APPLICATION OF VINYLSULFONIUM SALTS TO THE SYNTHESIS OF HETEROCYCLES

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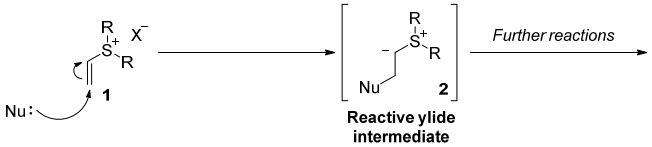
Abstract. *Vinylsulfonium salts are very useful reagents in the synthesis of heterocycles and carbocycles. Owing to their conjugate addition-type reactivity, they can react with nucleophiles to form sulfur ylides which can either react as a nucleophile or undergo proton transfer, followed by intramolecular cyclisation liberating sulfide, and the desired heterocycle. The first vinylsulfonium salt was reported over 100 years ago, however, their synthetic potential as annulation reagents was underexplored for decades until the 1960s. Since then, many variants of vinylsulfonium salts have been synthesised and utilised in many annulation reactions, demonstrating their synthetic capacity to form different ring sizes and build up molecular complexity in a single step.*

Contents

1. Introduction

This chapter will discuss the synthesis and use of vinylsulfonium salts in the synthesis of heterocycles. It is primarily a personal account detailing work by Aggarwal, McGarrigle and co-workers, however closely related work by other groups will also be included. Some earlier work is also included for historical context and to describe how vinylsulfonium salts can be accessed. A comprehensive review of all reactions of vinylsulfonium salts is beyond the scope.[1,2]

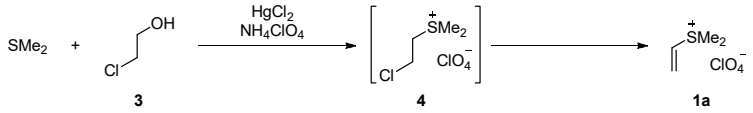
Vinylsulfonium salts **1** are highly reactive molecules in conjugate addition reactions with nucleophiles. Nucleophiles can attack the position of vinylsulfonium salts, and this generates a sulfur ylide **2** *in situ* which an undergo a diverse range of reactions such as intramolecular cyclisations, rearrangements processes or electrophilic trapping to yield different heterocycles (Scheme 1). This reactivity renders vinylsulfonium salts **1** as effective C_2 synthons and excellent annulation reagents.



Scheme 1. Generic reaction of vinylsulfonium salts with nucleophiles.

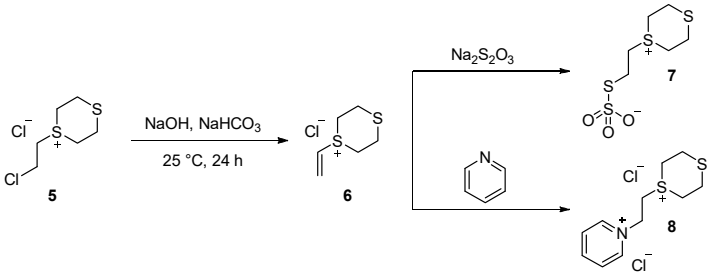
2. Synthesis of vinylsulfonium salts

Vinylsulfonium salts were first synthesised by Hofmann in 1912.[3] 2-Chloroethanol **3** was reacted with dimethylsulfide, in the presence of $HgCl_2$ and NH_4ClO_4, to give intermediate **4** which undergoes elimination to give vinylsulfonium salt **1a** (Scheme 2).



Scheme 2. First reported synthesis of a vinylsulfonium salt.[3]

Vinylsulfonium salts were absent in the literature for a period of time until work by Stahmann and co-workers.[4] They noted that mustard gas reacted to give a series of interesting sulfonium compounds which they further studied. Synthesis of derivatives of the sulfonium compounds led to the synthesis of vinylsulfonium salt **6** from sulfonium salt **5** (Scheme 3),Vinylsulfonium salt **6** was reacted with two different nucleophiles, sodium thiosulfate and pyridine. Compounds **7** and **8** were obtained, however, the products were not demonstrated to have any synthetic value. Nonetheless, this was the first demonstration of nucleophilic addition to vinylsulfonium salts, provoking future investigations in this chemistry.

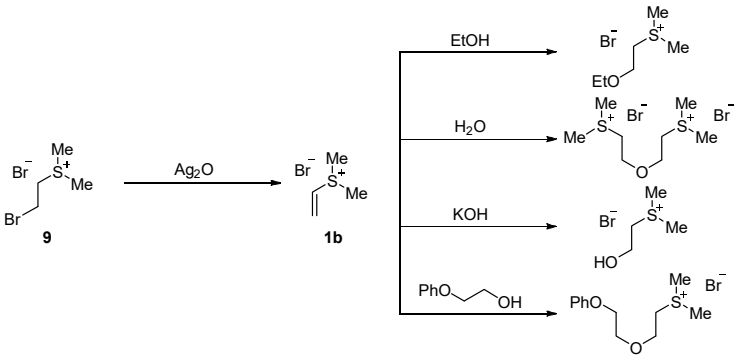


Scheme 3. Stahmanns's synthesis of vinylsulfonium salt **6** and reaction with nucleophiles.

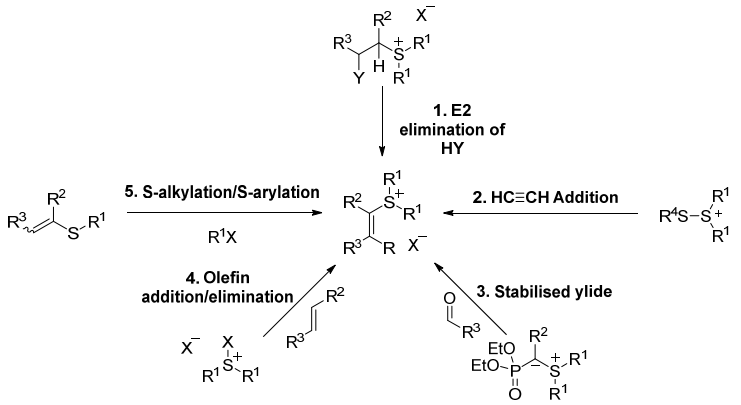
Following this report, Doering and Schreiber synthesised dimethylvinylsulfonium bromide **1b** and tested its reactivity in comparison to its vinylammonium analogue.[5] Vinylsulfonium salts were more reactive to nucleophiles than their vinylammonium salt counterparts as hydroxide readily added to vinylsulfonium salts, but no reactions were observed between reactions between hydroxide and vinylammonium salts. Doering proposed that this was due to the stabilisation effect of sulfur on the α-anion generated. Sulfonium salt **9** was synthesised *via* alkylation of corresponding sulfide with MeBr, the vinylsulfonium salt **1b** was then generated *via* an E2 elimination using silver oxide as base. The resulting vinylsulfonium salt **1b** was then reacted with a series of oxygen nucleophiles to give various sulfonium products (Scheme 4), although, the products were of not demonstrated to have a use in any specific application.

There are at least five strategies for the synthesis of vinylsulfonium salts (Scheme 5). The choice of method is dependent on the identity of the vinylsulfonium salt needed. Syntheses involving alkyne addition[6,7] (route 2, Scheme 5) and stabilised ylides[8] (route 3, Scheme 5) will not be discussed in detail in this chapter. E2 elimination to produce vinylsulfonium salts has already been noted, olefin addition/elimination and S-alkylation/arylation will be described further in this chapter.

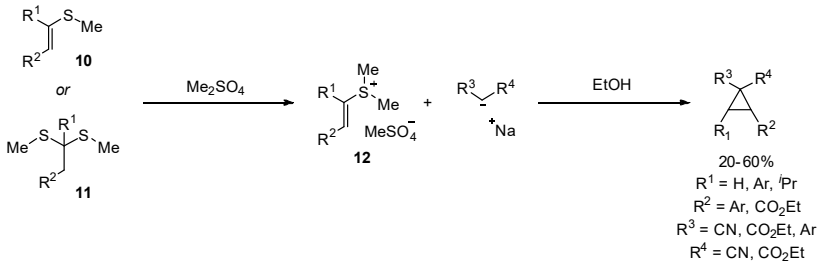
The first application of vinylsulfonium salts in synthesis was by Gosselck and co-workers in 1966.[9] They demonstrated the use of vinylsulfonium salts in the synthesis of cyclopropanes (Scheme 6). A range of substituted vinylsulfonium salts were synthesised through reaction of either vinyl sulfides **10** or disulfides **11** with Me_2SO_4 to produce vinylsulfonium salts **12**.[9,10] Vinylsulfonium salts were reacted with carbon nucleophiles in ethanol to produce a range of cyclopropanes. This was the first demonstration of the use of vinylsulfonium salts in annulation reactions.



