated at reflux for 18 h. The solvent and most of the excess diene were evaporated at reduced pressure to give the crude adduct **4b** as a mixture of separable diastereomers. A ^{1}H NMR spectrum was recorded of the crude reaction product (crude ratio of **4b**-*endo* : **4b**-*exo* 1.2 : 1) before separation by chromatography on silica gel using ethyl acetate–hexane (gradient elution 10–25% ethyl acetate) as eluent to give the less polar minor adduct diastereomer **4b**-*exo* (390 mg, 32%) as a colourless solid; mp 159–162 °C; Found C, 59.83; H, 5.70; N, 4.56; Cl, 11.10; S, 9.40. $C_{16}H_{18}NClO_2S$ requires C, 59.34; H, 5.60; N, 4.33; Cl, 10.95; S, 9.90; ν_{max}/cm^{-1} (KBr) 1669, 1522, 1032, 746; δ_H (270 MHz, $CDCl_3$) 0.80 (3H, t, *J* 4, $-CH_3$), 1.58–1.62 (1H, H_A of ABq, *J* 10, H-7′), 1.77–1.81 (1H, H_B of ABq, *J* 10, H-7), 2.73–3.02 (2H, m, NCH_2), 3.41 (1H, s, H-4), 3.48 (1H, s, H-1), 5.63 (1H, d, *J* 4, H-3), 6.58–6.64 (1H, m, H-5), 6.77–6.82 (1H, m, H-6), 6.91 (1H, br s, NH), 7.40–7.52 (3H, m, ArH), 7.78–7.90 (2H, m, ArH); δ_C (67.8 MHz, $CDCl_3$) 14.1 ($-CH_3$), 34.7 (NCH_2), 45.4 (C-7), 50.6 (C-4), 55.0 (C-1), 59.7 (C-3), 78.7 (C-2), 126.3 (aromatic CH), 129.0 (aromatic CH), 130.8 (aromatic CH), 135.3 (C-6), 139.7 (C-5), 141.5 (aromatic C), 167.2 (CO). MS *m*/*z* 323 (M^+, 7%), 198 (100, M^+-SOPh), 162 (46, M^+-SOPh-HCl), 91 (93); isotopic Cl pattern observed; 323, 325 (3 : 1 ^{35}Cl: ^{37}Cl); Found (HRMS, EI) *m*/*z* 323.0811. $C_{16}H_{18}N^{35}ClO_2S$ requires 323.0747. NOE studies on this compound, 270 and 300 MHz, irradiating at H-3 showed enhancement of H-4 and H-7′.

The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **4b**-*exo* recrystallised from ethyl acetate–hexane. Crystals of **4b**-*exo* are monoclinic, space group $P2_1/n$, formula $C_{16}H_{18}ClNO_2S$, M = 323.82, a = 9.9680(10) Å, b = 13.712(2) Å, c = 11.671(2) Å, β = 99.670(10)°, U = 1572.5(4) Å^3, $F(000)$ = 680, μ(Mo-Kα) 0.379 mm^{-1}, $R(F_o)$ = 0.044, for 1009 observed reflections with $I > 2\sigma(I)$, w$R_2(F^2)$ = for all 1800 unique reflections. Data in the θ range 2.31–27.46° were collected on a Nonius MACH3 diffractometer using Mo-Kα graphite monochromated radiation, λ = 0.71069 Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

