# Investigation of the chemoselective and enantioselective oxidation of α-thio-β-chloroacrylamides

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**Abstract**

Investigation of the chemoselective and enantioselective oxidation of α-thio-β-chloroacrylamides is described. The α-thio-β-chloroacrylamides can be selectively oxidized to either the racemic sulfoxide or the sulfone very efficiently. The asymmetric sulfur oxidation of α-thio-β-chloroacrylamides is also discussed, with sulfoxide enantioselectivites of up to 52% ee achieved using the Kagan oxidation, and up to 71% ee when the Bolm oxidation is employed. While the enantioselectivities achieved are modest, these are among the most highly functionalised sulfides investigated in catalytic asymmetric oxidation, and the resulting enantioenriched sulfoxides have significant synthetic potential.

## Introduction

Sulfoxides and sulfones are widely used in organic synthesis, particularly in carbon-carbon bond forming reactions.[1] These compounds are almost invariably prepared by oxidation of the corresponding thioethers. A variety of oxidants have been employed for this transformation.[2] Among the more common oxidants are *m*CBPA,[3] CHP,[4] $NaIO_4$,[5] MMPP,[6] oxone®,[7] $H_2O_2$[2] and $MnO_4^-$.[8]

The asymmetric synthesis of sulfoxides has received particular attention in recent years as the sulfoxide moiety has been shown to provide excellent stereochemical control as a chiral auxiliary. Also, many enantiopure sulfoxides are known to have high biological activity.[9] Several methods are available for the preparation of optically active sulfoxides. The most

generally used method is the Andersen method, which involves nucleophilic addition of alkyl or aryl ligands to diastereochemically pure chiral sulfinates.[10] Despite the high yields of enantiopure sulfoxides obtained using this method, its scope is limited due to the difficult preparation and limited availability of suitable chiral precursors. The development of chiral precursors that possess two leaving groups[11,12] and the use of carbanionic leaving groups[13] has extended the scope of this methodology.

An attractive alternative to nucleophilic displacement is asymmetric sulfur oxidation. Very efficient biological sulfide oxidations have been reported using both whole cell systems and isolated enzymes.[14,15] Metal-free asymmetric sulfur oxidation has been reported using oxaziridines[16] and hydroperoxides.[17] The most popular route to asymmetric sulfur oxidation is metal-catalysed oxidation. The titanium-based Kagan oxidation method was first reported in the 1980's and is one of the most widely used oxidation methods; the amount of water present in these reactions must be very carefully controlled.[18] The use of titanium/BINOL complex was later reported by Uemura *et al.*[19,20] A robust oxidation method based on vanadium was reported by Bolm and Bienewald in 1995.[21] This method involves the *in situ* formation of a catalyst from vanadyl acetylacetonate and a Schiff base. The oxygen source is hydrogen peroxide and critically the reaction is not moisture sensitive. Due to its ease of use, this method has attracted a lot of attention recently, including investigation of the nature of the species involved.[22,23]

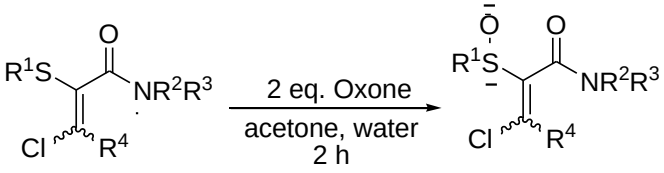
Following our recent report[24] of the highly efficient and stereoselective transformation of α-thioamides to the corresponding α-thio-β-chloroacrylamide derivatives on treatment with NCS, we describe here the chemoselective and stereoselective oxidation of the β-chloroacrylamides to the sulfoxide and sulfone levels to extend the scope of this methodology. While the enantioselectivities achieved in oxidation to the sulfoxide derivatives are modest (up to 71% ee), these are among the most highly functionalised sulfides investigated in catalytic asymmetric oxidation, and the resulting enantioenriched sulfoxides have significant synthetic potential, for example as Michael acceptors, dienophiles or dipolarophiles.[25] Asymmetric oxidation of aryl methyl sulfides is readily achieved with high enantioselectivity using the Kagan and Bolm methods, among others; however, successful extension to differently substituted sulfides, or sulfides bearing additional functionality, has been remarkably limited.

## Results and Discussion

### Oxidation of the β-chloroacrylamides to the racemic sulfoxide

The chemoselective oxidation of **1a** to the racemic sulfoxide was investigated using a range of oxidizing reagents. The use of $H_2O_2$, $KMnO_4$, peracetic acid and MMPP led to the recovery of the starting material **1a**, while *m*CPBA gave a 1:1 mixture of sulfide and sulfoxide. Employing 2 equivalents of oxone® as oxidant in an acetone/water mixture led to complete conversion to the sulfoxide **2a**, and this reaction has been extended to a series of derivatives as summarized in Table 1. While most of the compounds explored had *Z* stereochemistry, oxidation of a number of *E* isomers was also undertaken equally efficiently and selectively. Critically, there was no evidence of sulfone formation in any instance.

Table 1: Oxidation to the racemic sulfoxide




| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *E/Z* | Product | % Yield[Y] |
|---|---|---|---|---|---|---|
| Ph | Tol | H | H | *Z* | **2a** | 96 |
| Ph | Bn | H | H | *Z* | **2b** | 98 |
| Ph | *i*-Pr | H | H | *Z* | **2c** | 98 |
| Ph | Et | H | H | *Z* | **2d** | 57 |
| Ph | *n*-Bu | H | H | *Z* | **2e** | 98 |
| Ph | Allyl | H | H | *Z* | **2f** | 98 |
| Ph | H | H | H | *Z* | **2g** | 92 |
| Ph | 4-F-$C_6H_4$ | H | H | *Z* | **2h** | 95 |
| Ph | Me | Me | H | *E* | **2i** | 98 |
| *n*-Bu | 4-F-$C_6H_4$ | H | H | *Z* | **2j** | 95 |
| *n*-Bu | *n*-Bu | H | H | *Z* | **2k** | 80 |
| *n*-Bu | Bn | H | H | *Z* | **2l** | 68 |
| *n*-Bu | Tol | H | H | *Z* | **2m** | 67 |
| *n*-Bu | Ph | H | H | *Z* | **2n** | 76 |
| 4′-$MeOC_6H_4$ | Tol | H | H | *Z* | **2o** | 84 |
| 4′-$MeOC_6H_4$ | Bn | H | H | *Z* | **2p** | 93 |
| 4′-$MeOC_6H_4$ | Et | H | H | *Z* | **2q** | 96 |
| 4′-$NO_2C_6H_4$ | Tol | H | H | *Z* | **2r** | 84 |
| *i*-Bu | 4-F-$C_6H_4$ | H | H | *Z* | **2s** | 92 |
| *i*-Pr | 4-F-$C_6H_4$ | H | H | *Z* | **2t** | 88 |
| Me | 4-F-$C_6H_4$ | H | H | *Z* | **2u** | 92 |
| Me | *n*-Bu | H | H | *Z* | **2v** | 85 |
| Me | Bn | H | H | *Z* | **2w** | 82 |
| Bn | Bn | H | H | *Z* | **2x** | 79 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bn | 4-F-$C_6H_4$ | H | H | *Z* | **2y** | 65 |
| Bn | *n*-Bu | H | H | *Z* | **2z** | 58 |
| Bn | Tol | H | H | *Z* | **2aa** | 72 |
| Bn | Me | H | H | *Z* | **2ab** | 76 |
| Bn | Ph | H | H | *Z* | **2ac** | 76 |
| Bn | H | H | H | *Z* | **2ad** | 46 |
| Bn | Me | Me | H | *E* | **2ae** | 75 |
| Bn | Me | Me | H | *Z* | **2af** | 75 |
| Bn | 4-F-$C_6H_4$ | H | Me | *E* | **2ag** | 53 |
| Bn | 4-F-$C_6H_4$ | H | Me | *Z* | **2ah** | 83 |

