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# Chiral non-racemic sulfinimines: versatile reagents for asymmetric synthesis

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## 1. Introduction

Amines represent one of the nature's key functionalities. Their incorporation into a wide variety of motifs, from drugs and biologically active molecules to ligands for asymmetric catalysis, underlines their importance to modern chemistry. Despite their abundance in both natural and un-natural systems, however, methods for the preparation of chiral amines can often be difficult. This deficiency in synthetic methodology has been efficiently addressed in recent years through the emergence of enantiopure sulfoxide *N*-protecting groups, versatile substituents that can be incorporated into a wide range of imines and influence the stereochemistry of a variety of reactions, introducing high levels of stereocontrol.

While it is recognised that 1,2-nucleophilic additions to imine double bonds represent one of the most flexible approaches to amines and, more specifically chiral amines, N-substitution is generally required to domesticate the capricious nature of the imines. This has prompted the development of electronically and structurally diverse *N*-substituents. To be effective tools for the synthetic chemist, these substituents are required to be inexpensive and easy to synthesise, to provide direct preparation of stable imines from a broad spectrum of aldehyde and ketone precursors, to

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furnish activation of the imine double bond for nucleophilic attack, to ideally act as a chiral directing group and finally, once their role is complete, to be amenable to facile removal.

## 2. Background

*N*-Sulfinyl-imines (sulfinimines) represent an exceptional class of imines.[1] Their widespread application since their inception has led to the development of an array of chiral sulfinyl motifs, offering the opportunity to fine-tune the reactivity of the sulfinimines towards specific requirements (Fig. 1).

Sulfinimines, albeit in racemic form, were first introduced over 30 years ago with the synthesis of *p*-toluene-sulfinimines (*p*-TS-imines, **1**), through the oxidation of *p*-toluene-sulfenimines with *m*-CPBA, by Davis and co-workers.[2] The first synthesis of enantiomerically pure *p*-TS-imines was accomplished by Cinquini et al. in 1982 via reaction of metal ketimines with the Andersen reagent **7** (Scheme 1).[3] Applications of this budding class of chiral *N*-substituent were, however, slow to emerge, primarily due to the difficulty associated with their preparation. New methods were developed to overcome this hurdle, and their application began to spread. This new-found interest prompted investigations into varying the structural and electronic chemistry of the sulfoxide. Garcia Ruano et al. recognised that substitution of the *p*-toluene motif with a *tert*-butyl group significantly increased the stereoinduction observed in the aziridination of sulfinimines.[4] This substitution was perceived to also infer a subtle alteration in the electronic chemistry of the species, specifically with respect to interactions with Grignard reagents. At the time of this work, however, the synthesis of *tert*-butyl-sulfinimines (*t*-BS-imines, **2**) was not straightforward.

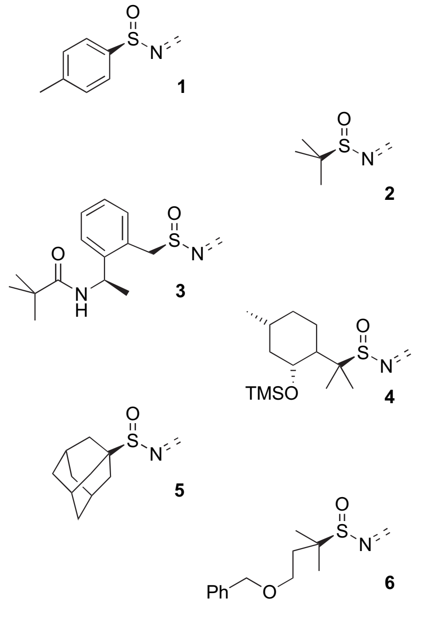
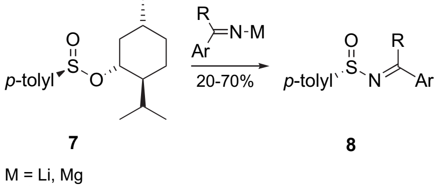


**Figure 1**.



**Scheme 1**.

It was in the mid-1990s that sulfinimine chemistry really blossomed; *p*-TS-imines were becoming recognised as valuable chiral ammonium synthons, and a novel direct entry into the *t*-BS-imines was developed. During their efforts to develop a new linker for solid-phase synthesis, Ellman et al. recognised a potential route for accessing *t*-BS-imines and subsequently reported the straightforward synthesis of *tert*-butyl-sulfinamide (*t*-BSA),[5] condensation of which with aldehydes and ketones provided direct entry to a broad range of *t*-BS-aldimines and *t*-BS-ketimines,[6] circumventing many of the problems previously associated with the preparation of sulfinimines.

At around the same time, other groups were investigating modifications of this concept. Wills et al. reported the synthesis of a recyclable chiral sulfinyl *N*-substituent, **3**, recycling of the chiral motif combined with the high stereocontrol induced making it particularly attractive.[7] Kawecki et al., emerging from a series of investigations focused on the interactions of sulfoxides with Lewis acids, described the development, generation and application of a novel chiral sulfoxide **4**.[8] Senanyake et al. have in the past three years developed an extremely facile entry to a broad, diverse range of chiral sulfoxides, each with individual, distinct chemical features (**5**, **6**).[9] In spite of these advances, however, the *p*-TS- and *t*-BS-imines remain the most popular substrates and have been applied in a panoply of asymmetric reactions. This work seeks to provide a general overview of the role of chiral sulfinimines in asymmetric synthesis, providing a taste for the chronological trends exhibited by these chiral synthons up until January 2006.

## 3. Synthesis of chiral sulfinimines

For any motif to be truly valuable as a synthetic tool, it is vital for it to be readily available. To this end, there has been a strong focus on the development of efficient routes for the direct, inexpensive synthesis of chiral sulfinimines. Examination of the chiral sulfinimine reveals three obvious disconnections, asymmetric oxidation, iminolysis of sulfinate esters and condensation of a sulfinamide with aldehydes and ketones (Fig. 2).

Each of these synthetic routes has been explored towards the development of an efficient synthesis of chiral sulfinimines.

### 3.1. Iminolysis

While the first sulfinimines were prepared by Davis et al.[2] it was Cinquini and co-workers who accomplished the first

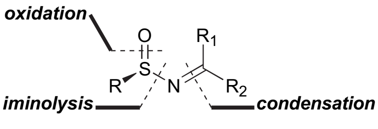
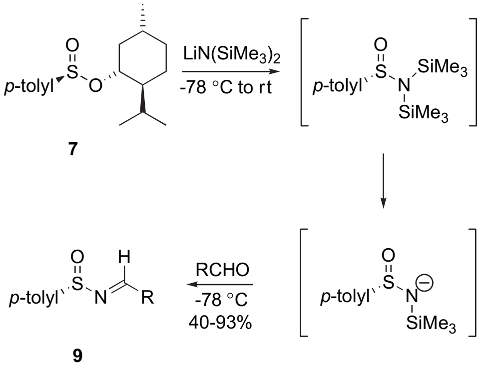


**Figure 2**.

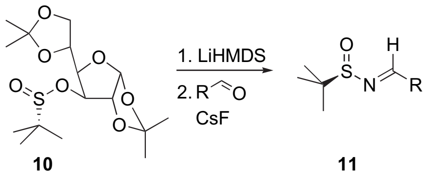
asymmetric synthesis of these chiral synthons.[3] Reaction of metal ketimines with the Andersen reagent **7** furnished a variety of sulfinimines **8** in 20–70% yield and high enantiopurity (Scheme 1).

While this methodology provided access to chiral sulfinimines, the scope of the reaction was severely limited, with only aromatic metallo-ketimines being suitable reagents, and the more sensitive aromatic and aliphatic aldehydes were precluded. In order to address this issue and expand the scope of accessible sulfinimines, Davis et al. developed a one-pot synthesis of sulfinimines from **7**, for the first time providing an efficient entry (40–93% yield, and >96% ee) to sulfinimines **9** derived from both aliphatic and aromatic aldehydes (Scheme 2).[10]



**Scheme 2**.

Exploiting the stereodirecting influence of the diacetone-D-glucose (DAG) developed by Alcudia et al.,[11] it is possible to prepare enantiomerically pure *t*-BS-imines (Scheme 3).[12] Both enantiomers of *S*-alkyl sulfinate ester **10** are accessible through judicious choice of conditions, subsequent fluoride-promoted condensation with both aldehydes and ketones revealing access to a range of *t*-BS-imines **11**.



**Scheme 3**.

More recently, Wills et al. have described the iminolysis of the recyclable chiral cyclic sulfinamide **12**.[7] Addition of metallo-imines to cyclic sulfinamide **12** resulted in the clean formation of aromatic sulfin-ketimines **13**. Subsequent removal of the sulfinyl group gave chiral amines **14** and chiral sulfinic acid **15**, which could be regenerated to the chiral cyclic sulfinamide **12** (Scheme 4). Many of the constraints associated with previous iminolysis methodologies were, however apparent, with only ketimines being suitable addition substrates and more sensitive, enolisable structures being precluded.

While the iminolysis of sulfinate esters provides access to a wide range of enantiopure sulfinimines, there are, unfortunately, a number of problems associated with this chemistry. The primary consideration is a practical one, isolation of the enantiomerically pure sulfinimines from the complex mixture of reagents and chiral auxiliaries employed prohibiting large-scale preparation using either Andersen's reagent or the DAG methodology.

### 3.2. Oxidation

Possibly the most rational approach to chiral sulfinimines **17** is through the asymmetric oxidation of sulfenimines **16**. There are two distinct methods for the introduction of asymmetry into the oxidation process (Fig. 3). One strategy is through the introduction of a stereo-inducing chiral centre into the sulfenimine, and thus an achiral oxidant can be employed. The alternative technique is to use a chiral oxidant, introducing asymmetry into achiral sulfenimines.

The first efficient chemo- and enantioselective oxidation of sulfenimines **18** was described by Davis et al. in 1992. Chiral *N*-sulfonyloxaziridines **20** were used as chiral oxidants to prepare both *R*- and *S*-sulfinimines **19** in 72–95% yield and 88–90% ee (Scheme 5).[13]

Davis demonstrated the generality of this procedure through the oxidation of a range of achiral sulfenimines. The

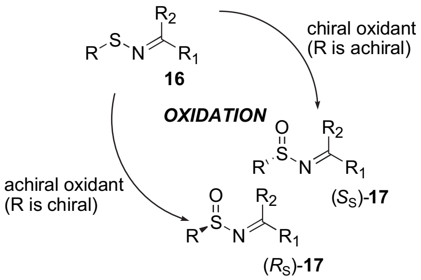
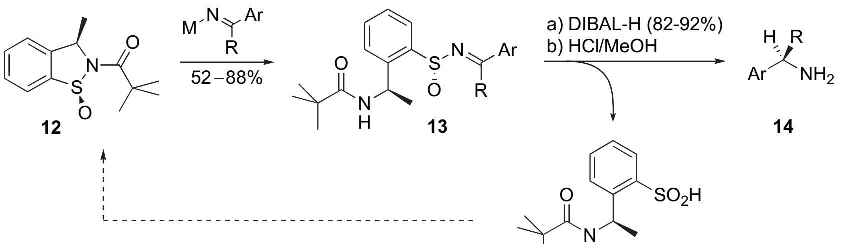
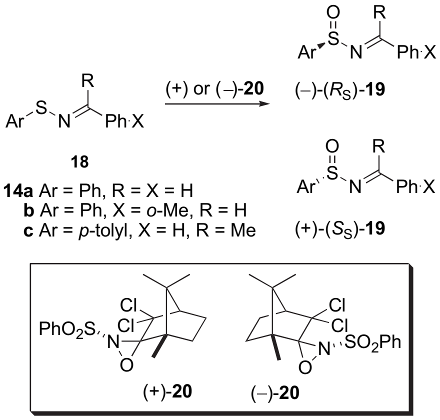


**Figure 3**.



Ar = Ph, *p*-tolyl
R = Me, Et, *i*-Pr, *t*-Bu

**Scheme 4**.



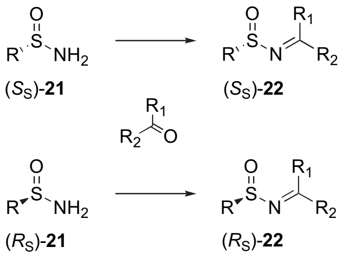
**Scheme 5**.

alternative approach, the diastereomeric oxidation of chiral, non-racemic sulfenimines, has also been reported.[14]

While asymmetric oxidation was found to provide access to a range of chiral sulfinimines in high ees, their application was limited, primarily due to the difficulty associated with the preparation of chiral *N*-sulfonyloxaziridines or the chiral sulfenimine starting materials.

### 3.3. Condensation

The most common and versatile method for the preparation of generic imines is through the condensation of an aldehyde or ketone with an amine, providing access to a diverse range of substituted imines. Thus, the obvious progression for the preparation of chiral sulfinimines **22** was the synthesis of chiral sulfinamides **21**, substrates for condensation with aldehydes and ketones (Scheme 6).

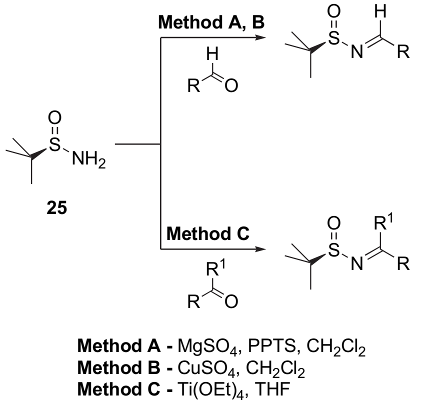


**Scheme 6**.

The first non-racemic sulfinamide was synthesised by Davis et al. in 1997. Isolated as a side product of their one-pot procedure for the direct preparation of chiral sulfinimines, *p*-toluene-sulfinamide (*p*-TSA) was found to condense with *p*-nitrobenzaldehyde in the presence of CsF. Other less reactive aldehydes were, however, found not to react with *p*-TSA, and it therefore appeared that the reaction was applicable to only a narrow range of substrates.

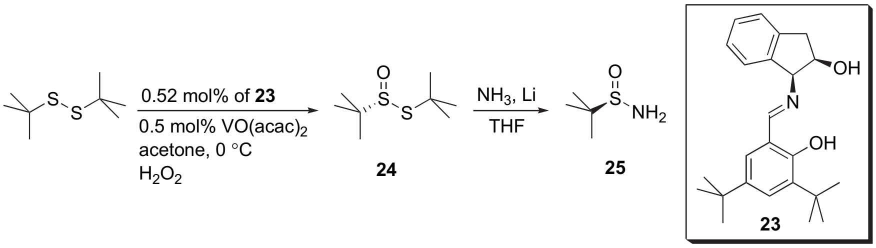
In the same year, Ellman et al. described the preparation and reaction of *t*-BSA **25**. The enantiomerically pure sulfinamide was synthesised through the reaction of lithium amide with chiral *tert*-butanethiosulfinate **24** (Scheme 7).

Although the initial procedure for acquiring the optically active *tert*-butanethiosulfinate **24** was found not to be amenable to large-scale preparation, subsequent investigations using the chiral ligand **23** have furnished conditions that allow the preparation of both enantiomers on the multi-kilogram scale in 68% overall yield and >99% ee.[15] Ellman's focus then switched to the condensation reaction between *t*-BSA and aldehydes and ketones (Scheme 8).[16] Direct condensation of *t*-BSA with aldehydes in the presence of $MgSO_4$ and PPTS provided both aromatic and aliphatic *t*-BS-imines in high yield (84–96%), with no sign of racemisation (Method A, Scheme 8). Under these conditions, however, large excesses of aldehydes were required, especially with unreactive substrates and efforts to react ketones met with little success. Use of the more Lewis-acidic $CuSO_4$ as both a desiccant and catalyst provided efficient access to *t*-BS-imines (40–96%), with many of the unreactive substrates only requiring small excesses of this reagent to provide satisfactory yields (Method B, Scheme 8). Despite the efficiency of $CuSO_4$, condensation with ketones was still not possible. To effect the condensation of *t*-BSA with ketones, a range of titanium(IV) salts were investigated (Method C, Scheme 8).



**Scheme 8**.

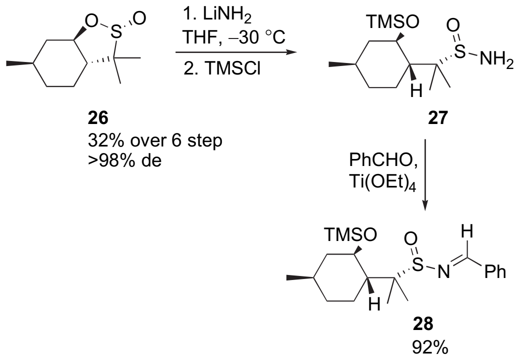
Ellman's studies revealed that $Ti(OEt)_4$ provided the best results, the condensation of unreactive aldehyde substrates being performed at room temperature, with mild warming



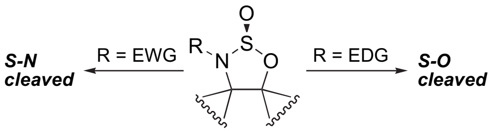
**Scheme 7**.

required to promote condensation with a wide range of ketones. This work established an efficient and reliable route for obtaining both *t*-BS-aldimines and *t*-BS-ketimines, significantly expanding the potential of chiral sulfinimines. The generality observed in the preparation of *t*-BS-imines through condensation of aldehydes and ketones with *t*-BSA was found to be true for the condensation with *p*-TS-amide (*p*-TSA).[17] Davis et al. screened a wide range of conditions for this condensation, finding that 4 Å molecular sieves or $Ti(OEt)_4$ were efficient desiccants for the procedure. Further to these investigations, a number of other conditions have been examined for the condensation reaction,[18,19] although few have approached the generality offered by those developed by Ellman and Davis.

From their experience gained in examining the interaction between chiral sulfinimines and Lewis acids,[8] Kawecki et al. proposed and developed the synthesis of a novel, recoverable chiral sulfinyl protecting group (Scheme 9).[8] Sultine **26**, prepared in six steps and 32% yield (>98% de), was reacted with lithium amide furnishing sulfinamide **27**. Condensation of **27** with benzaldehyde in the presence of $Ti(OEt)_4$ afforded sulfinimine **28** in 92% yield.



**Scheme 9**.



**Scheme 10**.

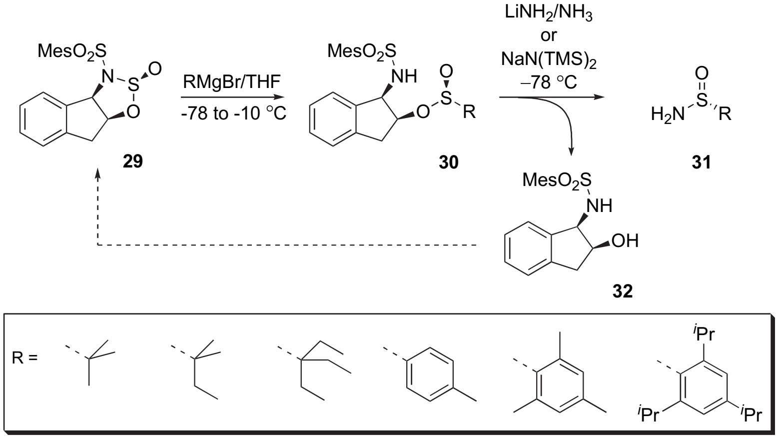
During their synthesis of the enantiomerically pure drug (*S*)-cetirizine, Senanayake et al. found that chiral sulfinimines, specifically *t*-BS-imines, were the most suitable intermediates for the drug's construction.[20] While the *t*-BS-imines provided acceptable results, however, their synthetic strategy required the preparation of structurally diverse aryl and alkyl sulfinamides for the fine-tuning of the diastereoselectivity of the organometallic addition. To fulfil this need, a general and practical modular synthesis of enantiopure tertiary alkyl and aryl sulfinamides was developed. Their approach was based upon the use of cyclic sulfinyl transfer agents. Over 30 years ago, Wudl and Lee demonstrated the utility of the (−)-ephedrine-derived *N*-methyl-1,2,3-oxathiazolidine-2-oxide in the synthesis of chiral sulfoxides. Exposure to carbon nucleophiles selectively cleaved the more reactive S–O bond (Scheme 10).

Senanayake et al. reasoned that a modification of the structure of the cyclic sulfinate would provide access to chiral sulfinamides. By building an electron-withdrawing group (EWG) rather than an electron-donating group (EDG) onto the nitrogen, the S–N bond would be activated and, thus upon exposure to a carbon nucleophile, the S–N bond would be cleaved in preference to the S–O bond giving silfinylester **30** (Scheme 11).

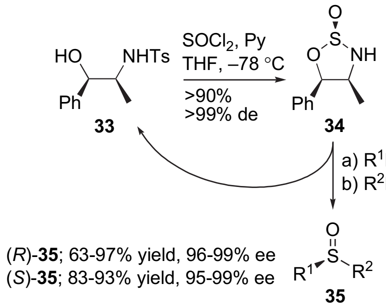
Not only does this chemistry provide access to a diverse range of chiral sulfinamides **31** in high yields and excellent enantiopurity, but, in addition, the valuable chiral amino alcohol **32** can be recovered and recycled to the cyclic sulfinate **29**, significantly increasing the efficiency of this chemistry.

More recent investigations have evaluated the use of other *N*-sulfonylamino alcohols as oxathiazolidine-oxide precursors. The inexpensive and readily available *N*-toluenesulfonylnorephedrine (*R*,*S*)-**33** was reported to be an excellent precursor to the corresponding oxathiazolidine-oxide **34**, exposure of which to a series of nucleophiles demonstrated its applicability to the preparation of chiral sulfoxides **35** (Scheme 12).