The more polar major adduct diastereomer **4b**-*endo* was isolated (510 mg, 42%) as a colourless solid; mp 161–163 °C (with decomposition); Found C, 59.82; H, 5.80; N, 4.41; Cl, 11.10; S, 9.90. $C_{16}H_{18}NClO_2S$ requires C, 59.34; H, 5.60; N, 4.33; Cl, 10.95; S, 9.90; ν_{max}/cm^{-1} (KBr) 1667, 1533, 1076, 1041, 755; δ_H (270 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7, $-CH_3$), 1.88–1.92 (1H, H_A of ABq, *J* 10, H-7′), 2.62–2.66 (1H, H_B of ABq, *J* 10, H-7), 2.69–2.99 (2H, m, NCH_2), 3.29 (1H, s, H-4), 3.74 (1H, s, H-1), 4.88 (1H, d, *J* 2, H-3), 6.08–6.13 (1H, m, H-5), 6.34–6.40 (1H, m, H-6), 6.48 (1H, br s, NH), 7.40–7.51 (3H, m, ArH), 7.82–7.91 (2H, m, ArH); δ_C (67.8 MHz, $CDCl_3$) 14.2 ($-CH_3$), 34.3 (NCH_2), 45.6 (C-7), 50.2 (C-4), 53.9 (C-1), 59.6 (C-3), 76.3 (C-2), 126.7 (aromatic CH), 129.1 (aromatic CH), 130.9 (aromatic CH), 135.5 (C-5), 138.5 (C-6), 141.4 (aromatic C), 166.0 (CO). MS *m*/*z* M^+ not seen, 272 (50%, M^+–Cl–O), 231 (35), 135 (63), 117 (85), 43 (100). NOE studies on this compound, 270 and 300 MHz, irradiating at H-3 showed enhancement of H-4 and H-5.

The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **4b**-*endo* recrystallised from ethyl acetate–hexane. Crystals of **4b**-*endo* are triclinic, space group $P\bar{1}$, formula $C_{16}H_{18}ClNO_2S$, M = 232.82, a = 8.221(4) Å, b = 9.997(3) Å, c = 10.709(6) Å, α = 114.90(4)°, β = 92.12(5)°, γ = 99.43(3)°, U = 782.0(6) Å^3, $F(000)$ = 340, μ(Mo-Kα) 0.381 mm^{-1}, $R(F_o)$ = 0.067, for 1828 observed reflections with $I > 2\sigma(I)$, w$R_2(F^2)$ = 0.155 for all 2668 unique reflections. Data in the θ range 2.11–25.33° were collected on a Nonius MACH3 diffractometer using Mo-Kα graphite monochromated radiation, λ = 0.71069 Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

Cu(II) Catalysed cycloadditions

$CuCl_2$ Catalysed cycloaddition of 3d with cyclopentadiene.

Method i. Freshly distilled cyclopentadiene (0.1 mL, 1.3 mmol) was added to a solution of the sulfoxide **3d** (50 mg, 0.2 mmol) in dichloromethane (1 mL). A catalytic amount of $CuCl_2$ (1% by weight *cf.* the sulfoxide) was added and the resulting brown suspension was stirred for 16 h when the reaction mixture was applied directly to the top of a column of silica gel. The product was eluted using ethyl acetate–hexane (gradient elution: 0–30% ethyl acetate) as eluent to give a mixture of unreacted sulfoxide **3d** (50% conversion by NMR) and the two adduct diastereomers **4d** in a ratio of **4d**-*endo* : **4d**-*exo* of 1.2 : 1. See supporting information for spectroscopic details.†

Method ii. Freshly distilled cyclopentadiene (0.1 mL, 1.3 mmol) was added to a solution of the sulfoxide **3d** (50 mg, 0.2 mmol) in dichloromethane (1 mL). A catalytic amount of $CuCl_2$ (1% by weight *cf*. the sulfoxide) was added and the resulting brown suspension was stirred for 16 h when a further addition of cyclopentadiene (0.1 mL, 1.3 mmol) was made. After stirring for

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an additional 26 h, the reaction mixture was applied directly to the top of a column of silica gel. The product was eluted using ethyl acetate–hexane (gradient elution: 0–30% ethyl acetate) as eluent to give two adduct diastereomers (no detectable starting material) **4d**-*exo* in a ratio of **4d**-*endo* : -*exo* of 1.4 : 1.

$CuCl_2$ Catalysed cycloadditions at reflux.

