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The chemistry of α, β-unsaturated sulfoxides and sulfones: an update

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REVIEW ARTICLE

The chemistry of α,β-unsaturated sulfoxides and sulfones: an update

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A comprehensive review of recent chemistry of α,β-unsaturated sulfoxides and sulfones is presented. Emphasis has been placed on new reactions and strategies, stereo- and enantio-selective reactions, and emerging areas of interest such as metal-mediated asymmetric synthesis, solid-phase organic synthesis (SPOS), and cascade or 'Domino' reactions.

Keywords: Vinyl sulfoxide; Vinyl sulfone; Asymmetric synthesis; Stereoselectivity; Conjugate addition; Tandem reactions; Cycloaddition; Metal-mediated

1. Introduction

Enantiopure sulfoxides have become one of the most important classes of chiral auxiliaries as a result of their ease of preparation, remarkable synthetic versatility, and straightforward removal [1–4]. α,β-Unsaturated sulfoxides have also been used extensively in asymmetric synthesis as versatile chiral reagents with the sulfinyl group playing the role of chiral auxiliary [5].

The related α,β-unsaturated sulfones are widely used as building blocks in synthetic organic chemistry [6]. In 1995, researchers from Khepri Pharmaceuticals first reported peptidyl vinyl sulfones **1** and **2** (figure 1) as potent and selective inhibitors of cysteine proteases [7]. Depeptide vinyl sulfones were found to be suitable for intracellular inhibition of depeptidyl peptidase I (DPPI) [8, 9]. The authors proposed that the inhibition mechanism involves a 1,4-conjugate addition of the thiol group of the cysteine active site to the vinyl sulfone **3** to give a covalently linked enzyme-inhibitor derivative **4** (scheme 1) [9]. It was suggested that the oxygen on the sulfonyl group may form hydrogen bonding with a histidine active site, which enhances the inhibition rate. *In vivo* evaluation of a peptidyl vinyl sulfone inhibitor of falcipain markedly delayed the progression of murine malaria [10, 11]. Peptidyl vinyl sulfones have also been reported to be useful inhibitors of the proteasome and of its bacterial homologue HsIVU [12]. α,β-Unsaturated sulfones have been discovered from a combinatorial library as leads for a new series of inhibitors of inducible VCAM-1 expression [13]. Recently, non-peptidyl vinyl

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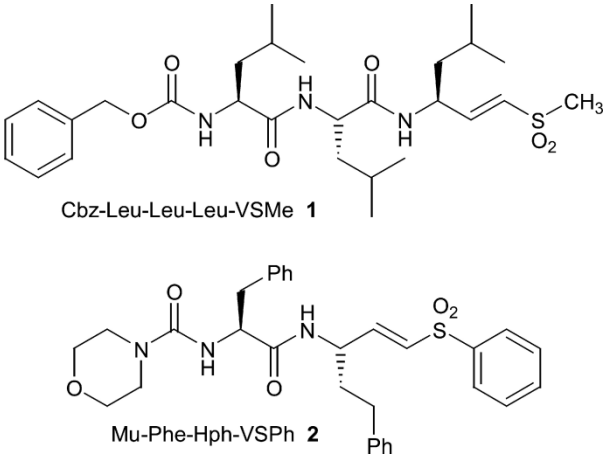
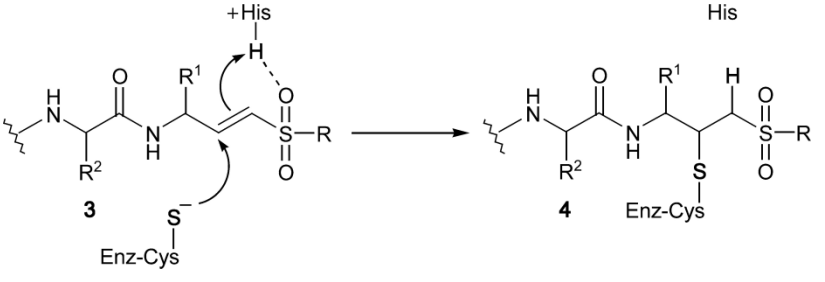


Figure 1.

sulfones have been shown to be promising inhibitors of SrtA, a transpeptidase required for cell wall protein anchoring and virulence in *Straphylococcus aureus* [14]. Thus, vinyl sulfones have a remarkable biomedical significance and will become increasingly important over the coming years.



SCHEME 1

This review continues from one that was recently published in a monograph of organosulfur chemistry [15]. The goal of the present review is to examine recent advances in chemistry of α,β-unsaturated sulfoxides and sulfones, focusing on those which have been published since 1998. Only the chemistry of vinyl (alkenyl) sulfoxides and sulfones will be considered. The synthesis of α,β-unsaturated sulfoxides and sulfones has already been reviewed extensively by Procter [2–4] and hence will be not covered here. The chemistry of other α,β-unsaturated sulfoxides and sulfones, such as dienyl, allenyl, and propargyl (alkynyl) sulfoxides and sulfones, is beyond the scope of this review.

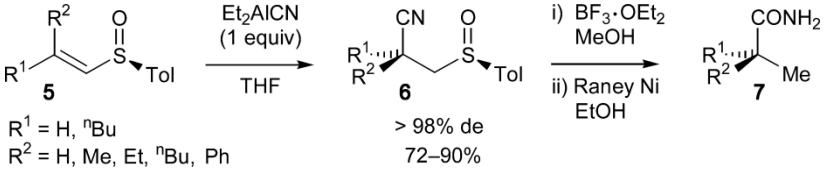
As with previous reviews in the series, emphasis has been placed on new reactions and strategies, stereo- and enantio-selective reactions, and emerging areas of interest such as metal-mediated asymmetric synthesis, solid-phase organic synthesis (SPOS), cascade or 'Domino' reactions, and solvent-free reactions.

2. Nucleophilic additions to α,β-unsaturated sulfoxides and sulfones

2.1 *Conjugate addition of carbon nucleophiles*

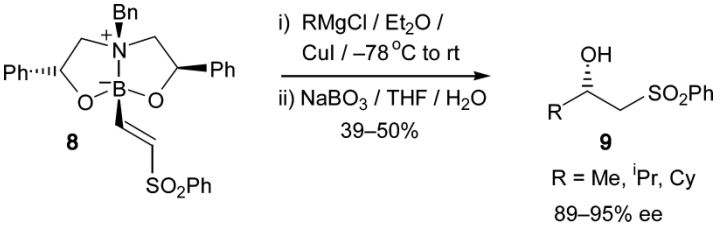
2.1.1 Intermolecular additions. Formation of carbon–carbon bonds with full control of stereochemistry is one of the major challenges in organic chemistry. Over the last ten years the sulfinyl group has been successfully employed to control the enantioselectivity of 1,4-additions of carbon nucleophiles to α,β-unsaturated sulfoxides [15]. In this section further advances in this important area will be highlighted.

García Ruano showed that the hydrocyanation of alkenyl sulfoxides **(5)** with Et_2AlCN takes place in a completely stereoselective manner to yield β-sulfinyl nitriles **(6)**. The chemical versatility of the cyano and sulfinyl groups allowed the creation of optically pure amides **(7)** containing tertiary or quaternary chiral centers (scheme 2) [16]. The same group subsequently utilized this highly stereoselective hydrocyanation of vinyl sulfoxides for the synthesis of the fungicide systhane [17].



SCHEME 2

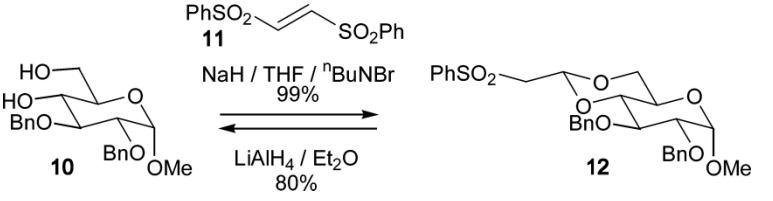
Solladié and co-workers employed a diastereoselective conjugate addition of a cuprate to the key sulfinylchromone precursor in the synthesis of (*R*)-(+)-5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavanone [18]. A recent communication reported the diastereoselective addition of carbon nucleophiles to vinyl sulfone-modified hex-2-enopyranosides and pent-2-enofuranosides [19]. Marsden reported the copper catalysed addition of Grignard reagents to a boron-substituted vinyl sulfone **8**. The dioxazaborocine chiral auxiliary proved to be an excellent stereocontrol element, and following oxidative removal, yielded β-hydroxy sulfones **(9)** with asymmetric induction up to 95% ee (scheme 3) [20].



SCHEME 3

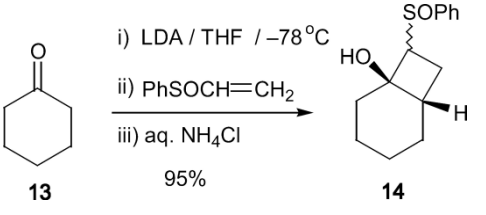
Percy and Blades reported a conjugate addition/sulfoxide elimination route to allylic difluorophosphonates. [(Diethoxyphosphinyl)difluoromethyl]lithium underwent cerium-mediated conjugate additions to cyclic vinyl sulfoxides. However, this reaction failed to occur with all but the simplest acyclic congeners [21]. Highly efficient, electrocatalytic conjugate additions of allyl sulfones to a variety of vinyl sulfones have been accomplished [22]. Phenylsulfonylethylidene (PSE) acetals have recently been reported as a new protecting group for

diols in carbohydrate chemistry [23]. This novel acetal **12** is formed by an addition–elimination reaction of the diol **10** to 1,2-bis(sulfonyl)ethene **11** (scheme 4).



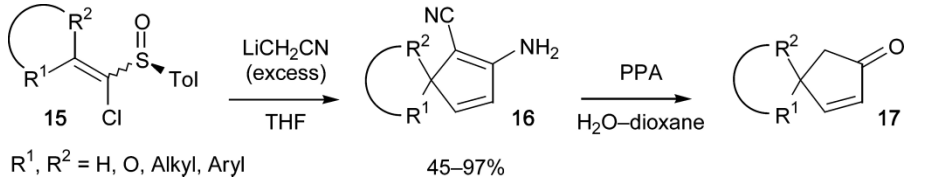
SCHEME 4

The synthesis of substituted quinolines was achieved *via* the Michael addition of the dianion of *N*-Boc-anilines, in the presence of CuCN and LiCl, to α-tolylsulfonyl-α,β-unsaturated ketones [24]. Novel sulfinylbicyclo[4.2.0]octanols **14** were formed upon treatment of the enolate generated from cyclohexanone **13** and LDA at $-78\,^{\circ}C$ with racemic phenyl vinyl sulfoxide (scheme 5) [25]. These bicyclooctanols **14** contained a *cis* ring junction as well as a bridgehead hydroxy group. The same workers extended this methodology to the synthesis of bicyclo[*n*.2.0]alkan-1-ols derived from cyclopentanone, cycloheptanone, and cyclooctanone [26]. Recently, a paper outlining their attempts to probe the mechanism of this novel cyclization was published [27].



SCHEME 5

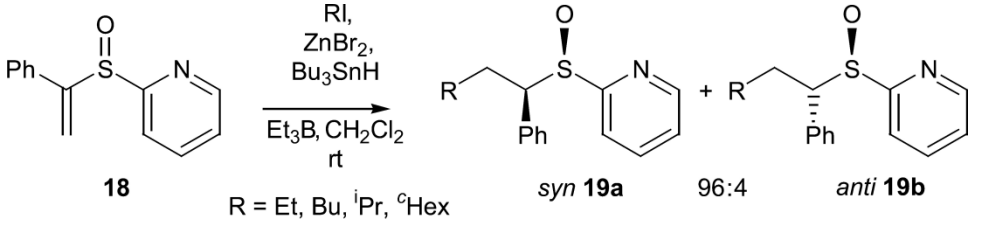
Satoh and co-workers have developed a novel cascade reaction in which three consecutive carbon–carbon bonds are formed in a one-flask multistep reaction [28, 29]. Treatment of α-chlorovinyl *p*-tolyl sulfoxides **(15)** with five equivalents of the lithium carbanion of acetonitrile at $-78\,^{\circ}C$ afforded cyclopentadienyl enaminonitriles **(16)** in high yields (scheme 6). This tandem reaction proceeds *via* an initial Michael-type addition of the lithium carbanion of acetonitrile to the vinyl sulfoxide. These enaminonitriles **(16)** were readily converted into the corresponding 4,4-disubstituted cyclopent-2-enone derivatives **(17)** including novel spiro-type compounds [29].