Scheme 4. Synthesis and reactions of vinylsulfonium salt **1b**.[5]

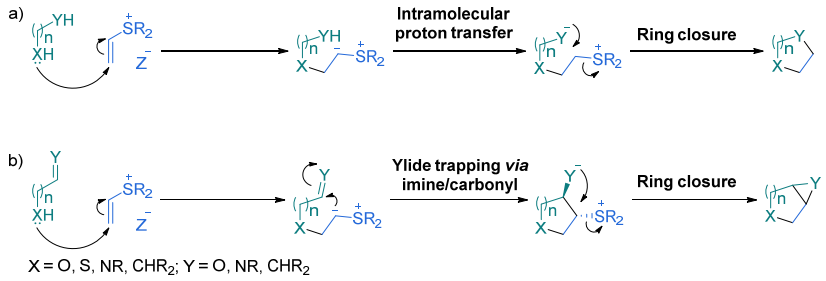


Scheme 5. Methods of synthesising vinylsulfonium salts.



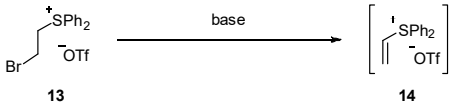
Scheme 6. First reported use of vinylsulfonium salts in annulation reactions.[9]

There are two main mechanistic pathways by which vinylsulfonium salts act as effective annulation reagents in organic synthesis (Scheme 7).[11,12] The first is exemplified in the work of Gosselck (Scheme 6). Nucleophiles can add to the β position of the vinyl system producing a sulfur ylide *in situ* which undergoes proton transfer followed by ring-closure and expulsion of sulfide (Scheme 7a). The second pathway also starts with nucleophilic addition generating a sulfur ylide, however, the sulfur ylide can undergo 1,2- or 1,4-addition to a pendant electrophile on the nucleophile. The resulting anion can then undergo ring-closure to give a fused bicyclic system (Scheme 7b). Thus, the vinylsulfonium salts enable the generation of some molecular complexity in one simple step.



Scheme 7. General mechanistic pathways of annulation reactions of vinylsulfonium salts.

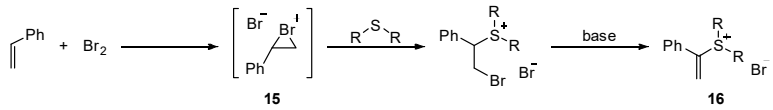
Vinylsulfonium salts are quite versatile molecules, however, as they are rather reactive, some decompose on the bench over time. One solution to this problem is *in situ* generation of vinylsulfonium salts (Scheme 8).[13] Treating sulfonium salt **13** with base generates the corresponding vinylsulfonium salt **14** *in situ,* which then reacts with nucleophiles. This method is much more attractive than working directly with the oily vinylsulfonium salt **14** as sulfonium salt **13** is a free-flowing crystalline material which is bench stable and now commercially available. This has been applied to the synthesis of many heterocyclic ring systems.[12]



Scheme 8. *In situ* generation of reactive vinylsulfonium salt species in annulation reactions.[13]

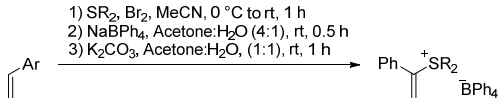
2.1. Synthesis of α-substituted vinylsulfonium salts

Vinylsulfonium salts are useful synthetic C_2 synthons in the synthesis of ring systems (*vide infra*) and thus additional substitution on the vinyl system adds further synthetic value to the reagent class. Gosselck reported the synthesis of α-substituted vinylsulfonium salts by alkylation and used them in cyclopropanations (*vide supra*).[9,10,14] α-Substituted vinylsulfonium salts were synthesised from alkenes by Chow and co-workers in the 1980s.[15,16] They demonstrated that following an electrophilic bromination of styrene, the bromonium intermediate **15** could be intercepted by a nucleophilic sulfide species and upon elimination, produced an α-substituted vinylsulfonium salt **16** (Scheme 9). They furthered this work by using alkyl-substituted alkenes and demonstrated the synthesis of α- and β-substituted vinylsulfonium salts. In 2011 Chandrasekaran and co-workers used the same route, but used bromoethylsulfonium salt to generate vinylsulfonium salts **16** *in situ* in cyclisation reactions.[17]



Scheme 9. Synthesis of α-substituted vinylsulfonium salts **16** by Chow and co-workers.[15,16]

Matlock *et al.* synthesised a range of α-substituted vinylsulfonium salts **17**[18,19] using methodology similar to that of Chow. It was found that there was a significant counter anion effect in their epoxyannulation reactions (*vide infra*) which proceeded *via* vinylsulfonium salts. Anion exchange to the tetraphenylborate salt (Scheme 10) gave more efficient reactions with less side-products. In addition, the tetraphenylborate salts were crystalline and bench stable without decomposition over 6 months. Subsequently other groups have used this methodology to access α-arylated vinylsulfonium salts to carry out vinylation[20] and other annulation reactions.[21]



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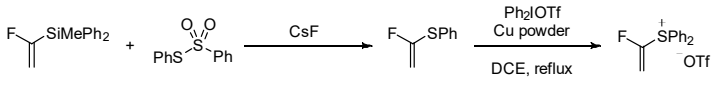
Scheme 10. The synthesis of α-arylated vinylsulfonium salts with counterion exchange.[18]

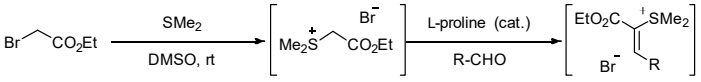
Hanamoto and co-workers demonstrated that they could introduce fluorine as the α-substituent and form a synthetically useful α-fluorovinylsulfonium salt.[22] Starting from α-(fluorovinyl)methyldiphenylsilane **18**, the corresponding sulfide **19** could be synthesised[23] and subsequently arylated using Ph_2IOTf in the presence of a catalytic amount of copper powder to give the α-substituted vinylsulfonium salt **20** (Scheme 11).



18 **19** **20**

Scheme 11. Synthesis of α-fluorovinylsulfonium salt **20**.[22]

Wu and Wu also reported an *in situ* synthesis of α,β-substituted vinylsulfonium salts **23**.[24] In their proposed mechanism, an S_N2 displacement of the bromide from bromoester **21**, forms the corresponding sulfonium salt **22** *in situ*; this is followed by a proline-catalysed Knoevenagel condensation to give the α-substituted vinylsulfonium salt **23** (Scheme 12).

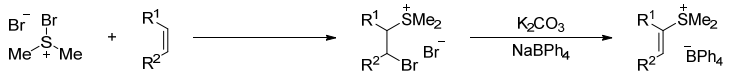


21 **22** **23**

Scheme 12. Synthesis of α-substituted vinylsulfonium salts **23** by Wu.[24]

2.2. Synthesis of β-substituted vinylsulfonium salts

Gosselck and co-workers first demonstrated the synthesis of β-substituted vinylsulfonium salts (*vide supra*).[9,10,14] Chow and co-workers also developed a method of synthesising α,β-substituted and β-*tert*-butyl-substituted vinylsulfonium salts **25** using an electrophilic addition of bromodimethylsulfonium bromide **24** to olefins followed by treatment with base and then ion exchange (Scheme 13).[15,16]

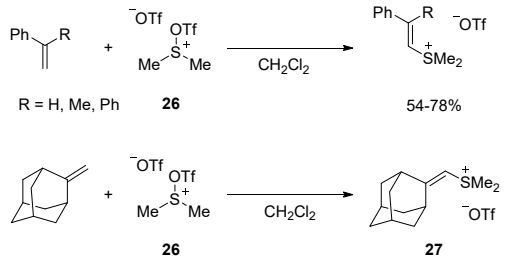


24 **25**

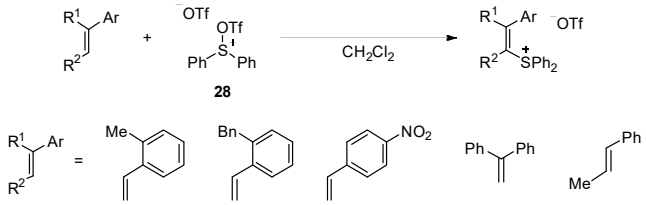
Scheme13. Chow and co-workers reported synthesis of α,β- and β-substituted vinylsulfonium salts.

