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Synthesis and reactivity of α-sulfenyl-β-chloroenones, including oxidation and Stille cross-coupling to form chalcone derivatives

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ABSTRACT

The synthesis of a range of novel α-sulfenyl-β-chloroenones from the corresponding α-sulfenylketones, *via* a NCS mediated chlorination cascade, is described. The scope of the reaction has been investigated and compounds bearing alkyl- and arylthio substituents have been synthesised. In most instances, the *Z* α-sulfenyl-β-chloroenones were formed as the major products, while variation of the substituent at the β-carbon position led to an alteration in stereoselectivity. Stille cross-coupling with the *Z* α-sulfenyl-β-chloroenones led to selective formation of *Z* sulfenyl chalcones, while the *E* α-sulfenyl-β-chloroenones did not react under the same conditions. Oxidation of the *Z* α-sulfenyl-β-chloroenones was followed by isomerisation, leading to the *E* α-sulfinyl-β-chloroenones. Stille cross-coupling with the *E* α-sulfinyl-β-chloroenones produced the *E* sulfinyl chalcones. Either the *E* or *Z* sulfinyl chalcones can be obtained by altering the sequence of oxidation and Stille cross-coupling.
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1. Introduction

Stereoselective construction of densely functionalised versatile building blocks which can be employed in organic synthesis remains a key objective [1–3]. Enones have been widely employed as synthetic intermediates over many decades [4–7]. Indeed, enones display interesting biological activity in their own right [8].

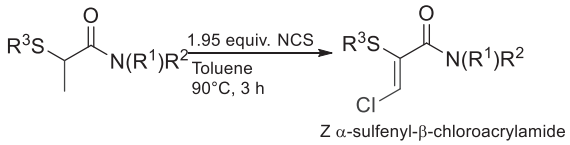
Our group has previously reported the discovery of a novel class of compounds, the α-sulfenyl-β-chloroacrylamides (Scheme 1) [9,10]. The transformation of α-sulfenylamides to the corresponding α-sulfenyl-β-chloroacrylamides, upon treatment with *N*-chlorosuccinimide, via a chlorination cascade, is both highly efficient and also stereoselective, yielding exclusively the *Z* stereoisomer. The mechanistic pathway has been explored in detail with the key reaction intermediates identified, including through use of ReactNMR [11]. Recently, the synthetic utility of the chlorination cascade has been enhanced through the use of continuous flow processing [12,13].

The scope of this transformation was investigated and compounds bearing alkyl- and arylthio substituents were synthesised as well as the series being extended to the ester, nitrile and Weinreb amide series [10,14]. The use of the novel α-sulfenyl-β-chloroacrylamides as Michael acceptors in nucleophilic addition/substitution reactions, as dienophiles in Diels-Alder cycloadditions, as well as their use in 1,3-dipolar cycloadditions [15,16] has been reported (Scheme 2). We have also reported the oxidation and subsequent reactivity of sulfoxide and sulfone derivatives of this series [15].

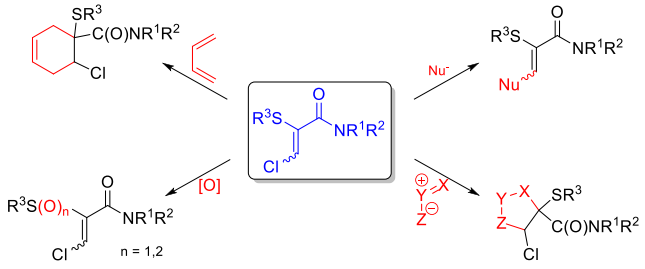
Herein, we report for the first-time, successful application of the chlorination cascade at the ketone level of oxidation to form the novel α-sulfenyl-β-chloroenones; previously, the chlorination cascade had been implemented with carboxylic acid derivatives only. The process optimisation and scope of this transformation is described. These novel compounds, as highly functionalised enones, offer greater synthetic potential than the previously reported α-sulfenyl-β-chloroacrylamides. Structurally similar compounds have been described only rarely in the literature, for example, Iwasaki *et al.* [17] reported the iron-induced

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Scheme 1. Synthesis of α-sulfenyl-β-chloroacrylamides.



Scheme 2. Reactivity of α-sulfenyl-β-chloroacrylamides.

chlorothiolation of internal alkynes with sulfenyl chlorides giving rise to a compound bearing the α-sulfenyl-β-chloroenone core framework.

Selective oxidation to the α-sulfinyl-β-chloroenones is described. Stille cross-coupling to introduce aryl substituents at the β-carbon was investigated, leading to 2-sulfenyl and 2-sulfinyl chalcones, with the stereochemical outcome dependent on the level of oxidation at sulfur. Chalcones, open chain flavonoids, are of keen interest due to their diverse biological activities, including anti-cancer and anti-malarial properties, among others, reported in the literature [18–20].

2. Results and discussion

2.1. Synthesis of α-chloroketones and α-sulfenylketones

The α-sulfenylketones (3a – 3ll, Table 1), the majority of which were novel, were readily prepared by reaction of known α-chloroketones with sodium thiolates as summarised in Scheme 3 (Full details provided in the supplementary information).

All but one of the α-chloroketones were prepared by treating a range of commercially available ketones with NCS and *p*-toluenesulfonic acid, while one made use of another literature procedure [21]. The α-sulfenylketones were selected to enable investigation of the impact of both steric and electronic effects on the outcome of the chlorination cascade. Use of aryl-, benzyl, alkylthio substituents and alkyl or aryl ketones were employed. The α-sulfenylketones were prepared in moderate to excellent yields.

2.2. Synthesis of α-sulfenyl-β-chloroenones

As summarised in Table 1 and Scheme 4, treatment of the α-sulfenyl aryl ketones with 1.95 equiv. of NCS in toluene at 90 °C for 16 h resulted in efficient transformation to the corresponding α-sulfenyl-β-chloroenones, typically in moderate to excellent yields.

It appears that a similar mechanistic pathway is followed for the chlorination cascade with the aryl ketone derivatives (Scheme 5), to that which had been studied in detail with the α-sulfenylamides [11]. Indeed, in the ^{1}H NMR spectra of the crude reaction mixtures, characteristic signals could be seen corresponding to the intermediates of the chlorination cascade proposed for the ketone series, namely the α,β-unsaturated ketones **C** and the dichlorides **D**, confirming that the mechanistic pathway proceeded similarly to that seen in the amide series (Scheme 4) (See supplementary information for full details). Interestingly, the α-chlorosulfide **B** intermediate of the NCS cascade was not seen in the preparation of the aryl ketones, while it was detected in the amide series.

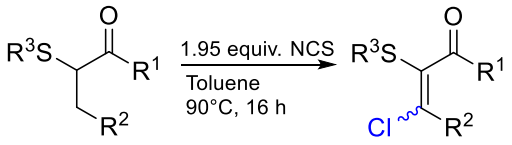
While the scope of the ketone derivatives investigated was substantially broader than the earlier study with the α-sulfenyl amides, for those derivatives which could be compared, the reaction was notably slower with the ketone derivatives than with the amide series, requiring 16 h at 90 °C for efficient transformation, while the amide transformation was generally complete within 2–3 h [10]. Although slower than the amide derivatives, the NCS cascade with the aryl ketone derivatives was seen to be more efficient than those of the corresponding ester and nitrile derivatives which required Lewis acid catalysis to effect the final transformation in the cascade [14]. Rapid heating of the reaction mixture on addition of NCS is critical for efficient transformation and, in practice, this was achieved by immersing the reaction flask in a pre-heated oil bath at 90 °C immediately following the NCS addition. When the reaction mixture was gradually heated to 90 °C, transformation through the reaction cascade was less efficient with increased amounts of the key intermediates, such as the α,β-unsaturated ketone and dichloride, evident in the ^{1}H NMR spectra of the crude product mixtures.

In contrast to the highly selective formation of the *Z* α-sulfenyl-β-chloroacrylamides, with the ketone series, a mixture of *E* and *Z* α-sulfenyl-β-chloroenones was formed in all cases, and, while in some instances these were separated by chromatography, in many cases they were isolated as a mixture with the *Z* isomer the major isomer formed for the majority of the propenones (**4a** – **4aa,** other than entries 3, 4, 16 and 23). The assignment of stereochemistry in the α-sulfenyl-β-chloroenones was undertaken by ^{1}H NMR spectroscopy utilising NOESY and comparative trends with the spectral features in the α-sulfenyl-β-chloroacrylamides, in which case some derivatives were definitively assigned by crystallography. Typically, the characteristic β-hydrogen singlet was significantly downfield in the *Z* isomer relative to the *E* isomer. There was minor alteration in *E*:*Z* ratios following chromatography, most notably for entries 4, 15, 18, 21 and 22.