Condensation of aldehydes and ketones with chiral sulfinamides has become the most prevalent route for the preparation of chiral sulfinimines. With methods established for access to a variety of both sulfinyl and imine substituents, the versatility of condensation as a preparative procedure



**Scheme 11**.



**Scheme 12**.

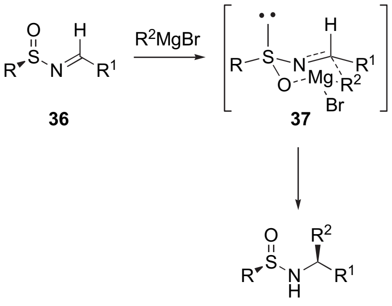
has significantly expanded the application of chiral sulfinimines in asymmetric synthesis.

## 4. Application of chiral sulfinimines as substrates in asymmetric synthesis

Since their inception, chiral non-racemic sulfinimines have played an increasingly significant role in the preparation of enantiopure amines. Their stereodirecting nature, the facile preparation of a diverse range of substrates and the subsequent possible removal of the protecting group have provoked widespread interest in their application. This section aims to provide a general overview of the role of chiral sulfinimines in asymmetric synthesis.

### 4.1. Synthesis of chiral amines

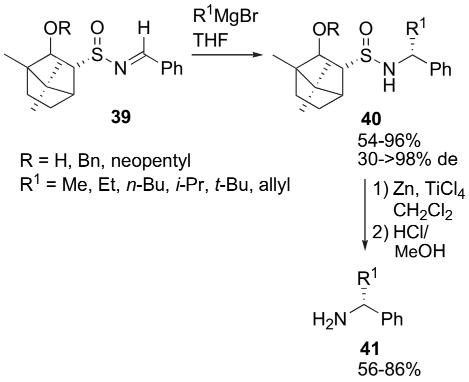
Nucleophilic 1,2-addition to an imine double bond is one of the most versatile and popular methods for the preparation of functionalised amines. With the incorporation of a stereodirecting motif in sulfinimines, the potential for the synthesis of chiral amines is evident. The typical means for such additions is through the reaction of aryl and alkyl carbanions, classically, Grignard reagents. Thus, it was proposed that addition of Grignard reagents to chiral sulfinimines **36** should, through transition state **37**, yield amines **38** with a high degree of stereoselectivity (Scheme 13).



**Scheme 13**.

The initial efforts to synthesise chiral amines from *p*-TS-imines, however, encountered problems. A prime example was reported in 1997 by Moreau et al., examining the addition of Grignard reagents to chiral *p*-TS-imines as a route for the synthesis of optically active 1,2-diphenylethylamines.[21] While the addition of benzylmagnesium bromide to the *p*-TS-imines furnished the desired sulfinamides in modest yield (55–76%) and stereoselectivity (60–74% de), exposure of the *p*-TS-imines under the same conditions to the more nucleophilic methylmagnesium bromide resulted in the displacement of the sulfinyl auxiliary and yielded none of the desired addition product.

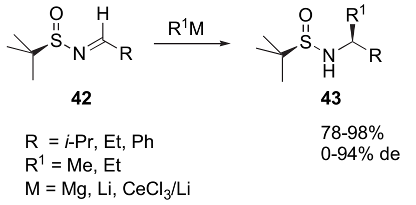
Thus, it became generally accepted that the more reactive Grignard reagents added exclusively to the sulfur of *p*-TS-imines, furnishing the *p*-tolyl methyl sulfoxides. These issues were overcome by the work of Yang et al. through the examination of an alternative *S*-substituent.[14] Reaction of the camphor-derived sulfinimines **39** with Grignard and other organometallic reagents was found to occur solely at the desired imine double bond, with no displacement being observed (Scheme 14).



**Scheme 14**.

A number of chemically diverse Grignard reagents were found to be suitable nucleophiles for this transformation, furnishing the chiral sulfinamides **40** in good yield and stereoselectivity. In addition, removal of the camphor-derived sulfinyl group was achieved in good yield to furnish the chiral amines **41**, with no loss in enantiopurity.

In 1997, Ellman et al. demonstrated the utility of *t*-BS-imines by the preparation of α-branched amines through the addition of Grignard reagents to these imines.[5] Ellman and co-workers later disclosed a report detailing the exploration of the synthesis of chiral amines through the addition of organometallic reagents to *t*-BS-imines.[22] They demonstrated that chiral amines **43** could be prepared in high yield (78–98%) and good diastereoselectivity (0–94% de) from the reaction of a diverse range of *t*-BS-imines **42** with a number of organometallic reagents (Scheme 15).



**Scheme 15**.

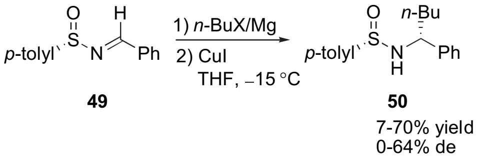
This work was further extended to encompass the reaction of *t*-BS-ketimines. Initial investigations found that both the rate and selectivity of the addition were disappointing. In order to both promote the rate and improve the selectivity of the reaction, a series of Lewis-acid additives were investigated.

The early results indicated that $Me_3Al$ was the Lewis acid of choice, providing yields of 26–93% with 26–99% de.[23] Further investigations, however, provided a more elegant solution.[24] It was found that employing $Ti(OEt)_4$ as a Lewis acid in the addition of organometallics to *t*-BS-imines promoted the rate and improved the diastereoselectivity of the reaction. With $Ti(OEt)_4$ being used to drive the condensation of *t*-BSA with ketones, the one-pot asymmetric synthesis of chiral *t*-BS-amines was realised (Scheme 16).

The use of $Ti(OEt)_4$ as the promoter in both condensation and reduction meant that chiral amines **48** could be prepared directly in one pot, with *t*-BS-ketimine **44** or *t*-BS-imines **45** and **46** not being isolated. Furthermore, Ellman and co-workers described the removal of the *t*-BS protecting group through acid-promoted methanolysis, a protocol shown to be applicable to an array of *t*-BS-aldimines and -ketimines. Addition of Grignard (M=MgBr) and organolithium (M=Li) reagents to the *t*-BS-ketimines followed by subsequent deprotection provided an efficient route to a wide range of chiral tertiary amines **48**. The stereochemical outcome of all their investigations were in keeping with the chelating transition state **37**.

While *t*-BS-imines are the preferred substrates for reactions with organometallic reagents due to the propensity for attack at the sulfur atom of *p*-TS-imines, a shrewd choice of both substrates and conditions has revealed a number of methods for organometallic addition to *p*-TS-imines. A prime example was reported by Chan et al. on the addition of *n*-butylmagnesium bromide to *p*-TS-imine **49** (Scheme 17).[25] Initial investigations gave the desired amine **50** in only 7% yield and as a 1:1 diastereomeric mixture, with the major product resulting from attack at the sulfur of the *p*-TS-imine. It was found, however, that premixing of the organometallic reagent with copper iodide not only improved the yield to 70%, but, in addition, increased the diastereoselectivity to 64% de. Thus, copper-mediated organometallic addition to *p*-TS-imines provides an efficient route to α-branched chiral amines.

Prakash et al. made use of the high stereodirecting nature of the *t*-BS-auxiliary in their synthesis of trifluoromethylated allylic amines.[26] Reaction of α,β-unsaturated *t*-BS-imines with $TMSCF_3$ in tetrahydrofuran furnished the corresponding allylic amines in 50–80% yield and >99% de. The application of this protocol to the *p*-TS-imines was later explored by Dolbier et al., but the yields (54–86%) and stereochemical induction (44–88% de) were observed to be significantly lower.[27]

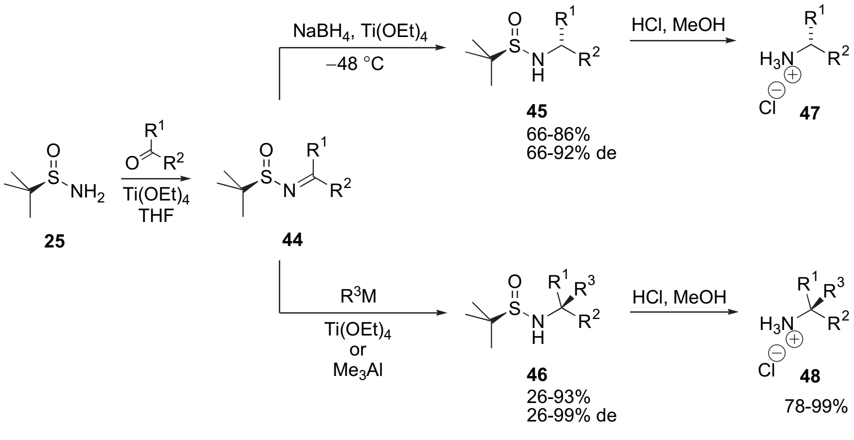


Scheme 17.

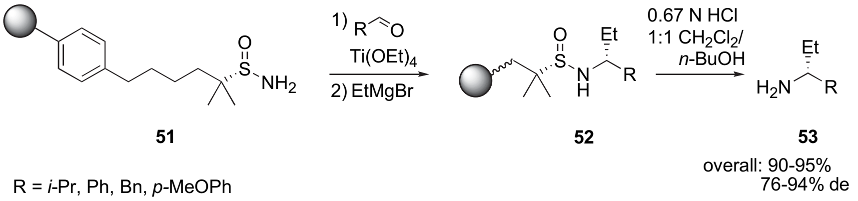
The routes of Ellman's interest in the field of chiral sulfinimines stem from research into the development of a novel solid-phase linker. In 2001, Ellman et al. reported on the synthesis and utility of a support-bound *tert*-butylsulfinamide derivative **51** (Scheme 18).[28] While many support-bound linkers have been developed for amines, few had incorporated the possibility to impart stereochemical information. Prepared in high yield, enantiopure **51** represents a stereodirecting solid-support linker, incorporating all the advantages displayed by the solution-phase *t*-BSA.

To correlate the solid- and solution-phase synthetic methods and demonstrate the practicality of the new technology, Ellman assessed the synthesis of chiral α-branched amines. Imine formation and addition of ethylmagnesium bromide were carried out under solution-phase optimised conditions. Subsequent cleavage from the solid-support-bound derivative **52** furnished the chiral amines **53** in near-quantitative yield over the three steps, albeit in a lower diastereomeric excess than the solution-phase counterparts. The utility of **51** was further demonstrated through the multistep synthesis of the more complex pavine and *iso*-pavine alkaloids.

Plobeck et al., during their investigations into the preparation of chiral diarylmethylamines, found that it was possible to implement a switch in the diastereoselectivity of the addition of the organometallic derivatives to *t*-BS-imines through judicious choice of reagents and conditions (Scheme 19).[29] While the addition of Grignard reagents afforded the expected *S*-amines **54**, reaction of the organolithium reagents in tetrahydrofuran furnished the *R*-amines **55**. To justify this change in stereochemical induction, which was observed

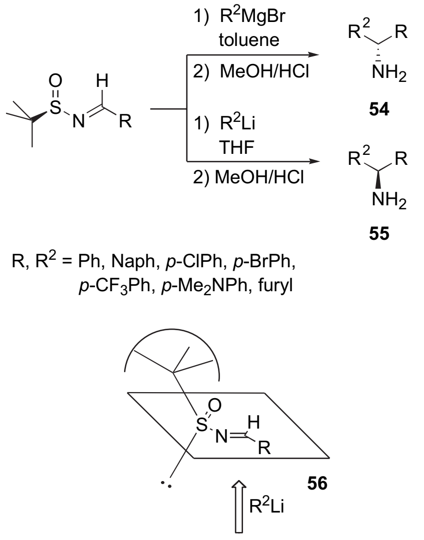


Scheme 16.



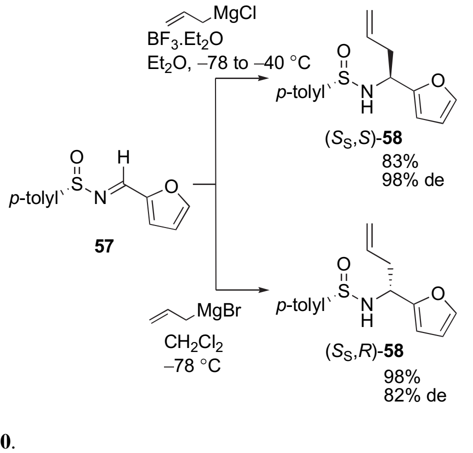
**Scheme 18**.

in a number of other instances, an open transition state **56** was adopted.



**Scheme 19**.

Shimizu et al. reported the addition of the more reactive allyl Grignard reagents to *p*-TS-imines.[30] An informed choice of the Grignard reagent and reaction conditions uncovered methods that furnished high diastereoselectivity and a reversal in the configuration of the newly formed chiral centre (Scheme 20). Addition of allylmagnesium bromide to **57** in $CH_2Cl_2$ furnished **58** in 98% yield with ($S_S$,*R*)-**58** in 82% de. On the other hand, in the addition of allylmagnesium chloride in ether, with $BF_3 \cdot OEt_2$ as an additive, ($S_S$,*S*)-**58** was observed to be the major diastereomer in 98% de and 83% yield.



**Scheme 20**.

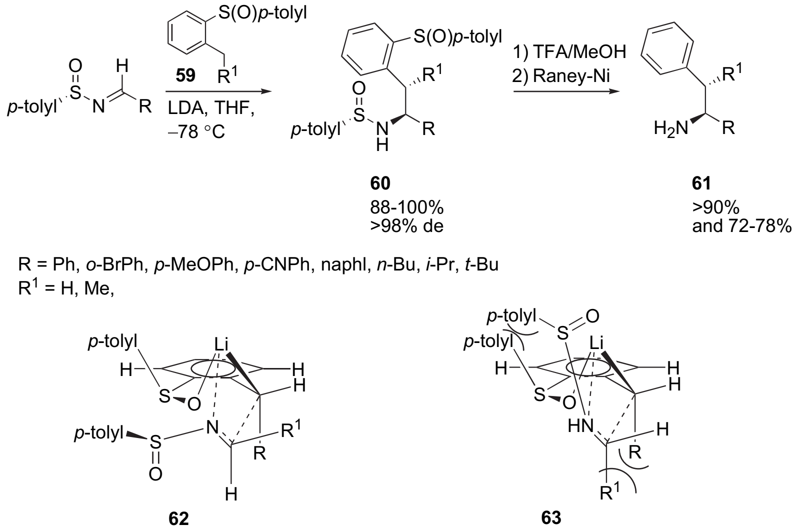
Prompted by reports of the difficulty of incorporating the benzyl motif into chiral amines through 1,2-nucleophilic addition to sulfinimines, primarily due to an unacceptably low stereoselectivity, Garcia Ruano et al. developed a new protocol to improve the stereoselective synthesis of 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines (Scheme 21).[31] Proposing that the inclusion of a chiral substituent at the *ortho*-position of the benzyl carbanion would increase the stereoselectivity of the reaction through a double stereodifferentiation effect, the reaction of the anion generated by deprotonation of sulfoxide **59** with a range of both aromatic and aliphatic *p*-TS-imines was examined.

Both aromatic and aliphatic sulfinimines proved to be suitable substrates for the procedure, affording sulfinamides **60** in high yield and exceptional stereoselectivity. Sequential removal of the *N*-sulfinyl group and the sulfoxide afforded the benzyl chiral amines **61** in good yield and optical purity. The exceptional stereoselectivity was rationalised by invoking a double stereodifferentiation effect. The matched pairing was found to be the *S*-isomer of the benzyl carbanion and the *S*-sulfinimine. In this instance, the reaction can proceed through either transition state **62** or **63**, but there are significantly less unfavourable steric interactions present in **62**, and thus the new chiral centre is formed almost exclusively as the *S*-isomer.

To demonstrate the utility of his new chiral sulfinamide, Kawecki explored the synthesis of chiral amines through the reaction of ethylmagnesium bromide with sulfinimine **64** (Scheme 22).[8] Comparative studies found that the reaction of sulfinimine **64** in $CH_2Cl_2$ furnished sulfinamide **65** in a comparable yield to the reaction of *t*-BS-imines, but notably with a higher diastereoselectivity (84% vs 98% de). The 8-menthylsulfinyl moiety was removed under acidic conditions, affording the desired amine and sulfinate **26**, which could be recycled.

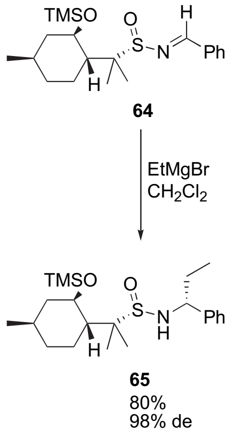
During a programme of research directed towards the stereoselective synthesis of organosilanes, Scheidt et al. reported the highly diastereoselective addition of silyl anions to *t*-BS-imines (Scheme 23).[32] Both aryl and branched alkyl *t*-BS-imines **66** were found to be suitable substrates for the addition, affording α-organosilanes **67** in good yield and stereoselectivity.

While the addition of Grignard and lithium reagents has proved to be a reliable method for the synthesis of chiral amines, these methods were, in general, intolerant to highly functionalised substrates. One example of the addition of a Grignard reagent to a complex, functionalised substrate was described by Overhand et al., where the addition of phenylmagnesium chloride to a sugar-based *t*-BS-imine provided the desired chiral amine in high stereoselectivity.[33] Full protection of the sugar alcohols was, however, required.

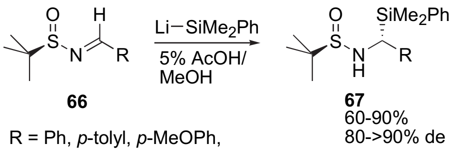


R = Ph, *o*-BrPh, *p*-MeOPh, *p*-CNPh, naphl, *n*-Bu, *i*-Pr, *t*-Bu
$R^1$ = H, Me,

**Scheme 21.**



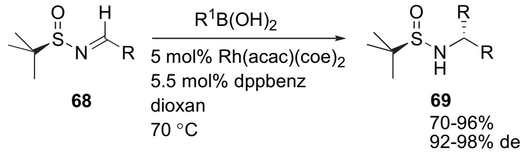
**Scheme 22.**



R = Ph, *p*-tolyl, *p*-MeOPh,
naphth, $PhCH_2{=}CH_2$, *t*-Bu

**Scheme 23.**

To address this issue, Ellman et al. investigated the addition of arylboronic acids to *t*-BS-imines.[34] While arylboronic acids are poor nucleophiles, rhodium(I)–phosphine complexes have been found to effectively catalyse their addition to *N*-sulfonyl-imines, and, thus, Ellman reasoned that *t*-BS-imines would be suitable substrates (Scheme 24).



R = *p*-tolyl, 2-phenylethyl, Ph
$R^1$ = Ph, *p*-MeOPh, *p*-$CF_3$Ph,
*m*-[C(O)Me]Ph, *p*-ClPh

**Scheme 24.**

The addition of arylboronic acids to both aliphatic and aromatic *t*-BS-imines **68** to form **69** was achieved in good yield (70–96%) and with high diastereoselectivity (92–98% de). Notably, Ellman reports the first rhodium(I)-catalysed addition of arylboronic acids to aliphatic imines **68** (R=2-phenylethyl), and demonstrates the functional group tolerance of the procedure with the addition of relatively sensitive substrates ($R^1$=3-acetylphenyl). The efficiency of the protocol was enhanced through the development of a one-pot procedure, leading from the aldehydes directly to the chiral amines **55**.

Recently, Batey et al. have disclosed their investigations on the rhodium-catalysed addition of arylboronic acids to chiral *t*-BS-imines, with conditions that require only room-temperature reaction and provide more facile practical conditions.[35]

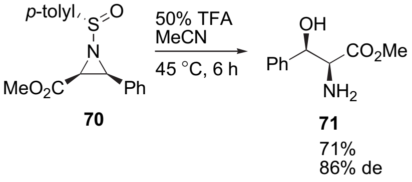
While it is clear that *t*-BS-imines have emerged as the favoured substrates for the synthesis of chiral amines, due to the lack of reaction of organometallics at sulfur, conditions have been established for the addition of organometallics to *p*-TS-imines. With the emergence of new techniques for nucleophilic addition to chiral sulfinimines, the range of substrates suitable for this transformation is set to expand.

### 4.2. Synthesis of chiral α-amino acids

The existence of α-amino acids as the building blocks of proteins and peptides in biological systems combined with their application as chiral synthons in modern organic chemistry has justified the continued efforts for the development of new and efficient methods for the preparation of an ever-expanding pool of these valuable chiral amines.

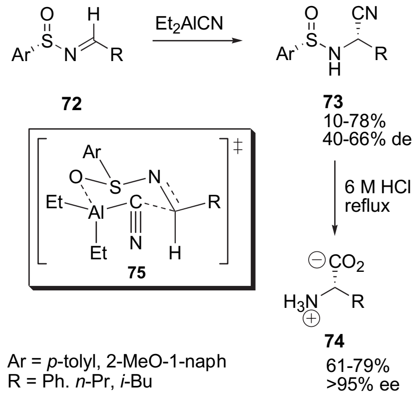
The first α-amino acid derived from a chiral sulfinimine was synthesised by Davis et al. in 1994.[36] To demonstrate the activating nature of the *p*-TS-sulfinyl group to promote the ring opening of an aziridine ring, exposure of aziridine **70** to 50%

aqueous TFA furnished the *syn*-β-phenylserine derivative **71** in 71% yield (Scheme 25).