Following Chow's reports, Nenajdenko and Balenkova described a related method of accessing β-substituted vinylsulfonium salts from alkenes and a sulfonium reagent **26**.[25,26] Reagent **26** can be formed from the reaction of DMSO and Tf_2O. It reacts with styrenes in CH_2Cl_2 to form the corresponding vinylsulfonium salts (Scheme 14). As well as styrenes, methyleneadamantane also reacts with **26** to form the β-substituted vinylsulfonium salt **27** (Scheme 14). They noted that demethylation can occur for these dimethylvinylsulfonium salts in reactions with nucleophiles.

Using the same approach as Nenajdenko and Balenkova, Mukaiyama and co-workers synthesised a range of β-arylated diphenylvinylsulfonium salts *in situ* from sulfonium reagent **28**, with one example of di-β-substitution and α,β-substitution, however the vinylsulfonium salts were mostly used *in situ (vide infra)*; only three examples were isolated (Scheme 15).[27]

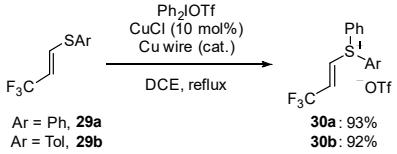


Scheme 14. Synthesis of β-substituted vinylsulfonium salt from sulfonium reagent **26**.[25,26]



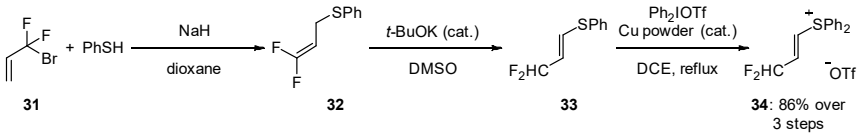
Scheme 15. Selected examples of β-arylated vinylsulfonium salts synthesised by Mukaiyama.[27]

β-Trifluoromethyl-substituted vinylsulfonium salts were synthesised by Hanamoto's research group *via* an S-arylation protocol.[28,29] Vinylsulfides **29** were subjected to reaction with Ph_2IOTf in the presence of CuCl and copper wire to form the vinylsulfonium salts **30** (Scheme 16). They also attempted to form the vinylsulfonium salt *via* S-methylation with MeI, however, no desired product was observed. They found that vinylsulfonium salt **30b** was oily and difficult to handle and thus, synthesised the diphenyl variant **30a**, which was crystalline solid and easy to handle.



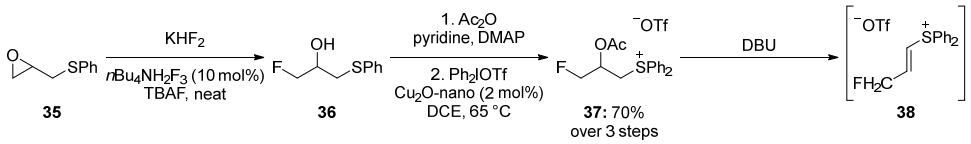
Scheme 16. Synthesis of β-CF_3 vinylsulfonium salts.[28,29]

Hanamoto and co-workers furthered this work in the synthesis of β-difluoromethylvinylsulfonium salts.[30] Reaction of thiophenol with halogenated olefin **31** gave allylsulfide **32**, which was then isomerised to **33** using a catalytic amount of *t*-BuOK. The vinylsulfide **33** was then subjected to their S-arylation protocol to give the β-difluoromethylvinylsulfonium salt **34** (Scheme 17).



Scheme 17. Synthesis of β-difluoromethylvinylsulfonium salt **34**.[30]

Hanamoto extended this work further and synthesised β-monofluoromethylvinylsulfonium salt **38**.[31] Epoxide **35** was ring-opened with KHF_2 to form **36**, followed by acetylation and copper-catalysed arylation to give the sulfonium salt **37** (Scheme 18). Sulfonium salt **37** could then generate the desired reactive β-substituted vinylsulfonium salt **38** with DBU as a base but this was reacted *in situ* as it was unstable.



Scheme 18. Synthesis of β-fluoromethylvinylsulfonium salt **38**.[31]

2.3. Synthesis of chiral vinylsulfonium salts

Jimenez and co-workers,[32,33] and later the Aggarwal group,[34,35] reported the synthesis of chiral vinylsulfonium salts (Figure 1). These salts were synthesised by alkylation with 2-bromoethyl triflate followed by elimination, a method that is useful for the synthesis of sterically hindered, less reactive, sulfides (Scheme 19). Using salts **39-41**, Jimenez and co-workers obtained moderate levels of enantioselectivity in asymmetric annulation reactions. The Aggarwal group synthesised chiral vinylsulfonium salt **42** and bromoethylsulfonium salt **43** derived from chiral sulfides that they developed in their work on catalytic asymmetric sulfur ylide epoxidation, aziridination and cyclopropanations.[36-40] Chiral vinylsulfonium salt **42** gave the best performance in asymmetric annulation reactions, forming fused epoxides with excellent enantioselectivity.[34,35]

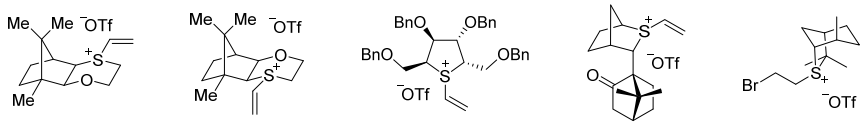
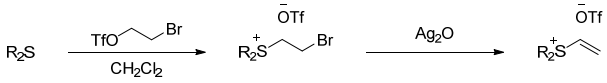


Figure 1. Examples of chiral vinylsulfonium salts and bromoethylsulfonium salt precursor prepared by the Jimenez (**39-41**)[32,33] and Aggarwal groups (**42** and **43**).[34,35]



Scheme 19. Synthesis of chiral vinylsulfonium salts.[34]

3. Synthesis of non-fused 3-membered heterocycles

3-Membered ring systems are of high interest to chemists, especially heterocyclic systems such as aziridines and epoxides.[41-44] Aziridines and epoxides are important as synthetic intermediates and are found in a wide range of natural products and biologically active compounds (Figure 2). Several methods to synthesise 3-membered heterocycles have been achieved using vinylsulfonium salts.

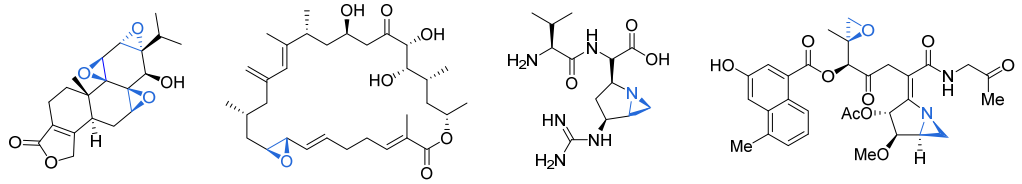
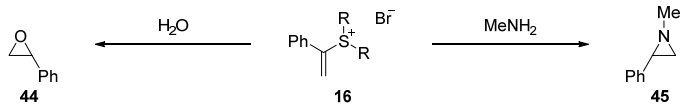


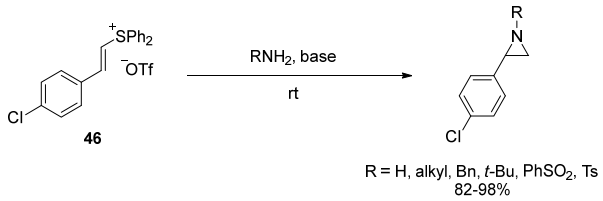
Figure 2. Examples of natural products containing epoxides/aziridines.

α-Substituted vinylsulfonium salts were applied to the synthesis of heterocycles by Chow and co-workers in the 1980s.[15] The α-substituted vinylsulfonium salt **16** formed the aziridine **45** and epoxide **44**, respectively (Scheme 20). The mechanism the reaction presumably follows a pathway similar to that in Scheme 7a.



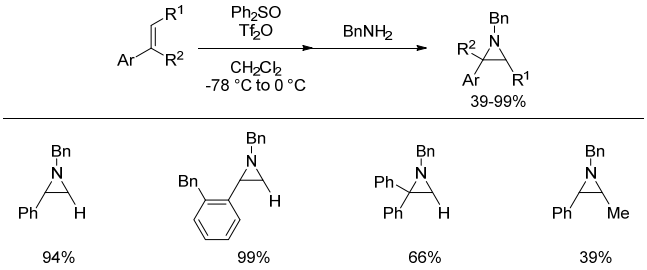
Scheme 20. Synthesis of epoxide and aziridine from α-substituted vinylsulfonium salt **16** by Chow and co-workers.[15,16]

Mukaiyama and co-workers demonstrated that aziridines could be synthesised from the corresponding amine/sulfonamide and a β-substituted diphenylvinylsulfonium salt **46** (Scheme 21).[45] The synthesis of aziridines was high yielding and could be carried out in solvents such as DMSO or THF, or neat without deleterious effect on the yield. *t*-$BuNH_2$ or NaH were both suitable bases in the reaction to generate the aziridine products.