With the extended chain ketones (entries 28–38, Table 1), formation of the α-sulfenyl-β-chloroenones proceeded with similar efficiency to that seen with the propenones, in contrast to the decrease in efficiency reported in the amide series [14,15]. This may be associated with the increased conformational flexibility in the transition state of the ketone series relative to the amides (Fig. 1). However, the stereochemical outcome in the formation of the α-sulfenyl-β-chloroenones was sensitive to the presence of an alkyl substituent at the β-carbon position with increased formation of the *E* isomer evident, and indeed in all cases, the *E* isomer was the major product from the reaction, in contrast to the *Z* isomer which dominated in the propenones. There was a notable decrease in stereoselectivity for the α-sulfenyl-β-chlorobutenones and α-sulfenyl-β-chloropentenones with crude *E*:*Z* ratios of 1.1–1.4:1 observed in the ^{1}H NMR spectra of the crude products, relative to that seen with the α-sulfenyl-β-chloropropenones (typically *E*:*Z* 1:2–1:4), indicating that while replacing the terminal hydrogen with an alkyl group had a significant effect on the stereochemical outcome, a change from β-methyl to β-ethyl had no significant impact on stereoselectivity.

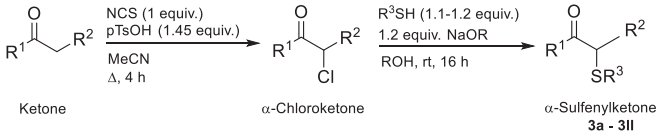
The altered outcome in terms of stereocontrol, relative to the amide series, may be rationalised as summarised in Fig. 1; as discussed previously [10], an intramolecular hydrogen bond in the α-sulfenylamides holds the intermediate carbocation in a conformation which leads selectively to the *Z* sulfenyl β-chloroacrylamide. In the ketones, conformational flexibility is greater in the sulfur stabilised carbocation, decreasing the steric interaction in the

Table 1
Synthesis of aryl α-sulfenyl-β-chloroenones.



Entry	Thioketone	R^1	R^3	R^2	β-Chloroenone	Crude *Z*:*E*[a]	% Yield *Z*[b]	% Yield *E*[b]	% Yield (overall)[b]	Purified *Z*:*E*[c]
1	**3a**	Ph	Ph	H	**4a**	2:1	–	–	68	2.2:1
2	**3b**	Ph	Bn	H	**4b**	1:1	–	–	86	1.1:1
3	**3c**	Ph	n-Bu	H	**4c**	1:1.8	–	–	75	1:1.5
4	**3d**	4-$MeOC_6H_4$	Ph	H	**4d**	1:1.75	–	–	88	1.6:1
5	**3e**	4-$MeOC_6H_4$	Bn	H	**4e**	3:1	–	–	57	4.3:1
6	**3f**	4-$MeOC_6H_4$	n-Bu	H	**4f**	2.1:1	–	–	89	2.3:1
7	**3g**	4-MeC_6H_4	Ph	H	**4g**	1.5:1	–	–	65	1.7:1
8	**3h**	4-MeC_6H_4	Bn	H	**4h**	2.5:1	40	16	56	–
9	**3i**	4-MeC_6H_4	n-Bu	H	**4i**	1.3:1	–	–	53	1.3:1
10	**3j**	4-MeC_6H_4	4-$ClC_6H_4CH_2$	H	**4j**	2.8:1	32	18	50	–
11	**3k**	4-MeC_6H_4	4-$MeOC_6H_4CH_2$	H	**4k**	2.6:1	39	12	51	–
12	**3l**	4-MeC_6H_4	4-$FC_6H_4CH_2$	H	**4l**	2.7:1	46	15	61	–
13	**3m**	4-MeC_6H_4	4-$MeC_6H_4CH_2$	H	**4m**	2.7:1	23	9	32	–
14	**3n**	4-ClC_6H_4	Ph	H	**4n**	1.7:1	–	–	53	2.1:1
15	**3o**	4-ClC_6H_4	Bn	H	**4o**	1.7:1	–	–	48	2.4:1
16	**3p**	4-ClC_6H_4	n-Bu	H	**4p**	1:2	–	–	66	1:1.3
17	**3q**	4-ClC_6H_4	4-$ClC_6H_4CH_2$	H	**4q**	2.7:1	20	16	36	–
18	**3r**	4-ClC_6H_4	4-$MeOC_6H_4CH_2$	H	**4r**	2.3:1	–	–	39	9:1
19	**3s**	4-ClC_6H_4	4-$FC_6H_4CH_2$	H	**4s**	2.2:1	–	–	62	2.5:1
20	**3t**	4-ClC_6H_4	4-$MeC_6H_4CH_2$	H	**4t**	2.5:1	33	13	46	–
21	**3u**	4-FC_6H_4	Ph	H	**4u**	1.3:1	–	–	63	3.8:1
22	**3v**	4-FC_6H_4	Bn	H	**4v**	1.4:1	–	–	76	2:1
23	**3w**	4-FC_6H_4	n-Bu	H	**4w**	1:1.2	–	–	73	1:1.1
24	**3x**	4-FC_6H_4	4-$ClC_6H_4CH_2$	H	**4x**	2.2:1	–	–	66	2.2:1
25	**3y**	4-FC_6H_4	4-$MeOC_6H_4CH_2$	H	**4y**	2.6:1	–	–	40	2.8:1
26	**3z**	4-FC_6H_4	4-$FC_6H_4CH_2$	H	**4z**	2.6:1	–	–	64	3:1
27	**3aa**	4-FC_6H_4	4-$MeC_6H_4CH_2$	H	**4aa**	2.3:1	45	17	62	–
28	**3bb**	Ph	Bn	Me	**4bb**	1:1.7	–	–	67	1:1.6
29	**3cc**	Ph	4-$ClC_6H_4CH_2$	Me	**4cc**	1:1.3	–	–	74	1:1.4
30	**3dd**	Ph	4-$MeOC_6H_4CH_2$	Me	**4dd**	1:1.2	29	25	54	–
31	**3ee**	Ph	4-$FC_6H_4CH_2$	Me	**4ee**	1:1.4	–	–	65	1:1.4
32	**3ff**	Ph	4-$MeC_6H_4CH_2$	Me	**4ff**	1:1.4	–	–	63	1:1.8
33	**3gg**	Ph	Ph	Me	**4gg**	1:1.4	–	–	50	1:1.2
34	**3hh**	Ph	Bn	Et	**4hh**	1:1.4	–	–	67	1:1.4
35	**3ii**	Ph	4-$ClC_6H_4CH_2$	Et	**4ii**	1:1.4	–	–	69	1:1.2
36	**3jj**	Ph	4-$MeOC_6H_4CH_2$	Et	**4jj**	1:1.2	–	–	65	1:1.3
37	**3kk**	Ph	4-$FC_6H_4CH_2$	Et	**4kk**	1:1.1	–	–	63	1:1.1
38	**3ll**	Ph	4-$MeC_6H_4CH_2$	Et	**4ll**	1:1.4	–	–	72	1:1.4

[a] Ratio of Z:E determined from the ^{1}H NMR spectrum of the crude product.
[b] Isolated yield after column chromatography.
[c] Z and E isomers could not be separated following column chromatography and were isolated as a mixture.



Scheme 3. Synthesis of α-chloroketones and α-sulfenylketones.

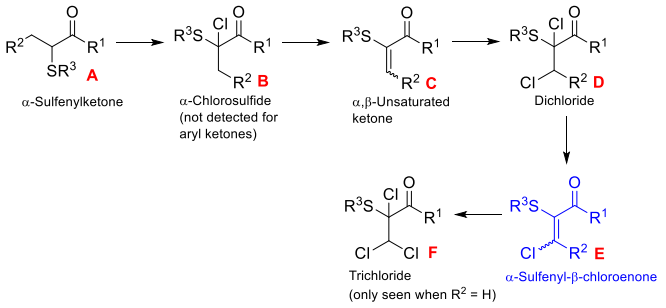
transition state, relative to the amide series, resulting in the formation of both *Z* and *E* sulfenyl β-chloroenones.