*$CuCl_2$ Catalysed cycloaddition of **3a** with cyclopentadiene.* Freshly distilled cyclopentadiene (0.1 mL, 1.1 mmol) was added to a solution of the sulfoxide **3a** (50 mg, 0.2 mmol) in the presence of a catalytic amount of CuCl (1% by weight *cf.* the sulfoxide) in dichloromethane (1 mL). The resulting brown suspension was heated to reflux. After refluxing for 18 h, the reaction mixture was applied directly to the top of a column of silica gel. The product was recovered using ethyl acetate–hexane (gradient elution: 0–30%) as eluent to give a mixture consisting of both adduct diastereomers (no detectable starting material) in a ratio of **4a**-*endo* : **4a**-*exo* of 1.8 : 1. See supporting information for spectroscopic details.†

$Cu(OTf)_2$ Catalysed cycloadditions at room temperature.

*$Cu(OTf)_2$ Catalysed cycloaddition of **3a** with cyclopentadiene.* Freshly distilled cyclopentadiene (0.1 mL, 1.1 mmol) was added to a solution of the sulfoxide **3a** (50 mg, 0.2 mmol) in dichloromethane (1 mL). A catalytic amount of $Cu(OTf)_2$ (1% by weight *cf.* the sulfoxide) was added and the resulting suspension was stirred for 16 h at room temperature when the reaction mixture was applied directly to the top of a column of silica gel. After stirring for 1 h the reaction mixture was blue in colour. The product was eluted using ethyl acetate–hexane (gradient elution: 0–30% ethyl acetate) as eluent to give two adduct diastereomers in a ratio of **4a**-*endo* : **4a**-*exo* of 8.8 : 1. See supporting information for spectroscopic details.†

$Cu(OTf)_2$ Catalysed cycloadditions at reflux.

*$Cu(OTf)_2$ Catalysed cycloaddition of **3c** with cyclopentadiene.* Freshly distilled cyclopentadiene (0.2 mL, 2.6 mmol) was added to a solution of the sulfoxide **3c** (50 mg, 0.2 mmol) in the presence of a catalytic amount of $Cu(OTf)_2$ (1% by weight *cf.* the sulfoxide) in dichloromethane (1.5 mL). The reaction solution was then heated to reflux. After about 30 min at reflux, the reaction solution was deep blue in colour. After refluxing for 2 h, the reaction mixture was applied directly to the top of a column of silica gel. The product was recovered using ethyl acetate–hexane (20 : 80) as eluent to give a mixture consisting of both adduct diastereomers (no detectable starting material) in a ratio of **4c**-*endo* : **4c**-*exo* of 6.2 : 1. See supporting information for spectroscopic details.†

Preparation of sulfide adducts

2-*exo*-Phenylthio-3-*exo*-chlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid *p*-tolylamide 6a-*endo* and 2-*endo*-phenylthio-3-*endo*-chlorobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid *p*-tolylamide 6a-*exo*. $CuCl_2$ (500 mg, 3.7 mmol) was added to a solution of the **5a** (750 mg, 2.5 mmol) in dichloromethane (15 mL) to give a brown suspension. Freshly distilled cyclopentadiene (2 mL) was added and the reaction suspension stirred for 48 h. More freshly distilled cyclopentadiene (1 mL) was added and the reaction mixture was again stirred for 48 h before a further cyclopentadiene addition was made. This process of fresh cyclopentadiene additions (1 mL aliquots) was repeated every 48 h until the reaction suspension had been stirred for a total of 10 days. A short column of silica gel was prepared using ethyl acetate–hexane as eluent (5 : 95) and the reaction mixture applied directly. A ^{1}H NMR spectrum of the crude product mixture was recorded which showed 77% conversion and a crude ratio of **6a**-*endo* : **6a**-*exo* of 4.0 : 1. The crude product was dissolved in dichloromethane (15 mL) and morpholine (124 mg, 1.4 mmol) was added. After stirring for 30 min, the reaction solution was washed with water (2 × 20 mL) and brine (20 mL), dried and concentrated at reduced pressure. Chromatography on silica gel using ethyl acetate–hexane (20 : 80) as eluent gave the adduct **6a** (590 mg, 65%) as a mixture of inseparable diastereomers (ratio of **6a**-*endo* : **6a**-*exo* of 3.0 : 1) as a sticky brown solid; Found C, 67.90; H, 5.67; N, 3.54; Cl, 9.96; S, 8.21. $C_{21}H_{20}NClOS$ requires C, 68.19; H, 5.45; N, 3.79; Cl, 9.58; S, 8.67. The NMR signals for each diastereomer could be distinguished:

Major diastereomer **6a**-*endo*: δ_H (270 MHz, $CDCl_3$) 1.79–1.83 (1H, H_A of ABq, dd, *J* 2, 9, H-7′), 2.29 (3H, s, Ar–CH_3), 2.59–2.63 (1H, H_B of ABq, *J* 9, H-7), 3.08 (1H, br s, H-4), 3.11 (1H, br s, H-1), 4.62 (1H, d, *J* 2, H-3), 6.11–6.25 (2H, symmetrical m, H-5, H-6), 7.01–7.47 (9H, m, ArH), 7.60 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 21.2 (Ar CH_3), 46.6 (C-7), 52.3 (C-1 or C-4), 54.0 (C-1 or C-4), 65.3 (C-3), 67.4 (C-2), 120.4 (aromatic CH), 129.2 (aromatic C), 129.5 (aromatic CH), 129.9 (aromatic CH), 132.7 (aromatic CH), 134.5 (aromatic C), 134.8 (aromatic CH), 135.4 (aromatic C), 136.0 (C-5), 138.3 (C-6), 169.9 (CO).

Minor diastereomer **6a**-*exo*: δ_H (270 MHz, $CDCl_3$) 1.76–1.80 (1H, H_A of ABq, *J* 9, one of CH_2-7), 2.29 (4H, s, one of CH_2-7, Ar CH_3), 3.29 (1H, br s, H-1 or H-4), 3.36 (1H, br s, H-1 or H-4), 5.19 (1H, d, *J* 4, H-3), 6.40–6.46 (1H, m, H-5 or H-6), 6.53–6.59 (1H, m, H-5 or H-6), 7.01–7.47 (9H, m, ArH), 8.35 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 21.2 (Ar CH_3), 46.4 (C-7), 50.6 (C-1 or C-4), 54.0 (C-1 or C-4), 66.0 (C-3), 68.1 (C-2), 120.7 (aromatic CH), 128.5 (aromatic C), 129.5 (aromatic CH), 129.9 (aromatic CH), 132.7 (aromatic CH), 134.5 (aromatic C), 134.8 (aromatic CH), 135.4 (aromatic C), 136.6 (C-5 or C-6), 137.5 (C-5 or C-6), 170.8 (CO).

MS *m*/*z* 369 (M^+, 1%), 334 (4, M^+–Cl), 260 (1, M^+–SPh), 196 (13), 149 (40), 109 (20, $[SPh]^+$), 91 (55), 66 (100), 39 (97).

Preparation of sulfone adducts

Method I: Diels–Alder cycloaddition of sulfone 9a.

2-*exo*-Benzenesulfonyl-3-*exo*-chlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid *p*-tolylamide 7a-*endo* and 2-*endo*-benzenesulfonyl-3-*endo*-chlorobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid *p*-tolylamide 7a-*exo*. A solution of *m*CPBA (116 mg of 70% pure material, 0.5 mmol) in dichloromethane (10 mL) was added to a solution of **3a** (300 mg, 0.9 mmol) in dichloromethane (10 ml) at 0 °C. The reaction solution was allowed to warm to room temperature and after stirring for 1.5 h, a further addition of *m*CPBA (116 mg of 70% pure material, 0.5 mmol) in dichloromethane (10 mL) was made. The reaction solution was stirred for a further 1.5 h when a final addition of *m*CPBA (116 mg of 70% pure material, 0.5 mmol) in dichloromethane (10 mL) was made. After stirring for a further 2 h, the reaction solvent was evaporated at reduced pressure. The resulting white solid was slurried in dichloromethane (8 mL) and freshly distilled cyclopentadiene (320 mg, 0.4 ml, 4.7 mmol) was added. The