Scheme 21. Synthesis of aziridines from β-arylated vinylsulfonium salt **46**.[45]

Mukaiyama also showed that aziridines could be synthesized directly from styrenes in a one-pot procedure. Thus, styrenes were reacted with diphenyl sulfoxide and trifluoromethanesulfonic anhydride to form the corresponding vinylsulfonium salt *in situ* followed by reaction with benzylamine to form the aziridine (Scheme 22). Using this one-pot protocol, alkenes could also be reacted to form the vinylsulfonium salt *in situ* followed by aziridination. Disubstituted vinylsulfonium salts could also be reacted to form the corresponding aziridine products, however, the yields were significantly lower, possibly due to steric constraints.



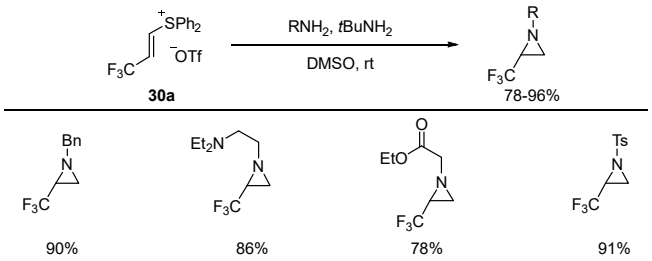
Scheme 22. Synthesis of aziridines from *in situ* generated vinylsulfonium salts.[45]

Hanamoto's group reacted β-CF_3-substituted vinylsulfonium salt **30a** with range of primary amines to form CF_3-substituted aziridines (Scheme 23).[28] The reactions were high yielding and even amino acids are tolerated in this system. The CF_3 group renders these compounds of high interest to medicinal chemists.

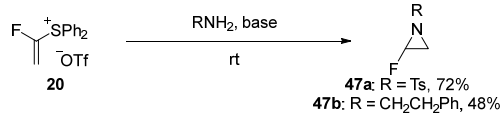
Hanamoto also applied the aziridination methodology to α-fluoro-substituted vinylsulfonium salt **20** to form fluorinated aziridines **47** (Scheme 24).[22] The main focus of this report was of the diastereoselective synthesis of fluorinated cyclopropanes, however, they reported two examples of fluorinated aziridines.

The Aggarwal group developed a three-component reaction to synthesize oxygen and nitrogen containing 3-membered rings (Scheme 25).[46] The process initiates *via* conjugate addition of a nucleophile to the vinylsulfonium salt **14**, followed by sulfur ylide-mediated epoxidation with aldehydes (see Scheme 7b). This enabled the synthesis of disubstituted epoxides. A broad range of nucleophiles were tolerated in the

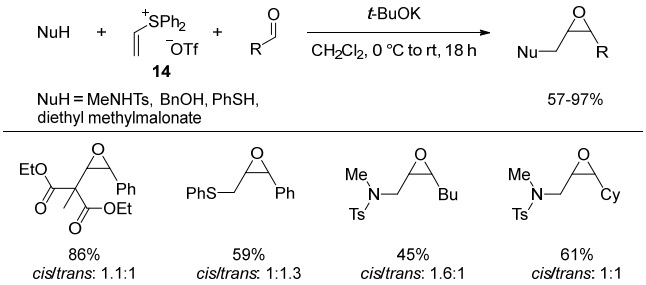
reaction along with a range of different aldehydes. However, the diastereoselectivity of the epoxidation reaction was poor.



Scheme 23. Synthesis of CF_3-containing aziridines.[28]

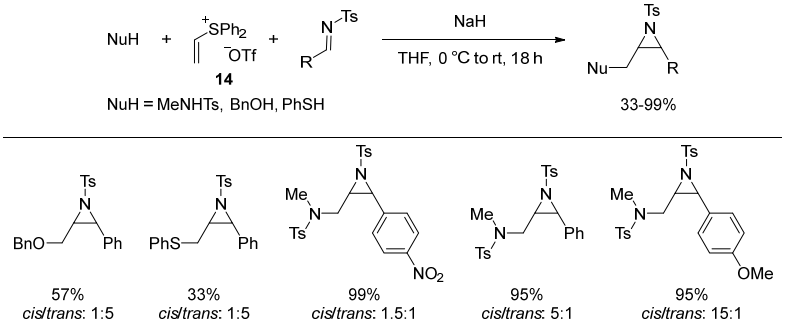


Scheme 24. Synthesis of monofluorinated aziridines **47**.[22]



Scheme 25. Three-component reaction of nucleophiles, vinylsulfonium salt **14** and aldehydes to form substituted epoxides.[46]

The methodology was also applied to reactions with imines to form aziridines. Nucleophiles were reacted with vinylsulfonium salt **14**, followed by sulfur ylide-mediated aziridination with the corresponding imine (Scheme 26).

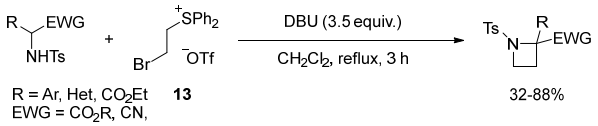


Scheme 26. Three-component reaction of nucleophiles, vinylsulfonium salt **14** and imines to form substituted aziridines.[46]

The diastereoselectivity of the reaction with imines was better than the epoxidation reactions and yields were generally higher for the aziridine products.

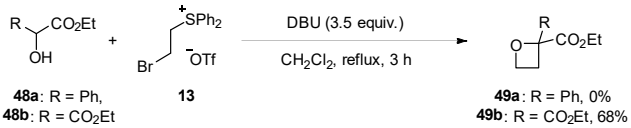
4. Synthesis of 4-membered heterocycles

The Aggarwal group have also applied vinylsulfonium salts in the synthesis of azetidines and oxetanes, with a proposed mechanism in line with that in Scheme 7a.[47] Protected amino acid derivatives were reacted with 2-bromoethylsulfonium triflate **13** and DBU to yield the 4-membered azetidine products in good to excellent yield (Scheme 27). Tosyl-protected substrates were higher yielding than those with Cbz protection.



Scheme 27. Preparation of azetidines from amino acid derived precursors.[47]

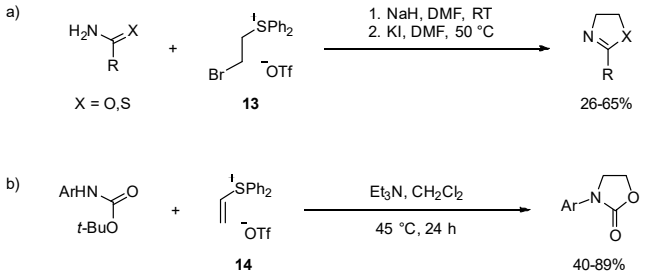
This reaction protocol was applied to the synthesis of an oxetane also. The initial reaction with ester **48a** gave no oxetane product **49a** (Scheme 28). However, on increasing the acidity of the α-proton through the use of a diester **48b**, the oxetane product **49b** was formed in 68% yield.



Scheme 28. Synthesis of oxetanes from reaction with vinylsulfonium salt precursor **13**.[47]

5. Synthesis of non-fused 5-membered heterocycles

Mukaiyama reported the synthesis of 5-membered heterocycles through the reactions of amides and thioamides with vinylsulfonium salts (Scheme 29a).[48] Yields were higher using **13** to generate the vinylsulfonium salt **14** *in situ* with potassium iodide as an additive, rather than using **14** directly. The mechanism is proposed to involve the sodium (thio)amide attacking the vinylsulfonium salt along the lines of Scheme 7a. Xie *et al.* adopted a similar approach using Boc-protected anilines for the synthesis of *N*-aryloxazolidin-2-ones (Scheme 29b).[49]

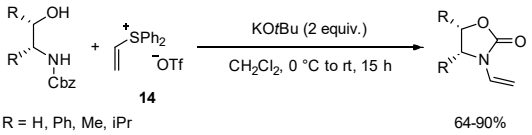


Scheme 29. Synthesis of 5-membered heterocycles using vinylsulfonium salts.[48,49]

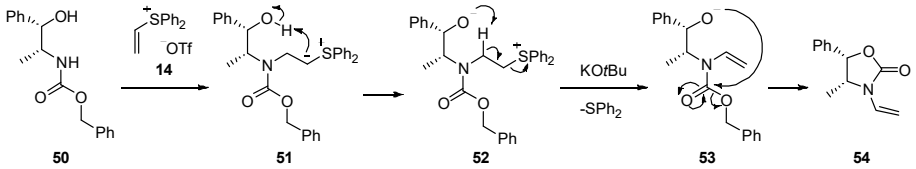
The Aggarwal group found that reaction of Cbz-protected β-amino alcohols with vinylsulfonium salt **14** gave a 5-membered *N*-vinyloxazolidinones (Scheme 30).[50] The reaction outcome was very sensitive to the identity of the nitrogen protecting group.