Interconversion of *Z* and *E* alkene isomers has been reported, especially in the presence of UV light [22], although this has not been observed in the α-sulfenyl-β-chloroacrylamides studied over the past decade. In contrast, some evidence of interconversion was seen with the ketone series. ^{1}H NMR spectra of samples of pure *Z*-**4h** and pure *E*-**4h**, taken after neat, bench-top storage at room temperature without protection from light, 4 months after initial characterisation, showed partial conversion to the opposite isomer, with the pure *Z* isomer seen to have interconverted to a larger degree than the corresponding pure *E* isomer (Fig. 2). Similar interconversion was seen with compound **4r** as detailed in the Supplementary Information.

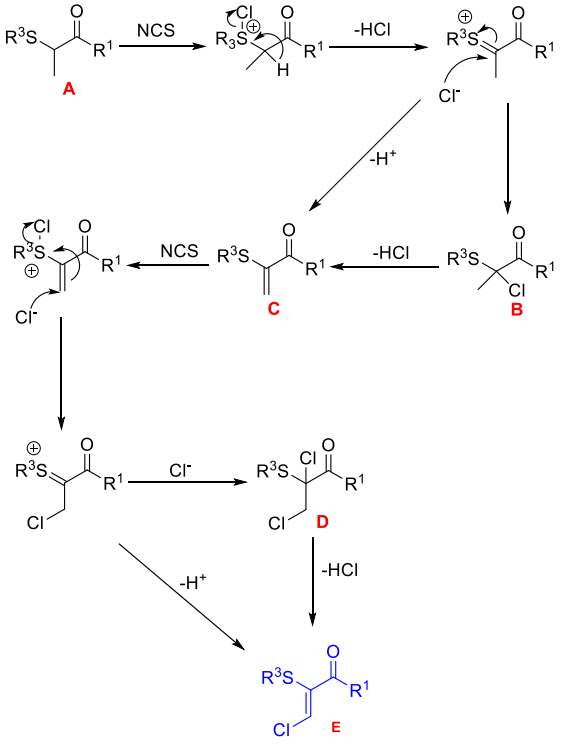
As summarised in Fig. 3, characteristic trends are evident in the ^{1}H NMR spectra of the *Z* and *E* isomers of the α-sulfenyl-β-chloroenones with the stereochemistry confirmed through NOESY studies.

Building on the success of the chlorination cascade in the α-sulfenyl aryl ketones, our attention next focussed on the corresponding alkyl ketones as summarised in Table 2 and Schemes 6 and 7.

To investigate the pathway and intermediates in the chlorination cascade with the alkyl α-sulfenylketones, 3-phenylthiobutanone **5a** was selected for investigation as the intermediates derived from this ketone were anticipated to have



Scheme 4. Characteristic components detected in the reaction mixtures of the chlorination cascade.



Scheme 5. Proposed mechanistic pathway for the formation of α-sulfenyl-β-chloroenones.

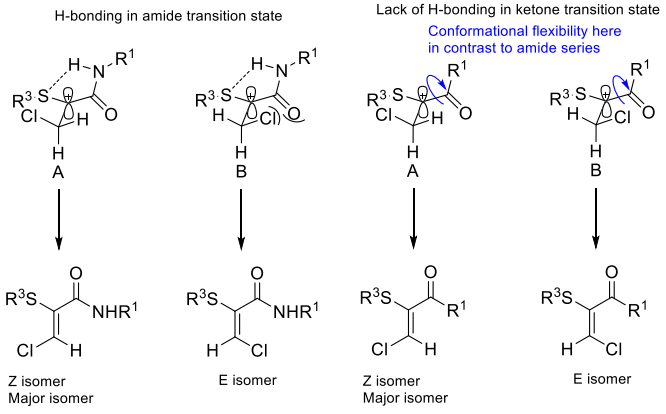


Fig. 1. Stereochemical control in the formation of α-sulfenyl-β-chloroacrylamides and α-sulfenyl-β-chloroenones.

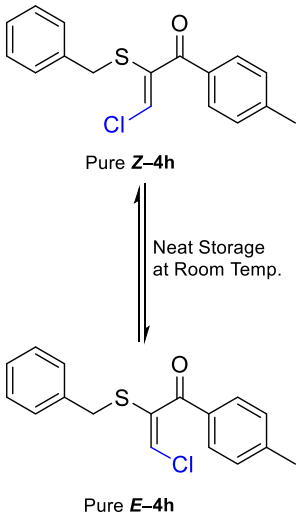


Fig. 2. Interconversion of *Z* and *E* α-sulfenyl-β-chloroenone **4h**.

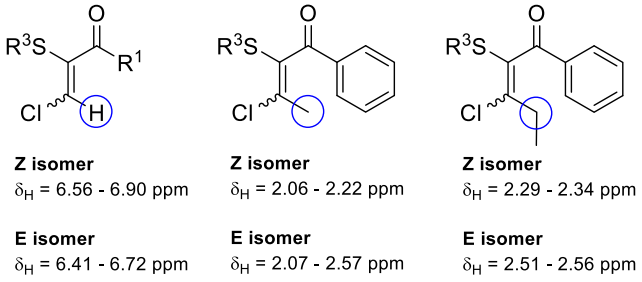
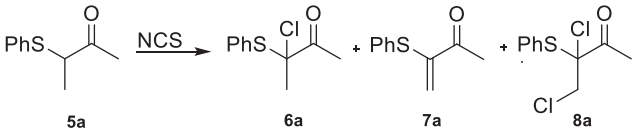


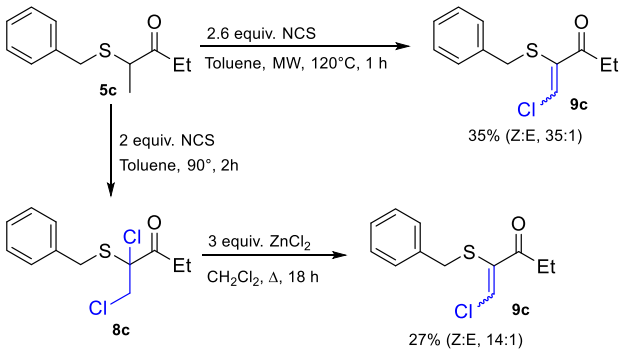
Fig. 3. Characteristic ^{1}H NMR signals of β-substituent signal in α-sulfenyl-β-chloroenones.

Table 2
Initial reactions of **5a** with *N*-chlorosuccinimide.

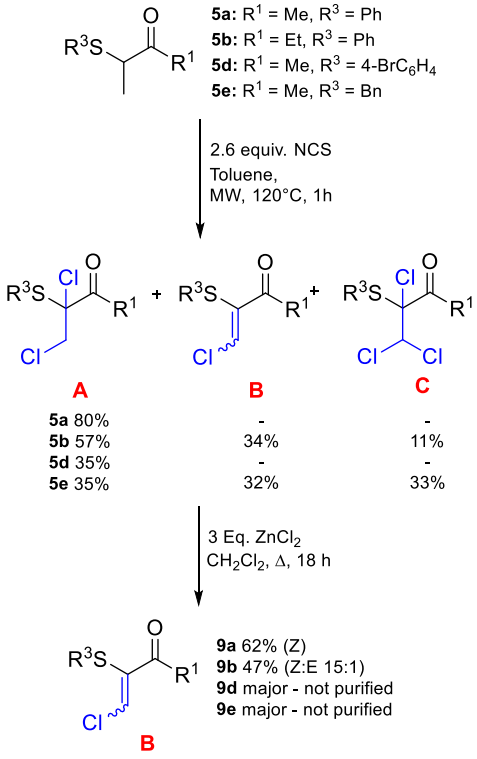


Entry	NCS (equiv.)	Time (h)	Temp (°C)	Solvent	crude product ratios[a]		
					6a %	7a %	8a %
1	1.10	3	0	CCl_4	56	N.D.	N.D.
2	1.90	2	25	Toluene	33	50	17
3	1.90	1	90	Toluene	14	9	77
4	2.05	2	90	Toluene	7	10	83
5	2.10	2	90	Toluene	31	N.D.	69
6	2.15	2	90	Toluene	20	N.D.	70
7	2.20	2	90	Toluene	N.D	N.D.	75
8	2.00	1	25	Toluene	30	27	43
9	2.60	0.5	120 (MW)	Toluene	8	N.D.	92
10	2.60	1	120 (MW)	Toluene	N.D.	N.D.	98

N.D. = not detected by ^{1}H NMR spectroscopy. MW = microwave heating at 200 W.
[a] % conversion to each product was estimated by integration of the ^{1}H NMR spectrum of the crude product mixture.



