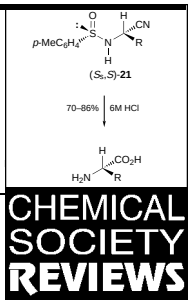
Asymmetric synthesis of amino acids using sulfinimines (thiooxime *S*-oxides)



CHEMICAL SOCIETY REVIEWS

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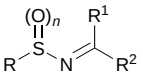
The occurrence of α- and β-amino acids in biological systems and their exceptional utility as chiral building blocks underlies the importance of new and improved methods for their synthesis in enantiomerically pure form. The intent of this review is to highlight the applications of a new class of chiral imine building block, sulfinimines (thiooxime *S*-oxides), for the enantioselective synthesis of amino acids and their derivertives.

1 Introduction

The *N*-sulfur bonding imines **1** are versatile intermediates in organic synthesis, particularly for the preparation of amine derivatives (Scheme 1).[1–3] Among them, sulfinimines (thiooxime *S*-oxide, *N*-alkylidenesulfinamides, **1b**) display unique reactivity and stereoselectivity due to the existence of the chiral electron withdrawing sulfinyl group. Like sulfoxides, sulfinimines undergo thermo-elimination to give sulfenic acids.[4–6] As expected, sulfinimines are strong Michael acceptors and undergo addition reactions with alcohols,[7] thiols,[8] amines,[9] hydrazines[9] and hydrides.[10–12] Sulfinimines also react with carbon nucleophiles.[12,13] More importantly, in many of these reactions, the chiral centre of the sulfur atom makes it possible to control these reactions in a highly diastereoselective manner. The purpose of this article is to review the asymmetric synthesis of amino acids and their derivatives from enantiomerically pure sulfinimines with particular attention to applications in the synthesis of biologically active molecules.



1a, *n* = 0, sulfenimine
b, *n* = 1, sulfinimine
c, *n* = 2, sulfonimine

Scheme 1

2 Preparation of enantiomerically pure sulfinimines

Several methods have been developed for the preparation of enantiomerically pure sulfinimines and can be divided into three categories: asymmetric oxidation of sulfenimines, asymmetric iminolysis of sulfinates (*e.g.* the Andersen's reagent), and asymmetric iminolysis of sulfinamides.

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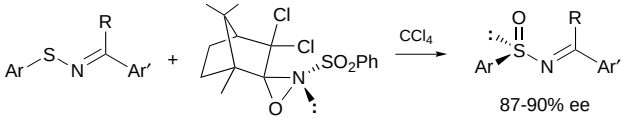
Bang-Chi Chen was born in Ruian, Zhejiang, China. He received his BS degree in 1984 from Hangzhou University. He worked for three years in Hangzhou University as an instructor while conducting research with Professor Xian Huang. In 1987 he joined Professor Davis at Drexel University in 1987 and received his PhD degree in organic chemistry 1991. In the same year he joined Bristol-Myers Squibb Company in Syracuse, New York as a Research Scientist and now is a Senior Research Investigator in the Department of Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, in Princeton, New Jersey. His research efforts have resulted in over 50 publications and patents.

Bang-Chi Chen

2.1 Asymmetric oxidation of sulfenimines

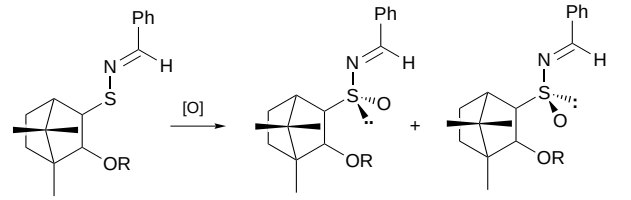
The chemoselective oxidation of sulfenimines **1a** to racemic sulfinimines **1b** without over-oxidation to sulfonimines **1c** was first reported by us over two decades ago.[7] The chemo- and stereo-selective oxidation of sulfenimines to enantiomerically enriched sulfinimines, however, was realized much more recently during our investigations of *N*-sulfonyloxaziridines (Scheme 2).[14,15] In these studies it was found that (−)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine **3** oxidizes sulfenimines **2** to give sulfinimines (R_s)-**4** in 87–90 ee and 89–96% yield. Simple crystallization upgrades **4** to enantiomeric purity.[15,16] The antipodal sulfinimines (S_s)-**4** can be readily prepared using enantiomeric oxaziridine (+)-**3**.



