CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Addition-substitution reactions of 2-thio-3-chloroacrylamides with carbon, nitrogen, oxygen, sulfur and selenium nucleophiles
Authors	Kissane, Marie;Murphy, Maureen;O'Brien, Elisabeth;Chopra, Jay;Murphy, Linda.;Collins, Stuart G.;Lawrence, Simon E.;Maguire, Anita R.
Publication date	2011-04-07
Original Citation	KISSANE, M., MURPHY, M., O'BRIEN, E., CHOPRA, J., MURPHY, L., COLLINS, S. G., LAWRENCE, S. E. & MAGUIRE, A. R., 2011. Addition-substitution reactions of 2-thio-3-chloroacrylamides with carbon, nitrogen, oxygen, sulfur and selenium nucleophiles. Organic & Biomolecular Chemistry, 9, 2452-2472. doi: 10.1039/C0OB00805B
Type of publication	Article (peer-reviewed)
Link to publisher's version	http://pubs.rsc.org/en/content/articlelanding/2011/ob/c0ob00805b - 10.1039/C0OB00805B
Rights	©2010, The Authors. Exclusive licence to publish RSC Publishing.
Download date	2026-11-04 11:05:36
Item downloaded from	https://hdl.handle.net/10468/602



UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

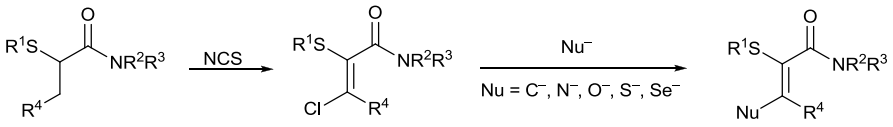
Addition-substitution reactions of 2-thio-3-chloroacrylamides with carbon, nitrogen, oxygen, sulfur and selenium nucleophiles

Marie Kissane,[a] Maureen Murphy,[a] Elisabeth O'Brien,[a] Jay Chopra,[a] Linda Murphy,[a] Stuart G. Collins,[a] Simon E. Lawrence[a] and Anita R. Maguire[b]*

[a]*Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Ireland*

[b]*Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Ireland*

email: a.maguire@ucc.ie



Abstract:

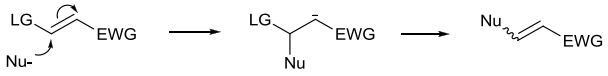
Synthetically versatile conjugate addition of a range of carbon, nitrogen, oxygen, sulfur and selenium nucleophiles to the highly functionalised 2-thio-3-chloroacrylamides is described. The stereochemical and synthetic features of this transformation are discussed in detail. In most instances, the nucleophile replaces the chloro substituent with retention of stereochemistry. With the oxygen nucleophiles, a second addition can occur leading to acetals, while with the nitrogen nucleophiles, *E*-*Z* isomerism occurs in the resulting enamine derivatives. The ratio of the *E*/*Z* isomers can be rationalised on the basis of the substituent and the level of oxidation.

Introduction

Nucleophilic addition to conjugatively unsaturated systems is a well established synthetic method.[1-4] Alkenes bearing electron-withdrawing groups such as esters, amides, ketones,

sulfones or nitriles can react with a wide range of nucleophiles (both carbon-based or heteroatom-based) in a conjugate fashion to generate a stabilised anion which is quenched by protonation or reaction with an electrophile. While α,β-unsaturated amides undergo conjugate addition they are, in general, the least reactive Michael acceptors and usually require basic conditions or acid catalysis.[2]

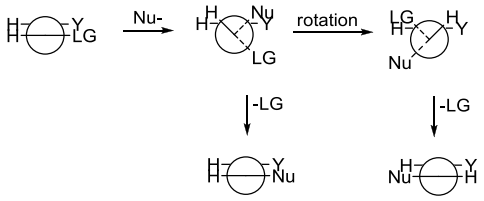
The presence of a leaving group on the β-carbon offers another possibility for reaction of the stabilised anion.[5] Displacement of the leaving group with reformation of the conjugated system can be envisaged as illustrated in Scheme 1.



Scheme 1

The rate of nucleophilic addition reactions is determined by the electrophilicity of the β-carbon. Rappoport has studied the nucleophilic substitution of vinylic halides bearing α-electron withdrawing groups, and has found that the reaction rate increases when the β-substitutent is changed from bromine to chlorine to fluorine.[6-8] This is due to the increasing electronegativity from bromine to fluorine rendering the β-carbon more electrophilic, rather than the leaving group ability, which increases in the reverse order.

Nearly complete retention of configuration has been observed in the substitution reactions of many vinyl chlorides and bromides.[9-12] However, partial or complete stereoconvergence is also possible,[13,14] particularly when the carbanionic carbon bears two strongly electron withdrawing groups. The retention or loss of stereochemistry may be rationalised by relating the ability of the C_2-C_3 single bond to rotate to the stability of the carbanion. The greater the stabilisation, the more time exists for rotation and therefore stereoconvergence to occur (Scheme 2).[6] Conversely, any factor that reduces the stability of the carbanion increases the possibility of retention. Anionic nucleophiles enhance leaving group expulsion and therefore promote retention.

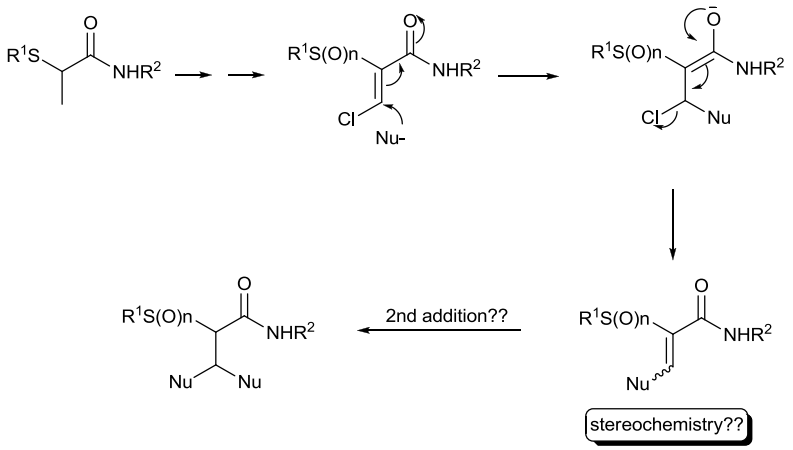


Scheme 2

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.[15] The chemoselective and stereoselective oxidation of the β-chloroacrylamides to the sulfoxide and sulfone levels of oxidation has extended the scope of this methodology.[16,17] The α,β-unsaturated system of the β-chloroacrylamides contains substituents with considerably different electronic properties. The amide group is electron withdrawing both inductively and by resonance delocalisation, although this effect is reduced somewhat by delocalisation of the nitrogen lone pair into the carbonyl. The sulfide substituent is inductively electron withdrawing, but can donate electron density to the β-carbon by resonance. Likewise, the chloride group is electron withdrawing inductively but can be resonance donating. While the sulfide group can confer nucleophilic character to the β-carbon, the combined effects of the amide and chloride groups are more significant, and overall lead to an electrophilic β-carbon.

A wide range of reaction pathways can be envisaged with these highly functionalised acrylamide derivatives, including Diels-Alder cycloadditions and 1,3-dipolar cycloadditions.[18,19] Potentially one of the most interesting and synthetically useful pathways is the addition of nucleophiles to the β-carbon. Conjugate addition followed by chloride displacement would be expected to lead to β-substitution. A wide range of nucleophiles can be envisaged, and if this substitution is widely applicable, it would allow access to a wide variety of differently substituted acrylamide derivatives.

Herein, we report the addition of a range of carbon, nitrogen, oxygen and sulfur based nucleophiles to the β-chloroacrylamides. We were particularly interested to determine if the product of a single nucleophilic addition with chloride displacement would be observed, or if a second addition of the nucleophile to the resulting Michael acceptor would occur. Furthermore, determination of the stereochemical features of the transformations was of interest (Scheme 3).



Scheme 3

Results and Discussion

Carbon Based Nucleophiles

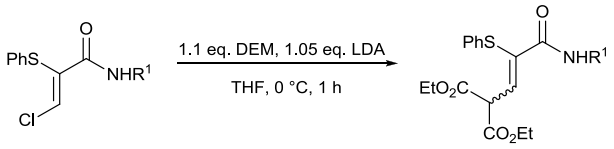
As the Michael addition of active methylene compounds to conjugated systems is one of the oldest and more useful carbon-carbon bond-forming reactions,[1,20] nucleophilic addition of the enolates of diethyl malonate and ethyl acetoacetate to the β-chloroacrylamides was studied initially. This work was later extended to the cyclohexanone enolate and a range of organocuprates.

Stabilised enolates

Investigation of the reaction of the β-chloroacrylamide **1a** with the diethyl malonate anion, generated using a range of bases and reaction conditions, was undertaken. While the employment of 2.1 equivalents of sodium ethoxide in ethanol with 2 equivalents of diethyl malonate yielded the substitution product **2a**, excess diethyl malonate was present in the product and a low yield (45%) was achieved. Use of a reduced amount of sodium ethoxide (< 2 eq.) or employment of other bases such as sodium hydride or potassium *t*-butoxide either led to incomplete reaction or side-product formation. Optimisation of the process was undertaken, and ultimately the addition of the lithium salt of diethyl

malonate (prepared from reaction of 1.1 equivalents of diethyl malonate with 1.05 equivalents of LDA in THF at 0 °C) to **1a** in THF at 0 °C for 1 h afforded the corresponding adduct **2a** in 80% yield. Extension of this reaction of the anion of diethyl malonate with the β-chloroacrylamides **1b** and **1c** gave the extended acrylamides **2b** and **2c** in yields of 72% and 88% respectively (Table 1). This indicates that the methodology is compatible with both aryl and benzyl amides, signifying that altering the acidity of the NH of the amides is not detrimental to the substitution process.

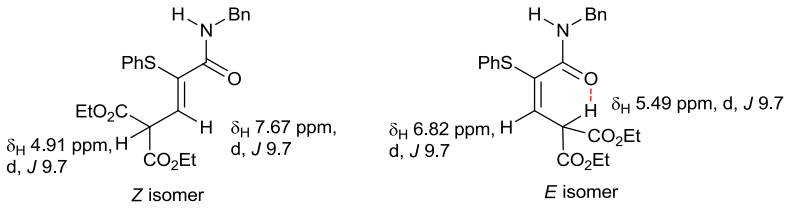
Table 1 Michael Addition of the Enolate of Diethyl Malonate



β-Cl	**R^1**	**Product**	***Z*:*E***	**% Yield**[a]
1a	Tol	**2a**	27:1	80
1b	(*S*)-CH(CH_3)Ph	**2b**	30:1	72
1c	Bn	**2c**	15:1	88

a) Isolated yield after chromatographic purification.

The malonate adducts **2a**−**2c** were isolated predominantly as one stereoisomer, with trace amounts of a minor isomer (~3-4%) in each case. The isomers were not separable by chromatography. Under the basic conditions, *E*-*Z* interconversion can be readily envisaged via an extended enolate. While the stereochemistry of the malonate adducts has not been definitively confirmed, the major isomer is believed to have *Z*-stereochemistry. In the ^{1}H NMR spectra, the signals for the characteristic vinylic proton in the two isomers are clearly resolved, appearing at δ_H 7.60-7.75 ppm in the major isomer and at higher field at δ_H 6.78-6.82 ppm in the minor isomer, reflecting a greater distortion from planarity in the conjugated system in the more sterically crowded *E*-isomer. Furthermore, the proton between the two ester groups in the minor isomer is significantly deshielded, consistent with hydrogen bonding to the amide oxygen (see for example Scheme 4).

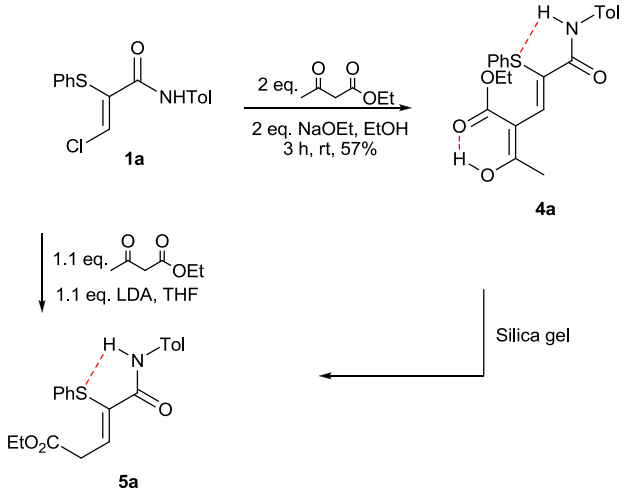


Scheme 4

Alkylation of the malonate adducts can be envisaged at either the α- or γ-position, and a brief exploration was undertaken to establish the potential synthetic utility of this transformation (see Supporting Information).

The next carbon-based nucleophile explored was the enolate of ethyl acetoacetate, with the outcome of the reaction dependant on the nature of the basic conditions employed (

Scheme 5).

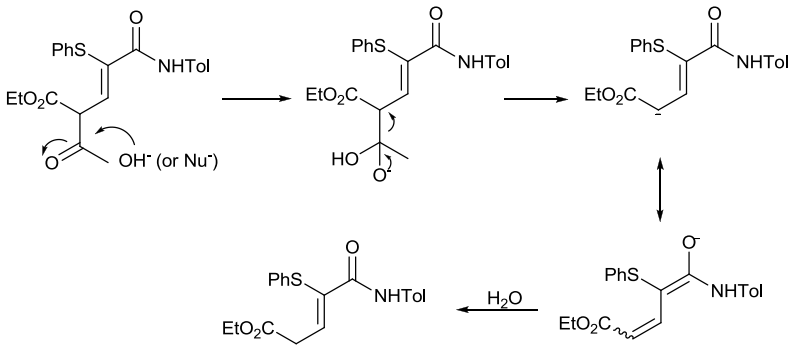


Scheme 5

Addition of a solution of the β-chloroacrylamide **1a** in ethanol to a solution of the sodium enolate of ethyl acetoacetate (prepared by reaction of 2 equivalents of sodium ethoxide with 2 equivalents of ethyl acetoacetate in ethanol) afforded the enol form of the substituted product **4a** in 57% yield following trituration in cold hexane. The enol form is presumably favoured due to extended conjugation and hydrogen bonding.

In contrast, employment of LDA as base led to the isolation of the deacylated compound **5a** in 22% yield following purification by chromatography on silica gel (
Scheme 5). Interestingly, this deacylated compound **5a** was also obtained in 34% yield when the product mixture from a sodium ethoxide/ethyl acetoacetate addition containing **4a** was purified by chromatography on silica gel.

Isolation of **5a** was rationalised by initial nucleophilic addition of the enolate of ethyl acetoacetate to **1a**, followed by a retro Claisen-type cleavage of the acetyl group (either in the reaction mixture or during the work-up) generating an extensively resonance stabilised enolate, which on protonation yielded the deacylated product **5a** (Scheme 6).



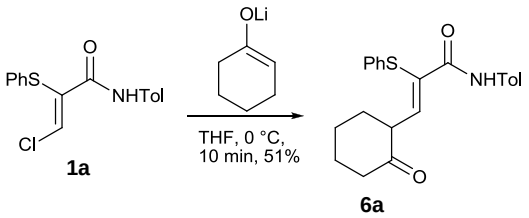
Scheme 6

Less stabilised enolates

As the β-substitution of the β-chloroacrylamides with carbon based nucleophiles stabilised by two electron-withdrawing groups had proven successful, investigation of the reaction with the less stabilised enolate/enol of cyclohexanone was studied under basic and acidic conditions.

Addition of a solution of the β-chloroacrylamide **1a** in THF to a solution of cyclohexanone enolate in THF (prepared by treatment of 1.1 equivalents of cyclohexanone with 1.1 equivalents of LDA in THF at 0 °C) afforded the cyclohexanoylacrylamide **6a** as the major product, as a single isomer, following stirring at 0 °C for 10 minutes and chromatographic purification (Scheme 7). The presence of the β-hydrogen doublet at δ_H 7.73 coupled to the α-hydrogen on the cyclohexanone, which

was evident as a multiplet at δ_H 3.73-3.89, confirmed the formation of **6a**. The stereochemistry of **6a** was tentatively assigned as *Z*, but was not confirmed.