SCHEME 6

However, if only three equivalents of the lithium carbanion of acetonitrile were used the Michael addition product was formed. Upon treatment with excess of lithium α-carbanion of the homologues of acetonitrile, and subsequent hydrolysis of the enaminonitrile products, the related 2,4,4-trisubstituted cyclopent-2-enone derivatives were obtained [30]. They also employed enantiopure α-chlorovinyl *p*-tolyl sulfoxides in order to extend this methodology to the asymmetric synthesis of both 4,4-disubstituted cyclopent-2-enones [31], including the asymmetric total synthesis of (+)-α-cuparenone [32], and 2,4,4-trisubstituted cyclopent-2-enones [33]. Conjugate additions of lithium ester enolates to α-chlorovinyl *p*-tolyl sulfoxides resulted in a novel synthesis of functionalized esters and lactones having a tertiary or a quaternary carbon at the 3-position [34, 35].

Toru reported that carbon radicals undergo β-addition to vinyl sulfoxides bearing the 2-pyridyl group (compound **18**). In the presence of bidentate Lewis acids high diastereoselectivities, for the *syn*-stereoisomer **19a**, were achieved in the hydrogenation of the resulting α-(arylsulfinyl)alkyl radicals (scheme 7) [36]. Toru and co-workers also showed that α-(1-hydroxyalkyl)vinyl sulfoxides and sulfones undergo highly diastereoselective tandem radical addition/hydrogenation reactions. Intramolecular hydrogen bonding played a key role on both the observed diastereoselectivity and reactivity [37].



SCHEME 7

2.1.2 S_N2' additions. Acyclic epoxy vinyl sulfoxides **(20)** and **(21)** (figure 2) undergo highly regio- and stereo-selective S_N2' displacements with lithium alkyl cyanocuprates in accord with a reinforcing/nonreinforcing scenario, with the sulfoxide being the predominant stereocontrolling element [38]. The observed reversal of selectivity is unprecedented and underlines the extremely useful and powerful stereocontrolling character of the sulfinyl functionality.

The same group reported that α′-alkylated γ-mesyloxy-(Z)-α,β-unsaturated sulfoxide **22** can also readily undergo stereoselective S_N2' displacement with lithium methyl cyanocuprate to yield vinyl sulfoxide **23a** with high diastereoselectivity (scheme 8) [39].

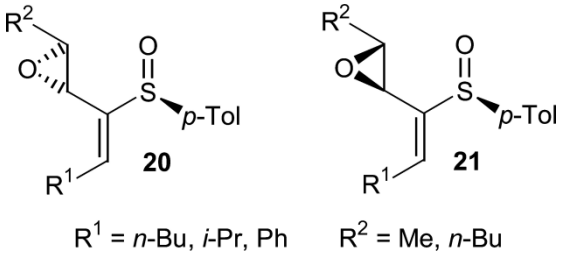
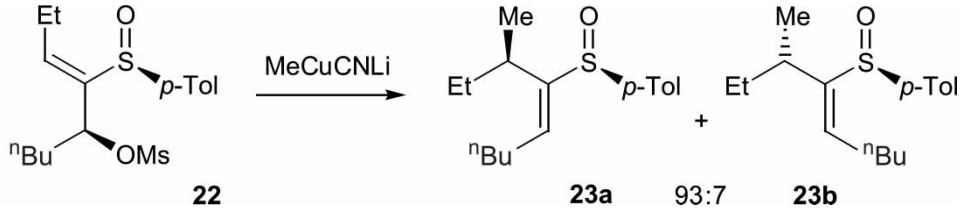


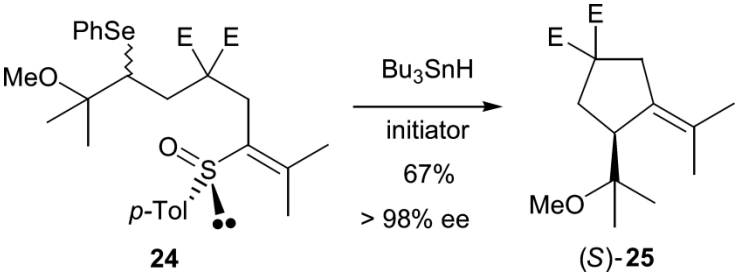
Figure 2.



22 23a 23b

SCHEME 8

2.1.3 Intramolecular additions. An asymmetric intramolecular 5-*exo-trig* radical cyclization using tethered vinyl sulfoxides was reported [40]. For example, vinyl sulfoxide **24** underwent a radical addition/elimination sequence to yield the cyclopentane derivative **25** with full control of the enantioselectivity (scheme 9). The enantiopure sulfinyl moiety served as a very efficient temporary chiral auxiliary in this tandem reaction. Interestingly, the enantioselectivity was reversed by introducing the bulky methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) Lewis acid into the reaction medium.



24 (*S*)-**25**

SCHEME 9

2.2 *Conjugate addition of heteroatom nucleophiles*

2.2.1 Intermolecular additions. Conjugate additions of nitrogen and oxygen nucleophiles to vinyl sulfoxides and vinyl sulfones have become a well established method of creating new carbon–heteroatom bonds. The resulting 1,4-addition products contain either the sulfinyl or sulfonyl moiety, which can readily undergo subsequent functional group transformations. Hence, conjugate additions of heteroatoms have played an important role in various syntheses of structurally complex or biologically important molecules (figure 3) [41–44]. The 1,4-addition of an allylic alcohol to phenyl vinyl sulfoxide followed by sulfoxide elimination and Claisen rearrangement provided the key precursor to spirobenzazepines **(26)** which are potent vasopressin receptor antagonists [41]. The key steps in the synthesis of the indolo[2,3-*a*]quinolizidine **27** were a conjugate addition of a piperidine nitrogen with phenyl vinyl sulfoxide, followed by a regioselective Pummerer reaction [42]. Ma and co-workers reported a short synthesis of the HIV-protease inhibitor nelfinavir **28** *via* a diastereoselective 1,4-addition of ammonia to an α,β-unsaturated sulfoxide derived from (*R*)-glyceraldehyde acetonide [43]. The reactivity of cyclopropanol vinyl sulfoxides toward addition of lithiated Schöllkopf bislactim ether provided a simple synthesis of a novel conformationally restricted analogue **29** of glutamic acid [44].

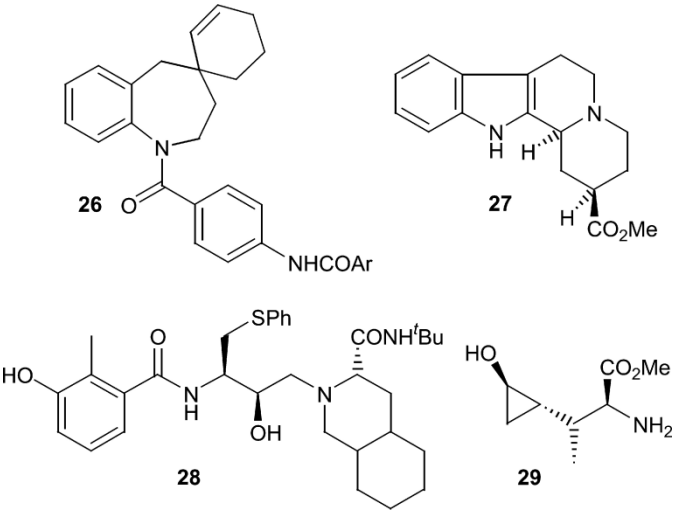
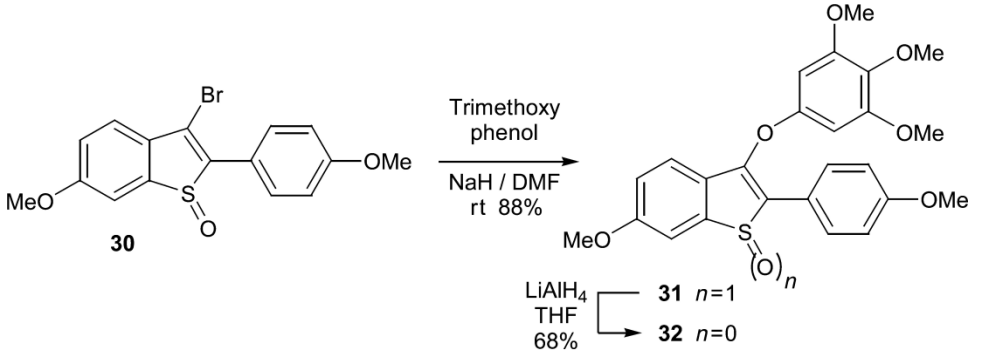


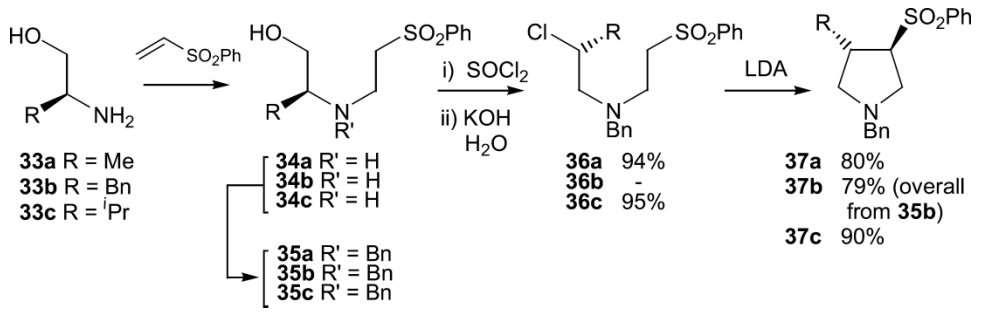
Figure 3.

A new anti-tublin ligand **32**, which exhibited strong cytoxic activity, was prepared from a 1,4-addition/elimination reaction on a bromo-substituted benzo[*b*]thiophene *S*-oxide precursor **30** (scheme 10) [45].



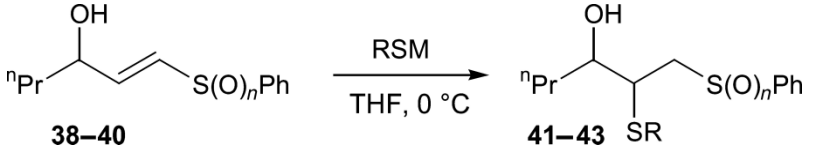
SCHEME 10

The 1,4-addition of nitrogen nucleophiles to vinyl sulfoxides and vinyl sulfones has provided novel approaches for the synthesis of various nitrogen heterocycles. Michael addition of allyl- or propargyl-amines to α-phenylselenenyl α,β-unsaturated sulfones followed by reductive radical cyclization yielded pyrrolidines [46]. Moody and co-workers developed a new protecting-group strategy in order to extend the scope of their modified Bischler indole synthesis. The most suitable protecting group, was the 2-sulfonylethyl group which was readily formed by the conjugate addition of the aniline precursor to phenyl vinyl sulfone [47]. Conjugate additions of amino alcohols derived from α-amino acids (aminols **33**) to phenyl vinyl sulfone, followed by *N*-benzylation, chlorination (*via* an aziridinium intermediate), and intramolecular alkylation, provided a convenient route to substituted pyrrolidines **(37)** (scheme 11) [48]. The conjugate addition–cyclization of piperidazine to enantiopure vinyl sulfoxides yielded bicyclic lactams, with high diastereoselectivity (95% de). One of these bicyclic lactams was then converted into the naturally occurring (*S*)-celacinnine [49].



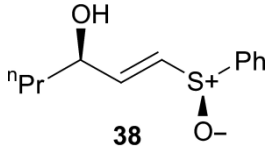
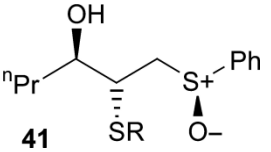
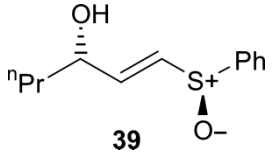
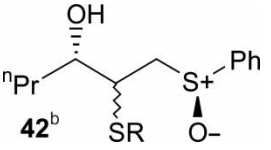
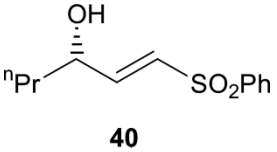
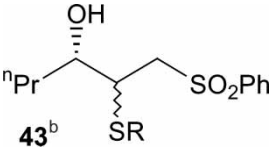
SCHEME 11

There has been considerable interest in the development of novel methodology for 1,4-additions of these and other heteroatom nucleophiles to vinyl sulfoxides and vinyl sulfones. Rayner and Forristal reported the first stereoselective conjugate addition of thiolate nucleophiles to both (*E*)-γ-hydroxy α,β-unsaturated sulfoxides, **38** and **39**, and (*E*)-γ-hydroxy α,β-unsaturated sulfone **40** (scheme 12) [50]. Moderate levels of diastereoselectivity were observed, with the two stereocontrolling elements, the hydroxy group and the sulfoxide, showing reinforcing and nonreinforcing control of stereoselectivity, depending on their relative configuration. Results are presented in table 1.



