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Asymmetric Carbon-Carbon Bond Formation Using Sulfoxide-Stabilised Carbanions

Andrew J. Walker

Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT. U.K.

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CONTENTS

1. INTRODUCTION.

The use of sulfoxides as chiral synthons in asymmetric synthesis is now a well-established and reliable strategy, and has been the subject of several excellent reviews.[1] Examples outside the area of this current review include the Michael addition of nucleophiles to activated α,β-unsaturated sulfoxides.[2] Posner and co-workers have applied this methodology with great effect to the asymmetric syntheses of a number of natural products with high enantiomeric excess (e.e.). Solladie has shown that β-ketosulfoxides can be stereoselectively reduced to afford either diastereomer under appropriate conditions,[3] and has accessed a variety of compounds in this

manner. Chiral α,β–unsaturated sulfoxides are very useful dienophiles in asymmetric Diels-Alder reactions, often reacting with high levels of discrimination.[4]

However, in some respects, the use of sulfoxides in asymmetric synthesis has been somewhat curtailed by the relative paucity of reliable, efficient methods for the asymmetric synthesis of a wide variety of sulfoxides. Therefore, this review is intended to outline some of the more recent developments in this area, with emphasis on general methods only. The reactions of sulfoxide-stabilised carbanions will then be discussed, incorporating some of the more fundamental studies as well as applications to asymmetric carbon-carbon bond formation, although some examples of racemic syntheses have been included for illustration.

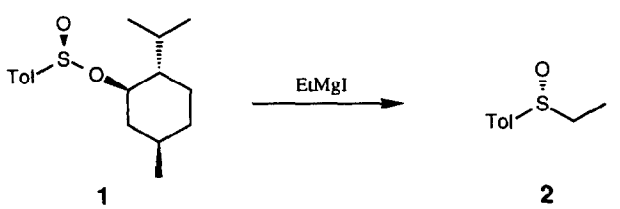
2. ASYMMETRIC SYNTHESIS OF SULFOXIDES.

Sulfoxides, to be effective synthetic tools for asymmetric carbon-carbon bond formation, are required in optically active form. In general, sulfoxides are configurationally stable under normal conditions.[5] Allyl sulfoxides are exceptions to this rule in that they racemise quite easily at ambient temperatures *via* a [2,3]-sigmatropic rearrangement.[6] There are several excellent reviews on this topic,[7] but this section is concerned only with recent developments, sub-divided into three main categories:-

1) chemical synthesis via nucleophilic substitution at sulfur.
2) enantioselective oxidation of prochiral sulfides.
3) kinetic resolution of sulfoxides.

2.1. NUCLEOPHILIC SUBSTITUTION AT SULFUR.

Until quite recently, the most popular means of preparing optically active sulfoxides was *via* the Andersen synthesis (**Scheme 1**).[8] The nucleophilic displacement of a menthylsulfinate ester **1** with Grignard reagents proceeds with clean inversion of stereochemistry at sulfur to afford the homochiral sulfoxide **2**.



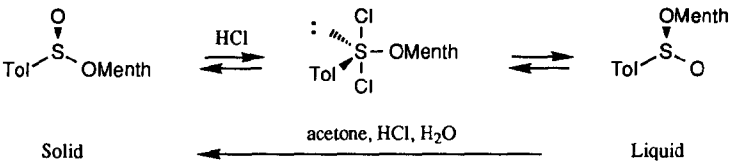
1 **2**

Scheme 1

Whilst stereochemically reliable, this approach has several limitations. The diastereomeric menthylsulfinate esters are prepared with low kinetic selectivity (2 or 3:1), and require separation before the next step. This becomes very tedious for liquid sulfinate esters, which includes most alkanesulfinate esters. Therefore, some important classes of sulfoxides are effectively inaccessible by this method.

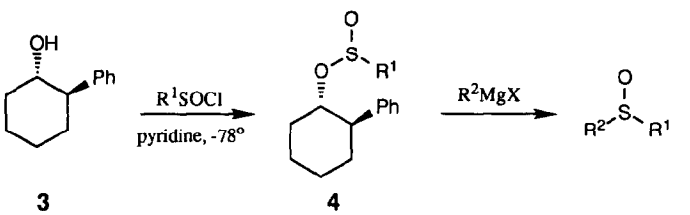
The low kinetic selectivity observed in the preparation of menthyl *p*-toluenesulfinate **1** can be circumvented by using an acid-catalysed epimerisation to equilibrate the diastereomeric esters (**Scheme 2**).[9] The less soluble isomer can be isolated in 90% yield after several days. Thus, the Andersen synthesis is still the most

popular way to prepare *p*-tolyl sulfoxides, and explains why the tolyl group has been the most common non-acidic (or spectator) group used in asymmetric synthesis *via* sulfoxides.



Scheme 2

In an analogous approach, Whitesell and Wong have recently shown that a range of sulfinate esters **4** can be prepared from their chiral auxiliary, (+)- or (-)-*trans*-2-phenylcyclohexanol **3**, with considerably better kinetic selectivity than observed with menthol (**Scheme 3**).[10] In all cases, the major diastereomer can be isolated by chromatography or recrystallisation. The sulfinate esters **4** undergo typical reactions with Grignard reagents to give the corresponding sulfoxides with excellent e.e.'s. Since both enantiomers of the auxiliary are readily available, this represents a flexible route to homochiral dialkyl, diaryl or alkylaryl sulfoxides.

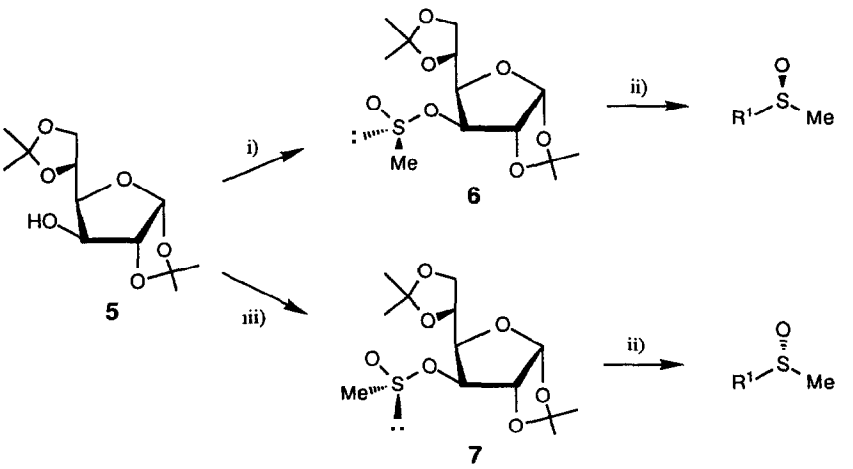


Scheme 3

A promising and potentially inexpensive route to homochiral methyl sulfoxides, using diacetone-D-glucose (DAG) **5** as the source of chirality, was disclosed by Llera and co-workers (**Scheme 4**).[11] Either methyl DAG-sulfinate diastereomer can be prepared in excellent yield and with high diastereoselectivity by the appropriate choice of base. Reaction in the presence of Hunig's base affords diastereomer **6**, whilst the use of pyridine gives **7**. Nucleophilic substitution proceeds cleanly with alkyl and aryl Grignard reagents to produce a variety of homochiral methyl sulfoxides. Extensions to the preparation of analogous aryl DAG-sulfinates are expected. This procedure is unique in that it utilises the cheap DAG as the sole source of chirality for either enantiomeric series.

Several workers have developed strategies based on a chiral sulfinyl group flanked by two different leaving groups. Two successive treatments with different organometallic reagents would thus afford homochiral sulfoxides.

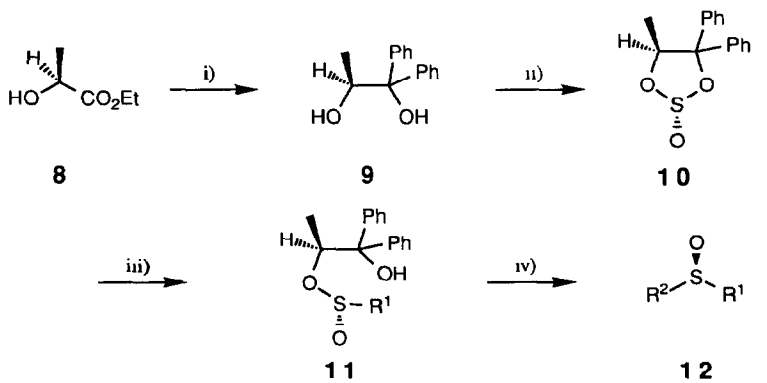
Kagan and co-workers, initially as a communication,[12] and recently as a full paper,[13] outlined their approach, using a chiral sulfite derived from (*S*)-ethyl lactate **8** (**Scheme 5**). The diol **9**, available by addition of 2 equivalents of PhMgBr, was treated with thionyl chloride to afford the crystalline sulfite **10**. Reaction with bulky organometallic reagents, such as *tert*-butylmagnesium bromide, proceeds with good (95:5) regioselectivity



Reagents: i) MeSOCl, Pr^i_2NEt, toluene, -78° ii) R^1MgX iii) MeSOCl, pyridine, toluene, -78°

Scheme 4

to afford the sulfinate **11**, derived from cleavage at the more hindered site. By contrast, regioselectivity is almost completely reversed when using small organometallic reagents (*ca.* 10:90). A second displacement reaction affords the homochiral sulfoxide **12** in quantitative yield (**Table 1**).



Reagents: i) 2 eq. PhMgBr ii) $SOCl_2$, Et_3N iii) R^1MgBr iv) R^2Met

Scheme 5

The generality (dialkyl, diaryl and alkylaryl) of this procedure, coupled with the commercial availability of (*R*)-isobutyl lactate, means that a wide range of sulfoxides can be easily accessed in either enantiomeric series.

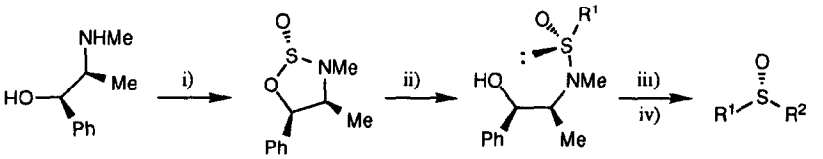
The regiochemical problems associated with this approach have been addressed by Benson and Snyder,[14] in a modification of some work published in the mid-70's by Wudl and Lee (**Scheme 6**).[15]

R^1	R^2	%e.e.
Bu^t	Bu^n	100
Bu^t	vinyl	100
Mesityl	Me	100
Mesityl	Ph	100
Bu^t	Me	100

Table 1

Treatment of the oxathiazolidine-S-oxide **14**, derived from ephedrine **13**, with freshly prepared Grignard reagents in toluene affords the sulfinamides **15** regiospecifically, in excellent yields. This is highly diastereoselective for alkyl and vinyl reagents; symmetrical diaryl sulfoxides are obtained using PhMgX. Addition of $AlMe_3$ to **15**, followed by addition of the appropriate Grignard reagent at -70°, gives good yields of the sulfoxides with excellent enantiomeric excess (**Table 2**).

$AlMe_3$ serves two purposes. First, the use of two equivalents of the potentially valuable organometallic reagent for the second displacement is no longer necessary, and secondly, the sulfinyl transfer route to sulfur epimerisation is eliminated. This was a serious drawback in the original procedure. Using this approach, homochiral dialkyl and alkylaryl sulfoxides can be prepared in good overall yield.



13 **14** **15**

Reagents: i) $SOCl_2$, Et_3N, 0° ii) R^1MgX, toluene, -40° iii) $AlMe_3$, CH_2Cl_2, r.t. iv) R^2Met, -70°

Scheme 6

R^1	R^2	%e.e.
Me	Ph	>99
Me	Bu^n	>99
Me	Bu^t	>99
vinyl	Ph	>99
allyl	Ph	>99*

* slowly racemises at room temp.

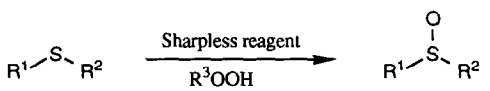
Table 2

2.2. ENANTIOSELECTIVE OXIDATION OF SULFIDES.

An attractive alternative to the "chemical" synthesis of homochiral sulfoxides, as outlined in Section 2.1., is *via* the asymmetric oxidation of prochiral sulfides with chiral oxidising agents. A number of workers have been active in this area in the past few years, and approaches can be broadly divided into two categories: 1) chemical oxidation and 2) enzymatic oxidation.