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reaction suspension was heated to reflux and total dissolution of the reaction mixture occurred. After 2 h at reflux, the reaction solution was dark green in colour. The solution was refluxed for a total of 18 h, then water (20 mL) was added and the phases separated. The organic fraction was washed with water (20 mL) and brine (20 mL) and concentrated at reduced pressure to give a brown solid. NMR analysis of this compound indicated formation of the sulfone adduct **7a** with a ratio of **7a**-*endo* : **7a**-*exo* of approximately 5.0 : 1. The crude reaction product was chromatographed on silica gel using ethyl acetate–hexane (40 : 60) as eluent to give **7a** (295 mg, 78%) with a ratio of **7a**-*endo* : **7a**-*exo* of 6.0 : 1 and spectroscopic details as reported below.

Method II: Oxidation of 4a.

2-*exo*-Benzenesulfonyl-3-*exo*-chlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid *p*-tolylamide 7a-*endo*, 2-*endo*-benzenesulfonyl-3-*endo*-chlorobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid *p*-tolylamide 7a-*exo* and 6-*endo*-benzenesulfonyl-7-*endo*-chloro-3-oxatricyclo[3.2.1.0]octane-6-*exo*-carboxylic acid *p*-tolylamide 8a. The sulfoxide adduct **4a** (200 mg, 0.5 mmol) was dissolved in dichloromethane (4 mL) and a sample of 0.4 mL (approximately 20 mg) removed for NMR spectroscopic analysis. The ratio of **4a**-*endo* : **4a**-*exo* in the reaction starting material was determined to be 1.3 : 1 by ^{1}H NMR spectroscopy. A solution of *m*CPBA (176 mg of 70% pure material, 0.7 mmol) in dichloromethane (4 mL) was added slowly to the adduct **4a** solution (180 mg, 0.5 mmol) and the reaction mixture stirred for 18 h. $NaHSO_3$ (10 mL of 10% solution) was added and the phases separated. The organic layer was washed with saturated $NaHCO_3$ (2 × 15 mL), water (2 × 15 mL) and brine (15 mL), dried and concentrated at reduced pressure to give the crude sulfone adduct **7a** with a ratio of **7a**-*endo* : **7a**-*exo* of 1.3 : 1. The crude product was purified by chromatography on silica gel using ethyl acetate–hexane (30 : 70) as eluent to give **7a** (168 mg, 89%), with the same ratio, as a colourless solid. Some over-oxidation (approximately 24% of the minor adduct diastereomer) to the epoxide **8a** was also evident.

7a: Found C, 62.29; H, 4.96; N, 3.99; Cl, 9.20; S, 8.20. $C_{21}H_{20}NClO_3S$ requires C, 62.75; H, 5.02; N, 3.49; Cl, 8.82; S, 7.98; The NMR signals for each diastereomer could be distinguished:

Major diastereomer **7a**-*endo*: δ_H (270 MHz, $CDCl_3$) 1.82–1.91 (1H, H_A of ABq, *J* 9, H-7′), 2.34 (3H, s, Ar–CH_3), 2.95–3.02 (1H, H_B of ABq, *J* 9, H-7), 3.14 (1H, br s, H-4), 3.91 (1H, br s, H-1), 4.78 (1H, d, *J* 2, H-3), 6.21–6.33 (2H, symmetrical m, H-5, H-6), 8.50 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 20.8 (*C*H$_3$, Ar–*C*H$_3$), 47.6 (*C*H$_2$, C-7), 50.8 (*C*H, C-1 or C-4), 53.4 (*C*H, C-1 or C-4), 59.6 (*C*H, C-3), 83.2 (*C*, C-2), 120.1 (*C*H, aromatic CH), 128.9 (*C*H, aromatic CH), 129.6 (*C*H, aromatic CH), 130.2 (*C*H, aromatic CH), 134.2 (*C*H, aromatic CH), 134.9 (*C*, aromatic C), 135.0 (*C*, aromatic C), 137.5 (*C*H, C-5 or C-6), 139.0 (*C*H, C-5 or C-6), 164.0 (*C*, CO).