2 (–)-**3** (R_s)-**4**

Scheme 2

Diastereoselective oxidation of sulfenimines has also been reported for the preparation of non-racemic sulfinimines (Scheme 3).[13] Oxidation of sulfenimines **5** with *m*-CPBA or MMPP afforded sulfinimines **6** in 83–99% yield. The diastereoselectivity, however, was highly dependent on the R group in the chiral auxiliary. For example, when R = H in **5** the sulfinimine (R_s)-**6** was obtained in diastereomerically pure form.

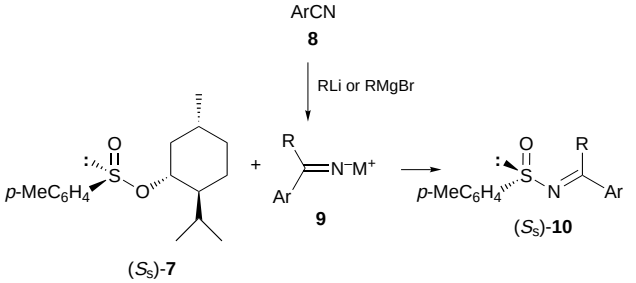


5 (R_s)-**6** (S_s)-**6**

Scheme 3

2.2 Asymmetric iminolysis of sulfinates

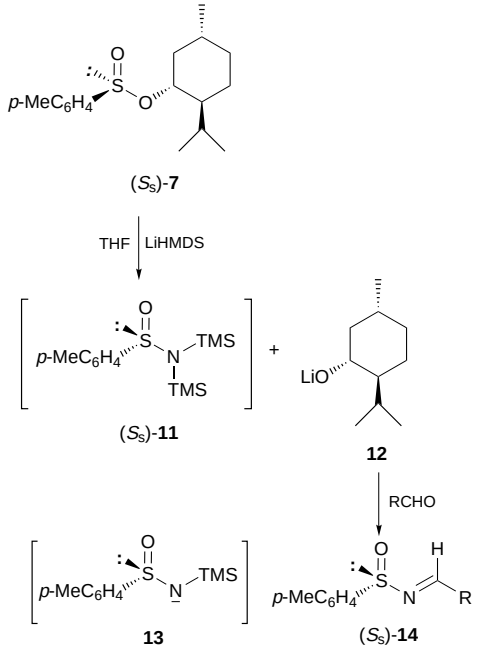
Another method for the preparation of sulfinimines is the iminolysis of sulfinates (Scheme 4). Enantiomerically pure sulfinimines **10** have been prepared from the Andersen's reagent **7** and imino-metallo reagents **9** in moderate to low yields.[10,12,17] This reaction is highly stereoselective, taking place at the chiral sulfur atom in an S_N2 fashion. The imino-metallo reagents **9** are usually prepared *in situ via* the reaction of aromatic nitriles **8** with lithium or Grignard reagents. This means that R and Ar in **10** cannot be hydrogen and alkyl, respectively.



(S_s)-**7** (S_s)-**10**

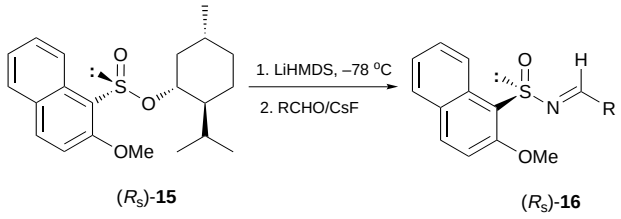
Scheme 4

Recently we devised an efficient 'one pot' procedure for the asymmetric synthesis of aromatic and aliphatic aldehyde derived sulfinimines **14** (> 95% ee) making these versatile building blocks available for the first time.[18,19] This procedure entails the reaction of *N*,*N*-bis(trimethylsilyl)-*p*-toluenesulfinamide **11**, prepared *in situ* by treatment of the Andersen's reagent **7** with lithium bis(trimethylsilyl)amide (LiHMDS), with aromatic or aliphatic aldehydes (Scheme 5). This method is highly effective for the preparation of arylidene and alkylidene sulfinamides **14** (R = aryl, alkyl) which are usually obtained in 57–90% yield. The mechanism of this transformation involves the reaction of silyl sulfinamide anion **13** with the aldehyde in a Peterson type olefination reaction. Anion **13** is thought to be generated by reaction of **11** with the by-product lithium menthoxide (**12**).[19]