ϒ Yields quoted are following purification by column chromatography or recrystallisation.

Each of the sulfoxides was isolated as a crystalline solid and purified by column chromatography or recrystallisation. The relative stereochemistry (*E*/*Z*) of the β-chloroacrylamides was retained on oxidation to the sulfoxides in all cases, as confirmed by single crystal X-ray crystallography of the *N*-ethyl derivative **2d** (Figure 1).

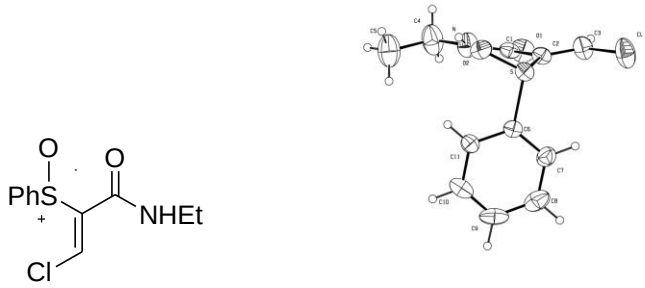



**Figure 1** A view of **2d** showing the structure and stereochemistry. Anisotropic displacement parameters are drawn at the 30% probability level.

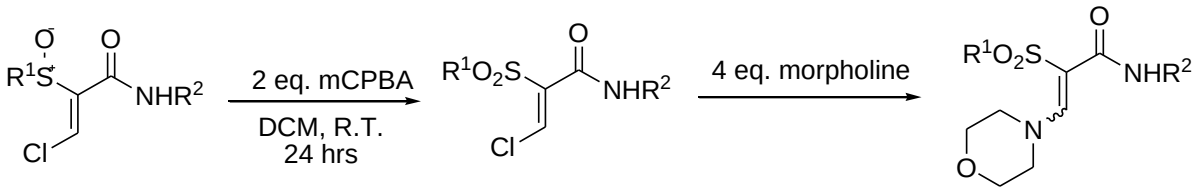
Analysis of the dihedral angles and rotation of the crystal structure illustrate that the sulfoxide moiety is twisted out of the plane of the acrylamide, presumably due to steric interactions between the phenyl ring of the sulfoxide and the chlorine atom. In all cases, an upfield shift in the $^1$H NMR spectrum of the β-hydrogen of approximately 0.15 ppm occurred on oxidation of the β-chloroacrylamides, reflecting a significant impact on the extent of resonance delocalization in the acrylamide system.

**Oxidation to the sulfone**

An investigation of the oxidation of the sulfoxide **2a** to the sulfone **3a** was undertaken with a range of oxidants, including $H_2O_2$, $KMnO_4$, peracetic acid, MMPP, Oxone® and *m*CPBA, with *m*CPBA the only oxidant resulting in oxidation to the sulfone. While the crude products were relatively clean by NMR, with sulfoxide oxidation complete, isolation of analytically pure sulfones from the oxidations is challenging, principally as the labile sulfones, potent Michael Acceptors, are not stable on silica gel. To overcome this issue, morpholine was added to the crude sulfones, triggering a substitution process to the β-amino derivatives as illustrated in Table 2. Critically, the morpholine adducts, which are stabilized by extensive delocalistion, are readily purified and characterized.

Following this protocol, a series of sulfoxides were treated with 2 equivalents of mCPBA in DCM. Following stirring at room temperature for 24 hours, 4 equivalents of morpholine was added. TLC analysis indicated reaction completion after 15 minutes and following purification by column chromatography, the morpholine adduct of the sulfone **4** was isolated (see Table 2).

Table 2: Oxidation to the sulfone




| $R^1$ | $R^2$ | Sulfone | % Yield |
|---|---|---|---|
| Ph | Tol | **4a** | 68 |
| Ph | Me | **4b** | 30 |
| Bn | Bn | **4c** | 42 |
| Bn | 4-F-$C_6H_4$ | **4d** | 43 |
| Bn | *n*-Bu | **4e** | 63 |
| Bn | Tol | **4f** | 56 |
| Bn | Me | **4g** | 38 |
| Bn | Ph | **4h** | 56 |
| Bn | H | **4i** | 37 |
| *n*-Bu | Bn | **4j** | 38 |
| *n*-Bu | Tol | **4k** | 45 |
| *n*-Bu | Ph | **4l** | 54 |

In conclusion, chemoselective oxidation of the β-chloroacrylamides to either the sulfoxide or sulfone level is readily achieved. For ease of characteristion, the sulfones were trapped as adducts with morpholine.

**Asymmetric Sulfur Oxidation of the β-Chloroacrylamides**

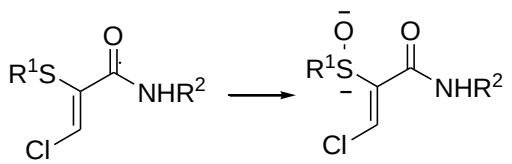
A number of methods for the enantioselective oxidation of the β-chloroacrylamides were examined, including Kagan Oxidation[18] and Bolm Oxidation.[21]

*Kagan Oxidation*

When the β-chloroacrylamide **1a** was oxidised under the standard Kagan conditions employing a ratio of $Ti(O^iPr)_4$ : (+)-DET : $H_2O$ : β–chloroacrylamide of 1 : 2 : 1 : 2, using cumene hydroperoxide (2 equivalents, *i.e.* equimolar with the sulfide) as oxidant, the conversion of the β-chloroacrylamide **1a** to the sulfoxide **2a** was determined to be 46% by $^1H$ NMR spectroscopy of the crude reaction product. Following removal of the 2-phenylpropan-2-ol by-product by distillation, the sulfoxide **2a** was isolated in 30% yield after chromatography on silica gel. However, the enantiomer ratio of the product was then determined to be just 12% ee by chiral HPLC. The standard Kagan oxidation of methyl tolyl sulfide using the same reagents was undertaken to ensure the oxidising agent was correctly formed. Methyl tolyl sulfoxide was isolated in 84% ee, a value which compares quite favourably with the reported value of 89% ee.[26]

Extension of the initial work with sulfoxide **2a** to the enantioselective oxidation of a series of β-chloroacrylamides using the Kagan reagent was next undertaken as summarized in Table 3. In all cases, with the exception of entry 10, (+)-DET was used and the *S*-sulfoxide series was formed.