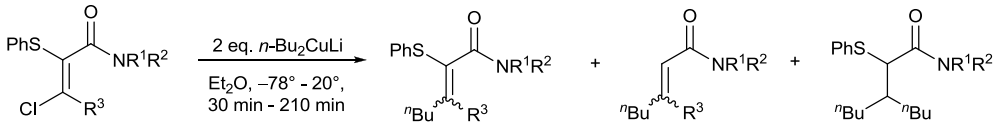
Scheme 7

While the yield is modest (51%), this result confirms that more reactive enolates can be successfully employed in the β-substitution process. Varying the reaction conditions by decreasing the temperature and increasing the number of equivalents of the cyclohexanone enolate did not lead to improved yields. The substitution of **1a** was also attempted under acidic conditions by reaction of the trimethylsilyl enol ether of cyclohexanone with either a Lewis acid or fluoride ion; the starting material **1a** was isolated unchanged from these conditions.

Organocuprates

Encouraged by successful reaction with the cyclohexanone enolate, reaction of organocuprates with β-chloroacrylamides was next explored.[21,22] The reactivity of the β-chloroacrylamides **1a**, **1c**–**1g** towards *n*-Bu_2CuLi (generated using the conditions described by Dieter)[23] was explored initially (Table 2).

Table 2 Michael Addition of n-*Bu_2CuLi to β-Chloroacrylamides*



	7	8	9
R^1 = Tol, R^2 = H, R^3 = H **1a**	**7a**	**8a**	**9a**
R^1 = Bn, R^2 = H, R^3 = H **1c**	**7c**	**8c**	**9c**
R^1 = Me, R^2 = Me, R^3 = H **1d**	**7d**	**8d**	
R^1 = Et, R^2 = H, R^3 = H **1e**	**7e**		**9e**
R^1 = *i*Pr, R^2 = H, R^3 = H **1f**	**7f**		**9f**
R^1 = Tol, R^2 = H, R^3 = Me **1g**	**7g**		

Entry	β-Cl	R^1	R^2	R^3	ratios				
					7	**:**	**8**	**:**	**9**
1	**1a**	Tol	H	H	1 Trace[a]	:	1.26	:	
2	**1c**	Bn	H	H	1	:	0.3	:	N.D.[a, b]
3	**1d**	Me	Me	H	1.48	:	1	:	N.D.[c]
4	**1e**	Et	H	H	major		N.D.		Trace
5	**1f**	*i*Pr	H	H	major		N.D.		Trace
6	**1g**	Tol	H	Me	major		N.D.		N.D.

a) By integration of the ^{1}H NMR spectra of the crude products
b) N.D. = not detected

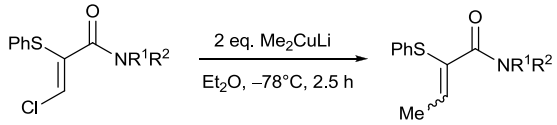
c) Ratio of isolated products

Reaction of the β-chloroacrylamides with *n*-butyl cuprate led to a complex mixture of products, with the mono-substituted product the major product isolated as a mixture of *E* and *Z* isomers in most cases (entries 2−5, Table 2). The major isomer is believed to be the *Z* isomer. Once again the β-H signal in the ^{1}H NMR spectra is characteristic of the stereochemistry, with the major isomer appearing at lower field (δ_H ~7.66 ppm *c.f.* δ_H ~6.66 ppm), reflecting a distortion from planarity in the more sterically hindered *E* isomer. The side-products formed included the desulfurised product (entries 1−3, Table 2) and the di-addition product (entries 1, 4−5, Table 2). The methodology was also successfully applied to the extended acrylamide **1g**, with the mono-substitued product **7g** isolated as a single isomer, tentatively assigned as *Z* (entry 6, Table 2).

The recovery of the desulfinylated products **8a**, **8c** and **8d** and diphenyldisulfide demonstrates the relatively labile character of the carbon-sulfur bond. In order to determine if the loss of the sulfide group occurs prior to or after substitiution of the β-chloroacrylamides by the organocuprates, a sample of the adduct **7c** was exposed to the reaction conditions; a mixture of the adduct **7c** and the di-adduct **9c** was recovered, with no evidence by ^{1}H NMR analysis for the presence of the desulfinylated product **8c**. It thus seems likely that C-S bond cleavage occurs earlier in the reaction sequence.

As some success had been achieved for the *n*-butyl cuprate additions, the reaction of the methyl cuprate with β-chloroacrylamides was next attempted. A Me_2CuLi solution was prepared using a 2:1 ratio of methyl lithium and copper iodide in ether at –78 °C, and this mixture was subsequently added to a solution of the β-chloroacrylamide in ether at –78 °C. Table 3 summarises the results of these investigations. The reaction proved to be much cleaner than the *n*-butyl cuprate additions, with no evidence for the formation of other side-products, albeit with modest yields.

Table 3 Reaction of Me_2CuLi with β-Chloroacrylamides



Entry	β-Cl	R^1	R^2	Product	% Yield[a]
1	**1a**	Tol	H	**10a**[b]	30
2	**1b**	(*S*)-CH(CH_3)Ph	H	**10b**[b]	44
3	**1c**	Bn	H	**10c**[b]	75
4	**1d**-*Z*	Me	Me	**10d**[c]	34
	1d-*E*	Me	Me	**10d**[d]	71
6	**1e**	Et	H	**10e**[b]	34
7	**1f**	*i*Pr	H	**10f**[b]	20
8	**1h**	Allyl	H	**10h**[e]	42
9	**1i**	*n*Bu	H	**10i**[b]	29
10	**1j**	Me	H	**10j**[b]	29
11	**1k**	H	H	**10k**[f]	39

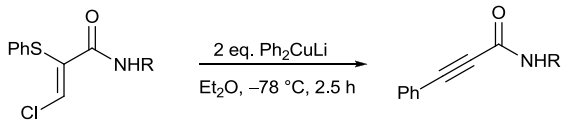
a) Isolated yield after chromatographic purification
b) Trace amount of the E isomer detected by ^{1}H NMR spectroscopy.
c) Isolated as an inseparable mixture of *Z* and *E* isomers of **10d** in a ratio of 4:1 following chromatography. This ratio changed to 1:1 after 3 weeks.

d) Isolated as an inseparable mixture of *Z* and *E* isomers of **10d** in a ratio of of 3:8 initially and a ratio of 1.1:1 following chromatography. This ratio changed to 1.4:1 after 2 days.
e) Crude ratio of **10h**-*Z* : **10h**-*E* 1: 0.1. Ratio after chromatographic purification was **10h**-*Z* : **10h**-*E* 1: 0.05.
f) The *E* isomer was not detected by ^{1}H NMR spectroscopy.

The addition products **10a**–**10j** were isolated as a mixture of *E* and *Z* isomers, with the major isomer tentatively assigned as *Z*, while the *E* isomer was not detected by ^{1}H NMR spectroscopy for **10k**. Reaction of two equivalents of Me_2CuLi with one equivalent of the tertiary β-chloroacrylamide *Z*-**1d** proved interesting (entry 4, Table 3). Following chromatographic purification, the adduct **10d** was isolated as an inseparable mixture of the *Z* and *E* isomers in a ratio of 4:1. When a ^{1}H NMR spectrum of **10d** (which had been stored at room temperature) was recorded 3 weeks later, the *Z* : *E* ratio had changed to 1 : 1. On repeating the reaction with the *E* isomer of **1d**, a similar result was observed. The initial ratio of *Z* : *E* of **10d** was 3 : 8 and following chromatography the ratio had changed to 1.1 : 1 (*Z*:*E*). After storage for 2 days at room temperature, the *Z* : *E* ratio had changed to 1.4 : 1. Evidently, the *E* and *Z* isomers of **10d** can interconvert slowly. In contrast, there was no evidence for isomerisation of the corresponding *n*-butyl adducts **7d**.

The addition of an aryl group to the β-chloroacrylamides was investigated next. It was anticipated that addition of Ph_2CuLi [prepared by reacting two equivalents of phenyl lithium with one equivalent of copper(I) iodide in ether at –78 °C] to the β-chloroacrylamides would afford the corresponding β-phenylacrylamides. However, following the work-up, the alkynamides **11a**−**11c** were isolated (Table 4). Significantly, analogous products were never detected using the alkyl cuprates.

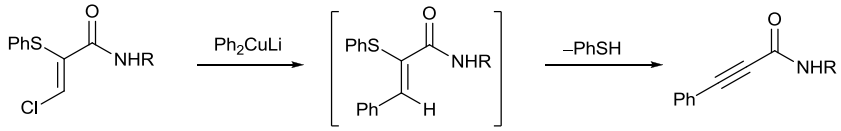
Table 4 Reaction of Ph_2CuLi with the β-Chloroacrylamides



β-Cl	R	Product	% Yield[a]
1a	Tol	**11a**	31
1c	Bn	**11c**	83
1f	*i*Pr	**11f**	77

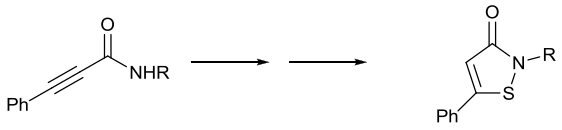
a) Isolated yield after chromatographic purification.

Elimination of thiophenol occurs under the basic reaction conditions (Scheme 8), possibly due to the increased acidity of the β-H, activated by the adjacent phenyl group, relative to the analogous *n*-butyl (**7a**−**7g**) or methyl adducts (**10a**−**10k**).



Scheme 8

The alkynamides **11a** and **11c** are known compounds, and are intermediates in the synthesis of 2,5-diarylisothiazolones **12a** and **12c** (Scheme 9), inhibitors of cytokine induced cartilage destruction.[24]

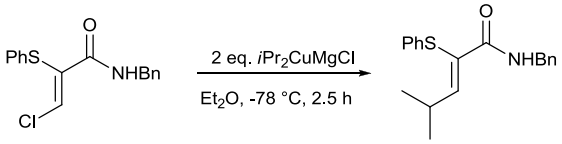


R = Tol **11a** **12a**

R = Bn **11c** **12c**

Scheme 9

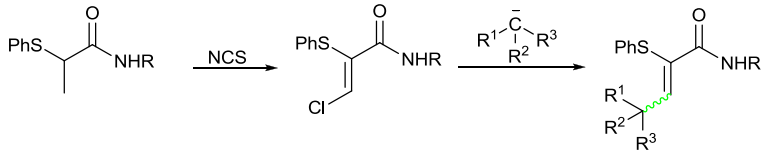
The reaction of the β-chloroacrylamide **1c** with organocuprates derived from Grignard reagents was also explored; a number of commercially available Grignard reagents (RMgX) were used to generate organocuprates by reaction with copper(I) iodide, with starting material isolated on employment of MeMgBr/CuI, PhMgBr/CuI and *i*PrMgBr/CuI. The best result was achieved using *i*Pr_2CuMgCl, affording a 1.13 : 1 ratio of starting material **1c** to the adduct **13c** (Scheme 10). The adduct **13c** was predominantly one product, presumably *Z*, with a trace amount of a minor isomer. It is clear that the nature of the halide has a significant influence on the reaction.



1c **13c**

Scheme 10

Thus, substitution at the β-position is possible using carbon nucleophiles ranging from reactive systems to stabilised enolates. The yields are modest, but they proceed with good retention of stereochemistry, and generally the mono-substituted adducts can be isolated. The overall transformation from the α-phenylthioamides to the carbon adducts reflects C-C bond formation at an originally unactivated methyl group, and is therefore synthetically useful (Scheme 11).

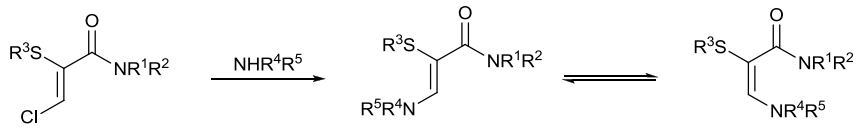


Scheme 11

Nitrogen Nucleophiles

Introduction of nitrogen atoms to a carbon framework is particularly important in the synthesis of biologically active molecules such as amino acids, β-amino acids or alkaloids.[25,26] Amines are excellent nucleophiles, reacting readily with even poorly electrophilic species.[27]

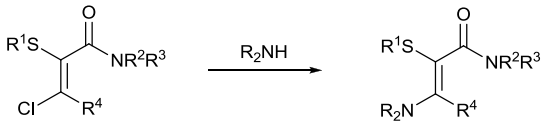
The reaction of primary or secondary amines with β-chloroacrylamides was envisaged to follow the pathway outlined in Scheme 12 to generate enaminoamide derivatives. Nucleophilic addition at the β-carbon followed by elimination of chloride would produce enaminoamides which are stabilised by extensive resonance delocalisation. Indeed, rapid interconversion of the *E* and *Z* isomers is envisaged in these systems, in contrast to all other derivatives investigated during this work, due to the extended conjugation. The addition of a second equivalent of amine should be disfavoured as delocalisation of the nitrogen lone pair significantly reduces the electrophilicity of the β-carbon.



Scheme 12

The reaction of β-chloroacrylamides with amines to produce β-enaminoamides was initially explored using the secondary amines dimethyl-, diethyl- and diisopropylamine and morpholine. Table 5 summarises the results of these experiments.

Table 5 Addition of Secondary Amines to the β-Chloroacrylamides



Entry	β-Cl	R	R^1	R^2	R^3	R^4	Product	Time (h)	% Yield
1	**1a**	Me	Ph	Tol	H	H	**14a**[a]	0.25	75[b]
2	**1v**	Me	Bn	Bn	H	H	**14v**[a]	0.25	78[c]
3	**1a**	Et	Ph	Tol	H	H	**15a**[a]	0.1	73[b]
4	**1v**	Et	Bn	Bn	H	H	**15v**[a]	0.25	95[c]
5	**1a**	*i*Pr	Ph	Tol	H	H	**16a**[d]	1	Quant.[c]
6	**1a**	$(CH_2CH_2)_2O$	Ph	Tol	H	H	**17a**[e]	0.2	67[b]
7	*E*-**1d**	$(CH_2CH_2)_2O$	Ph	Me	Me	H	**17d**[f]	23	Quant.[c]
8	**1f**	$(CH_2CH_2)_2O$	Ph	*i*-Pr	H	H	**17f**[e]	0.5	88[g]
9	*Z*-**1l**	$(CH_2CH_2)_2O$	Ph	(*S*)-$CHCH_3Ph$	H	Et	**17l**[e,h]	22	Quant.[c]
10	*E*-**1l**	$(CH_2CH_2)_2O$	Ph	(*S*)-$CHCH_3Ph$	H	Et	**17l**[e,i]	96	Quant.[c]
11	*Z*-**1m**	$(CH_2CH_2)_2O$	Ph	Tol	H	Et	**17m**[e,j]	16	Quant.[c]
12	*Z*-**1n**	$(CH_2CH_2)_2O$	Ph	Ph	Ph	H	**17n**[e,k]	3	88[l]
13	**1o**	$(CH_2CH_2)_2O$	Bn	4-F-C_6H_4	H	H	**17o**[e]	0.2	71[c]
14	**1p**	$(CH_2CH_2)_2O$	Bn	*n*-Bu	H	H	**17p**[e]	0.2	75[c]
15	**1q**	$(CH_2CH_2)_2O$	Bn	Tol	H	H	**17q**[e]	0.5	87[l]

a) A solution of the amine in ethanol was added to the β-chloroacrylamide.
b) Isolated yield after recrystallisation.
c) Crude yield, further purification was not required.
d) The β-chloroacrylamide was added to neat DIPA.
e) 2.5 equivalents of morpholine were added to a dichloromethane solution of the β-chloroacrylamide.
f) 5 equivalents of morpholine were required for completion of reaction.
g) Isolated yield after trituration from ether and hexane
h) Isolated as a 1:1.3 mixture of the *E* and *Z* isomers of **17l**.
i) Isolated as a 1.2:1 mixture of the *E* and *Z* isomers of **17l**.
j) Isolated as a 4:1 mixture of the *E* and *Z* isomers of **17m**.
k) Isolated as a 1:10 mixture of the *E* and *Z* isomers of **17n**.
l) Isolated yield after chromatographic purification.

The β-chloroacrylamides **1a** and **1v** were added to an ethanolic solution of dimethylamine and diethylamine, and the β-chloroacrylamide **1a** was added to neat diisopropylamine; the resulting solutions were then stirred at room temperature. The

reaction progess was monitored by TLC analysis and very efficient substitution of the chloride by the amines was observed (entries 1−5, Table 5). An excess of the amine was employed due to amine salt formation with the HCl released in the substitution. Significantly, only one isomer of the enaminoamides **14a**, **14v**, **15a**, **15v** and **16a** was evident by ^{1}H NMR spectroscopy in each of the transformations. The slower conversion of **1a** when treated with DIPA reflects the poorer nucleophilicity of this amine,[27] although it is notable that the addition of DIPA proceeded very efficiently under these mild conditions. Although the enaminoamides **14a** and **15a** were purified by recrystallisation, in general the crude products were found to be of sufficient purity to use in subsequent reactions.