Scheme 5

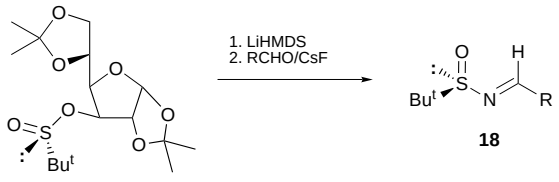
Another enantiomerically pure sulfinate available for the preparation of sulfinimines is menthyl 2-methoxy-1-naphthalenesulfinate **15** (Scheme 6).[20] In a manner similar to that outlined in Scheme 5, enantiomerically pure sulfinimines such as **16** were also obtained.[21,22]



(R_s)-**15** (R_s)-**16**

Scheme 6

S-Alkyl sulfinimines can also be prepared using this method (Scheme 7). Thus reaction of sulfinate **17** with LiHMDS, followed by addition of the aldehyde in the presence of CsF afforded *S*-*tert*-butyl sulfinimines **18** in enantiomerically pure form.[23]

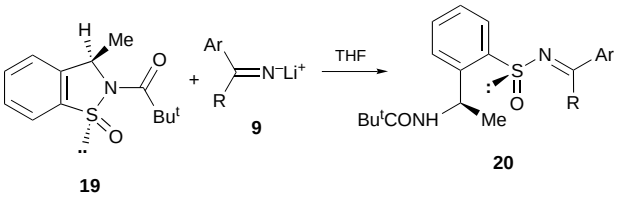


17 **18**

Scheme 7

2.3 Asymmetric iminolysis of sulfinamides

Analogous to the iminolysis of sulfinates, Wills and co-workers reported that the reaction of sulfinamide **19** with the lithiated imines **9** gave sulfinimines **20** as a single isomer (Scheme 8).[24,25] As noted in the other examples, an S_N2 inversion of the chiral centre at sulfur atom is observed and R and Ar in **20** cannot be H or alkyl, respectively.

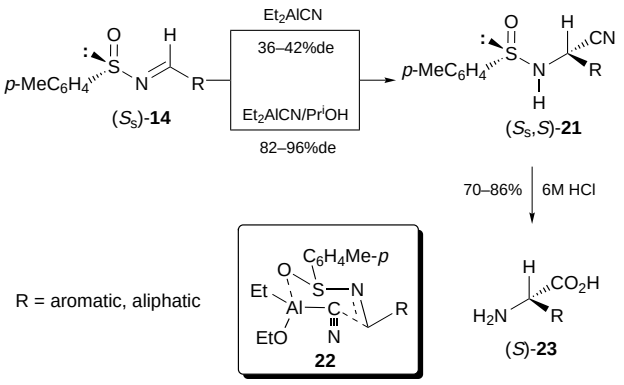


19 **9** **20**

Scheme 8

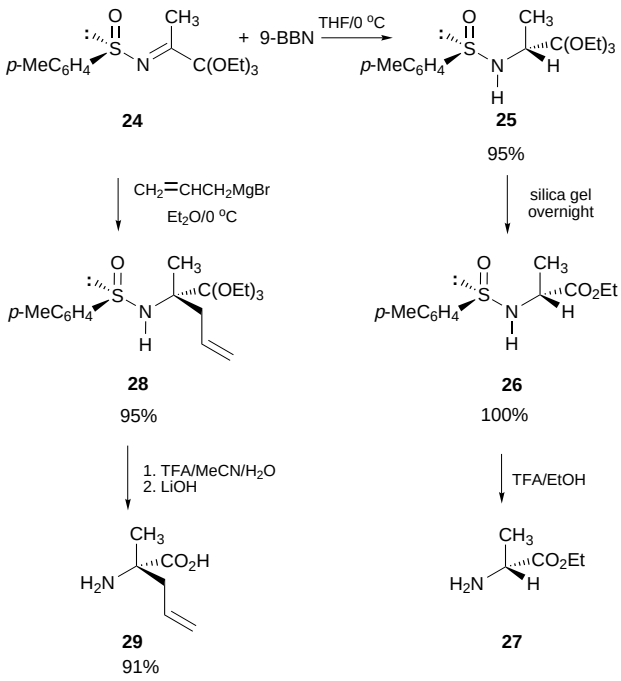
3 Asymmetric synthesis of α-amino acids from sulfinimines