Scheme 6. Reaction of **5c** under both microwave and thermal conditions.



Scheme 7. Synthesis of alkyl α-sulfenyl-β-chloroenones using optimised conditions.

clearly distinguishable methyl singlets in the ^{1}H NMR spectra of the crude product mixtures.

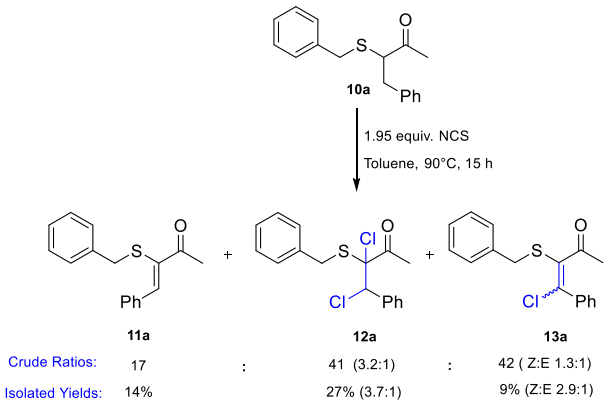
As summarised in Table 2, the α-sulfenylketone **5a** was exposed to increasing amounts of NCS and increasing temperatures in toluene under both thermal and microwave conditions, or in carbon tetrachloride at 0 °C. At low temperatures and low equivalents of NCS, the α-chlorosulfide **6a** was the major product from the reaction as seen from Entry 1. Increasing the temperature from 0 °C to 25 °C led to a mixture of the α-chlorosulfide **6a**, the α,β-unsaturated ketone **7a** and the dichloride **8a**. Entries 4 to 7 in Table 2 show that increasing the reaction temperature to 90 °C and using 2 equivalents of NCS led to the dichloride **8a** being the major product from the reaction. The reaction was also investigated under microwave conditions, proving the dichloride could be successfully formed using this method. In contrast to the results with the aryl ketones (Table 1), there was no evidence for the formation of the α-sulfenyl-β-chloroenone **9a** during this study. Clearly, replacing the aryl ketone with a methyl ketone results in stabilisation of the dichloride, presumably associated with the decreased conjugation which destabilises the sulfur stabilised carbocation. The conditions subsequently employed for the formation of the dichloride **8a** were 2 equivalents of NCS in toluene at 90 °C for 2 h. Subsequent reaction of **8a** with zinc chloride as the Lewis acid furnishes the desired α-sulfenyl-β-chloroenone **9a**.

As summarised in Scheme 6, transformation of the α-benzylsulfenyl ketone **5c** to the α-sulfenyl-β-chloroenone **9c** can be conducted directly by effecting the chlorination cascade under microwave heating or alternatively, in a two-step sequence forming initially the dichloride **8c** in toluene at 90 °C for 2 h, followed by exposure to zinc chloride to effect elimination of HCl to provide the α-sulfenyl-β-chloroenone **9c**.

Furthermore, as summarised in Scheme 7, when the α-sulfenyl ketones **5a**, **b**, **d,** and **e** were subjected to the chlorination cascade under microwave conditions, both the dichlorides **A** and the α-sulfenyl-β-chloroenones **B** were seen in the crude product mixtures, with the HCl elimination completed on exposure to zinc chloride. While the ease of the final HCl elimination leading to the α-sulfenyl-β-chloroenones is sensitive to the substituents, from a synthetic perspective, exposure to zinc chloride effectively completes the process leading to the products in good yields following chromatographic purification. Formation of the *Z* isomer predominated throughout the series, in agreement with the observations with the aryl ketones, but to an even greater extent (relative to Table 1). Interestingly, the stereochemical outcome is comparable to that seen with the ester and nitrile derivatives [14].

In contrast to the secondary amide series [9,10,14,15], where the efficiency of the reaction cascade was relatively insensitive to substituent alteration, it is interesting to see increased sensitivity to differences in substitution in the ketone series, with aryl ketones leading efficiently to the α-sulfenyl-β-chloroenones while alkyl ketones require more forcing conditions to complete the reaction cascade in some instances. However, from a synthetic perspective, it is clear that access to the *Z* α-sulfenyl-β-chloroenones is readily achieved, albeit in some cases requiring the use of a Lewis acid to complete the final elimination step.

Investigation of the chlorination cascade was undertaken with 4-phenyl ketone **10a** to establish the impact of an aryl substituent at the β-position on both the efficiency and stereoselectivity of the chlorination sequence (Scheme 8). Under the standard reaction conditions, characteristic signals were seen in the ^{1}H NMR spectra of the crude product mixture confirming the presence of the enone **11a**, the dichloride **12a** and the α-sulfenyl-β-chloroenone **13a**, indicating that the efficiency of the transformation through the



Scheme 8. Reaction of α-sulfenylketone **10a** with NCS.

cascade was somewhat less efficient than with the other derivatives, possibly due to the stability associated with the extended conjugation in the enone **11a** [23].

Notably, an interesting observation was made on the relative stability of the two diastereomers of the dichloride **12a.** On extended storage at room temperature (40 months), one of the two diastereomers was seen to convert completely to a mixture of *Z* and *E* α-sulfenyl-β-chloroenones **13a** (*E*:*Z*, 1:2), indicating that, for stereoelectronic reasons, the HCl elimination is favoured in one diastereomer over the other, presumably due to the relative stability of the trans co-planar orientation leading to the α-sulfenyl-β-chloroenones.

Having established that the chlorination cascade successfully leads to α-sulfenyl-β-chloroenones, attention focussed on the potential synthetic utility of these highly functionalised enones. While 2-sulfenyl chalcones are rare in the literature, Reddy and coworkers [24] have reported the synthesis and biological evaluation in cytotoxicity screens of a series of *E* 2-sulfenyl chalcones, noting in particular the importance of a nitro substituent on the styryl ring. Accordingly, we envisaged that transformation of the novel α-sulfenyl-β-chloroenones to the *Z* 2-sulfenyl chalcones, by palladium-mediated cross-coupling, would provide access to these compounds for further biological evaluation and in particular, to establish the impact of the stereochemistry.

As summarised in Table 3, Stille cross-coupling of the α-sulfenyl-β-chloroenones with a number of aryl stannanes [25–27] proved effective in forming a range of novel 2-sulfenyl chalcones with yields of up to 92%, using reaction conditions described by Aguilar-Aguilar and Peña-Cabrera [28]. Interestingly, the efficiency of the cross-coupling was impacted by the nature of the substituent on the aryl stannane, with better yields obtained when using substituted aryl stannanes [25–27] (**36b**–**36f**) compared to the unsubstituted phenyl stannane **36a** (Table 3, Entries 3 and 24). Use of the 4-nitro phenyl stannane **36f** [27] in the cross-couplings was of particular interest as Reddy has highlighted the significance of the nitro substituent in the bioactivity profile of related *E* sulfenyl chalcones, and notably, the efficiencies of the couplings were very effective with this stannane. Alteration of the substituent of the aryl ketone (R^1) did not notably affect the efficiency of the cross-coupling, while alteration of the substituent on the thio benzyl group (R^3) had more of an impact with no cross-coupling evident in the crude product mixture for the 2-(*p*-methoxybenzyl)sulfenyl-3-chloroenones (Entry 11 and 19). Interestingly, while the *Z* α-sulfenyl-β-chloroenones undergo efficient cross-coupling with the aryl stannanes, it appears that the *E* α-sulfenyl-β-chloroenones do not react under the same conditions. In entry 9, where the starting enone **4h** was predominantly *E*, there was no evidence of cross-coupling while in many of the other entries, the *E* α-sulfenyl-β-chloroenone was present as a minor component in the starting material and in most instances was recovered unchanged following the cross-coupling reaction. In most instances, the *Z* chalcone predominated in the reaction product and for many of the compounds was isolated as a single stereoisomer following chromatography (Entries 1–7, 10, 16–18, 20–27). On prolonged storage, there is some evidence of isomerisation to form minor amounts of the *E* isomer. From a synthetic perspective, the fact that the *E* α-sulfenyl-β-chloroenones did not undergo cross-coupling but were recovered from the reaction mixtures enabled isolation and characterisation of the pure *E* α-sulfenyl-β-chloroenones. While the efficiencies of the cross-couplings as evidenced by the ^{1}H NMR spectra of the crude product mixtures was typically greater than 70%, the isolated yields in some cases were negatively impacted by the challenge of separation from bi-aryl side product **37** [29] formed from the stannane **36f** [27]. The cross-couplings were initially conducted at room temperature for 2 h but in some instances, extending the reaction time and/or increasing the temperature increased the efficiency of transformations (Entries 8, 10–15, 17–21).