Table 3: Asymmetric Oxidation using the Kagan Oxidation




| 1 | **$R^1$** | **$R^2$** | **Method** | **Sulfoxide** | **% Conv.†** | **% Yield‡** | **% ee§** | **[α]ϒ** |
|---|---|---|---|---|---|---|---|---|
| 2 | Ph | Tol | A | **2a** | 46 | 30 | 12 | - |
| 3 | Ph | Et | A | **2d** | 0 | - | - | - |
| 4 | *n*-Bu | Bn | A | **2l** | 0 | - | - | - |
| 5 | 4-$NO_2$-$C_6H_4$ | Tol | A | **2r** | 20 | 9 | 4 | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 | 4-MeO-$C_6H_4$ | Tol | A | **2o** | 40 | 28 | 30¶ | - |
| 7 | *n*-Bu | Tol | A | **2m** | 60 | 49 | 51 | -84 |
| 8 | Ph | 4-F-$C_6H_4$ | A | **2h** | 60 | 40 | 25 | - |
| 9 | *n*-Bu | 4-F-$C_6H_4$ | A | **2j** | 100 | 68 | 51 | -98 |
| 10 | *n*-Bu | 4-F-$C_6H_4$ | A | **2j** | 100 | 68 | 52 | +94 |
| 11 | Me | Tol | A | **2ai** | 100 | 66 | 39 | -72 |
| 12 | Me | 4-F-$C_6H_4$ | A | **2u** | 72 | 65 | 43 | - |
| 13 | *i*-Bu | 4-F-$C_6H_4$ | A | **2s** | 75 | 68 | 17 | |
| 14 | *i*-Bu | Tol | A | **2aj** | 73 | 65 | 7 | |
| 15 | Ph | Tol | B | **2a** | 13 | 9 | 15 | - |

Method A: Standard Kagan oxidation using (+)-DET except entry 10, which used (-)-DET

Method B: Modified Kagan oxidation using 0.1 equivalents of the catalyst

† As determined by $^1$H NMR spectroscopy of the crude product mixture

‡ Yield after chromatography on silica gel

§ Enantiomer ratios were determined by chiral HPLC using IPA/hexane as mobile phase on a Chiralcel AS column detected at λ 254 nm

ϒ All optical rotations were recorded as solutions in DCM (c 1.3-2.0)

¶ As determined by chiral shift NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent

Significantly, oxidation is only observed for *N*-aryl derivatives, with partial or complete oxidation to the sulfoxides seen under the standard Kagan oxidation conditions, albeit with modest enantioselectivity.

Investigation of the impact of substitution on the phenylthio group was first explored. Introduction of *p*-nitro or methoxy groups resulted in a decrease in the efficiency of oxidation, but the enantioselectivity altered significantly, reflecting the variation in the electronic properties of the sulfide. In the presence of 4-MeO-$C_6H_4$ group (Table 3, entry 6), an increase in selectivity to 30% ee resulted, while in the presence of 4-$NO_2$-$C_6H_4$ group (Table 3, entry 5) a decrease to 4% ee resulted, *c.f.* 12% ee in the unsubstituted derivative (Table 3, entry 1).

Investigation of the alkylthio derivatives proved interesting. Replacement of the phenylthio moiety with the more electron donating *n*-butylthio group resulted in improved conversion

and enantioselectivity (Table 3, entry 7), with 51% ee achieved on employment of the *N*-tolyl group.

The effect of the nature of the amide group was next examined. It had already been shown that on replacement of *N*-tolyl amide with the relatively less electron withdrawing *N*-benzyl or *N*-ethyl group, no oxidation occurred. We thus decided to look at incorporating a more electron withdrawing amide by synthesizing the *N*-4-fluoroaniline phenylthio and *n*-butylthio derivatives.

When the β-chloroacrylamides **1h** and **1j** were exposed to the standard Kagan oxidation conditions, an improvement in both reaction efficiency and selectivity was recorded for both compounds compared to **1a**. For **1h** (Table 3, entry 8), the increase in the degree of conversion was moderate, up from 46% for **1a** to 60% for **1h**, as was the increase in the enantioselectivity, up from 12% ee for **1a** to 25% ee for **1h**. Some of the sulfoxide (+)-**2h** isolated from the oxidation of **1h** was recrystallised from ether/hexane and the mother liquor was found to contain (+)-**2h** in 32% ee. Subsequent analysis of the solid isolated from the recrystallisation showed the sulfoxide precipitates racemically.

The use of **1j** (Table 3, entry 9) gave much better results than those obtained with any other β-chloroacrylamide. Complete conversion of the β-chloroacrylamide **1j** to the corresponding sulfoxide **2j** occurred, with **2j** isolated in 68% yield after removal of the 2-phenyl-2-propanol and chromatography of the residue on silica gel. Analysis of the enantiomer ratio of the material by chiral HPLC showed almost identical selectivity to that seen with **2m**, with the sulfoxide **2j** having 51% ee. The result of this reaction suggests that the amide substituent is important in relation to the extent of oxidation achieved, while the enantioselectivity of the reaction is determined by the nature of the sulfide moiety.

On scale up of this reaction to 2 mmol of the β-chloroacrylamide **1j**, the enantioselectivity was virtually identical to that obtained in the smaller scale (0.70 mmol) reactions. When the opposite (-)-enantiomer of diethyl tartrate was employed in preparing the catalyst complex, as expected the opposite enantiomer of the sulfoxide **2j** predominated in the product. Analysis of this material by chiral HPLC showed the material to again have 52% ee, with the *R*-enantiomer predominant. As the sulfoxide **2j** is an oil, recrystallisation of the product to increase the enantiomer ratio was not possible.

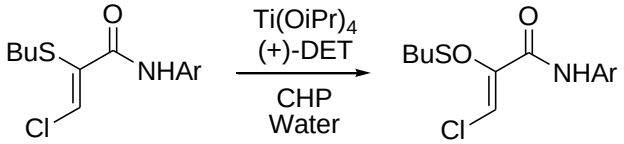
The effect of the sulfide substituent of the β-chloroacrylamide on the outcome of the asymmetric oxidation, using the Kagan procedure, has been shown above to be quite significant. As replacement of the arylthio substituent with *n*-butyl thio resulted in significantly improved enantioselectivity, further investigation of *N*-alkyl thio derivatives was undertaken. The methanethio sulfides **1ai** and **1u** were investigated, as the optimum results in sulfur oxidation have been achieved with methyl aryl sulfides, while the *i*-butyl derivatives **1s** and **1aj** were explored to determine the impact of branching in the alkylthio chain on the enantioselective oxidation.