As an extension of the Strecker synthesis, first reported in 1850, addition of cyanide to sulfinimines is expected to give α-amino nitriles which on hydrolysis give α-amino acids. Our initial attempts to add common cyanide sources such as KCN, TMSCN, *etc.* to sulfinimines were unsuccessful.[26] However, reaction of sulfinimine (S_s)-**14** with diethylaluminium cyanide afforded a mixture of diastereoisomers **21** in good yield, but modest diastereoselectivity; *e.g.* 36–42% (Scheme 9).[26] Formation of the major product (S_s,*S*)-**21** is consistent with complexation of Et_2AlCN with the sulfinyl oxygen activating the imine for intramolecular cyanide addition *via* chair-like transition state **22**. Significantly, it was observed that addition of ethyl(alkoxy)aluminium cyanide [Et(R′O)AlCN], prepared by treatment of Et_2AlCN with isopropyl alcohol (R′OH), to the sulfinimine results in a dramatic improvement in the diastereoselectivity (de), *e.g.* from 36–42% to 82–94%.[27] The enhanced des are attributed to the reduced Lewis acidity of Et(R′O)AlCN *vs.* Et_2AlCN which makes it more selective. Simple crystallization of the amino nitriles affords a diastereomerically pure product **21** (> 96% de) in good yield. Acid catalysed hydrolysis of the diastereomerically pure **21** not only removes the sulfinyl auxiliary, but hydrolyses the nitrile group, affording the enantiomerically pure (> 95% ee) α-amino acids **23**. Importantly, racemization of the sensitive arylglycines was not detected in this practical asymmetric Strecker synthesis.



Scheme 9

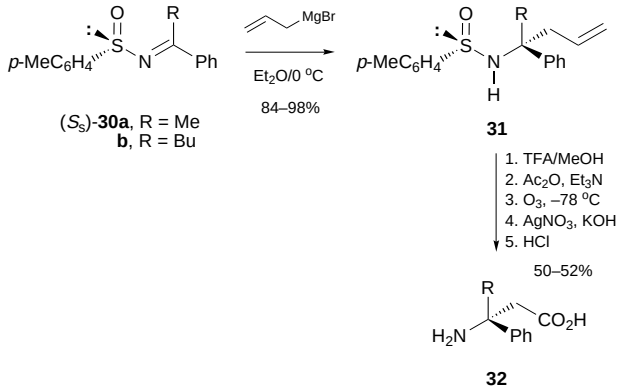
A new method for the synthesis of α-amino acids from sulfinimines was reported by Hua and co-workers (Scheme 10).[28] Reaction of sulfinimine **24** with 9-borabicyclo[3.3.1]nonane gave **25** exclusively in 95% yield.[28] Hydrolysis of the ortho-ester on silica gel followed by removal of the *N*-sulfinyl group resulted in formation of alanine ethyl ester **27** in excellent yield. Similarly, reaction of **24** with allylmagnesium bromide afforded **28** in 95% yield as a single isomer. The high stereoselectivity observed with the allyl Grignard reagent was attributed to a chair-like six-membered transition state.[12,13,28] Compound **28** has been converted to (*S*)-2-amino- 2-methylbut-4-enoic acid **29** in 91% yield. The sulfinimine **24** was prepared in 68% yield by treatment of the Andersen reagent (R_s)-**7** with the imino-metallo reagent prepared from triethoxyacetonitrile and methyllithium.