The treatment of **1a** with morpholine was particularly efficient, resulting in rapid and clean transformation to the *Z*-β-morpholinoacrylamide **17a**. The effect on the morpholine substitution of variation in the amide and sulfide substitutents was then investigated (entries 6−15, Table 5). In most instances, the β-morpholinoacrylamides were analytically pure and no purification was required. For the primary and secondary β-chloropropenamides, the morpholine adducts were isolated as the *Z*-isomers exclusively (entries 6—8 and 13−15, Table 5), while employment of the tertiary and extended chain acrylamides led to a mixture of *E* and *Z* isomers (entries 9−11, Table 5). The tertiary and extended chain acrylamides required much longer reaction times (entries 7, 9−12, Table 5), presumably due to steric (for the extended chain acrylamides) and conformational effects (for the tertiary acrylamides). In order to determine if the stereochemistry of the β-chloroacrylamides influenced the efficiency and/or stereochemical outcome of the reaction, the *Z* and *E* isomers of the β-chloropentenamide **1l** were reacted separately with morpholine. It was found that *Z*-**1l** had completely reacted with morpholine after 22 h while *E*-**1l** had not been completely transformed even after 96 h. Thus, the *Z* isomer reacts much more efficiently in nucleophilic substitutions. This is also reflected in the longer reaction times required for the reaction of *E*-**1d** than *Z*-**1n** (entries 7 and 12, Table 5).

The observation of only one enaminoamide isomer on treatment of **1a** and **1v** with the secondary amines dimethylamine and diethylamine, on treatment of **1a** with diisopropylamine and of **1a**, **1d**, **1f** and **1o**−**1q** with morpholine is significant. When a

secondary amine reacts with a β-chloroacrylamide, two conformations leading to chloride loss can be envisaged. Kinetically, formation of the *Z* isomer *via* **A** is favoured due to unfavourable steric interactions in **B** (Figure 1). However, extensive resonance delocalisation in the enaminoamides is expected to allow rapid interconversion between the *E* and *Z* isomers and therefore it is believed that the thermodynamically determined ratio is observed. For the enaminoamides **14a**, **14v**, **15a**, **15v**, **16a**, **17a**, **17d**, **17f** and **17o**−**17q** the *Z* isomer is strongly favoured, and indeed in practice the *E* isomer cannot be detected by ^{1}H NMR spectroscopic analysis.

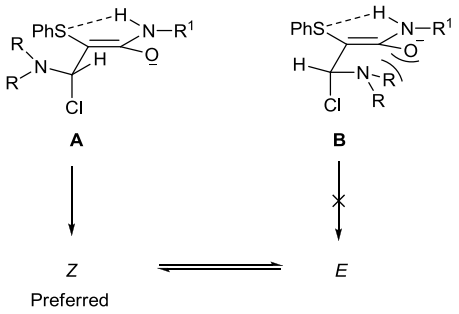
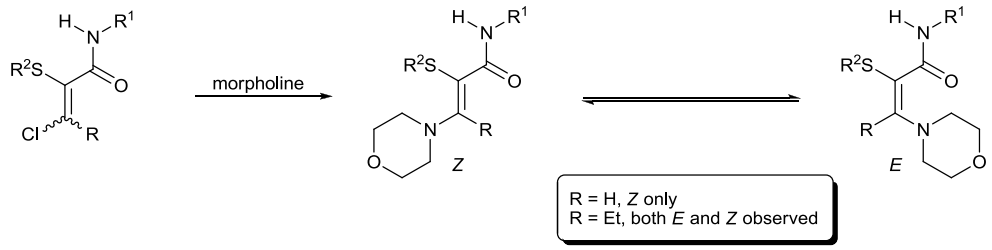


Figure 1

With the extended chain β-chloroacrylamides **1l** and **1m**, formation of two isomers of the enaminoamides is observed, reflecting a decrease in the energy difference between the two isomers (Scheme 13). Similarly, with the tertiary propenamide *Z*-**1n**, formation of both *E* and *Z* isomers of the morpholine adduct is observed, albeit with the *Z* isomer dominating (*E*:*Z* 1:10). The different conformational properties of the tertiary amides have been previously observed to affect the stereochemical outcome due to the absence of the intramolecular hydrogen bond, for example in the chlorination reaction.[15]



Scheme 13

Evidence for the delocalisation of the nitrogen lone-pair was seen in the ^{1}H and ^{13}C NMR spectra of enaminoamides **14a**, **15a** and **16a**. For example, in the ^{1}H NMR spectrum of the dimethylamino adduct **14a**, the signal for the methyl groups (δ_H 3.35-3.65) was shifted considerably downfield compared to the amine (δ_H 2.42). In addition, the signal was broadened due to restricted rotation; both features indicate extensive delocalisation of the nitrogen lone-pair into the conjugated system. Also, in the ^{13}C NMR spectrum, a broad signal was evident for the methyl groups at δ_C 42.7.

In the ^{1}H NMR spectrum of the *E* and *Z* isomers of the *N*-tolyl-β-morpholinopentenamide **17m**, signals due to the morpholino substituent of the minor isomer *Z*-**17m** were present at δ_H 3.40-3.43, while the corresponding signals for the major isomer *E*-**17m** were evident at δ_H 2.85-2.89. As the latter signals are very similar to the chemical shifts of the methylene hydrogens in free morpholine (which are seen at δ_H 2.85-2.91), it is evident that the extent of delocalisation of the nitrogen lone pair into the conjugated system in the *E* isomer is much less than in the *Z* isomer. Examination of the structures illustrated in Figure 2 indicates that 1,3-allylic strain in the *E* isomer would result in more 'out of plane' rotation of the morpholine substituent, leading to poor overlap of the nitrogen lone-pair with the π-orbitals of the conjugated system.

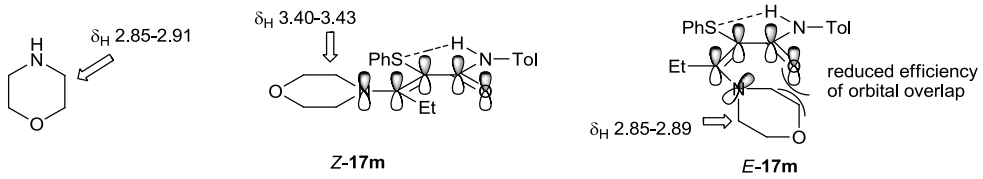
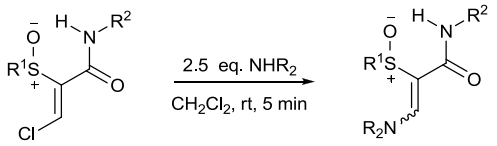


Figure 2

The reactivity of a range of sulfoxide derivatives of the β-chloroacrylamides with the secondary amines diethylamine, diisopropylamine, piperidine and morpholine was also studied, with the stereochemical outcome dependant on the nature of the amine and sulfoxide employed (Table 6).

Table 6 Addition of Secondary Amines to the Sulfoxides

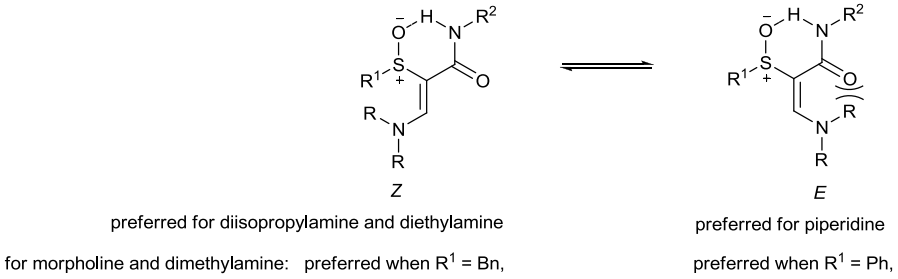


Entry	*Z*-Sulfoxide	R	R^1	R^2	Product	*Z*:*E*[a]	% Yield[b]
1	**18a**	*i*Pr	Ph	Tol	**19a**	1.7:1	87
2	**18a**	Et	Ph	Tol	**20a**	1.8:1	93[d]
3	**18b**	Et	Me	4-F-C_6H_4	**20b**	3.0:1	-[c]
4	**18g**	Et	Bn	Bn	**20g**	5.0:1	92[d]
5	**18a**	Me	Ph	Tol	**21a**	1:1.2	94[d]
6	**18g**	Me	Bn	Bn	**21g**	2.9:1	89[d]
7	**18a**	$(CH_2)_5$	Ph	Tol	**22a**	1:1.7	59
8	**18b**	$(CH_2)_5$	Me	4-F-C_6H_4	**22b**	1:1.1	-[c]
9	**18a**	$(CH_2CH_2)_2O$	Ph	Tol	**23a**	1:3	64
10	**18b**	$(CH_2CH_2)_2O$	Me	4-F-C_6H_4	**23b**	1:1	65
11	**18c**	$(CH_2CH_2)_2O$	Ph	Et	**23c**	1:3.8	72
12	**18d**	$(CH_2CH_2)_2O$	Bn	4-F-C_6H_4	**23d**	2.4:1	87[d]
13	**18e**	$(CH_2CH_2)_2O$	Bn	*n*Bu	**23e**	1.6:1	80[d,e]
14	**18f**	$(CH_2CH_2)_2O$	Bn	Tol	**23f**	1.9:1	85[d]

a) Determined by integration of the β-hydrogen signal for each isomer in the ^{1}H NMR spectrum.
b) Isolated yield after chromatography unless otherwise stated.
c) This compound readily decomposed to a complex mixture of unidentifiable products before purification and full characterisation could be conducted.
d) Purification was not required.
e) **23e** was also synthesised from *E*-**18e** in 67% yield (ratio of *Z*:*E* 1.6:1).

As observed with the sulfides, the sulfoxides **18a**−**18g** proved to be very efficient Michael acceptors with the secondary amines as nucleophiles, and the reactions were generally complete within 5 minutes by TLC analysis. In each instance, the enamino adducts were isolated as an inseparable mixture of *E* and *Z* isomers, in contrast to the results with the sulfide series. The isomers were distinguished by the position of the β-hydrogen signals; the β-hydrogen signal of the *E* isomer is typically 1 ppm upfield from the corresponding signal in the *Z* isomer.

On employment of diisopropylamine and diethylamine as nucleophiles the *Z* isomer of the sulfoxide adduct is favoured (entries 1–4, Table 6), due to steric interactions of the amino substituent with the amide group in the *E* isomer (Scheme 14).



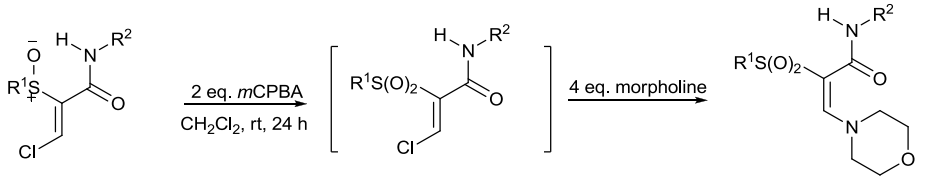
Scheme 14

Interestingly, on reaction of dimethylamine, the *E* isomer is the major isomer obtained for the benzenesulfinyl adduct **21a**, while the *Z* isomer is favoured for the more conformationally flexible benzylsulfinyl adduct **21g**. Reaction of the conformationally constrained secondary amines piperidine and morpholine resulted in the *E* isomer predominating in most cases (entries 7−14, Table 6). Due to the intramolecular hydrogen bond between the oxygen of the sulfoxide and the amide proton, the sulfoxide adduct is held in a very rigid conformation, resulting in a significant interaction between the amino substituent and the sulfoxide in the *Z* isomer and the amide substituent in the *E* isomer. When piperidine is used as the nucleophile, the *E* isomer is favoured for both the benzenesulfinyl adduct **22a** and the methylsulfinyl adduct **22b**, although to a greater extent for the benzenesulfinyl adduct (entries 7 and 8, Table 6).

Addition of morpholine to the sulfoxides led to some very interesting trends; on employment of the benzenesulfinyl derivatives **18a** and **18c**, the *E* isomer is preferred (entries 9 and 11, Table 6). On changing to the methylsulfinyl derivative **18b**, an equimolar mixture of *E* and *Z* isomers are formed due to reduced steric interaction between the smaller methyl group and the morpholino substituent (entry 10, Table 6). The introduction of the more conformationally flexible benzyl group at the sulfur centre leads to the *Z* isomer as the major isomer, as the benzyl group can accomodate the morpholino substituent more readily (entries 12−14, Table 6).

The addition of morpholine to a range of sulfone derivatives was also investigated, with the results summarised in Table 7.[16]

Table 7 Addition of Morpholine to the Sulfones



***Z*-Sulfoxide**	**R^1**	**R^2**	***E*-Adduct**	**% Yield**[a]
18a	Ph	Tol	**24a**	68
18d	Bn	4-F-C_6H_4	**24d**	43
18e	Bn	*n*-Bu	**24e**	63
18f	Bn	Tol	**24f**	56
18g	Bn	Bn	**24g**	42
18h	Bn	Me	**24h**	38
18i	Bn	Ph	**24i**	56
18j	Bn	H	**24j**	49
18k	Ph	Me	**24k**	24
18l	*n*-Bu	Bn	**24l**	38
18m	*n*-Bu	Tol	**24m**	45

a) Isolated yield after chromatographic purification.

The synthesis of the sulfone adducts **24a**, **24d**−**24m** has already been described, where the morpholino adducts were employed to enable characterisation of the more labile β-chlorosulfones.[16] In each instance the *E* isomer was formed exclusively, confirmed by single crystal X-ray diffraction on a sample of **24a** recrystallised from dichloromethane/hexane (See supporting information). Clearly, the introduction of a second oxygen atom at the sulfur centre increases the steric demand at this centre, pushing the equilibrium completely towards the *E* isomer (Figure 3).

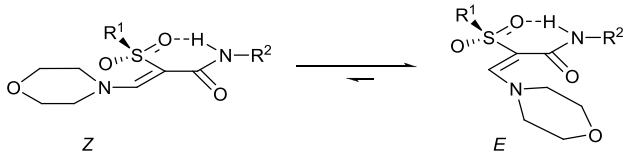
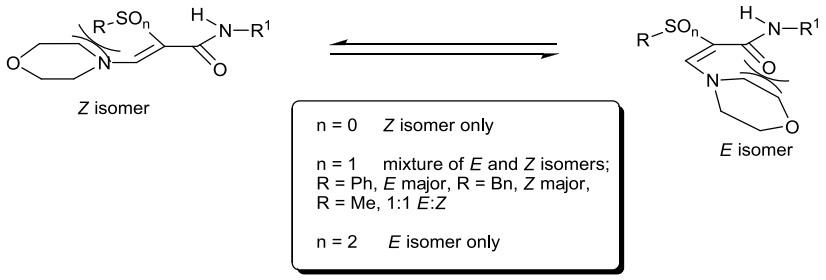


Figure 3

The crystal structure reveals the existence of a hydrogen bond from the amide proton to an oxygen of the sulfone, leading to a highly organised and rigid six-membered structure. Interestingly, the acrylamide unit is quite distorted from planarity, reflecting limited conjugation between nitrogen and the acrylamide system.