When the methanethio derivatives **1ai** and **1u** were subjected to the standard Kagan oxidation conditions, a decrease in enantioselectivity was observed when compared to the *n*-butylthio derivatives (Table 3, entries 11 & 12), while Kagan oxidation of the *i*-butyl sulfides **1s** and **1aj** led to recovery of the corresponding *S*-iso butyl sulfoxides **2s** and **2aj** with poor enantiomer ratios of 17% ee and 7% ee respectively (Table 3, entries 13 & 14). Clearly, branching had a detrimental effect on the enantioselectivity, while interestingly the methanethio derivatives did not mimic methyl aryl sulfides.

In 1996, Kagan published a truly catalytic version of his chiral titanium derived catalyst for the asymmetric oxidation of sulfides to sulfoxides.[27] The complex employed differed from the original system in that water was replaced with 4 equivalents of isopropanol, 1 equivalent of 4A molecular sieves were added and the overall ratio of the catalyst complex to the sulfide was reduced from 2:1 to 0.1:1. Oxidation of **1a** and **1m** was attempted using this procedure. Oxidation of **1a** using this method resulted in poorer conversion to the sulfoxide **2a**, with a slight increase in the enantioselectivity to 15% ee (Table 3, entry 15). No oxidation occurred when **1m** was employed using this method.

In a 1995 paper, Kagan[28] explored the possibilities of increasing the selectivity of the oxidation by varying parameters such as temperature, time, rate of addition and aging of the catalyst complex. Up to this point, the optimum conditions as reported in an Organic Synthesis paper[26] had been employed. It was clear that in order to increase the selectivity of the reaction for the optimum substrate **1j**, we needed to further examine the oxidation conditions. To this end, a number of reactions were conducted, as outlined in Table 4, where temperature, the number of equivalents of the titanium complex and the rate of addition of the oxidant were examined.

Table 4 Optimisation of Kagan Oxidation of **1j**




Ar = 4-F-$C_6H_4$

| Conditions | Conversion[a] | ee[b] |
|---|---|---|
| Standard conditions<br>1:1:2:2:2 ratio of Ti:Water:DET:Sulfide:Oxidant[c]<br>Reagent prepared as described[c], CHP added in one lot at –20 °C | >95% | 53%[d] |
| CHP added in 6 portions over 1 hour | >95% | 52% |
| Full equivalent of titanium complex | >95% | 51% |
| Full equiv. of Ti complex and CHP added in 6 portions over 1hr | >95% | 52% |
| Reaction conducted at –50 °C for 18 hours | 30% | 37% |
| Reaction conducted at 4 °C for 18 hours | >95% | 40% |
| Reaction conducted at room temperature for 18 hours | >95% | 32% |
| Standard conditions[c] on 2.00 mmol scale | >95% | 51% |
| Standard conditions[c] using (-)-DET | >95% | 52%[e] |

a: As estimated by $^1$H NMR spectroscopy at 60MHz in $CDCl_3$ of the crude reaction mixture.

b: As estimated by chiral HPLC using a Chiralcel AS column at ambient temperature in 90/10 hexane/isopropanol, detection at 254nm.

c: As reported by Kagan, H. B. *et al*[26]

d: An optical rotation of this sample was recorded; $[\alpha]_{20}^{D}$ -98 (c 1.3 in DCM)

e: As expected, the enantioselectivity in the sulfoxide was reversed; $[\alpha]_{20}^{D}$ +94 (c 1.7 in DCM).

The conclusion which can be drawn from these experiments is that none of the modifications resulted in improved enantioselectivity relative to the standard Kagan conditions. Addition of the oxidant, CHP, in 6 portions over 1 hour, use of a full equivalent of the titanium complex and a combination of both all gave material with effectively the same enantioselectivity. Only when the reaction was conducted at lower temperature (-50 °C) was less than complete conversion obtained and the slower rate of the reaction was accompanied by a reduction in enantioselectivity. Conducting the reaction at 4 °C or at room temperature also gave poorer

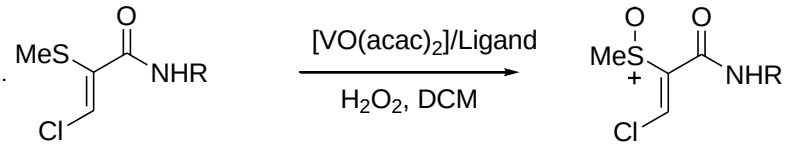
enantioselectivity, suggesting that –20 °C is at or near the optimum temperature for the oxidation, as reported by Kagan.[26]

In summary, the optimum enantioselectivity achieved with the Kagan oxidation was 51% ee with the *n*-butyl thio derivative **2j**. Interestingly, only *N*-aryl amides undergo the oxidation. Enantioselectivity is enhanced by the presence of the *N*-4-fluoroaniline substituent.

*Bolm Oxidation*

Asymmetric oxidation of the β-chloroacrylamides using the Bolm method was also explored. Initially, a number of reactions were conducted on the *S*-methyl derived β-chloroacrylamides, where the influence of temperature, scale and ligand was examined in detail (Table 5).