Scheme 10

4 Asymmetric synthesis of β-amino acids from sulfinimines

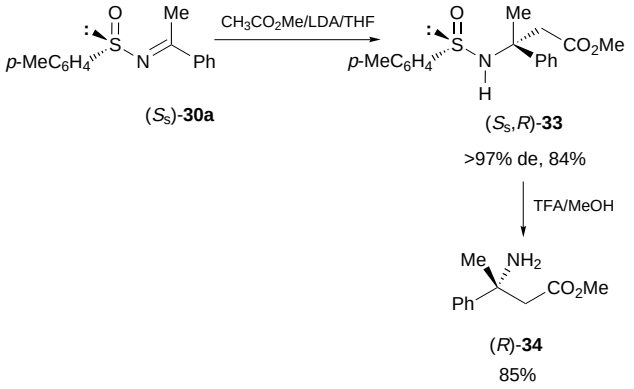
β-Amino acids are important constituents of natural products and precursors of the β-lactam class of antibiotics. By taking advantage of the high diastereoselectivity obtained in the addition of allyl Grignard reagent to sulfinimines,[12,13,28] Hua *et al.* developed a method for the synthesis of β-amino acids (Scheme 11).[12] Diastereoselective addition of allylmagnesium bromide to sulfinimines (S_s)-**30** gave sulfinamides **31** in 82–98% de and 92–96% yield.[12] Following separation of the diastereoisomers, sulfinamides **31** were converted to β-amino acids **32** in 50–52% yield *via* a sequence of reactions.



Scheme 11

A simpler route to β-amino acids involves the diastereoselective addition of enolates to enantiopure sulfinimines (Scheme 12).[16,29–31] For example, treatment of (S_s)-sulfinimine

30a with the lithium enolate of methyl acetate afforded β-amino ester **33** in > 97 de and 84% yield.[16] Removal of the *N*-sulfinyl group with TFA afforded β-phenylalanine **34** in 85% yield.[16]



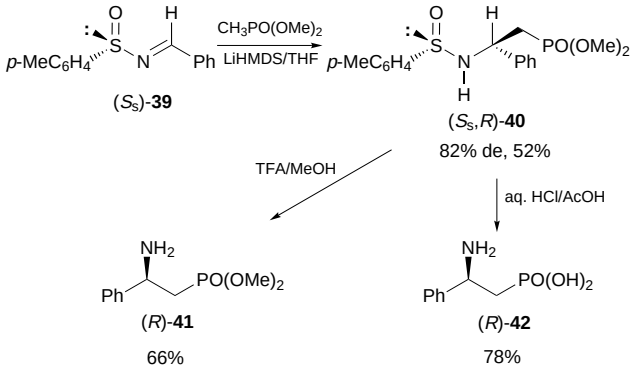
Scheme 12

Fujisawa and co-workers reported the addition of the enolate of *tert*-butyl acetate to sulfinimine **35**.[32] Interestingly, the lithium enolate gave (*S*s,*S*)-**37** while the titanium enolate afforded (*S*s,*R*)-**37**. A non-chelated transition state was used to explain the formation of (*S*s,*S*)-**37** while a six-membered chair-like transition state containing a four-membered metallocycle and/or a seven membered counterpart was attributed to the formation of the (*S*s,*R*)-**37**. Treatment of (*S*s,*S*)-**37** with TFA gave β-amino acid **38** in 70% yield,[32] Scheme 13.

Mikolajczyk *et al.* reported that the addition of α-phosphonate carbanions to sulfinimines gives rise to β-amino phosphonic acids (Scheme 14).[33] For example, reaction of sulfinimine **39** with the lithium α-phosphonate carbanion afforded **40** in 82% de which can be isolated in 52% yield, diastereomerically pure, by flash column chromatography. Treatment of **40** with TFA–MeOH gave dimethyl β-aminophosphonate **41** in 66% yield. On the other hand, β-amino phosphonic acid **42** was obtained in 78% yield by treating **40** with HCl–AcOH. A seven-membered chelated transition state was proposed to explain the stereochemistry of the product.