2.2.1. CHEMICAL OXIDATION.

Independently, Kagan,[16] and Modena,[17] discovered that application of a modified Sharpless asymmetric epoxidation procedure to prochiral sulfides furnished a wide range of alkylaryl sulfoxides with variable e.e.'s (**Table 3**). Kagan's optimised conditions involved the use of *tert*-butyl hydroperoxide as oxidant in the presence of a stoicheiometric amount of the modified Sharpless reagent [$Ti(OPr^i)_4$: (+)-DET : H_2O in a ratio of 1:2:1], whereas the Modena variant involved a ratio of 1:4:2 of $Ti(OPr^i)_4$: (+)-DET : Bu^tOOH.



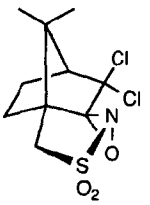
Entry	R^1	R^2	R^3OOH	Yield	%e.e.
1	*p*Tol	Me	Bu^t	90	89
2	"	Et	"	71	74
3	"	CH_2CO_2Me	"	81	64
4	*o*-anisyl	Me	"	58	86
5	2-napthyl	Me	"	88	90
6	"	Pr^n	"	78	24
7	2-pyridyl	Me	"	63	77
8	Bu^t	Me	"	72	53
9	*p*Tol	Me	$PhC(Me)_2$	-	96
10	*o*-anisyl	Me	"	-	93

Table 3

Kagan has actively developed this reaction,[18] and has demonstrated the scope and limitations of this approach. The use of cumene hydroperoxide appears to result in an increase in the optical purity of the sulfoxide, and, to some extent, allows the reaction to proceed in a catalytic sense. Whilst the approach appears viable for a wide range of aryl methyl sulfoxides, increasing the steric bulk of the alkyl chain results in a decrease in optical purity. Dialkyl sulfoxides are generally obtained with low enantioselectivity.

Davis and co-workers have developed the use of enantiomerically pure *N*-sulfonyl- **15** and *N*-sulfamyloxaziridines **16** for the asymmetric oxidation of sulfides with modest success.[19,20] More recently, they reported that (-)-α,α-dichlorocamphorsulfonyloxaziridine, **17**, was a highly effective reagent for this

transformation,[21] and appeared to be quite insensitive to changes in the substrate (**Table 4**). In many cases, the optical purity of the sulfoxide was greater than *via* the modified Sharpless approach, and either enantiomeric series can be synthesised by suitable choice of the oxaziridine.



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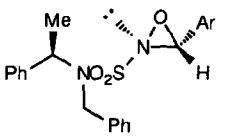

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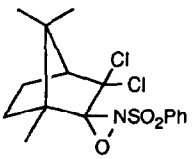

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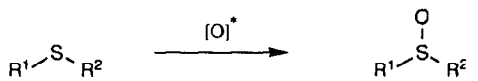


R^1	R^2	% e.e.
*p*Tol	Me	95
"	Bu^n	90
"	Pr^i	95
Ph	vinyl	60
"	CH_2CO_2Me	65
Bu^t	Me	84

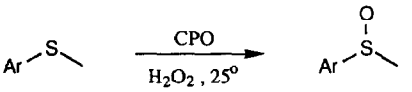
Table 4

In a different approach, Sakuraba *et. al.* have recently reported that a variety of alkylaryl sulfides undergo enantioselective oxidation in crystalline cyclodextrin complexes with quite modest selectivity.[22]

2.2.2. ENZYMATIC OXIDATION.

The biotransformation of sulfides to sulfoxides has been comprehensively reviewed recently by Holland.[23] In general, enzymatic methods do not provide a general, high-yielding route to sulfoxides with high e.e., but excellent results can be achieved with certain substrates.

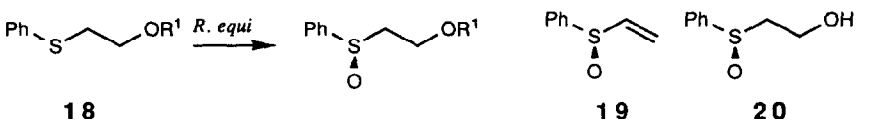
It was shown recently that chloroperoxidase-catalysed oxidation (CPO) of prochiral sulfides, using H_2O_2 or Bu^tOOH as the stoicheiometric oxidant, is very effective in providing a variety of important aryl methyl sulfoxides with high e.e.[24] The enantioselectivity in the CPO reaction is sensitive to steric and electronic factors, and it was found that *p*-substituted aryl sulfides were generally prepared with the highest e.e. (**Table 5**).



Aryl methyl sulfide	% Yield	% e.e.
p-Tol	98	91
Ph	100	98
p-MeOPh	72	90
o-MeOPh	24	27
$PhCH_2$	100	90
2-pyridyl	100	99
p-FPh	100	97

Table 5

Homochiral 2-hydroxyethyl- and vinyl sulfoxides can be prepared using *Rhodococcus equi* IFO 3730 (**Scheme 7**).[25] Best results were obtained with the methyl or MOM ethers (>99% e.e.) of the parent sulfide **18**. Elimination of methanol afforded the vinyl sulfoxide **19**, whilst MOM-deprotection gave the hydroxysulfoxide **20**. Both classes of compound are valuable synthons for asymmetric synthesis.

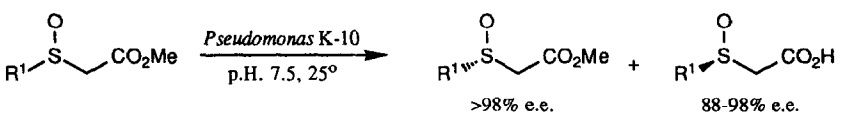


Scheme 7

The comparable effectiveness of the chemical and enzymatic oxidation on a limited number of vinyl sulfides was recently reported.[26] Whilst fungal cultures afforded some vinyl sulfoxides with excellent enantioselectivity, no clear pattern emerged with respect to substrate.

2.3. KINETIC RESOLUTION OF SULFOXIDES.

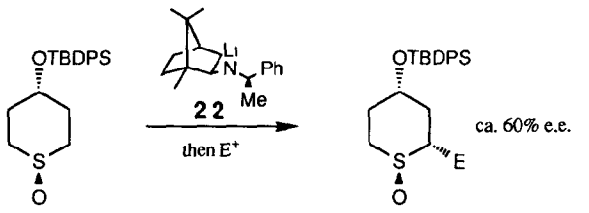
Ohta and co-workers have reported that enzyme-mediated hydrolysis of some racemic sulfinyl acetates and propionates using *Carynebacterium equi* IF 3730 returns the unreacted sulfoxide with 90-97% e.e.[27] Burgess has developed this approach (**Scheme 8**), and prepared homochiral sulfinyl acetates of a quite general



Scheme 8

nature using a more readily available biological system.[28] Enzymic hydrolysis of a number of arene- and alkanesulfinyl acetates using *Pseudomonas* K-10 afforded both the unreacted sulfinyl acetate and the acid with excellent e.e.

In a conceptually different approach, Simpkins *et. al.* have shown that deprotonation of an appropriate cyclic sulfoxide **21** using a homochiral lithium amide base **22** afforded non-racemic products **23** after quenching with suitable electrophiles (**Scheme 9**).[29] To date, optical yields are modest, but further improvements are anticipated.



Scheme 9

3. REACTIONS OF SULFOXIDE-STABILISED CARBANIONS.

3.1 WITH 1,2-ASYMMETRIC INDUCTION.

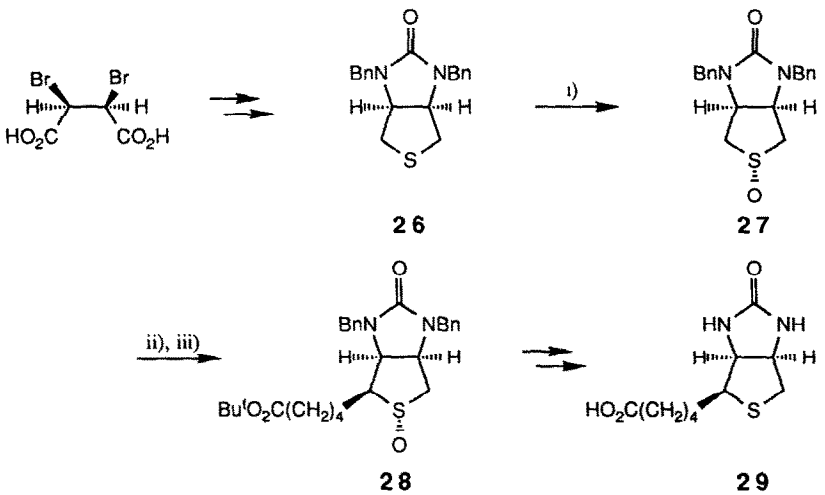
This section is concerned with the reactions of α-sulfinyl carbanions that involves 1,2-asymmetric induction, and embraces alkylation, deuteration, carbonation, acylation and halogenation reactions. The relative lack of synthetic applications of this class of reaction reflects the need for a means of removing the sulfinyl auxiliary with conservation of the induced chirality. These reactions have therefore been studied mainly from an academic viewpoint, but have provided information relating to the various factors that influence the reactions of sulfoxide-stabilised carbanions.

Durst and co-workers found that methylation and deuteration of benzyl sulfoxides proceeded with good diastereoselectivity to give the *syn*- and *anti*-products respectively.[30] Intensive studies of these basic reactions have shown that the stereoselectivity is dependent on the electron-donating ability of the electrophile (**Scheme 10**).[31,32] Biellmann proposed the following generalisation: electrophiles with the abilty to coordinate to the metal counterion, e.g. D_2O, CO_2,[33] tend to react with "retention", from the same side of the anion as the cation **24**.

Scheme 10

Electrophiles, such as MeI, that do not coordinate to the cation, approach from the less hindered face of the anion, with "inversion" **25**.

The first successful application of the alkylation strategy was reported by Marquet and co-workers in the total synthesis of *dl*-biotin.[34] The approach took advantage of the high *trans*-selectivity in the alkylation of cyclic sulfides (**Scheme 11**). The bicyclic sulfide **26**, prepared from *meso*-dibromosuccinic acid, was selectively oxidised using sodium periodate to the *exo*-sulfoxide **27** in excellent yield. The required alkyl residue was introduced using a diglyme/HMPA solvent mixture to afford the advanced intermediate **28** with complete stereocontrol. Standard deprotection gave biotin **29**.

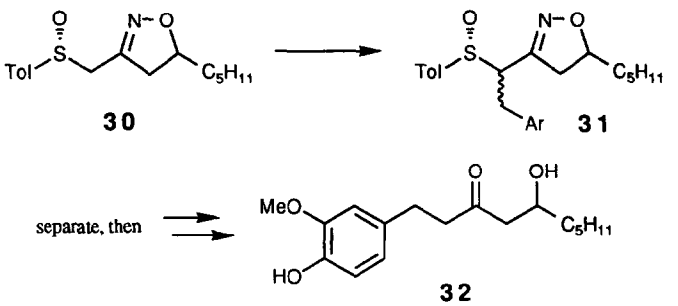


Reagents: i) $NaIO_4$ ii) MeLi iii) $I(CH_2)_4CO_2Bu^t$, HMPA

Scheme 11

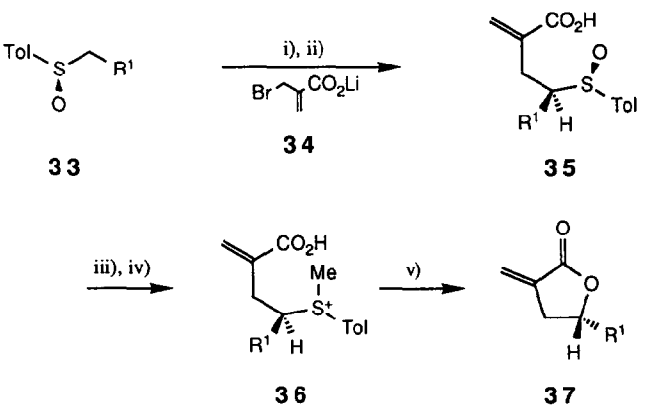
Simpkins has also observed this *trans*-selectivity, in trapping experiments, after enantioselective deprotonation of cyclic sulfoxides using homochiral lithium amide bases.[29,35] Desulfurisation revealed the acyclic product. Cinquini *et.al.* have successfully synthesised (*S*)-(+)-gingerol *via* the alkylation of enantiomerically pure isoxazolines **30**, prepared with poor kinetic selectivity using the Andersen method (**Scheme 12**).[36] Homochiral isoxazolines and β-hydroxyketones can be prepared *via* reductive desulfurisation. Alkylation with the benzylic bromide gave **31**. Desulfurisation, followed by debenzylation, afforded gingerol **32** with >96% e.e.