As anticipated, while Reddy [24] had reported the synthesis and biological evaluation of related *E* sulfenyl chalcones, formation of the *Z* sulfenyl chalcones as the major product provides access to the complementary series for evaluation. Extending this work to generate the 2-sulfinyl chalcones was next explored with particular interest in establishing the impact of increasing the oxidation level at sulfur on both the efficiency and the stereochemical outcome of the Stille cross-coupling. Reddy [24] noted the impact of sulfur oxidation on the biological activity of chalcones and, accordingly, it was of interest to determine whether similar results would be seen with these derivatives.

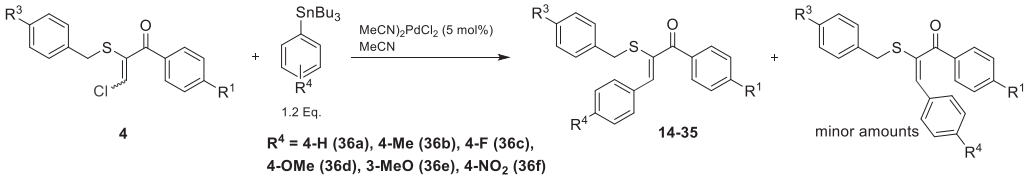
Oxidation of the α-sulfenyl-β-chloroenones to the corresponding sulfoxides was readily achieved using Oxone® as summarised in Table 4. Chemoselective oxidation to the sulfoxide level was very efficient with only minor amounts of the sulfone by-product present (less than 10%) in the ^{1}H NMR spectra of the crude product mixtures (Entries 1–3, 6). Interestingly, while exclusively the *Z* sulfenyl β-chloroenones **4** were employed for the oxidation in most cases (Entries 1–5) or as the major component (Entry 6), ^{1}H NMR spectroscopy of the crude product mixtures indicated the presence of both *Z* and *E* isomers of the α-sulfinyl-β-chloroenones **38**, and, following either chromatography or recrystallisation, the products were isolated as exclusively *E* sulfinyl β-chloroenones *E*-**38**. Evidently, the *E* sulfoxides are more stable, with the position of thermodynamic equilibrium altered on sulfur oxidation and, in addition, interconversion of the *E*-**38** and *Z*-**38** isomers is relatively facile, notably faster than at the sulfide level of oxidation. In some instances, a minor amount of a by-product (**39**) can be seen in the ^{1}H NMR spectra (less than 6%, Entries 3, 5, 6), presumably formed by over oxidation to the α-sulfonyl-β-chloroenone followed by hydrolysis and retro-Claisen condensation (Fig. 4). It is clear that the rate of addition of water to the α-sulfonyl-β-chloroenone is enhanced by oxidation from the sulfide to sulfone level of oxidation.

As summarised in Table 5, the Stille couplings with the *E* sulfinyl β-chloroenones *E*-**38** proved effective leading to the *E* sulfinyl chalcones *E*-**40** as the principal product in all cases, with the *Z* sulfinyl chalcones *Z*-**40** isolated as a minor product in some instances (Entries 1 and 7) and detected in the ^{1}H NMR spectra of the crude product mixtures. With a halogenated substituent on the benzyl sulfinyl moiety, extended reaction times were required for reaction completion but in all cases, reactions were conducted at room temperature. Notably, the stereochemistry of the *E* sulfinyl β-chloroenones *E*-**38** was retained to a very large extent during the Stille cross-coupling and there was no evidence of isomerisation of the *E* sulfinyl chalcones *E*-**40** following storage over a prolonged period, consistent with these being the thermodynamically preferred isomers. It appears that at the sulfoxide level of oxidation, the reactivity of the *E* sulfinyl β-chloroenones *E*-**40** towards Stille cross-coupling is greater than that seen at the sulfide level of oxidation, where the *E* sulfenyl β-chloroenones *E*-**4** did not react under these conditions.

As the sequence involving sulfur oxidation followed by Stille cross-coupling of *E*-sulfinyl-β-chloroenones led to the *E* sulfinyl chalcones, access to the complimentary *Z* sulfinyl chalcones was investigated using the alternative approach of conducting the Stille cross-coupling to form the *Z* sulfenyl chalcones prior to sulfur oxidation; the key question to be addressed was whether the *Z* stereochemistry in the chalcone would be retained on sulfur oxidation.

As summarised in Table 6, the *Z* sulfenyl chalcones **20**–**24** and **26**–**29** were oxidised to the corresponding sulfinyl chalcones **40**

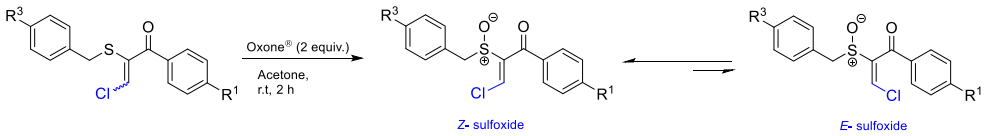
Table 3
Synthesis of Chalcone derivatives from α-sulfenyl-β-chloroenone precursors.



Entry	β-Chloroenone *Z:E*	R^1	R^3	R^4	Temp.	Time (h)	Relative Ratios[a]		% Yield[b]	Purified *Z:E*[c]
							4 *Z:E*	Chalcone *Z:E*		
1	**4e** 4:1	OMe	H	4-Me	rt	2	9% *E* only	**14** (91%) *Z* only	86	*Z* only
2	**4e** 4:1	OMe	H	4-F	rt	2	18% 1:3	**15** (82%) *Z* only	66	*Z* only
3	**4e** 4:1	OMe	H	H	rt	2	39% 2:1	**16** (59%) *Z* only	59	*Z* only[d]
4	**4e** 4:1	OMe	H	4-OMe	rt	2	9% *E* only	**17** (91%) *Z* only	70	*Z* only
5	**4e** 4:1	OMe	H	3-OMe	rt	2	10% *E* only	**18** (90%) *Z* only	83	*Z* only
6	**4e** 4:1	OMe	H	4-NO_2	rt	2	9% *E* only	**19** (90%) *Z* only	87	*Z* only
7	**4h** 5.2:1	Me	H	4-NO_2	rt	2	24% 1.8:1	**20** (76%) *Z* only	18	*Z* only
8	**4h** 14:1	Me	H	4-NO_2	rt	24	4% *E* only	**20** (79%) *Z* only	38	10.6:1
9	**4h** 1:18	Me	H	4-NO_2	rt	2	1:11	-	–	–
10	**4j** 4.5:1	Me	Cl	4-NO_2	rt	5	6% *E* only	**21** (94%) *Z* only	43[e]	*Z* only
11	**4k** 68:1	Me	OMe	4-NO_2	reflux	3	24:1	–	–	–
12	**4l** 3.4:1	Me	F	4-NO_2	rt	5	77% 3.2:1	**22** (23%) 9.6:1	4	4.9:1
13	**4l** 3.4:1	Me	F	4-NO_2	reflux	5	26% 1:1.4	**22** (74%) 6.3:1	28	3.2:1
14	**4o** 2.4:1	Cl	H	4-NO_2	rt	5	7% *E* only	**23** (93%) 8.4:1	64	4.6:1
15	**4q** 1.7:1	Cl	Cl	4-NO_2	reflux	5	11% *E* only	**24** (89%) 8.3:1	47	31:1
16	**4r** 9:1	Cl	OMe	4-NO_2	rt	2	55% 5.4:1	**25** (45%) *Z* only	9[f]	*Z* only
17	**4s** 2.5:1	Cl	F	4-NO_2	rt	5	17% 1.2:1	**26** (83%) *Z* only	18	*Z* only
18	**4x** 2.2:1	F	Cl	4-NO_2	reflux	5	26% 1:3.7	**27** (74%) 8.8:1	20	*Z* only
19	**4y** 2.8:1	F	OMe	4-NO_2	reflux	13	2.7:1	–	–	–
20	**4z** 3:1 **14:1**	F	F	4-NO_2	rt	6	10% *E* only	**28** (90%) *Z* only	24	*Z* only
21	**4aa**	F	Me	4-NO_2	rt	24	7% *E* only	**29** (93%) *Z* only	51	*Z* only
22	**4v** 2.2:1	F	H	4-Me	rt	2	–	**30** (100%) *Z* only	92	*Z* only
23	**4v** 2.2:1	F	H	4-F	rt	2	22% 1:1.2	**31** (78%) *Z* only	75	*Z* only
24	**4v** 2.2:1	F	H	H	rt	2	63% 2.5:1	**32** (37%) *Z* only	35	*Z* only
25	**4v** 2.2:1	F	H	4-OMe	rt	2	12% *E* only	**33** (88%) *Z* only	77	*Z* only
26	**4v** 2.2:1	F	H	3-OMe	rt	2	30% 1:2	**34** (70%) *Z* only	65	*Z* only
27	**4v** 2.2:1	F	H	4-NO_2	rt	2	14% 1:4	**35** (80%) *Z* only	78	*Z* only

[a] Determined by integration of key signals in ^{1}H NMR spectrum of crude product mixtures.
[b] % yield after purification by column chromatography on silica gel.
[c] Ratio of Z:E chalcone products determined by integration of key signals in 1H NMR spectrum of product mixtures.
[d] 14% Z β-chloroenone starting material remaining in sample.
[e] Approximately 90% pure by ^{1}H NMR spectroscopy.
[f] Contains *approx.* 22% bi-aryl **37**.

