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Sulfimides (Sulfilimines): Applications in Stereoselective Synthesis

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SULFIMIDES (SULFILIMINES): APPLICATIONS IN STEREOSELECTIVE SYNTHESIS

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Aspects of the chemistry of sulfimides (sulfilimines) which are of importance in stereoselective synthesis are reviewed. The three principal sections cover bonding and configuration, preparation of enantiomerically enriched sulfimides from chiral and achiral starting materials and applications of chiral sulfimides in stereoselective synthesis, including stereospecific conversion to other chiral sulfur compounds, stereospecific electrocyclic reactions, diastereoselective and enantioselective reactions. Parallels are drawn with related reactions of other chiral sulfur compounds.

Keywords: Enantioselective reactions; stereoselective reactions; stereospecific reactions; sulfilimines; sulfimides

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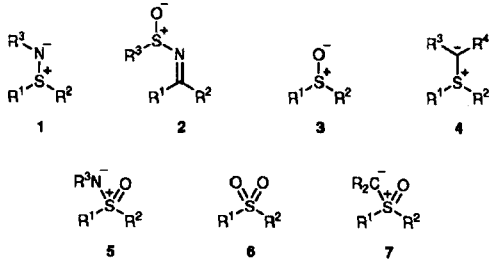
1. INTRODUCTION



Compounds of general structure **1** are usually known as either "sulfimides" (IUPAC) or "sulfilimines" (*Chemical Abstracts*), although the names "iminosulfurane", "aminosulfurane" and "sulfimine" have also been applied. At Warwick we prefer the term sulfimide, not least because of the confusing similarity between "sulfilimine" and "sulfinimine". The latter refers instead to compounds **2**. Sulfimides **1** are the nitrogen analogues of sulfoxides **3** and sulfonium ylides **4** in the same way that sulfoximides (sulfoximines) **5** are the nitrogen analogues of sulfones **6** and oxosulfonium ylides **7**. The chemistry of sulfimides has

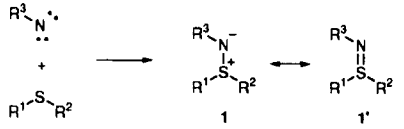
been reviewed comprehensively on a number of occasions,[1–6] most recently in 1993.[6] Therefore, it appeared inappropriate to produce a further all-embracing review of the subject. Applications of sulfimides in stereoselective synthesis have been very limited compared to those of the analogous chiral sulfoxides, sulfonium ylides and sulfoximides, on which there are useful reviews.[7] However, there has been a resurgence of interest in stereoselective reactions of sulfimides. It is thus hoped that this review will both be timely and stimulate further applications of sulfimides in stereoselective synthesis.

2. BONDING AND CONFIGURATIONAL ASPECTS

2.1. Stereochemical Consequences of the Nature of the S–N Bond

The nature of the sulfur–nitrogen bond in sulfimides has been the subject of a good deal of controversy,[3,6] which this author is not well-qualified to assess! A simple way to appreciate the problem is to approach the bonding as did Clarke *et al.* in 1927.[8] They imagined a sulfimide as being a sulfide–nitrene adduct (for the synthetic realisation of this see Section 3.3.3). Hence, one of the two sulfur lone pairs is donated to the electron deficient nitrene, leaving both heteroatoms with a full eight electron complement, a positive charge on sulfur and a negative charge on nitrogen (Scheme 1).

Although the charge-separated representation **1** is the most widely used, it is also common, as with sulfoxides etc., to draw a formal double bond, such as in **1′**, so neutralising the charges, despite the fact that, as pointed out by Oae, it is most unusual to draw a carbon–sulfur double bond when representing a sulfonium ylide **4**.[9] In fact, the sulfur has no vacant p orbitals to accept a share of the electron pair from the nitrogen, hence d orbitals would have to be used. However, there is no evidence for the existence of $p\pi$–$d\pi$ bonding in sulfimides and it has been