In these examples, stereoselective removal of the auxiliary was not required. Such a strategy was employed by Bravo and co-workers in the synthesis of homochiral α-methylene butyrolactones (**Scheme 13**).[37] The homochiral sulfoxides **33** were deprotonated using a variety of bases, and alkylated with lithium α-bromomethyl acrylate **34** to give diastereomeric mixtures of the corresponding sulfinyl acids **35** in excellent yields. A slightly more diastereoselective alkylation was observed when using the very bulky lithiumtetramethylpiperidide base, although chemical yields were lower. The sulfinyl group was stereoselectively



Scheme 12

removed using a 3-step process. This involved reduction to the sulfide, selective methylation to give the sulfonium salt **36**, and intramolecular nucleophilic displacement of the sulfonium group with clean inversion to furnish the lactones **37**. This displacement of a sulfonium salt by an internal nucleophile represents one of the very few methods to stereoselectively remove the sulfinyl moiety after asymmetric C-C bond formation.

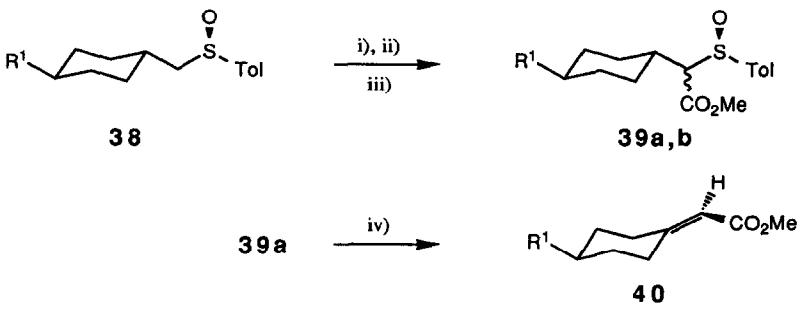


Reagents: i) Base, -78° ii) **34** iii) NaI, TFAA iv) Me_3OBF_4 , -45° v) Bu^tOK, 0°

Scheme 13

Solladie has used the stereospecific nature of the pyrolytic elimination of sulfoxides to obtain substituted alkylidenecyclohexanes possessing axial chirality (**Scheme 14**).[38] Carbonation of the tolyl sulfoxide **38** proceeded with moderate selectivity to afford the ester **39** after methylation. Pyrolytic elimination to give the unsaturated ester **40** was used to confirm the absolute configurations of the products.

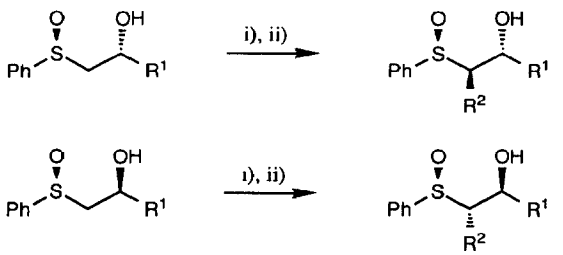
Bromination of the same sulfoxide **38** proceeded with complete diastereoselectively to give the α-bromosulfoxide, which was cleanly dehydrosulfinylated to the corresponding bromoalkene without racemisation.[39]



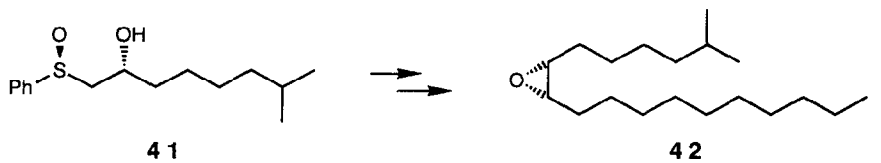
Reagents: i) MeLi ii) CO_2 iii) MeI iv) Δ

Scheme 14

Alkylation of β-hydroxysulfoxides has been shown to proceed with high 1,2-asymmetric induction (**Scheme 15**). The hydroxyl group controls the stereochemistry of the alkylation , and the products were 2,3-*anti* in the case of substituted hydroxysulfoxides.[40,41] This high *threo*-selectivity was applied to the synthesis of both enantiomers of disparlure **42**, using the reduction/alkylation/displacement procedure outlined previously.[41] The pheromone was obtained in 42% yield from **41** *via* the stereoselective alkylation of the dianion.

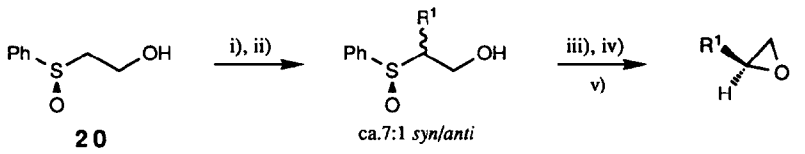


Reagents: i) 2MeLi ii) R^2X



Scheme 15

In the absence of a β-substituent, the alkylation proceeds with high 1,2-*syn* selectivity.[42] The stereochemistry of the products from the alkylation of 2-phenylsulfinyl ethanol **20** were again elucidated by conversion to the known epoxides (**Scheme 16**).

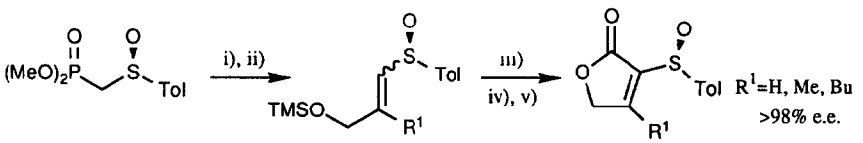


20 ca.7:1 *syn/anti*

Reagents: i) 2.2 eq. LDA ii) R^1X iii) $TiCl_4$, $NaBH_4$ iv) Me_3OBF_4 v) NaOH

Scheme 16

Vinyl sulfoxides undergo clean deprotonation at the α-position,[43] generating the *E*-vinyl anion stereoselectively. This anion has been trapped with D_2O, MeI, allyl bromide and benzyl bromide to form reagents for asymmetric synthesis. An example is outlined in **Scheme 17**.[44] Wittig reaction of the homochiral phosphonate **43** affords the vinyl sulfoxide **44** as a mixture of geometric isomers. Lithiation gives solely the *E*-lithio derivative; carbonation, followed by an acidic work-up, furnishes the homochiral 2-(*p*-tolylsulfinyl)-2-butenolide **45** in good overall yield.

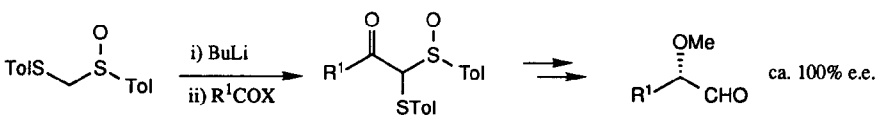


43 **44** **45**

Reagents: i) BuLi ii) ketone iii) LDA iv) CO_2 v) TsOH

Scheme 17

Acylation of sulfoxides allows reliable access to β-ketosulfoxides, which have been used to great effect in asymmetric synthesis. However, there are few synthetic applications of this acylation procedure involving 1,2-asymmetric induction, since the products are stereochemically unstable.[45] Guanti and co-workers have synthesised both enantiomers of a protected α-hydroxyaldehyde *via* acylation.[46] In this case, excellent 1,2-control was observed, and the resulting ketones were selectively transformed to the target compounds (**Scheme 18**).



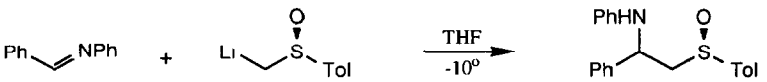
Scheme 18

Bravo and Resnati have described the regioselective acylation of α-haloesters using sulfoxides.[47] Depending on the acylating agent, β-ketosulfoxides that were homochiral at S, at S and the α-carbon, or at S and the α'-carbon, could be isolated.

Additions to electrophiles with 1,3-asymmetric induction are intrinsically of more interest synthetically, since the sulfinyl auxiliary can be removed without compromising the stereochemical integrity of the newly-formed chiral centre. Developments and applications in this area shall now be discussed with respect to the nature of the electrophile.

3.2. WITH IMINES.

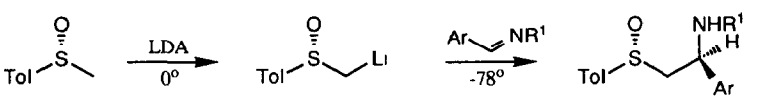
The first report of the addition of α-sulfinyl carbanions to imines was disclosed by Tsuchihashi and co-workers in 1973.[48] Addition of the sulfoxide **46** to *N*-benzylideneaniline **47** afforded the β-aminosulfoxide **48** in 70% yield (**Scheme 19**). It was also noted that **46** added to benzonitrile to give the iminosulfoxides, which were immediately reduced to a 1:1 mixture of aminosulfoxides. These could be separated *via* fractional crystallisation in poor yield.



47 **46** **48**

Scheme 19

The original workers stated that the product was isolated as a single diastereomer, but a more rigorous study showed that **48** was recovered as a 3:1 mixture after work-up.[49] The temperatures of deprotonation and of imine addition were shown to be significant, and optimised conditions were developed (**Scheme 20**). A deprotonation temperature of 0° was found to be optimal, and it was suggested that a chelated anion, with no external coordination to Li^+ by di-isopropylamine, was responsible for the improved diastereoselectivity (92:8). The study revealed that *N*-alkylimines were not suitable substrates for addition.

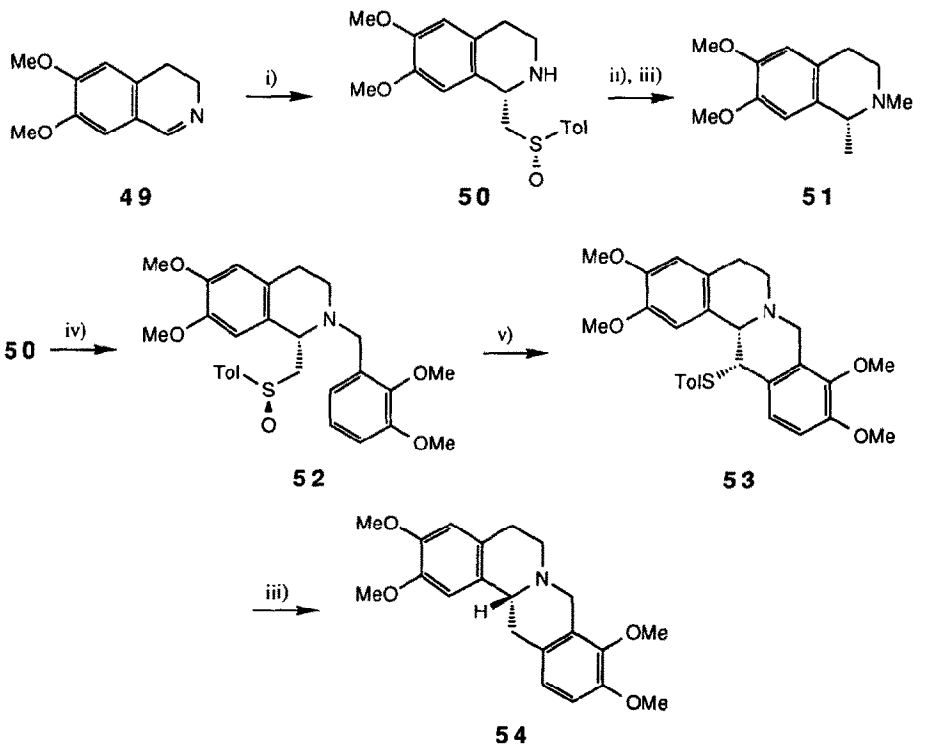


Scheme 20

Kinetically- and thermodynamically-controlled addition of (*R*)-(+)-methyl *p*-tolyl sulfoxide **46** to imines was reported to proceed with modest stereoselectivity.[50] Equilibration between the diastereomeric adducts was thought to be taking place over the timescale of the reaction. In general, product diastereoselection was poorer under thermodynamic control than under kinetic control. This methodology was recently applied to the synthesis of (*R*)-(+)-carnegine **51** and (*R*)-(+)-tetrahydropalmatine **54** (**Scheme 21**).[51]

Addition of **46** to the imine **49** under equilibrium-controlled conditions gave the adduct **50** with excellent diastereoselectively (92:8). Reductive alkylation of the major isomer with formaldehyde, followed by simple desulfurisation, afforded (*R*)-(+)-carnegine **51**. For the synthesis of tetrahydropalmatine, reductive

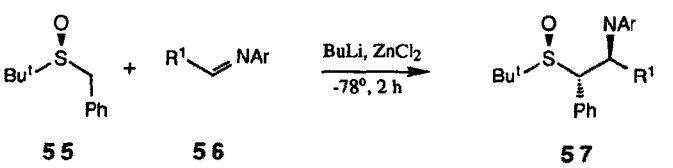
alkylation with 2,3-dimethoxybenzaldehyde gave the sulfoxide **52** in 87% yield. An intramolecular Pummerer reaction was used to construct the tetracyclic ring system **53**, followed by reductive desulfurisation to give the target compound **54**.