**Scheme 25**.

While this reaction demonstrated the activating ability of the *p*-TS-group towards aziridine ring opening, it does not represent an efficient synthesis of α-amino acids. In the same year, however, Davis et al. published the first of a series of articles on the development of a highly efficient route to chiral α-amino acids.[37] The asymmetric Strecker synthesis of α-amino acids has become a cornerstone of this field of chemistry. The addition of cyanide to a chiral imine and subsequent hydrolysis of the nitrile furnishes the desired amino acid. The auxiliary controlled nucleophilic addition of cyanide to non-racemic imines had, however, encountered several hurdles; only modest levels of diastereoselectivity had been observed (22–60% de) and, subsequently, the removal of the *N*-substituent without decomposition or epimerisation of the α-amino acid proved challenging. Prompted by these shortcomings, Davis et al. investigated the use of enantiopure *p*-TS-imines in the Strecker synthesis[37] (Scheme 26). Their initial efforts using common cyanide sources such as KCN, CuCN and TMSCN met with disappointing results and, in general, there was no reaction, with only poor yields being obtained when addition did occur, even in the presence of Lewis-acid catalysts. Undeterred, diethylaluminium cyanide ($Et_2AlCN$) was examined as a source of cyanide. While there was only limited precedence for this reagent, Davis rationalised that the strong Lewis-acid nature of the reagent would increase the likelihood of addition to *p*-TS-imines **72**; complexation with the sulfinyl oxygen would not only activate the imine double bond to addition, but would also provide a mechanism for the intramolecular delivery of cyanide **75**.



**Scheme 26**.

The major diastereomeric α-amino nitriles **73** could be isolated by chromatography, and interestingly the sulfinimines with the 2-methoxy-1-naphthyl substituent were not only easier to separate but the addition appeared to proceed with higher diastereoselectivity. Removal of the sulfinyl group and hydrolysis of the nitrile were achieved in refluxing HCl, and hence, both aromatic and aliphatic chiral α-amino acids **74** were prepared in good yield and excellent enantiopurity.

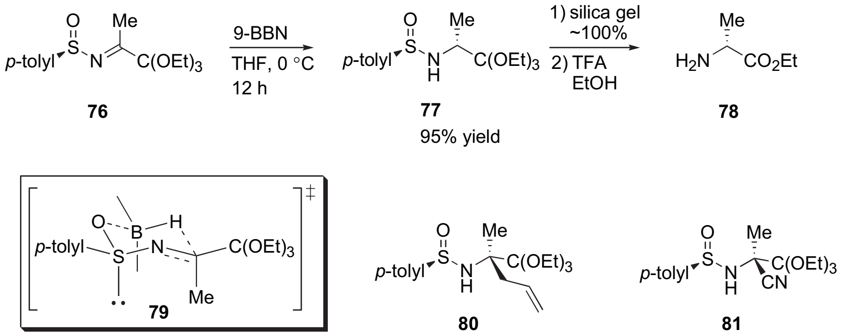
Hua et al. adopted an alternative approach to chiral α-amino acids (Scheme 27).[38] Reduction of *p*-TS-imine **76** was carried out with a number of reagents, both lithium aluminium hydride and diisobutylaluminium hydride giving a mixture of *R*-and *S*-diastereomers. However, reduction with 9-BBN yielded exclusively ($R_S$,*R*)-**77**. Hydrolysis of the *ortho* ester **77** on silica gel followed by ethanolysis afforded the alanine ethyl ester **78**.

An explanation for the stereoselective reduction was proposed in the form of the six-membered transition state **79**. The boron chelates with the sulfinyl oxygen, and hence the hydride reagent approaches from the *si*-face of the sulfinimine. Hua's investigations were extended by examining the addition of alternative nucleophiles to *p*-TS-imine **76**. Sulfinimine **76** underwent a completely stereoselective addition of allylmagnesium bromide to give **80** in 95% yield, subsequent deprotection and hydrolysis affording the corresponding α-amino acid. Treatment of **76** with $Et_2AlCN$ gave a 92% yield of both the *S*- and *R*-diastereomers of nitrile **81** in a 7:4 ratio.

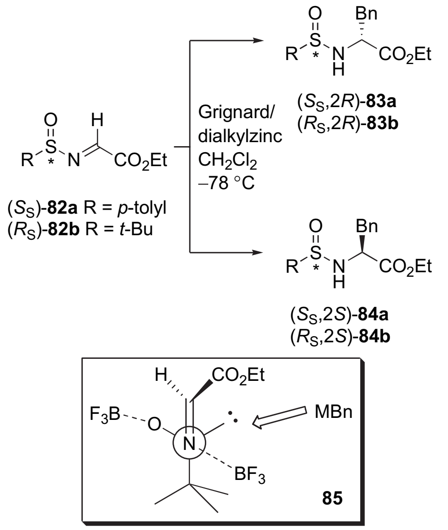
While the *p*-TS-imine asymmetric Strecker reaction provided access to a range of chiral α-amino acids, the diastereoselectivities were still only modest at best. Seeking to improve the stereoselectivity of this reaction, Davis et al. examined the reaction conditions.[39] Having realised that the Lewis acidity of the cyanide source was significant to this reaction, this aspect was considered. It was observed that pre-complexation of the $Et_2AlCN$ with 2-propanol resulted in a dramatic improvement in the diastereoselectivity, from 40–66% to 82–86% de, of the *p*-TS-imine Strecker reaction. Addition of 2-propanol to $Et_2AlCN$ results in the formation of an ethylaluminium cyanide, alkoxide Et(*i*-PrO)AlCN. It is thought that the lower Lewis acidity of the alkoxide complex relative to the $Et_2AlCN$ is responsible for the greater diastereoselectivity observed.

An alternative disconnection investigated by Davis et al. for the synthesis of α-amino acids provided some interesting results that furnished a procedure complementary to the *p*-TS-imine-based Strecker modification.[40] Glyoxylate imines have previously been employed in the preparation of un-natural α-amino acids, but the effectiveness of this route has been hampered by a lack of stereoselectivity. Proposing that the attachment of a sulfinyl group to the imino-nitrogen could introduce a level of stereocontrol over the reaction, Davis investigated the reaction of a series of glyoxylate sulfinimines (Scheme 28).

Initial investigations revolved around the reaction of *p*-TS-imine **82a** and, while the addition of BnMgCl occurred regioselectively at the desired imino carbon providing a diastereomeric mixture of amines **83** and **84**, with **83a** as the major diastereomer (*R*/*S* 82:12) in 56% yield, the mixture was found to be inseparable. The modest yield was attributed to a competing oligomerisation pathway and the associated sulfinyl displacement reaction recurrent in *p*-TS-imine



**Scheme 27**.

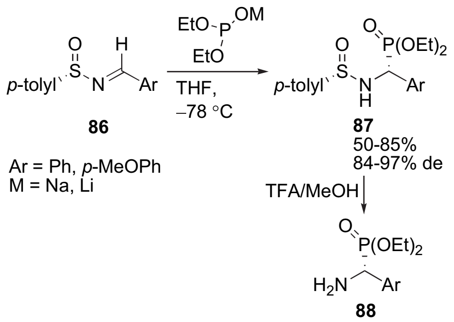


**Scheme 28**.

chemistry. Introduction of 2 equiv of the Lewis acid, $BF_3\cdot OEt_2$, to the reaction significantly decreased not only the oligomerisation, but, unfortunately, also the yield of the amino acid. It was thought that overactivation of the sulfinyl group promoted displacement of the sulfoxide by the organometallic reagent. Davis envisaged that the more sterically demanding *t*-BS-imine would reduce the likelihood of reaction at sulfur.

Initial results from the reaction of BnMgCl with *t*-BS-imine **82b** were disappointing, with significant levels of both oligomerisation and displacement at sulfur observed, but the diastereoselectivity was seen to have improved and the isomers were found to be separable by chromatography. Further investigation found that the addition of 2 equiv of $BF_3\cdot OEt_2$ and the use of 2 equiv of the organometallic reagent provided conditions that effectively eliminated oligomerisation and the displacement of the sulfoxide, delivering the protected α-amino acid **83b** in 88% de and 70% isolated yield. These conditions were found to be efficient for a number of both aromatic and aliphatic organometallic reagents (Bn, Ph, Et, Me). The sense of stereoinduction is opposite to that previously observed. To rationalise this observation, Davis proposed the open transition state **85**. Coordination of $BF_3$ to the sulfinyl oxygen and to the imino-nitrogen sterically shields the *si*-face of the imine to afford the Cram product. This observed difference is due to the presence of the ester functionality, and it was speculated that chelation of the incoming organometallic reagent with the ester carbonyl disrupts and prevents the formation of the commonly favoured chelated transition state. This inversion of the observed stereoinduction provides a method complementary to Davis's modification of the Strecker reaction. This chemistry was more recently put to interesting use *en route* to the synthesis of the un-natural amino acid, L-α-(1-cyclobutenyl)glycine.[41] Thus, the chiral centre was set up through the asymmetric directing power of the chiral sulfinyl group on the addition of 1-cyclobutenylmagnesium chloride on the *t*-BS-imine glyoxylate.

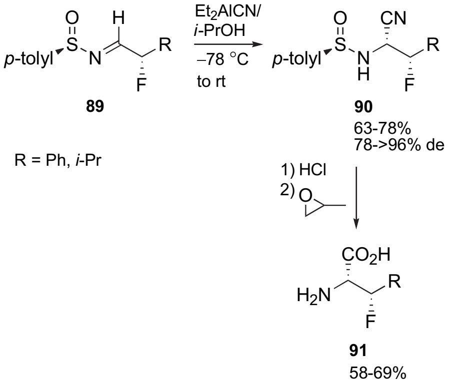
The wide range of biological activity exhibited by α-amino phosphonic acids as surrogate α-amino acids, primarily as antagonists in the metabolism of amino acids, has resulted in a number of routes for their preparation. In 1997, Evans et al. took advantage of the stereodirecting nature of the *p*-TS auxiliary in the synthesis of these biologically interesting compounds (Scheme 29).[42] Both lithium and sodium phosphites were added to a range of aromatic *p*-TS-imines **86**, with the corresponding *p*-TS-α-amino phosphonates **87** isolated in high yield and diastereoselectivity. The lithium phosphites were observed to provide marginally better yields and stereoselectivities, with the stereoinduction consistent with an open, non-chelating transition state. Subsequent deprotection was accomplished in high yield, furnishing the desired α-amino acid surrogates **88**.



**Scheme 29**.

As a continuation of their studies into the application of the sulfinimine-mediated asymmetric Strecker synthesis and, in particular, its application to the preparation of β-substituted α-amino acids, Davis et al. published a series of papers in 1999–2000 detailing the synthesis of structurally diverse β-substituted α-amino acids.

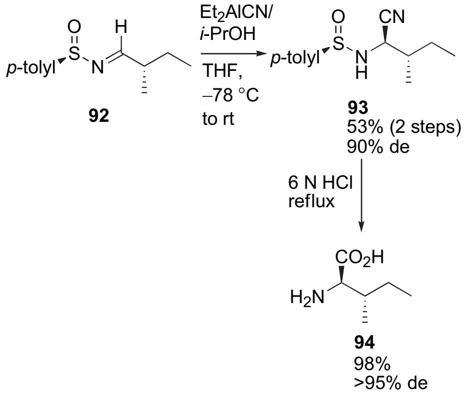
Shrewd inclusion of a fluorine atom into a structure has the capacity to significantly enhance the biological properties and, in this respect, β-fluoro α-amino acids are of particular interest. Many of the previous strategies for synthesising these halogenated amines displayed low yields and a tendency for defluorination during the deprotection of the amine. In 1999, Davis et al. described a direct approach to these biologically interesting compounds (Scheme 30).[43]



**Scheme 30.**

Addition of cyanide to α-fluoro p-TS-imines **89** through optimised reaction of Et$_2$AlCN/i-PrOH furnished β-fluoro α-amino nitriles **90** in high yield (63–78%) and diastereomeric excess (78 to >96% de). Subsequent treatment with 6 N HCl and propylene oxide afforded β-fluoro α-amino acids **91** in good yield with no racemisation observed. Notably, the stereoselectivity of the reaction was observed to be unaffected by the presence of the α-fluoro chiral centre, with the sulfinyl group found to be the sole influence over the topicity of the nucleophilic cyanide addition.

In 1999, Joullié et al. disclosed the synthesis of the β-methyl α-amino acid (2R,3S)-alloisoleucine via the sulfinimine-mediated Strecker reaction (Scheme 31).[44] Addition of cyanide to the crude p-TS-imine **92** afforded α-amino nitrile **93** in good yield and high diastereoselectivity. It was observed that, in accordance with previous findings, the adjacent chiral centre played no role in the stereoselectivity of the reaction, and rather the sulfinyl group was the sole influence on the topicity of the cyanide delivery. Subsequent deprotection under standard conditions provided the un-natural α-amino acid **94** in high yield.



**Scheme 31.**

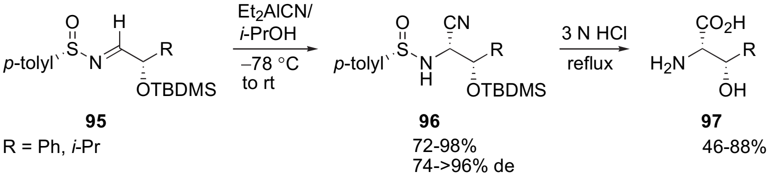
β-Hydroxy α-amino acids are not only an important class of biologically active compounds, but, in addition, they are useful chiral building blocks in organic synthesis. In 2000, Davis et al. described a general route to β-hydroxy α-amino acids (Scheme 32).[45] Reaction of p-TS-imines **95** under the optimised Strecker conditions afforded α-amino nitriles **96** in good yield (72–98%) and good diastereoselectivity (74–96% de). Davis et al. demonstrated the generality of this procedure through preparation of all four stereoisomers of phenylserine and (2R,3S)-β-hydroxyleucine. Investigation of the factors influencing the stereoselectivity of the reaction revealed that a double stereodifferentiation effect was present, where the chirality of the resident hydroxyl moiety influences the asymmetric induction. This effect was, however, observed to be relatively weak, with the mismatched pair proceeding with 74% and 87% de, while the matched pair presented >96% de. It is suggested that the reason this double stereodifferentiation effect is observed for these substrates, yet not for the α-methyl or α-fluoro substrates, is due to the greater steric presence of the TBDMS protecting group.

Hydrolysis of the diastereomerically pure α-amino nitriles was accomplished by refluxing with 3 N HCl, delivering amino acids **97** in 46–88% yield and >95% enantiomerically pure.

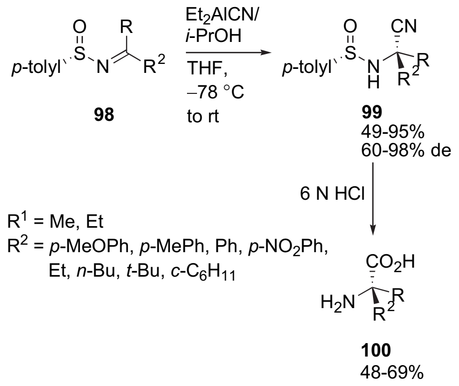
Davis successfully prepared the surrogate β-hydroxy α-amino phosphonates through the addition of metal dialkyl phosphites to O-protected α-hydroxy p-TS-imines.[46] The chiral motifs were prepared in good yield (68–74%) and high diastereoselectivity (86 to >94% de). The addition was observed to be subject to a similar double stereodifferentiation effect, though again the sulfinyl group was found to exert the primary influence.

Another avenue of structural investigation for α-amino acids is the investigation of α-alkyl α-amino acids. Davis proposed that application of the sulfinimine-mediated asymmetric Strecker reaction to sulfin-ketimines would provide a straightforward route for the synthesis of these sterically congested amines (Scheme 33).[47]

Reaction of ethylaluminium cyanoisopropoxide with p-TS-ketimines **98** gave α-amino nitriles **99** in good yield (49–95%) and diastereoselectivity (60–98%), with the



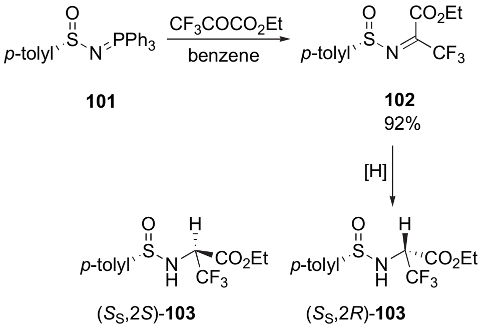
**Scheme 32.**



**Scheme 33**.

stereoselectivity of the reaction in accordance with the chelating six-membered transition state **75**. Hydrolysis to α-alkyl α-amino acids **100** was achieved through refluxing in 6 N HCl. To ascertain the effect of a more sterically demanding sulfinyl group on the diastereoselectivity of the reaction, Davis examined the cyanide addition to *t*-BS-ketimines. While the crude yield and diastereoselectivities (64–84% de) were comparable, unlike the *p*-TS-α-amino nitriles, the *t*-BS analogues could not be easily separated by flash chromatography. In addition, removal of the *t*-BS protecting group was found to be challenging. Later in the same year, this chemistry was applied to the synthesis of the di-α-amino acids, (2*S*,6*S*)-diaminopimelic acid and *meso*-(2*S*,6*R*)-diaminopimelic acid, providing an efficient entry to these biologically interesting compounds.[48]

Zanda et al. developed a novel, *p*-TS-imine-mediated synthesis of trifluorinated α-amino acids **103** (Scheme 34).[49] The Staudinger reaction of **101** proceeded in high yield, affording *p*-TS-imine **102**. The sulfinyl group was found to direct the stereoselectivity of the reduction of imine **102**. The sense and extent of the reduction were observed to be dependent upon the hydride source employed.



| | (SS,2S)-103 | | (SS,2R)-103 | |
|---|---|---|---|---|
| DIBAL-H | 1 | : | 4 | 52% |
| 9-BBN | 20 | : | 1 | 78% |

**Scheme 34**.

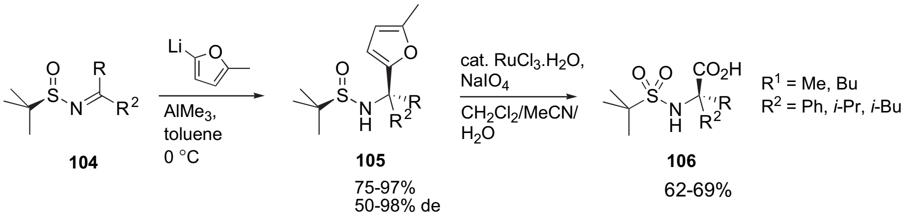
Reduction with 9-BBN occurred in high yield and stereoselectivity, rationalised by the six-membered transition state **79** proposed by Hua, while DIBAL-H proceeded with significantly lower yield and diastereoselectivity, the fact that both diastereomers are readily accessible from the same enantiomer of the *p*-TS-imine making this as an attractive route. Hydrolysis afforded 3,3,3-trifluoroalanine.

Ellman et al. also considered the synthesis of α,α-disubstituted amino acids **106** from sulfin-ketimines **104**, but an alternative disconnection was examined (Scheme 35).[50] Nucleophilic addition of a masked carboxylic acid to sulfin-ketimines and subsequent oxidation and deprotection provides direct access to α,α-disubstituted amino acids.

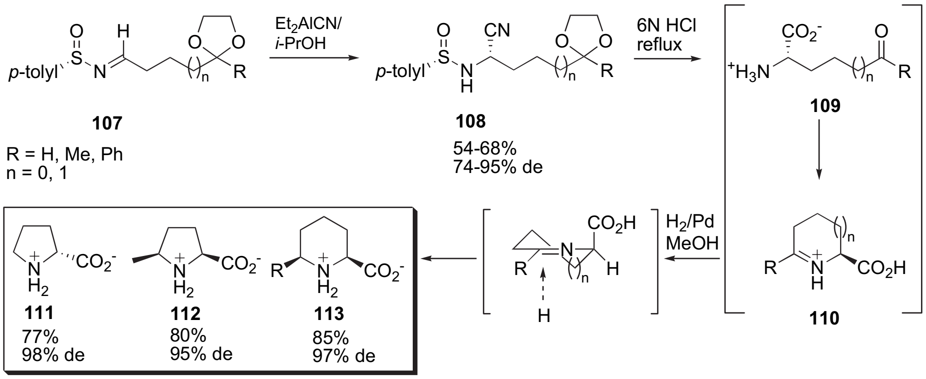
Addition of 5-methylfuryllithium at 0 °C furnished **105** in good yield (75–90%) and excellent diastereoselectivity (50–98% de), and the reaction was found to be general over a range of both aromatic and aliphatic substrates. Oxidation of both the sulfinyl and furyl groups afforded the *tert*-butylsulfonyl- (Bus-) protected α,α-disubstituted amino acids **106** in good yield (62–69%), with no racemisation observed. The utility of Bus-protected α,α-disubstituted amino acids in peptide synthesis was then examined, with two coupling conditions evaluated, in both instances the protecting group remaining untouched. Removal of the Bus protection was achieved through exposure to TfOH/$CH_2Cl_2$ in good yield (65%).

In 2001, Davis et al. focused their interest on the application of the sulfinimine-mediated Strecker reaction on the synthesis of cyclic α-amino acids.[51] Previous methods for the synthesis of these structurally interesting motifs had been hampered by their reliance upon proteinogenic amino acids as building blocks, hence making access to both enantiomers difficult. The Davis strategy revolved around the Strecker reaction of masked oxo *p*-TS-imines **107** (Scheme 36).