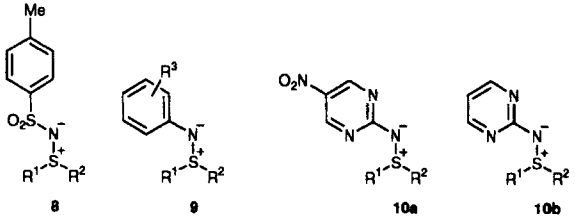


SCHEME 1

proposed that the overlap of the nitrogen p orbitals with the more diffuse sulfur d orbitals is too small to be significant.[3,6] In short, the best representation of a sulfimide is probably **1**. This certainly helps explain the fact, of relevance to this review, that no stereoisomers due to restricted rotation about the S–N bond have been reported, whereas this might have been expected if a true double bond, such as that in imines, existed. This conclusion is supported by calculations which show very low barriers to rotation about a relatively weak sulfur–nitrogen bond.[10]

2.2. Configuration at Sulfur

For a compound to be of use in stereoselective synthesis it should preferably be an isolable, reasonably stable species and it must certainly be chiral! As mentioned in Section 2.1, the negative charge on nitrogen in sulfimides **1** cannot readily be stabilised by the positive sulfur centre. Therefore, it should not be surprising that the most stable sulfimides are those bearing nitrogen substituents which are able to stabilise this negative charge.[1–6] For example, a large number of *N*-sulfonyl and *N*-acyl sulfimides have been isolated, with *N*-tosyl analogues **8** being particularly common.[1] The *N*-aryl analogues **9** are also well-known, with electron-withdrawing aryl groups providing the most stable examples.[1] This picture is supported by calculations which predict the S–N bond in the 5-nitropyrimidyl sulfimide **10a** to be longer than that in **10b**, whereas the *N*-pyrimidyl bond is predicted to be shorter.[11]



8 **9** **10a** **10b**

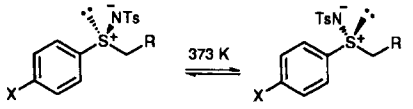
So, sulfimides with substituents which can stabilise the negative charge on nitrogen are potentially useful in synthesis, due to their excellent stability. The second criterion is that they should be chiral. In fact, most information on this point relates to *N*-tosyl sulfimides **8**, of which a good number of non-racemic examples are known (for examples of non-racemic sulfimides and their preparation see Section 3).[3,6]

1a **1b** **11a** **11b**

If groups R^1 and R^2 of sulfimide **1** are different *and remembering that the lone pair is counted as a fourth group* the sulfur atom is a centre of chirality and two enantiomers **1a** and **1b** can exist. We should recall that amines **11** meet the same criteria (if the three R groups are different), but in most amines the lone pair tunnels from one side of the nitrogen centre to the other at ambient temperature, causing inversion of configuration at nitrogen and precluding isolation of enantiomers.[12] For *N*-tosyl sulfimides this phenomenon does not occur appreciably at ambient temperatures. However, it was demonstrated that at 100 °C the enantiomerically enriched sulfimides **12** rapidly racemise, with little dependence on either the sulfur substituents or the solvent.[13] Hence, sulfimide-mediated stereoselective synthesis at elevated temperatures should be contemplated with caution. Indeed, if the ambient temperature on Earth was 100 °C, this review would be very short! It should be noted that racemisation of sulfoxide analogues at 100 °C is much slower.[13]

Following this study, the mechanism of racemisation, which is a *unimolecular* reaction, was discussed.[13] The possibility of heterolysis and recombination of C–S or N–S bonds was ruled out by the absence of both solvent polarity effects and substituent effects which would have been expected for polar intermediates. An analogous homolysis–recombination would be expected to lead to by-products which were not observed. Hence, a pyrimidal inversion mechanism was proposed, as for sulfoxides. This conclusion was also reached by Darwish and Datta, who measured a comparable rate constant for racemisation of **12** (R = H, X = Me).[14] They also ruled out a further alternative mechanism for the racemisation by demonstrating that decomposition to the sulfide and tosyl nitrene and recombination was not occurring since no cross-over products were isolated when a slightly different sulfide was added to the reaction mixture.