Reagents: i) **46** ii) $HCHO$, $NaCNBH_3$ iii) Raney Nickel iv) $ArCHO$, $NaCNBH_3$ v) TFAA, Δ

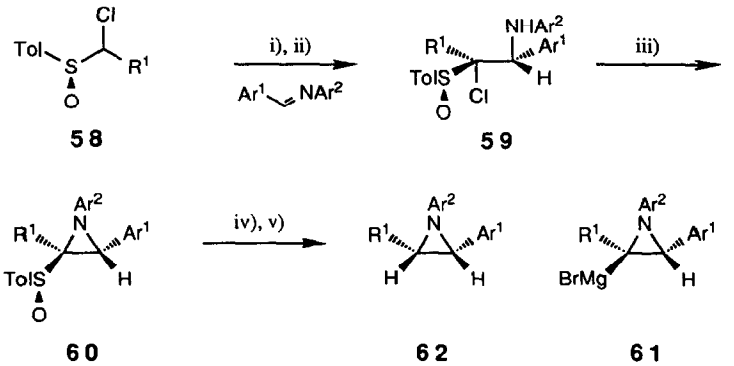
Scheme 21

A bulkier spectator group was shown to confer excellent diastereoselectivity in the reaction of benzyl sulfoxides to *N*-arylimines (**Scheme 22**).[52] The *tert*-butyl sulfoxide **55** reacted with imines **56**, having R^1 = alkenyl or aryl, under kinetic conditions to afford the *anti*-adducts **57** as essentially single diastereomers. Poor selectivity was again observed with alkyl imines, and it was suggested that groups able to stabilise an incipient charge in the transition state were important for good selectivity and reactivity.



Scheme 22

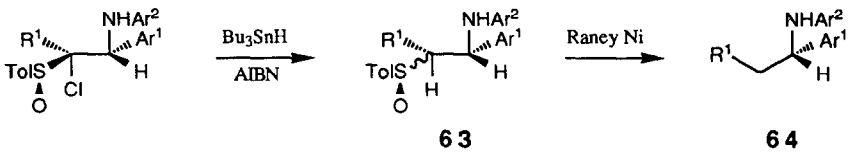
More complex sulfoxides also undergo smooth addition to *N*-arylimines. Work by Yamakawa and co-workers has realised an asymmetric synthesis of (*Z*)-*N*-arylaziridines *via* the addition of 1-chloroalkyl *p*-tolyl sulfoxides to aryl imines (**Scheme 23**).[53,54] Deprotonation of the sulfoxide **58** using LDA, followed by reaction with an appropriate imine, yields the chloroamines **59** as single diastereomers in excellent yield. Cyclisation to the sulfinylaziridines **60** proceeds smoothly using Bu^{t}OK. Stereospecific desulfinylation using ethylmagnesium bromide affords the aziridines **62** *via* the Grignard intermediate **61**.



Reagents: i) LDA ii) imine iii) Bu^{t}OK iv) EtMgBr v) H_2O

Scheme 23

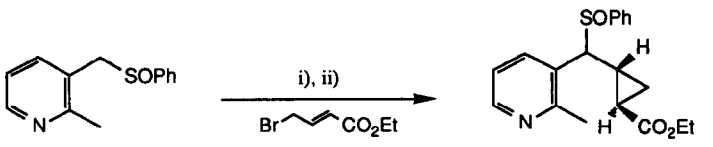
This methodology was also applied to the asymmetric synthesis of secondary amines **64** *via* a radical dehalogenation/ reductive desulfurisation procedure. Unfortunately, the radical reaction gave inseparable 1:1 mixtures of the β-aminosulfoxides **63** (**Scheme 24**).



Scheme 24

3.3. WITH α,β-UNSATURATED CARBONYL COMPOUNDS.

As early as 1973, Schlessinger showed that dithioacetal-S-oxide behaved as an acyl anion equivalent in the conjugate addition to enones.[55] Of more interest was the report that the benzylic sulfoxide **65** reacted in a 1,4-manner with ethyl 4-bromocrotonate **66** to afford the cyclopropane **67** as a single diastereomer in 53% yield (**Scheme 25**).[56] Although they were not able to extend this to simple ene esters, this represented the first evidence that the conjugate addition of simple sulfoxides was a diastereoselective process.

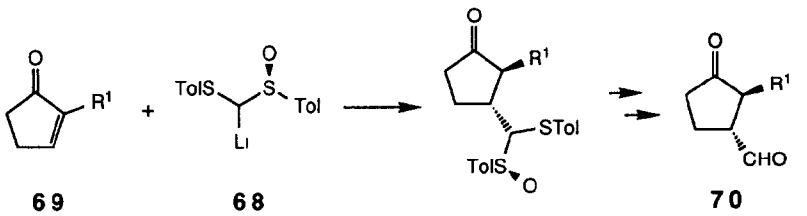


65 66 67

Reagents: i) LDA, THF, TMEDA, -78° to -20° ii) **66** , -78°

Scheme 25

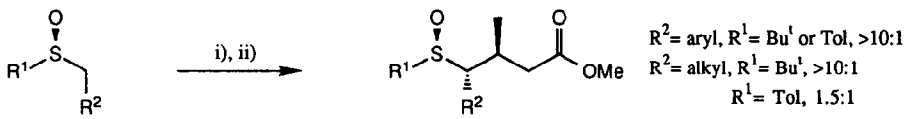
Other examples of 1,4-additions of benzylic sulfoxides were reported in the context of annulation chemistry.[57,58] No mention of stereoselectivity was made as the resulting Michael adducts were aromatised to functionalised phenols. Conjugate addition of the chiral acyl anion equivalent **68** to 2-alkylcyclopentanones **69** afforded the adducts with good 1,3- and 1,4-induction, but with poor 1,2-induction (**Scheme 26**).[59] These were converted into interesting homochiral prostanoid intermediates **70**. However, the generality of this procedure is in doubt, as a C-2 substituent is required for high diastereoselectivity.



69 68 70

Scheme 26

Recently, it has been demonstrated that alkyl and benzyl *tert*-butyl sulfoxides react with acyclic α,β-unsaturated esters with excellent regio- and stereoselectivity (**Scheme 27**).[60,61] The *t*-butyl alkyl sulfoxides gave much higher selectivity in the conjugate addition than the more commonly-used *p*-tolyl sulfoxides, although both spectator groups were equally effective in controlling the addition of benzyl sulfoxides.

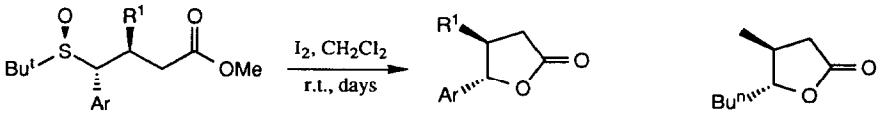


Reagents: i) LDA, THF, -78° ii) methyl crotonate, THF, -78°

Scheme 27

A very useful transformation of *tert*-butyl benzyl conjugate adducts was recently reported by the same workers (**Scheme 28**).[62] Treatment of the adducts **71** with a positive iodine source, such as I_2 or NIS, generated the γ-butyrolactones **72** in good yield and with excellent *trans:cis* selectivity (>92:8). This represents a

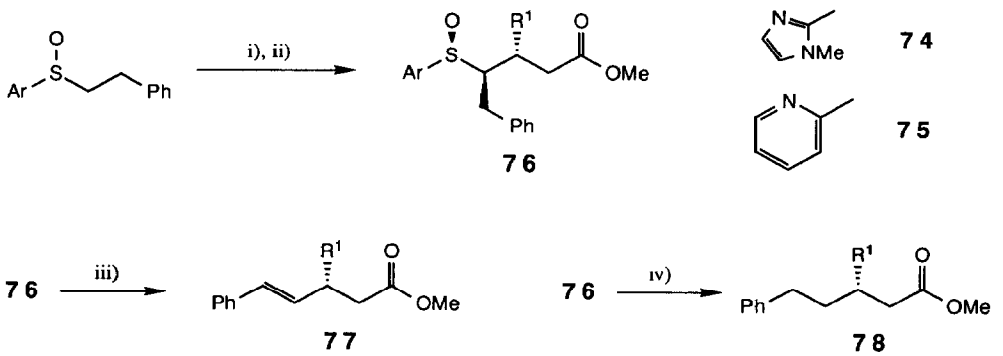
novel method for the removal of the sulfinyl moiety, stereoselectively replacing a C-S bond with a more synthetically useful C-O bond. A racemic synthesis of *quercus* lactone **73** was described using this procedure.



71 **72** **73**

Scheme 28

In an extension of the above reaction, two heteroaromatic alkyl sulfoxides **74** and **75** were shown to add remarkably cleanly to α,β-unsaturated esters with excellent diastereoselectivity (**Scheme 29**).[63] Pyrolytic elimination of the adduct **76** under mild conditions or reductive desulfurisation using nickel boride afford the alkene **77** and alkane esters **78** respectively.

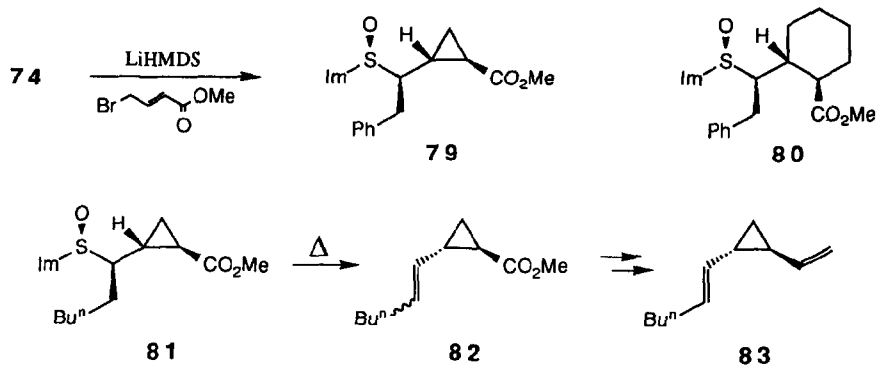


Reagents: i) LiHMDS, -78° ii) ene ester iii) Δ, $CHCl_3$ iv) $NaBH_4$, $NiCl_2.6H_2O$

Scheme 29

In addition, it was found that the imidazolyl sulfoxide **74** participated in MIRC (Michael Induced Ring Closure) reactions to generate the cyclopropane **79** and the cyclohexane **80** as single diastereomers in good yield. This methodology was employed in a concise synthesis of dictyopterene A **83** (**Scheme 30**).[64] The cyclopropane **81** was prepared in 72% yield as a single diastereomer. Thermolysis gave the vinyl cyclopropane **82** as a mixture of isomers. Standard transformations afforded dictyopterene A in 50% overall yield over 6 steps.