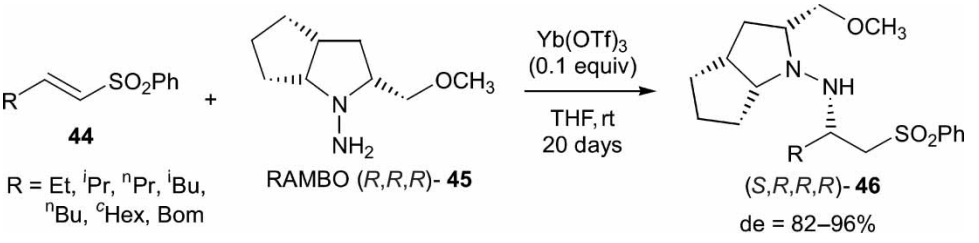
SCHEME 12

Table 1. Conjugate addition of thiolates to (*E*)-γ-hydroxy α,β-unsaturated sulfoxides and (*E*)-γ-hydroxy α,β-unsaturated sulfones.

Entry	Substrate	Thiolate (RSM)	Product	Yield (%)	de	Major product
1		NaSMe[a]	**41a**	63	18	
2		LiS^{n}Bu	**41b**	54	48	
3	**38**	LiS^{i}Pr	**41c**	73	62	**41**
4		NaSMe[a]	**42a**	69	30	
5		LiS^{n}Bu	**42b**	85	0	
6	**39**	LiS^{i}Pr	**42c**	85	0	**42**[b]
7		NaSMe[a]	**43a**	70	30	
8		LiS^{n}Bu	**43b**	93	33	
9	**40**	LiS^{i}Pr	**43c**	83	50	**43**[b]

[a]Reaction carried out at 25 °C. [b]Stereochemistry of major product not determined.

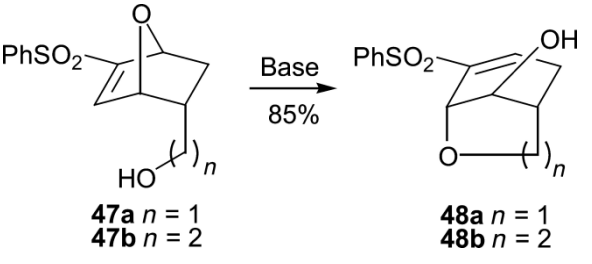
N-Alkylhydroxylamines have been shown to undergo highly stereoselective *cis* addition to α,β-unsaturated sulfones [51]. Lewis acids have recently been used in several aza-Michael additions to vinyl sulfones. Enders reported the $Yb(OTf)_3$-catalysed asymmetric Michael addition of enantiopure ammonia equivalents, such as **45**, to (*E*)-vinyl sulfones **(44)** (scheme 13) [52]. The addition products **(46)** were obtained with diastereoselectivities of up to 96%. After reductive cleavage of the stereocontrol element, subsequent diastereoselective α-alkylation yielded biologically interesting and synthetically valuable α-alkyl-β-amino sulfones [52]. The diastereoselective addition of amines to carbohydrate-derived vinyl sulfones has been reported [53] and provides a highly flexible methodology for the synthesis of new classes of deoxyamino sugars.



SCHEME 13

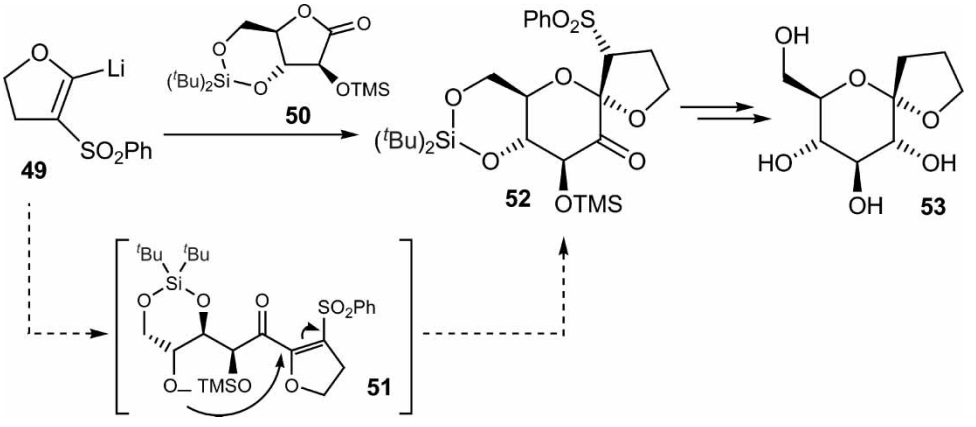
With the increase of environmental consciousness in chemical research, the solvent-free Michael addition has become increasingly important. A very recent paper highlighted heteroatom nucleophilic addition to vinyl sulfones promoted by the $CeCl_3 \cdot 7H_2O$/NaI system supported on alumina under solvent-free conditions [54]. The cerium: (III) salt acts as a Lewis acid promoter of these Michael reactions. They offer the advantage of low toxicity, ease of handling, low cost, and stability in the presence of moisture.

2.2.2 Intramolecular additions. Prunet and co-workers described a short route to protected *syn*-1,3-diols by intramolecular conjugate addition of a hemiacetal anion made *in situ* from δ-hydroxy vinyl sulfones, benzaldehyde and a catalytic amount of base [55]. A recent route to 6-oxabicyclo[3.2.1]octen-8-ol **48a** and 2-oxabicyclo[3.3.1]nonen-9-ol **48b** skeletons *via* intramolecular Michael addition–S_N2' ring openings of 7-oxabicyclic sulfones, **47a** and **47b** respectively, has been reported (scheme 14) [56]. Tanaka and co-workers described highly diastereoselective tetrahydrofuran and tetrahydropyran ring formations *via* intramolecular conjugate additions of the appropriate enantiopure vinyl sulfoxides [57].



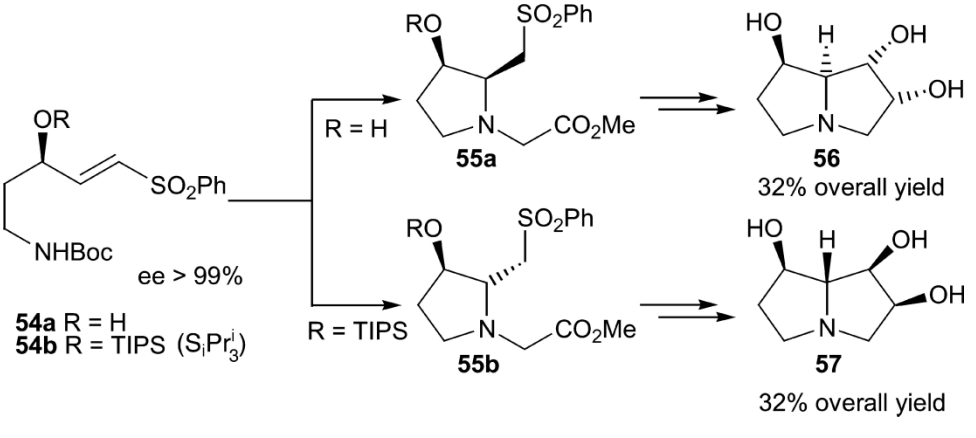
SCHEME 14

A new approach to the stereoselective synthesis of [4.5]spiroketal moiety **53** of papulacandins was developed [58]. The process takes place by reaction of the α-lithiated carbanion of β-sulfonyldihydrofuran **49** with lactone **50** at $-78\,^{\circ}C$ to give the alkoxy intermediate **51** (scheme 15). The intermediate then undergoes intramolecular conjugate addition to the α,β-unsaturated sulfone moiety to stereoselectively provide the 1,6-dioxaspiro[4.5]decane **52** as a single isomer.



SCHEME 15

Carretero and co-workers have continued to develop novel and efficient approaches to polyhydroxylated pyrolizidines and indolizidines [59–62]. Following *in situ* deprotection with CF_3CO_2H the readily available enantiomerically pure γ-hydroxy-α,β-unsaturated sulfones **54a** and **54b** underwent stereoselective intramolecular conjugate addition (scheme 16) [59]. Interestingly, whereas the cyclization of **54a** (R = H) was *cis*-stereoselective, that of **54b** (R = $SiPr^i_3$) was *trans*-stereoselective. The respective pyrrolidines **55a** and **55b** were then converted into the desired enantiopure 1,2,7-trihydroxylated pyrrolizidines **56** and **57**.

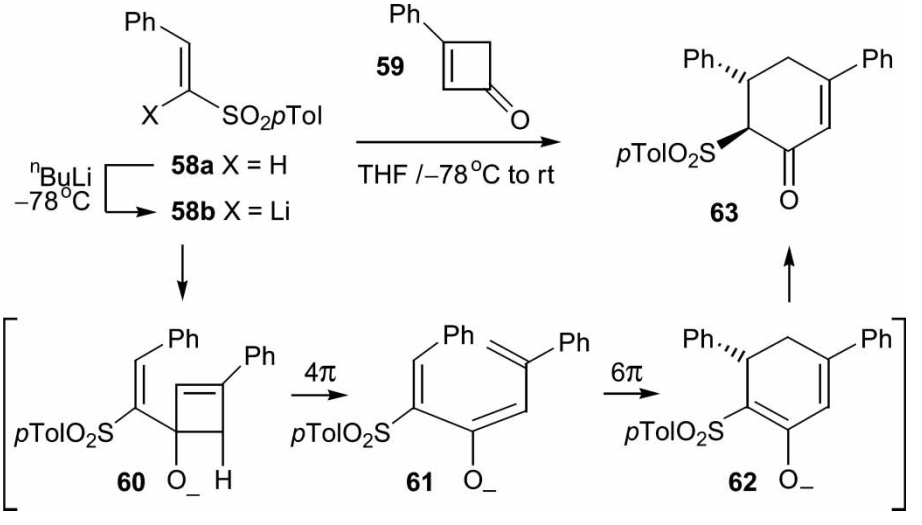


SCHEME 16

The same group also applied the same methodology for the construction of the related indolizidine alkaloids. They reported the synthesis of stereoisomers of castanospermine [60], (−)- and (+)-slaframine [61], and (−)-swainsonine and 1,2-di-*epi*- swainsonine [62].

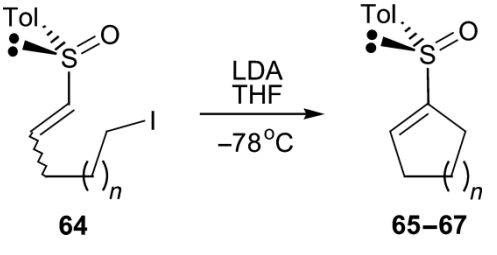
3. Functionalized α,β-unsaturated sulfoxides and sulfones as nucleophiles

Treatment of the cyclobutenone **59** with α-lithio α,β-unsaturated sulfone **58b** resulted in a novel cascade sequence yielding a highly functionalized cyclohexenone **63**, whose structure was unequivocally established by X-ray crystallographic analysis (scheme 17) [63]. The authors proposed the following reaction sequence: attack of the vinyl anion on the carbonyl of **59**, a charge accelerated four-electron conrotatory ring opening of the cyclobutane **60**, and finally a 6π-electrocylcic ring closure (6π-ERC) of hexatriene **61** to yield enolate **62**. Back and co-workers recently reported the synthesis of quinolizidine alkaloids. One of the key steps was an intramolecular acylation of a α-lithiovinyl sulfone [64].



SCHEME 17

Tanaka and co-workers investigated intramolecular alkylation of various β-ω-halogenoalkyl)-substituted vinylic sulfoxides **(64)**. Upon treatment with LDA in THF at −78 °C the α-sulfinyl carbanion generated from the vinylic sulfoxides cyclized at the α-sulfinyl position to give cycloalk-1-enyl sulfoxides **65–67** with a five- to seven-membered ring (scheme 18) [65, 66]. Not only the (*E*)-isomer but also the (*Z*)-isomer cyclized *via* a rapid inversion of the olefin geometry. No loss of optical purity was observed during isomerization. Results are given in table 2. Various cycloalk-1-enyl sulfoxides, including a fused ring and a polyoxygenated ring, were also synthesized [66].



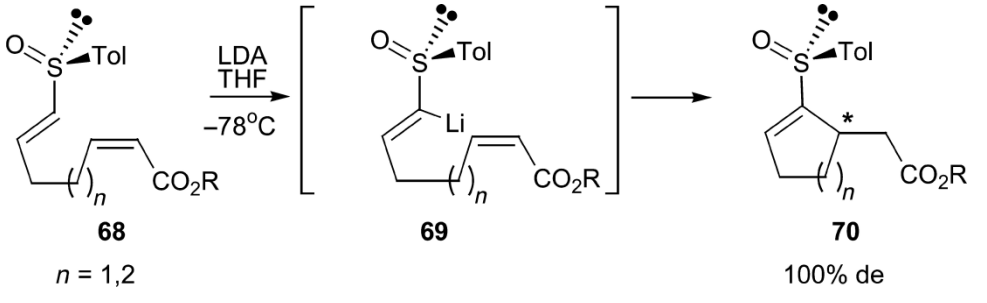
SCHEME 18

The same group also reported the first example of an asymmetric intramolecular Michael reaction using α-lithiated vinylic sulfoxides as the Michael donor [67, 68]. Michael addition of

Table 2. Cyclization of (*E*)- and (*Z*)-**64**.