Comparing the morpholine adducts at the sulfide, sulfoxide and sulfone levels of oxidation leads to some interesting trends. For the sulfide adducts **17a**–**17i** (Table 5), steric interaction between the morpholino group and the carbonyl group of the amide in the *E*-isomer results in the exclusive formation of the Z-isomer in all instances. For the sulfoxide adducts **23a**–**23f**, a mixture of *E*- and *Z*-isomers are obtained, with the *Z*-isomer the major isomer for the benzylsulfinyl adducts **23d**–**23f** (Table 6). Clearly, the introduction of the oxygen atom at the sulfur centre together with the alteration to a six-membered hydrogen bonded system leads to increased steric hindrance in the *Z*-isomer between the morpholino group and the benzyl substituent. Therefore, the conformational mobility in the six-membered hydrogen bonded system involving oxygen is significantly less than in the five-membered hydrogen bonded system involving sulfur. However, the interaction between the morpholino group and the amide carbonyl in the *E*-isomer is more sterically demanding, and thus the *Z*-isomer is the major isomer obtained. Interestingly, in the addition of morpholine to benzenesulfinyl derivatives, the *E*-isomer was the major isomer obtained, and employment of methylsulfinyl derivatives led to an equimolar mixture of the *E*- and *Z*-isomers. For the benzenesulfinyl derived adducts, the interaction between the phenyl group attached to the sulfur centre and the morpholino substituent is significant and pushes the equilibrium in the direction of the *E*-isomer. Employment of the smaller methyl group reduces the steric interaction with the morpholino substituent leading to a 1:1 mixture of the *E*- and *Z*-isomers. Introduction of the more conformationally flexible benzyl group at the sulfur centre leads to the *Z*-isomer as the major isomer, presumably as the benzyl group can adjust to accommodate the morpholino substituent more easily than an *S*-aryl group. It is interesting to note that formation of the *Z*-isomer is slightly more favourable in the *S*-benzyl derivatives than in the *S*-methyl derivatives, although energetically the difference is very small. Thus, in

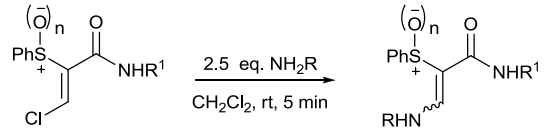
addition to a steric effect, it is likely that there is also a more subtle electronic effect operating. Finally, the introduction of a second oxygen atom at the sulfur centre increases the steric interaction in the *Z*-isomer, and the *E*-isomer is formed essentially exclusively at the sulfone level of oxidation. Thus, the steric demand of the sulfur substituent increases gradually from the sulfide (*Z*-isomer exclusively) to the sulfoxide (mixture of *Z*- and *E*-isomers) to the sulfone (*E*-isomer exclusively) (Scheme 15).



Scheme 15

Nucleophilic addition by primary amines to the sulfides and sulfoxides was next explored (Table 8). Once again, efficient nucleophilic substitution took place with the primary amines, and as highly conjugated enaminoamides are formed, there is no evidence for the second addition of a nucleophile. Interestingly, each of the products existed exclusively as the enamino tautomers, with no evidence for the corresponding imine tautomers.

Table 8 Addition of Primary Amines to β-Chloroacrylamides



Entry	β-Cl	n	R	R^1	Product	*Z*:*E*[a]	% Yield[b]
1	**1a**	0	Me	Tol	**25a**	1:3[c]	Quant.[d]
2	**1b**	0	$CH(CH_3)Ph$	(*S*)-$CH(CH_3)Ph$	**26b**	1:3	57
3	**18a**	1	Me	Tol	**27a**	*E* only	60
4	**18c**	1	Me	Et	**27c**	*E* only	93
5	**18a**	1	*i*Pr	Tol	**28a**	*E* only	81

a) Determined by integration of the β-hydrogen sugnal for each isomer in the ^{1}H NMR spectrum.
b) Isolated yield after chromatographic purification unless otherwise stated.
c) The *E* and *Z* isomers were found to interconvert on silica gel or on storage at room temperature.
d) Crude yield.

The primary amine was added neat to a dichloromethane solution of the sulfide or sulfoxide, and the reactions were complete within 5 minutes. The stereochemical outcome was dependant upon the oxidation level at the sulfur centre.

Addition of methylamine to the sulfide **1a** afforded the adduct **25a** as a 3:1 mixture of the *E* and *Z* isomers which slowly interconverted on silica gel or on storage at room temperature, confirmed by two-dimensional TLC analysis. Partial separation of the isomers was possible by chromatography on silica gel. The characteristic signals of the enamine proton and the β-hydrogen in the ^{1}H NMR spectrum are depicted in Figure 4.

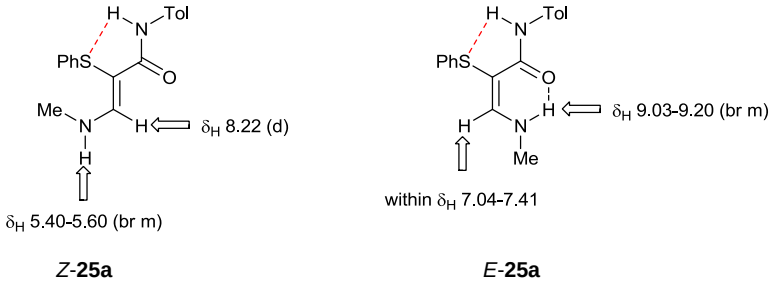


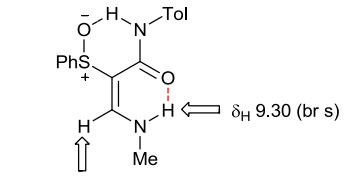
Figure 4

Assignment of the relative stereochemistry was based on the downfield shift of the enamine proton in the *E* isomer; the enamine proton for the less polar *E* isomer was evident at δ_H 9.03-9.20, while the enamine proton for the more polar *Z* isomer was present at δ_H 5.40-5.60.[28] Again, the signal for the β-hydrogen of the *Z* isomer appeared further downfield at δ_H 8.22 than the corresponding signal in the *E* isomer, which lay within the aromatic region (δ_H 7.04-7.41). This assignment is consistent with the polarity, where *E*-**25a** is less polar, having more extensive intramolecular hydrogen-bonding.

The chiral sulfide **1b** was treated with a racemic mixture of α-methylbenzylamine to yield a 3:1 mixture of the *E* and *Z* isomers of **26b**, each as a mixture of two diastereomers. As the *E* and *Z* isomers interconverted on silica they were not isolable separately. Though the ratio of the *E* and *Z* isomers was 3:1, the difference between the amounts of diastereomers of each geometrical isomer was negligible. The chiral amide auxiliary is too remote to influence the selectivity of the attack at the β-carbon.

Significantly, the stereochemistry and particularly the number of intramolecular hydrogen bonds in the *E* and *Z* isomers influence the physical properties of the compounds. Not only do they have different polarities on silica gel (R_f values were 0.5 apart in both **25a**-*E*/*Z* and **26b**-*E*/*Z*), their solubilities in the same solvent differ substantially. The *E* isomers of both **25a** and **26b** are eluted with ethyl acetate-hexane (25:75), while the more polar Z isomers require the addition of ethanol (for **25a**) or dichloromethane (for **26b**) to the eluent for elution from silica gel.

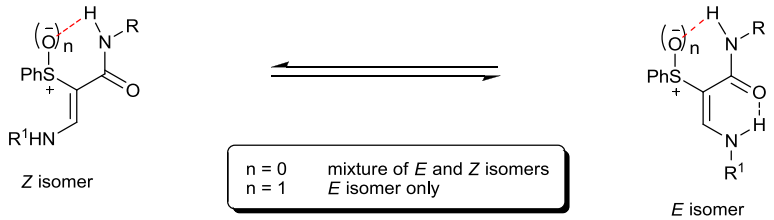
Interestingly, addition of methylamine and isopropylamine to the sulfoxides afforded the adducts **27a**, **27c** and **28a** as single stereoisomers, assigned as *E* by comparison of the ^{1}H NMR spectroscopic data with that of the sulfide adducts **25a** and **26b** (see for example Figure 5).



27a

Figure 5

Thus, in the sulfoxide the *E* isomer, stabilised by two intramolecular hydrogen bonds, is significantly more stable than the *Z* isomer. In contrast, at the sulfide level of oxidation, both the *E* and *Z* isomers are observed, indicating that the decreased steric interactions in the *Z* isomer compensate for the loss of enamine to carbonyl hydrogen bond in the *E* isomer. The steric constraints in the sulfoxide are clearly greater than that in the sulfide, even though both are hydrogen bonded to the amide (Scheme 16).



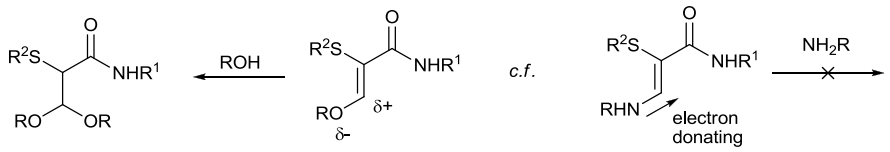
Scheme 16

Finally, treatment of the sulfide **1a** with ammonia and hydroxylamine results in chloride substitution analogous to the reaction with amines, but in these instances resulted in relatively complex mixtures of products due to the potential for both *E* and *Z* isomer formation and imine-amine tautomerisation (see Supporting Information).

Thus, primary and secondary amines act as very effective nucleophiles leading to single nucleophilic addition and chloride substitution at the sulfide, sulfoxide and sulfone levels of oxidation. Unlike all other compounds studied during this work (*i.e.* β-chloroacrylamides and the carbon and oxygen based adducts), rapid equilibration between *Z* and *E* isomers is seen in the amine adducts, enabled by extensive resonance conjugation in enaminoamides (Scheme 12). Thus, while the *Z*/*E* ratios in all the other nucleophilic substitutions appear to reflect kinetic features, with the amino adducts in general the thermodynamic ratio of *Z* and *E* isomers is observed. Interestingly, the ratio of these isomers can be rationalised based on the level of sulfur oxidation and the steric effect of the thio and amide substituents. Intramolecular hydrogen bonding plays a very strong role in determining the *Z*/*E* ratio. In general, the enaminoamides are very stable compounds, presumably reflecting the extended conjugation, and indeed formation of these derivatives enabled characterisation of the more labile β-chlorosulfones.

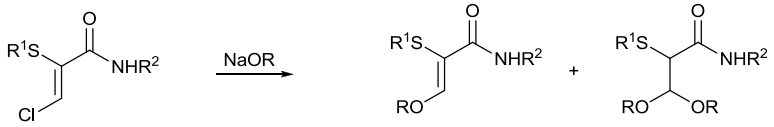
Oxygen Nucleophiles

Reaction of alkoxides with the β-chloroacrylamides was expected to follow a similar pathway to that of the amines, although in contrast to the nitrogen-substituted acrylamides in which the β-carbon was no longer nucleophilic, it was envisaged that the β-alkoxyenamides formed by addition of alkoxide may be susceptible to a second addition of nucleophile, leading to the disubstituted product due to the strongly inductive electron withdrawing effect of the oxygen substituent, which renders the β-carbon electrophilic, despite the potential for resonance delocalisation (Scheme 17). This would lead to an interesting series of acetal derivatives.



Scheme 17

Exploratory experiments involved treating a sample of **1a** with two equivalents of freshly prepared sodium ethoxide or methoxide in ethanol or methanol. Treatment of **1a** with two equivalents of sodium methoxide gave a mixture of two products within 30 min; both the β-methoxyacrylamide **33a** and the β,β-dimethoxypropanamide **34a** were isolated in a 1:5 ratio after aqueous workup. Similarly, treatment of **1a** with two equivalents of sodium ethoxide gave a mixture of β-ethoxyacrylamide **35a** and β,β-diethoxypropanamide **36a**, but in a ratio of 1:1.5. The reaction of the benzylthio β-chloroacrylamide **1v** with two equivalents of sodium methoxide and sodium ethoxide was also investigated. A mixture of the β-methoxyacrylamide **33v** and the β,β-dimethoxypropanamide **34v** were obtained in a ratio of 1:1.8 on reaction with sodium methoxide, while the β-ethoxyacrylamide **35v** and the β,β-diethoxypropanamide **36v** were obtained in a ratio of 1:1.2 on reaction with sodium ethoxide (Scheme 18).

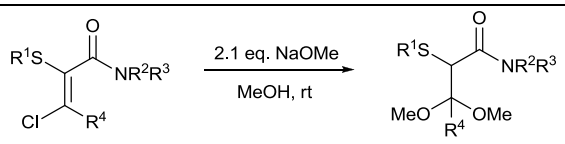


R^1 = Ph, R^2 = Tol	**1a**	R=Me	**33a**	1 :	**34a**	5.0
		R=Et	**35a**	1 :	**36a**	1.5
R^1 = Bn, R^2 = Bn	**1v**	R=Me	**33v**	1 :	**34v**	1.8
		R=Et	**35v**	1 :	**36v**	1.2

Scheme 18

As the dimethoxyamides were of interest from a synthetic perspective, the conditions for their formation were optimised and it was found that use of 2.1 equivalents of sodium methoxide in methanol at room temperature resulted in clean transformation of the β-chloroacrylamides to the acetals. The scope of the transformation to the acetal was established as summarised in Table 9.

Table 9 Formation of β,β-Dimethoxyamides



Entry	β-Cl	R^1	R^2	R^3	R^4	Acetal	Time (h)	% Yield
1	**1a**	Ph	Tol	H	H	**34a**	1	91[a]
2	**1b**	Ph	(*S*)-$CHCH_3Ph$	H	H	**34b**	2	89[b]
3	**1f**	Ph	*i*Pr	H	H	**34f**	1	86[a]
4	**1g**	Ph	Tol	H	Me	**34g**	22	91[a]
5	**1k**	Ph	H	H	H	**34k**	16	79[a]
6	**1n**[c]	Ph	Ph	Ph	H	**34n**	19	92[a]
7	**1r**	*n*Bu	Tol	H	H	**34r**	1	82[b]

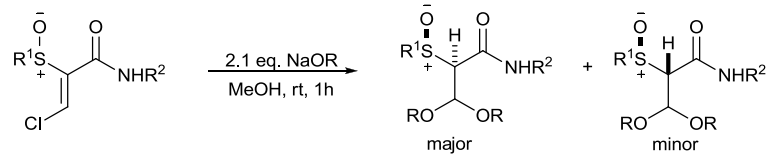
a) Crude yield, further purification was not required.
b) Isolated yield after chromatographic purification.
c) 1:1 mixture of the *E* and *Z* isomers.

In all cases, transformation to the acetal was achieved in good yield. In most instances, the products were found to be of sufficient purity to use in subsequent transformations without further purification. The secondary propanamides reacted efficiently within 1 hour (entries 1−3, 5, Table 9), while the primary, tertiary and extended amides necessitated longer reaction times (entries 4, 6 and 7, Table 9).

Due to the absence of the intramolecular hydrogen bond, the conformational features of the tertiary amide derivative **34n** differed from those of the corresponding secondary amides **34a**, **34b**, **34f**, **34k**, **34n**, **34r**. Thus, the ^3J coupling between the β-hydrogen and the α-hydrogen in **34a**, **34b**, **34f**, **34k**, **34n**, **34r** is typically 4 Hz, while in the tertiary amide **34n** an 8 Hz coupling is observed.

The formation of the dimethoxyamide derivatives of the sulfoxides was also explored. Table 10 summarises the results of these experiments.

Table 10 Formation of α-Sulfinyl-β,β-Dimethoxyacrylamides



Entry	Sulfoxide	R	R^1	R^2	Acetal	d.r.[a]	% yield[b]
1	**18a**	Me	Ph	Tol	**37a**	1.8:1	56 + 27[c]

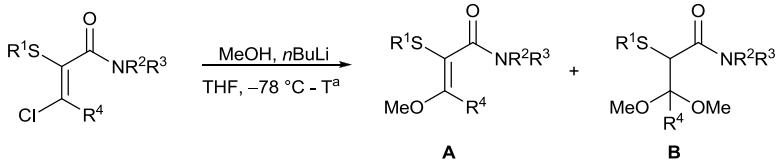
2	**18g**	Me	Bn	Bn	**37g**	6.6:1	42 + 11[c]
3	**18a**	Et	Ph	Tol	**38a**	2.0:1	44 + 20[c]
4	**18g**	Et	Bn	Bn	**38g**	1.1:1	90[d]

a) d.r. = diastereomeric ratio of the crude product by ^{1}H NMR spectroscopy.
b) Yield after chromatographic purification
c) A pure sample of the major isomer was obtained by column chromatography. The minor isomer was contaminated with the major isomer in each instance.
d) Isolated as a mixture of the major and minor diastereomers.

Treatment of the sulfoxides **18a** and **18g** with 2.1 equivalents of sodium methoxide led to a mixture of two diastereomers of the corresponding dimethoxyacrylamides **37a** and **37g** (entries 1 and 2, Table 10). It was possible to obtain a pure sample of the major isomer of **37g** by chromatography on silica gel. Similarly, reaction of **18a** and **18g** with 2.1 equivalents of sodium ethoxide led to a diastereomeric mixture of the diethoxyacrylamides **38a** and **38g** (entries 3 and 4, Table 10). The relative stereochemistry of the major isomer of the acetal **38a** was determined by single crystal X-ray diffraction after recrystallisation of a sample from acetonitrile/acetone (See Supplementary Information).