The effect on the configurational stability of changing the substituent on nitrogen is of importance. As noted above, increasingly electron-demanding substituents on nitrogen stabilise sulfimides in general.[1 6] Oae and Furukawa showed that, fortunately for sulfimide-mediated



12 X = Me, H, Cl; R = H, Ph

13 R = *p*-$MeOC_6H_4SO_2$, *p*-$MeC_6H_4SO_2$, $C_6H_5SO_2$, *p*-$ClC_6H_4SO_2$, ^{i}PrCO, MeCO, PhCO, CF_3CO, CH_2CH_2CN, H

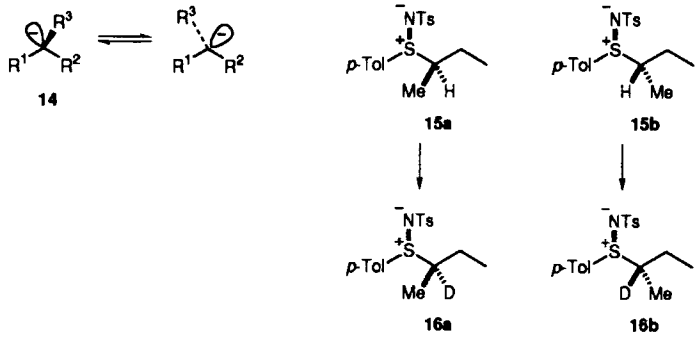
asymmetric synthesis, this increased electron demand also leads to more configurationally stable sulfimides. Hence, with sulfimides **13**, the rate of racemisation decreased through the arylsulfonyl series *p*-MeO to *p*-Cl and the trifluoroacetyl derivative was the slowest of the *N*-acyl sulfimides to racemise.[15] Menon and Darwish also obtained rate constants for the racemisation of an *N*-acetyl sulfimide.[16]

It seems that, in general, more electronegative groups on sulfur stabilise the pyrimidal ground state and hence increase configurational stability, which is why sulfoxides are more configurationally stable than even the most stabilised sulfimides. The reasons for this were discussed at length by Oae and Furukawa.[3] Increasing the electronegativity of the heteroatom will increase the s character of the sulfur lone pair orbital. Hence, the barrier to achieving the planar, sp^2 transition state for pyramidal inversion will be higher. However, the observed effect of varying the sulfur substituents cannot be rationalised in this way. Therefore, Oae and Furukawa proposed that the trend is due to increased repulsion between the lone pairs on sulfur and those on the heteroatom (one for carbon, two for nitrogen, three for oxygen), which is a simple and convincing explanation.[3]

2.3. Configuration of Sulfimidyl-stabilised Carbanions

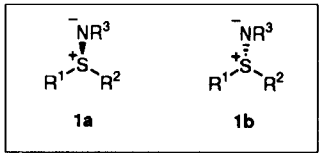
Carbanions which are stabilised by a sulfimidyl group have been employed to good effect in stereoselective syntheses (see Sections 4.2 and 4.3). It is thus important to appreciate issues regarding the configurations of such carbanions. Discussion here will be limited to the case of *N*-tosyl sulfimides.

Simple carbanions are formulated as rapidly interconverting pyramidal structures **14** (cf. Section 2.2). However carbanions stabilised by, for example, a carbonyl group are considered to be *planar*, due to conjugation with the carbon–oxygen π bond. As was discussed in Section 2.1, there is no evidence for a sulfur–nitrogen π bond.[3] Hence, stabilisation of the carbanion by a sulfimidyl group, although it undoubtedly occurs,[1–6] is not due to overlap with a π bond. Therefore, the carbanion does not need to be planar.



One investigation of this phenomenon has been published. A group from Milan prepared two diastereoisomeric sulfimides **15a** and **15b** and carried out an H–D exchange experiment with $NaOCD_3$ in CD_3OD.[17] Diastereoisomer **15a** yielded only **16a** with the same relative configuration. Isomer **15b** reacted analogously. This demonstrates that the intermediate carbanion is not planar and is reasonably stable towards pyramidal inversion, otherwise both **15a** and **15b** would have led to the same mixture of **16a** and **16b**.