Amino alcohol **50** was subjected to reaction with vinylsulfonium salt **14** and KO*t*-Bu as base in CH_2Cl_2 (Scheme 31).[50] Through analysis of reaction mixtures *via* nanospray mass spectrometry, key reaction

intermediates in the formation of the *N*-vinyloxazolidinones could be detected. Reaction of **50** with vinylsulfonium salt **14** forms intermediate **51**, which undergoes intramolecular proton transfer to give **52**. The alkoxide anion initiates an E2 elimination to give the *N*-vinylcarbamate **53** and under the basic conditions, the alkoxide attacks the carbonyl to give **54**. It was noted that if Boc or Bz were used as protecting groups the reaction follows a similar pathway initially, but that cyclisation does not occur and polar products from addition of a second equivalent of vinylsulfonium salt **14** were detected. Use of sulfonamide or sulfinamide protecting groups generated morpholines (*vide infra*).

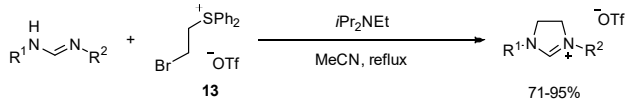


Scheme 30. Synthesis of *N*-vinyloxazolidinones from Cbz-protected amino alcohols.[50]



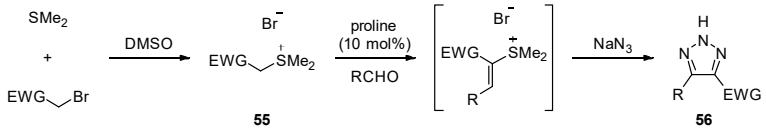
Scheme 31. Proposed reaction pathway for the formation of *N*-vinyloxazolidinone **54**.[50]

N-Heterocyclic carbenes (NHCs) have been of widespread interest as ligands and organocatalysts[51,52] since first synthesised by Arduengo.[53] Imidazolium and imidazolinium salts are precursors to NHCs, thus synthetic methods to generate these compounds are important. The Aggarwal group developed a synthesis of such imidazolinium salts *via* the use of vinylsulfonium salts. Reaction of formamidines with sulfonium salt **13** in the presence of Hünig's base in MeCN under reflux gives the corresponding imidazolinium salt in good to excellent yields (Scheme 32).[54] Mechanistically the proposed reaction pathway involves generation of vinylsulfonium salt *in situ* and then is in line with that in Scheme 7a. The method could be used to form unsymmetrical imidazolinium salts from the corresponding formamidines, while symmetrical formamidines could be formed *in situ* to give a one-pot method directly from amines and triethyl orthoformate. The method was particularly efficient for very hindered amines which are more challenging with other methods.



Scheme 32. Synthesis of imidazolinium salts.[54]

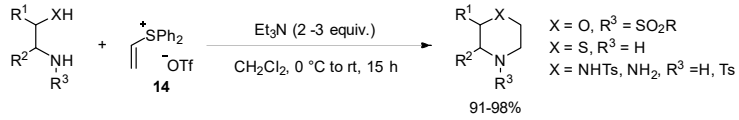
Wu and Wu reported a synthesis of triazoles which is proposed to proceed through *in situ* generated α-ester-substituted vinylsulfonium salts (Scheme 33).[24] The method has a wide scope, rapidly assembling the heterocycle from commercially available components.



Scheme 33. Synthesis of triazoles **56** *via* vinylsulfonium salts generated *in situ*.[24]

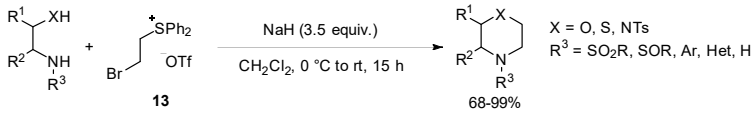
6. Synthesis of non-fused 6-membered heterocycles

In 2014, Njardarson analysed all U.S. FDA approved small molecule drugs[55] and found that 21% (71 compounds) contained saturated 6-membered *N*-heterocycles with an additional heteroatom. Morpholines and piperazines are some of the most important pharmacophores in medicinal chemistry.[55-57] The Aggarwal group described an operationally simple method of synthesising such compounds using vinylsulfonium salt **14** as the annulating reagent.[58] β-Amino alcohols/thiols/amines were reacted with **14** to afford the desired 6-membered heterocycle in excellent yields (Scheme 34). Mechanistically, these reactions are proposed to proceed via the pathway described in Scheme 7a.



Scheme 34. Synthesis of 6-membered heterocycles from **14**.[58]

Although the method to access the 6-membered heterocycles was effective, it suffered from the need to prepare and isolate the oily and unstable vinylsulfonium salt **14**. Thus, the Aggarwal group developed the method further through the use of the bench-stable vinylsulfonium salt precursor **13** to generate **14** *in situ*.[13] Reaction of β-amino alcohols/thiols/amines with **13** with NaH as base gave the 6-membered heterocyclic products in excellent yields (Scheme 35). The protocol also tolerated aryl and heteroaryl *N*-substituents whereas previously for amino alcohols only sulfonamide-protected amines were shown to work. Using vinylsulfonium salt precursor **14** was more operationally simple than using vinylsulfonium salt **14** due to its crystallinity and long shelf life. Later it was shown that sulfinamide-protected amino alcohols were suitable substrates, whereas CBz-protected amino alcohols gave *N*-vinyloxazolidinones (Scheme 31).[50,59] The sulfinamide group was easily removed to give free morpholines. For the synthesis of thiomorpholines and piperazines no amine protecting groups were needed.



Scheme 35. Preparation of 6-membered heterocycles from reactions with vinylsulfonium salt precursor **13**.[13]

This methodology has been used in several drug development programmes as evidenced in the patent and peer-reviewed literature (Figure 3).[52,60-66]

Chen, Xiao *et al.* later showed the method could be extended to oxazino[4,3-a]indoles **58**,[67] with KOH as base giving the best yields (Scheme 36).

Using α-arylated vinylsulfonium salt **59**, the Aggarwal group extended their method to the synthesis of more heavily substituted morpholines and piperazines (Scheme 37).[19] A broad range of 6-membered heterocycles were accessed with this methodology and with high diastereoselectivity in most cases.

The origin of the high diastereoselectivity was investigated and a rationale proposed (Scheme 38). Amino alcohol **60** reacts with **59** *via O*-attack on sulfonium salt **59**, giving two possible chair-like diastereomeric transition states, **61** and **62,** for cyclisation. The major diastereomer results from the reaction proceeding through **61**, where all substituents are pseudoequatorial while the minor diastereomer arises from **62** where the phenyl substituent is pseudoaxial. Transition state **61** gives a congested conformer of the product which then ring flips to a more favoured conformer. When the corresponding β-phenylvinylsulfonium salt was used in place of **59** in these reactions, there was little to no diastereoselectivity observed.