Table 5: Bolm Oxidation of the S-Methyl β-Chloroacrylamides

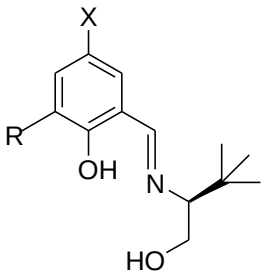



R=4-F-$C_6H_4$ **1v** **2v**
R=*n*-Bu **1v** **2v**
R=Bn **1w** **2w**

| Entry | R | Ligand | Temp. (°C) | %Conversion[1] | Yield[2] (%) | Enantioselectivity[3] (% ee) |
|---|---|---|---|---|---|---|
| 1 | 4-F-$C_6H_4$ | **5a** | ambient | 72 | 51 | 45 |
| 2 | 4-F-$C_6H_4$ | **5a** | 0 | 100 | 70 | 71 |
| 3 | 4-F-$C_6H_4$ | **5a** | -20 | 100 | 81 | 69 |
| 4 | 4-F-$C_6H_4$ | **5a** | -30 | 100 | 73 | 61 |
| 5[4] | 4-F-$C_6H_4$ | **5a** | -20 | 100 | 81 | 71 |
| 6[5] | 4-F-$C_6H_4$ | **5a** | -20 | 100 | 82 | 53 |
| 7[5] | 4-F-$C_6H_4$ | **5a** | -20 | 100 | 85 | 62 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8[5] | 4-F-$C_6H_4$ | **5a** | -20 | 100 | 82 | 63 |
| 9 | 4-F-$C_6H_4$ | **5b** | ambient | 100 | 67 | 72 |
| 10 | 4-F-$C_6H_4$ | **5b** | -20 | 60 | 41 | 60 |
| 11 | 4-F-$C_6H_4$ | **5c** | ambient | 100 | 87 | 23 |
| 12 | 4-F-$C_6H_4$ | **5d** | ambient | 95 | 66 | 71 |
| 13 | 4-F-$C_6H_4$ | **5d** | -20 | 60 | 41 | 61 |
| 14 | 4-F-$C_6H_4$ | **5e** | ambient | 95 | 62 | 66 |
| 15 | 4-F-$C_6H_4$ | **5e** | -20 | 68 | 51 | 70 |
| 16 | 4-F-$C_6H_4$ | **5f** | ambient | 85 | 71 | 70 |
| 17 | 4-F-$C_6H_4$ | **5f** | -20 | 100 | 86 | 71 |
| 18 | 4-F-$C_6H_4$ | **5g** | ambient | 100 | 82 | 70 |
| 19 | 4-F-$C_6H_4$ | **5g** | -10 | 100 | 85 | 51 |
| 20 | 4-F-$C_6H_4$ | **5h** | ambient | 47 | 30 | 36 |
| 21 | 4-F-$C_6H_4$ | **5h** | 0 | 45 | 32 | 30 |
| 22 | 4-F-$C_6H_4$ | **5h** | -10 | 40 | 37 | 20 |
| 23 | 4-F-$C_6H_4$ | **5h** | -20 | 51 | 32 | 71[7] |
| 24 | 4-F-$C_6H_4$ | **5i** | ambient | 44 | 32 | 24 |
| 25 | 4-F-$C_6H_4$ | **5i** | 0 | 40 | 30 | 34 |
| 26 | 4-F-$C_6H_4$ | **5i** | -10 | 80 | 55 | 68 |
| 27 | 4-F-$C_6H_4$ | **5i** | -20 | 32 | 24 | 22 |
| 28 | 4-F-$C_6H_4$ | **5j** | ambient | 100 | 88 | 56 |
| 29 | 4-F-$C_6H_4$ | **5j** | -20 | 100 | 87 | 56 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 30 | Bn | **5a** | ambient | 62 | 50 | 30 |
| 31 | Bn | **5a** | -10 | 100 | 85 | 61 |
| 32 | Bn | **5a** | -20 | 100 | 82 | 59 |
| 33 | *n*-Bu | **5a** | ambient | 40 | 31 | 35 |
| 34 | *n*-Bu | **5a** | -20 | 100 | 72 | 71 |
| 35[6] | *n*-Bu | **5a** | -20 | 20 | 7 | 71 |
| 36 | *n*-Bu | **5k** | -20 | 0 | - | - |




R=H, X=$NO_2$ **5a**

R=X=H **5b**

R=$Bu^t$, X=$NO_2$ **5c**

R=Me, X= H **5d**

R=H, X=Me **5e**

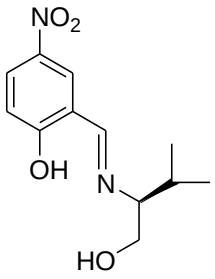
R=H, X=$Bu^t$ **5f**

R=H, X = Cl **5g**

R=X=I **5h**

R=X=Br **5i**

R=X=$Bu^t$ **5k**




**5j**

1. Estimated from integration of $^1$H NMR spectra of crude samples.

2. Yields quoted are following chromatography

3. Enantiomer ratios were determined using chiral HPLC using IPA/hexane as mobile phase on a Chiralcel AS column detected at λ 254 nm

4. This reaction was carried out on a 1g scale (4 mmol).

5. This reaction was carried out on a 2.5 g scale. On this scale the enantioselectivity of the product was seen to decrease even when the hydrogen peroxide was added over 16 hours using a syringe pump.

6. This reaction was worked up after 2 hours (16 hours in all other cases)

7. >98% ee was achieved on recrystallisation from 1:1 mixture of hexane/chloroform

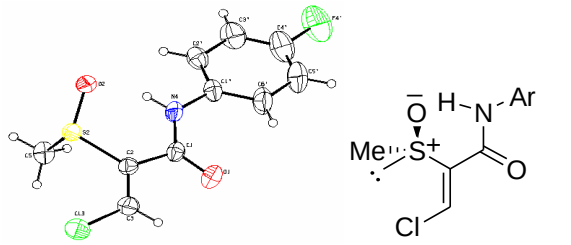
The initial reaction involved the oxidation of the *S*-methyl β-chloroacrylamide **1u** using the original Bolm conditions {1 mol% [$VO(acac)_2$], 1.5 mol% ligand, 1.1 eq. $H_2O_2$, rt, DCM} with ligand **5a**. $^1$H NMR spectroscopy of the crude reaction mixture showed 72% conversion of β-chloroacrylamide **1u** to the corresponding sulfoxide **2u**. Following chromatography, sulfoxide **2u** was isolated in 51% yield with 45% ee (Table 5, entry 1). Decreasing the temperature of the reaction increased the conversion (quantitative at -30 °C or 0 °C) and the ee of the resultant sulfoxide **2u**, with the optimum enantioselectivity obtained at -20/0 °C (Table 5, entries 1-4). This transformation was scaled up successfully from using 1 mmol (0.25 g) to 4 mmol (1.00 g) of β-chloroacrylamide **1u**, but when increased to 10 mmol, the enantioselectivity decreased slightly to 62 or 63% ee, even when the oxidant was added slowly over 16 h. The conversion (100%), yield (81%) and the enantioselectivity (71% ee) obtained on a 4 mmol scale were consistent with those obtained on a 1 mmol scale (Table 5, entry 3 versus entry 5).

Since the enantioenriched *S*-methyl sulfoxide **2u** is a solid, enhancement of the enantiomer ratio by recrystallisation was attempted. Following slow (*ca*. 2 weeks) vapour diffusion recrystallisation from chloroform/hexane (1:1), a number of distinct crystals were obtained. Analysis of the resulting crystals and the mother liquor showed that individual enantiopure crystals of **2u** could be obtained but this method was not practical for producing synthetically useful amounts of enantiopure **2u**.

The *S* absolute stereochemistry was determined by single crystal X-ray diffraction on an enantiopure crystal of **2u**. Critically, chiral LC demonstrated that this is the major enantiomer formed in the Bolm oxidation using the *S* ligand. The absolute stereochemistry of the other sulfoxide derivatives was assigned by analogy on the basis of similar profiles in chiral LC and direction of specific rotations. The *S* sulfoxides **2u-w**, are formed selectively

using the *S* ligand in the Bolm oxidation. This is consistent with the stereoselectivity which has been reported previously.[21,23,29]

**Figure 2:** A view of **2u** showing the structure and absolute stereochemistry. Anisotropic displacement parameters are drawn at the 30% probability level.




An investigation on the impact of the nature of the ligand on the Bolm oxidation of β-chloroacrylamide **1u** was then explored. Ligands **5a-k** were selected for investigation based on literature reports by Bolm and others.[21,30] For the Bolm oxidation of alkyl aryl sulfides, **5h** has proven to be highly enantioselective, with 97% ee achieved for methyl naphthylsulfoxide.[30] Sulfide oxidation of **1u** was achieved with varying efficiency and enantioselectivity using ligands **5a-k**.