Treatment of the masked oxo sulfinimines **107** with $Et_2AlCN$/*i*-PrOH afforded α-amino nitriles **108** in good yield (54–68%) and high diastereoselectivity (74–95% de). Hydrolysis of the diastereomerically pure α-amino nitriles in refluxing HCl accomplished a number of operations in a single pot; hydrolysis of the sulfinyl group was accompanied by conversion of the nitrile into the acid, and the protected acetal is unmasked to give the intermediate aldehydes/ketone **109**, which undergoes cyclisation in situ, furnishing the iminium ion **110**, which was carried through a hydrogenation crude, producing the cyclic α-amino acids **111–113** in high



**Scheme 35**.



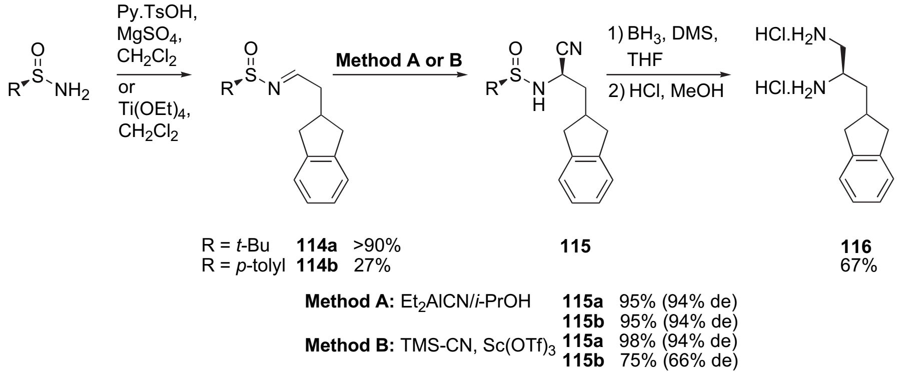
Scheme 36.

yield (77–85%) and excellent diastereoselectivity (95–98% de).

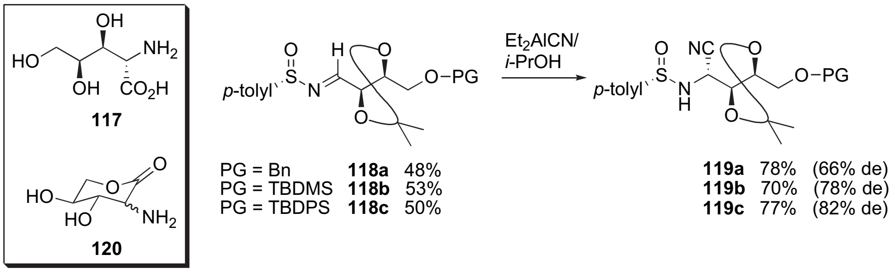
During a programme of research directed towards the preparation of imidazoles as potential antidepressants, Cordi et al. investigated the application of the sulfinimine-mediated asymmetric Strecker reaction as a facile method for the preparation of one of the key intermediates.[52] During these investigations, the suitabilities of the *p*-tolyl- and *t*-BS-imines were compared and an alternative cyanide source was investigated (Scheme 37).

Condensation with *t*-BSA to form sulfinimine **114a** occurred in high yield, and it was noted that the sulfinimine was highly stable and easily isolated, while condensation with *p*-TSA under typical conditions furnished sulfinimine **114b** in disappointing yield and the sulfinimine itself was found to readily decompose. Two cyanide-delivery reagents were examined. The Strecker conditions developed by Davis et al. afforded α-amino nitriles **115a** and **115b** in high yield and diastereoselectivity (Method A). The second delivery agent examined was TMSCN, previously thought to be inactive towards sulfinimines, and it was found to react at temperatures above 10 °C in the presence of an activating Lewis acid. After extensive screening, scandium triflate was found to deliver the best yield and diastereoselectivity (Method B). Subsequent reduction and deprotection efficiently provided the desired di-amine intermediate **116**.

Through a series of reports, Davis et al. have demonstrated that the sulfinimine-mediated Strecker synthesis is an efficient, versatile and stereoselective method for the synthesis of a diverse range of α-amino acids. There were, however, limitations highlighted, primarily the ability to prepare the desired sulfinimine, and the compatibility of the functional groups with the hydrolysis conditions. To this end, Davis sought a highly substituted α-amino acid that would provide a good test for these criteria. Thus, the synthesis of polyoxamic acid **117** was investigated (Scheme 38).[53] Sulfinimine **118** was prepared in modest yield, with the extent of the



Scheme 37.



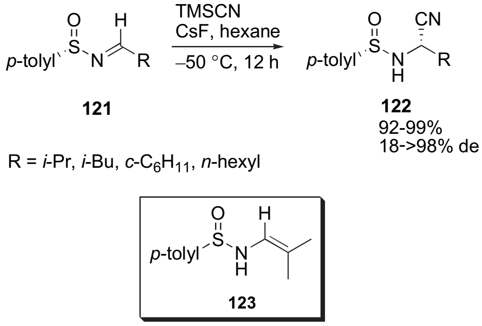
Scheme 38.

condensation found to be almost independent of the protecting group employed.

Hydrocyanation of **118a–c** afforded the corresponding α-amino nitriles **119a–c** in good yield (70–78%) and modest to good diastereoselectivity (66–82% de). Alteration of the conditions failed to provide a significant improvement. Stereochemical investigations revealed that the chiral sulfinyl moiety was the sole stereodirecting factor with no double stereodifferentiation effect observed.

In previous examples of the sulfinimine-mediated Strecker reaction, the hydrolysis of the nitrile and concomitant removal of the sulfinyl group is accomplished in a simple one-pot operation. Application of the normal conditions to **119a** resulted in decomposition. Exposure of **119a** to moist ethereal HCl removed both the ketal and sulfinyl moieties, but conditions could not be found for the reductive removal of the benzyl group. Exposure of **119c** to refluxing HCl also resulted in decomposition, as did exposure to moist ethereal HCl. Thus sequential removal of the TBDPS with TBAF and the sulfinyl moiety with ethereal HCl was accomplished. Hydrolysis of the nitrile functionality was executed using moist ethereal HCl, but rather than the desired acid, lactone **120** was isolated. Efforts to remove the TBDMS group in **119b** were unsuccessful.

Recently, an alternative, yet complementary, approach to Davis's modification to the Strecker synthesis was reported by Hou and Dai.[54] Whilst Davis's work was efficient in the generation of α-amino acids, there were some practical considerations and limitations evident in the generality in the procedure, and thus Hou and Dai sought to address these by the consideration of an alternative source for the cyanide anion. While Davis's early work had established that when aromatic *p*-TS-imines were treated with TMSCN and CsF in tetrahydrofuran no reaction occurred, from previous experience Hou and Dai had observed that the presence of a fluoride anion acted as a trigger to promote the reaction of silicon reagents. On revisiting the conditions initially investigated by Davis et al., it was observed that TMSCN, in the presence of CsF, successfully adds to the C=N bond of *p*-TS-imines **121**, provided that there is an enolisable proton α to the imine bond (Scheme 39).



**Scheme 39.**

With yields of the α-amino nitriles **122** >90% and the diastereoselectivities >95%, the application of the more robust TMSCN as a cyanide-delivery reagent has only one obvious limitation. Identification of enamine **123** from the reaction mixture suggests it is an intermediate in the mechanism, lending weight to the argument that only enolisable imines are suitable substrates for these conditions, a rationale further supported by the lack of reaction with non-enolisable *p*-TS-imines.

Extending their work on the synthesis of cyclic α-amino acids, Davis et al. reported the construction of cyclic α-amino phosphonic acids via masked oxo *p*-TS-imines (Scheme 40).[55] Reaction of the masked oxo *p*-TS-imines **124** with 2 equiv of lithium diethyl phosphate furnished the α-amino phosphonates **125** in high yield and diastereoselectivity. Subsequent hydrolysis and hydrogenation of the major diastereomers **126** afforded the cyclic α-amino phosphonates **127–129** in modest to good yield with no loss of enantiopurity observed.

Further to these investigations, Davis examined the reaction of masked oxo *p*-TS-ketimines towards the asymmetric synthesis of quaternary cyclic α-amino phosphonates. While the masked oxo *p*-TS-ketimines did prove to be suitable substrates for this reaction, lower yields and diastereoselectivities were observed.

Recently, Avenoza et al. have exploited the sulfinimine-mediated Strecker synthesis for the straightforward preparation of both (*S*)- and (*R*)-α-phenylserine.[56] Hydrocyanation of the *t*-BS-imines afforded the corresponding α-amino nitriles in only modest yield (52%) and stereoselectivity (62% de). Subsequent deprotection and hydrolysis provided rapid access to the structurally interesting α,α-disubstituted amino acids.

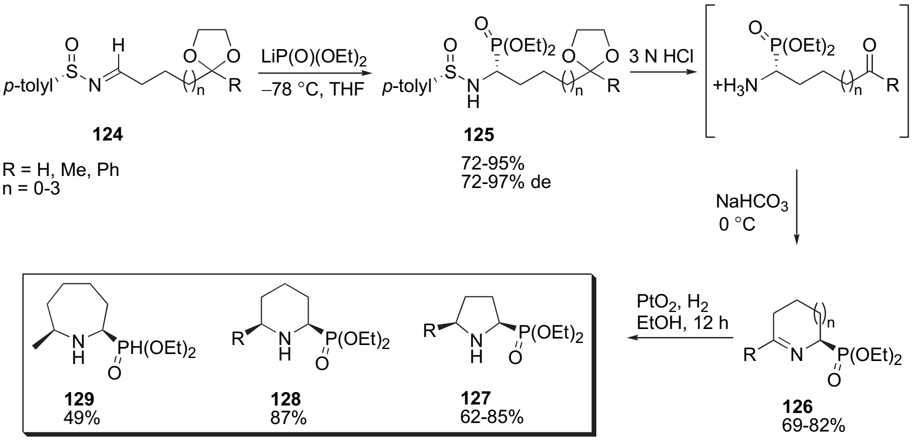
The sulfinimine-mediated asymmetric Strecker synthesis developed by Davis et al. has provided a direct and efficient route to a wide range of chiral non-racemic α-amino acids. Modifications have extended the applicability of this procedure, and alternative cyanide sources have been investigated. Both *p*-TS- and *t*-BS-imines have been shown to be suitable chiral precursors for α-amino acids.

### 4.3. Synthesis of chiral β-amino acids

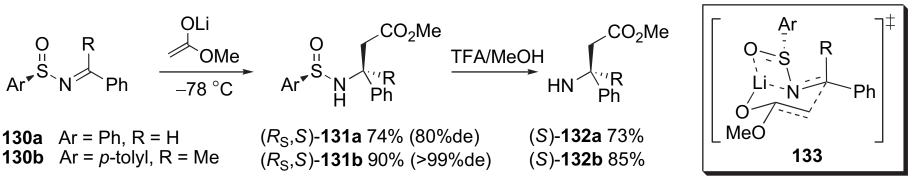
β-Amino acids have recently received significant attention as the fundamental building blocks of β-peptides. Previous methods for their preparation have relied upon either the homologation of α-amino acids or the addition of various nucleophiles to imines. While these methods have been effective, efficient and more general means are still sought.

In 1992, Davis et al. first described the synthesis of enantiomerically pure *p*-TS-imines through the asymmetric oxidation of sulfenimines with chiral oxaziridines.[13] To demonstrate the capacity of the *p*-TS-imines towards asymmetric synthesis, the preparation of non-racemic β-amino acids was tackled (Scheme 41).

Thus, addition of lithium enolate to enantiopure sulfinimines **130a**,**b** furnished the sulfinamides **131a**,**b** in good yield and diastereoselectivity and, notably, the *p*-tolyl-sulfinyl group afforded significantly higher levels of diastereoselectivity. Further, no enolisation of **130b** was observed. Hydrolysis, with no loss of enantiopurity, was achieved with TFA in methanol, affording β-amino acids **132a**,**b** in good yield.



Scheme 40.

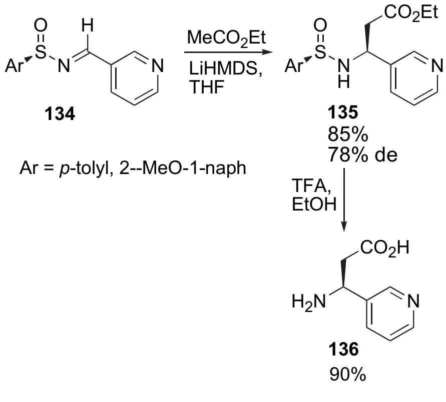


Scheme 41.

Davis proposed the Zimmerman–Traxler-type six-membered transition state **133** to rationalise the stereochemical outcome. Chelation of the incoming lithium enolate with the sulfinyl oxygen ensures delivery to the *si*-face of the sulfinimine.

During studies towards the synthesis of (*R*)-β-phenylalanine, an important constituent of a number of biologically interesting compounds, Davis et al. re-examined the conditions of enolate addition to *p*-TS-imines.[57] While the lithium enolate in tetrahydrofuran afforded the corresponding sulfinamide in 74% yield and 80% de, the use of the sodium enolate in diethyl ether boosted the yield to 84% in >96% de. Thus, sodium enolates became the favoured reagents.

Extending the scope of their β-amino acid protocol, Davis et al. reported the asymmetric synthesis of (*S*)-ethyl-β-amino-3-pyridinepropanoate **136**, a key building block of a peptidomimetic of fibrinogen and an orally active antiplatelet agent (Scheme 42).[58] It was anticipated that the basic pyridine unit would present complications, and thus this synthesis provided a test of the robustness of the procedure. Hence, while the sodium enolate in diethyl ether had been established as the most efficient conditions, the insolubility of sulfinimine **134** precluded these conditions. Therefore a re-examination of the conditions was required.

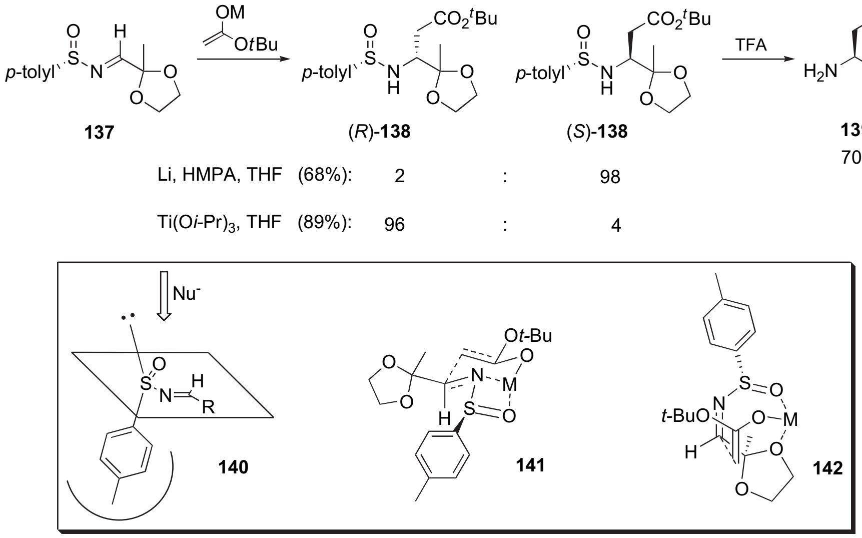


Scheme 42.

While it was found that the lithium enolate of ethyl acetate effected the desired transformation in acceptable yield, the *p*-tolyl-substituted sulfinamide diastereomers were found to be inseparable. Fortunately however, the 2-methoxynaphthyl derivatives were found to be readily separable by flash chromatography. Hydrolysis of sulfinimine **135** with TFA presented β-amino acid **136**, in 90% yield, with the enantiomeric purity shown to be >97% ee.

*En route* towards the synthesis of chiral β-lactams, Fujisawa et al. observed an interesting feature of the reactivity of different metal enolates with *p*-TS-imines to make β-amino acids.[59] It was realised that it was possible to control the sense of stereoinduction through judicious choice of reagent, thus effectively making both enantiomers of the newly formed stereocentre available from the same starting material (Scheme 43). A rationale for the observed switchover in stereoselectivity was provided through a consideration of the chelated and non-chelated transition states. Addition of the lithium enolate in tetrahydrofuran with HMPA as an additive causes the counterion effect to be negated by solvent effects, and thus the open transition state **140** predominates, resulting in *si*-face attack of sulfinimine **137**.

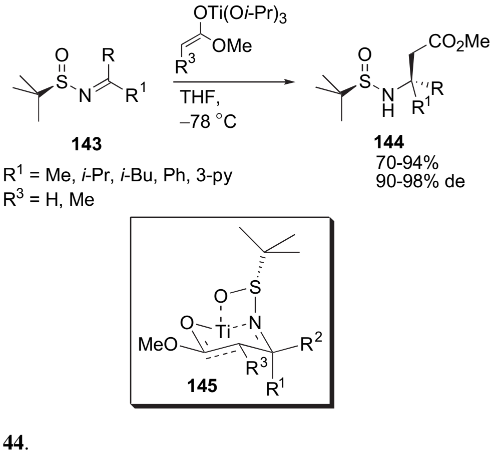
On the other hand with the titanium enolate, however, the more covalent nature of the bonding interactions leads to the predominance of the Zimmerman–Traxler-type six-membered transition state **141** and/or the seven-membered counterpart **142**, delivering the enolate to the *re*-face of the



Scheme 43.

sulfinimine. Both sets of conditions furnish sulfinamide **139** in good yield and high diastereoselectivity. Hydrolysis of (*S*)-**138** afforded the β-amino acid that was taken forward for the synthesis of β-lactams.

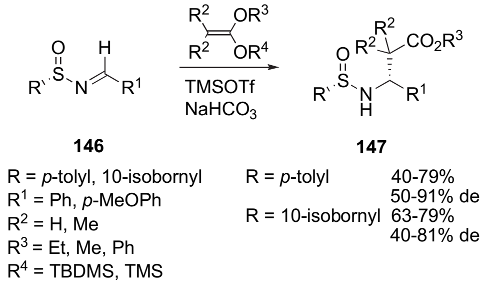
The synthesis of β-amino acids through the addition of metal enolates to *p*-TS-imines prompted Ellman et al. to examine the application of *t*-BS-imines **143**, proposing that the greater stereodirecting influence of the *tert*-butyl-sulfinyl group would result in the preparation of highly enantio-enriched β-amino acids **144**.[60] Having screened a series of both metals and solvents, Ellman established that the reaction of titanium enolates in tetrahydrofuran provided both the best yield and stereoselectivity (Scheme 44). Notably, a significant improvement in diastereoselectivity (74–96% de) was observed upon increasing the number of equivalents of titanium from 1 to 2. The scope of the reaction was then examined, and aryl, branched alkyl and unbranched alkyl *t*-BS-imines were all found to be suitable substrates for titanium enolate addition.



Scheme 44.

The stereochemical outcome of these transformations was in agreement with the previously proposed Zimmerman–Traxler-type six-membered transition state **145**. In addition to these studies, Ellman evaluated the impact of a substituent on the enolate ($R^3$). Preliminary results indicated that more substituted enolates remained efficient nucleophiles. Further work examined the application of the *t*-BS auxiliary as a Boc surrogate in the synthesis of more elaborate structures, where it proved to be both efficient and easy to remove.

An alternative approach to enantiopure β-amino acids was taken by Kawecki, investigating the addition of silyl ketene acetals to chiral *p*-TS-imines (Scheme 45).[61] A range of Lewis acids were screened to promote the reaction, with the most efficient system proving to be in the presence of TMSOTf. With efficient conditions in hand, the substituent tolerance for both the *p*-TS-imine and ketene was examined, and both aromatic and aliphatic substituted structures were observed to be suitable substrates. Focus then turned to the addition of silyl ketene acetals to 10-isobornyl-sulfinimines.



Scheme 45.

Addition of the silyl ketene acetal to the 10-isobornyl-sulfinimines was seen to only occur under the optimised conditions in the presence of TMSOTf. Upon reaction, however, the protected β-amino acid derivatives were provided in good yield and stereoselectivity. Subsequent to Kawecki's work, Skrydstrup et al. reported on the reaction of a similar system with *t*-BS-imines.[62] Reaction of silyl ketene acetals with *t*-BS-imines was found to proceed with similar yields (50–95%) and stereoselectivities (60–94% de).

Silverman et al. disclosed a protocol for the traceless solid-phase synthesis of chiral 3-aryl β-amino acid-containing peptides in 2000.[63] The key chiral-inducing step was a *t*-BS-imine-mediated titanium enolate addition, which proceeded in high yield (79%) and excellent diastereoselectivity (>99% de).

In 2002, Ellman et al. disclosed a full account of their investigations into the asymmetric addition of enolates to *t*-BS-imines.[64] It was found that *t*-BS-imines **149** were ideal precursors for the synthesis of β-substituted α,β- and β,β-disubstituted, α,β,β- and α,α,β-trisubstituted and α,α,β,β-tetrasubstituted β-amino acid derivatives (Scheme 46).

Screening of the enolate addition conditions primarily with acetate enolates ($R^3$=$R^4$=H) furnished a series of the β-amino esters **149** in high yield (70–95%) and excellent diastereoselectivity (90–98% de) and firmly established the optimal conditions for the reaction. Application of these conditions to facilitate the addition of α-substituted ester enolates ($R^3$=Me, Bn, *p*-MeOPh; $R^4$=H) to *t*-BS-imines afforded access to α-substituted β-amino acids in high yield (65–96%) and generally good diastereoselectivity (18–92% de). Further it was found that α,α-disubstituted enolates ($R^3$=$R^4$=Me, $-(CH_2)_5-$) could be employed, providing α,α,β-trisubstituted and α,α,β,β-tetrasubstituted β-amino esters in moderate to good yield (65–86%) and excellent diastereoselectivity (98% de in all cases). In all instances, the major diastereomer was correctly predicted by the Zimmerman–Traxler six-membered transition state **150** previously invoked. With a diverse range of variously substituted β-amino acid derivatives to hand, Ellman's focus turned to the application of the *t*-BS group as a versatile protecting group, providing the means for incorporating *t*-BS-β-amino esters into a series of more complex structures.