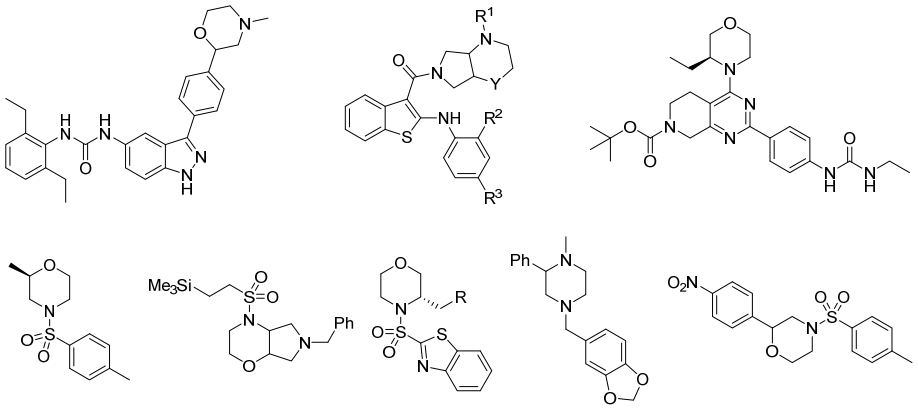
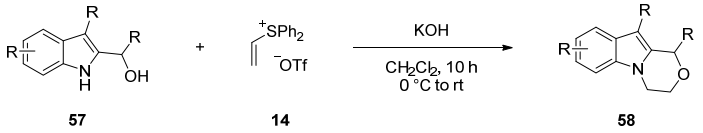
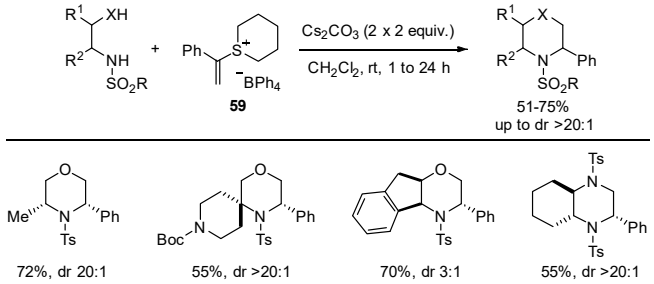


Figure 3. Examples of morpholines and piperazines synthesised using vinylsulfonium salts in papers and patents from pharmaceutical companies.[52,60-66]



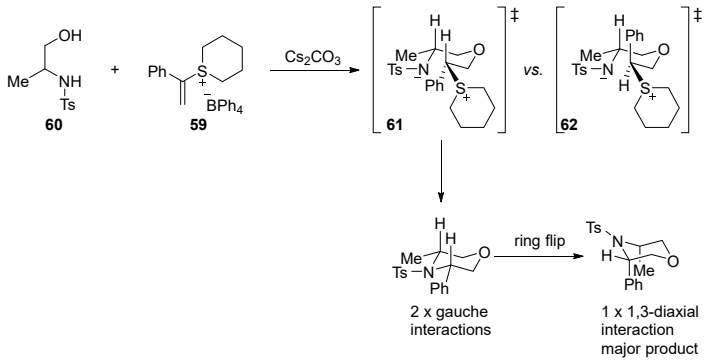
57 **14** **58**

Scheme 36. Synthesis of oxazino[4,3-a]indoles using vinylsulfonium salts.[67]



72%, dr 20:1 55%, dr >20:1 70%, dr 3:1 55%, dr >20:1

Scheme 37. Preparation of substituted morpholines and piperazines from vinylsulfonium salt **59**.[19]



2 x gauche interactions

1 x 1,3-diaxial interaction major product

Scheme 38. Rationale for the observed regio- and diastereoselectivity in cyclisation reactions with salt **59**.[19]

7. Synthesis of non-fused 7-membered heterocycles

7-Membered heterocycles are a privileged class of compounds in medicinal chemistry, particularly when fused to an aromatic system.[68-70] Particularly well-known examples being the naturally occurring antitumor antibiotic anthramycin **63**[71] and one of the most frequently prescribed medications in the world, diazepam (Valium) **64** (Figure 4).[72] Another drug example within the 1,4-benzodiazepine family is the antileishmanial drug **65** (Figure 4).[73]

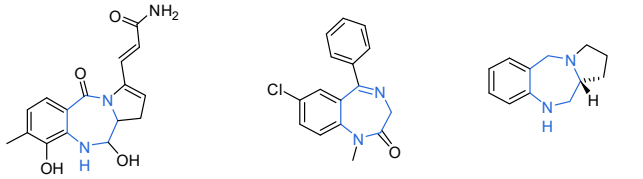
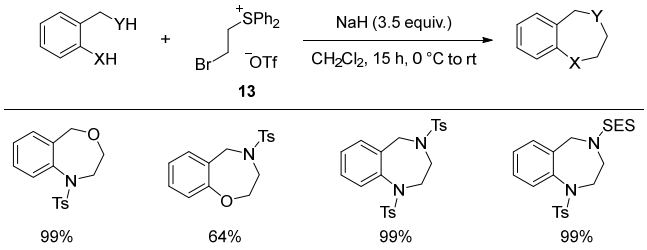


Figure 4. Exemplars of 7-membered heterocycle-containing fused aromatics in medicinal chemistry.

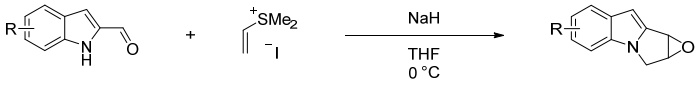
The Aggarwal group showed that reaction of 1,3-amino alcohols/1,3-diamines with vinylsulfonium salt precursor **13** yielded the corresponding 7-membered heterocycles in good to excellent yield (Scheme 39).[13] Mechanistically these reactions are proposed to follow the pathway in Scheme 7a. The products of these reactions can be further derivatised to synthesise more complex targets. This method has also been taken up by the pharmaceutical industry.[52]



Scheme 39. Synthesis of 7-membered heterocycles from **13**.[13]

8. Synthesis of fused bicyclic heterocyclic ring systems

Garst reported the use of butadienylsulfonium salts in epoxyannulation reactions.[74] Later, Jimenez reported the use of dimethylvinylsulfonium iodide **67** for the synthesis of a fused ring as a key step in their synthesis of a mitomycin skeleton (Scheme 40). Mechanistically the reaction is proposed to proceed *via* the pathway shown in Scheme 7b.

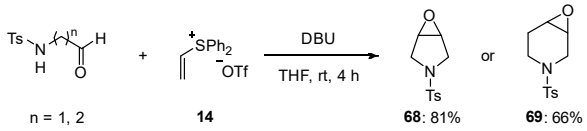


Scheme 40. Jimenez's synthesis of fused bicyclic ring systems using vinylsulfonium salts.[32,75-77]

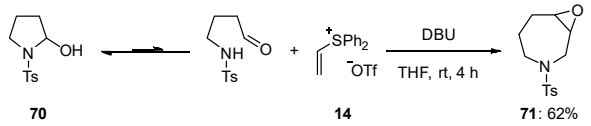
The Aggarwal group explored the synthesis of fused heterobicyclic systems starting from γ-aminoaldehydes.[34] Using vinylsulfonium salt **14** in reactions with aminoaldehydes, bicyclic heterocycles **68** and **69** could be formed in good to excellent yield (Scheme 41).

Reacting γ-hemiaminal **70** with vinylsulfonium salt **14** gave product **71** in 62% yield (Scheme 42). The starting material **70** is in equilibrium with the open chain aldehyde, which can react like other aminoaldehydes leading to the formation of epoxide-fused azepines. This was further explored and it was

found that substituted hemiaminals can form azepines with good diastereocontrol under the reaction conditions.[78]

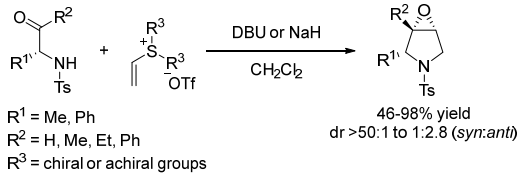


Scheme 41. Synthesis of heterobicyclic molecules.[34]



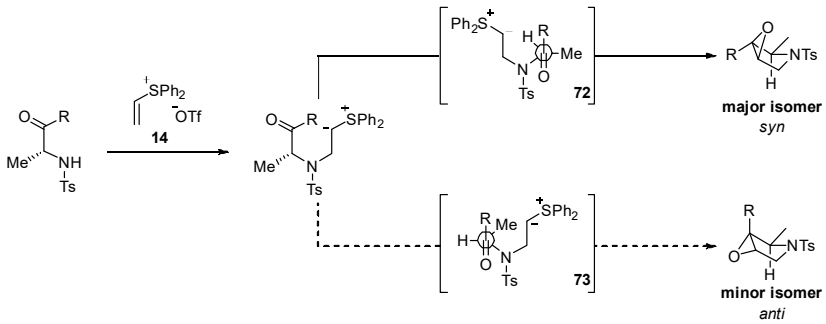
Scheme 42. Synthesis of fused 7-membered epoxide-fused heterocycles.