Table 4
Oxidation of α-sulfenyl-β-chloroenones to sulfoxides.



Entry	β-Chloroenone	*Z*:*E* ratio S.M.[a]	R^1	R^3	Sulfoxide[b]	Crude *Z*:*E*[c]	% Yield *E*[d]
1	**4h**	*Z* only	Me	H	**38h** 96%	1:15	53[e]
2	**4m**	*Z* only	Me	Me	**38m** 89%	*E* only	37[e]
3	**4t**	*Z* only	Me	Cl	**38t** 88%	2.8:1	76[f]
4	**4aa**	*Z* only	Me	F	**38aa** 98%	1:1.03	77[f]
5	**4q**	*Z* only	Cl	Cl	**38q** 90%	2.4:1	39[f]
6	**4z**	4.3:1	F	F	**38z** 88%	1.5:1	54[f]

[a] Z:E ratio of α-sulfenyl-β-chloroenone starting material used.
[b] % of sulfoxide product estimated from ^{1}H NMR spectrum of the crude product mixture.
[c] Z:*E* ratio of the sulfoxide products estimated from ^{1}H NMR spectrum of the crude product mixture.
[d] Yield of *E* sulfoxide following purification.
[e] Purified by recrystallisation from methanol.
[f] Purified by column chromatography on silica gel.

using Oxone® to enable comparison with the stereochemical outcome when the Stille coupling was conducted at the sulfoxide level of oxidation (Table 6). In most cases (other than Entry 8) the oxidation was efficient with little or none of the sulfone formed, as evidenced by the ^{1}H NMR spectra of the crude product mixtures. However, for the para-halo aryl ketones **23**, **24**, **26**–**29**, it was necessary to increase the temperature of the reaction mixtures to 30–35 °C (Entries 5–7) or the reaction time (Entries 4–9) to achieve efficient oxidation. It is clear that the oxidation of the *Z* sulfenyl chalcones is considerably slower than that of the corresponding *Z* sulfenyl β-chloroenones **4** (Table 4). Examination of the ^{1}H NMR spectra of the crude product mixtures showed that the principal isomer of the sulfoxides formed was the *Z* isomer, although there were minor amounts of the *E* isomer detectable in the crude product mixtures. On purification and storage, there was evidence of further isomerisation to the *E* sulfinyl chalcones **40**, the thermodynamically more stable isomer. In most instances, the *Z* and *E* stereoisomers were inseparable, however, both isomers of **40s** were recovered as pure components.

As summarised in Scheme 9, complementary stereochemical outcomes can be achieved by altering the sequence of sulfur oxidation and Stille cross-coupling. Thus, when the *Z* sulfenyl β-chloroenones **4** are subjected to Stille cross-coupling, the *Z* sulfenyl chalcones **14**–**35** are formed, which on oxidation, produce selectively the *Z* sulfinyl chalcones **40**. In contrast, oxidation of the *Z* sulfenyl β-chloroenones **4** forms the *E* sulfinyl β-chloroenones **38**, which form selectively the *E* sulfinyl chalcones **40** on Stille cross-coupling.

Finally, Stille cross-couplings were undertaken using the β-chloroacrylate **41** [14], and β-chloroacrylamides **42** [10] and **43** [30], with the first two compounds at the sulfide level of oxidation, while **43** [30] was at the sulfoxide level of oxidation (Table 7). It is clear that the extent of conversion within 2 h is substantially less than that seen in the α-sulfenyl-β-chloroenone series, although, the sulfoxide **43** [30] was more reactive than the sulfides **41** [14] and **42** [10]. Once again, the *Z* stereochemistry was retained in the Stille cross-coupling with the *Z* chalcones **44**–**46** formed with no evidence of the *E* isomer detected in contrast to the outcome of the cross-couplings with the α-sulfenyl-β-chloroenones. The relative stereochemistry was confirmed by single crystal X-ray crystallography of **46** as illustrated in Fig. 5 revealing a strong intramolecular hydrogen bond (1.88 Å) between the amide proton and the oxygen of the sulfoxide group. The carbonyl group is distorted somewhat from planarity presumably due to the conformational constraints of this intramolecular hydrogen bond. The aryl ring at the β-position lies in the same plane as the acrylamide, indicating effective conjugation.

Preliminary one-dose (10 μM) screening of the *Z* sulfenyl and *E* sulfinyl chalcones against a range of cancer cell lines was undertaken (NCI, see SI for details); a number of the compounds displayed significant activity in terms of inhibiting cell growth, with cytotoxicity evident in some instances, with nine compounds progressed for five-dose screening. In the case of the *Z* sulfenyl chalcones, the substituent at both the R^1 and R^3 positions had a notable impact on the inhibition of cell growth with the greatest inhibition seen for compound **27** with fluoro (R^1) and chloro (R^3) substituents, with a mean growth of 49.6% seen across all 60 cancer cell lines. The most significant level of inhibition with **27** was seen against the colon cell line HCT-116, with a cell growth of −59.9%.

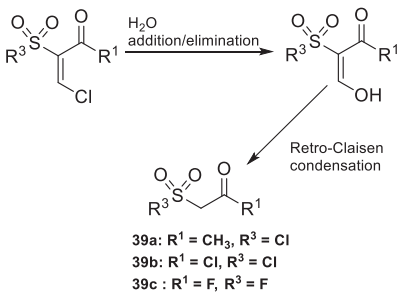
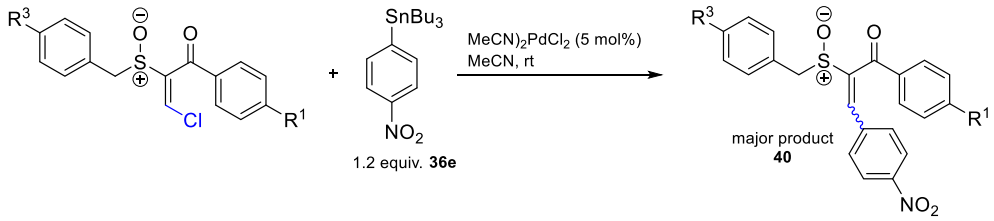


Fig. 4. Formation of retro-Claisen impurity from sulfone by-product.

Table 5
Synthesis of Chalcones using sulfoxide derivatives of α-sulfinyl-β-chloroenones.



Entry	β-Chloroenone *Z:E*	R^1	R^3	Time (h)	Relative Ratios[a]		% Yield *E*[b]	% Yield *Z*[b]
					14 *Z:E*	Chalcone *Z:E*		
1	**38h** *E* only	Me	H	2	8% *E* only	**40h** (92%) 1:4.5	47	8
2	**38m** *E* only	Me	Me	5	–	**40m** (90%) *E* only	70	–
3	**38aa** *E* only	Me	F	24	–	**40aa** (99%) 1:31	74	–
4	**38q** *E* only	Cl	Cl	21	22% *E* only	**40q** (78%) 1:5.7	45	–
5	**38z** *E* only	F	F	21	–	**40z** (92%) 1:35	69	–
6	**38t** *E* only	Me	Cl	26	–	**40t** (96%) *E* only	46	–
7	**38t** 5:1[c]	Me	Cl	21	39% 1:1	**40t** (56%) 2.5:1[d] 1:2.7[e]	22	10

[a] Determined by integration of key signals in ^{1}H NMR spectrum of crude product mixtures.
[b] % yield after purification by column chromatography on silica gel.
[c] Reaction was carried out immediately after sulfur oxidation to minimise conversion of *Z*-**14t** to *E*-**14t**.
[d] *Z:E* ratio estimated from ^{1}H NMR spectrum of crude product. *Z* isomer is the major product.
[e] *Z:E* ratio estimated from ^{1}H NMR spectrum of major impure fraction following initial column chromatography.