While the acetals are readily accessed, in general for alkoxide additions to multiple bonds, monoaddition is difficult to control.[29-32] However, as the β-methoxypropenoate and propenamide units are very important for the fungicidal activity of several agrochemicals,[33-36] the monoaddition of methoxide anion to the β-chloroacrylamides was investigated in more detail. A number of experiments were conducted on the β-chloroacrylamide **1a**, in which the effect of solvent, temperature, counterion and base were investigated. The optimum conditions for monoaddition were found to be addition of 1.4 equivalents of lithium methoxide (generated from *n*-butyllithium in methanol) to a solution of **1a** in THF at –78 °C, and the reaction mixture was then allowed to warm slowly over 3 hours to –5 °C. On employment of these conditions, the monoaddition product **33a** and the acetal **34a** were produced in a 9:1 ratio respectively, with no other side-products detected. The formation of the acetal could never be completely avoided.
The scope of the monoaddition was then investigated by employment of various sulfide, amide and β-alkyl substituents on the β-chloroacrylamide (Table 11).

Table 11 Reaction of β-Chloroacrylamides with Lithium Methoxide



β-Cl	R^1	R^2	R^3	R^4	T^a/ °C	Time/h	Product		% Yield (A)[b]	A:B[c]
1a	Ph	Tol	H	H	–5	3.5	**33a**	**34a**	60	9:1
1g[d]	Ph	Tol	H	Me	20	18[e]	**33g**	**34g**	-[f]	1:1
1h	Ph	Allyl	H	H	0	2	**33h**	**34h**	69	20:1
1n[d]	Ph	Ph	Ph	H	20	18	**33n**	**34n**	11	1:2
1r	*n*Bu	Tol	H	H	10	4	**33r**	**34r**	30	3:1

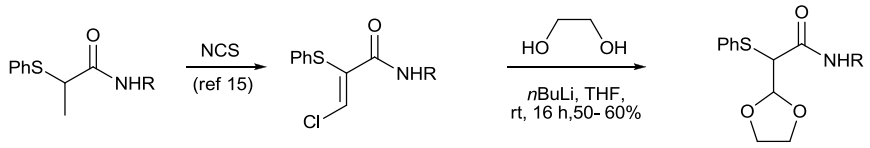
a) Temperature at which the reaction was complete.
b) Isolated yield following chromatographic purification.
c) Ratio of β-methoxyacrylamide **A** to β,β-dimethoxyadduct **B** after chromatography.
d) 1:1 mixture of the *E* and *Z* isomers.
e) The reaction was incomplete on reaching room temperature and was allowed to stir at room temperature overnight.
f) Isolated as a 1:1 inseparable mixture with **34g**.

The yields, reaction times and levels of purity vary considerably on variation of the sulfide, amide and β-alkyl substituents. In most instances, the monoadduct was isolated as the *Z* isomer exclusively. The *N*-tolyl- and *N*-allyl-β-chloroacrylamides **1a** and **1h** gave the monoaddition products **33a** and **33h** in yields of 60% and 69% respectively, along with small amounts of the β,β-dimethoxypropanamides **34a** and **34h**. Changing the α-thio substituent from phenylthio to *n*-butylthio reduces the electrophilicity of the β-carbon and in turn the efficiency of the transformation, with **33r** isolated in 30% yield. Treatment of a 1:1 mixture of the *E* and *Z* isomers of the tertiary *N*,*N*-diphenyl-β-chloroacrylamide **1n** with lithium methoxide gave complete transformation of the starting material only after 18 hours; the acetal **34n** was the major product isolated from the reaction in 31% yield, with the monoaddition product **33n** obtained in just 11% yield.

Reaction of a 1:1 mixture of the *E* and *Z* isomers of the butenamide **1g** with lithium methoxide resulted in incomplete reaction even after stirring at room temperature overnight, presumably due to decreased rate of addition at the substituted β-carbon. The product contained an equimolar inseparable mixture of the monoadduct **33g** and the acetal **34g**. Interestingly, **33g** was formed as a mixture of the *Z* and *E* isomers in a 5:1 ratio.

Thus, while formation of the β-methoxyacrylamide derivatives can be achieved, it is not possible to completely prevent competing acetal formation. As the *E* isomer was only observed for the butenamide **33g**, there is no evidence for thermodynamic equilibration in the enol ethers, in contrast to the enamino derivatives.

The reactivity of the β-chloroacrylamides towards a range of diols was also explored. On treatment of ethylene glycol with 2 equivalents of *n*-butyllithium in THF at 0 °C and subsequent addition of the β-chloroacrylamides **1a** or **1c**, the 1,3-dioxolanes **39a** and **39c** were isolated as white crystalline solids in yields of 60% and 50% respectively after chromatographic purification (Scheme 19). This offers a practical synthetic method for converting the unfunctionalised methyl group of an α-thioamide to an acetal in two rapid, efficient and easily conducted steps.

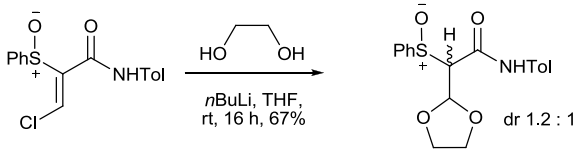


R = Tol **1a** **39a**

R = Bn **1c** **39c**

Scheme 19

The reaction of ethylene glycol with the sulfoxide **18a** was also explored under identical conditions to those described above for the sulfide derivatives. Analagous to the reaction of the sulfoxides with the alkoxides, a mixture of two diastereomers of the 1,3-dioxolane adduct **40a** was obtained in a 1.2:1 ratio (Scheme 20).



Scheme 20

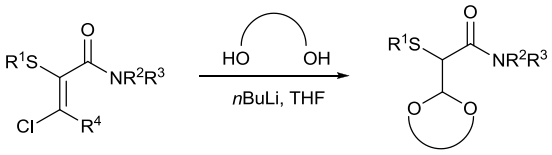
As the synthesis of **39a**, **39c** and **40a** had proceeded so efficiently, the synthesis of acetals derived from chiral diols which could serve as chiral synthons was investigated. Chiral acetals have been widely used as auxiliaries and can be easily removed after exerting their stereocontrol.[37] Chiral acetals are normally prepared under acidic conditions,[38,39] whereas the acetals are prepared under basic conditions during this work.

Four C_2-symmetric diols were employed; (2*R*,3*R*)-2,3-butanediol **41a**, (2*S*, 3*S*)-2,3-butanediol **41b**, (2*R*,4*R*)-2,4-pentanediol **41c** and (2*R*,3*R*)-diethyl tartrate **41d**. Table 12 summarises the results of these investigations.



41a **41b** **41c** **41d**

Table 12 Reaction of β-Chloroacrylamides with Chiral Diols



β-Cl	R^1	R^2	R^3	R^4	Diol	Product	% Yield[a]	d.r.[b]
1a	Ph	H	Tol	H	**41a**	**42a**	65	56:44
1a	Ph	H	Tol	H	**41b**	**43a**	43	53:47
1a	Ph	H	Tol	H	**41c**	**44a**	52	50:50
1a	Ph	H	Tol	H	**41d**	**45a**	66	58:42
1b	Ph	H	(*S*)-CH(CH$_3$)Ph	H	**41a**	**42b**	68	53:47
1b	Ph	H	(*S*)-CH(CH$_3$)Ph	H	**41b**	**43b**	75	51:49
1c	Ph	H	Bn	H	**41a**	**42c**	64	53:47
1c	Ph	H	Bn	H	**41b**	**43c**	51	52:48
1c	Ph	H	Bn	H	**41c**	**44c**	61	50:50

1c	Ph	H	Bn	H	**41d**	**45c**	-[c]	57:43
1g[d]	Ph	Tol	H	Me	**41a**	**42g**	45	54:46
1g[d]	Ph	Tol	H	Me	**41c**	**44g**	33	73:27
1h	Ph	H	Allyl	H	**41a**	**45h**	83	52:48
1h	Ph	H	Allyl	H	**41c**	**44h**	53	51:49
1k	Ph	H	H	H	**41a**	**42k**	80	53:47
1k	Ph	H	H	H	**41c**	**44k**	63	50:50
1n[d]	Ph	Ph	Ph	H	**41a**	**42n**	75	56:44
1n[d]	Ph	Ph	Ph	H	**41c**	**44n**	71	51:49
1n[d]	Ph	Ph	Ph	H	**41d**	**45n**	47	59:41
1r	*n*-Bu	H	Tol	H	**41a**	**42r**	26	50:50
1r	*n*-Bu	H	Tol	H	**41c**	**44r**	25	53:47
1s	*n*-Bu	H	Bn	H	**41a**	**42s**	39	50:50
1s	*n*-Bu	H	Bn	H	**41b**	**43s**	20	50:50

a) Isolated yield after chromatographic purification.
b) d.r.=diastereomeric ratio following chromatographic purification.
c) **41c** was isolated as a 1:2 mixture with diethyl tartrate.
d) 1:1 mixture of the *E* and *Z* isomers.

Two equivalents of *n*-butyllithium were added to a solution of the diol in THF at 0 °C and following stirring for ten minutes, a THF solution of the β-chloroacrylamide was added. When the 2,3-butanediols **41a** and **41b** and diethyl tartrate **41d** were employed, the reaction was conducted at room temperature, whereas the reaction of the β-chloroacrylamides with the deprotonated 2,4-pentanediol **41c** was faster and was therefore conducted at 0 °C to minimise side-product formation. Dioxolanes were produced from treatment of β-chloroacrylamides with butanediols, while dioxanes were generated from reaction with pentanediol. Purification by chromatography on silica gel was necessary for isolation of analytically pure acetals; however, the crude product in each case was essentially one compound (as a mixture of two diastereomers) by ^{1}H NMR spectroscopy.

Analysis of the diastereomeric ratios of the purified products outlined in Table 12 show that the dioxolanes derived from the butanediols **41a** and **41b** and the dioxanes were formed without any significant diastereoselectivity, with the ratio of diastereomers

always close to 1:1. The dioxane **44g** produced from a 1:1 mixture of the *E* and *Z* isomers of the β-chlorobutenamide **1g** and the pentanediol **41c** showed a modest preference for one diastereomer of the acetal (d.r. 73:27). A slight diastereomeric excess was also seen on use of diethyl tartrate **41d** with **1a**, **1c** and **1n**.

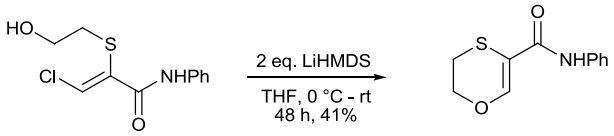
The yields were lower for the acetals derived from the *n*-butylthio-β-chloroacrylamides **1r** and **1s**, possibly reflecting enhanced electron donation from the alkylthio substituent decreasing the electrophilicity of the Michael acceptor, and for the acetals derived from the β-chlorobutenamide **1g**, presumably for steric reasons.

In the reactions of the chiral β-chloroacrylamide **1b**, there was no detectable difference in the diastereocontrol, indicating that the amide auxiliary has little or no impact on this.

As seen with the dimethoxyacrylamides, the coupling constants for the CHS and CH-2′ protons in the tertiary amide (7−8 Hz) is notably different to that in the secondary amides (2−4 Hz), reflecting a conformational change in the absence of the intramolecular hydrogen bond.

The scope of the alkoxide substitution reaction was then extended to include intramolecular substitution. While it proved difficult to prevent double addition with intermolecular alkoxide substitution, it was envisaged that control may be possible in an intramolecular fashion.

Treatment of the β-chloroacrylamide *Z*-**1t**[40] with two equivalents of LiHMDS (generated *in situ* from HMDS and butyllithium) in THF afforded the carboxin **46a** in 41% yield following stirring at room temperature for 48 hours (Scheme 21).

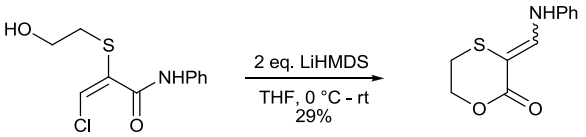


Z-**1t** **46a**

Scheme 21

The extension of this methodology to the *E* isomer of **1t** led to the formation of the oxathianone **47a**, with no evidence for the presence of the analogous carboxin. The oxathianone **47a** is presumably formed by nucleophilic displacement of anilide by the alkoxide, followed by nucleophilic substitution of chloride by the displaced aniline. The

oxathianone was isolated as a single isomer, but the relative stereochemistry has not been confirmed (Scheme 22).



***E*-1t** **47a**

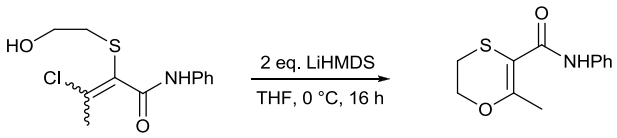
Scheme 22

Carboxins are of biological importance, as compounds of this type are active components of commercially available pesticides and fungicides (for example Vitavax® **46b** and Plantavax® **46c**).



46b **46c**

The scope of this methodology was then extended to the *E*- and *Z*-β-chlorobutenamides **1u**-*E*/*Z*; treatment of the *E* isomer of **1u** with two equivalents of LiHMDS yielded the carboxin **46b** in 7% yield, while **46b** was isolated in 11% yield on reaction of the *Z* isomer of **1u** (Scheme 23).



1u-*E* **46b** (7%)

1u-*Z* **46b** (11%)

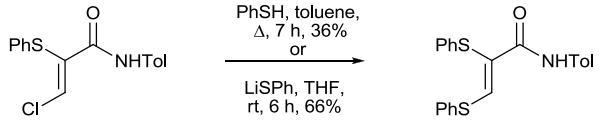
Scheme 23

Thus, the β-chloroacrylamides act as very efficient Michael acceptors in reactions with oxygen based nucleophiles. A second addition of the oxygen nucleophiles readily occurs, leading to a range of novel acetals, however it is possible to stop the reaction at the monoaddition product to yield the corresponding β-methoxypropenamides. The use of diols as nucleophiles results in very efficient cyclic acetal formation. In an intramolecular sense, monoaddition is more readily controlled, as might be expected.

Sulfur Nucleophiles

Analogous to oxygen based nucleophiles, sulfur based nucleophiles usually require formation of at least a catalytic amount of the anion.[41] Thiolates are less basic but more nucleophilic than alkoxides.

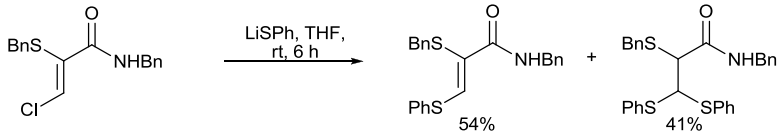
The β-chloroacrylamide **1a** was initially treated with 1.1 equivalents of benzenethiol in toluene at reflux for 7 hours, leading to a complex mixture of products. The major product was the β-phenylthioacrylamide **47a**, isolated as a white crystalline solid in 36% yield. Substitution of the chloride in **1a** by thiophenol under neutral conditions is significant, and is consistent with the increased nucleophilicity of the thiol compared to ethanol and methanol. On employment of basic conditions (1.1 equivalents of lithium thiolate, generated *in situ* from reaction of benzenethiol and *n*-buthyllithium), an improved yield of 66% was obtained for the β-phenylthioacrylamide **47a** (Scheme 24).



1a **47a**

Scheme 24

Meanwhile, treatment of the benzylthio β-chloroacrylamide **1v** under the basic conditions described above resulted in a mixture of the mono- and diaddition products **47v** and **48v**. Following chromatographic purification, **47v** and **48v** were isolated in yields of 54% and 41% respectively (Scheme 25).

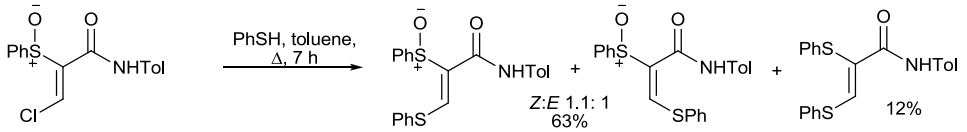


1v **47v** **48v**

Scheme 25

Finally, treatment of the sulfoxide **18a** with 1.1 equivalents of benzenethiol in toluene at reflux for 7 hours, led to a 1.1:1 mixture of the *Z* and *E* isomers of the monoaddition product **49a**, in addition to 12% of the sulfide **47a** (Scheme 26). Following chromatographic purification, the *Z* and *E* isomers of **49a** were isolated as an inseparable

mixture in 63% yield in the same *Z*:*E* ratio as a white solid, and **47a** was isolated as a white solid in 12% yield.

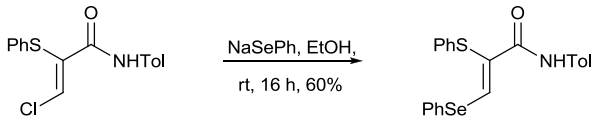


18a **49a-*Z*** **49a-*E*** **47a**

Scheme 26

Selenium Nucleophiles[42]

One equivalent of sodium phenyl selenide, prepared as described by Sharpless[43] by treatment of diphenyl diselenide in ethanol with two equivalents of sodium borohydride, was added to an ethanolic solution of **1a**. Following stirring at room temperature for 16 hours, the β-phenylselenoacrylamide **50a** was isolated as a single isomer, presumably *Z*, in 60% yield (Scheme 27).