### 4.4. Synthesis of chiral non-racemic amino alcohols

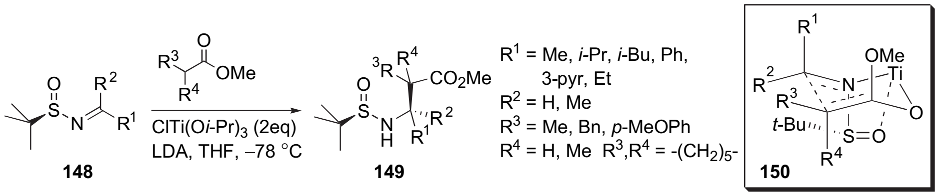
The 1,2- and 1,3-amino alcohol motifs are recurrent throughout drugs and natural products and have been widely employed in many chiral ligands for asymmetric catalysis. While many methods have been developed for the asymmetric synthesis of these valuable structural patterns, their varied applications warrant continued interest in new and diverse methods for their preparation.

Expanding upon the work of Bravo et al.,[65] Garcia Ruano and co-workers sought to develop a general procedure for the synthesis of chiral 1,2-amino alcohols via the Pummerer reaction of β-amino sulfoxides.[66] For this to be efficient, an expedient route to β-amino sulfoxides was required, and thus Garcia Ruano chose to examine the reaction of lithium anions with chiral *p*-TS-imines (Scheme 47). Building upon their previous experience, a chiral sulfoxide was incorporated into nucleophile **152** to induce a double stereodifferentiation effect, their reasoning being that this would increase the diastereoselectivity of the reaction.

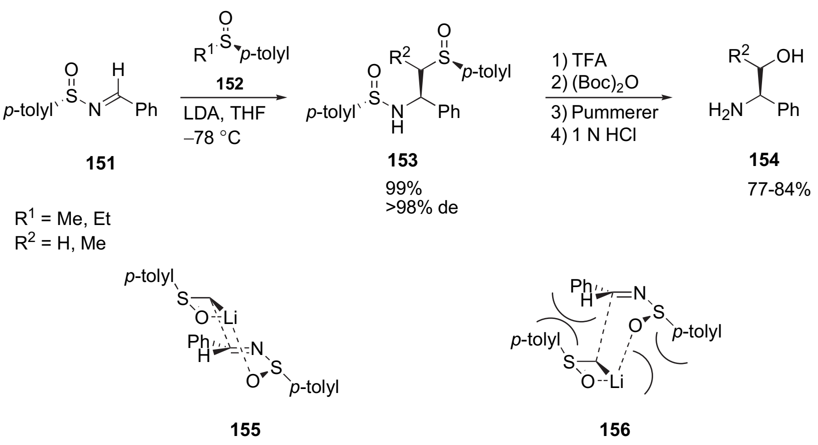
Reaction of the lithium anions of **152** with *p*-TS-imine **151** furnished chiral sulfinamides **153** in near-quantitative yield and excellent diastereoselectivity. The transition states **155** and **156** are for the matched pair, which, in this case, was found to be the *S*-sulfinimine and *R*-sulfoxide. Chelation of the incoming nucleophile is preferred for **155**, due to significantly reduced steric interactions. Exchange of the nitrogen protecting group and subsequent Pummerer reaction afforded the 1,2-amino alcohols **154** in good yield.

Barrow et al., through an adaptation of the methodologies developed by Davis and Ellman, described a novel *t*-BS-imine-mediated asymmetric synthesis of 1,2-amino alcohols **160** from protected α-alkoxy imines **157** and **158** in 2001 (Scheme 48).[67]

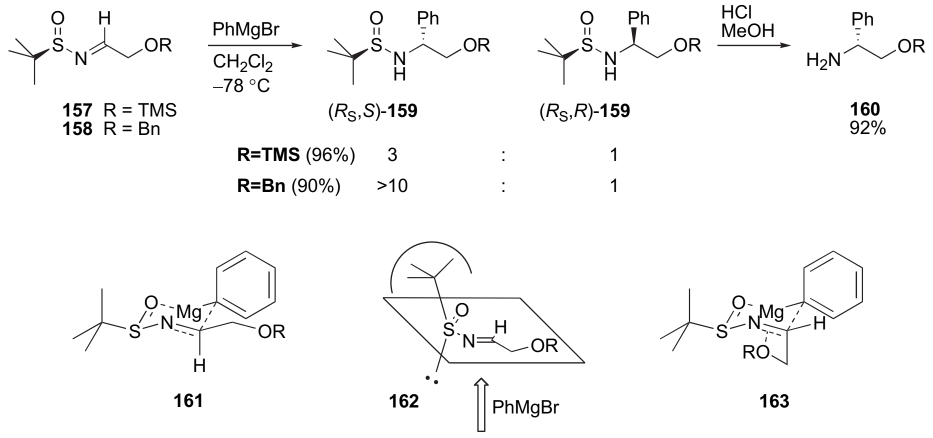
Initially, Barrow screened a range of conditions for the addition of phenylmagnesium bromide or phenyllithium to



**Scheme 46.**



**Scheme 47.**

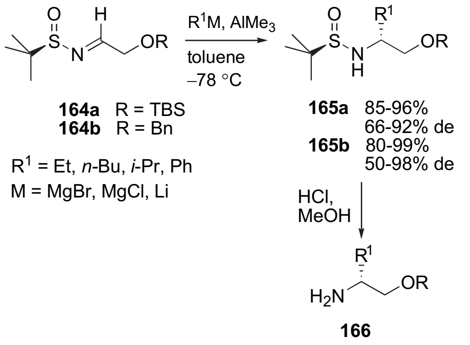


Scheme 48.

*t*-BS-imines **157** and **158**. In general, the yield of sulfinamide **159** was high (>80%), but the diastereoselectivity of the reaction was found to be highly dependent on the conditions employed. With tetrahydrofuran present in the solvent system, a modest selectivity towards the expected ($R_S$,*R*)-**159** was observed, which was thought to proceed through transition state **161**. Reactions performed in $CH_2Cl_2$, however, favoured the formation of the ($R_S$,*S*)-**159** isomer. This reversal in selectivity has been previously observed, and the open transition state **162** was used to rationalise the stereochemistry. Barrow put forward the chelated bicyclic transition state **163**, in which the imine has isomerised to the *Z*-conformation, the behaviour which has previously been observed.[22] Further support for this premise was found when sulfinimine **158** was subjected to the reaction conditions. It was found that sulfinimine **158** was significantly more selective and less dependent upon the solvent environment, thought to be due to the superior co-ordinating power of the benzyloxy group, hence stabilising **163**. Once the optimal conditions were established, the scope of the reaction was examined, with a series of both aryl and alkyl Grignard reagents adding to sulfinimines **158** in good yield (44–100%) and modest stereoselectivity (23–80% de).

Later in the same year, Ellman et al. published their findings on the synthesis of 1,2-amino alcohols **166** from *t*-BS-imines.[68] These workers employed the substrates previously examined by Barrow for their investigations. Preliminary studies focused on screening the conditions for the addition. Drawing on previous experience, it was observed that the addition of a Lewis acid improved not only the yield of the reaction, but also the stereocontrol of the addition. The addition of *tert*-butylmagnesium chloride was found to proceed most satisfactorily in toluene in the presence of aluminium trichloride (Scheme 49).

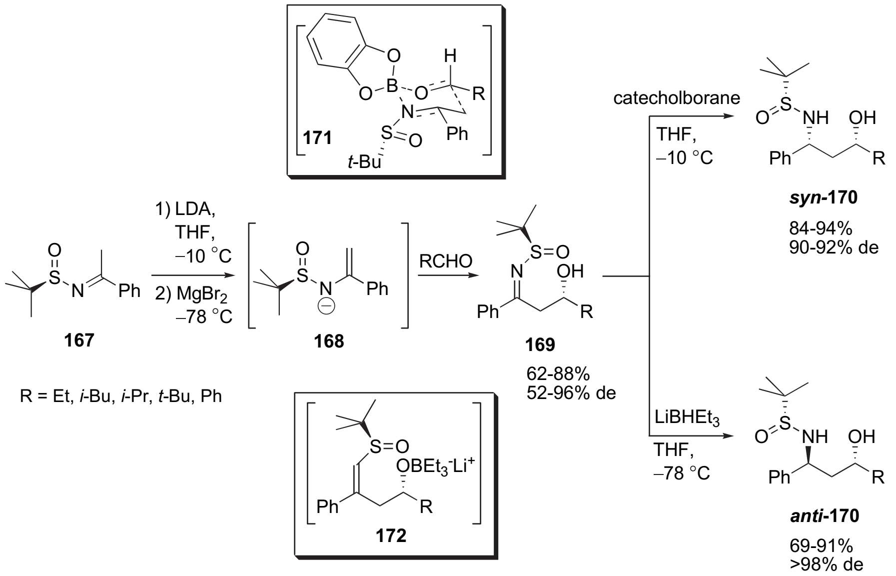
These conditions were found to be the most efficient for both the benzyl and silyl ethers, affording sulfinamides **165** in high yields and stereoselectivities. The stereoinduction observed was in line with Barrow's results, and thus Ellman invoked a similar argument. Further results, however, highlighted that the true mechanism was still not fully understood. Addition to a *t*-BS-ketimine was found to proceed in modest yield (42–52%) and diastereoselectivity (44–70% de), yet the stereochemistry of the resulting sulfinamides was the reverse of the aldimine substrates and, in line with previous Grignard additions, was presumably via transition state **150**, the α-chelating group therefore having no effect on the facial selectivity of *t*-BS-ketimines.



Scheme 49.

In 2002, Ellman et al. disclosed a report detailing their work on a remarkable new feature of chiral sulfinimine chemistry.[69] While the asymmetric addition to sulfinimines had been used extensively, despite the importance of metalloenamines as enolate equivalents, the use of metalloenamines derived from sulfinimines had not previously been described. Ellman proposed that the addition of a *t*-BS-metalloenamine to an aldehyde would occur stereoselectively, furnishing the chiral β-hydroxyl *t*-BS-imines, which, upon reduction and subsequent deprotection would afford direct entry to a wide range of chiral 1,3-amino alcohols (Scheme 50).

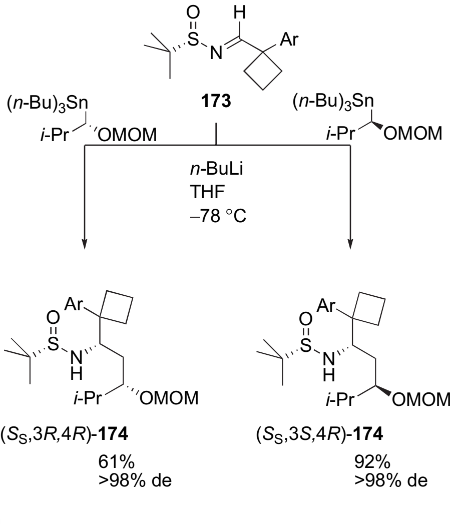
Generation of the *t*-BS-metalloenamine **168** from **167** was found to be best accomplished with lithium diisopropylamine, the addition of $MgBr_2$ significantly increasing both the yield and stereoselectivity of the transformation. Addition to a number of both aryl and alkyl aldehydes to form **169** was accomplished in good yield and diastereoselectivity. Reduction to the 1,3-amino alcohols was found to be highly dependent upon the reagent employed. Both catecholborane and $LiBHEt_3$ carried out the reduction in high yield, with catecholborane affording *syn*-**170** and $LiBHEt_3$ presenting the *anti*-**170**. It was proposed that chelation of the catecholborane with the sulfinyl group (**171**) stabilised isomerisation of the imine to the *Z*-geometry, hence the *anti*-stereoselectivity,



**Scheme 50**.

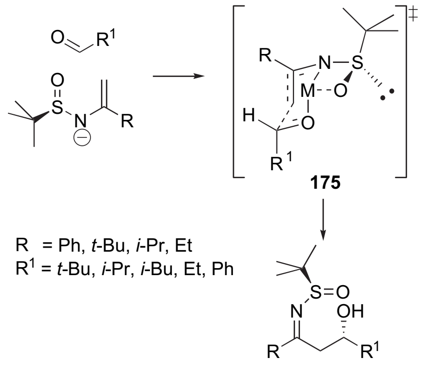
while no such stabilisation is present upon reaction with $LiBHEt_3$ (**172**).

Senanayake et al. developed an efficient method for the synthesis of both *syn*- and *anti*-1,2-amino alcohols from a common *t*-BS-imine starting material **173** (Scheme 51).[70] Addition of the stannanes proceeded in good yield (61–92%) and excellent diastereoselectivity (>98%), affording the protected 1,2-amino alcohols **174**. Deprotection through exposure to HCl in methanol furnishes the desired chiral 1,2-amino alcohols in 83–89% yield.



**Scheme 51**.

In 2003, Ellman et al. disclosed a detailed account of their extended studies on the formation of *t*-BS-metalloenamines and their application in the synthesis of 1,3-amino alcohols.[71] Having established the optimal conditions in the preliminary report,[69] Ellman's focus turned to the scope of the reaction. A range of both aryl and alkyl aldehydes were found to be suitable substrates for the addition reaction, as were a series of more complex *t*-BS-metalloenamines, with both aryl and alkyl side chains incorporated. In all cases, the reaction proceeded in good to high yield (50–92%) and high stereoselectivity (54–98% de). To rationalise the stereochemical outcome, Ellman proposed the transition state **175** to access the major diastereomer (Scheme 52).

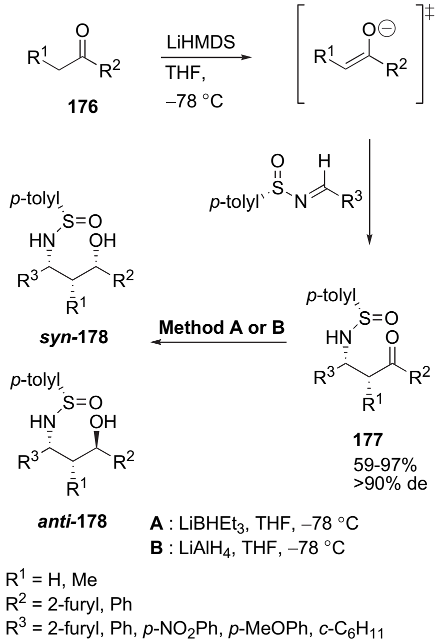


**Scheme 52**.

The practical nature of the reaction of *t*-BS-metalloenamines was further exemplified by Ellman through the synthesis of two alkaloid natural products (−)-halosaline and (−)-8-epi-halosaline.

Nelson et al. employed an alternative strategy for the construction of 1,3-amino alcohols.[72] Addition of ketone enolates **176** to *p*-TS-imines was found to occur stereoselectively, to afford the corresponding chiral β-amino ketones **177**. Subsequent reduction provided direct access to amino alcohols **178** (Scheme 53).

The addition of a number of ketone enolates to a range of aryl- and alkyl-*p*-TS-imines was achieved in high yield (59–97%) and generally excellent diastereoselectivity (>90%). A range of conditions were screened for the reduction and, while the majority of conditions were efficient, two sets in particular afforded noteworthy results. Reduction with $LiBHEt_3$ in tetrahydrofuran furnished the 1,3-amino alcohols **178** in a 92:8 ratio in favour of the *syn*-isomer (Method A). On



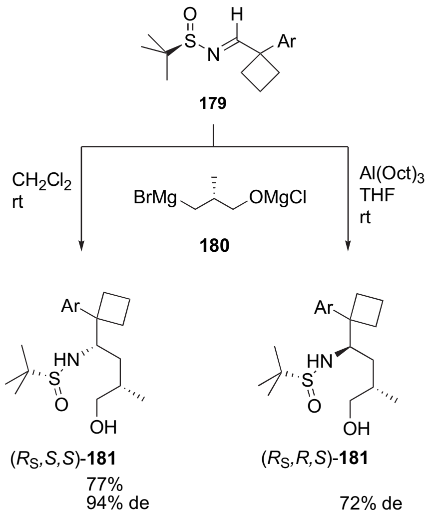
Scheme 53.

the other hand, reduction with $LiAlH_4$ in tetrahydrofuran provided the amino alcohols in a 29:71 population in favour of the *anti*-isomer (Method B). Hence, a careful choice of conditions allows selection between the *syn*- and *anti*-isomer from the same starting material.

In a recent report, Garcia Ruano et al. expand upon their investigations into the synthesis of chiral 1,2-amino alcohols through the reaction of chiral lithium anions with *p*-TS-imines.[73] Further to their previous studies, the reaction of the *p*-TS-ketimine derived from acetophenone was investigated and the influence of the sulfinyl substituent examined. As observed before, the excellent diastereoselectivity of the reaction was the result of a double stereodifferentiation effect, with the *S*-sulfinimine and *R*-sulfoxide making up the matched pair. The addition to the sulfinimine occurred with high yield (67–83%) and excellent stereoselectivity (>98% de). Interestingly, changing to the naphthyl-sulfinimine in place of the *p*-TS-imine produced some anomalous results, with disappointing yields and diastereoselectivities observed.

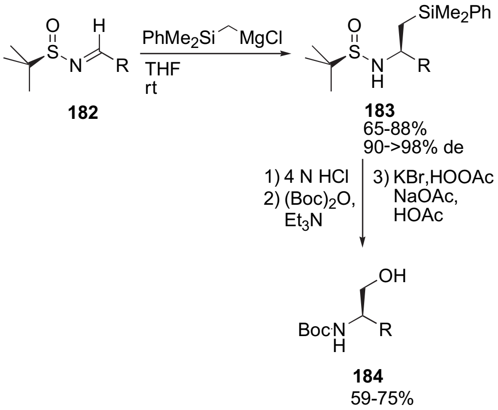
*En route* to the synthesis of biologically active sibutramine analogues, Senanayake et al. exploited the chiral influence of the *t*-BS-auxiliary in the preparation of 1,4-amino alcohols.[74] Seeking to analyse the biological potential of all stereoisomers of the target molecule, Senanayake reported the efficient stereoselective synthesis of all four stereoisomers (Scheme 54). It was observed that it was possible to obtain both enantiomers of 1,4-amino alcohols **181** from a single enantiomer of *t*-BS-imine **179**. Addition of the Grignard reagents (*S*)-**180** or (*R*)-**180** to a common sulfinimine led to a new chiral centre with the *R*-configuration.

The same reaction carried out in $CH_2Cl_2$, however, led to a new stereocentre with *S*-configuration being formed. Subsequent deprotection afforded the corresponding 1,4-amino alcohols.



Scheme 54.

Very recently, Kim et al. reported their findings on the development of an alternative route to chiral 1,2-amino alcohols.[75] Using the dimethylphenylsilyl group as a masked hydroxy equivalent, the addition of [(dimethylphenylsilyl)-methyl]magnesium chloride to *t*-BS-imines **182** and subsequent Fleming–Tamao oxidation of silanes **183** was found to provide an effective entry to the desired chiral alcohols **184** (Scheme 55).



Scheme 55.

A screen of the conditions established that the most efficient reaction, in terms of both the yield and stereoselectivity, was carried in tetrahydrofuran at room temperature. The configuration of the newly formed chiral centre was found to favour the *R*-isomer, which is in accordance with the six-membered chelated transition state commonly invoked for the addition of Grignard reagents. With these conditions established, the focus was turned to the scope of the reaction. Both alkyl and aryl *t*-BS-imines were found to be suitable substrates, undergoing the addition in good yield (65–88%) and excellent diastereoselectivity (90 to >98% de). Subsequent conversion into the Boc-protected amine and Fleming–Tamao oxidation afforded the chiral 1,2-amino alcohols in good yield (59–75%).

Thus through the addition of a variety of organometallic reagents or the development of a new aspect to sulfinimine chemistry in the case of Ellman's metalloenamine chemistry, it has been shown that a variety of chiral 1,2-, 1,3- and 1,4-amino alcohols are readily accessible in only a few steps from sulfinimines.

### 4.5. Synthesis of chiral 1,2-amino sulfides

1,2-Amino sulfides have, in recent years, received a good deal of interest from the synthetic community; not only have they found application as N, S ligands in asymmetric synthesis, but they are also common as a subunit in a number of biologically active molecules. In 2005, drawing upon their previous experience,[76] Garcia Ruano et al. published an expedient synthesis of chiral 1,2-amino sulfides **186** through the addition of a suitably substituted benzyl carbanion to chiral *p*-TS-imines **185** (Scheme 56).[77]

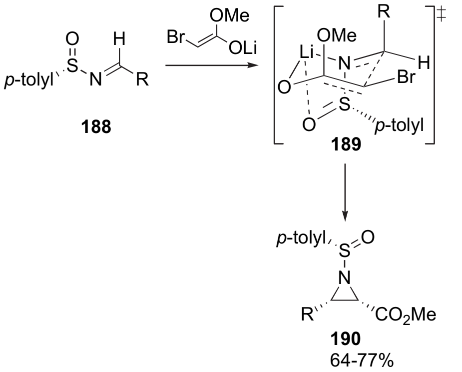
Under optimised conditions, the addition of the benzyl carbanion to the *p*-TS-imine was found to be a rapid and efficient reaction. It was observed that there was a double stereodifferentiation effect at work, with the matched pair having the *S*-configuration around both the *p*-TS-imine and the chiral sulfoxide present in the nucleophile; under these conditions, exceptional stereoselectivity was observed. Using *tert*-butyllithium to remove the sulfoxide, with subsequent deprotection of the amine with HCl, revealed direct access to chiral *anti*-1,2-amino sulfides **187**.