Interestingly, the *E* sulfinyl chalcones displayed enhanced biological activity compared with their sulfenyl counterparts, with the impact of altered substitution patterns evident once again. Notably, compound **40h** displayed a mean growth of just 6.7% across all 60 cancer cell lines. The *E* sulfinyl chalcones were most active against renal, colon and melanoma cell lines, while the *Z* sulfenyl chalcones were most effective against a number of leukaemia and colon cancer cell lines. Although a direct comparison of biological activity cannot be made due to the opposite stereochemistry of the *Z* sulfenyl and *E* sulfinyl chalcones, the *E* sulfinyl chalcones were notably more active than the *Z* sulfenyl derivatives, presumably due to the impact of sulfur oxidation on their ability to act as Michael acceptors. Interestingly, Reddy [24] reported a loss of activity in the *E* α-benzylthiochalcones when oxidised to either the sulfoxide or sulfone level of oxidation.

3. Conclusion

The chlorination cascade with α-sulfenylketones on heating with NCS follows a similar mechanistic pathway to that seen with the α-sulfenylamides, leading to novel α-sulfenyl-β-chloroenones in a synthetically useful manner with modest stereocontrol, typically with the *Z*-propenones as the major product from the transformation. The influence of the substituents on the ketone impacted on the efficiency of the chlorination cascade, but in all instances, the α-sulfenyl-β-chloroenones were readily isolated either directly from the chlorination cascade (for aryl ketones) or on exposure to the Lewis acid zinc chloride which effects the final HCl elimination (alkyl ketones). Access to the synthetically versatile α-sulfenyl-β-chloroenones broadens substantially the synthetic potential of application of this chlorination methodology, previously explored only at the carboxylic acid level of oxidation.

Interestingly, on oxidation of the *Z* sulfenyl β-chloroenones, while the *Z* sulfinyl β-chloroenones were the initial direct products, these rapidly isomerised to the thermodynamically more stable *E* sulfinyl β-chloroenones. The Stille cross-coupling with the novel sulfenyl or sulfinyl β-chloroenones **4**/**38** provided an efficient route to the *Z* sulfenyl **14**—**35** or *E*/*Z* sulfinyl **40** chalcones; at the sulfide level of oxidation, the *Z* stereochemistry is retained in the Stille cross-coupling while at the sulfoxide level, the stereochemical outcome is determined by the sequence of oxidation and Stille cross-coupling, providing access to either the *E* or the *Z* sulfinyl chalcone isomer as the major product. This sequence illustrates the synthetic potential of combining the chlorination cascade with subsequent transformations, leading to stereoselective bond formation at the previously unactivated methyl substituent.

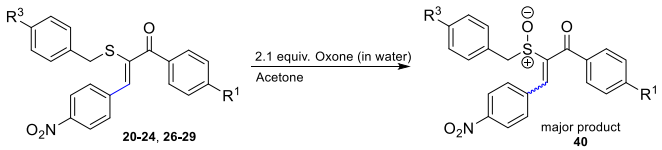
4. Experimental

4.1. General procedures

All commercial reagents were used without further purification.

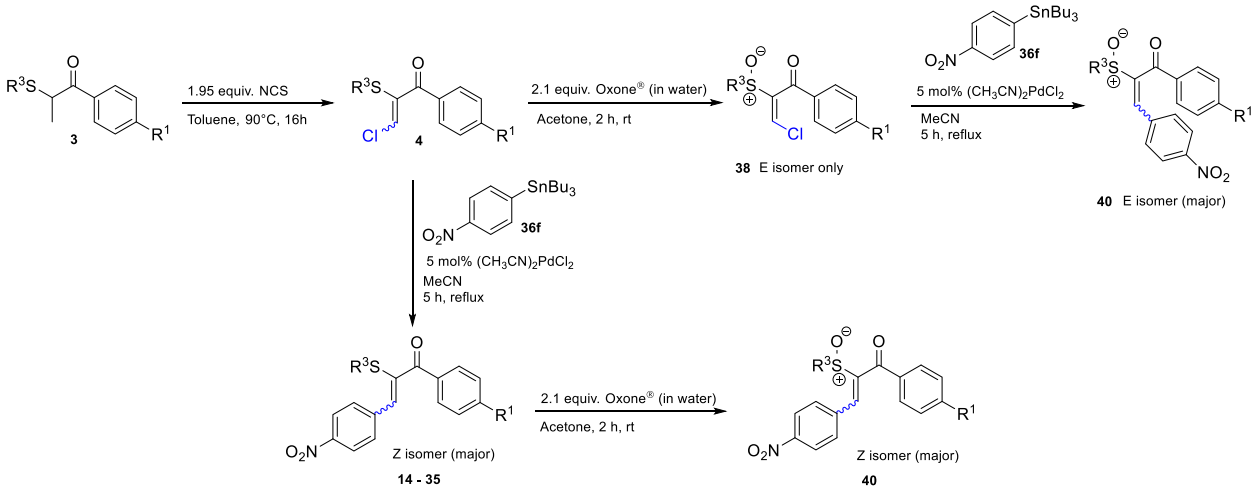
Proton (300 MHz) and carbon (75 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. All spectra were recorded at 300 K (27 °C) in deuterated chloroform (CDCl3) using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants (J) are expressed in Hertz (Hz). Splitting patterns in 1H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), qd (quartet of doublets), and m (multiplet). 13C NMR spectra were assigned with the aid of DEPT experiments.

Table 6
Oxidation of chalcone derivatives.



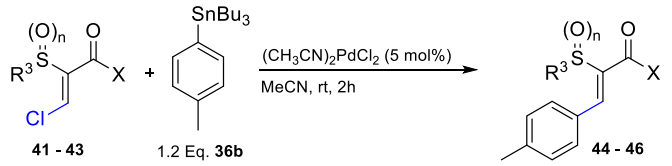
Entry	Starting Material *Z:E*	R^1	R^3	Time (h)	Temp (C)	Relative Ratios[a]			% Yield[b]	Purified *Z:E*[c]
						S.M. *Z:E*	Sulfoxide *Z:E*	Sulfone		
1	**20** *Z* only	Me	H	2	rt	6% *Z* only	**40h** 86% 11:1	8%	47	4:1
2	**21** *Z* only	Me	Cl	2	rt	25 *Z* only	**40j** 75% 4.5:1	–	59	8:1
3	**22** *Z* only	Me	F	2	rt	6% *Z* only	**40l** 94% 16:1	–	53	11.5:1
4	**29** *Z* only	F	Me	6	rt	29% *Z* only	**40aa** 71% 6.3:1	–	33	1:1.3
5	**27** *Z* only	F	Cl	7.5	35	7.5% *Z* only	**40x** 91% 10.4:1	1.5%	76	7:1
6	**28** *Z* only	F	F	7.5	35	1.5% *Z* only	**40z** 92.5% 7:1	6%	70	6:1
7	**23** *Z* only	Cl	H	9.5	30	13% *Z* only	**40o** 87% 4:1	–	73	1:1.6
8[d]	**24** *Z* only	Cl	Cl	4	rt	–	**40q** 52% *Z* only	48%	56	*Z* only
9	**26** *Z* only	Cl	F	23	rt	18% *Z* only	**40s** 82% 5:1	–	51	39% *Z*[e] 12% *E*

[a] Determined by integration of key signals in ^{1}H NMR spectrum of crude product mixtures.
[b] % yield after purification by column chromatography on silica gel.
[c] Products isolated as a mixture after column chromatography. Ratios determined by integration of key signals in ^{1}H NMR spectrum of purified material.
[d] After initial stirring at room temperature for 2 h, 28% conversion of starting material was observed. 1 Eq. of mCPBA in dichloromethane was subsequently added and the reaction was stirred at room temperature for 1 h.
[e] Isomers were separated following column chromatography on silica gel.



Scheme 9. The impact of alternating the sequence of sulfur oxidation and Stille cross-coupling on the stereochemical outcome.

Table 7
Synthesis of chalcones from β-chloroacrylates and β-chloroacrylamides.