Minor diastereomer **7a**-*exo*: δ_H (270 MHz, $CDCl_3$) 1.50–1.76 (2H, ABq, *J* 9, CH_2-7), 2.34 (3H, s, Ar-CH_3), 3.29 (1H, br s, H-4), 3.60 (1H, br s, H-1), 5.33 (1H, d, *J* 4, H-3), 6.46–6.53 (1H, m, H-5), 6.66–6.72 (1H, m, H-6), 8.78 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 20.8 (*C*H$_3$, Ar–*C*H$_3$), 47.1 (*C*H$_2$, C-7), 50.8 (*C*H, C-1 or C-4), 51.7 (*C*H, C-1 or C-4), 62.3 (*C*H, C-3), C-2 obscured by $CDCl_3$ at 76.5–77.5, 120.1 (*C*H, aromatic CH), 129.0 (*C*H, aromatic CH), 129.6 (*C*H, aromatic CH), 130.2 (*C*H, aromatic CH), 134.2 (*C*H, aromatic CH), 134.9 (*C*, aromatic C), 135.0 (*C*, aromatic C), 135.7 (*C*H, C-5 or C-6), 136.0 (*C*H, C-5 or C-6), 164.7 (*C*, CO).

The aromatic protons for both diastereomers were observed at δ_H (270 MHz, $CDCl_3$) 7.11–7.20 (2H, m, ArH), 7.29–7.48 (4H, m, ArH), 7.52–7.64 (1H, m, ArH), 7.79–7.90 (2H, m, ArH).

MS *m*/*z* 401 (M^+, 9%), 366 (39, M^+–Cl), 260, 262 (100, M^+–SO_2Ph), 224 (37), 121 (50), 77 (87); isotopic Cl pattern observed; 401, 403 (3 : 1 ratio ^{35}Cl: ^{37}Cl); Found (HRMS, EI) *m*/*z* 401.0826. $C_{21}H_{20}N^{35}ClO_3S$ requires 401.0852.

Characteristic signals for the epoxide **8a** were observed at δ_H (270 MHz, $CDCl_3$) 3.81–3.84 (m, H-2 or H-4), 4.18–4.21 (m, H-2 or H-4), 5.33 (d, *J* 4, H-7), 8.68 (br s, NH) and δ_C (67.8 MHz, $CDCl_3$) 24.0 (C-8), 44.9, 48.6, 49.0 (3 signals for 4 CH's, C-1, C-2, C-4, C-5), 163.5 (CO).