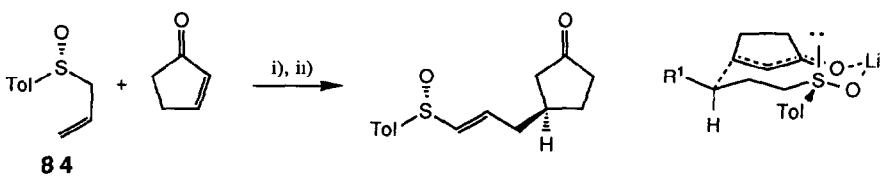
Initial work by Japanese chemists related to the conjugate addition of allyl sulfoxides to Michael acceptors was concerned with the synthesis of prostanoid intermediates.[65] In a series of studies into the scope of this addition to cyclic enones, it has been shown that excellent regio- and stereoselectivity is observed for simple



Scheme 30

allyl sulfoxides.[66,67] Extension to allylic sulfoxides substituted at C-1 and C-2 resulted in poor diastereoselectivity in most cases.[68]

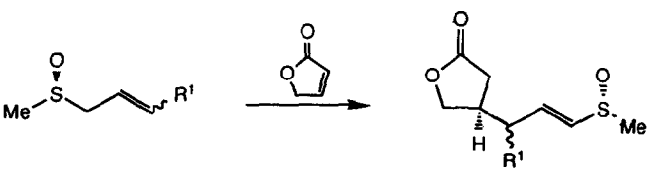
The regiospecific asymmetric conjugate addition of (*R*)-(+)-allyl *p*-tolyl sulfoxide **84** to various cyclic enones afforded good isolated yields of the γ-substituted adducts with good to excellent diastereomeric excess (**Scheme 31**).[66] A number of 3-substituted γ-butyrolactones and cyclopentanones were synthesised with high e.e. in this way. The selectivity was explained in terms of a 10-membered "*trans*-decalyl" transition state.[67]



Reagents: i) LDA, THF, -78° ii) enone , -78°

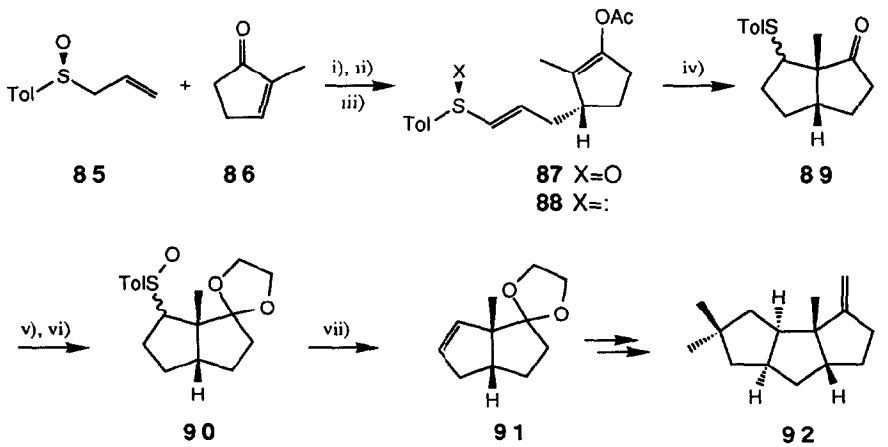
Scheme 31

For γ-substituted allyl sulfoxides, the tolyl spectator group and the γ-substituent are pseudoequatorial and the sulfur lone pair is pseudoaxial. The tolyl group projects away from the enone, and therefore the alkene geometry in the starting sulfoxide determines the diastereomeric distribution in the product (**Scheme 32**).



Scheme 32

Hua and co-workers have applied this chemistry to a number of elegant syntheses of natural products. An asymmetric total synthesis of (+)-hirsutene was initiated by the 1,4-addition of (*S*)-(-)-allyl *p*-tolyl sulfoxide **85** to 2-methyl-2-cyclopentanone **86**, followed by treatment with acetyl chloride, to give the enol acetate **87** in 86% yield and with 94% d.e. (**Scheme 33**).[69] Deoxygenation to the sulfide **88** was followed by intramolecular cyclisation to yield a mixture of diastereomeric sulfides **89**. Ketalisation was followed by oxidation to the bicyclic sulfoxide **90**. Dehydrosulfinylation proceeded smoothly to the alkene **91**, from which (+)-hirsutene **92** was synthesised.



85 **86** **87** X=O **88** X=: **89** **90** **91** **92**

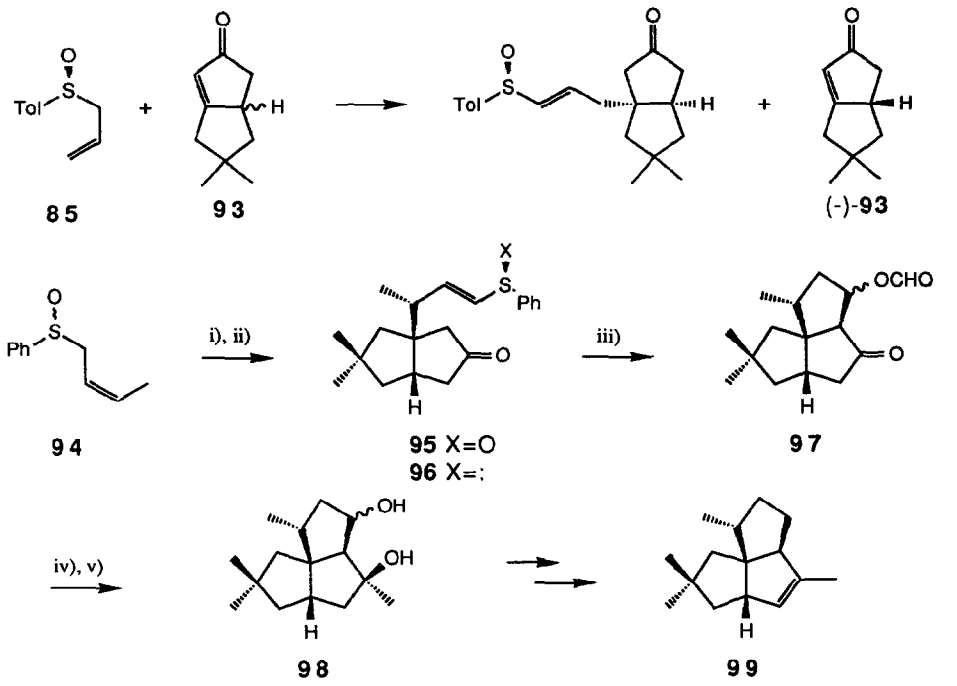
Reagents: i) LDA, -78° ii) **86** iii) AcCl iv) $TiCl_4$ v) $HOCH_2CH_2OH$, TsOH vi) mCPBA vii) DBN, PhMe

Scheme 33

A similar strategy was employed in the asymmetric synthesis of (+)-pentalenene.[70] The *si*-selectivity of the conjugate addition of allyl sulfoxides was used to kinetically resolve the Michael acceptor **93** (**Scheme 34**). Reaction of the *dl*-enone with 0.5 eq. of (*S*)-allyl *p*-tolyl sulfoxide **85** afforded good yields of the homochiral acceptor **93**. Treatment of (-)-**93** with 2 eq. of *dl*-(*Z*)-crotyl phenyl sulfoxide **94** effected another kinetic resolution to afford the required adduct **95** with 82% e.e. The sulfide **96** was cyclised to give the formate **97** in 60% yield. Hydrolysis, followed by treatment with MeMgBr, gave the diol **98**, which was converted into (+)-pentalenene **99** *via* standard transformations.

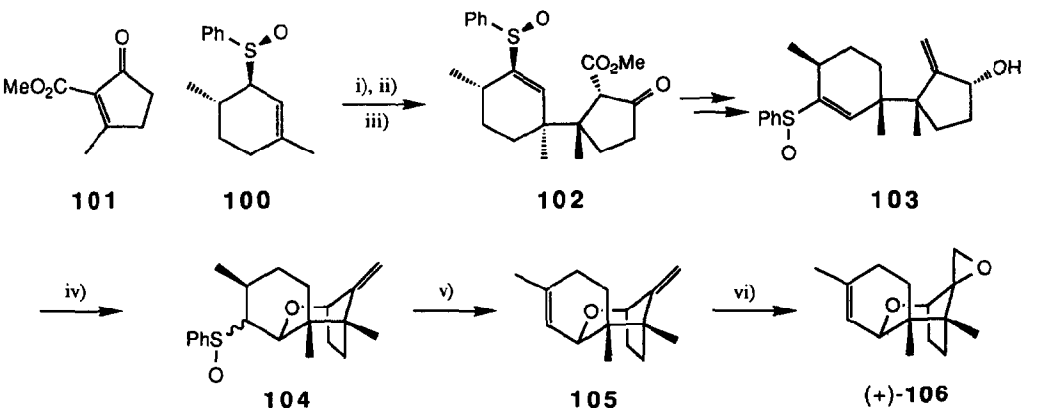
The synthesis of *dl*-pentalenolactone E methyl ester was prepared in an analogous manner to those seen above.[71] Extension of this methodolgy to more complex sulfoxides and Michael acceptors has been shown to be practical, and has been applied by Hua to the enantioselective total synthesis of (+)-12,13-epoxytrichothec-9-ene (**Scheme 35**).[72]

For enones substituted at C-3, activation was required for reaction to occur. Thus, the homochiral cyclic allyl sulfoxide **100** added smoothly to the enone **101** to afford the adduct **102** with 94% d.e. Routine transformations gave the vinyl sulfoxide **103** in good overall yield. The sulfinyl auxiliary was then used to construct the cyclic ether **104** *via* an intramolecular Michael addition to a vinyl sulfoxide. Pyrolytic elimination to the diene **105** was followed by selective epoxidation to give (+)-12,13-epoxytrichothec-9-ene **106**. The



Reagents: i) LDA, -78° ii) 0.5 eq. of (-)-93 iii) HCO_2H, TFA, 60° iv) H^+ v) MeMgBr

Scheme 34



Reagents: i) LDA, -78° ii) **101** iii) AcOH, -78° iv) KOH, Bu^tOH v) Δ , DABCO vi) mCPBA

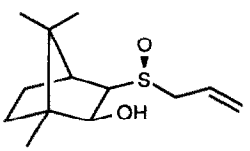
Scheme 35

antipode of **106** was also synthesised.

The use of allyl sulfoxides in asymmetric C-C bond formation is potentially limited by the availability of homochiral starting materials, since many are stereochemically labile *via* a [2,3]-sigmatropic rearrangement. One approach to this problem has been to use a chiral auxiliary as the spectator group, and transfer the chirality fromthe auxiliary to the S centre *via* the [2,3]-rearrangement. Thus, the equilibrium may now be biased in favour of a single sulfoxide diastereomer.

Haynes and co-workers have developed a camphor-based approach, and shown that a number of 3-*exo*-(allylsulfinyl)isoborneols **107** can be prepared with high levels of diastereoselectivity.[73] These sulfoxides are stereogenically stable at ambient temperatures, but heating at 145°C quantitatively transforms them into their sulfur epimers. The allyl sulfoxides add to cyclic enones with excellent levels of diastereoselectivity, but with only modest conversion.