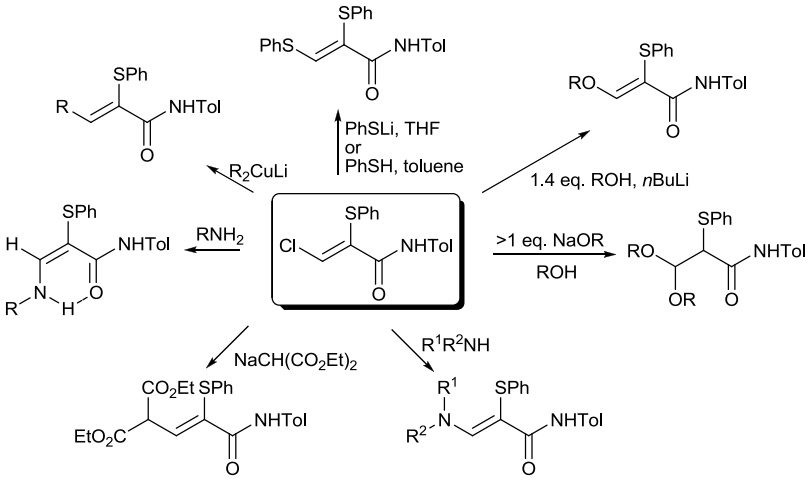


1a **50a**

Scheme 27

Conclusion

The β-chloroacrylamides at the sulfide, sulfoxide and sulfone levels of oxidation act as very efficient Michael acceptors, and readily undergo substitution reactions with carbon, nitrogen, oxygen, sulfur and selenium based nucleophiles, demonstrating that the carbon framework can be easily extended and new functionality introduced at the β-position as summarised in Scheme 28 for the sulfides. In most instances, the nucleophile replaces the chloro substituent with retention of stereochemistry. With the oxygen nucleophiles, a second addition can occur leading to acetals, while with the nitrogen nucleophiles, *E*-*Z* isomerism occurs in the resulting enamine derivatives. The ratio of the *E*/*Z* isomers can be rationalised on the basis of the substituent and the level of oxidation.



Scheme 28

Experimental

All solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorous pentoxide and ethyl acetate was distilled from potassium carbonate, ethanol and methanol were distilled from magnesium in the presence of iodine. Acetone was distilled from potassium permanganate and toluene was distilled from sodium and stored over 4Å molecular sieves. Dimethylformamide was stored overnight over calcium hydride, then distilled and stored over 4 Å molecular sieves. Organic phases were dried using anhydrous magnesium sulphate.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker (300 MHz) NMR spectrometer. ^{1}H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a Jeol GSX (270 MHz) NMR spectrometer. ^{1}H (60 MHz) NMR spectra were recorded on a Jeol PMX-60SI spectrometer. All spectra were recorded at room temperature (~20^{o}C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm) and coupling constants in Hertz (Hz).

Elemental analyses were performed by the Microanalysis Laboratory, National University of Ireland, Cork, using a Perkin-Elmer 240 elemental analyzer. Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus. Mass spectra were recorded on a Kratos Profile HV-4 double focusing high resolution mass

spectrometer (EI), a Waters/Micromass LCT Premier Time of Flight spectrometer (ESI) and a Waters/Micromass Quattro Micro triple quadrupole spectrometer (ESI). Infrared spectra were recorded as potassium bromide (KBr) discs for solids or thin films on sodium chloride plates for oils on a Perkin-Elmer Paragon 1000 FT-IR spectrometer.

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

The syntheses of β-chloroacrylamides **1a**-**1u**, sulfoxides **18a**-**18m** and sulfone adducts **23a**-**23m** have been described elsewhere.[15,16]

Selected experimental data, including representatives of each of the synthetic methods, are given below-full experimental procedures and spectral data for all the compounds described in the paper are given in the ESI.

Addition of Carbon Nucleophiles

Addition of the enolate of diethyl malonate

***N*-(4-Methylphenyl)-4,4-di(ethoxycarbonyl)-2-(phenylthio)-2-pentenamide 2a**

Diisopropylamine (0.5 mL, 3.6 mmol) was added to a flask containing THF (20 mL). The stirred solution was cooled to 0 °C and *n*-butyllithium (1.5 mL, 1.6 M in hexane, 3.78 mmol) was added dropwise *via* syringe. After 20 min, diethyl malonate (0.6 mL, 3.6 mmol) was added and the reaction mixture was stirred for a further 20 min. A solution of **1a** (1.00 g, 3.3 mmol) in THF (20 mL) was then added dropwise. A bright yellow colour appeared instantly. After 1 h the reaction was complete (by TLC analysis) and was quenched with saturated aqueous ammonium chloride (20 mL). CH_2Cl_2 (20 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with aqueous sodium bicarbonate (2 × 10 mL), brine (2 × 10 mL), dried and evaporated to give **2a** as a yellow, low-melting solid. Purification by chromatography using ethyl acetate-hexane (20:80) as eluent gave **2a** (1.23 g, 80%) as a yellow, crystalline solid. The product contained a minor isomer which could not be separated by chromatography. The ratio was estimated to be (27:1) by

^{1}H NMR spectroscopic integration; mp 68−70 °C; (Found C, 64.56; H, 5.77; N, 2.95; S, 7.13. $C_{23}H_{25}NO_5S$ requires C, 64.62; H, 5.89; N, 3.28; S, 7.50%); ν_{max}/cm^{-1} (KBr) 3354 (br NH), 1749, 1736 (CO ester), 1664 (CO α,β-unsaturated amide); δ_H (270 MHz, $CDCl_3$) 1.29 (6H, t, *J* 7, 2 × C*H*$_3$CH$_2$O), 2.31 (3H, s, ArC*H*$_3$), 4.22 (4H, q, *J* 7 , 2 × C*H*$_2$O), 4.94 [1H, d, *J* 10, C(4)*H*], 7.06-7.57 (9H, m, Ar*H*), 7.75 (1H, d, *J* 10, C*H*(3)=), 8.62 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 20.8 (Ar*C*H$_3$), 54.4 [*C*(4)H], 62.1 (*C*H$_2$O), 120.1, 127.2, 127.8, 129.0, 129.2 (aromatic *C*H), 132.3, 133.1, 134.5, 134.7 (quaternary aromatic *C* and S*C*=), 141.2 (*C*H=), 160.9 (*C*O amide), 166.3 (*C*O ester); MS *m/z* 427 (M^+, 25%), 381 (25%), 267 [30%, M^+-CH$_2$(CO$_2$Et)$_2$], 109 (91%). Signals for the minor isomer were seen in ^{1}H and ^{13}C NMR spectra at 5.42 [1H, d, *J* 10, C(4)*H*], 6.82 (1H, d, *J* 10, C*H*=); all other signals were identical to the major isomer.

Alkylation of 2c

***N*-Phenylmethyl-4,4-di(ethoxycarbonyl)-2-phenylthiohept-2,6-dienamide 3a**

Potassium carbonate (0.19 g, 1.41 mmol) was added to a solution of **2c** (0.30 g, 0.70 mmol) in acetonitrile (6 mL). A solution of allyl bromide (0.12 mL, 1.41 mmol) in acetone (3 mL) was added and the reaction mixture was stirred overnight under nitrogen. Ether (10 mL) was added to precipitate the salts, and the mixture was filtered through a celite plug. The filtrate was then dried and the solvent evaporated to give the crude product as a brown oil. Following chromatography on silica gel using 15:85 ethyl acetate-hexane, **3a** was isolated as a white solid (0.09 g, 27%); mp 66−68 °C; (Found C, 66.99; H, 6.15; N, 3.07; S, 7.10; $C_{26}H_{29}NO_5S$ requires C, 66.79; H, 6.25; N, 2.90; S, 6.86 %); ν_{max}/cm^{-1} (KBr) 3374 (NH), 1738 (CO saturated ester), 1666 (CO amide); δ_H (300 MHz, $CDCl_3$) 1.19 (6H, t, *J* 7.1, 2 × OCH$_2$C*H*$_3$), 2.93 [2H, d, *J* 7.4, C(5)*H*$_2$], 3.96-4.21 (4H, 2 × sym m, 2 × OC*H*$_2$CH$_3$), 4.36 (2H, d, *J* 5.8, NC*H*$_2$Ph), 5.07-5.17 [2H, m, C(7)*H*$_2$=], 5.71-5.88 [1H, m, C(6)*H*=], 6.73-6.80 (2H, m, Ar*H*), 6.94-7.27 (9H, m, Ar*H*, br s at 7.00 for N*H*), 7.97 [1H, s, C(3)*H*=]; δ_C (75.5 MHz, $CDCl_3$) 14.3 (CH$_3$, OCH$_2$*C*H$_3$), 41.7 [CH$_2$, *C*(5)H$_2$], 44.5 (CH$_2$, N*C*H$_2$Ph), 60.7 [C, *C*(4)], 62.4 (CH$_2$, O*C*H$_2$CH$_3$), 120.1 [CH$_2$, *C*(7)H$_2$=], 127.0, 127.6, 127.8, 128.9, 129.0 [CH, aromatic *C*H, *C*(6)H=], 129.6 (C, =*C*SPh), 129.7, 132.5 [CH, aromatic *C*H, *C*(6)H=], 134.3, 138.0 (C, aromatic *C*), 146.2 [CH, *C*(3)H=], 164.1 (C, amide *C*O), 169.3 (C, ester *C*O); MS *m/z* 467 (6%, M^+), 394 [3%, (M-CO$_2$Et)$^+$], 84 (100%).

Addition of the enolate of ethyl acetoacetate

_N_-(4-Methylphenyl)-4-ethoxycarbonyl-2-(phenylthio)-5-oxo-2-hexenamide 4a

Ethyl acetoacetate (0.17 g, 1.32 mmol) was added to a freshly prepared solution of sodium ethoxide [using sodium (30 mg, 1.32 mmol) and ethanol (10 mL) at 0 °C] and stirred for 30 min. A solution of β-chloroacrylamide **1a** (0.2 g, 0.66 mol) in ethanol (3 mL) was added. After stirring for 3 h (while slowly returning to room temperature), the reaction mixture was quenched with water (10 mL). CH_2Cl_2 (20 mL) was added and the phases were separated. The organic layer was washed with brine (2 × 10 mL), dried and evaporated. Excess ethyl acetoacetate was removed under vacuum at 1 mmHg. Purification by recrystallisation from ether-CH_2Cl_2-hexane (10:5:75) gave what is tentatively assigned as **4a** (29 mg, 11%) as white crystals in enol tautomeric form; mp 184−185 °C; ν_{max}/cm^{-1} (KBr) 3480 (br NH), 1711 (CO conjugated ester), 1654, 1592 (CO α,β-unsaturated amide); δ_H (270 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7, *CH*$_3$CH$_2$O), 2.34 (3H, s, ArC*H*$_3$), 2.42 [3H, s, C(6)*H*$_3$], 4.19 (2H, q, *J* 7, OC*H*$_2$), 7.01-7.57 (11H, m, Ar*H* and C(5)*H*= and N*H*); δ_C (67.8 MHz, $CDCl_3$) 14.1 (CH_3, *C*H$_3$CH$_2$O), 19.4 [CH_3, *C*(6)H$_3$], 21.2 (CH_3, Ar*C*H$_3$), 60.9 (CH_2, *C*H$_2$O), 109.6 [C, *C*(4)], 127.5, 128.6, 129.5, 130.6, 134.0 (CH, Ar*C*H), 128.2, 131.8, 139.2 (3 × C, aromatic *C* and PhS*C*=), 135.8 [CH, *C*(3)H], 150.6 (C, =*C*OH), 160.8, 165.4 (2 × C, *C*O amide, *C*O ester).

Addition of n-Bu$_2$CuLi

_N_-(4-Methylphenyl)-2-(phenylthio)-*Z*-2-heptenamide 7a

Ether (25 mL) was added to a flask containing CuI (250 mg, 1.32 mmol) which had been freshly purified. The suspension was cooled to −30 °C, *n*-butyllithium (1.65 mL, 1.6 M in hexane, 2.64 mmol) was added and stirring was continued for 30 min, after which time the solution was brown and opaque. The reaction mixture was cooled to –78 °C and β-chloroacrylamide **1a** (0.20 g, 0.66 mmol) in ether (10 mL) was added quickly. The reaction was complete after 30 min at a reaction temperature of –50 °C. Saturated aqueous ammonium chloride (10 mL) was added and stirred for 15 min while the reaction mixture was warmed to room temperature. Saturated aqueous ammonium chloride (10

mL) and ether (10 mL) were added and the solution was filtered through a layer of celite. Separation of the phases followed by washing of the organic phase with brine (2 × 20 mL), drying and evaporation gave a yellow oil. Purification by chromatography using ethyl acetate-hexane (5:95) as eluent gave **7a**-*Z* (85 mg, 40%) as a light yellow solid; mp 43−45 °C; (Found C, 73.40; H, 7.00; N, 4.21; S, 9.84. $C_{20}H_{23}NOS$ requires C, 73.81; H, 7.21; N, 4.30; S, 9.85%); ν_{max}/cm^{-1} (film) 3354 (br NH), 1674, 1594 (CO α,β-unsaturated amide); δ_H (270 MHz, $CDCl_3$) 0.92 [3H, t, *J* 7, C(7)H_3], 1.29-1.37 [2H, m, C(6)H_2], 1.40-1.54 [2H, m, C(5)H_2], 2.28 (3H, s, ArCH_3), 2.49-2.58 [2H, dt, *J* 7, 7, C(4)H_2], 7.06-7.38 (9H, m, Ar*H*), 7.75 [1H, t, *J* 7, C(3)*H*=], 8.79 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 13.4 [CH_3, *C*(7)H_3], 20.3 (CH_3, Ar*C*H_3), 22.0 [CH_2, *C*(6)H_2], 28.9 [CH_2, *C*(5)H_2], 30.0 [CH_2, *C*(4)H_2], 119.6, 125.9, 126.7, 128.9 (CH, aromatic *C*H), 125.7, 133.6, 134.2, 134.7 (4 × C, aromatic *C* and S*C*=), 153.5 [CH, C(3)H=], 161.8 (C, *C*O); MS *m/z* 325 (M^+, 17%), 149 (15%), 107 [22%, $(NHTol)^+$], 96 (100%). A compound which was detected in a mixture of side-products was tentatively assigned as **21**-*E* (total wt = 5 mg, 2 %). δ_H (270 MHz, $CDCl_3$) 0.93 [3H, t, *J* 7, C(7)H_3], 1.36-1.57 [4H, m, C(6)H_2, C(5)H_2], 2.27 (3H, s, ArCH_3), 2.76-2.79 [2H, dt, *J* 7, 7, C(4)H_2], 6.74 [1H, t, *J* 7, C(3)*H*=], 7.05-7.29 (9H, m, Ar*H*), 8.49 (1H, br s, N*H*).

Addition of Me_2CuLi

_N_-Benzyl -2-phenylthio-2-butenamide 10c

CuI (0.42 g, 2.18 mmol) was suspended in dry ether (20 mL) and the flask was cooled to –78 °C under nitrogen. Methyl lithium (2.7 mL, 1.6 M solution in ether, 4.36 mmol) was added and the mixture was stirred for 10 min, during which time it changed from yellow to colourless. In a separate flask, **1c** (0.33 g, 1.09 mmol) was dissolved in ether (20 mL) and also cooled to –78 °C. The organocuprate solution was then allowed to settle and added to the solution of **1c** using a cannula. The reaction vessel was maintained at –78 °C for 2.25 hours, and on removal from the cold bath the reaction was rapidly quenched with saturated aqueous ammonium chloride (5 mL). After stirring for 10 min, the solution was filtered through a celite plug, the layers were separated and the aqueous layer was washed with ether (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, and the solvent evaporated at reduced pressure to give the crude product, which was shown by ^{1}H NMR spectroscopic

analysis to contain a 1:16 ratio of starting material to the *Z* isomer of the adduct **10c**. After chromatography, the pure product **10c** was isolated as an off-white solid (0.11 g, 75%); ν_{max}/cm^{-1} (film) 3355 (NH), 1653 (CO), 1608, 1581 (C=C), 1511; δ_H (300 MHz, $CDCl_3$) 2.09 [3H, d, *J* 7.0, C(4)*H*$_3$], 4.43 (2H, d, *J* 5.9, NC*H*$_2$Ph), 6.89-6.99 (2H, m, Ar*H*), 7.10-7.39 (9H, m, N*H*, Ar*H*), 7.75 (1H, q, *J* 7.0, C(3)*H*=); δ_C (75.5 MHz, $CDCl_3$) 16.7 [CH_3, *C*(4)H_3], 43.9 (CH_2, N*C*H_2), 126.1, 126.9 (CH, aromatic *C*H), 127.0 (C, aromatic *C*), 127.2 127.7, 128.5, 129.3 (CH, aromatic *C*H), 134.8, 137.9 (C, aromatic *C*, =*C*S), 148.1 [CH, *C*(3)H=], 164.3 (C, *C*O); MS *m/z* 283 (M^+, 48%), 268 [5%, $(M\text{-}CH_3)^+$], 174 [8%, $(M\text{-}PhS)^+$], 149 [21%, $(PhS{=}C{=}CHCH_3)^+$], 134 [24%, $(CONHCH_2Ph)^+$], 106 [45%, $(NHCH_2Ph)^+$], 91 [100%, $(CH_2Ph)^+$], 77 [23%, $(C_6H_5)^+$].