### 4.6. Synthesis of chiral aziridines

Aziridines are a representative of the first, and most simple of, heterocyclic systems, characterised by the presence of two carbon atoms and one heteroatom. Their simplicity, however, belies their importance to organic chemistry. Aziridines and, in particular chiral aziridines, are increasingly being exploited in organic synthesis. Elaboration via ring opening or ring expansion provides direct access to a host of structural motifs.[78]

Combining a long-standing interest in aziridines and the application of chiral *p*-TS-imines, Davis et al. developed the asymmetric aza-Darzens reaction for the synthesis of *cis*-*p*-TS-aziridine-2-carboxylic acids **190** (Scheme 57).[36] The addition of the lithium enolate of methyl-2-bromoacetate was found to add selectively to a series of both non-enolisable and enolisable *p*-TS-imines **188** in good yield (64–77%), with, in most cases, only the cis-isomer being observed. The high cis-stereoselectivity was rationalised by invoking the six-membered transition state **189**.

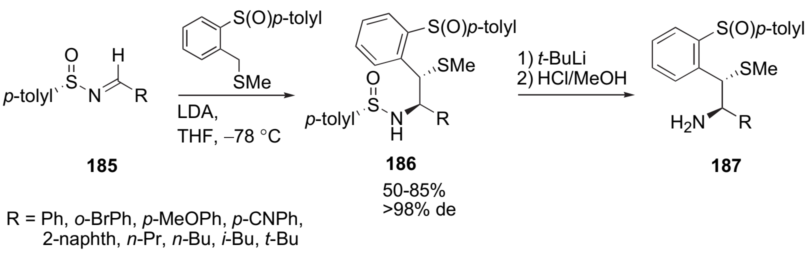
To demonstrate the application of *p*-TS-aziridines, Davis investigated the reaction of **190**. It was demonstrated that the sulfinyl auxiliary could be easily oxidised to the toluenesulfonyl group, thus making it a substrate for the plethora of ring-opening reactions previously established for that motif. Removal of the sulfinyl group upon exposure to TFA revealed direct access to N–H aziridines, versatile intermediates in synthesis. Further, it was shown that the *p*-TS auxiliary provides enough activation to the aziridine ring to direct ring opening, thus bypassing the need to oxidise to the more-electron-withdrawing sulfonyl substituent.



Scheme 57.

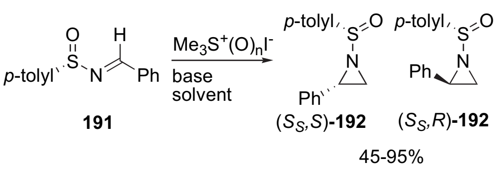
Supplementary to their report on the synthesis of *cis*-*p*-TS-aziridine-2-carboxylic acids, Davis et al. demonstrated the practicality of these small molecules through the synthesis of the antibiotic, (+)-thiamphenicol, using the chiral aziridine backbone to install the stereochemistry of this molecule.[79]

In 1995, Garcia Ruano et al. reported the results of their evaluation of a *p*-TS-imine-mediated modification of the classic Corey–Chaykovsky methylene-transfer reaction.[80] Reaction of the activated sulfonium ylides, dimethylsulfonium methylide and dimethyloxosulfonium methylide with chiral non-racemic *p*-TS-imines **191** was found to furnish chiral aziridines **192** in good yield (Scheme 58). From screening the reaction conditions, two clear trends emerged, it was observed that the nature of the major diastereomer was dependent upon the methylene-transfer reagent employed, with the reaction with dimethylsulfonium methylide selecting for the *S*-isomer and dimethyloxosulfonium methylide for the *R*-isomer. The solvent polarity was found to have a significant effect upon the diastereoselectivity; as the polarity of the solvent was increased, the diastereoselectivity of the reaction was improved, with solvents such as DMSO and DMF for dimethylsulfonium methylide and toluene for dimethyloxosulfonium methylide proving optimal. Further, it was



Scheme 56.

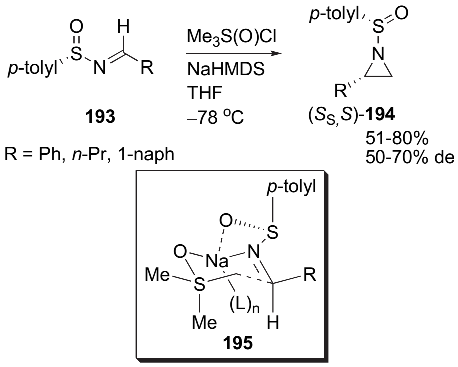
found that the stereoselectivity of the reaction was independent of the metal ion present.



**Scheme 58**.

Deprotection of the chiral aziridines was accomplished through treatment with methyllithium, affording the N–H aziridine, through which the stereochemical assignments were made. In an ensuing report in the same year, however, these assignments were brought into question.

Diversifying from the development of the sulfinimine-mediated aza-Darzens aziridine synthesis, Davis et al. reported their findings on the addition of dimethyloxosulfonium methylide to *p*-TS-imines (Scheme 59).[81] Having screened a number of conditions for the reaction of the activated ylide with both alkyl- and aryl-*p*-TS-imines **193**, it was observed that the use of solvents other than tetrahydrofuran resulted in significantly lower yields. The optimal base in terms of both yield and stereoselectivity was found to be sodium bis(trimethylsilyl)amine (NaHMDS).



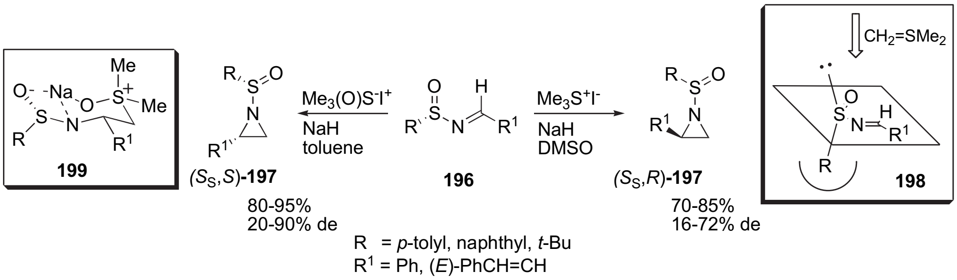
**Scheme 59**.

While the extent of the diastereoselectivity was not astonishing, *p*-TS-aziridine **194** diastereomers were separable. The absolute assignment of stereochemistry was achieved through oxidation to the known *N*-tosyl-aziridine with *m*-CPBA, establishing that the reaction of dimethyloxosulfonium methylide with (*S*)-*p*-TS-imine is selective towards ($S_S$,*S*)-**194** isomer, not ($S_S$,*R*)-**194** isomer as previously thought. The stereochemical outcome was in agreement with a six-membered transition state **195** proposed by Davis. Further confirmation of the assignment was gained upon removal of the *p*-TS-auxiliary, with methyllithium affording the known (*S*)-phenylaziridine.

In 1996, Garcia Ruano et al. disclosed a report containing a full account of their investigations into the reaction of activated sulfur ylides with sulfinimines.[12] Prompted by the disappointing diastereoselectivity observed both by themselves and Davis on the reaction of *p*-TS-imines with methylene-transfer reagents, Garcia Ruano et al. examined the influence of the substituent on the sulfinyl sulfur on the stereochemical outcome of the aziridination. Using the optimal conditions discovered in their previous investigations, the reaction of both dimethylsulfonium methylide and dimethyloxosulfonium methylide with *p*-TS-, naphthyl- and *t*-Bu-imines **196** was investigated (Scheme 60). A number of trends became clear from their enquiries. Again, it was realised that, for all substrates, an opposite sense of diastereoselection occurred at the newly formed C-2 carbon when using different methylene-transfer reagents. Thus, ($S_S$,*S*)-**197** are the major products with dimethyloxosulfonium methylide in toluene, while ($S_S$,*R*)-**197** are formed preferentially upon reaction with dimethylsulfonium methylide in DMSO. These stereochemical assignments are in line with Davis's previous observation.

With respect to the influence of the sulfur substituent on the stereoselectivity of the aziridination, it was observed that an increase in the steric bulk of the substituent was accompanied by an increase in the diastereoselection. Thus, changing from the *p*-TS-imines to the naphthyl-sulfinimines resulted in an increase in the diastereomeric excess with both ylides, the improvement being much more pronounced when the *t*-BS-imines were examined, providing even greater levels of stereocontrol. Garcia Ruano proposed that the observed disparity in the stereochemical outcome of the reaction with the two ylides was attributable to the difference in the chelating character of the reagents. With the non-chelating dimethylsulfonium methylide, the nucleophilic attack is directed to the least-hindered face of sulfinimine **198**. The presence of the oxygen on the dimethyloxosulfonium methylide, however, provides the opportunity for the intermediate betaine to be stabilised through chelation with sodium. Thus, the conformation of the transition state **199** is favoured over the more hindered form in which the R group would clash with the axial methyl of the ylide.

Such was the success of the sulfinimine-mediated aza-Darzens protocol developed by Davis et al. that it was investigated whether aziridine-2-phosphonates could be prepared



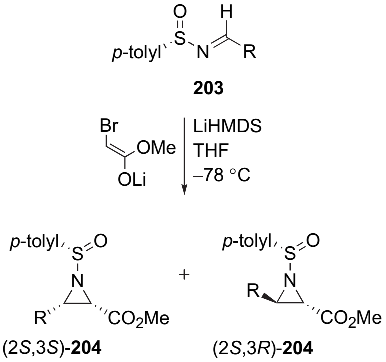
**Scheme 60**.

by an analogous method.[82] As surrogates for carboxylic acids, amino phosphonates have received significant interest and, it was for these reasons, that aziridine-2-phosphonates were thought to be valuable targets.[83] Using the conditions previously optimised for the aza-Darzens chemistry, the reaction between *p*-TS-imines **200** and the lithium anion of diethyl chloromethylphosphonate was found to give none of the desired aziridines **202** (Scheme 61). Rather, the major products were the α-chloro-β-amino adducts **201**. Isolation and treatment of the sulfinamide diastereomers **201** with 2 equiv of sodium hydride furnished the aziridine-2-phosphonates **202** in good yield.

The stereochemical outcome observed was consistent with previous phosphite and α-phosphonate additions to chiral sulfinimines, the nucleophile attacking the least-hindered face in an open, non-chelated transition state. Treatment of the *cis*-aziridine-2-phosphonates **201** with 50 equiv of TFA removed the sulfinyl group in 84% yield. Interestingly, under similar conditions, the less stable *trans*-aziridines were found to afford mainly the ring-opened product, while conducting the reaction at 0 °C with only 5 equiv of TFA delivered the N–H aziridine in 91% yield. Davis demonstrated the potential of the aziridine-2-phosphonates through ring opening to afford the α-amino phosphonates and hydrogen abstraction to give the azirine-2-phosphonates.

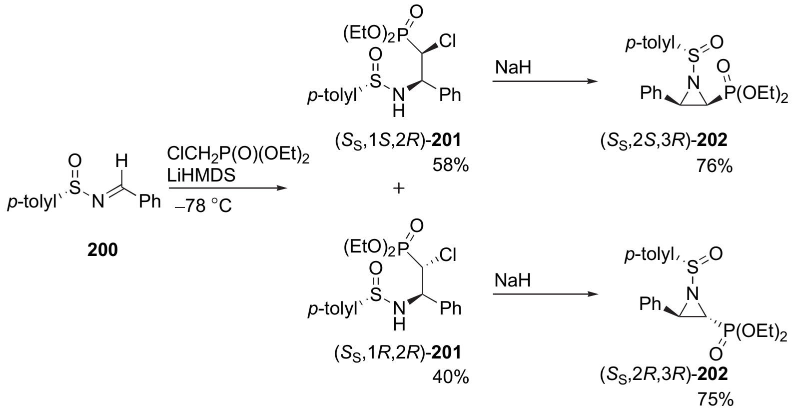
To demonstrate the practicality of the sulfinimine-mediated aza-Darzens synthesis of the aziridine-2-carboxylate esters, it was applied as a key step in the synthesis of a variety of chiral amine motifs. In 1999, Davis published a report summarising these applications and describing their exploration of this simple aziridination procedure (Scheme 62).[84] A wide range of α-haloesters were screened to find the best conditions for the addition to *p*-TS-imine. While, in general, these reactions occurred with high stereoselectivities (68–98% de), the yields were disappointing. The best results were observed for the lithium enolate of methyl α-bromoacetate, with high selectivity (>90% de) and yield. Aziridination was found to be general for aromatic, aliphatic and α,β-unsaturated *p*-TS-imines **203** furnishing the *cis*-aziridines **204** in good yield (50–77%).

The preparation of aziridines directly from the Andersen derivative that is the sulfinimine precursor was investigated and, while the aziridines could be prepared in high yields (55–93%), the stereoselectivity observed was significantly lower (42–90% de). In addition, the reaction of the enolates with *p*-TS-ketimines was briefly examined. Reaction with the sulfinimine derived from acetophenone proved sluggish, however, and required thermal encouragement. There were also significant side reactions competing with the desired aziridination, primarily the formation of the *p*-TS-imine enolate and further side reactions which markedly reduced the yield. To demonstrate the aziridine-2-carboxylate motif's potential for further elaboration, a number of transformations were carried out on the chiral cis-substrates. Deprotection of the ring nitrogen was achieved through exposure to either TFA or methylmagnesium bromide. The ring opening of the chiral aziridines was shown to provide direct access to chiral α-amino acids, a strategy previously employed by Davis. Oxidation of the sulfinyl group was shown to furnish the corresponding *N*-tosyl aziridines, the activating nature of which is key to many aziridine transformations.



**Scheme 62**.

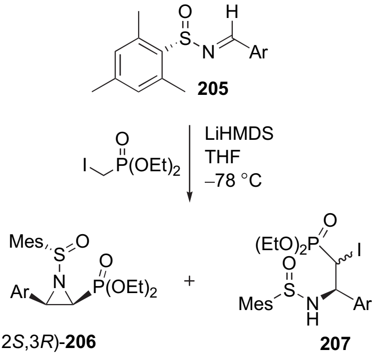
Building upon their preliminary results on the synthesis of *p*-TS-aziridine-2-phosphonates, Davis et al. published a detailed report on their extended investigations.[85] While, at this stage, it remained necessary to isolate the intermediate α-chloro-β-amino adducts and subsequently cyclise them to synthesise the aziridines in acceptable yields and stereoselectivities, the protocol was shown to be practical for a wide range of aromatic *p*-TS-imines. Further, the influence of the sulfinyl auxiliary on the reaction was investigated. Reaction of the anion derived from either iodo or tosyl phosphonate with *t*-BS-phenyl-imine and LiHMDS formed the aziridine-2-phosphonate directly, as a single isomer in 82% and



**Scheme 61**.

32% yield, respectively. Unfortunately, however, removal of the *tert*-butylsulfinyl auxiliary proved challenging. Thus, Davis's investigations into the synthesis of aziridine-2-phosphonates from sulfinimines were continued.

In a report later in 2003, Davis disclosed an improved synthesis of aziridine-2-phosphonates.[86] Seeking to combine the advantageous features of both the *t*-BS- and *p*-TS-imines, *N*-sulfinyl auxiliaries large enough to produce high diastereoselectivities in the aza-Darzens reaction and to allow selective deprotection using Grignard reagents. Thus the *N*-(2,4,6-trimethylphenylsulfinyl) (Mes-sulfinyl) auxiliary was examined (Scheme 63). Using a modification of the procedure developed by Senanayake, in which LiHMDS was favoured over NaHMDS as it proved to impart better enantioselectivity, Davis prepared a range of Mes-sulfinimines **205**.

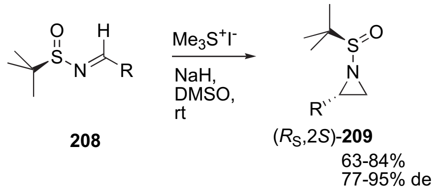


Ar = *p*-MeOPh, Ph, *p*-$CF_3$Ph, *p*-$NO_2$Ph

**Scheme 63**.

Under the previously optimised conditions, reaction of Mes-sulfinimines containing the phenyl and *para*-methoxyphenyl motif underwent aziridination to form aziridine-2-phosphonates **206** as single diastereomers, in one pot with 75% and 78% isolated yield, respectively. Substrates containing electron-withdrawing functionalities, such as *p*-trifluoromethylphenyl and *p*-nitrophenyl Mes-sulfinimines, however, reacted to produce a complex mixture of the desired aziridine diastereomers and isomeric mixtures of the β-amino-α-iodophosphonates **207**, which could not be separated. This was in contrast to the *p*-TS analogues, which were found to be separable; this divergence in physical properties is thought to be due to the increased lipophilicity associated with the Mes-sulfinyl group. Exposure of the Mes-aziridine-2-phosphonates to 2 equiv of methylmagnesium bromide furnished the deprotected N–H aziridines in 72–77% yield with no loss of optical purity. Though the application of Mes-sulfinimines appears not to be general, the diastereoselectivities associated with the system provided a significant improvement on those associated with the *p*-TS-imines and, with the demonstrated facile removal of the Mes-sulfinyl auxiliary, this is an efficient and direct route to the synthesis and further elaboration of chiral aziridine-2-phosphonates.

To determine the functionality tolerated by the sulfur ylide-mediated aziridination of chiral sulfinimines, Stockman et al. explored the reaction of *t*-BS-imines with dimethylsulfonium methylide in greater detail (Scheme 64).[87] Their initial investigations screened a series of conditions to determine the optimal reaction of dimethylsulfonium methylide with *t*-BS-imines. In line with the findings of Garcia Ruano et al., deprotonation with sodium hydride in DMSO provided both the best yield and stereoselectivity.

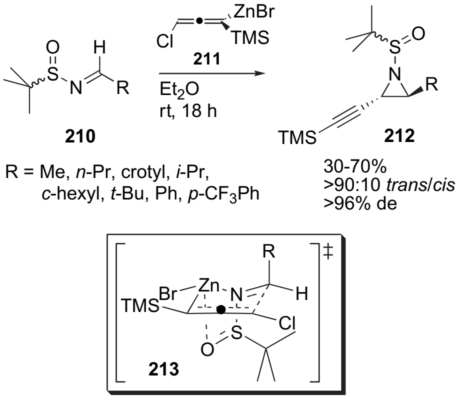


R = Ph, (*E*)-HC=CHPh, *p*-MeOPh, 2-pyl,
3-pyl, furyl, *c*-$C_6H_{11}$, *n*-$C_5H_{11}$

**Scheme 64**.

Both aromatic and enolisable aliphatic *t*-BS-imines **208** were found to be suitable substrates for the procedure, affording aziridines ($R_S$,2*S*)-**209** in high yields and stereoselectivities. Notably, the reactions were found to be complete within 10 h, signifying a remarkably more rapid process than those observed by both Davis and Garcia Ruano. The selective formation of the *S*-chiral centre within the aziridine ring is in line with the previously observed reaction, where it was proposed that the selectivity originated from an open transition state with the *si*-face protected by the steric bulk of the auxiliary and the nucleophile attacking the open *re*-face. The stereochemical assignments were confirmed by an X-ray crystal structure.

Extending their previous experience in the synthesis of *N*-benzyl and *N*-TMS ethynylaziridines, Ferreria et al. examined the reaction of allenylzinc **211** with racemic *t*-BS-imines **210** (Scheme 65).[88] With their established procedures only requiring minor modifications, both aromatic and aliphatic *t*-BS-imines were found to be suitable substrates, accessing the corresponding ethynylaziridines **212** in generally good yield (35–70%), high trans/cis selectivity (>90:10) and excellent diastereoselectivity (>96% de of the trans-isomer). Further, the procedure was found to be applicable to a limited range of *t*-BS-ketimines, albeit in lower yields. In all cases, however, the reaction was found to be rather sluggish, requiring 18 h and with the allenylzinc reagents required in significant excesses (3–6 equiv).

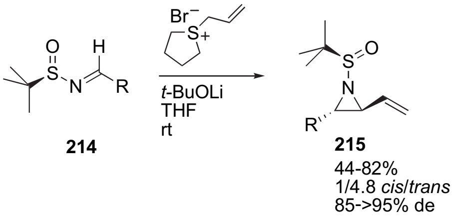


R = Me, *n*-Pr, crotyl, *i*-Pr,
*c*-hexyl, *t*-Bu, Ph, *p*-$CF_3$Ph

**Scheme 65**.

The relative stereochemistry of the aziridines was confirmed through comparison with the X-ray crystal structure of the *t*-BS-phenyl-ethynylaziridine. The high predilection for the trans-isomer was rationalised through the Zimmerman–Traxler-type transition state **213**. While these preliminary investigations were carried out on racemic *t*-BS-imines, the scope of the reaction was established and the stereoselectivities observed revealed the potential for the synthesis of optically pure chiral ethynylaziridines.

Building upon their previous investigations into the reaction of activated sulfur ylides with *t*-BS-imines, Stockman et al. disclosed their exploration of the reaction of *S*-allyl sulfur ylides with chiral *t*-BS-imines for the synthesis of chiral vinylaziridines **215** (Scheme 66).[89] Initial investigations revolved around the optimisation of the conditions; a series of solvents and bases were analysed, with generation of the ylide with LiO*t*-Bu in tetrahydrofuran providing the best balance of high yield and good cis/trans selectivity. In all cases examined, irrespective of base or solvent, the diastereoselectivity observed was excellent (generally >95%).

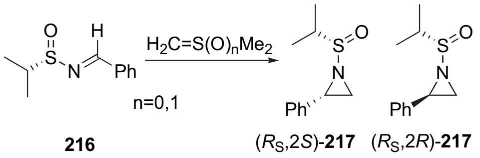


**Scheme 66**.

With efficient conditions established, the focus was turned to the generality of the reaction. Aromatic, heterocyclic and branched and cyclic aliphatic *t*-BS-imines **214** were all found to be suitable substrates, providing the corresponding *t*-Bs-vinylaziridines **215** in good yield and excellent diastereoselectivity. The excellent diastereoselectivity was rationalised by invoking an open transition state, with the ylide attacking the less hindered *re*-face of the (*R*)-*t*-BS-imine. The removal of the *t*-BS-auxiliary was achieved through exposure to HCl in dioxan, furnishing the stable hydrochloride salt of the N–H aziridine in >90% yield, thus increasing the potential for elaboration of the chiral vinylaziridines.