Oxidation of adducts

2-*exo*-Benzenesulfonyl-3-*exo*-chlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid *p*-tolylamide 7a-*endo* and 2-*endo*-benzenesulfonyl-3-*endo*-chlorobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid *p*-tolylamide 7a-*exo*. A solution of *m*CPBA (37 mg of 70% pure material, 0.2 mmol) in dichloromethane (2 mL) was added to a solution of **6a** (50 mg, 0.1 mmol) in dichloromethane (5 mL). Before addition of the *m*CPBA solution, the ratio of **6a**-*endo* : **6a**-*exo* was estimated at 3.1 : 1 by ^{1}H NMR spectroscopy of a representative sample. After stirring for 18 h, 0.5 mL of the reaction solution was removed and the solvent evaporated at reduced pressure. NMR analysis (^{1}H NMR spectroscopy) of this sample showed 80% conversion of the sulfide adduct **6a** to the corresponding sulfoxide adduct **4a** with a ratio of **4a**-*endo* : **4a**-*exo* of 3.1 : 1. A solution of *m*CPBA (40 mg of 70% pure material, 0.2 mmol) in dichloromethane (1 mL) was added to the reaction solution before stirring for a further 18 h when a sample (1 mL) was removed and analysed by ^{1}H NMR spectroscopy which showed 68% sulfone adduct **7a**, 32% sulfoxide adduct **4a**-*endo* and an adduct ratio of **7a**-*endo* : **7a**-*exo* of 3.0 : 1. No evidence of the sulfoxide adduct of the minor diastereomer **4a**-*exo* was seen. A final addition of *m*CPBA (20 mg of 70% pure material, 0.1 mmol) in dichloromethane (1 mL) was made to the reaction solution and, after stirring for 18 h, the reaction was worked up as described for **7a** to give a white solid. NMR analysis of this material showed the major diastereomer to be approximately 90% converted to **7a**-*endo* while some over-oxidation of the minor diastereomer **7a**-*exo* to the epoxide **8a**-*exo* was also observed.

3, 4-Dimethyl-*N*-4-methylphenyl-benzamide 12a.

Method a: Sealed tube. A solution of the sulfoxide **3a** (100 mg, 0.3 mmol), 2, 3-dimethylbutadiene (1.0 mL, 8.1 mmol) in toluene (2.0 mL) was charged to a tube which was then sealed. The tube was heated in an oil bath at 100 °C for 18 h before cooling to room temperature. The crude reaction solution was applied directly to a column of silica gel. The reaction product was eluted using ethyl acetate–hexane (gradient elution, 0–20% ethyl acetate) as eluent to give the crude product (110 mg). Purification by chromatography on silica gel using ethyl acetate–hexane (gradient elution, 10–20% ethyl acetate) as eluent gave **12a** (65 mg, 87%) as a colourless solid; mp 123–125 °C; Found C, 79.65; H, 7.12; N, 5.83. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.16; N, 5.85; ν_{max}/cm^{-1} (KBr) 1652 (CO), 1521, 1319, 807; δ_H (270 MHz, $CDCl_3$) 2.30 (6H, s, 2 × ArCH_3), 2.32 (3H, s, ArCH_3), 7.09–7.22 (3H, m, ArH), 7.49–7.67 (4H, m,

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ArH), 7.86 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 19.7 (CH_3, 2 × $ArCH_3$ overlapping), 20.9 (CH_3, $ArCH_3$), 120.4 (*C*H, 2 × aromatic CH), 124.4 (*C*H, aromatic CH), 128.4 (*C*H, aromatic CH), 129.6 (*C*H, 2 × aromatic CH), 130.0 (*C*H, aromatic CH), 132.8 (*C*, aromatic C), 134.0 (*C*, aromatic C), 135.8 (*C*, aromatic C), 137.2 (*C*, aromatic C), 140.8 (*C*, aromatic C), 165.8 (*C*, CO). MS *m/z* 239 (M^+, 20%), 133 (100), 105 (40), 77 (72).