In 1990, Swindell reported that a series of allylic sulfoxides **108** could be prepared in racemic form, but with complete control over the S stereocentre.[74] The spectator group was synthesised *via* Ulmann coupling and thiol subtitution, and oxidation of the sulfide gave either diastereomer under selective conditions. This class of sulfoxide was shown to react with cyclopentenone with excellent regio- and stereoselectivity, in the manner predicted by the "*trans*-decalyl" model (**Scheme 36**).[75]



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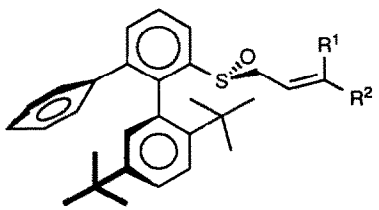
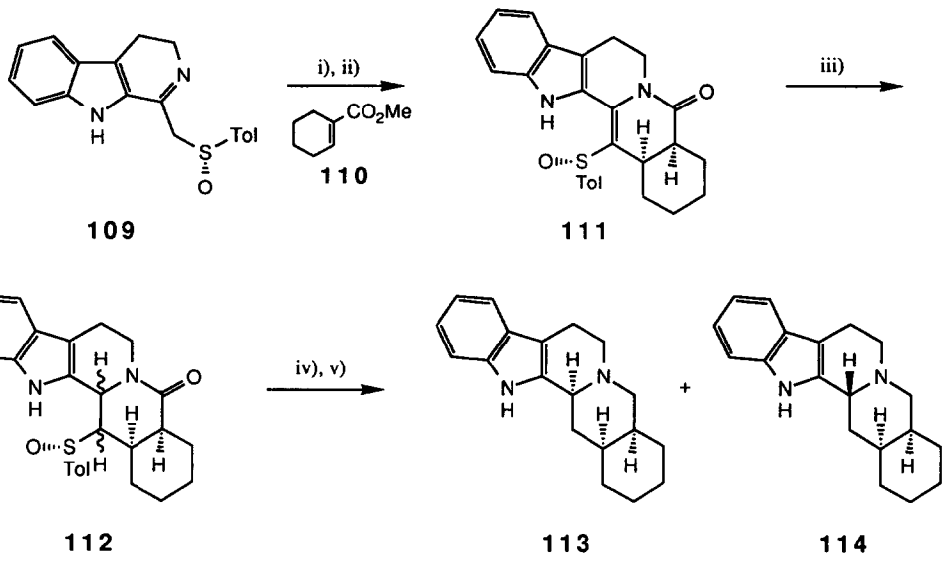


108

Scheme 36

The 1,4-addition of α-sulfinylketimines to α,β-unsaturated esters has been reported recently.[76] Whilst very modest diastereoselectivity was observed in the addition to acyclic ene esters, much better results were obtained using cyclic *exo*-esters, such as **110** (**Scheme 37**).This has been used to assemble chiral indolizines. The ketimine sulfoxide **109** reacted with the unsaturated ester **110** to afford the tetracyclic vinyl sulfoxide **111**. This reaction proceeds through the α-carbon, and is not related mechanistically to the conjugate additions of allyl sulfoxides discussed previously. The enamine was reduced to give a separable mixture of sulfoxide diastereomers **112**. Further reduction resulted in the asymmetric synthesis of (-)-allo-yohimban **113** and its C-3 epimer **114**.



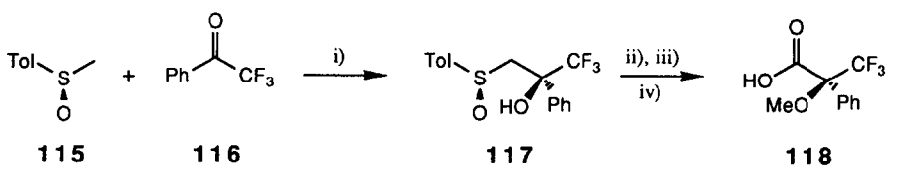
Reagents: i) 2 eq. LDA ii) **110**, 60°, 14 h iii) $NaCNBH_3$, AcOH, cat. TFA iv) Raney Ni v) $LiAlH_4$

Scheme 37

3.4. WITH CARBONYL COMPOUNDS.

A very large number of workers have investigated the addition of α-sulfinyl carbanions to carbonyl compounds, and of necessity, this section concentrates on those which have resulted in good diastereoselectivity, and in applications to asymmetric synthesis.

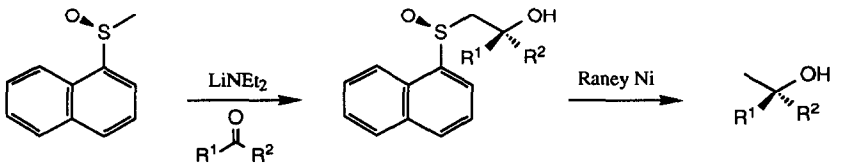
The addition of methyl sulfoxides to carbonyl compounds generally leads to poor 1,3-asymmetric induction, although Resnati has recently reported moderate (3:1) selectivity in the reaction of methyl *p*-tolyl sulfoxide **115** to 1,1,1-trifluoroacetophenone **116** (**Scheme 38**).[77] The major isomer **117** was converted into the Mosher acid **118** *via* a Pummerer rearrangement.



Reagents: i) LDA ii) MeI iii) TFAA iv) $NaClO_2$

Scheme 38

Recently, the use of a 1-naphthyl spectator group afforded the corresponding adducts with excellent d.e. for aryl aldehydes and sterically unencumbered aryl alkyl ketones (**Table 6**).[78] Dialkyl and branched alkyl aryl ketones gave poorer results. Desulfurisation gave the corresponding alcohols (**Scheme 39**).



Scheme 39

R^1	R^2	% d.e.
Ph	Me	100
Ph	Pr	100
Ph	Pr^i	44
Ph	Bu^t	50
Et	Me	6

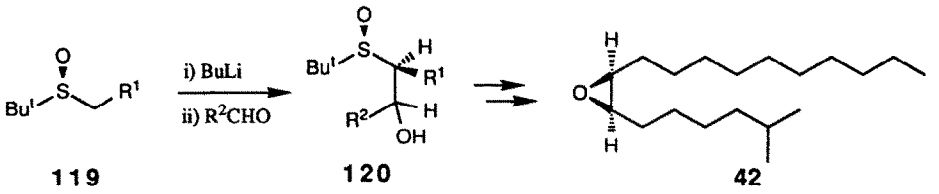
Table 6

Braun and Hild demonstrated that transmetallation from lithium to zinc improved the selectivity of the addition of methyl *p*-tolyl sulfoxide to benzaldehyde from 1:1 to 4:1.[79] In a more detailed study, Solladie reported a similar result upon counterion exchange.[80] It was also shown that the use of a spectator group (Ar) with the ability to coordinate to the metal internally improved 1,3-asymmetric induction (**Table 7**). A similar effect was observed recently, where a binaphthyl sulfoxide with an appropriately positioned hydroxyl group gave a 4:1 mixture of diastereomers on addition to benzaldehyde.[81]

Ar	Base	Yield	ratio
*p*Tol	LDA	95	1:1
*p*Tol	LDA+$MgBr_2$	95	1:1
*p*Tol	LDA+$ZnBr_2$	35	4:1
2-pyridyl	LDA	90	4:1

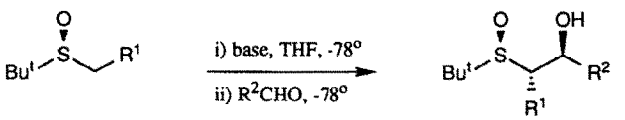
Table 7

Subtituted sulfoxides can react with good 1,2- and 1,3-asymmetric induction, but, in general, the reaction of simple alkyl sulfoxides with aldehydes is not a selective process. For example, the synthesis of (+)- and (-)-disparlure **42** required the separation of the 1.5:1 mixture of β-hydroxysulfoxides **120** obtained from the sulfoxide **119** (**Scheme 40**).[82] Cyclisation using the standard 3-step procedure gave (+)- and (-)-disparlure **42** from the appropriate carbonyl adduct.



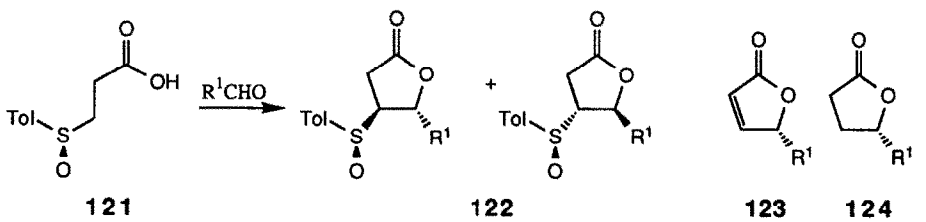
Scheme 40

This use of the *tert*-butyl spectator group has been found to be effective by several workers. In combination with a zinc counterion,[52] benzyl sulfoxides were found to add with good diastereoselectivity to aldehydes. A more wide-ranging study into the factors that affect the addition of *tert*-butyl alkyl sulfoxides to aldehydes revealed some interesting trends (**Scheme 41**).[83] Addition to unhindered aldehydes generally gave poor results, whereas the use of either bulkier sulfoxides or of hindered aldehydes resulted in improved stereoselectivity, the *anti*-diastereomer predominating. Complete stereocontrol was observed over the α-centre, with moderate control over the β-centre. These results emphasise the superiority of the *tert*-butyl group over the *p*-tolyl group, although this has not been used in a synthetic application to date.



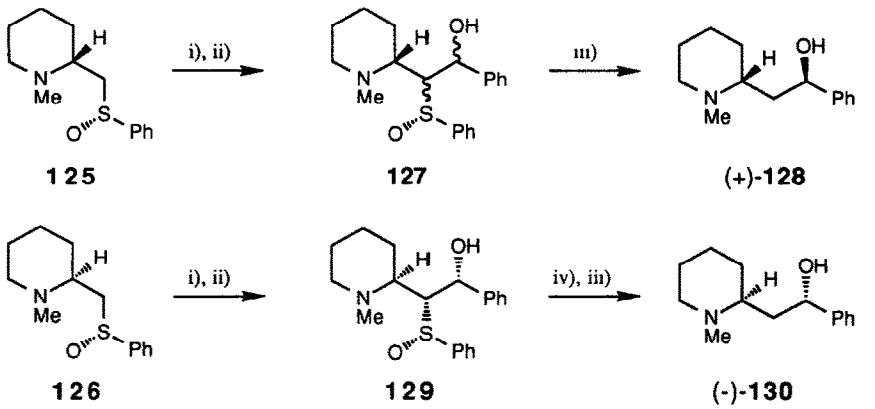
Scheme 41

Bravo and co-workers have used the intrinsically poor diastereoselectivity of *p*-tolyl sulfoxides in the addition to aldehydes to prepare both enantiomeric series of butenolides **123** (**Scheme 42**).[84,85] The sulfoxide **121** reacts under standard conditions with a variety of aldehydes to afford separable 1.5:1 mixtures of the diastereomeric lactones **122**. Thermal elimination gives the synthetically useful homochiral butenolides **123**, whereas desulfurisation affords the saturated γ-butyrolactones **124**. Addition to ketones gives γ-disubstituted lactones.



Scheme 42

In a more stereochemically complex situation, Pyne introduced the carbinol functionality of (+)- and(-)-sedamine in an asymmetric manner using the sulfoxides **125** and **126** (**Scheme 43**).[86] Deprotonation of **125**

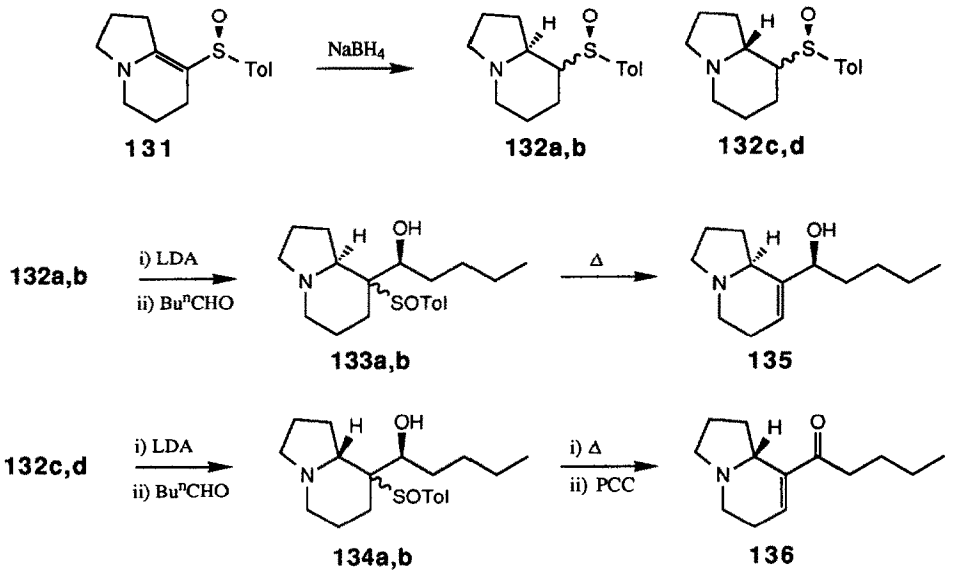


Reagents: i) LDA ii) PhCHO iii) Raney Ni iv) Al/Hg

Scheme 43

and reaction with benzaldehyde gave a mixture of four diastereomers **127**. Direct treatment of one of the minor adducts with Raney Nickel gave (+)-sedamine **128**. Under identical conditions, the diastereomeric starting sulfoxide **126** afforded a 6:1:1 mixture of adducts with PhCHO. The major isomer **129** was converted into (-)-sedamine **130** *via* the sulfide.