Substrate	Product	*n* (ring size)	Yield (%)
(*E*)-**64a**	**65**	1 (5)	81
(*E*)-**64b**	**66**	2 (6)	82
(*E*)-**64c**	**67**	3 (7)	79
(*Z*)-**64a**	**65**	1 (5)	66
(*Z*)-**64b**	**66**	2 (6)	71
(*Z*)-**64c**	**67**	3 (7)	64

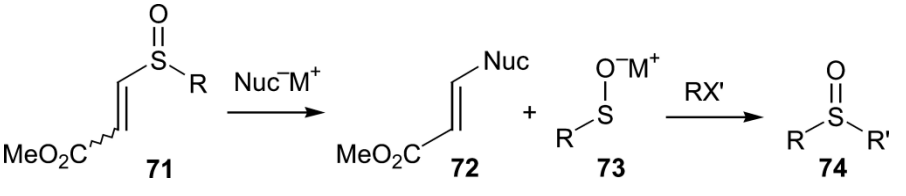
the α-lithiated vinylic sulfoxide **68** to (*Z*)-enoates proceeded with high stereoselectivity to give **70** having a stereogenic center with the (*R*)-configuration at the β-position of the ester in the cyclopentene ring formation (scheme 19). The selectivity was reversed in the six-membered ring formation. On the other hand, the corresponding (*E*)-enoates provided Michael adducts with poor diastereoselectivity [67].



SCHEME 19

4. Elimination reactions of α,β-unsaturated sulfoxides and sulfones

This section focuses upon transformations in which the sulfinyl or sulfonyl group is expelled during the course of the reaction. O'Donnell and Schwan reported that methyl β-sulfinyl acrylate esters **(71)** undergo addition/elimination reactions with oxygen and sulfur nucleophiles [69, 70]. The sulfinyl moiety acts as a leaving group and the resulting sulfenate anions **(73)** were trapped with a variety of electrophiles to yield the corresponding sulfoxides **(74)** (scheme 20). Results are presented in table 3.



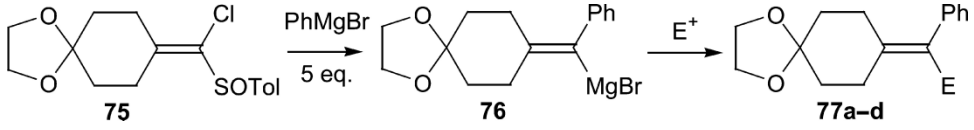
SCHEME 20

Naso investigated the elimination of carbanionic leaving groups from sulfoxides. Treatment of optically pure (*S*)-1-bromovinyl *p*-tolyl sulfoxide with Grignards reagents caused the release of the vinyl leaving group and led to the full inversion of configuration of the sulfoxide [71]. Satoh generated magnesium alkylidene carbenoids from 1-halogenovinyl sulfoxides through ligand-exchange reactions of sulfoxides with alkyl Grignard reagents. The resulting

Table 3. Addition-elimination of β-sulfinyl acrylate esters for the generation of sulfenate anions and subsequent quenching to the sulfoxide.

R	Nuc^-M^+	RX′	Yield of **74** (%)
p-Tol	MeO^-Na^+	BnBr	84
n-C_6H_{13}	MeO^-Na^+	MeI	83
p-Tol	*c*-$C_6H_{11}O^-Li^+$	BnBr	85
Bn	*c*-$C_6H_{11}S^-Li^+$	BnBr	75

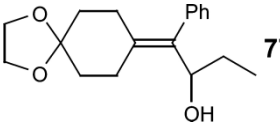
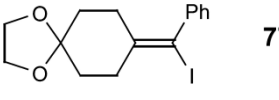
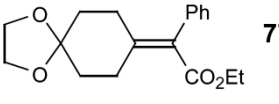
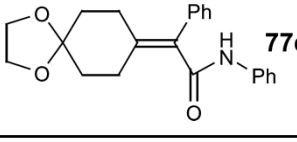
carbenoids reacted with aldehydes to give adducts in moderate yields [72]. 1-Chlorovinyl sulfoxide **75** reacted with excess of phenylmagnesium bromide to give an alkenyl Grignard reagent **76** bearing an aryl group. This reacted with several electrophiles to give tetrasubstituted olefins **(77)** in moderate to good yields (scheme 21) [72]. Results are presented in table 4.



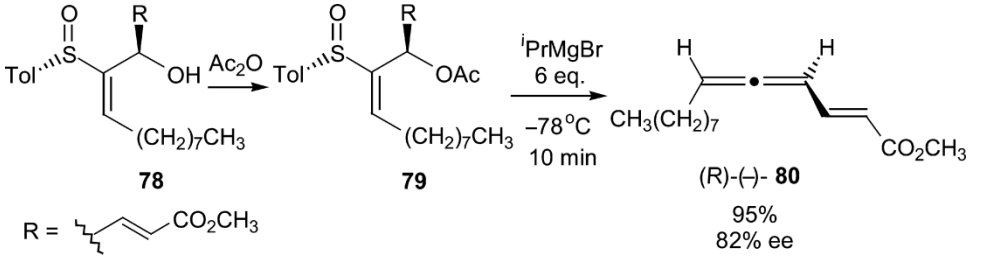
SCHEME 21

Marek and Farhat developed a novel method of desulfonylation. Treatment of vinyl sulfones with bis(cyclopentadienyl)zirconacyclopropane resulted in vinyl organozirconium derivatives, which were readily hydrolysed to yield the corresponding alkenes [73–75]. In all cases, complete isomerization of the stereochemistry was observed with only the *E*-isomer being obtained. Evans reported the asymmetric dihydroxylation of vinyl sulfones [76]. This provided an efficient route to the synthetically useful enantiomerically enriched α-hydroxy carbonyl molecules *via* the 1,2-elimination of the intermediate α-hydroxy sulfone.

Table 4. Reaction of chlorovinyl sulfoxide **75** with PhMgBr followed by some electrophiles.

Electrophile	Product/Yield (%)
CH_3CH_2CHO	 **77a** (81)
I_2	 **77b** (53)
$ClCO_2Et$	 **77c** (65)
PhNCO	 **77d** (87)

The sulfoxide–metal exchange reaction of β-acetoxy sulfoxides or β-mesyloxy sulfoxides with a Grignard reagent or alkyllithium at low temperature gave allenes in good yields [77, 78]. Enantiomerically pure allenes were synthesized from enantiopure 2-substituted ethenyl *p*-tolyl sulfoxides. A short asymmetric synthesis of (*R*)-(−)-methyl tetradeca-2,4,5-trienoate **80**, a male bean weevil sex attractant, from the enantiopure alkenyl sulfoxide **78** was realized by this method (scheme 22) [78].



SCHEME 22

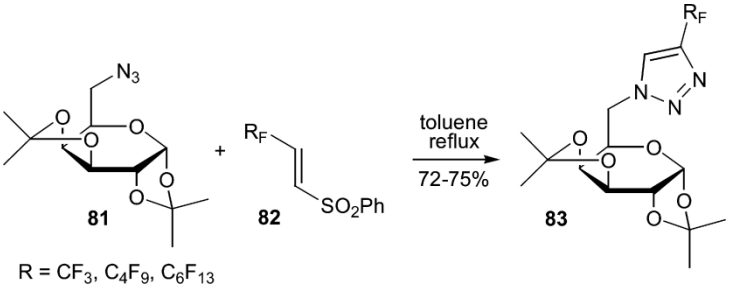
Malacria and co-workers described an unprecedented radical β-elimination of vinyl sulfoxides as a new route to functionalized allenes [79, 80]. Interestingly, this reaction did not proceed with either the sulfinyl or sulfonyl moieties. Toru reported the desilylsulfinylation of 2-(trimethylsilyl)vinyl sulfoxides to yield optically pure propargylic alcohols [81].

5. Cycloaddition reactions of α,β-unsaturated sulfoxides and sulfones

5.1 *[3+2] Cycloadditions*

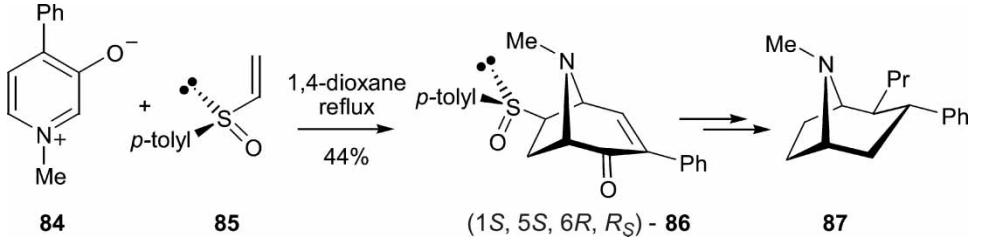
Various α,β-unsaturated sulfoxides and sulfones have been exploited as dipolarophiles in 1,3-dipolar cycloadditions, reacting with a variety of 1,3-dipoles such as azomethine ylides, azides, nitrones, oxidopyridinium betaines and diazoalkanes.

A stereoselective dipolar cycloaddition of an *N*-substituted azomethine ylide with phenyl vinyl sulfone produced a *trans*-2,5-dialkylpyrrolidine that was further transformed into the dendrobatid alkaloid indolizidine 239CD [82]. Novel reversed nucleosides **(83)**, with a fluoroalkyl-substituted 1,2,3-triazole linked to the C-atom 6 of D-galactose, were synthesized by 1,3-dipolar cycloadditions of the monosaccharide azide **81** and perfluoroalkyl phenyl vinyl sulfones **(82)** (scheme 23) [83].



SCHEME 23

(*R*)-p-Tolyl vinyl sulfoxide **85** underwent asymmetric 1,3-dipolar cycloaddition with oxidopyridinium betaine **84** with good diastereoselectivity but only moderate π-facial selectivity. The products were separated by flash chromatography and the major *exo* cycloadduct **86** was converted into the corresponding 2β-alkyl-3α-phenyltropane **87** (scheme 24) [84]. The same group utilized this protocol for the enantioselective synthesis of 7-fluoro-3-(*p*-fluorophenyl)-2-propyltropanes [85].



SCHEME 24

The ability of the sulfinyl group to control the π-facial selectivity in the asymmetric Diels–Alder reaction [15, 86] has provided impetus for the use of enantiomerically pure α,β-unsaturated sulfoxides as dipolarophiles. However, higher levels of reactivity and π-facial selectivity are usually achieved if the dipolarophile contains additional activating groups as well as the sulfinyl moiety (figure 4).