Prompted by their initial results on the reaction of allenylzinc **211** with racemic *t*-BS-imines, Ferreira et al. took the logical progression and examined the reaction with enantiomerically pure *t*-BS-imines.[90] As expected, the non-racemic substrates performed with similar reactivity to their racemic counterparts, with both aromatic and aliphatic *t*-BS-imines furnishing the ethynylaziridines in good yield (54–70%) displaying a high predilection for the trans-isomer (90:10) and excellent diastereoselectivity (>96% de). In an effort to reduce the long reaction time and large excesses of allenylzinc required to achieve these reactions, Ferreira considered the reaction of *p*-TS-imines. While the *p*-TS-imines all exhibited a much higher reactivity, consequently requiring less allenylzinc (1.5–3 equiv) and being complete in significantly shorter times, disappointing levels of diastereoselectivity were observed. Removal of the *t*-BS-auxiliary was achieved through treatment with HCl in methanol. Overall, a series of aromatic and aliphatic chiral, non-racemic ethynylaziridines were prepared in good yield and stereoselectivity.

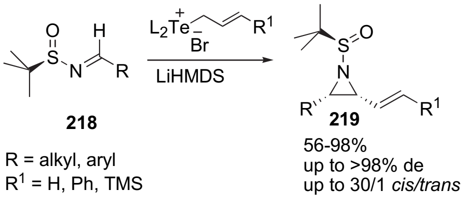
Recently, Fernandez et al. re-examined the reaction of chiral sulfinimines with the activated sulfonium ylides, dimethylsulfonium methylide and dimethyloxosulfonium methylide, to demonstrate the application of a new class of chiral sulfinimines.[91] Fernandez reports on the development of the *iso*-propyl-sulfinyl (*i*-PS) auxiliary **216**, and its application to the synthesis of chiral terminal aziridines **217** (Scheme 67). Recognising that the trend was towards more sterically encumbered sulfur substituents, the *i*-PS-imines were designed to play an intermediary role between the *p*-TS- and the *t*-BS-imines.



**Scheme 67**.

The results reported suggest that the *i*-PS auxiliary does indeed react with a rapid nature with the *p*-TS-imines and induces stereoinfluence similar to that of the *t*-BS-imines. The aziridines were formed with the same sense of stereoinduction as previously observed for the addition of activated sulfur ylides to sulfinimines.

Very recently, Tang et al. disclosed a report on the reaction of telluronium ylides with *t*-BS-imines **218** in the synthesis of chiral, non-racemic *cis*-vinylaziridines **219** (Scheme 68).[92] Optimisation of the conditions provided an efficient protocol that was applied to the synthesis of a diverse range of aromatic, aliphatic and unsaturated aliphatic *cis*-vinylaziridines. In addition, the *t*-BS-ketimine derived from acetophenone underwent the aziridination in good yield (76%) and high stereoselectivity (30/1 cis/trans, >98% de). Further studies examined the aziridination mediated by different telluronium ylides. Interestingly, replacing the TMS group with a proton diminished both the yield and stereoselectivity.

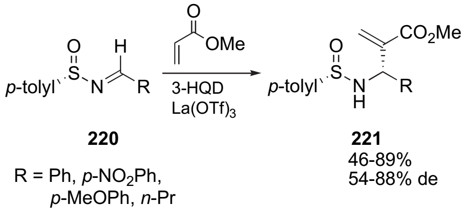


**Scheme 68**.

Aziridines have been shown to be efficient precursors to a number of interesting motifs, and, with their potential for elaboration, either through ring expansion or ring opening, and now through the reaction of chiral non-racemic sulfinimines, a number of efficient routes for the preparation of the valuable chiral aziridines have been developed.

### 4.7. Synthesis of chiral β-hydroxy-α-methylene esters

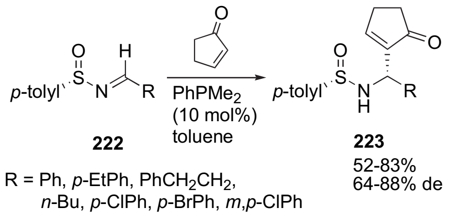
The Baylis–Hillman reaction provides an efficient direct entry into substituted esters, ketones and nitriles. In an effort to assert stereocontrol over the reaction, Aggarwal et al. investigated whether the *N*-sulfinimines **220** would be activated enough to undergo the coupling reaction to **221** (Scheme 69).[93] A range of conditions were examined for the addition of methyl acrylate to *p*-TS-phenyl-imine, and it was observed that the most efficient reaction was achieved in the presence of 3-hydroxyquinuclidine (3-HQD) as an amine catalyst and lanthanide-based Lewis acids, affording the desired β-hydroxy-α-methylene ester in high yield (89%) and modest diastereoselectivity (64% de). It was also observed that the major isomer had the *S*-configuration around the new chiral centre, rationalised by a six-membered Zimmerman–Traxler-type transition state.



**Scheme 69.**

In an effort to improve the rather disappointing diastereoselectivity of the transformation, the reaction with the bulkier *t*-BS-imines was examined. Reaction with the *t*-BS-analogues furnished increased levels of diastereoselection, but the yields were significantly diminished, leading to the conclusion that the *p*-TS-imines were the most suitable substrates for the Baylis–Hillman reaction.

In the same year, Shi et al. reported their findings on the sulfinimine-mediated catalytic asymmetric Baylis–Hillman reaction (Scheme 70).[94] Drawing upon their previous experience with the catalytic Baylis–Hillman reaction, a range of conditions were screened. Reaction of **222** in toluene in the presence of 10 mol % of the Lewis acid dimethylphenylphosphine, afforded the β-hydroxy-α-methylene amides **223** in high yield (83%) and good diastereoselectivity (86% de).

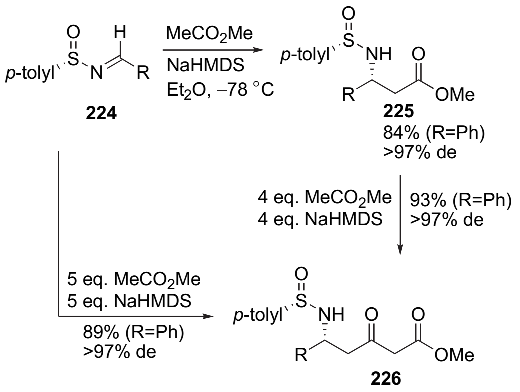


**Scheme 70.**

The scope of the reaction was then examined and both alkyl and aryl-*p*-TS-imines were found to be suitable substrates for the addition.

## 5. Chiral sulfinimines as building blocks for synthesis

Designed polyfunctionalised chiral building blocks (DPFCBs) have been developed to overcome the problems associated with using chiral-pool derivatives. The DPFCBs are engineered to avoid many of the manipulations and protecting-group transformations inherent in the use of natural sources. Spurred on by the growing popularity of chiral sulfinimines in asymmetric synthesis, Davis et al. introduced a new class of DPFCBs; *N*-sulfinyl δ-amino β-keto esters such as **226**.[95] The utility of these new building blocks for the synthesis of alkaloids was illustrated in the concise synthesis of (*R*)-2-phenylpiperidine **229** (see Scheme 72) and (−)-SS20846A **232** (see Scheme 73). A flexible approach for the synthesis of these highly functionalised systems was adopted and two routes were developed from **224**, allowing a modular design of the substrates (Scheme 71).



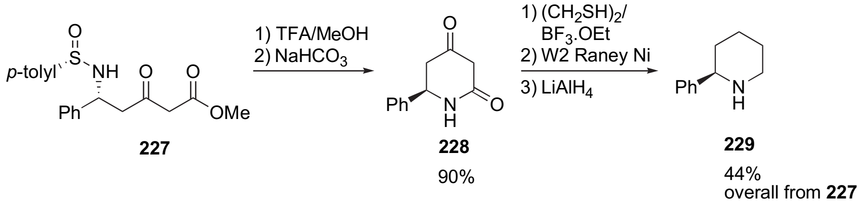
**Scheme 71.**

While the one-step procedure is more succinct, the two-step route was envisioned to provide the opportunity, where the initial enolate addition is not selective enough, to enrich the optical purity of the intermediate **225**. Notably, it was observed that, in solution, 5–10% of the δ-amino β-keto esters existed in the enol form. Thus having established an efficient route for the synthesis of chiral δ-amino β-keto esters, Davis's focus turned to the application of the building blocks (Scheme 72).

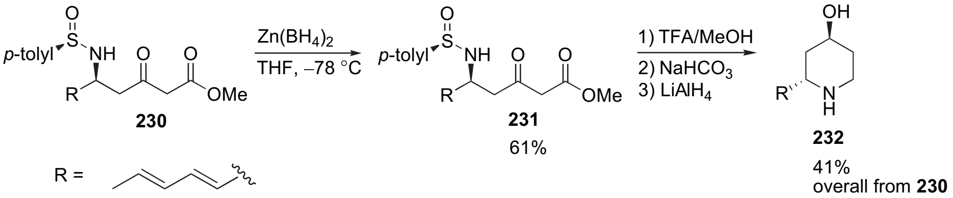
Deprotection and subsequent cyclisation of **227** afforded piperidinedione **228** as a single isomer. Succeeding transformations afforded (*R*)-2-phenylpiperidine **229** in 44% overall yield over four steps from δ-amino β-keto ester **227**. The modular nature of these building blocks allows the incorporation of motifs at different stages of the synthesis, and hence (2*S*,4*S*)-SS20846A **232** was synthesised in 41% overall yield over four steps, via **231**, from **230** (Scheme 73).

These concise, efficient asymmetric syntheses demonstrate the power of the δ-amino β-keto esters as chiral building blocks.

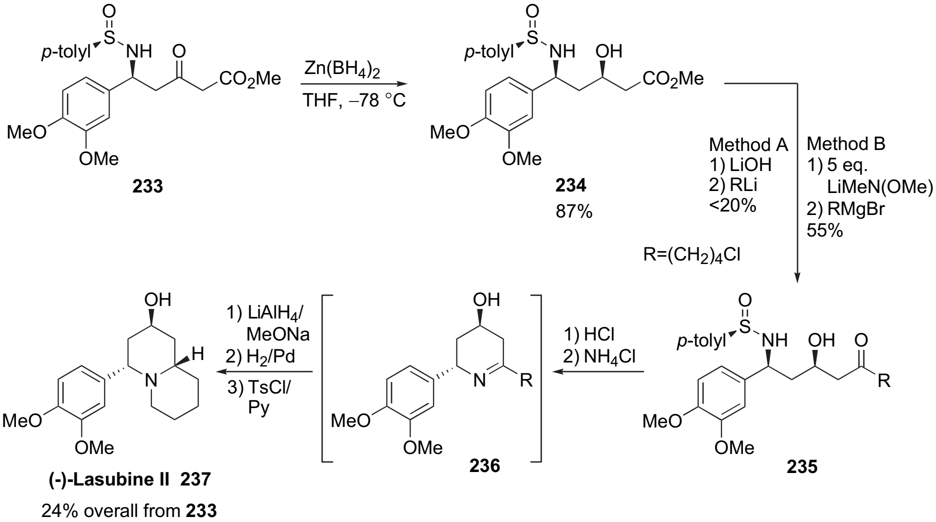
To further demonstrate the practicality of the δ-amino β-keto esters to asymmetric synthesis, Davis embarked upon the synthesis of the challenging (−)-lasubine II skeleton **237**, one of the lythracease class of alkaloids (Scheme 74).[96] During the course of their synthesis, it was found necessary to incorporate the benzyl chain at the β-amino alcohol **234** stage, as efforts to introduce this structure further in the synthesis met with disappointing results. Thus hydrolysis of the ester with subsequent addition of the corresponding organolithium reagent afforded ketone **235**, though in only 20% yield (Method A). As an alternative route, conversion into the Weinreb amide and addition of the corresponding Grignard reagent furnished ketone **235**, albeit in two steps, in 55% yield (Method B).



**Scheme 72**.



**Scheme 73**.



**Scheme 74**.

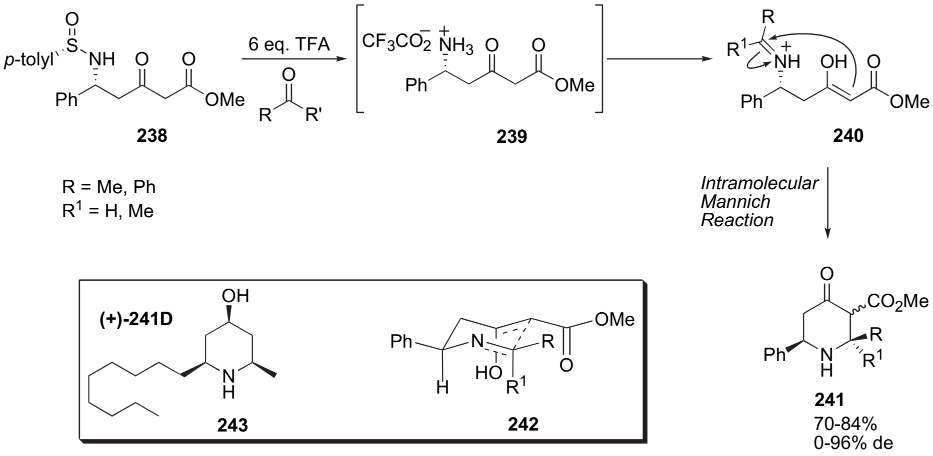
Deprotection of the sulfinyl group and subsequent elaboration of the resulting cyclised product provided direct access to (−)-lasubine II **237** in 24% overall yield in six steps from δ-amino β-keto ester **233** as a single isomer.

In a modification to the synthesis of (−)-lasubine II **237**, Davis et al. described the synthesis of *trans*-2,6-disubstituted piperidines, and thereafter the preparation of (−)-lasubine I.[97] Screening a set of conditions for the reduction of **236**, they found that using a mixture of diisobutylaluminium hydride and *n*-butyllithium afforded the trans-isomer, rather than the previously favoured cis-ring system, in 68% yield and 98% de.

Stemming from the observation that 5–10% of the δ-amino β-keto esters exist as the enol form in solution, Davis sought to exploit this property in the application of the δ-amino β-keto esters towards new chiral skeletons.[98] It was reasoned that if an iminium ion could be generated, it would react with the enol form via an intramolecular Mannich reaction, providing direct access to the 2,3,4,6-tetrasubstituted piperidine skeleton (Scheme 75). It was found that, after removal of the sulfinyl group of **238**, an iminium ion **240** could be generated from **239** and a number of different aldehydes and ketones. The intramolecular Mannich reaction furnished piperidines **241** in high yield (70–84%) with generally good stereoselectivity (1:1 to 98:2 cis/trans). The high predilection for the cis-isomer was rationalised by invoking the chelated six-membered transition state **242**, in which the sterically large substituents preferentially occupy the equatorial positions, leading to the cis-isomer.

The efficacy of the intramolecular Mannich reaction was further demonstrated by Davis et al. through the asymmetric synthesis of the dendrobate alkaloid (+)-241D **243**, achieved in five steps from the δ-amino β-keto ester in 36% yield and >97% de.

As a test of the intramolecular Mannich reaction of the sulfinimine-derived δ-amino β-keto esters, Davis et al. embarked upon the synthesis of the quinolizidine alkaloids, (−)-epimyrtine and (+)-myrtine.[99] *En route* to these functionalised piperidines, the scope of the reaction was briefly examined. Overall, the expediency of this procedure was



**Scheme 75**.

again highlighted, providing a short and efficient asymmetric synthesis of these alkaloids, with (−)-epimyrtine synthesised in six steps and 41% overall yield from the corresponding sulfinimine.

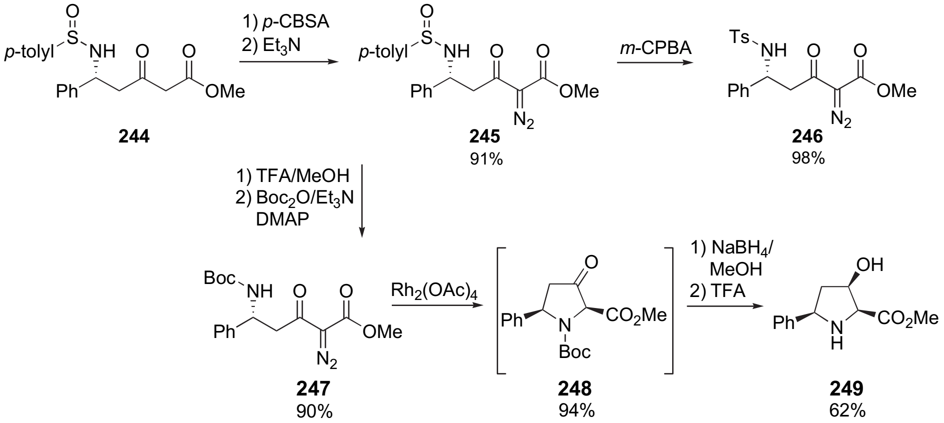
Seeking to expand the versatility of the new δ-amino β-keto ester building blocks, a method for the coupling of the δ-amino with the α-carbon was reported by Davis et al., providing expedient entry to the proline skeleton. To accomplish the desired cyclisation, Davis chose to exploit metal carbenoid chemistry (Scheme 76).[100] The requisite chiral diazo compound **245** was synthesised in high yield from δ-amino β-keto ester **244**. As metal carbenoid insertion into the N–H bond of a sulfinamide was unprecedented, however, preliminary investigations revolved around insertion into the corresponding *N*-tosyl derivative **246**, accessed through oxidation of the sulfoxide. Unfortunately, treatment of the *N*-tosyl derivative with 3 mol % $Rh_2(OAc)_4$ resulted in a complex mixture of inseparable products. Hence, sulfinamides **245** were converted into the *N*-Boc derivative **247**, which, upon treatment with 3 mol % $Rh_2(OAc)_4$ afforded the desired oxo-proline **248** in near-quantitative yield and as a single diastereomer. It was observed, however, that the stereochemical purity of the compound eroded in solution and upon further purification, and thus proline **248** was taken on directly, reduction, deprotection and subsequent purification affording the major cis-isomer **249** in 62% yield.

The effectiveness of this new strategy for the synthesis of the chiral proline skeleton was demonstrated through the concise synthesis of (2*R*,5*R*)-5-phenylpyrrolidine-2-carboxylate, a key structural feature of (+)-RP66803, a non-peptide cholecystokinin antagonist.

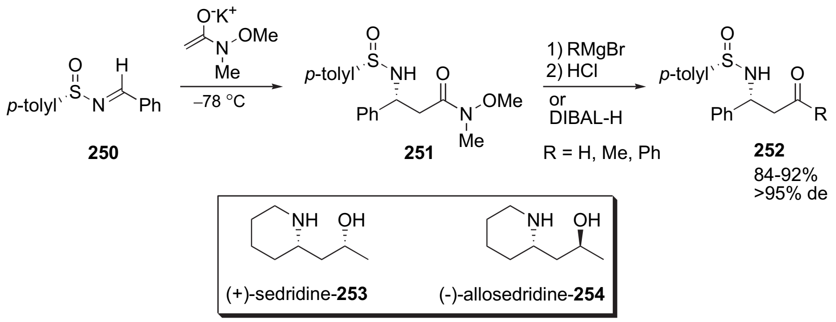
In 2003, Davis et al. published a detailed report on their exploration of the scope and limitations of the rhodium-mediated N–H insertion of δ-amino α-diazo compounds.[101] It was found that the exceptional cis-stereoselectivity was general to a wide range of substituent patterns. Further, it was found that many of the substrates examined possessed greater stability relative to Davis's previous results.

A further illustration of the potential of the α-diazo δ-amino β-keto ester building blocks was presented in 2004, through the efficient asymmetric synthesis of the potent antifungal and antibiotic agent, (+)-preussin.[102] The asymmetric synthesis was accomplished in seven steps and 23% overall yield from the δ-amino β-keto ester.

Prompted by previous results of their work, Davis et al. reported a general solution to the construction of enantiopure β-amino carbonyl compounds via the new sulfinimine-derived chiral building blocks, *N*-sulfinyl β-amino Weinreb amides.[103] Addition of the potassium enolate of the commercially available *N*-methoxy-*N*-methylacetamide to chiral



**Scheme 76**.

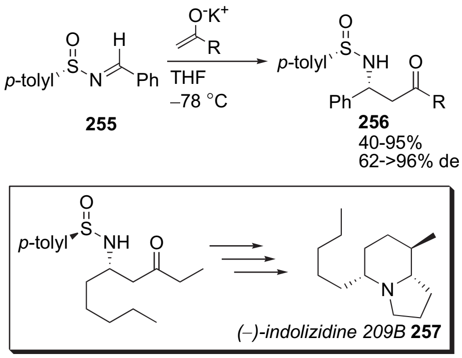


**Scheme 77**.

*p*-TS-imine **250** was found to provide β-amino amide **251** in good yield and high diastereoselectivity (Scheme 77). Addition to *p*-TS-phenyl-imine, however, afforded low diastereoselectivities (56% de), though this was observed to be the exception. Variation of the sulfinyl substituent resulted in a reduction in both yields and stereoselection.

It was found that the β-amino Weinreb amides **251** react well with a variety of organometallic reagents to afford the corresponding β-amino carbonyl compounds **252** in good yield (84–92%), with no loss in stereochemical purity. As a demonstration of the virtue of these new building blocks, the asymmetric synthesis of the sedum alkaloids, (+)-sedridine **253** and (−)-allosedridine **254**, was completed, indicating the potential access to a wide range of enantiopure β-amino carbonyl compounds.