Using achiral vinylsulfonium salt and enantiopure aminoaldehydes and ketones it was found that high levels of diastereoselectivity were achieved in the epoxyannulation reactions with good to excellent yields (Scheme 43).[79]



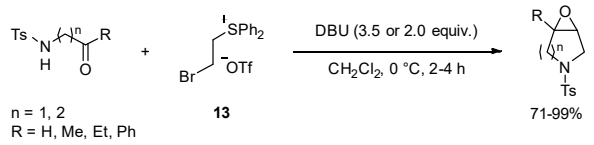
Scheme 43. Diastereoselective synthesis of pyrrolidine-fused epoxides.[79]

The diastereoselectivity was rationalised by considering the two Felkin-Ahn transition states **72** and **73** (Scheme 44). The two main factors influencing the diastereoselection are (i) preferential approach of the ylide over the H substituent rather than the methyl group (favouring transition state **72**) and (ii) steric repulsion between the carbonyl R substituent and methyl group (favouring transition state **72**). These factors both favour the formation of the major *syn* isomer and not the *anti*-product.



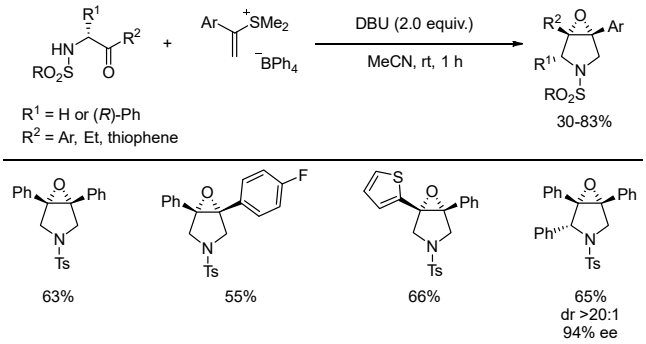
Scheme 44. Proposed model for substrate-controlled diastereoselective epoxyannulation.

Later they replaced vinylsulfonium salt **14** with its precursor **13** (Scheme 45)[35] making the epoxyannulation reactions operationally simpler and giving higher yields in comparison to the direct use of vinylsulfonium salt **14**.



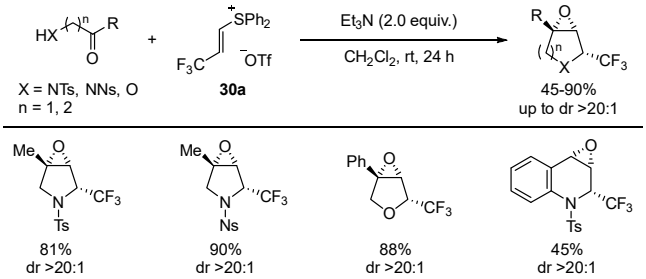
Scheme 45. Reactions of aminoaldehydes and aminoketones with sulfonium salt **13**.[35]

Reactions of aminoketones with α-substituted vinylsulfonium salts were also explored (Scheme 46).[18] This enabled the synthesis of di and tri-substituted pyrrolidine-fused epoxides in good to excellent yields.



Scheme 46. Reaction of aminoketones with α-substituted vinylsulfonium salts with product examples.[18]

The CF_3 functionality was also introduced into fused epoxide bicyclic systems by using β-substituted vinylsulfonium salt **30a** (Scheme 47). Good yields and excellent diastereocontrol were observed in these reactions.



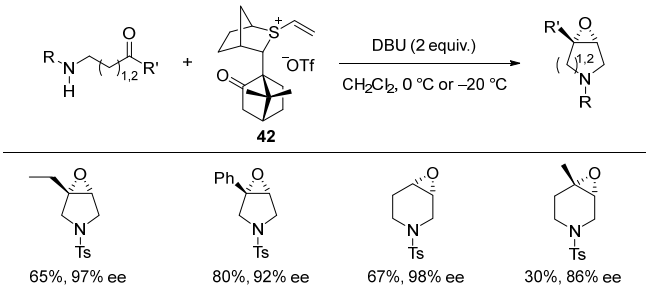
Scheme 47. Synthesis of CF_3-substituted epoxide-fused heterocycles using **30a**.

Having developed a new protocol for the synthesis of bicyclic systems, the Aggarwal group rendered the process asymmetric through the use of chiral vinylsulfonium salts. Aminoaldehydes or aminoketones were reacted with chiral vinylsulfonium salt **42** to form a range of enantioenriched fused epoxides (Scheme 48). The products could be formed in good to excellent yield with high enantioselectivity.[34]

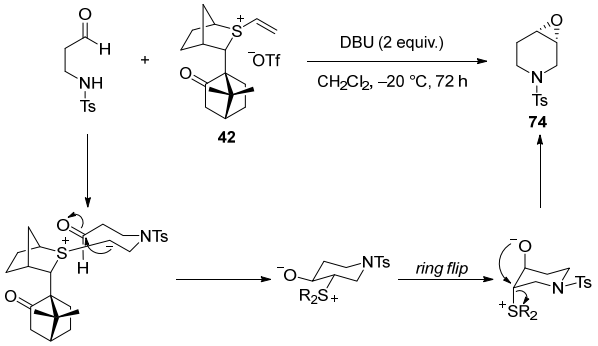
The following stereochemical model was proposed for the selectivity for product **74** (Scheme 49). The aminoaldehyde is deprotonated and attacks the chiral vinylsulfonium salt forming a sulfur ylide *in situ*. Sulfur ylide attack on the aldehyde follows through a chair-like transition state, with the rear face of the ylide preferred as the front face is blocked. The resulting *trans*-betaine intermediate undergoes a ring flip and displacement of sulfide gives epoxide **74**.

Then reactions were conducted whereby both substrate and reagent could exert control and they investigated which one would be the dominant factor.[79] When the substrate and reagent favoured the same

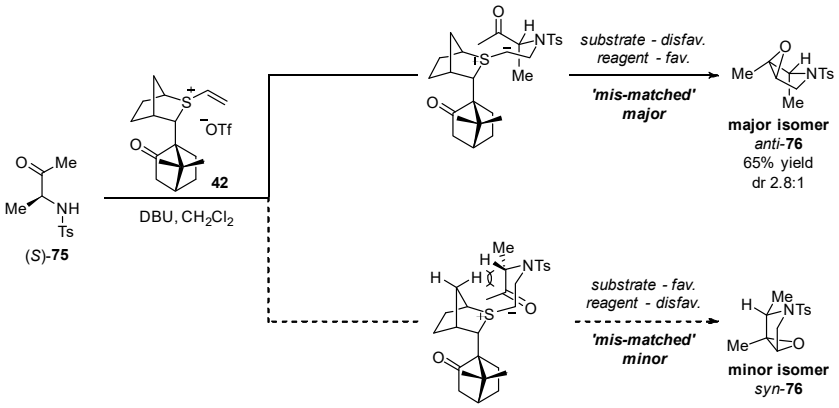
product (matched cases), the *syn* product was formed with excellent diastereoselectivity. However, in the mis-matched cases, the *anti*-product *anti*-**76** was obtained, showing that the reagent dominated the outcome of the reaction (Scheme 50).



Scheme 48. Asymmetric annulation reactions using chiral vinylsulfonium salt **42**.[34]



Scheme 49. Proposed model for asymmetric induction in epoxyannulations with salt **42**.[79]

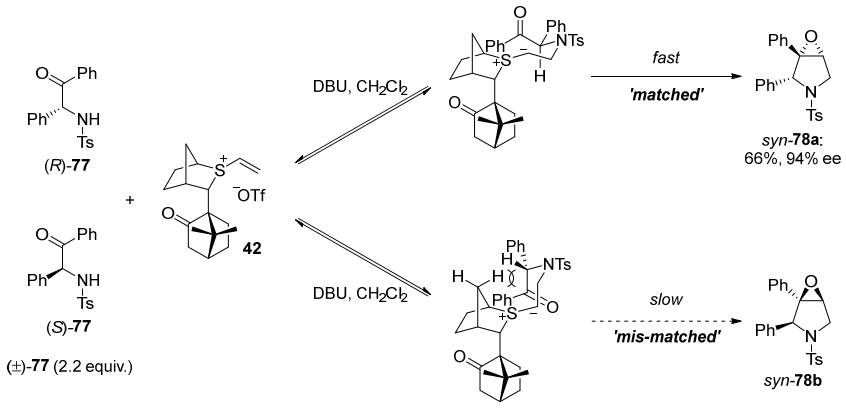


Scheme 50. Proposed model for 'mis-matched' reaction of (*S*)-amido methyl ketone and salt **42**.[79]