Entry	Starting Material *Z:E*	X	R^3	n	Relative Ratios[a] S.M.	Chalcone	% Yield *Z*[b]
1	**41** *Z* only	OMe	Ph	0	55%	**44** (45%) *Z* only	45
2	**42** *Z* only	NHBn	Bn	0	89%	**45** (11%) *Z* only	10
3	**43** *Z* only	NHTol	Ph	1	38%	**46** (62%) *Z* only	59

[a] Determined by integration of key signals in ^{1}H NMR spectrum of crude product mixtures.
[b] % yield after purification by column chromatography on silica gel.

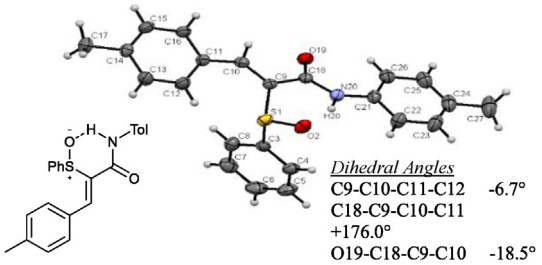


Fig. 5. Single crystal X-ray data of **46**.

Compounds which were assigned with the aid of DEPT experiments were assigned by identifying the carbon type (CH3, CH2, CH or C).

Infrared spectra were measured using universal ATR sampling accessories on a PerkinElmer Spectrum Two spectrometer. Flash chromatography was performed using Kieselgel silica gel 60, 0.040–0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV (254 nm) light detection and vanillin staining.

Nominal mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionisation (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 ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

4.2. Procedure for synthesis of compound ***4d***

N-Chlorosuccinimide (0.248 g, 1.9 mmol, 1.95 eq) was added in one portion to a solution of the sulfide 1-(4-methoxyphenyl)-2-(phenylthio)propan-1-one **3d** (0.232 g, 0.9 mmol) in toluene (10 mL). The flask was immediately immersed in an oil bath at 90 °C and heating was maintained for 16 h with stirring. The reaction mixture was cooled to 0 °C and the succinimide by-product was removed by filtration. The solvent was evaporated at reduced pressure to give the crude product as an orange oil and a mixture of *E* and *Z* isomers in a ratio of 1:1.7. Following purification by column chromatography on silica gel using hexane-ethyl acetate (98:2) as eluent, the β-chloroenone **4d** (0.241 g, 88%) was isolated as a yellow oil and a mixture of *Z* and *E* isomers *Z*-**4d** and *E*-**4d** in a ratio of 1.6:1; νmax/cm^{-1} (film) 3058 (CH), 2934 (CH), 1659 (CO), 1598 (aromatic), 1253.

Z-**4d** (more polar): δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 9.0, ArH), 7.20–7.29 (2H, m, ArH), 7.10–7.16 (3H, m, ArH), 6.83 (2H, d, *J* 9.0, ArH), 6.79 (1H, s, CHCl), 3.83 (3H, s, OCH3); δ_C (75.5 MHz, $CDCl_3$) 189.2 (C), 163.8, 140.4 (2 x C), 132.6, 131.9 (2 x CH), 130.9, 129.1 (2 x C), 129.0, 128.1 (2 x CH), 126.0 (CH), 113.6 (CH), 55.5 (CH_3).

E-**4d** (less polar): δ_H (300 MHz, $CDCl_3$) 7.84 (2H, d, *J* 9.0, ArH), 7.38–7.44 (3H, m, ArH), 7.20–7.29 (2H, m, ArH), 6.90 (2H, d, *J* 9.0, ArH), 6.64 (1H, s, CHCl), 3.85 (3H, s, OCH3); δ_C (75.5 MHz, $CDCl_3$) 189.6 (C), 164.3 (C), 135.4 (C), 132.4, 132.1 (2 x CH), 131.2 (C), 129.3, 128.5 (2 x CH), 127.5 (C), 121.0 (CH), 114.0 (CH), 55.6 (CH_3).

HRMS (ES+): Exact mass calculated for $C_{16}H_{14}O_2S^{35}Cl[M+H]^+$ 305.0403. Found 305.0390; *m/z* (ES+) 305.1 [($C_{16}H_{13}O_2S^{35}Cl$)+H^+], 100%, 307.0 [($C_{16}H_{13}O_2S^{37}Cl$)+H^+], 40%.

4.3. Procedure for synthesis of compound ***31***

The β-chloroenones *Z*-**4v** and *E*-**4v** (ratio 2.2:1) (150 mg, 0.5 mmol) and the arylstannane, tributyl(4-fluorophenyl)stannane **36c** (227 mg, 0.6 mmol) were dissolved in anhydrous acetonitrile (5 mL) under nitrogen. The mixture was then purged with nitrogen for 5 min whereupon the palladium catalyst, $(CH_3CN)_2PdCl_2$ (5%) was added and the reaction mixture was stirred at room temperature for 2 h. The mixture was then washed with hexane (3 × 20 mL) to remove the tin by-products and the remaining acetonitrile phase was evaporated under reduced pressure to give the crude chalcone as a yellow oil. ^{1}H NMR analysis showed the crude product to contain 22% β-chloroenone starting material as a mixture of *Z* and *E* isomers *Z*-**4v** and *E*-**4v** in a ratio of 1:1.2 and 78% *Z* chalcone **31**. This was purified by column chromatography on silica gel using hexane-ethyl acetate (98:2) as eluent to give the *Z* chalcone **31** (137 mg, 75%) as a yellow oil; νmax/cm^{-1} (film) 3032 (CH), 1657 (CO), 1598 (aromatic), 1505, 1236, 846; δ_H (400 MHz, $CDCl_3$) 7.53–7.72 (4H, m, ArH), 7.15 (5H, s, ArH), 7.02–7.09 (4H, m, ArH), 6.94 [1H, s, C(3)H], 4.00 (2H, s, SCH_2); δ_C (75.5 MHz, $CDCl_3$) 192.4 (C), 165.5 (C),162.8 (C), 138.6 (CH), 137.2, 135.2 [2 x C], 133.5 (C), 132.5 (CH), 132.4 (CH), 130.8 (C), 129.4, 128.5, 127.3 (3 x CH), 115.5 (CH), 115.4 (CH), 36.7 (CH_2); HRMS (ES+): Exact mass calculated for $C_{22}H_{17}SOF_2$ [M + H^+] 367.0968. Found 367.0960; *m/z* (ES+) 367.3 [($C_{22}H_{16}SOF_2$)+H^+], 100%.

4.4. Procedure for synthesis of compound ***38h***

A solution of Oxone® (824 mg, 1.3 mmol) in water (5 mL) was added dropwise to a stirring solution of the sulfide *Z*-**4h** (203 mg, 0.6 mmol) in acetone (10 mL) at room temperature. A white precipitate formed immediately. After stirring for 2 h, water (15 mL) was added and the aqueous solution was extracted with dichloromethane (3 × 15 mL). The organic layers were washed with water (2 × 10 mL) and brine (10 mL), dried, and concentrated under reduced pressure to give a yellow solid. 1H NMR spectroscopy showed this product to contain 90% of the *E* sulfoxide *E*-**38h** with approx. 6% of the *Z* sulfoxide *Z*-**38h**. The product was recrystallised from methanol to give the sulfoxide *E*-**38h** (112 mg, 53%) as an off-white solid (mp 86–88 °C); νmax/cm^{-1} (neat) 3048, 1654 (C=O), 1599, 1284, 1225, 1175, 1061 (S–O), 704; δ_H (400 MHz, $CDCl_3$): 7.85 (2H, d, *J* 8.1, ArH), 7.27–7.38 (7H, m, ArH), 6.57 (1H, s, CHCl), 4.36 (1H, B of AB system, J_{AB} 13.0, one of SCH 2),4.14 (1H, A of AB system, J_{AB} 13.0, one of SCH 2), 2.45 (3H, s, $ArCH_3$); δ_C (100 MHz, $CDCl_3$): 189.6 (C), 146.2, 142.8, 133.0 (3 × C), 131.1, 130.0, 129.8 (3 × CH), 128.6 (CH), 128.4 (CH), 128.1 (C), 127.9 (CH), 59.8 (CH_2), 21.9 (CH_3); HRMS (ES+): Exact mass calculated for $C_{17}H_{16}O_2S^{35}Cl$ [M + H^+] 319.0560. Found 319.0550; *m/z* (ES+) 319.2 [($C_{17}H_{15}O_2S^{35}Cl$)+H^+], 11%.

CCDC 2050621 (Compound **46**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132091.

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