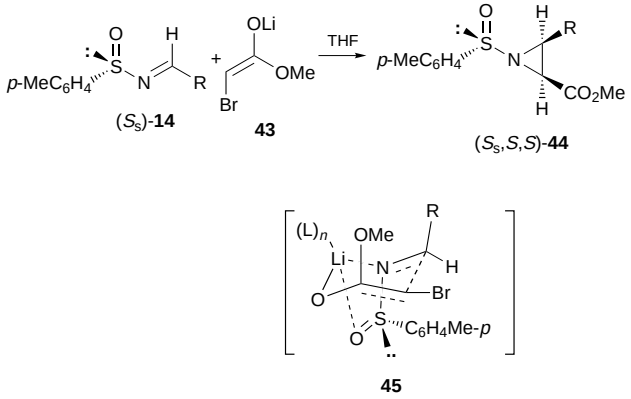
5 Asymmetric synthesis of aziridine-2-carboxylate esters from sulfinimines

Aziridine-2-carboxylate esters are a special class of amino acids. Enantiomerically pure aziridine-2-carboxylic acids are versatile intermediates for the asymmetric synthesis of many biologically active materials because they undergo highly regio- and stereo-controlled ring opening reactions with nucleophiles to give β-substituted α-amino acids.[34] In this regard, we developed a highly diastereoselective Darzens' type condensation involving addition of the lithium enolate of α-bromoacetate



Scheme 14

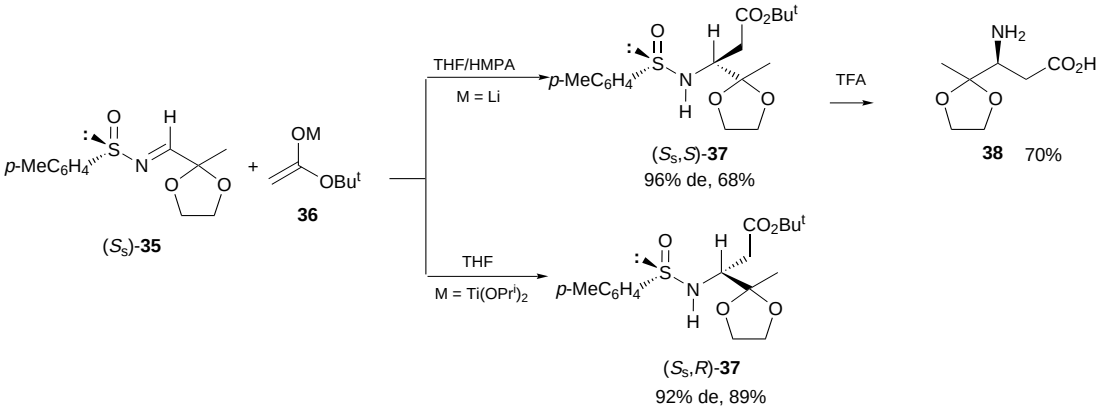
to sulfinimines (*S*s)-**14** for the preparation of *cis*-aziridine-2-carboxylates (Scheme 15).[35] The corresponding *N*-sulfinylaziridine-2-carboxylic esters (*S*s,*S*,*S*)-**44** were obtained in 94–98 de and 60–74% yield. A chair-like transition state **45** was suggested as being responsible for the high selectivity and stereochemistry. α-Substituted aziridine-2-carboxylates can be prepared in a similar manner.[36]



Scheme 15

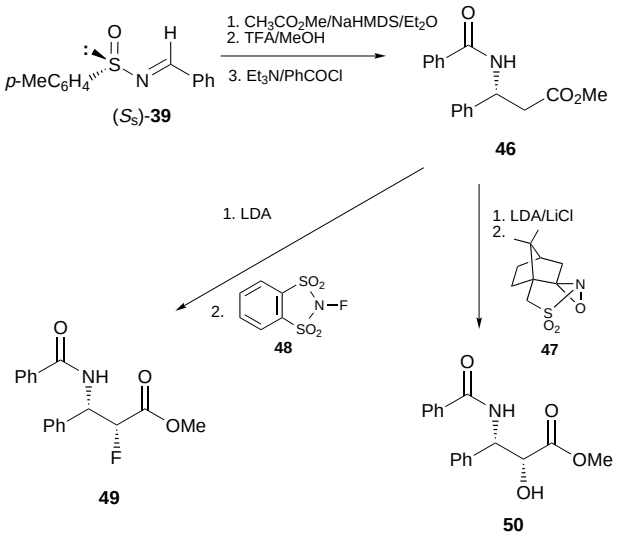
6 Applications in the synthesis of biologically important molecules