Addition of Ph_2CuLi

***N*-Benzyl-3-phenylpropynamide 11c**

To a solution of CuI (0.38 g, 1.98 mmol) in ether (30 mL) at –78 °C was added phenyl lithium (2.2 mL, 1.8 M solution in ether, 3.96 mmol) by syringe. This was stirred for 10 min under nitrogen. In a separate flask **1c** (0.30 g, 0.99 mmol) was dissolved in ether (20 mL) and cooled to –78 °C. The cuprate solution was added to the reaction vessel using a cannula, and the reaction mixture stirred for 2 h at –78 °C, at which point it was allowed to warm to room temperature. The reaction was quenched with aqueous ammonium chloride (5 mL) and filtered to remove the copper salts. The layers were separated and the aqueous layer washed with ether (10 mL). The combined organic layers were dried, and the solvent evaporated at reduced pressure to give the crude product mixture as an oil. After chromatography on silica gel using 20:80 ethyl acetate/hexane as eluent, the propynamide **11c** was isolated as an oil (0.19 g, 83%); ν_{max}/cm^{-1} (film) 3279 (NH), 3061, 3032 (CH), 2222 (C≡C), 1636 (CO); δ_H (270 MHz, $CDCl_3$) 4.49 (2H, d, *J* 5.9, NC*H*$_2$Ph), 6.55 (1H, br s, N*H*), 7.05-7.60 (10H, m, Ar*H*); δ_C (67.8 MHz, $CDCl_3$) 43.9 (N*C*H_2Ph), 83.0, 85.0 (*C*≡*C*), 120.2 (aromatic *C*), 127.2, 127.9, 128.7, 129.0, 129.7, 132.1 (aromatic *C*H), 137.4 (aromatic *C*), 153.3 (*C*O).

Addition of $iPr_2CuMgCl$

***N*-Benzyl-4-methyl-2-(phenylthio)-2-pentenamide 13c**

CuI (0.26 g, 1.35 mmol) was dissolved in ether (20 mL) and cooled to –78 °C. *i*-Propyl magnesium chloride (1.4 mL, 2.0 M solution in ether, 2.71 mmol) was added by syringe and the solution was stirred for 15 min. The starting material **1c** (0.21 g, 0.68 mmol) was dissolved in ether (10 mL) at room temperature and this solution was added to the reaction vessel by syringe, and this mixture was stirred for 2.5 h. The reaction was then quenched with water (10 mL) and the solution was filtered through a Celite® plug. The layers were separated, and the aqueous layer was washed with ether (2 × 10 mL). The combined organic layers were dried, and the solvent was evaporated to give a crude mixture containing a 1.13:1.0 ratio of starting material to product **13c**-*Z*, which also contained a trace of **13c**-*E*; mp 83−85 °C; ν_{max}/cm^{-1} (film) 3334 (NH), 1652 (CO), 1607, 1583 (C=C), 1513; δ_H (300 MHz, $CDCl_3$) 1.08 [6H, d, *J* 6.7, $CH(CH_3)_2$], 3.00-3.18 [1H, m, $CH(CH_3)_2$], 4.02 (2H, d, *J* 5.9, NCH_2Ph), 6.87-6.96 (2H, m, Ar*H*), 7.10-7.38 (9H, m, Ar*H*, N*H*), 7.48 [1H, d, *J* 9.9, C(3)*H*=]; δ_C (75.5 MHz, $CDCl_3$) 21.9 [CH_3, $CH(CH_3)_2$], 30.4 [CH, $CH(CH_3)_2$], 43.9 (CH_2, NCH_2Ph), 123.4 (C, aromatic *C*), 126.1, 126.8, 127.2, 127.2, 128.5, 129.4 (CH, aromatic *C*H), 135.2, 137.9 (C, aromatic *C*, =*C*S), 159.1 [CH, *C*(3)H=], 164.4 (C, *C*O); MS *m/z* 311 (M^+, 73%), 268 [17%, $(M-C_3H_7)^+$], 177 [13%, $(CH=CSPhCONH)^+$], 162 [16%, $(CH=CSPhCO)^+$], 110 (42%, PhSH), 106 [35%, $(NHCH_2Ph)^+$], 91 [100%, $(CH_2Ph)^+$], 77 [34%, $(C_6H_5)^+$]. The *E* isomer **13c**-*E* was tentatively identified by a signal at δ_H 6.45 [d, *J* 10.0, =C(3)*H*].

Nitrogen Nucleophiles

Addition of primary and secondary amines

N-(4-Methylphenyl)-3-*N*′,*N*′-dimethylamino-2-(phenylthio)propenamide 14a

β-Chloroacrylamide **1a** (200 mg, 0.66 mmol) was added to dimethylamine (5.6 M in ethanol, 3 mL, 17 mmol) with stirring. After stirring for 15 min the reaction was complete (by TLC analysis) and CH_2Cl_2 (10 mL) and water (10 mL) were added. The phases were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with aqueous saturated aqueous ammonium chloride (2 × 10 mL), brine (2 × 10 mL), dried and evaporated to give β-aminopropenamide **14a** (177 mg, 85%) as a white, crystalline solid. Purification by recrystallisation from ethanol gave **14a** (0.16 g, 75 %) as a white, crystalline solid; mp

124−125 °C; (Found C, 69.02; H, 6.40; N, 9.28; S, 10.20. $C_{18}H_{20}N_2OS$ requires C, 69.20; H, 6.45; N, 8.97; S, 10.26%); ν_{max}/cm^{-1} (KBr) 3338 (br NH), 1652, 1583 (CO α,β-unsaturated amide); δ_H (270 MHz, $CDCl_3$) 2.26 (3H, s, ArC*H*$_3$), 3.18 [6H, s, N(C*H*$_3$)$_2$], 7.04-7.39 (9H, m, Ar*H*), 8.29 [1H, s, C(3)*H*=], 8.86 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 20.7 (CH_3, Ar*C*H$_3$), 42.7 [CH_3, br, N(*C*H$_3$)$_2$], 83.0 (S*C*=), 119.7, 124.8, 125.2, 128.7, 129.2 (aromatic *C*H), 132.5, 136.5, 139.5 (quaternary aromatic *C*), 154.1 [*C*(3)H=], 167.1 (*C*O); MS *m/z* 312 (M^+, 15%), 285 (13%), 271 (15%), 178 (12%).

Addition of hydroxylamine

_N_-(4-Methylphenyl)-3-oxime-2-(phenythio)propanamide 29a

A solution of **1a** (0.15 g, 0.50 mmol) in ethanol (5 mL) and water (1mL) was stirred at room temperature. Potassium carbonate (83 mg, 0.78 mmol) and hydroxylamine hydrochloride (72 mg, 1.04 mmol) were added and the reaction mixture was warmed at 60 °C for 1 min. After stirring for 5 h at room temperature, the reaction was complete by TLC analysis, and CH_2Cl_2 (10 mL) and saturated aqueous ammonium chloride (10 mL) were added. The phases were partitioned and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried and evaporated. Purification by trituration with hexane gave **29a**-*Z* and **29a**-*E* (0.11 g, 74%) *Note:* The *E* and *Z* isomers interconvert on silica gel (2 D analysis), and slowly on standing at room temperature. Thus a pure sample of either isomer could not be obtained; mp 124−126 °C; (Found C, 63.64; H, 5.70; N, 9.16; S, 10.44. $C_{16}H_{16}N_2O_2S$ requires C, 63.98; H, 5.37; N, 9.33; S, 10.67%); ν_{max}/cm^{-1} (KBr) 3281 (br NH), 1654, 1597 (CO α,β-unsaturated amide); δ_H (270 MHz, acetone-d_6) tentatively assigned *Z;* 2.27 (3H, s, ArC*H*$_3$), 4.69 (1H, d, *J* 8, C*H*S), 7.11-7.54 (9H, m, Ar*H*), 7.59 (1H, d, *J* 8 C*H*=N), 9.50 (1H, br s N*H*Tol), 10.11-10.27 (1H, br s, O*H*); tentatively assigned *E;* 2.27 (3H, s, ArC*H*$_3$), 3.09 (1H, br s, O*H*), 5.39 (1H, d, *J* 8, C*H*S), 7.00 (1H, d, *J* 8, C*H*=N), 7.11-7.54 (9H, m, Ar*H*), 9.50 (1H, br s, N*H*Tol); δ_C (67.8 MHz, acetone-d_6) 20.8 (Ar*C*H$_3$), 46.0, 53.1$^{\diamond}$ (*C*HS), 120.5, 128.9, 130.0, 130.4, 133.5 (aromatic *C*H), 134.2, 134.3$^{\diamond}$, 137.0$^{\diamond}$, 137.1 (quaternary aromatic *C*), 146.5, 147.3$^{\diamond}$ (*C*H=N), 166.2, 166.4$^{\diamond}$ (*C*O); MS *m/z* 300 (M^+, 1%), 284 (10%, M^+-O), 268 (2%, M^+-NHOH), 110 (78%), 107 (100%).

[◊]Major isomer.

Ratio:	in acetone-d_6	1: 1.37 (*Z:E*)
	in deuterated methanol	1:1.03 (*Z:E*)
	in deuterated DMSO-d_6	1:1.43 (*Z:E*)

Addition of ammonia

_N_-(4-Methylphenyl)-3-amino-2-(phenythio)propenamide 30a and 31a

Aqueous ammonia (35%, 73 μl, 1.45 mmol) was added to a solution of **1a** (200 mg, 0.66 mmol) in acetone (4 mL). After 74 h the reaction was incomplete by TLC analysis, and a further aliquot of aqueous ammonia (73 μl, 1.45 mmol) was added. Following 24 h of stirring at room temperature, only trace amounts of **1a** remained. CH_2Cl_2 (10 mL) and saturated aqueous ammonium chloride (10 mL) were added and the phases separated, the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried and evaporated, Purification by chromatography using ethyl acetate-hexane (20:80) as eluent gave a mixture of tautomers and geometrical isomers (140 mg, 75%), which could not be isolated; mp 83−85 °C; (Found C, 67.05; H, 5.90; N, 9.92; S, 11.52. $C_{16}H_{16}N_2OS$ requires C, 67.58; H, 5.67; N, 9.85; S, 11.28%); ν_{max}/cm^{-1} (KBr) 3363 (br NH), 1651, 1590 (CO α,β-unsaturated amide); The following signals were distinguishable in the ^1H NMR spectrum: δ_H (270 MHz, $CDCl_3$) 1.37 (d, *J* 12), 2.01, 2.07 (2 × s), 2.27 (3 H, s, ArC*H*$_3$), 2.59, 2.67 (2 × s), 5.20-5.50 (br s), 7.05-7.39 (9 H, m, Ar*H*), 8.35 (t, *J* 7), 8.35, 8.40 (s), 8.48 (br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) major peaks at 20.8, 119.9, 125.4, 129.2, 150.6; MS *m/z* 284 (M^+, 15%), 224 (18%), 149 (25%), 134 [22%, $(PhS{=}C{=}CH)^+$], 107 (100%).

Oxygen Nucleophiles

Formation of β,β-dimethoxyamide

_N_-(4-Methylphenyl)-3,3-dimethoxy-2-(phenylthio)propanamide 34a

From a solution of sodium (50 mg, 2.17 mmol) in methanol (10 mL), a 6.4 mL portion was added to a solution of **1a** (0.20 g, 0.66 mmol) in methanol (4 mL). After stirring for 1h the reaction was complete by TLC analysis. Saturated aqueous ammonium chloride (10 mL) and ether (15 mL) were added and the phases were separated. The aqueous layer was extracted with ether (2 × 5 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried and evaporated to give **34a** (199 mg, 91%) as a white, crystalline solid which did not require further purification; mp 103−105 °C; (Found C, 64.83; H, 6.69; N, 4.40; S, 10.20. $C_{18}H_{21}NO_3S$ requires C, 65.23; H, 6.39; N, 4.23; S, 9.67%); ν_{max}/cm^{-1} (KBr) 3282 (br NH), 1657, 1599 (CO amide); δ_H (270 MHz, $CDCl_3$) 2.30 (3H, s, ArC*H*$_3$), 3.48 (3H, s, OC*H*$_3$), 3.53 (3H, s, OC*H*$_3$), 3.98 (1H, d, *J* 4, C*H*S), 4.80 [1H, d, *J* 4, C(3)*H*], 7.09-7.47 (9H, m, Ar*H*), 8.54 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 20.9 (Ar*C*H$_3$), 56.3, 56.9 (O*C*H$_3$), 58.0 (*C*HS), 105.3 [*C*(3)H], 120.5, 127.6, 128.9, 129.3, 129.9 (aromatic *C*H), 133.8, 134.2, 135.1 (aromatic *C*), 166.6 (*C*O); MS *m/z* 331 (M^+, 25%), 271 (33%), 75 {100%, $[CH(OMe)_2]^+$}.

Reaction with lithium methoxide

_N_-(4-Methylphenyl)-_Z_-3-methoxy-2-(phenylthio)propenamide 33a

A 1 mL aliquot of a solution of methanol (87 μl, 2.16 mmol) in THF (5 mL) was added to a flask containing THF (2 mL), and the solution was cooled to 0 °C. *n*-Butyllithium (0.29 mL, 1.6 M in hexane, 0.46 mmol) was added and the reaction mixture was stirred for 10 min before cooling to –78 °C. A solution of **1a** (100 mg, 0.33 mmol) in THF (2 mL) was also cooled to –78 °C and the methoxide solution was added slowly by syringe. The reaction mixture was allowed to warm up slowly in the cooling bath. After stirring for 3.5 h at a temperature of –5 °C, the reaction was complete by TLC analysis and was quenched with aqueous saturated aqueous ammonium chloride (10 mL). The aqueous phase was extracted with ether (2 × 10 mL), the combined organic layers were washed with brine (2 × 10 mL), dried and evaporated to give crude mixture containing **34a** and **33a** (1:6). Purification by chromatography using ethyl acetate-hexane (25:75) as eluent gave **33a** (59 mg, 60%) (with < 10% dimethoxypropanamide **34a**) as a white, crystalline solid; ν_{max}/cm^{-1} (KBr) 3349 (br NH), 1656, 1598 (CO amide); δ_H (270 MHz, $CDCl_3$)

2.28 (3H, s, ArC*H*$_3$), 4.00 (3H, s, OC*H*$_3$), 7.07-7.47 (9H, m, Ar*H*), 8.17 [1H, s, C(3)*H*=], 8.70 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 20.8 (Ar*C*H$_3$), 62.6 (O*C*H$_3$), 101.5 (S*C*=), 120.0, 126.0, 126.4, 128.7, 128.9 (aromatic *C*H), 133.8, 135.0, 135.3 (aromatic *C*), 163.3 (*C*O), 166.1 [*C*(3)H=]; MS *m/z* 299 (M^+, 100%), 193 (50%, M^+-NHTol), 165 (50%, M^+-CONHTol).