In summary, the temperature at which optimum selectivity occurs varies depending on the structure of the ligand. For example, with **5h** 71% ee was achieved at -20 °C (Table 5, entry 23), while with **5d** similar enantioselectivity was achieved at room temperature (Table 5, entry 12).

Replacement of the *t*-Bu substitutent with *i*-Pr in **5j** resulted in efficient oxidation but decreased enantioselectivity relative to **5a** (56% ee versus 71% ee), highlighting the importance of a bulky substituent at this position. The presence of a H, Me or halo substituent at C-3 of the ligand is readily tolerated, but introduction of a *t*-Bu group at this position results in a dramatic decrease in enantioselectivity (Table 5, entry 11). The presence of a H, Me, *t*-Bu, $NO_2$ or halo substituent at C-5 can be tolerated. The optimum enantioselectivity with each of the ligands was 70-71% ee.

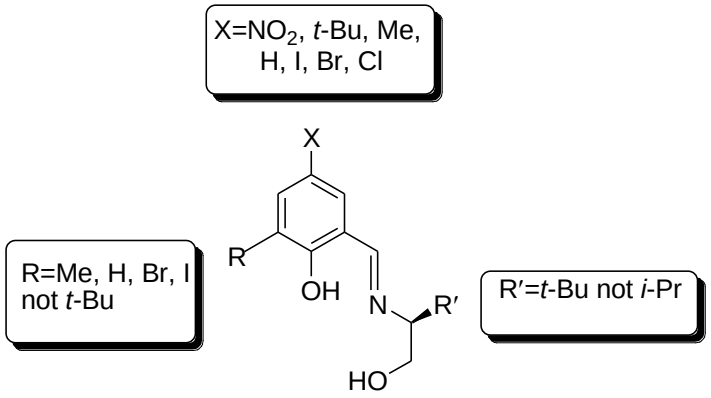


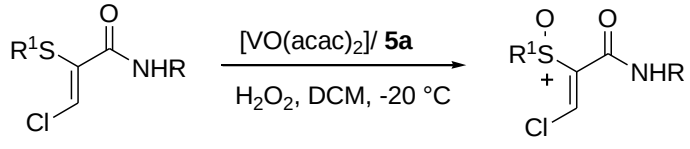

**Figure 3**

The impact of the electronic effect of the amide substituent was next investigated by replacing the *N*-aryl substituent with *N*-benzyl (**1w)** or *N*-alkyl (**1v)** using ligands **5a** and **5u.** In both oxidations with ligand **5a**, the conversions and the ee's tended to increase on decreasing the reaction temperature (Table 5, entries 30-35). Optimum enantioselectivities of 61% ee (**2w**) and 71% ee (**2v**) were achieved. When the oxidation of **1v** was repeated and worked up after 2 hours compared to 16 hours under standard conditions, the extent of conversion was significantly decreased, but critically the enantioselectivity of oxidation to the sulfoxide was unaffected, indicating that it is not affected by progress of the reaction.

The Bolm oxidation of β-chloroacrylamide **1v** was also conducted in the presence of ligand **5k** at -20 °C. Interestingly, the presence of the bulky t-butyl groups on ligand **5k** inhibited the reaction completely (Table 5, entry 36).

To investigate the impact of substrate structure on the Bolm oxidation, a study of the Bolm oxidation of β-chloroacrylamides **1s**, **1ak** and **1t** under various reaction conditions was then conducted, and the optimum results of this work are outlined in Table 6. The results obtained are similar to those obtained with the methanethio derivatives, with 67-71% ee achieved, indicating that increasing the steric hindrance adjacent to the sulfur does not noticeably affect the enantioselectivity.

Table 6: Bolm Oxidation of β-chloroacrylamides **1s**, **1ak** and **1t**



| $R^1$ | R | Sulfoxide | Eq. $H_2O_2$ | % Conversion† | % Yield‡ | Enantioselectivity (% ee)# |
|---|---|---|---|---|---|---|
| *i*-Bu | 4-F-$C_6H_4$ | **2s** | 2.0 | 73 | 59 | 67 |
| *i*-Bu | Tol | **2ak** | 1.1 | 91 | 72 | 71 |
| *i*-Pr | 4-F-$C_6H_4$ | **2t** | 1.1 | 100 | 76 | 71 |

†Estimated from integration of $^1$H NMR spectra of crude samples

‡Yields quoted are following chromatography

# Enantiomeric ratios were determined by chiral HPLC using IPA/hexane as mobile phase on a Chiralcel AS column detected at λ 254 nm

In summary, the outcome of the Bolm oxidation of the β-chloroacrylamides is rather insensitive to variation of the sulfide structure and the electronic properties of the ligand. The only significant effect observed during the course of this work was steric *i.e*. there was a dramatic fall off in the enantioselectivity of the sulfide oxidation in all cases when ligands **5c** and **5k**, both bearing a *t*-butyl group on the C-3 position of the aromatic ring, were employed in the Bolm oxidation of the β-chloroacrylamides. Interestingly, this contrasts with Bolm's results where he described higher enantioselectivity using ligand **5c** bearing the 3-*t*-butyl group compared to the less sterically hindered ligand **5a**.[21] However, in 2005 Zeng reported that ligands derived from 3,5-di-*tert*-butylsalicylaldehyde gave lower enantioselectivity in the sulfoxidation of thioanisole than those derived from less sterically hindered salicylaldehyde.[31] In general, the maximum enantioselectivity obtained for the sulfoxides was *ca.* 70% ee. However, the temperature at which this maximum occurred varied depending on the sulfide and ligand employed. Also, the predominant enantiomer in all cases was identified by X-ray crystallography and chiral HPLC as the *S* enantiomer, when the *S* ligand was employed.

The nature of the catalytically active species has been discussed extensively by Bryliakov,[29] Zeng,[31] Bolm[32-34] and Ellman.[35] It is clear that the presence of a *t*-Bu group at C-3 hinders approach of the sulfide to the reacting vanadium complex (Figure 4), thereby allowing achiral oxidation to compete with the enantioselective vanadium catalysed oxidation.