Enantiomerically pure sulfinimines have found a new role in the asymmetric synthesis of biologically important nitrogen containing molecules. This section highlights some of these applications. For example, sulfinimine **39** has been used in the synthesis of the Taxol C-13 side chain **50**[16] and its fluoro analogue **51** as outlined in Scheme 16.[30] Novel aspects of these syntheses are the highly diastereoselective *syn* hydroxylation of



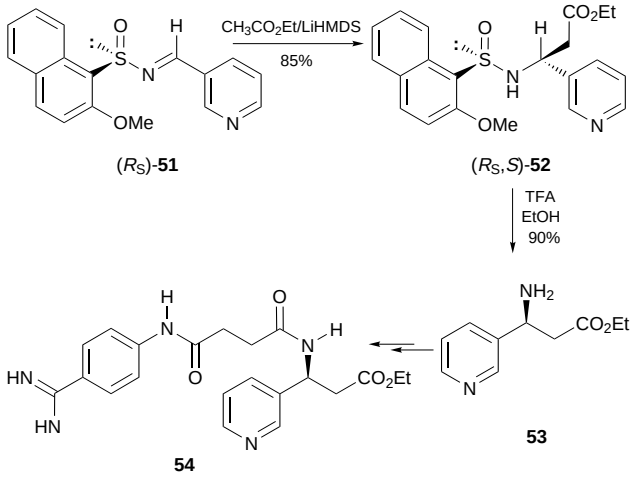
Scheme 13

the enolate of **46** with (+)-(camphorylsulfonyl)oxaziridine **47** and the fluorination of **46** with the electrophilic fluorinating reagent *N*-fluoro-*o*-benzenedisulfonimide **48**.



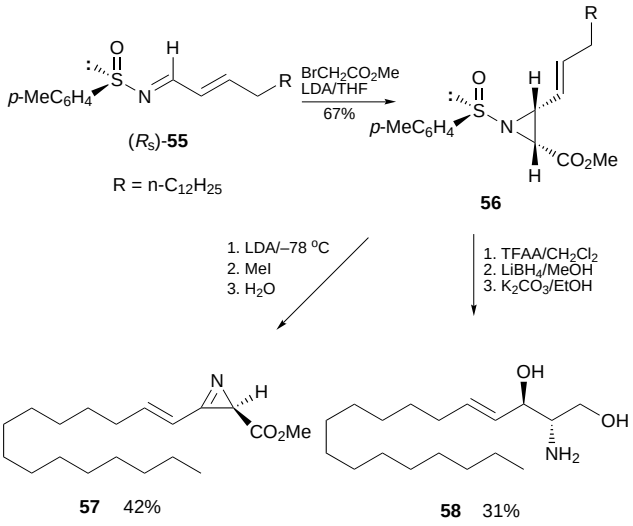
Scheme 16

(*S*)-Ethyl β-amino-3-pyridinepropanoate **53** is a key component of **54**, a peptidomimetic for the Arg-Gly-Asp-Phe sequence of fibrinogen, and may be useful in the treatment of heart disease (Scheme 17). This compound is conveniently prepared from sulfinimine **51** in >97% ee and 68% overall yield.[21]



Scheme 17

(*R*)-(−)-Dysidazirine **57** is a cytotoxic antitumour antibiotic, isolated from a marine sponge,[37] belonging to the smallest class of nitrogen-unsaturated heterocycles 2*H*-azirines (Scheme 18). Its first enantioselective synthesis was recently reported by us by treating enantiomerically pure *N*-sulfinylaziridine **56**, prepared from sulfinimine **55**, with lithium diisopropylamide (LDA).[38] D-*erythro*-Sphingosine **58**, the major constituent of the lipid backbone of the sphingolipids which play important roles in cell recognition events, was synthesized from the same aziridine.[39] This was accomplished using a new trifluoroacetic anhydride (TFAA) induced Pummerer-type rearrangement of **56** discovered in our laboratory.[39] The *threo* isomer of **58** is available by treatment of **56** with aqueous trifluoroacetic acid.



Scheme 18

(+)-Thiamphenicol **62a** and its fluorinated analogue, (−)-florfenicol **62b** are broad spectrum synthetic antibacterial agents used in the animal health industry (Scheme 19). *threo*-(1*R*,2*R*)-(−)-1-[(4-Methylthio)phenyl]propane-1,3-diol **61** is a common precursor to both these compounds, the manufacture of which involves a multi-step sequence ending with a classical resolution of racemic **61**. This compound is conveniently prepared from the enantiomerically pure sulfinimine **59** *via* aziridine **60**.[40] Conversion of **61** to thiamphenicol is straightforward involving treatment with dichloroacetyl chloride and oxidation with *m*-chloroperbenzoic acid (*m*-CPBA).