In 2003, Davis et al. published an alternative approach to the β-amino carbonyl chiral building blocks.[104] Rather than synthesis via the Weinreb amide as previously described, the direct addition of methyl ketone enolates to enantiopure sulfinimines **255** was found to provide direct access to the protected amino ketones **256** (Scheme 78). The reaction of a number of ketones was investigated. Through a screen of the conditions, it was found that the potassium enolates provided both the highest yields and diastereoselectivities. The stereochemical outcome was found to be in accordance with the established six-membered chelated transition state. To illustrate the utility of their methodology, Davis et al. described the concise asymmetric synthesis of (−)-indolizidine 209B **257**, a member of the dendrobatide family of alkaloids.



**Scheme 78**.

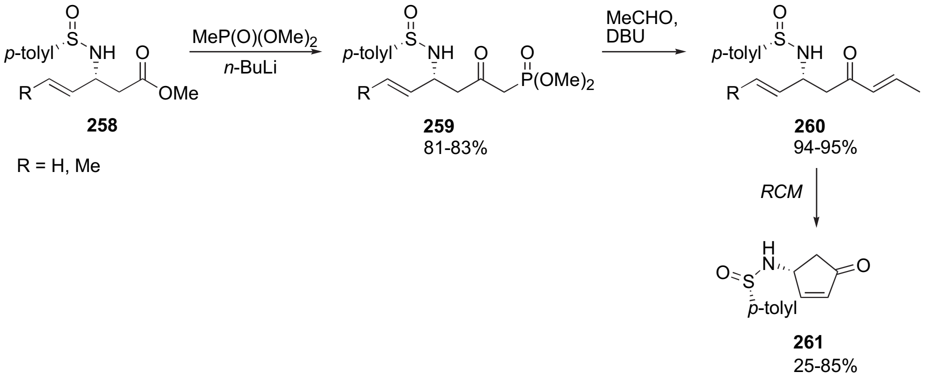
During their studies towards the asymmetric synthesis of carbocyclic nucleoside building blocks, Davis et al. described a new modification of the sulfinimine-derived δ-amino β-keto ester motif.[105] Seeking to synthesise a substrate for ring-closing metathesis (RCM) that incorporated the possibility for flexible substitution at both the alkenes and nitrogen to activate the system to metathesis, δ-amino β-ketophosphonates **259** were examined (Scheme 79).

Treatment of the *p*-TS imine-derived β-amino esters **258** with lithium dimethyl methylphosphonate furnished β-ketophosphonates **259** in high yield. Subsequent reaction with acetaldehyde provided direct access to the α,β-unsaturated amino ketones **260** in very high yield. A wide screen of conditions for the ring-closing metathesis was conducted, including both the first- and second-generation catalysts and analysing the effect of the sulfur substituent. Reaction of **260**, however, provided carbocycle **261** in good yield as a single isomer.

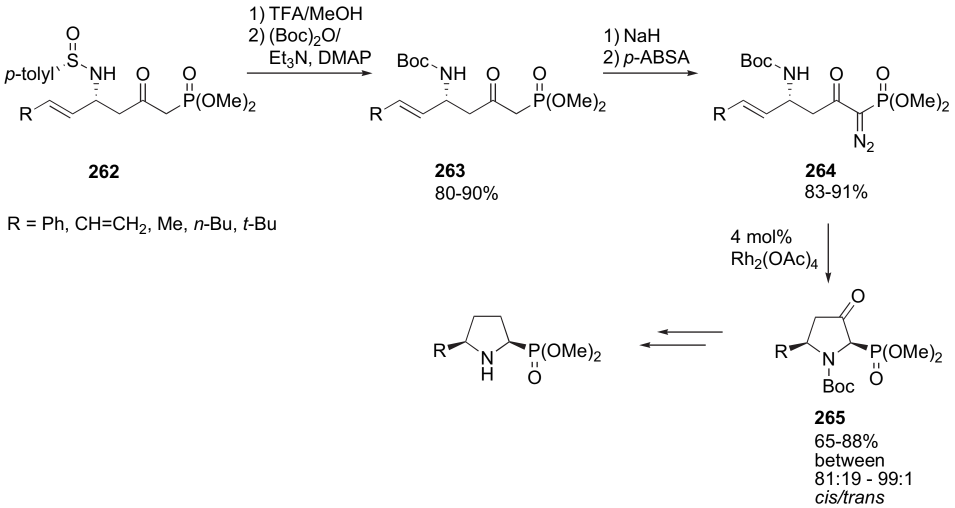
Expanding on their interest in the asymmetric synthesis of α-amino phosphonic acids as surrogate amino acids, Davis et al. described the efficient asymmetric synthesis of cis-5-substituted pyrrolidine-2-phosphonates from β-ketophosphonates (Scheme 80).[106] Conversion of the sulfinyl β-ketophosphonate into the *N*-Boc derivative occurred in high yield (80–90%) and, after some optimisation, the diazo functionality was efficiently installed (83–91%). Treatment of **264** with 4 mol % of $Rh_2(OAc)_4$ delivered the corresponding 3-oxopyrrolidine phosphonate **265** in high yield (65–88%), with the cis/trans ratio of the crude product varying between 81:19 and >99:1.

The new β-ketophosphonate building block provides efficient entry to chiral, non-racemic *cis*-5-substituted pyrrolidine-2-phosphonates, valuable proline surrogates, during which the first metal carbenoid N–H insertion reaction from a α-diazophosphonate was reported.

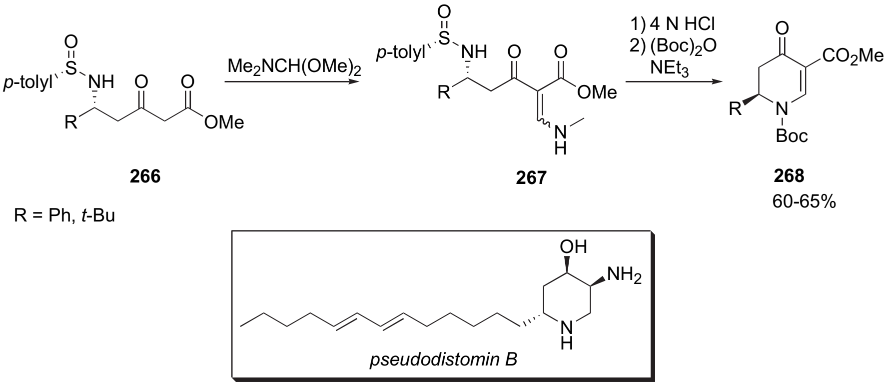
Very recently, Davis et al. introduced a new perspective to their intramolecular Mannich reaction of δ-amino β-keto esters.[107] Seeking to find an entry into the 2,4,5-trisubstituted piperidine ring system, Davis rationalised that an initial reaction with formaldehyde or its equivalent would set up the requisite Mannich precursor. Initial investigations revolved around the reaction of a number of formaldehyde equivalents to the δ-amino β-keto esters and, while the iminium ion was detected in a number of these instances, it was in unacceptably low yields, with a number of undesired side reactions competing. Thus, Davis's focus turned to the reaction of δ-amino β-keto ester enaminones **267** (Scheme 81).



**Scheme 79**.



**Scheme 80**.



**Scheme 81**.

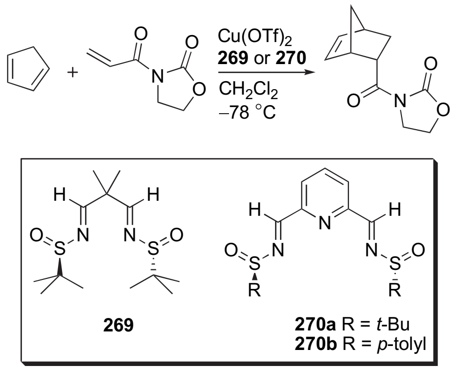
Treatment of δ-amino β-keto esters **266** with 10 equiv of dimethylformamide dimethyl acetal furnished the desired enaminones **267**, which, upon direct deprotection and treatment with Boc anhydride, afforded piperidines **268** in 60–65% from the δ-amino β-keto esters as a single isomer.

The practicality of this strategy for the construction of 2,4,5-trisubstituted piperidines was demonstrated through the synthesis of pseudodistomin B, one of the first isolated piperidine marine alkaloids.

## 6. Application of chiral sulfinimines as ligands for asymmetric synthesis

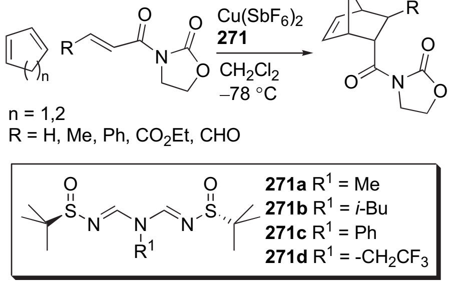
The drive towards the development of catalytic methods is particularly apparent in the field of asymmetric synthesis, primarily as it provides the opportunity to introduce asymmetry through the use of sub-stoichiometric amounts of valuable chiral-inducing agents. One of the most widely employed methods is through the use of chiral ligands. In the vast majority of chiral ligands, the stereodirecting effect relies upon stereocentres located at carbon. While the construction of ligands incorporating chiral sulfoxides as the stereodirecting moiety had been observed,[108] the chemistry was relatively underdeveloped. It was Ellman et al. who instigated a series of investigations into the practicality of chiral ligands based upon sulfinimines for asymmetric Lewis-acid catalysis.

Ellman's initial investigations into the application of sulfinimines in chiral ligands focused on the construction of the $C_2$-symmetric ligands **269** and **270**,[109] designed to be analogous to the highly successful bisoxazoline ligands (Scheme 82).[110] The reaction they chose in order to test the activity of these novel catalytic systems was the Lewis-acid-catalysed Diels–Alder reaction. Their initial results showed that, while the novel ligands proved to present good catalytic activity, the asymmetric induction was disappointing.



**Scheme 82**.

Reaction with ligand **269** showed good conversion (100% yield), but with essentially no stereoselectivity (80% de, 6% ee). Ligand **270a** was found to be less active (35–100% yield), but did present moderate levels of stereoinduction (88% de, 30–72% ee). Reaction in the presence of **270b** proceeded in both low yield (50%) and stereoinduction (88% de, 37% ee), and this discrepancy is thought to be due to the decreased steric presence of the *p*-tolyl group, in comparison to the *tert*-butyl-group. Developing their strategy further, Ellman et al. sought to synthesise a ligand that contained a rigid backbone, which contained a more basic donor atom to increase the co-ordinating capability of the ligand. To this end, the bis(sulfinyl)imidoamidine (SIAM) ligand **271** was prepared (Scheme 83).

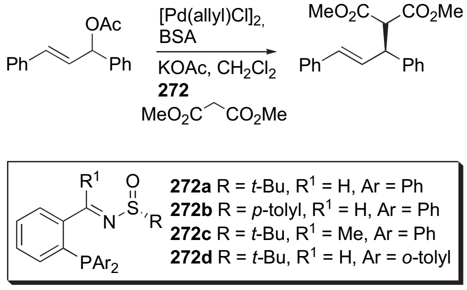


**Scheme 83**.

It was found that reaction in the presence of the complex of **271a** with Cu($SbF_6$) resulted in a greatly accelerated reaction (100% conversion in 0.1–16 h) with exceptional levels of both enantio- and diastereoselectivity (32 to >98% ee, 90 to >98% de). A range of dienophiles were examined to give a preliminary determination of the substrate tolerance of the catalyst system. Even with less electrophilic substrates, it was possible to find conditions that afforded high yields and stereoinduction. Notably, having observed that the use of excess ligand with respect to the amount of copper employed did not slow down the reaction, as had been seen in previously more established systems, it was deduced that the Cu(II)-SIAM complex exists as a rare $M_2L_4$ quadruple-stranded helicate.

Such was the success of their preliminary studies that Ellman et al. expanded their investigations on the development of sulfinimine-based ligands for asymmetric Lewis-acid catalysis, summarised in a full account in 2003.[111] Further to their introductory report, the full range of ligands examined was detailed. In addition, exploration of the SIAM ligands was described. A range of $C_2$-symmetric ligands **271a–d** were synthesised to investigate the impact of differential substitution at the internal nitrogen upon the ligand activity. Interestingly, substitution on the internal nitrogen appeared to have no detrimental effects, with the catalyst systems maintaining high yields and stereoinduction, exposing the potential for further elaboration and possible attachment to a solid support. In addition, the substrate scope of the reaction was expanded. The system was found to tolerate not only a wide range of chemically diverse dienophiles, but also cyclic and acyclic dienes, albeit in lower yield and stereoselectivity. Thus, the novel sulfinimine-based SIAM ligands were shown to be efficient in a chiral catalytic system for a broad range of substrates. Their modular design offers the potential for elaboration at a number of sites, hence widening their appeal. Their application in the asymmetric catalysis of a more complex real system was described by Murai, Ishihara and co-workers in the synthesis of the spirocyclic core of gymnodimine.[112]

Encouraged by the success of the sulfinimine-based SIAM ligands for Lewis-acid catalysis, Ellman et al. turned their focus to the synthesis of alternative novel ligands incorporating the chiral sulfinimines as asymmetric inducers. Building on the success of previous *P*,*N* ligands the use of sulfinimine-based *P*,*N* ligands **272** to introduce asymmetry in palladium-catalysed allylic alkylations was explored (Scheme 84).[113] The sulfinimine-based chiral scaffold was designed to incorporate a chelating phosphine and an $sp^2$ nitrogen in positions that are relative to the chiral centre and that are analogous to the phosphinooxazoline skeleton.



**Scheme 84**.

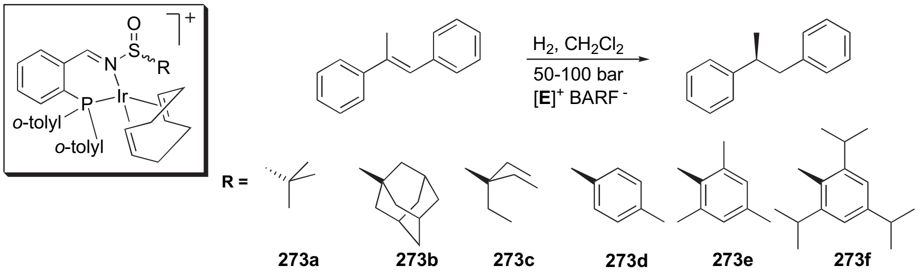
Initial investigations sought to optimise the conditions of the reaction and, for this purpose, ligand **272a** was employed. Gratifyingly high levels of conversion were observed, though with disappointing enantioselectivity (43–67% ee). Switching to a less polar solvent was found to result in a significant improvement in the stereoselectivity of the reaction. Thus, reaction in dichloromethane with $[Pd(allyl)Cl]_2$ was found to be optimal. While the transformation was now affording high yields and stereoselectivities (86–88% ee), it was deemed, however, to be inhibitively slow (>25 h).

The focus was then turned to the investigation of the effect of altering the substitution patterns on the ligand backbone. Substituting the sulfinyl *tert*-butyl with a *p*-tolyl group (**272b**) resulted not only in a slower transformation, but isolation of the product in a racemic form. Introduction of a methyl group onto the ligand scaffold (**272c**) provided a modest increase in the rate of reaction (5 h), though the stereoinduction was found to be unacceptably low (56% ee). From clues gained through further structural analysis, Ellman chose to investigate the effects of varying the phosphorous substituents. Incorporation of *ortho*-toluene groups into the structure (**272d**) was found to provide a series of significant improvements in the system. While reaction with ligand **272a** had required a loading of 5 mol % and low concentrations (0.07 M), in order to provide an effective transformation, reaction with **272d**, while still requiring low concentrations, provided high yields and high levels of stereoinduction (93–96% ee), and significantly shorter reaction times (<1 h). Thus, sulfinimine-based ligands had been shown to be applicable to asymmetric Pd-catalysed alkylations.

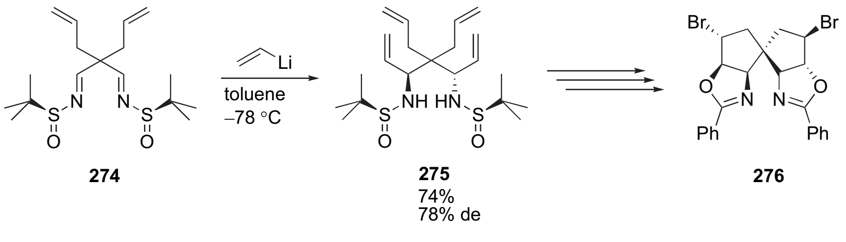
Prompted by the reports from Senanayake et al. on the facile synthesis of a variety of structurally diverse sulfinamides, Ellman et al. chose to expand the scope of their investigations on the effect of the sulfinyl substituent on the sulfinimine-based ligands activity; previously only the *tert*-butyl and *p*-tolyl groups had been considered. The system in which they chose to test the various ligands was a second transition-metal-catalysed reaction, the iridium-catalysed asymmetric hydrogenation of olefins (Scheme 85).[114]

Optimisation of the reaction was carried out using ligand **273a**. In line with previously established iridium catalysis systems, it was found that chlorinated solvents were required for efficient turnover, with dichloromethane providing complete conversion within 1 h and 94% ee. In addition, it was found that the counterion played a critical role, with the non-co-ordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (BARF) providing the most efficient catalysis. With the optimum conditions established and the catalytic system working efficiently, the Ellman group turned their focus to examining the effect of the sulfur substituent on the reaction of the chiral ligands. It was expected that increasing the steric bulk of the sulfinamide component would correspond with an improvement in the enantioselectivity. Reaction with ligands **273b** and **273c**, however, resulted in a reduction in both the rate and selectivity. In line with their previous observations, reaction with the ligands derived from arenesulfinyl imines **273d–f** was significantly impaired. These results only highlighted the negative impact of incorporating an aryl group at this position, with almost no reaction and effectively no selectivity observed. Ligands **273a–c** provided constantly better transformations with higher yield (58–99%) and stereocontrol (84–94% ee), with **273d–f** providing generally lower yields (52–99%) and significantly lower stereocontrol (5–7% ee). While the scope of this reaction was not examined, the asymmetric iridium-catalysed hydrogenation was found to be highly efficient in the reduction of α,β-unsaturated esters and allylic alcohols.

Recently, Kato et al. disclosed a report on their synthesis of a novel spirocyclic bis(oxazoline) chiral ligand **276** (Scheme 86).[115] While sulfinimines are not incorporated into the final skeleton, the stereochemistry of the ligand is set up through exploiting the stereodirecting nature of *t*-BS-imines.



**Scheme 85**.



**Scheme 86**.

Addition of vinyllithium to **274** afforded the bis-sulfinamide **275** in good yield, deprotection and subsequent modification leading to the ring-closing metathesis substrate providing direct access to the novel ligand skeleton **276**.

## 7. Conclusions

In summary, Ellman et al. have developed a novel class of sulfinimine-based chiral ligands. In both the SIAM and *P,N*-sulfinyl imine ligands derive their stereochemical induction derives from the stereogenic sulfur atoms. Not only have these ligands been found to be efficient for a range of substrates, but in addition they have been applied in more complex systems, with little decrease in efficiency or stereoselectivity observed.

The recent widespread application of sulfinimines has helped to establish them as key chiral *N*-auxiliaries in the direct, asymmetric preparation of amines. They have proved to be efficient *N*-protecting groups, domesticating the capricious nature of the imine double bond, while providing suitable activation for the reaction with a diverse range of nucleophiles. Facile deprotection of the sulfinyl group provides access to substrates for further elaboration. Two classes of chiral sulfinimines have emerged as the reagents of choice, their application having been so extensive that the sulfinamides are now commercially available. Both *p*-TS-imines and *t*-BS-imines display characteristics peculiar to their chemical makeup. Between them, these two classes have been applied to a vast range of reactions and have demonstrated the high stereodirecting nature of these chiral sulfoxides. The difference in chemistry between the *p*-tolyl- and *tert*-butyl groups highlights the influence the *S*-substituent has on the reactivity of the sulfinimines. With new modular routes being developed for the preparation of a variety of *S*-substituted chiral sulfinamides, the potential for these highly efficient chiral *N*-auxiliaries is vast. Undoubtedly, the exploration and application of new and variously substituted sulfinimines will help to realise and expand the potential of chiral sulfinimines in asymmetric synthesis.

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## Biographical sketch

**Daniel Morton** was born in Louth, UK (1979). He received his MChem in 2001 from the University of East Anglia (UK), where he remained and under the joint supervision of Dr. Robert Stockman and Professor Robert Field obtained his PhD in 2005 for work on the reaction of sulfur ylides with *tert*-butylsulfinimines for the synthesis of chiral aziridines. He is currently employed at Leeds University as a postdoctoral fellow in the group of Professor Adam Nelson, where he is involved in studies towards the total synthesis of the polycyclic ether, hemibrevetoxin B.

**Robert Stockman** was born in Castle Cary, Somerset, UK. He obtained his B.Sc. in Chemistry at the University of Bath in 1994, which incorporated a year spent in the Process Chemistry group at SmithKline Beecham in Great Burgh. He then moved to the University of Bristol to undertake a Ph.D. in the group of Professor Tim Gallagher, studying the utility of pyrrolidin-3-ones as building blocks for the synthesis of indolizidines and phakellin. In January 1998, he then moved to work as a postdoctoral fellow with Professor Philip Magnus, FRS, at the University of Texas at Austin, where he worked on the syntheses of nakadomarin and manzamine A. In July 1999, he was appointed as a Lecturer in Organic Chemistry at the University of East Anglia. His research interests encompass the development of new methods for the asymmetric synthesis of functionalised heterocycles and the use of combined two-directional synthesis/cascade approaches for target- and diversity-oriented synthesis.