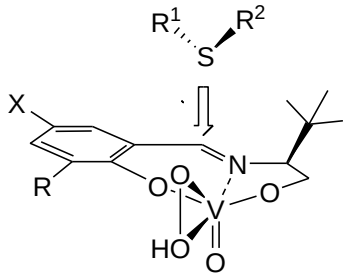
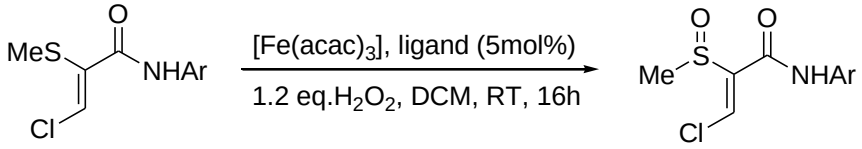



**Figure 4**

Following the development of the vanadium catalysed process, Bolm has reported that aryl alkyl sulfides can be rapidly oxidised to give chiral sulfoxides with enantioselectivities up to 90% ee using an iron catalyst formed *in situ* from $Fe(acac)_3$ and Schiff base ligands **5g-5i**.[36] Significantly, Bolm has reported improved stereoselectivities in the iron catalysed sulfide oxidation in the presence of additives such as substituted benzoic acids although use of these additives was not explored in this work.[37] Accordingly, the iron catalysed asymmetric oxidation of sulfide **1u** was explored using ligands **5a**, **5g-5i** as outlined in Table 7.

Table 7: $Fe(acac)_3$ catalysed Bolm Oxidation




Ar = 4-F-$C_6H_4$

| Entry | Ligand | Temp. (°C) | %Conversion[1] | Yield[2] (%) | Enantioselectivity[3] (% ee) |
|---|---|---|---|---|---|
| 1 | **5h** | ambient | 44 | 28 | 23 |
| 2 | **5i** | ambient | 41 | 26 | 30 |
| 3 | **5i** | -10 | 21 | 19 | 38 |
| 4 | **5g** | ambient | 42 | 31 | 14 |
| 5 | **5a** | ambient | 46 | 34 | 17 |

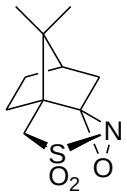
1 Estimated from integration of $^{1}$H NMR spectra of crude samples.

2 Yields quoted are following chromatography.

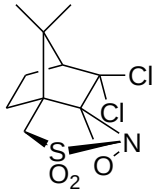
3 Enantiomeric ratios were determined using chiral HPLC using IPA/hexane as mobile phase on a Chiralcel AS column detected at λ 254 nm. As in the vanadium system, the *S* enantiomer was obtained when the *S* ligand was employed.

The efficiency and the enantioselectivity of the oxidation to form the methyl sulfoxide **2u** are lower than the results obtained with the vanadium based system. Decreasing the reaction temperature appears to have a positive impact on the enantioselectivity of sulfoxide **2u,** albeit with associated decrease in conversion (Table 7, entry 3).

The Page oxidation[38] (with oxaziridines **6a** and **6b** and sulfides **1a** and **1j**) and enzymatic oxidation[39] (with **1a** and chloroperoxidase, CPO from *Calsariomyces fumago*) were also explored. However, no conversion to the sulfoxides was observed under these conditions.




**6a**




**6b**

## Conclusion

Enantioselective oxidation of the β-chloroacrylamides to the analogous sulfoxides can be achieved using the Kagan oxidation with titanium catalysis or the Bolm oxidation with vanadium or iron based systems. Enantioselectivites of up to 71% ee were obtained across a range of derivatives using the vanadium catalyst with Schiff base ligands. Investigation of the synthetic utility of the resulting highly functionalised sulfoxides as Michael acceptors, dienophiles and dipolarophiles is currently underway in our laboratory.

## 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. Organic phases were dried using anhydrous magnesium sulphate. All commercial reagents, including *N*-chlorosuccinimide, were used without further purification.

$^{1}$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.

**Single crystal X-ray crystallographic analysis**

Data was collected on a Nonius MACH3 diffractometer using Mo-K$\alpha$ graphite monochromated radiation, $\lambda$ = 0.7107 Å, and corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full-matrix least-squares using all $F^2$ data. The SHELXS, SHELXL-97[40] and PLATON[41] suite of programs were used. All non-hydrogen atoms were refined with anisotropic displacement factors. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom. The *S*

enantiomer for **2u** was confirmed unambiguously using the Flack parameter. Full structural data have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference numbers 676357 and 676358.

*Typical experimental procedures are given below. Full details for all of the compounds are included in the supplementary information.*

**_N_-4'-Methylphenyl-_Z_-3-chloro-2-(benzenesulphinyl)propenamide 2a**

A solution of Oxone® (6.08 g, 9.88 mmol) in water (30 ml) was added dropwise to a stirred solution of *N*-4'-methylphenyl-*Z*-3-chloro-2-(phenylthio)-propenamide **1a** (1.50 g, 4.94 mmol) in acetone (120 ml) at room temperature. A colourless precipitate formed immediately. The reaction mixture was stirred for 2 h and was then checked for completion by TLC. Water (200 ml) was added and the aqueous solution extracted with DCM (3 x 75 ml). The combined extracts were washed with water (2 x 100 ml) and brine (100 ml), dried and concentrated to give **2a**. The crude product was purified by chromatography on silica gel using ethyl acetate–hexane (20:80) as eluent to give the sulfoxide **2a** (1.52 g, 96%) as a colourless solid; mp 128-129.5 $^{o}$C; Found C, 60.40; H, 4.61; N, 4.17; Cl, 11.53; S, 9.80. $C_{16}H_{14}NClO_2S$ requires C, 60.09; H, 4.41; N, 4.38; Cl, 11.09; S, 10.03; $\nu_{max}/cm^{-1}$ (KBr) 1671 (CO), 1612, 1555, 1512, 1319, 1034 (SO), 726; $\delta_H$ 2.30 (3H, s, Ar-$CH_3$), 7.08-7.18 (2H, m, ArH), 7.39-7.56 (5H, m, ArH), 7.67-7.79 (2H, m, ArH), 7.83 (1H, s, CHCl=), 10.37 (1H, b s, NH); $\delta_C$ 20.80 (*C*$H_3$Ar), 120.69 (aromatic CH), 124.14 (aromatic CH), 129.50 (aromatic CH), 129.73 (aromatic CH), 131.84 (aromatic CH), 134.63 (quaternary aromatic or SC=), 134.67 (quaternary aromatic or SC=), 137.40 (*C*HCl=), 138.77 (quaternary aromatic C or SC=), 141.07 (quaternary aromatic C or SC=), 158.12 (CO); MS *m/z* 319 ($M^+$, 84%), 226 (47), 213 (12, $M^+$-NHTol), 134 (73, $[PhS=C=CH]^+$), 125 (100, $[SOPh]^+$), 77 (95); isotopic Cl pattern observed; 319, 321 (3:1 ratio $^{35}Cl$:$^{37}Cl$). Found (HRMS, EI) *m/z* 319.0377. $C_{16}H_{14}N^{35}ClO_2S$ requires 319.0434.