Aggarwal reported that the *C*2-symmetric vinyl sulfoxide, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide **88** (figure 4), underwent 1,3-dipolar cycloaddition reaction with a range of 3-oxidopyridinium betaines in high yield and with 100% diastereoselectivity [87]. García Ruano and co-workers reported that methyl (*S*)-2-(*p*-tolylsulfinyl)acrylate **89** (figure 4) underwent 1,3-dipolar cycloaddition with *N*-substituted azomethine ylides with complete regio- and *endo*-selectivities [88]. Nevertheless, two diastereoisomers (75–88% de) resulting from the *anti* dipole/*s-cis* dipolarophile and *syn* dipole/*s-trans* dipolarophile approaches respectively, were obtained. Enantiomerically pure 2,5-dihydro-1*H*-pyrroles were readily obtained from the cycloadducts by pyrolytic desulfinylation [88]. The dipolarophilic reactivity of enantiopure (*Z*)-3-(*p*-tolylsulfinyl)acrylonitriles **(90)** has been evaluated with diazoalkanes (scheme 25) [89]. 3-Cyanopyrazoles **(96)** were obtained with **90a** (R = H), but with **90b–d** (R = Bn, ^{n}Bu,

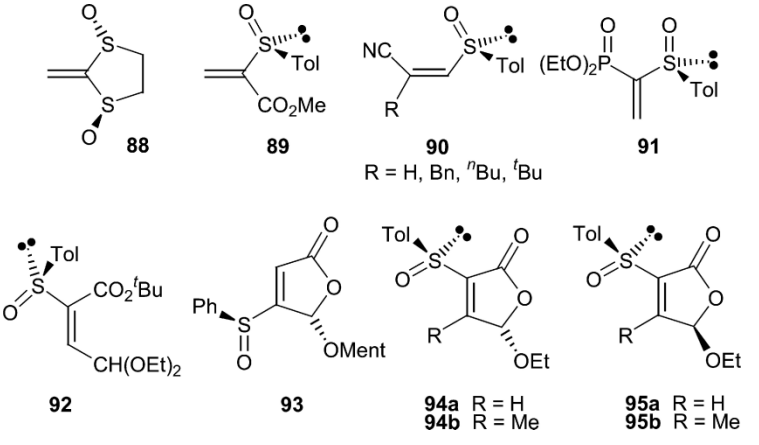
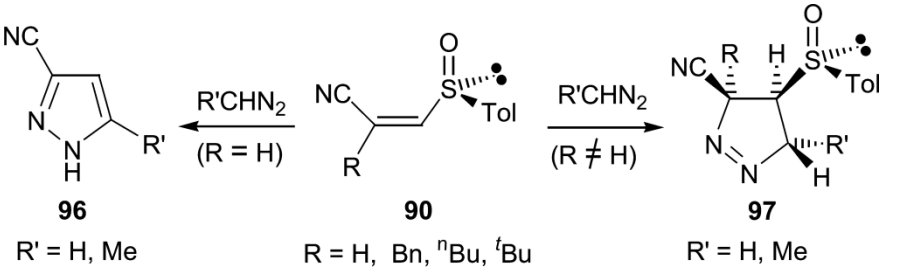


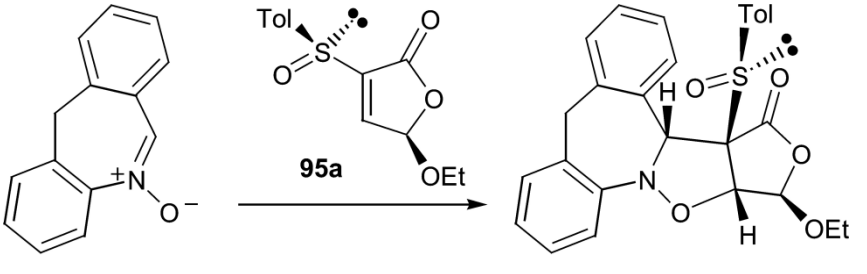
Figure 4.

^{t}Bu) only one pyrazoline cycloadduct **(97)** was formed, in high yield and with complete control of the regioselectivity and the *endo*/*exo* and π-facial selectivities. In a subsequent communication the same group reported that thermolysis of the related enantiopure sulfonylpyrazolines, easily obtained from (*Z*)-3-(*p*-tolylsulfinyl)acrylonitriles **(90)**, afforded sulfonylcyclopropanes in a completely stereoselective manner in almost quantitative yields [90].



SCHEME 25

Midura, Krysiak and Mikołajczyk reported that the 1,3-dipolar cycloaddition of diazoalkanes to (*S*)-(+)-α-(diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide **91** (figure 4) proceeded with full control of diastereoselectivity [91]. With diazopropane the pyrazoline cycloadduct underwent decomposition to yield the corresponding cyclopropane with preservation of the configurational integrity [91]. The asymmetric 1,3-dipolar cycloadditions of diazoalkanes to (5*S*, S_S)-5-[(1*R*)-menthyloxy]-4-(phenylsulfinyl)furan-2(5*H*)-ones **93** (figure 4) was described [92]. Only moderate π-facial selectivity was observed. The role of steric and electronic interactions in the stereocontrol of the asymmetric 1,3-dipolar reactions of 5-ethoxy-3-[(*S*)-*p*-tolylsulfinyl]furan-2(5*H*)-ones **94a–b** and **95a–b** (figure 4) was described [93]. The 1,3-cycloaddition reactions of various nitrile oxides with *tert*-butyl (*E*)-4,4-diethoxy-2-(*p*-tolylsulfinyl)but-2-enoate **92** (figure 4) yielded isoxazoles [94]. However, (5*S*, S_S)- and (5*R*, S_S)-5-ethoxy-3-(*p*-tolylsulfinyl)furan-2(5*H*)-ones, **94a** and **95a** (figure 4), when treated with benzonitrile oxide afforded isoxazolines [94]. Interestingly, in both cases the observed regioselectivity was opposite to that exhibited by dipolarophiles lacking the sulfinyl group. Both these heterocycles were independently transformed into the corresponding isoxazolopyridazinones in high yields by reaction with hydrazine hydrate [95]. The addition of nitrone **98** to enantiomerically pure furanone **95a** required less than 5 min at room temperature to exclusively afford the *endo*-furoisoxazoloazepine **99** (scheme 26) [96]. Manipulation of **99** allowed for the synthesis of optically pure isoxazoloazepines and pyrroloazepines. However, the other furanone **94a** (figure 4), with the opposite configuration at carbon-5, gave a mixture of three stereoisomers.

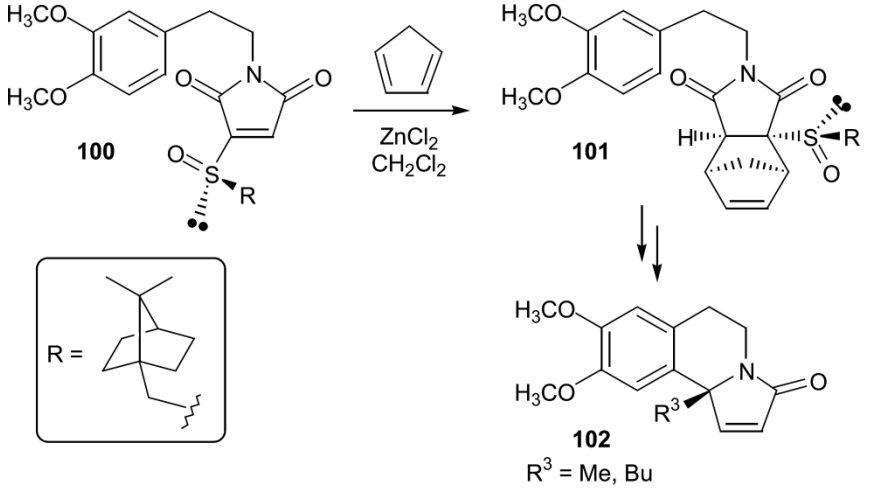


SCHEME 26

5.2 *[4+2] Cycloadditions*

The asymmetric Diels–Alder reaction has become one of the most powerful tools in asymmetric synthesis due to its capacity for creating up to four chiral centers in one step, often in a highly stereoselective manner. A review of asymmetric [4+2] cycloadditions mediated by sulfoxides, connected to either the dienophile or the diene, has been published in a monograph of organosulfur chemistry [97]. Recent advances in this area using vinyl sulfoxide and vinyl sulfone dienophiles will be considered. However, Diels–Alder reactions of sulfinyl-1,3-dienes is beyond the scope of this review.

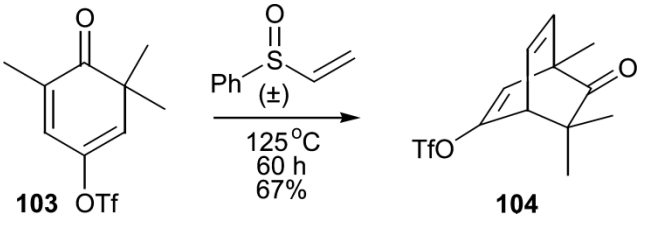
A stereoselective [4+2] cycloaddition of an enantiopure vinyl sulfoxide was one of the keys steps in the enantioselective synthesis of dihydropyrrolo[2,1-*a*]isoquinolones **(102)** [98]. The Diels–Alder reaction of the required sulfinylmaleimide **100** with cyclopentadiene, in the presence of $ZnCl_2$, afforded the corresponding sulfinylnorbornenimide **101** in excellent yield and as a single diastereoisomer (scheme 27) [98].



SCHEME 27

Aversa and co-workers investigated the Diels–Alder reactivity of enantiopure sulfinyl dienophiles with a carbohydrate attached to the sulfoxide moiety [99]. Unfortunately, their reactivity was very low (about half of a month was required for the cycloaddition to be completed) and the cycloadducts spontaneously underwent regioselective elimination of sulfenic acid.

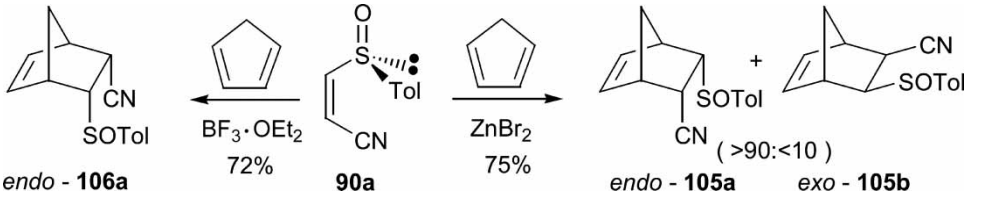
Phenyl vinyl sulfoxides have been employed as acetylene equivalents in Diels–Alder reactions. Cycloaddition of 2,6,6-trimethyl-4-trifloxycyclohexa-2,4-dienone **103** with (±)-phenyl vinyl sulfoxide, followed by thermally induced *syn* elimination of the sulfoxide, yielded the bicyclo[2.2.2]octadienone **104** in good yield (scheme 28) [100].



SCHEME 28

(1-Fluorovinyl) phenyl sulfoxide underwent a Diels–Alder reaction with the very reactive diene, 1,3-diphenylisobenzofuran, to give the corresponding fluorinated naphthalene derivative [101]. (*E*)-3-(Phenylsulfonyl)prop-2-enenitrile can act as a cyanoacetylene equivalent in [4+2] cycloaddition reactions [102]. The cycloadducts underwent base catalysed elimination of benzenesulfinic acid to yield α,β-unsaturated nitriles. Aggarwal reviewed the utilization of α,β-unsaturated sulfoxides and sulfones as ketene equivalents in [4+2] cycloadditions [103].

The sulfinyl group has been shown to control the π-facial selectivity in the asymmetric Diels–Alder reaction [15, 86]. Higher levels of reactivity and π-facial selectivity are usually achieved if the dienophile contains additional activating groups as well as the sulfinyl moiety (figure 4). García Ruano studied the cycloaddition reactions of enantiomerically pure (5*S*, S_S)-5-[(1*R*)-menthyloxy]-4-(phenylsulfinyl)furan-2(5*H*)-ones **93** (figure 4) and other related 4-thio-substituted 5-alkoxyfuranones [104]. The same group also investigated the dienophilic behaviour of enantiopure (*Z*)-3-(*p*-tolylsulfinyl)acrylonitriles **(90)** (figure 4) [105, 106]. The most significant finding of the asymmetric Diels–Alder reactions of **90a** with cyclopentadiene was the total π-facial selectivity, which was readily inverted by using BF_3 as a catalyst (scheme 29) [105]. High π-facial selectivity was also observed in the cycloaddition of **90a** with furan and acyclic dienes [106].



SCHEME 29

The authors suggested that electrostatic repulsion between the C≡N and S–O dipoles restricts the conformational mobility around the C–S bond. Thus, the approach of the diene is from the least hindered face of the dienophile (Face A: that bearing the lone electron pair) in the predominant rotamer **90a** (figure 5). A cyclic oxosulfonium intermediate **107** was proposed in order to account for the reversal in π-facial selectivity observed with BF_3 (figure 5) [106].

García Ruano outlined the Diels–Alder cycloadditions of the enantiomerically pure (*E*)-3-formyl 2-sulfinylacrylonitrile **108** and its diethyl acetal derivative **109** (figure 6) with

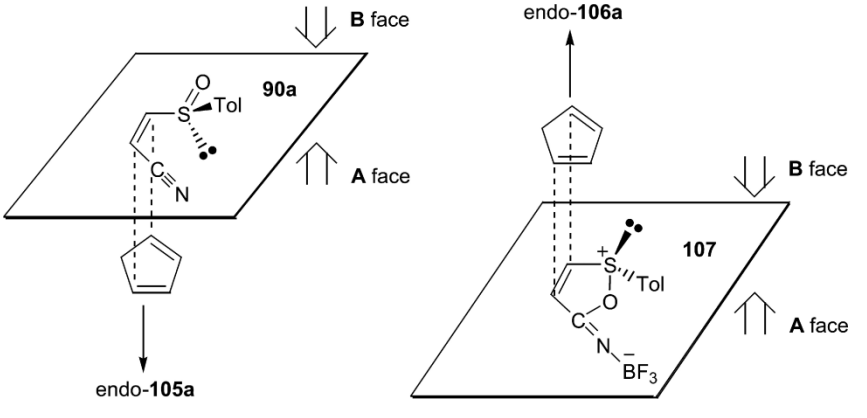


Figure 5.