Addition of ethylene glycol

2-[*N*-(4-Methylphenyl)-2-(phenylthio)acetamide]-1,3-dioxolane 39a

n-Butyllithium (0.33 mL, 1.6 M in hexane, 0.52 mmol) was added to a solution of ethylene glycol (34 μl, 0.55 mmol) in THF (2 mL) at 0 °C. The solution was removed from the ice bath and allowed to warm to room temperature over 10 min. A solution of **1a** (80 mg, 0.26 mmol) in THF (2 mL) was added rapidly to the reaction mixture. After stirring for 16 h the reaction was complete by TLC analysis, and saturated aqueous ammonium chloride (10 mL) and CH_2Cl_2 (10 mL) were added. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried and evaporated to give the crude acetal. Purification by chromatography using ethyl acetate-hexane (30:70) as eluent gave **39a** (51 mg, 60%) as a white, crystalline solid; mp 102−104 °C; (Found C, 65.60; H, 5.54; N, 4.49; S, 9.40, $C_{18}H_{19}NO_3S$ requires C, 65.63; H, 5.81; N, 4.25; S, 9.73%); ν_{max}/cm^{-1} (KBr) 3305 (br NH), 1657, 1605 (CO amide); δ_H (270 MHz, $CDCl_3$) 2.30 (3H, s, ArC*H*$_3$), 3.91-4.03 (2H, m, C*H*$_2$O), 4.07-4.20 (3H, contains d, *J* 2, C*H*S at δ_H 4.13) 5.49 [1H, d, *J* 2, C(3)*H*], 7.10-7.47 (9H, m, Ar*H*), 8.58 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 20.8 (Ar*C*H$_3$), 58.7 (*C*HS), 65.8, 66.1 (2 × *C*H$_2$O), 102.8 (*C*HO), 119.9, 127.6, 129.3, 129.4, 131.0 (aromatic *C*H), 133.4, 134.2, 134.9 (aromatic *C*), 165.9 (*C*O); MS *m/z* 329 (M^+, 2%), 257 [1%, M^+-$CO_2(CH_2)_2$].

Addition of chiral diols

(4*R*,5*R*)-4,5-Dimethyl-2-[*N*-(4-methylphenyl)-2-(phenylthio)acetamide]-1,3-dioxolane 42a

n-Butyllithium (0.83 mL, 1.6 M in hexane, 1.32 mmol) was added to a solution of (2*R*, 3*R*)-2,3-butanediol **41a** (125 mg, 1.39mmol) in THF (3 mL) at 0 °C. The reaction

mixture was removed from the ice bath and stirred at room temperature for 10 min. A solution of **1a** (0.20 g, 0.66 mmol) in THF (3 mL) was added and a strong yellow colour developed. The reaction was complete by TLC analysis after stirring for 2 h at room temperature, and saturated aqueous ammonium chloride (10 mL) and ether (20 mL) were added. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried and evaporated. Purification by chromatography using ethyl acetate-hexane (10:90 to 25:75) as eluent gave the two diastereomers (56:44) of **42a** (0.15 g, 65%) as a white, crystalline solid; mp 86−88 °C; $[\alpha]_{20}^{D}$ –16.53 (*c* 7 in ethanol); (Found C, 67.52; H, 6.70; N, 4.40. $C_{20}H_{23}NO_3S$ requires C, 67.20; H, 6.49; N, 3.92%); ν_{max}/cm^{-1} (KBr) 3307 (br NH), 1660, 1605 (CO amide); δ_H (270 MHz, $CDCl_3$) 1.24-1.36 [6H, m, C*H*$_3$C(4) and C*H*$_3$C(5)], 2.30 (3H, s, ArC*H*$_3$), 3.70-3.91 [2H, m, C(4)*H* and C(5)*H*], 4.05, 4.07 (1H, d, *J* 2, C*H*S), 5.58, 5.63 [1H, d, *J* 2, C(2)*H*], 7.09-7.48 (9H, m, Ar*H*), 8.55 (1H, br s, N*H*); δ_C (67.8 MHz, $CDCl_3$) 16.2, 16.4, 16.88, 16.91 [*C*H$_3$C(4) and *C*H$_3$C(5)], 20.8 (Ar*C*H$_3$), 58.5, 59.3 (*C*HS), 79.4, 79.7, 80.3, 80.5 [*C*(4)H and *C*(5)H], 101.7, 101.9 [*C*(2)H], 119.6, 119.9, 127.4, 127.5, 129.0, 129.4, 130.7, 131.0 (aromatic *C*H), 133.6, 133.8, 135.0, 135.1 (aromatic *C*), 166.0, 166.1 (*C*O); MS *m/z* 357 (M^+, 2%), 267 (4%), 115 {100%, $[CCH_3(OCHCH_3)_2]^+$}.

Intramolecular nucleophilic addition

5,6-Dihydro-1,4-oxathiine-2-carboxanilide 46a

n-Butyllithium (1.19 mL, 1.9 mmol) was added to a solution of HMDS (0.53 mL, 1.99 mmol), in THF (8 mL) at 0 °C and the reaction mixture was stirred for 20 min. This solution was added dropwise to a stirred solution of *N*-phenyl-*Z*-3-chloro-2-[2-(hydroxyethyl)thio]propanamide **46a** (0.45 g, 1.73 mmol) in THF (5 mL) also at 0 °C. The flask was removed from the ice bath and the reaction temperature was allowed to increase to room temperature. Stirring was continued for 48 h followed by quenching with saturated aqueous ammmonium chloride (10 mL). CH_2Cl_2 (20 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was washed with brine (3 × 20 mL), dried and evaporated to

dryness to give a viscous oil (367 mg, quantitative). Purification by chromatography using ethyl acetate-CH_2Cl_2-hexane (25:5:70) as eluent gave **46a** (156 mg, 41%) as a yellow crystalline solid; mp 131−133 °C; (Found C, 59.60; H, 5.07; N, 5.96; S, 14.72. $C_{11}H_{11}NO_2S$ requires C, 59.71; H, 5.01; N, 6.33; S, 14.49%); ν_{max}/cm^{-1} (KBr) 3216 (br NH), 1632, 1602 (CO α,β-unsaturated amide); δ_H (270 MHz, $CDCl_3$) 3.01 (2H, dd, *J* 5, 5, C*H*$_2$S), 4.42 (2H, dd, *J* 5, 5, C*H*$_2$O), 7.07-7.64 (5H, m, Ar*H*), 7.64 (1H, br s, N*H*), 7.75 [1H, s, C(3)*H*=]; δ_C (67.8 MHz, $CDCl_3$) 24.1 (*C*H$_2$S), 66.3 (*C*H$_2$O), 101.8 (S*C*=), 119.9, 124.2, 129.0 (aromatic *C*H), 137.8 (aromatic *C*), 148.5 (O*C*H=), 162.6 (*C*O); MS *m/z* 221 (M^+, 50%), 129 (100%, M^+ -PhNH), 93 [82%, $(PhNH_2)^+$], 101 (18%, M^+ -CONHPh), 77 (32%).

Sulfur Nucleophiles

***N*-(4-Methylphenyl)-2,3-di(phenylthio)propenamide 47a**

A) Using thiophenolate anion

n-Butyllithium (0.45 mL, 1.6 M in hexane, 0.73 mmol) was added to a stirred solution of thiophenol (81 μl, 0.79 mmol) in THF (2 mL) at 0 °C. After stirring for 10 min at 0 °C and for 20 min at room temperature, a solution of **1a** (0.20 g, 0.66 mmol) in THF (3 mL) was added. After 2 h a further equivalent of lithium thiophenolate [from *n*-butyllithium (0.41 mL, 1.6 M in hexane, 0.66 mmol) and thiophenol (75 μl, 0.73 mmol)] was added. The reaction was complete by TLC analysis after 6 h and saturated aqueous ammonium chloride (10 mL) and ether (20 mL) were added. The phases were separated, the aqueous phase was extracted with ether (2 × 10 mL) and the combined organic layers were washed with brine (3 × 10 mL), dried and evaporated. Trituration with hexane gave **47a** (165 mg, 66%) as a white, crystalline solid; mp 108−110 °C; spectroscopic characteristics are identical to those described previously.[15]

B)Using thiophenol

Thiophenol (74 μl, 0.73 mmol) was added to a solution of **1a** (0.20 g, 0.66 mmol) in toluene (4 mL). The reaction mixture was stirred initially at room temperature for 2 h and

then at reflux for 7h. CH_2Cl_2 (10 mL) was added and the organic phase was washed with aqueous NaOH (1 M, 2 × 10 mL), water (10 mL), brine (10 mL), dried and evaporated. Purification by chromatography using ethyl acetate-hexane (5:95) as eluent gave **47a** (90 mg, 36%) as a white, crystalline solid; mp 108−110 °C; spectroscopic characteristics are identical to those described previously.[15]

Selenium Nucleophiles

***N*-(4-Methylphenyl)-*Z*-3-(phenylseleno)-2-(phenylthio)propenamide 50a**

Sodium borohydride (25 mg, 0.66 mmol) was added portionwise to a stirred solution of diphenyl diselenide (99 mg, 0.33 mmol) in dry ethanol (2 mL). The solution turned colourless indicating the formation of sodium phenylselenide. This solution was transferred by cannula to a stirred solution of **1a** (0.20 g, 0.66 mmol) in dry ethanol (3 mL). The reaction was complete by TLC analysis after stirring at room temperature for 16 h and water (10 mL) was then added to quench the excess reagent. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried and evaporated. Purification by chromatography using ethyl acetate-hexane (5:95) as eluent gave **50a** (0.17 g, 60%) as a light yellow, crystalline solid; mp 86−88 °C; (Found C, 62.50; H, 4.56; N, 3.56; S, 8.01. $C_{22}H_{19}NOSSe$ requires C, 62.26; H, 4.51; N, 3.30; S, 7.55%); ν_{max}/cm^{-1} (KBr) 3253 (br NH), 1643, 1593 (CO α,β-unsaturated amide); δ_H (270 MHz, $CDCl_3$) 2.28 (3H, s, ArC*H*$_3$), 7.06-7.64 (9H, m, Ar*H*), 8.69 (1H, br s, N*H*), 9.04 [1H, s, C(3)*H*=]; δ_C (67.8 MHz, $CDCl_3$) 20.9 (Ar*C*H$_3$), 119.9 (aromatic *C*H), 122.7 (aromatic *C* or S*C*=), 126.8, 127.4, 128.6, 129.5, 130.1, 131.2 (aromatic *C*H), 132.9 (aromatic *C* or S*C*=), 133.4, 133.5 (aromatic *C*H), 134.2, 135.1 (aromatic *C* or S*C*=), 157.0 [*C*(3)H=], 160.5 (*C*O); MS *m/z* 425 (M^+, 100%), 377 (21%), 348 (1%, M^+-Ph), 268 (33%, M^+-PhSeH), 134 [100%, $(PhS{=}C{=}CH)^+$].

Acknowledgements

IRCSET, Forbairt, Merck and University College Cork are gratefully acknowledged for funding of this work. The authors wish to thank final year project students M. Brennan,

D. Foley and F. O'Donoghue for input on some aspects of this work. Rigaku are acknowledged for crystal structure determination of **24a**.

1. P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis (Tetrahedron Organic Chemistry)*, Permagon Press, Oxford, **1992**.
2. B.E.Rossiter and N.M.Swingle, *Chem.Rev.*, **1992**, *92*, 771.
3. J.Comelles, M.Moreno-Manas, and A.Vallribera, *Arkivoc*, **2005**, 207.
4. H.C.Guo and J.A.Ma, *Angew.Chem., Int.Ed.*, **2006**, *45*, 354.
5. V. J. Lee, *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I. eds., Permagon Press, New York, **1991**, Chapter 1.2.
6. Z.Rappoport, *Acc.Chem.Res.*, **1981**, *14*, 7.
7. Z.Rappoport and A.Gazit, *J.Org.Chem.*, **1985**, *50*, 3184.
8. B.Avramovitch, P.Weyerstahl, and Z.Rappoport, *J.Am.Chem.Soc.*, **1987**, *109*, 6687.
9. A.M.Aguiar and D.J.Daigle, *J.Org.Chem.*, **1965**, *30*, 3527.
10. D.Dodd, M.D.Johnson, B.S.Meeks, D.M.Titchmarsh, K.Nguyen Van Duong, and A.Gaudemer, *J.Chem.Soc., Perkin Trans.2*, **1976**, 1261.
11. C.V.Maffeo, G.Marchese, F.Naso, and L.Ronzini, *J.Chem.Soc., Perkin Trans.1*, **1979**, 92.
12. Z.Rappoport and A.Topol, *J.Chem.Soc., Perkin Trans.2*, **1975**, 982.
13. J.C.Chalchat and F.Theron, *Bull.Soc.Chim.Fr.*, **1974**, 953.
14. J.D.Park and E.W.Cook, *Tetrahedron Lett.*, **1965**, 4853.
15. M.Murphy, D.Lynch, M.Schaeffer, M.Kissane, J.Chopra, E.O'Brien, A.Ford, G.Ferguson, and A.R.Maguire, *Organic & Biomolecular Chemistry*, **2007**, *5*, 1228.
16. M.Kissane, D.Lynch, J.Chopra, S.E.Lawrence, and A.R.Maguire, *Tetrahedron: Asymmetry*, **2008**, *19*, 1256.
17. M.Kissane, S.E.Lawrence, and A.R.Maguire, *Tetrahedron Asymmetry*, **2010**, *21*, 871.
18. M.Kissane, S.E.Lawrence, and A.R.Maguire, *Org.Biomol.Chem.*, **2010**, *8*, 2735.

19. M.Kissane, S.E.Lawrence, and A.R.Maguire, *Tetrahedron*, **2010**, *66*, 4564.

20. M. E. Jung, *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I. eds., Premagon Press, New York, **1991**, Chapter 1.1.

21. H.Nagashima, N.Ozaki, M.Washiyama, and K.Itoh, *Tetrahedron Lett.*, **1985**, *26*, 657.

22. J.L.Coke, H.J.Williams, and S.Natarajan, *J.Org.Chem.*, **1977**, *42*, 2380.

23. R.K.Dieter and L.A.Silks, III, *J.Org.Chem.*, **1986**, *51*, 4687.

24. S.W.Wright, J.J.Petraitis, B.Freimark, J.V.Giannaras, M.A.Pratta, S.R.Sherk, J.M.Williams, R.L.Magolda, and E.C.Arner, *Bioorg.Med.Chem.*, **1996**, *4*, 851.

25. G.Cardillo and C.Tomasini, *Chem.Soc.Rev.*, **1996**, *25*, 117.

26. N.Sudhakar, G.Srinivasulu, G.S.Rao, and B.V.Rao, *Tetrahedron: Asymmetry*, **2008**, *19*, 2153.

27. H.K.Hall, Jr., *J.Org.Chem.*, **1964**, *29*, 3539.

28. Rajappa *et al.* have reported that the chemical shift of an enamine proton which is hydrogen bonded to oxygen is shifted downfield relative to the non-hydrogen bonded proton (A.N. Dixit, K.V. Reddy, A.R. Deshmukh, S. Rajappa, B. Ganguly, J. Chandrasekhar, *Tetrahedron*, **1995**, *51*, 1437)

29. S.Cossu, O.De Lucchi, F.Fabris, R.Ballini, and G.Bosica, *Synthesis*, **1996**, 1481.

30. C.Guillot and C.Maignan, *Tetrahedron Lett.*, **1991**, *32*, 4907.

31. D.K.Kim, K.Kim, J.Lim, and K.H.Kim, *J.Heterocycl.Chem.*, **1995**, *32*, 1625.

32. S.Blaya, R.Chinchilla, and C.Najera, *Tetrahedron*, **1995**, *51*, 3617.

33. R.Rossi, F.Bellina, and A.Carpita, *Synlett*, **1996**, 356.

34. J.Peralta, J.P.Bullock, R.W.Bates, S.Bott, G.Zepeda, and J.Tamariz, *Tetrahedron*, **1995**, *51*, 3979.

35. S.Zapf, A.Werle, T.Anke, D.Klostermeyer, B.Steffan, and W.Steglich, *Angew.Chem., Int.Ed.Engl.*, **1995**, *34*, 196.

36. K.A.Wood, D.A.Kau, S.K.Wrigley, R.Beneyto, D.V.Renno, A.M.Ainsworth, J.Penn, D.Hill, J.Killacky, and P.Depledge, *J.Nat.Prod.*, **1996**, *59*, 646.

37. A.Alexakis and P.Mangeney, *Tetrahedron: Asymmetry*, **1990**, *1*, 477.

38. T.Tsunoda, M.Suzuki, and R.Noyori, *Tetrahedron Lett.*, **1980**, *21*, 1357.

39. I.Coric, S.Vellalath, and B.List, *J.Am.Chem.Soc.*, **2010**, *132*, 8536.

40. M.Kissane, M.Murphy, D.Lynch, A.Ford, and A.R.Maguire, *Tetrahedron*, **2008**, *64*, 7639.

41. D.Enders, K.Luettgen, and A.A.Narine, *Synthesis*, **2007**, 959.

42. S.Santoro, B.Battistelli, L.Testaferri, M.Tiecco, and C.Santi, *Eur.J.Org.Chem.*, **2009**, 4921.

43. K.B.Sharpless and R.F.Lauer, *J.Am.Chem.Soc.*, **1973**, *95*, 2697.