**_N_-Benzyl- 3-morpholino-2-(benzylsulfonyl)propenamide 4c**

A solution of *m*CPBA (0.51 g of 65% pure material, 1.9 mmol) in dichloromethane (5 mL) was added dropwise to a stirring solution of the sulfoxide *N*-benzyl-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **2c** (0,32 g, 1.0 mmol) in dichloromethane (15 mL). Following

stirring at room temperature for 24 h, TLC analysis showed that all the sulfoxide starting material had been consumed and morpholine (0.33 mL, 3.8 mmol) was added directly to the reaction mixture. The reaction progress was monitored by TLC, which indicated that the reaction was complete after 5 minutes and the work-up involved washing with water (3 x 10 mL) and brine (10 mL). Following drying using anhydrous magnesium sulphate and evaporation of the solvent at reduced pressure, the crude sulfone **4c** was obtained as a brown oil. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 20-50% ethyl acetate) and the pure *sulfone* **4c** (0.16 g, 42%) was isolated as a white solid, mp 177-180 °C; (Found C, 62.67; H, 5.96; N, 6.72; S, 8.20. $C_{21}H_{24}N_2O_4S$ requires C, 62.98; H, 6.04; N, 6.99; S, 8.01%); $\nu_{max}/cm^{-1}$ (KBr) 3378 (NH), 3028 (CH), 2968 (CH), 1640 (CO), 1595 (NH bend), 1508, 1439 (CN stretch), 1352 (asymmetric $SO_2$ stretch), 1120 (symmetric $SO_2$ stretch); $\delta_H$ (300 MHz, $CDCl_3$) 3.29-3.36 [4H, m, NC(2′)$H_2$ and NC(6′)$H_2$], 3.64-3.70 [4H, m, OC(3′)$H_2$ and OC(5′)$H_2$], 4.14 (2H, s, SC$H_2$), 4.44 (2H, d, *J* 6.0, C$H_2$NH), 6.83 [1H, s, C(3)*H*N=], 7.22-7.37 (10H, m, Ar*H*), 7.59 (1H, b s, N*H*); $\delta_c$ (75.5 MHz, $CDCl_3$) 42.7 ($CH_2$, *C*$H_2$NH), 51.1 [$CH_2$, broad, NC(2′)$H_2$ and NC(6′)$H_2$], 60.2 ($CH_2$, SC$H_2$), 65.5 [$CH_2$, OC(3′)$H_2$ and OC(5′)$H_2$], 96.8 [C, *C*(2)S], 126.5, 126.8, 127.4, 127.5, 127.7, 130.1 (CH, aromatic *C*H), 137.3 (C, aromatic *C*), 151.5 [CH, *C*(3)HN=], 161.3 (C, *C*O); m/z (ESI) 401 ($[M+H]^+$, 100%).

**Asymmetric Oxidation of 1a to (-)2a using the Kagan Procedure**

Freshly distilled titanium isopropoxide (bp 43-5$^o$C at 0.04 mm Hg) (0.10 ml, 0.33 mmol) was added to a solution of (+)-diethyl tartrate (bp 100$^o$C at 0.1mm Hg) (0.11 ml, 0.66 mmol) in freshly double distilled ($P_2O_5$ and $CaH_2$) DCM (2.75 ml) in a round bottomed flask under a nitrogen atmosphere. On addition of the $Ti(O^iPr)_4$, the reaction solution turned yellow. Water (6 μl, 0.33 mmol) was then added from a micro syringe as slowly as possible. On completion of the water addition, the reaction solution was stirred at room temperature for 25 minutes. A solution of the β-chloroacrylamide **1a** (200 mg, 0.66 mmol) in freshly double distilled DCM (1 ml) was added and the reaction solution cooled to –30$^o$C by careful addition of dry ice to an acetone bath. The reaction solution was maintained at –30$^o$C for 40 minutes, then cumene hydroperoxide (0.12 ml, 0.66 mmol) was added dropwise from a micro syringe. The reaction solution was stirred at –30 $^o$C for 5 minutes, then the reaction flask was transferred to a freezer at –21 $^o$C. After 18 h, the flask was removed from the freezer and the

contents allowed warm to room temperature. Water (0.1 ml) was added and the solution stirred for 2 h during which time a gel formed. The gel was removed by filtration through a bed of celite which was then washed with DCM to ensure complete recovery of the product (the total volume of DCM after washing was 100 ml). Aqueous NaOH (2 ml of 2M solution) and brine (1 ml) were added and the reaction mixture was stirred for 90 minutes. At this point, more brine (50 ml) was added and the phases separated. The organic layer was washed with brine (50 ml), dried and evaporated at reduced pressure to give a mixture of the sulfoxide **2a** [46% conversion by $^1$H NMR spectroscopy (60 MHz)], the β-chloroacrylamide **1a** (54%) and 2-phenylpropan-2-ol. The 2-phenylpropan-2-ol was removed by bulb-to-bulb distillation at reduced pressure (100$^o$C at 2 mm Hg). Following chromatography on silica gel using ethyl acetate/hexane (gradient elution 5-30% ethyl acetate) as eluent, the sulphoxide (-)-**2a** was recovered (62 mg, 30%) as a colourless solid with 12% ee (Enantiomeric excess determined by HPLC on a chiral AS column using hexane:IPA 90/10 as mobile phase detected at λ 254nm. The major enantiomer eluted before the minor. Spectral characteristics were as reported previously.

**General Bolm procedure – Room temperature**

$VO(acac)_2$ (2.6 mg, 0.01 mmol) was added to a round bottomed flask containing the ligand (0.015 mmol) in DCM (2 ml). The resulting solution was stirred at room temperature for five minutes, then a solution of the appropriate β-chloroacylamide (1 mmol) in DCM (2.00 ml) was added. $H_2O_2$ (0.13 ml, 30%, 1.1 mmol) was added to the resulting solution. The reaction mixture was then stirred at room temperature for a further 16 h. Water (5 ml) was added and the phases separated; the organic layer was washed with water (2x 5 ml) and brine (5 ml), dried and concentrated at reduced pressure to the crude product. Following chromatography on silica gel using ethyl acetate and hexane (20:80), the sulfoxide was recovered. The enantiomeric excess was determined by chiral HPLC.

**General Bolm procedure – Low temperature**

$VO(acac)_2$ (2.6 mg, 0.01 mmol) was added to a round bottomed flask containing the appropriate ligand (0.015 mmol) in DCM (2 ml). The resulting solution was stirred at room

temperature for five minutes, then a solution of the appropriate β-chloroacylamide (1 mmol) in DCM (2.0 0ml) was added. The temperature was then lowered to the required value. $H_2O_2$ (0.13 ml, 30%, 1.1 mmol) was added to the resulting solution at this temperature. The reaction mixture was then stirred at this temperature for a further 16 h. Water (5 ml) was added and the phases separated; the organic layer was washed with water (2x 5 ml) and brine (5 ml), dried and concentrated at reduced pressure to give the crude product. Following chromatography on silica gel using ethyl acetate and hexane, the sulfoxide was recovered. The enantiomeric excess was determined by chiral HPLC. Note: A similar procedure was employed for reactions carried out at elevated temperatures, except in these experiments the $H_2O_2$ was added before heating commenced.

Details of the outcome of the Kagan and Bolm oxidations are summarised in Tables 3-6.

**Acknowledgements**

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