Method b: Microwave conditions. 2,3-Dimethyl-1,3-butadiene (1.5 mL, 6.3 mmol) and **3a** (0.2 g, 0.6 mmol) were placed in a sealed microwave reaction vessel with stirring and subsequently heated for 30 min at 300 W at 100 °C. The excess diene was then evaporated at reduced pressure to give the crude product as an orange oil. Following purification by column chromatography using hexane–ethyl acetate as eluent (gradient elution 5–20% ethyl acetate), **12a** was obtained as a white solid (0.08 g, 59%); (Found C, 80.16; H, 7.21; N, 5.59. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.16; N, 5.85%); ν_{max}/cm^{-1} (KBr) 3337 (NH), 2916 (CH), 1652 (CO), 1611, 1596, 1521; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, one of $ArCH_3$), 2.34 (6H, s, 2 × $ArCH_3$), 7.17 (2H, d, *J* 8.4, Ar*H*), 7.24 [1H, d, *J* 7.6, aromatic C(5)*H*], 7.52 (2H, d, *J* 8.4, Ar*H*), 7.58 [1H, dd, *J* 7.6, 1.6, aromatic C(6)*H*], 7.65 [1H, d, *J* 1.6, aromatic C(2)*H*], 7.72 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 19.78, 19.82, 20.9 (3 × CH_3, 3 × $ArCH_3$), 120.2, 124.3, 128.3, 129.5, 129.9 (5 × CH, 5 × aromatic *C*H), 132.6, 134.0, 135.6, 137.2, 140.9 (5 × C, 5 × aromatic *C*), 165.7 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1388. Found 240.1391; *m/z* (ES+) 240.0 {[($C_{16}H_{17}NO$)+H^+], 100%}.

(1*R,6*R**)-1-(Phenylthio)-6-chloro-3,4-dimethyl-*N*-(4-methylphenyl)cyclohex-3-enecarboxamide 13a.** 2,3-Dimethyl-1,3-butadiene (1.4 mL, 6.6 mmol) and *N*-(4-fluorophenyl)-*Z*-3-chloro-2-(phenylthio)propenamide **5a** (0.2 g, 0.6 mmol) were placed in a sealed microwave reaction vessel with stirring and subsequently heated for 120 min at 300 W at 180 °C. The excess diene was then evaporated at reduced pressure to give the crude product as a pale yellow solid. Following purification by column chromatography using hexane–ethyl acetate 85 : 15 as eluent, the substituted cyclohexene product **13a** was obtained as a white solid (0.2 g, 91%), mp 112–114 °C; Found C, 68.30; H, 6.37; N, 3.67; S, 8.67; Cl, 8.78. $C_{22}H_{24}ClNOS$ requires C, 68.46; H, 6.27; N, 3.63; S, 8.31; Cl, 9.19%; ν_{max}/cm^{-1} (KBr) 3332 (NH), 2922 (CH), 1679 (CO), 1517; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s, one of CH_3), 1.67 (3H, s, one of CH_3), 1.82 [1H, br d, A of AB system, J_{AB} 18.0, one of C(2)H_2], 2.35 (3H, s, $ArCH_3$), 2.57–2.67 [1H, m, one of C(5)H_2], 2.80–2.96 [2H, m, one of C(5)H_2 & one of C(2)H_2], 4.76 [1H, dd, *J* 9.6, 6.0, C(6)*H*], 7.19 (2H, d, *J* 8.4, Ar*H*), 7.27–7.34 (2H, m, Ar*H*), 7.35–7.42 (1H, m, Ar*H*), 7.43–7.48 (2H, m, Ar*H*), 7.50–7.55 (2H, m, Ar*H*), 9.76 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 17.9, 18.3, 20.9 (3 × CH_3, 3 × CH_3), 38.4, 40.1 [2 × CH_2, *C*(2)H_2 & *C*(5)H_2], 61.6 [CH, *C*(6)H], 65.3 [C, *C*(1)], 120.1 (CH, aromatic *C*H), 122.7, 124.0 [2 × C, *C*(3) & *C*(4)], 128.9 (CH, aromatic *C*H), 129.3 (C, aromatic *C*), 129.59, 129.62 (2 × CH, 2 × aromatic *C*H), 134.5, 135.0 (2 × C, 2 × aromatic *C*), 136.5 (CH, aromatic *C*H), 169.6 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{22}H_{25}NOS^{35}Cl$ $[M+H]^+$ 386.1345. Found 386.1338; *m/z* (ES+) 388.0 {[($C_{22}H_{24}NOS^{37}Cl$)+H^+], 40%}, 386.0 {[($C_{22}H_{24}NOS^{35}Cl$)+H^+], 100%}.

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