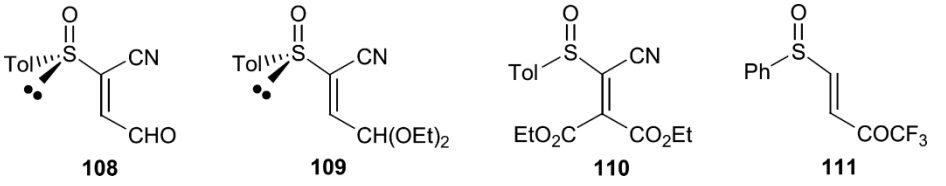


Figure 6.

cyclopentadiene [107]. The highest stereoselectivities were observed with the acetal **109** under $Eu(fod)_3$ catalysis. The presence of a third electron withdrawing group on the double bond of (±)-3,3-bis(ethoxycarbonyl)-2-(*p*-tolylsulfinyl)acryonitrile **110** (figure 6) caused a decrease in the energy barrier for the pyramidal inversion of the sulfinyl sulfur, thus making racemization easier. This is the first evidence about the influence of the electronic effects of substituents at the double bond in the configurational stability of vinyl sulfoxides [108]. The novel dienophile (*E*)-1,1,1-trifluoro-4-(phenylsulfinyl)but-3-en-2-one **111** (figure 6) underwent Diels–Alder reaction with 1,3-dienes to afford the corresponding CF_3-containing mono- and poly-cycloadducts [109].

Several research teams have shown that the sulfinyl group, situated on a quinone (figure 7), was able to control the regiochemistry of sulfinyl quinone cycloadditions with a range of substituted alkenes [86, 110–117]. High *endo* and π-facial diastereoselective reactions were always achieved, due to efficient differentiation of the diastereotopic faces of the quinone by the sulfoxide.

The regioselectivity of Diels–Alder reactions of the (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **112b** can be directed by the adequate choice of thermal or $ZnBr_2$-catalysed conditions [110]. This allowed the stereoselective synthesis of two regioisomers of tetrahydrochrysenequinones **118** and **119** from Dane's diene **115** with enantiomeric excesses up to >97% (scheme 30; table 5). Once the *endo*-cycloadducts **116** and **117** were formed, elimination of sulfenic acid occurred spontaneously, allowing the recovery of the quinone skeleton.

The resolution of racemic vinyl cyclohexenes upon reaction with enantiomerically pure (*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **113a** occurred when the substituent at the cyclohexene system was at the C-4, C-5, and C-6 positions [111]. With diene (±)-**120**, bearing an OTBDMS (*text*-butyldimethylsiloscy) group at C-6, tetracyclic quinine (+)-**121** was formed with 86% ee (scheme 31). Once again this domino Diels–Alder reaction/sulfoxide elimination occurred spontaneously in a single step. The same approach was also applied to the asymmetric synthesis of (–)-deoxytetrangomycin [112] and (+)-rubiginone B_2 and (+)-ochromycinone [113]. Rubiginones A_2 and C_2 were also synthesized in enantiomerically pure form (ee >97%) *via* the Diels–Alder reaction of racemic 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **113b**

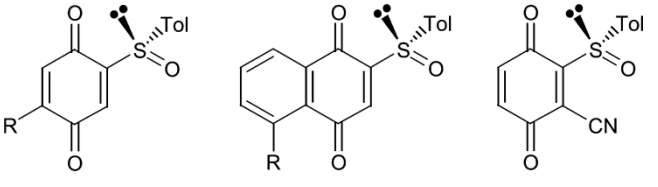
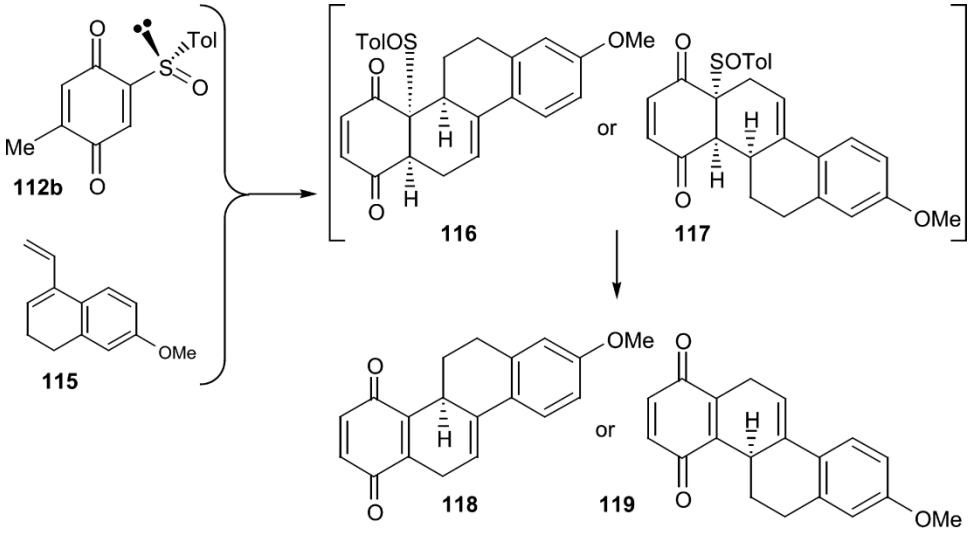


Figure 7.

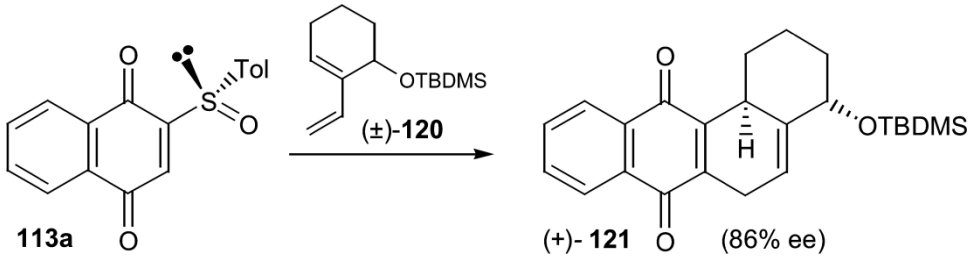


SCHEME 30

Table 5. Diels–Alder reaction of Dane's diene **115** and enantiopure sulfinylquinone (+)-**112b**.

Lewis acid	Product/Yield (%)	Product/ee (%)
	(+)-**118** (81)	(+)-**118** (80)
$ZnBr_2$	(−)-**119** (53)	(−)-**119** (>97)

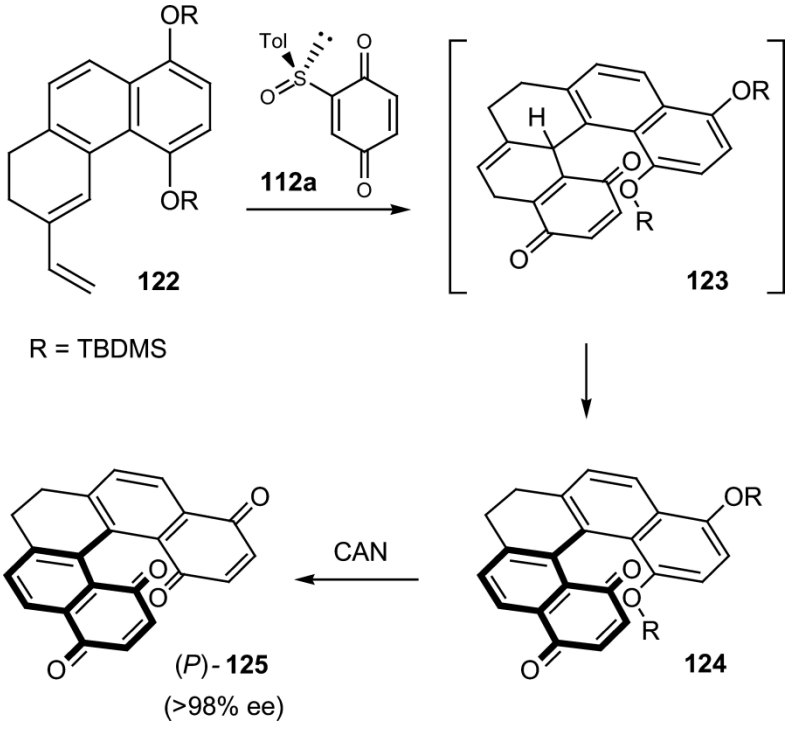
(figure 7) and a enantiopure diene [86]. A recent review highlighted these and other advances in the synthesis of naturally occurring quinones [114].



SCHEME 31

Carreño reported the first asymmetric synthesis of dihydrobenzo[*c*]phenanthrene-1,4-quinones with helical chirality [115]. The same group subsequently synthesized enantio-enriched dihydro[5]helicenequinones and bisquinones (50 → 98% ee) from the (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **112b** [116]. A domino Diels–Alder cycloaddition/sulfoxide elimination/partial aromatization, in which the absolute configuration was defined in the final aromatization step, yielded helicene (*P*)-**125** (scheme 32). Recently García Ruano reported

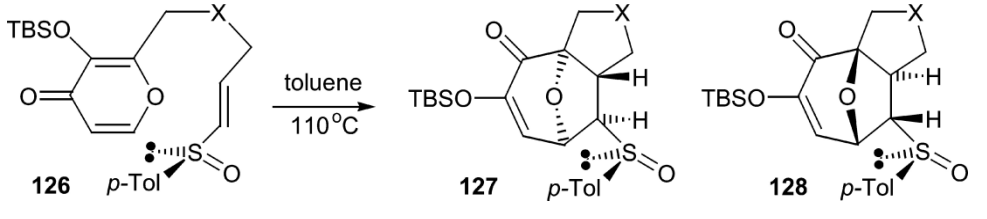
the dienophilic behaviour of (*S*)-2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone **114** (figure 7) [117].



SCHEME 32

5.3 *[5+2] Cycloadditions*

A highly diastereoselective thermal [5C+2C] intramolecular pyrone–vinyl sulfoxide **(126)** cycloaddition was achieved by employing an *endo*-placed homochiral *p*-tolylsulfinyl group (scheme 33; table 6) [118]. The resulting major oxabicylic adducts **(127)**, by virtue of their high functionalization, were readily converted into stereochemically enriched seven-membered carbocycles or tetrahydrofurans. This was demonstrated by a concise synthesis of (+)-nemorensic acid [118].



SCHEME 33

Table 6. Cycloaddition of pyrones **126a–c**.

Pyrone	X	Yield (%)	**127**:**128**	(t/h)
126a	$C(CN)_2$	98	**127a**:**128a** (91:9)	10
126b	$C(CO_2Et)_2$	99	**127b**:**128b** (97:3)	3.5
126c	S	95	**127c**:**128c** (93:7)	46

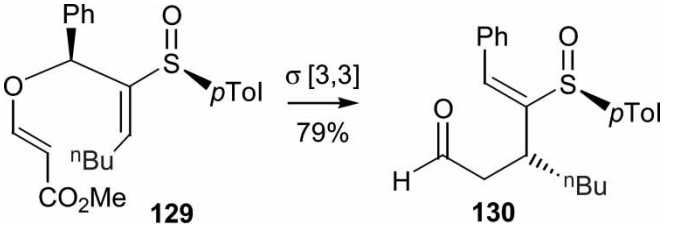
6. Rearrangements involving α,β-unsaturated sulfoxides and sulfones

6.1 *Pummerer reactions*

The vinylogous Pummerer reaction continues to be a very useful synthetic transformation. More than two decades ago the Marino group developed a powerful sulfoxide-directed lactonization (Marino's annulation reaction) of vinyl sulfoxides with a dichloroketene [119]. Bravo and co-workers extended the scope of this reaction to the sulfoxide-directed lactonization of (*R*)-(*E*)-β-fluoroalkyl vinyl sulfoxides with excellent stereocontrol to yield enantiomerically pure γ-butyrolactones [120]. This highly stereoselective reaction has recently been utilized by Marino to enantiospecifically set up a quaternary carbon in the total synthesis of the structurally complex alkaloid (+)-aspidospermidine [121].

6.2 *Sigmatropic rearrangements*

The Claisen rearrangement is well established as an efficient method to achieve one of the main challenges for chemists, which is the stereoselective formation of carbon–carbon bonds in acyclic systems. Two groups have developed asymmetric variants of this [3,3]-sigmatropic transposition involving removable sulfinyl chiral auxiliaries. Vinyl sulfoxide **129**, bearing a sulfinyl moiety at C-5, underwent highly selective Claisen rearrangements with concurrent decarboxylation (scheme 34). This strategy allowed for the creation of up to two new asymmetric centers with regeneration of the valuable vinyl sulfoxide moiety in an expedient manner [122].