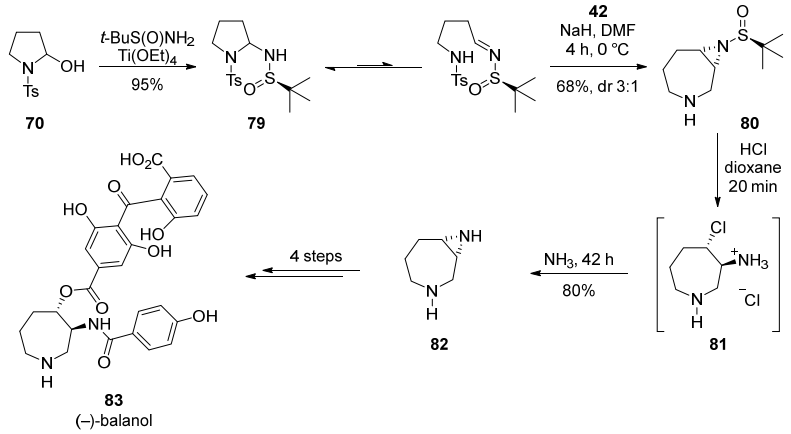
The same authors then showed that they could exploit this difference in rates in the form of a kinetic resolution of (±)-**77** (Scheme 51). They found that using 2.2 equiv. of (±)-**77** with respect to (+)-chiral vinylsulfonium salt **42**, they could obtain the *syn*-product **78a** in 66% yield and 94% ee.[79]

They also demonstrated a related aziridination instead of an epoxidation in a formal synthesis of (–)-balanol (Scheme 52).[34] Starting from hemiaminal **70**, reaction with (*R*)-*tert*-butyl sulfinamide gave

product **79**. This was then reacted with chiral vinylsulfonium salt **42** to give aziridine **80** in 68% yield. Although the dr was only 3:1, the diastereomers were separated by flash column chromatography. The aziridine **80** was deprotected with anhydrous HCl, which gave the ring-opened product **81**. However, the authors found that upon treatment with sat. aq. ammonia solution, they could obtain the desired key intermediate **82** thus, completing the formal synthesis of (−)-balanol **83**.



Scheme 51. Kinetic resolution of (±)-**77**.[79]



Scheme 52. Formal synthesis of (−)-balanol **83**.[34]

Cyclopropane-fused bicyclic systems were also of interest to the Aggarwal group. A wide range of bioactive molecules contain such scaffolds such as boceprevir,[80] a hepatitis C treatment, trovafloxacin,[81] an antibiotic or bicifadine,[82] an analgesic (Figure 5).

Vinylsulfonium salts were used to synthesise cyclopropane-fused pyrrolidines. A range of allylic amines were reacted with vinylsulfonium salts to give the cyclopropanated bicycle in good yield and excellent diastereoselectivity (Scheme 53).[83] It was shown that α or β-substituted vinylsulfonium salts could also be used in the reaction and under the similar reaction conditions the highly-substituted cyclopropanated products were obtained in high yield and excellent diastereoselectivity.[18,83] One example each of an analogous tetrahydrofuran and a piperidine were also reported.

Expanding this methodology further, a range of aza-Morita-Baylis-Hillman adducts[84] were reacted with vinylsulfonium salt precursor **13** (Scheme 54).[83] Esters gave good yields of cyclopropylpyrrolidines

with excellent diastereoselectivity, whereas the α,β-unsaturated ketone gave the corresponding product in poor yield due to the competing epoxyannulation reaction dominating.

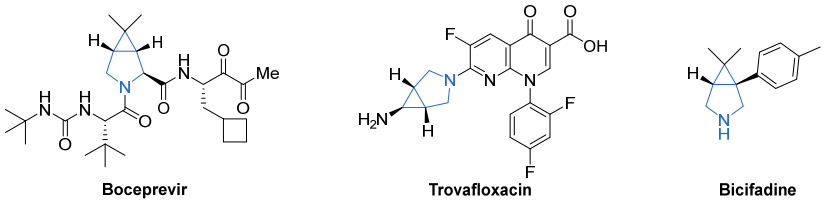
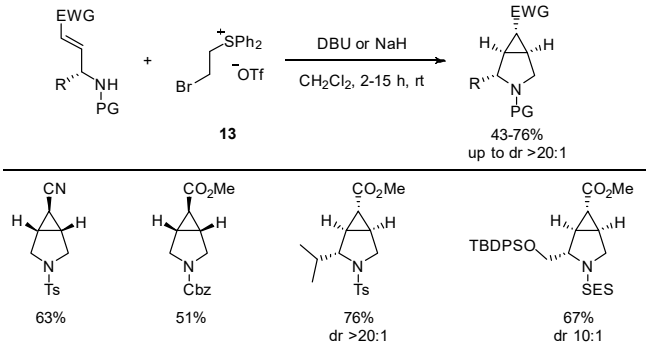
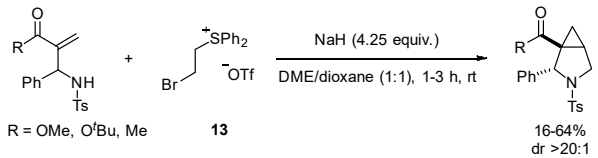


Figure 5. Exemplar of drugs containing the 3-azabicyclo[3.1.0]hexane motif.



Scheme 53. Synthesis of cyclopropane-fused bicycles using salt **13**.[83]



Scheme 54. Reactions of aza-Morita-Baylis-Hillman adducts with salt **13**.[83]

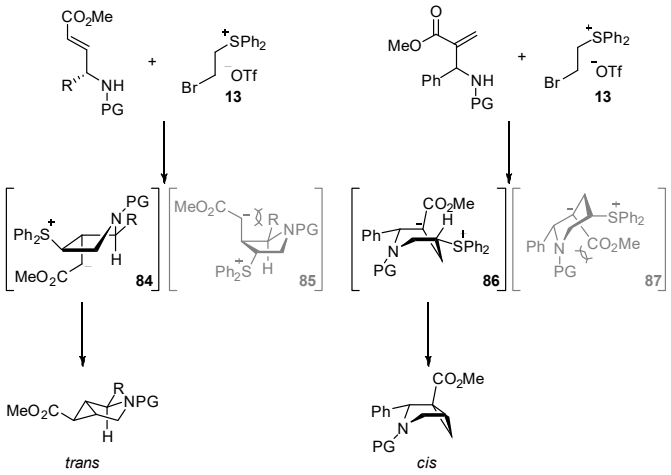
The origin of selectivity was proposed to arise from non-bonded steric interactions in the transition state (Scheme 55). Transition states **84** and **86** contain less steric interactions than **85** or **87**, leading to the preferential formation of *trans* isomers for internal allylic amines and *cis* products when using the aza-Morita-Baylis-Hillman adducts.

This methodology was then applied in a formal synthesis of trovafloxacin (Scheme 56). Starting from allylic amine **88**, the key bicyclic core **89** was synthesised using the methodology. Saponification followed by Schmidt reaction gave **90**. Deprotection of **91** gave the known bisamine **92**, completing the formal synthesis.

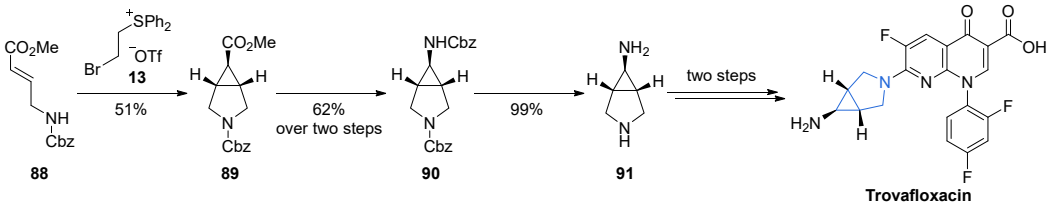
9. Conclusions

Vinylsulfonium salts have been used for the synthesis of a wide range of heterocycles from 3- to 7-membered rings. The synthesis of fused heterocycles incorporating epoxides, aziridines and cyclopropanes has been a very successful strategy. The majority of examples make use of unsubstituted vinyldiphenylsulfonium triflate **14** or its more easily handled, commercially available, precursor **13**, however, the use of enantiopure sulfonium salts and substituted sulfonium salts has also been demonstrated. There are many instances where reagent- or substrate-control have been used to obtain products with good to excellent diastereocontrol. Excellent enantioselectivity has been achieved in epoxyannulation reactions. The methods developed are of particular relevance to the pharmaceutical industry and indeed are seen to be in

use in that industry. We fully expect to see further developments in the applications of vinylsulfonium salts in the future.



Scheme 55. Origin of selectivity in the formation of the cyclopropanated pyrrolidines.[83]



Scheme 56. Formal synthesis of trovafloxacin.

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