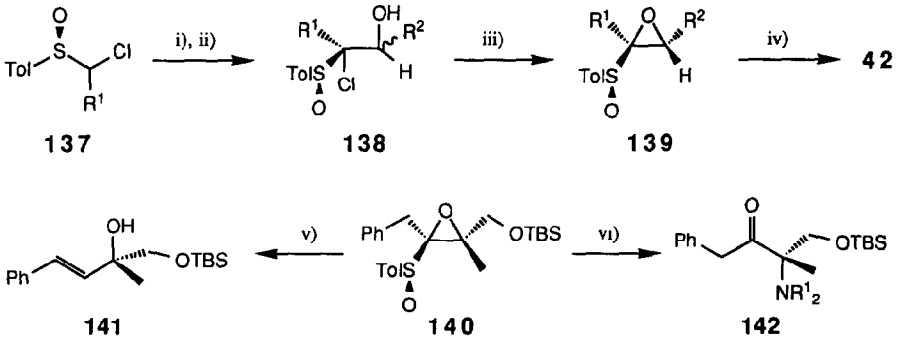
Hua has applied the aldol-type reaction to the asymmetric total synthesis of (+)-elaeokanine A and (-)-elaeokanine B (**Scheme 44**).[87] The β-aminosulfoxides **132a-d** were obtained from the reduction of the β-



Scheme 44

enaminosulfoxide **131**, prepared as seen previously. Reaction of the individual isomers, **132a,b** and **132c,d**, with butanal afforded a 2:1 mixture of only two diastereomers, **133a,b** and **134a,b**, in each series. Pyrolytic elimination of the sulfinyl moiety from **133a,b** gave (-)-elaeokanine B **135** in excellent yield, whilst elimination, followed by oxidation, of **134a,b** gave (+)-elaeokanine A **136**.

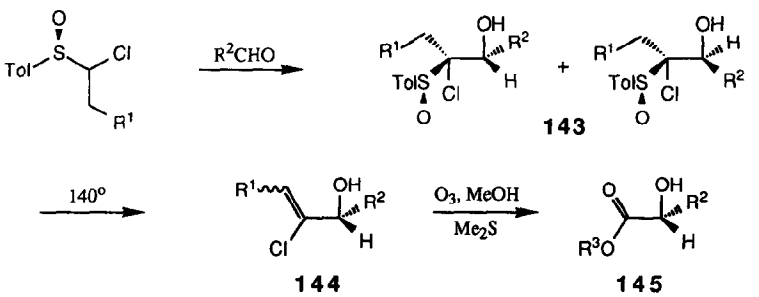
The addition of 1-chloroalkyl *p*-tolyl sulfoxides to carbonyl compounds has been used to synthesise a number of optically active compounds (**Scheme 45**).[88] The homochiral starting sulfoxides **137** reacted with aldehydes with low diastereoselection, and the adducts **138** were cyclised to give the diastereomeric epoxides **139**. A brief synthesis of (+)-disparlure **42** was completed by stereospecific desulfinylation. An alternative desulfinylation procedure afforded the allylic alcohol **141** from the benzyl adduct **140**, whilst the nucleophilic opening of the epoxide with secondary amines gave α-aminoketones **142**. All the compounds were obtained with excellent e.e.'s after the necessary separation of the initial carbonyl adducts.



Reagents: i) LDA ii) R^2CHO iii) Bu^tOK iv) BuLi, -100° v) 3 eq. BuLi, -40° vi) $R^1{}_2NH$

Scheme 45

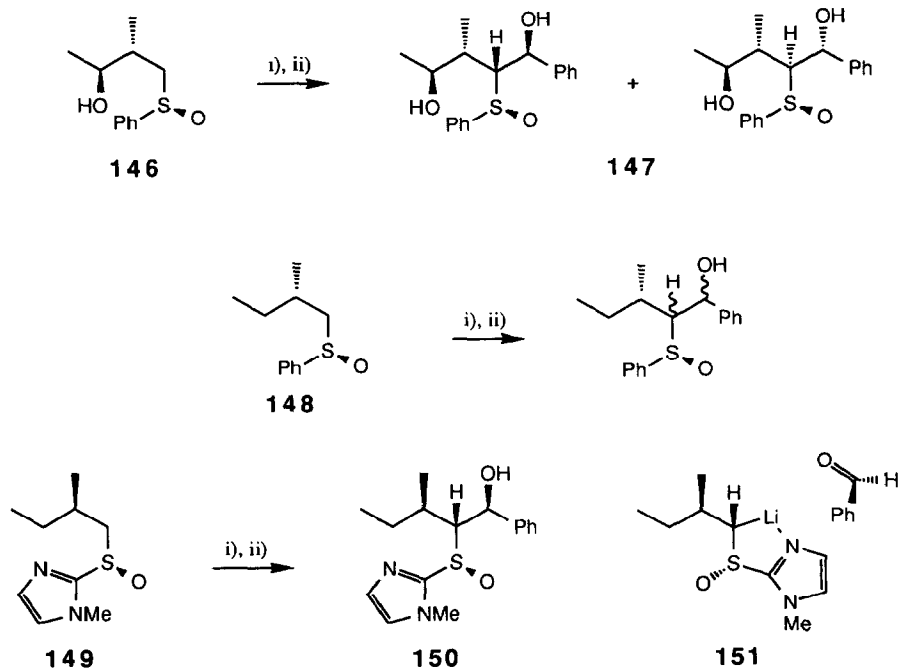
An application of this methodology to the asymmetric synthesis of α-hydroxyesters is shown in **Scheme 46**.[89] The very poor selectivity in the initial carbonyl addition allows both enantiomers of the target esters to be accessed. Separation of the carbonyl adducts **143** was followed by pyrolytic elimination to give the alkenes **144**. Ozonolysis in an alcoholic solvent afforded the appropriate α-hydroxyesters **145** with excellent



Scheme 46

e.e. Propargylic alcohols can also be prepared by a variation of this method in excellent yields.[90]

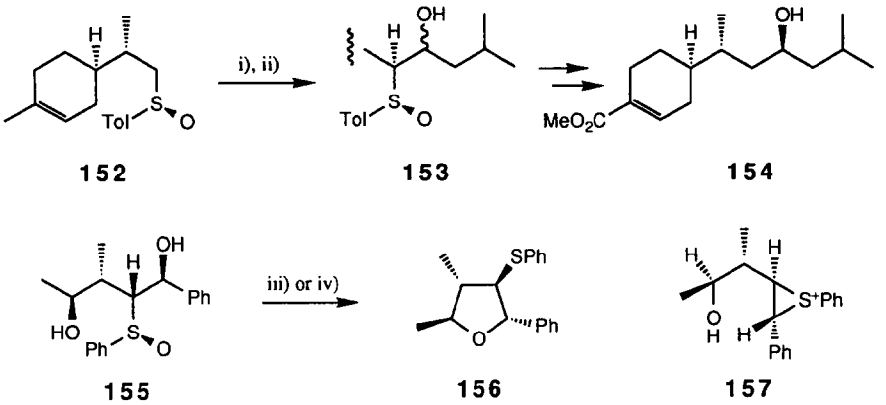
Williams has demonstrated that good 1,3-stereocontrol can be achieved in carbonyl additions using γ-hydroxysulfoxides (**Scheme 47**).[91] The sulfoxide **146** was reacted with benzaldehyde to give the adducts **147** with good (10:1) diastereselectivity. It was suggested that coordination effects were important in determining the stereoselectivity of the addition. The much poorer diastereoselectivity (9:9:2:1) in the addition of the desoxy analogue **148** appeared to support this hypothesis. Introduction of a spectator group with the ability to coordinate internally re-established a high degree of stereocontrol. The use of an imidazolyl spectator group **149** gave a very satisfactory 5:1 mixture of diastereomers **150** in good yield. Reaction, with the phenyl group disposed to the less hindered face of the metallocyclic intermediate **151**, was held to account for the observed stereoselectivity.



Reagents: i) LDA ii) PhCHO

Scheme 47

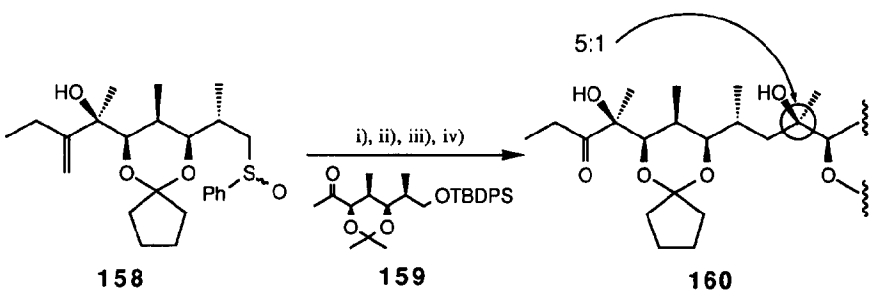
These results have been applied synthetically (**Scheme 48**).[92,93] The absence of a hydroxy group resulted in a poor 1.5:1 mixture of adducts **153**, epimeric at the carbinol centre, from the addition of the sulfoxide **152** to 3-methylbutanal. The major adduct was converted into (+)-juvabiol **154** *via* standard transformations.[92] The same workers have used the hydroxyl-controlled aldol reaction to synthesise a variety of stereochemically complex tetrahydrofurans.[93] The adduct **155** was smoothly converted into the tetrahydrofuran **156**, either by treatment with acetyl bromide at 0°, or by a reduction/methylation procedure. The reaction is thought to proceed *via* an episulfonium salt **157**.



Reagents: i) LDA ii) 3-methylbutanal iii) AcBr, CH_2Cl_2, 0° iv) BH_3, then Me_2SO_4

Scheme 48

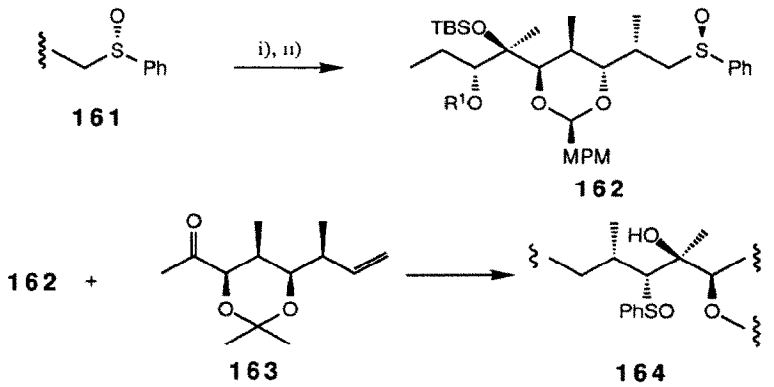
Sulfoxides have been used in coupling protocols in macrolide synthesis (**Scheme 49**). Stork and co-workers reported that a 5:1 mixture of diastereomers was obtained in the coupling of the racemic sulfoxide **158** with the functionalised ketone **159**.[94] Unmasking of the carbonyl compound and reductive desulfurisation gave an advanced acyclic intermediate for Erythronolide A **160**. Masamune has also used such a coupling procedure in the synthesis of the C1-C12 unit of the aglycon of Amphotericin B.[95] A 15:1 mixture of diastereomers was obtained from the reaction of a racemic sulfoxide and a complex aldehyde. The high selectivity can probably be attributed to the nature of the carbonyl compounds rather than to the presence of a γ-alkoxy substituent within the sulfoxide.



Reagents: i) 2 eq. LDA, -78° ii) **159** iii) O_3 iv) Raney Ni

Scheme 49

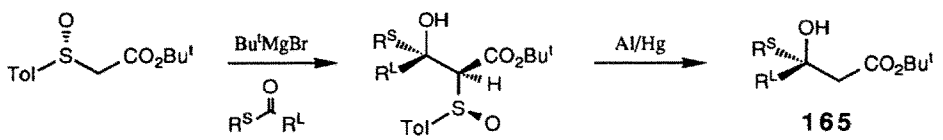
In contrast, sulfoxide configuration was found to be important in an alternative synthesis of Erythronolides A and B (**Scheme 50**).[96] The reaction of the (*R*)-sulfoxide **162** with the complex ketone **163** proceeded with 7:1 selectivity at the carbinol centre **164**. In contrast, the (*S*)-sulfoxide **161** did not react at all under the reaction conditions. Isomerisation at S circumvented this synthetic problem.