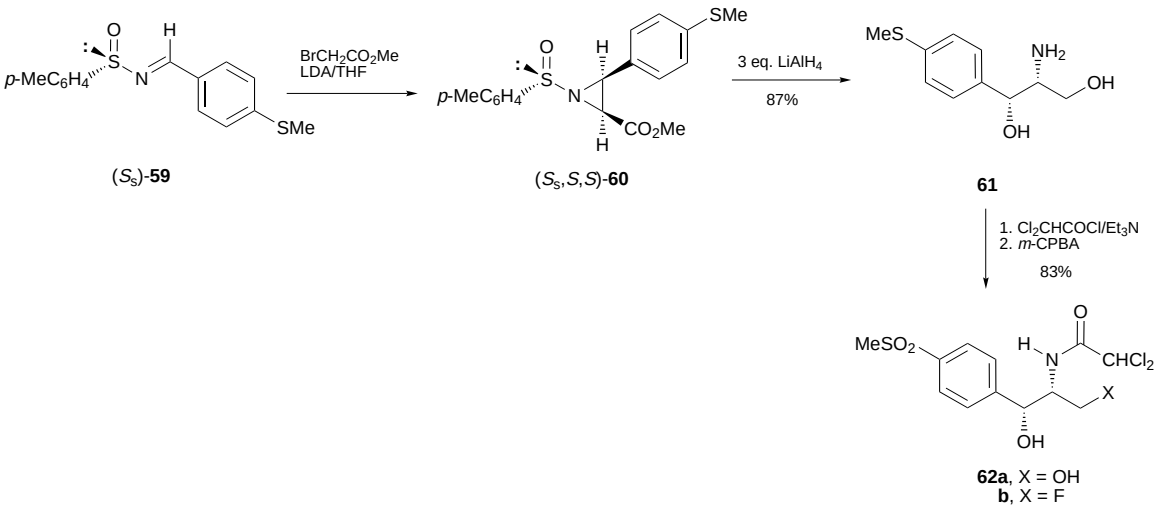
α-Alkyl-α-amino acids are important in the study of enzyme mechanism and in altering the conformational properties of peptides. Once incorporated into peptides these amino acids result in increased rigidity enhancing stability and altering secondary structures. These amino acids can be prepared from sulfinimine derived *N*-sulfinylaziridines such as **63** because they undergo highly regio- and stereo-selective hydrolysis to give, for example α-methyl-β-phenylserine **64** (Scheme 20).[36]

7 Conclusions

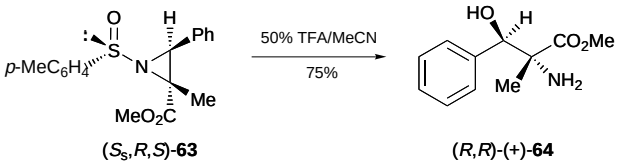
The work outlined in this brief review illustrates the applications of sulfinimines (thiooxime *S*-oxides) **1b** as chiral imine building blocks for the asymmetric synthesis of α- and β-amino acids, aziridine-2-carboxylate esters and other biologically relevant molecules. The usual limitations of imines in these reactions, low reactivity, enolization and poor stereocontrol, are avoided with sulfinimines because the chiral sulfinyl group activates the C–N bond for addition and is a powerful stereodirecting group. Furthermore, the product sulfinamides [ArS(O)NH-CHRR′] represent readily separable diastereoisomers that on hydrolysis afford the primary amine derivative without racemization. An added advantage of the sulfinyl group is that it can be used for further elaboration of the product; *e.g.* Pummerer rearrangements and oxidation to sulfonamides, a useful amine activating and protecting group.

8 Acknowledgements

It is a pleasure to acknowledge the important efforts of our coworkers whose names appear in the references. Our own



Scheme 19



Scheme 20

contributions to this review were supported by the National Science Foundation and the National Institutes of Health.

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