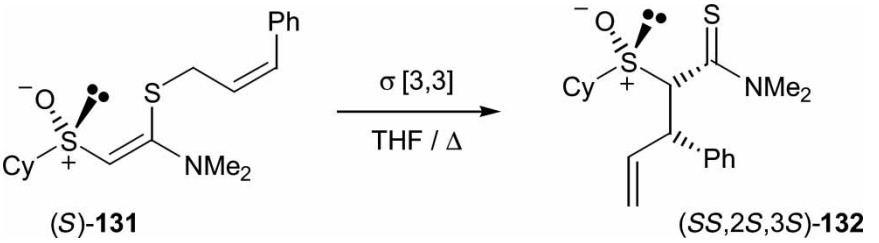


129 **130**

SCHEME 34

Metzner reported the first examples of asymmetric thio-Claisen rearrangements induced by an enantiopure cyclohexylsulfinyl group [123]. They developed a powerful general protocol for the synthesis of the required ketene aminoacetal substrates with full control of both the configuration of the sulfoxide and the geometry of their double bonds. One notable example was the Claisen rearrangement of the substrate **131** to form thioamide **132** as a single isomer (scheme 35). The stereochemical course of this [3,3] sigmatropic transposition was confirmed by X-ray analysis of the corresponding amide and was explained by an electronic model.

It was shown that the (*ZE*)-cinnamyl substrates proceed through a boat transition state rather than the usual chair transition state [123].



(*S*)-**131** (*SS*,2*S*,3*S*)-**132**

SCHEME 35

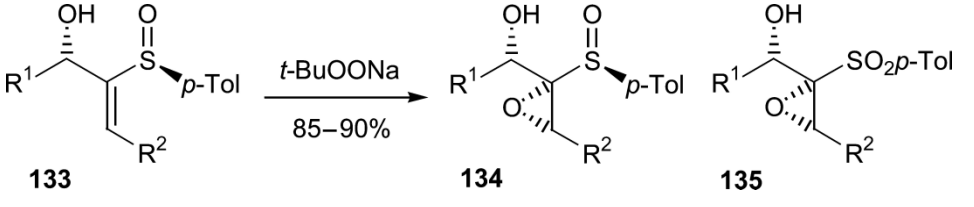
7. Epoxidation and cyclopropanation reactions of α,β-unsaturated sulfoxides and sulfones

7.1 *Epoxidation reactions*

There continues to be considerable interest in the stereoselective preparation of hetero-substituted oxiranes using nucleophilic epoxidation of electron-deficient alkenes such as vinyl sulfoxides and vinyl sulfones.

Aggarwal described a highly diastereoselective epoxidation of ketene dithioacetal dioxides [124]. The synthetic utility of the diastereoisomerically pure spirocyclic *bis*-sulfinyl oxirane products was demonstrated by the synthesis of two amino amides with complete control over the newly generated stereocenter [124]. The stereoselective epoxidation of vinyl sulfones derived from isopropylideneglyceraldehyde has also been reported [125].

Acyclic α′-(1-hydroxyalkyl)vinyl sulfoxides undergo highly stereoselective metal-catalysed epoxidation reactions in the presence of 5% $VO(acac)_2$ and 1.5 equivalents of ^{t}BuOOH [126]. A full account of the nucleophilic epoxidation of a variety α′-(1-hydroxyalkyl)vinyl sulfones and sulfoxides was outlined by de la Pradilla [127]. The sulfones gave rise to *anti* oxiranes with modest (*E*) or excellent (*Z*) selectivities and in good yields. The (*E*)-sulfoxides displayed low reactivity within a reinforcing/nonreinforcing scenario. The use of ^{t}BuOOLi in Et_2O allowed for a highly *syn*-selective epoxidation–oxidation. The reinforcing (*S*, S_S) diastereoisomers **(133)** yielded hydroxy sulfinyloxiranes **(134)** with high yields and selectivities (scheme 36; table 7). In contrast, the (*R*, S_S) diastereoisomers **(136)** showed diminished reactivities and a very substrate-dependent stereochemical outcome (scheme 37; table 8). The same group also reported that the nucleophilic epoxidation of simple (γ-silyloxy)vinyl sulfoxides takes place with complete stereocontrol and high yields [128]. For substrates bearing an additional substituent at the γ-position, once again a reinforcing/nonreinforcing scenario was operative. Roberts and co-workers recently reported an asymmetric epoxidation of some aryl alkenyl sulfones using a modified Juliá–Colonna procedure [129].

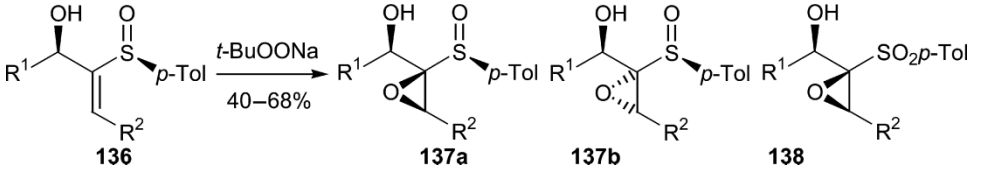


133 **134** **135**

SCHEME 36

Table 7. Epoxidation of (S, S_S)-(Z)-hydroxy vinyl sulfoxides.

	Substrate	**134**:**135**
133a	R^1 = Et, R^2 = n-Bu	100:0
133b	R^1 = Ph, R^2 = n-Bu	98:2
133c	R^1 = Et, R^2 = Ph	100:0



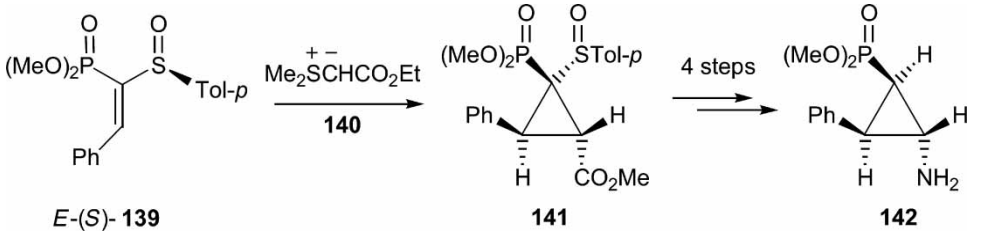
SCHEME 37

Table 8. Epoxidation of (R, S_S)-(Z)-hydroxy vinyl sulfoxides.

	Substrate	**137a**:**137b**:**138**
136a	R^1 = Et, R^2 = n-Bu	67:33
136b	R^1 = Ph, R^2 = n-Bu	78:4:18

7.2 *Cyclopropanation reactions*

Mikołajczyk and Midura have made further advances in the asymmetric cyclopropanation of chiral α-phosphorylvinyl sulfoxides. The cyclopropanation was initially performed with two sulfur ylides, namely dimethyl(oxo)sulfonium methylide and diphenylsulfonium isopropylide. Only moderate stereoselectivity (3:1 ratio) was observed for the first ylide. However, a high level of asymmetric induction was observed with the latter, leading to a 92:8 mixture of two diastereoisomers [130]. The cyclopropanation of (E)-(S)-(1-dimethoxyphosphoryl-2-phenyl)vinyl p-tolyl sulfoxide **139** with ethyl (dimethylsulfanylidene)acetate (EDSA) **140** occurred in a highly diastereoselective manner with three new chiral centers being formed. The major product **141** was then converted into the enantiopure (2R)-amino-(1R)-cyclopropanephosphonic acid **142**, a constrained analogue of the $GABA_B$ antagonist (scheme 38) [130]. They also applied this methodology to the synthesis of enantiopure cyclopropylphosphonate analogues of purine nucleotides, which are constrained forms of antiviral alk-1-enylphosphonic acid derivatives of purines [131].



SCHEME 38

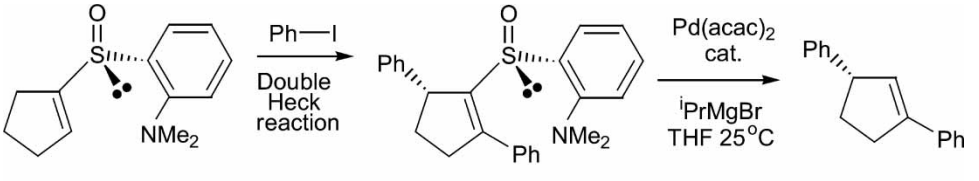
A recent collaboration between this group and García Ruano studied the asymmetric cyclopropanation of (5*S*, S_S)-5-ethoxy-3-(*p*-tolylsulfinyl)furan-2(5*H*)-one **94a** (figure 4) with sulfonium ylides [132]. Very high π-facial selectivity and *endo* selectivity was observed with diphenylsulfonium ylides, whereas reactions with dimethylsulfonium ylides occurred with only moderate π-facial selectivity and *exo* selectivity.

8. Metal-catalysed reactions of α,β-unsaturated sulfoxides and sulfones

Although the sulfinyl group has proved to be an efficient and widely used chiral auxiliary in many classical reactions, such as Diels–Alder reactions and nucleophilic additions, little was known about its use in processes catalysed by transition metals. However, in the last few years the Carretero research group have reported the first examples of vinyl sulfoxides in several cornerstone asymmetric metal-catalysed processes such as the Heck and Pauson–Khand reactions.

8.1 *Heck reactions*

Carretero and co-workers reported the enantioselective synthesis of tetrahydrofurans from the Heck reaction of enantiomerically pure 3-arylsulfinyl-2,3-dihydrofurans with aryl iodides [60, 133, 134]. An application of this methodology is the asymmetric synthesis of (*S*)-1,3-diphenylcyclopentene **145** *via* a double Heck reaction of the 1-sulfinylcyclopentene **143** with iodobenzene followed by palladium-catalysed reductive desulfurization of the sulfoxide **144** (scheme 39) [134–136]. This work illustrates that sulfoxides are excellent stereochemical controllers in intermolecular Heck reactions. It should be noted that the 2-(*N,N*-dimethylamino)phenyl substituent was necessary in order to obtain high stereoselectivity, presumably *via* co-ordination of the Pd atom with the nitrogen.



(*R*)- **143**
ee = 97%

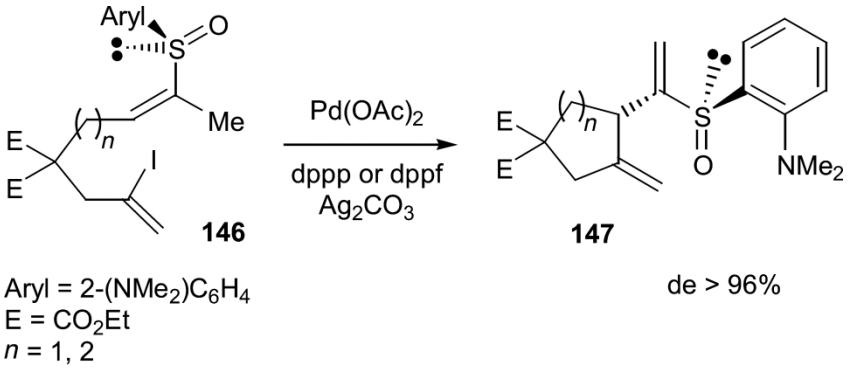
144
de = 97%

(*S*)-**145**
ee = 94%

SCHEME 39

The same group subsequently utilized this approach for intramolecular Heck reactions of vinyl sulfoxides. The central C2–C3 bond of 1-sulfinyl-1,3-dienes was constructed *via* an intramolecular Heck type vinylation reaction on simple α,β-unsaturated sulfoxides [137]. (*Z*)-2-Iodo-1,6- and 1,7-dienes **(146)** containing the 2-(*N,N*-dimethylamino)phenylsulfinyl group yielded cyclic compounds **(147)** of high enantiomeric purity (scheme 40) [138]. Owing to the availability of starting dienes in enantiomerically pure form and the development of procedures for the cleavage of the chiral auxiliary, this methodology constitutes an alternative to the enantioselective Heck reaction based upon the use of chiral ligands.

They also described the first example of the synthesis of β, β^1-disubstituted α,β-unsaturated sulfoxides by highly stereoselective Heck arylation of readily available (*E*) and (*Z*)



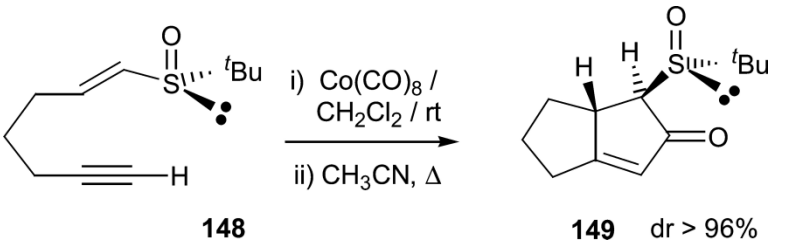
SCHEME 40

β-substituted vinyl sulfoxides [139]. Once again the authors postulated that the dimethylamino group facilitated the Heck reaction due to its capability to act as an internal ligand in the palladium-catalysed pathway. However, in their attempt to extend this methodology they observed an unusual palladium-catalysed cascade arylation of (*E*)-α,β-unsaturated phenyl sulfones [140, 141]. In the presence of excess of iodobenzene/$AgCO_3$, an intramolecular four component cascade reaction yielded 1-phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrenes in which four C–C bonds were formed in a single step. Recently, Kabalka developed a novel synthesis of β-arylvinyl phenyl sulfones *via* a Mizoroki–Heck-type reaction of boronic acids with phenyl vinyl sulfones [142].