Reagents: i) TFAA, THF, collidine, -60° ii) THF, H_2O

Scheme 50

A significant improvement in 1,3-asymmetric induction has been observed in the addition of α-sulfinyl esters to aldehydes. The sulfinyl group effectively acts as a chiral auxiliary for the enolate anion in aldol reactions. High diastereoselectivity in the aldol-type condensation of the α-sulfinyl ester with a variety of aldehydes was first observed by Solladie and Mioskowski in 1977 (**Scheme 51**).[97] The use of *tert*-butylmagnesium bromide as base was found to be essential for good results, whilst no condensation products were recovered using sodium hydride or alkyllithiums. Desulfurisation gave the aldol products **165** with variable e.e.'s (**Table 8**).

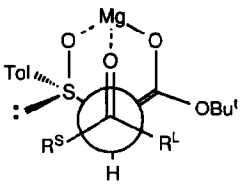


Scheme 51

R^S	R^L	% e.e.
H	Ph	91
Me	Ph	62
H	*n*-C_7H_{15}	86
Me	cyclohexyl	95

Table 8

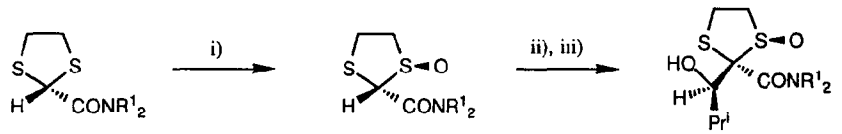
The mechanistic model proposed involves the coordination of the carbonyl compound to the magnesium counterion in a six-membered chelate (**Scheme 52**). This occurs on the less hindered face, that is, *anti* to the aryl group, and with the small carbonyl substituent directed towards the sulfinyl group. The relative ease of



Scheme 52

preparation makes them powerful tools in the synthesis of β-hydroxy acids. Related acid derivatives, such as α-sulfinylamides,[98] thioacetamides,[99] hydrazones,[100] and oxazolines,[101] have been investigated, and been shown to give modest to good diastereoselectivity in the addition to aldehydes. Again, the use of a magnesium counterion was found to be most effective.

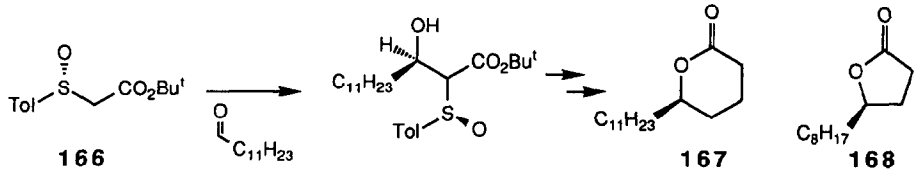
In a recent paper, Di Furia and co-workers have extended this to the use of *trans*-2-*N*,*N*-dialkylacetamide-1,3-dithiolane-S-oxide, prepared using the modified Sharpless procedure in homochiral form (**Scheme 53**).[102] Reaction of the magnesium enolate with a model aldehyde afforded a single diastereomer in 82% yield. It is anticipated that further work on this type of system will be forthcoming.



Reagents: i) Ti(IV), (+)-DET, TBHP, -20° ii) Bu^{t}MgBr iii) Pr^{i}CHO

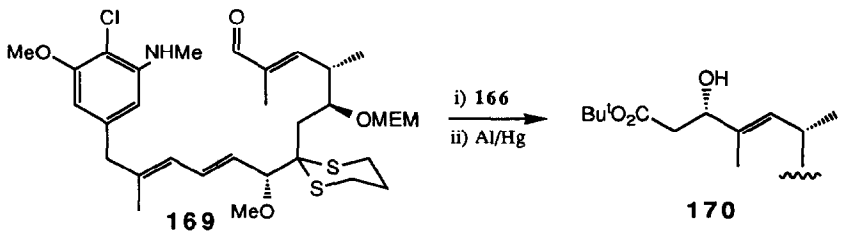
Scheme 53

Applications of this chemistry include the preparation of (*R*)-(-)-mevalonolactone,[103] (*R*)-(-)-gingerol,[104] and the asymmetric synthesis of two insect pheromones,[105] (*R*)-(+)-δ-*n*-hexadecanolactone **167** and (*R*)-(+)-γ-*n*-dodecanolactone **168** (**Scheme 54**). The synthesis of **167** involved an initial carbonyl addition using the α-sulfinyl ester **166**, followed by desulfurisation, homologation and lactonisation, to give the pheromones with >80% e.e.



Scheme 54

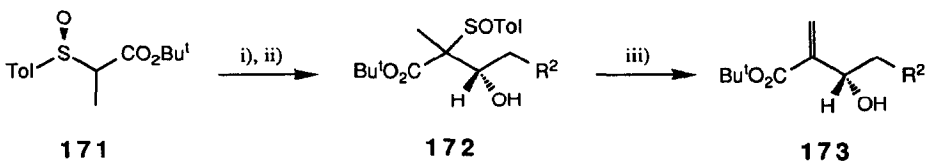
Application of this methodology in a more complex situation was used in the later stages of a total synthesis of maytansine (**Scheme 55**).[106] The unsaturated aldehyde **169** reacted smoothly with the α-sulfinyl ester **166** to afford the β-hydroxy ester **170** with an estimated 86% e.e. This alcohol was later converted into



Scheme 55

the natural product.

Pyrolytic elimination of the sulfinyl moiety after carbonyl condensation was employed in the asymmetric synthesis of a number of α-(hydroxyalkyl)acrylates (**Scheme 56**).[107] The reaction of a variety of aldehydes with the substituted sulfoxide **171** afforded the usual adducts **172**. Thermolysis gave the allylic alcohols **173** with 75% e.e.

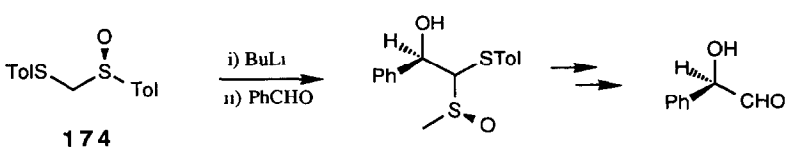


171 **172** **173**

Reagents: i) Bu^{t}MgBr ii) R^{2}CH$_2$CHO iii) Δ, CaCO$_3$

Scheme 56

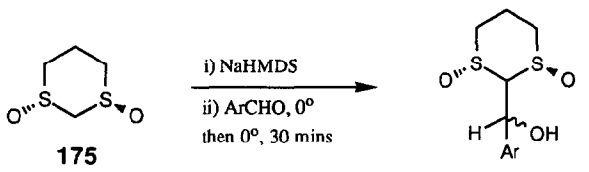
Chiral acyl anion equivalents also add with high levels of stereocontrol to carbonyl compounds. Initial work by Scolastico demonstrated that (+)-*p*-tolyl *p*-tolylthiomethyl sulfoxide **174** reacted with benzaldehyde to ultimately afford the α-methoxyaldehyde, after standard transformations (**Scheme 57**).[108] De Lucchi and co-workers have more recently demonstrated that a binapthyl analogue of **174** reacted with benzaldehyde to afford a single diastereomer in excellent yield.[109]



174

Scheme 57

A variation on this theme is the addition of *bis*-sulfoxides with C_2-symmetry. Aggarwal has shown that the cyclic *bis*-sulfoxide **175** reacts with aromatic aldehydes under thermodynamic control to afford the corresponding adducts with excellent diastereoselectivity (**Scheme 58**).[110,111] Deprotonation using NaHMDS, reaction with the aromatic aldehyde at 0° and equilibration of the initially formed adducts over 30 mins was required for good results.[111] A few representative results are shown in **Table 9**.

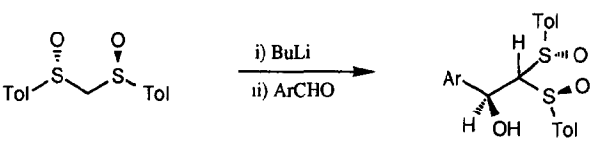


Scheme 58

Ar	d.e.	yield of major isomer
Ph	92	87
3-MeOPh	90	64
3,4-TBDMSOPh	92	74
4-NO_2Ph	90	42

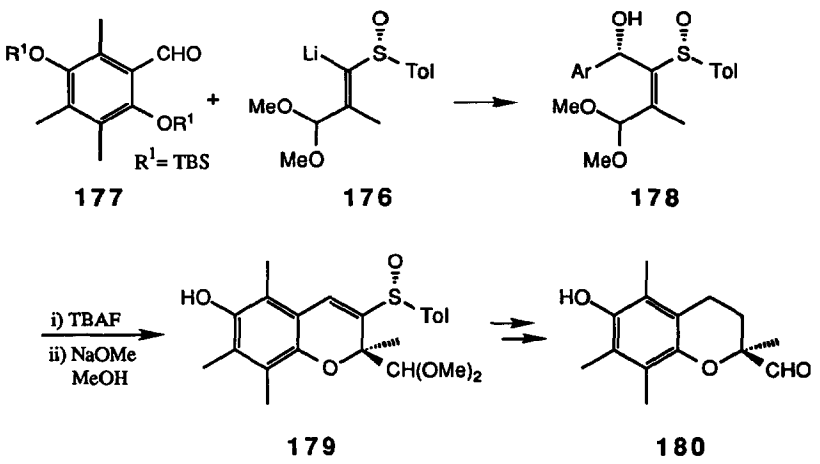
Table 9

Similar results were obtained using the acyclic *bis*-sulfoxide, although again the excellent diastereoselectivity was restricted to aromatic aldehydes (**Scheme 59**).[112]



Scheme 59

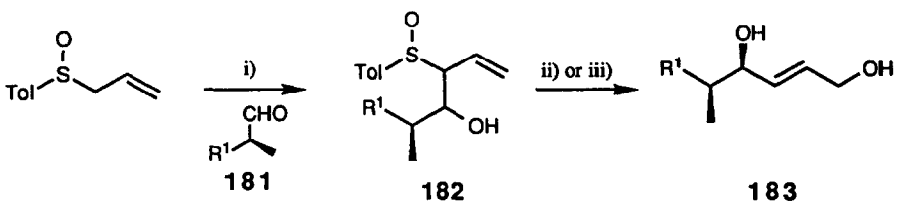
The addition of allyl and vinyl sulfoxides to carbonyl compounds has not received the same intensive investigation as for alkyl sulfoxides. Early examples of the addition of vinyl sulfoxides to aldehydes include the work of Okamura *et. al.*,[113] and of Posner and co-workers.[114] Whilst the alcohols were obtained in good yields and with high *E/Z* ratios, a thorough study of this reaction failed to result in high levels of diastereoselectivity. However, in an isolated paper, Solladie and Moine have shown that this type of reaction can be selective (**Scheme 60**).[115] The vinyl sulfoxide **176** added smoothly to the aromatic aldehyde **177** to give the β-hydroxysulfoxide **178** in 75% yield as a single diastereomer. Deprotection was followed by a Michael-type addition with concomitant dehydration to give the key chromene **179** in excellent yield. Standard transformations afforded the aldehyde **180**, the chroman ring of α-tocopherol.



177 176 178 179 180

Scheme 60

The use of allyl sulfoxides for the addition to carbonyl compounds has again been somewhat limited by the availability of homochiral starting materials and by the potential stereochemical lability of the adducts. Whilst some Australian workers have reported poor results with a series of aromatic aldehydes,[116] Annunziata *et. al.* have observed fair to excellent degrees of stereoselectivity in the reaction of racemic allyl sulfoxides with chiral aldehydes **181 (Scheme 61)**.[117] A mixture of α- and γ-products are formed, with α- predominant **182.** Conversion of these sulfoxides into allylic alcohols can be carried out in one pot to afford useful levels of diastereoselectivity in the preparation of functionalised diols **183.**



181 182 183

Reagents: i) LDA, HMPA ii) $P(OMe)_3$ iii) Et_3N, MeOH

Scheme 61

4. SUMMARY.

It is clear that sulfoxides are extremely useful reagents for asymmetric C-C bond formation. The large number of reliable methods for the preparation of homochiral sulfoxides now available, as discussed in Section 2, makes them a very attractive class of chiral nucleophile, and, with continuing developments in sulfoxide methodology, they represent a powerful tool for the synthetic chemist.

ACKNOWLEDGEMENT:- I would like to thank Dr. Mike Casey for his advice and encouragement.

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