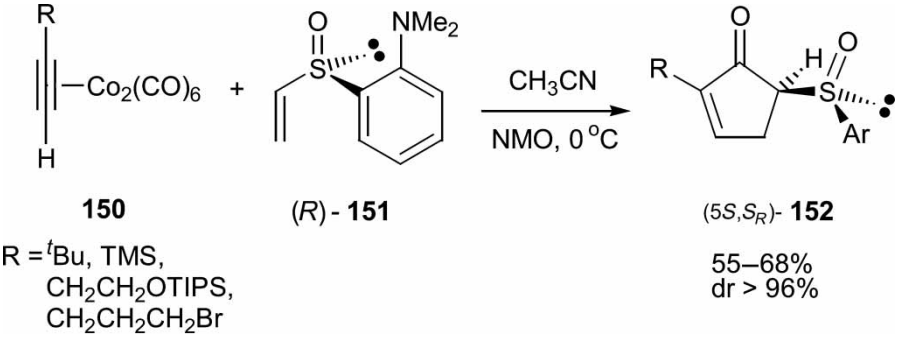
8.2 *Pauson–Khand reactions*

In the field of organic chemistry, the search for new and more efficient methods of carbon-skeleton formation for application to generate frameworks of complex molecules continues to be a fertile area of research. Over the past few decades, the Pauson–Khand reaction [143, 144], in which a cyclopentenone framework is constructed, has received great attention due to its potential application in complex molecule synthesis. Previously, it was well documented that alkenes substituted with electron-withdrawing groups were unsuitable substrates in Pauson–Khand (PK) reactions, because after the olefin-insertion step the mechanism evolves by β-H elimination rather than by carbonyl insertion, leading to conjugated dienes instead of cyclopentenones [145, 146]. However, Carretero demonstrated that the sulfinyl group can be used as a novel and efficient chiral auxiliary in an intramolecular asymmetric PK reaction of the readily available (*S*)-1-(*tert*-butylsulfinyl)hept-1-en-6-yne **148**, affording a single isomer **149** (scheme 41) [147]. The phenylsulfonyl group has also been employed in intramolecular PK reactions. Both racemic and enantiopure γ-oxygenated α,β-unsaturated sulfones underwent cyclization. Interestingly, a reversal of selectivity was observed, with the *endo* product, rather than the expected *exo* product, being obtained [148, 149]. The intramolecular PK reaction of 1-sulfinyl-1,6-enynes and 1-sulfonyl-3-oxygenated 1,6-enynes has been outlined in a recent microreview [150].

The same group also explored the ability of sulfoxide-based chiral auxiliaries in the much less thermodynamically favourable intermolecular processes. They reported the first asymmetric version of intermolecular PK reactions of acyclic alkenes [151]. Both racemic and enantiopure vinyl sulfoxides **151** reacted under very mild conditions with terminal alkynes **(150)** to yield 5-sulfinylcyclopent-2-enones **(152)**. The 2-(*N,N*-dimethylamino)phenylsulfinyl group afforded by far the most synthetically interesting results. Not only was it the most



SCHEME 41



SCHEME 42

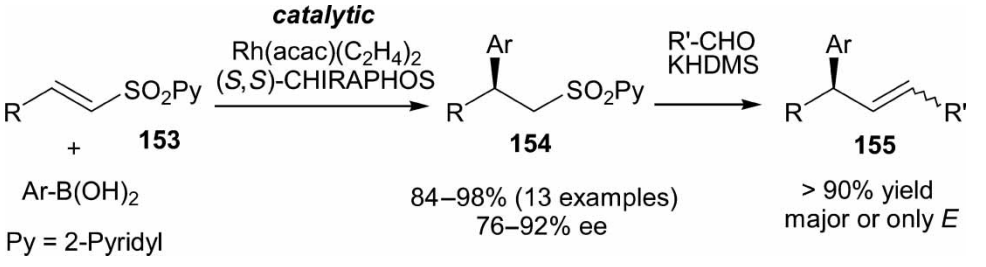
reactive alkene but also the reaction was completely regioselective and highly stereoselective (scheme 42).

A recent review outlined the Pauson–Khand reactions of alkenyl sulfoxides and alkenyl sulfones and their applications in asymmetric synthesis [152]. Another recent publication outlined applications of this methodology to the enantioselective synthesis of natural cyclopentanoids [153]. Carretero and co-workers have also developed a new version of the molybdenum-mediated PK reaction which takes place under very mild conditions and which tolerates a very broad range of 1,6- and 1,7-enyne substrates, including (*E*)-1-phenylsulfonyl-1,6-enynes [154].

8.3 *Other metal-catalysed reactions*

Carretero and Mavleón recently developed the first catalytic procedure for the enantioselective conjugate addition of carbon nucleophiles to α,β-unsaturated sulfones **(153)** [155]. The success of this Rh-catalysed addition of boronic acids relies heavily on the use of α,β-unsaturated 2-pyridyl sulfones as key rhodium-co-ordinating substrates and CHIRAPHOS as the optimal chiral ligand. This methodology has a broad scope regarding both the arylboronic acid and the sulfone substrate, affording conjugate addition products **(154)** in excellent yields and high enantioselectivities (scheme 43). The efficient elimination of the pyridylsulfonyl group by Julia–Kocienski olefination offers a new approach to the enantioselective synthesis of allylic substituted alkenes **(155)** [155].

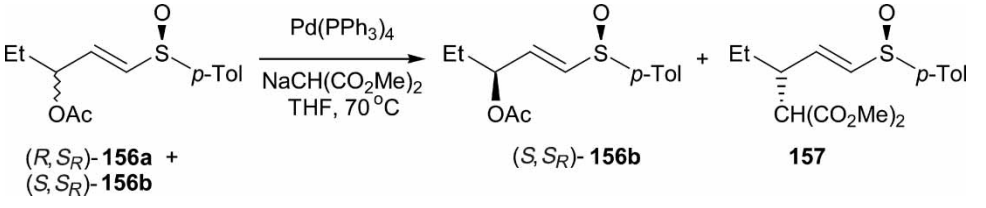
Grela and Bieniek demonstrated that vinyl sulfones readily participate in the Cross–Metathesis reaction with terminal olefins, leading to synthetically useful β-functionalized α,β-unsaturated sulfones with an excellent (*E*)-selectivity under mild conditions [156, 157]. The robust 'second generation' ruthenium complexes gave the highest yields, while the highly active Schrock catalyst was found to be incompatible with vinyl sulfones. However, both



SCHEME 43

molybdenum- and ruthenium-based complexes were found to be incompatible with vinyl sulfoxides [157].

Llera and co-workers reported the first example of palladium-mediated allylic substitutions on enantiomerically pure γ-oxygenated α,β-unsaturated sulfoxides [158]. Excellent regio- and stereo-selectivities were observed using sodium dimethyl malonate. The reactivity of these substrates was controlled by both the chiral sulfinyl group and the size of the alkyl group attached to the terminus of the allylic system. Interestingly, the presence of an (*R*)-configured chiral sulfinyl group allowed for the discrimination between allylic acetates **156a** and **156b**. Only the allylic acetate **156a**, with the (*R*)-configuration at carbon, reacted to give the substitution product **157**, whereas the allylic acetate **156b**, possessing the (*S*)-configuration at carbon, remained unaffected under these experimental conditions (scheme 44).



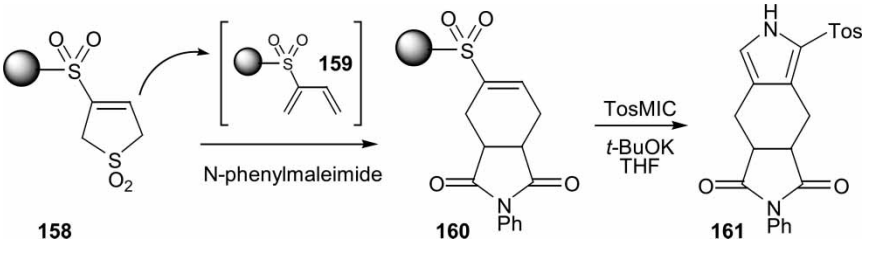
SCHEME 44

Carretero also reported the palladium-catalysed nucleophilic allylic substitution of the carbonate derivatives of γ-hydroxy-α,β-unsaturated sulfones with soft nucleophiles such as malonates, β-keto esters, 1,3-diketones, and α-sulfonyl ketones [159]. For several of these nucleophiles they observed a cascade process, *via* initial γ-regioselective allylic substitution and further intramolecular conjugate addition of the enol moiety to the α,β-unsaturated sulfone to yield 2,3,4,5-tetrasubstituted dihydrofurans [60, 159].

A new one-pot hydroaminovinylation reaction of vinyl sulfones, catalysed by a zwitterionic rhodium complex, was described by Alper and co-workers [160]. Balme and co-workers reported a novel synthesis of polysubstituted 4-(phenoxymethyl)-3-pyrrolines by a sequential one-pot coupling of three components: a propargylamine, a vinyl sulfone, and a phenol derivative [161]. This methodology is based upon the sequential integration of a Cu-catalysed cycloaddition and a Pd-catalysed allylic substitution reaction. Such 'domino' reactions are of great importance owing to their enormous potential for combinatorial applications and their economical and environmental significance. The same three-component coupling strategy was recently utilized for the synthesis of a variety of five-membered nitrogen heterocylces: pyrrolidines, pyrrolines, pyrroles, and γ-lactams [162].

9. Miscellaneous reactions of α,β-unsaturated sulfoxides and sulfones

Fuelled by a rapidly growing interest in combinatorial chemistry, solid-phase organic synthesis (SPOS) is under intensive application and research [163]. It enjoys several advantages over solution-phase synthesis: reactions can be driven to completion by the use of excess of reagent, and product isolation by simple filtration is operationally simple and time efficient. SPOS normally involves a 'linker' that connects the reactive center to an inert polymer support. Aryl vinyl sulfones have been used as a 'linker' for the SPOS of amines, such as *N*-benzyltetrahydroisoquinoline, albeit in low yields [164]. Kurth demonstrated that the polymer-bound vinyl sulfone **158** provides a versatile and useful traceless linker [165]. Thermolytic extrusion of SO_2 from **158** generated polymer-bound 2-(phenylsulfonyl)-1,3-butadiene **159** *in situ*, which underwent Diels–Alder cycloaddition with *N*-phenylmaleimide to furnish vinyl sulfone resin **160**. A specific cleavage protocol, using (*p*-tolylsulfonyl)methyl isocyanide (TosMIC), generated a heterocyclic pyrrole ring **161** with simultaneous cleavage of the sulfone linker (scheme 45).



SCHEME 45

Aversa and co-workers discovered a mild, efficient, and seemingly general method of converting vinyl sulfoxides into aldehydes or ketones [166, 167]. This iodotrimethylsilane-promoted C–S cleavage of vinyl sulfoxides, generally not easy to achieve, into the corresponding carbonyl compounds allows for numerous subsequent synthetic transformations. Block reported that α,β-unsaturated chloromethyl sulfones serve as 'prepackaged' Ramberg–Bäcklund reagents, which, following an appropriate first step such as Diels–Alder cycloaddition, react with base giving Ramberg–Bäcklund products [168]. He also reported the first example of a tandem reaction sequence incorporating an ene-reaction with Ramberg–Bäcklund elimination [168]. A review by Taylor highlighted developments in Ramberg–Bäcklund chemistry, including the epoxy-Ramberg–Bäcklund rearrangement and the tandem conjugate addition-Ramberg–Bäcklund rearrangement of vinyl sulfones [169]. Epoxy vinyl sulfoxides underwent an efficient stereoselective base-induced rearrangement to generate enantiopure hydroxy 2-sulfinyl dienes [170]. Quinuclidine-based catalysts were utilized by Aggarwal in the Baylis–Hillman reaction. Not only were the reactions more efficient and faster than previously reported, but slow-reacting substrates such as vinyl sulfones could be employed [171].

10. Summary and conclusions

The sulfinyl group has established itself as an excellent stereocontrolling element, and in many cases complete π-facial selectivity is observed. Hence, enantiomerically pure α,β-unsaturated sulfoxides have become increasingly important as Michael acceptors, dienophiles,

and dipolarophiles. In addition to the sulfinyl group being widely used as a chiral auxiliary in many classical reactions, significant advances have been made in their utilization in processes catalysed by transition metals. Recently, vinyl sulfoxides have proved to be excellent substrates in several cornerstone asymmetric metal-catalysed processes such as the Heck and Pauson–Khand reactions. In the last few years, vinyl sulfones have been shown to exhibit remarkable biomedical significance. Thus, both vinyl sulfoxides and vinyl sulfones will become increasingly important over the coming years.

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