2.4. Conclusion to Section 2



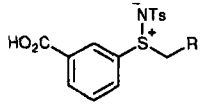
Sulfimides with two different sulfur substituents, in which the substituent on nitrogen is able to stabilise the negative charge on nitrogen,

are stable compounds which can be isolated as single enantiomers at ambient temperature, but which racemise at elevated temperatures, probably by pyramidal inversion at sulfur. It is recommended that representations **1a** and **1b** be used to denote enantiomeric sulfimides, although for convenience the lone pair may be omitted, as in the boxed structures **1a** and **1b**. An alternative representation **1′** with a sulfur–nitrogen double bond is misleading (i) in terms of what is known about the S–N bond, (ii) in that it invites consideration of isomers due to restricted rotation around the S–N bond, which are not known, and (iii) because it implies possible stabilisation of α-carbanions through a planar π system, when in fact the carbanion appears to have a degree of configurational integrity.

3. SYNTHESIS OF NON-RACEMIC SULFIMIDES

3.1. By Resolution

The first non-racemic sulfimide was reported in 1927.[8] *S*-(*m*-Carboxyphenyl) *S*-methyl *N*-tosyl sulfimide **17a** was resolved to provide both enantiomers in optically pure form. The brucine salt which recrystallised preferentially from acetone yielded, after decomposition of the salt with hydrochloric acid, the (−)-isomer with an $[\alpha]_D$ of −338°. The more soluble brucine salt was recovered from the filtrate and the chiral base was changed from brucine to cinchonidine. The new salt could be recrystallised from ethanol to optical purity and, after liberation of the free acid, the (+)-isomer was isolated, its $[\alpha]_D$ being +337°.



17 a, R = H; **b**, R = Me

The ethyl analogue **17b** of **17a** was also resolved in a similar way, in 1928.[18] It was noted that, unlike its sulfoxide analogue, the racemate and the enantiomerically pure compound have similar melting points and solubility properties, suggesting that sulfimide **17b** does not crystallise as a racemate.

Further examples of resolutions of sulfimides have been reported. The *ortho* analogue of **17a** (Compound **36** in Section 3.2) was partly resolved, but could not be recrystallised to optical purity.[19] An *N*-acetyl sulfimide was resolved *via* its dibenzoyl hydrogen tartrate salt[16] and a "free" sulfimide, that is one where the nitrogen substituent is hydrogen, was resolved using α-bromocamphorsulfonic acid.[20]

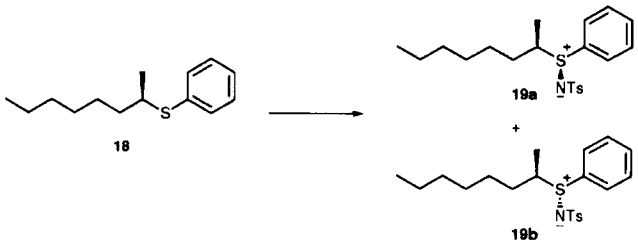
3.2. From Non-racemic Starting Materials

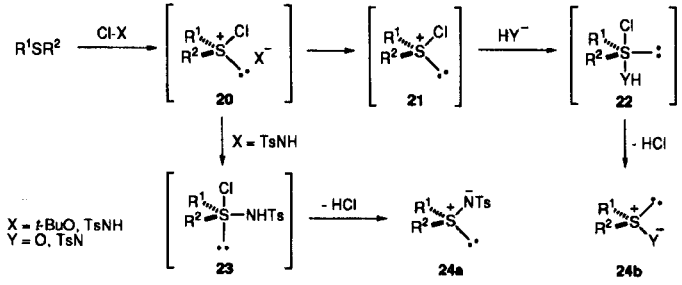
Two approaches have been used to prepare enantiomerically enriched sulfimides from non-racemic starting materials: to use a non-racemic sulfide, yielding a mixture of diastereoisomers (Section 3.2.1); to use an enantiomerically enriched chiral-at-sulfur starting material and convert it to a sulfimide through a stereospecific reaction (Section 3.2.2).

3.2.1. From Non-racemic Sulfides

In 1980 Ruff and Kucsman published a study of the conversion of an enantiomerically pure *R* sulfide **18** into sulfoxide/sulfimide mixtures using (i) *t*-BuOCl then NaNHTs and (ii) chloramine-T (TsNClNa).[21] One diastereosiomer was isolated and proposed to be R_CS_S by comparison of its ORD curves with those of a related *S* sulfimide. Intriguingly, the major diastereoisomeric sulfimide was the R_CS_S isomer **19a** with the two-step method (i) and the R_CR_S isomer **19b** when chloramine-T was used, although R_CS_S sulfoxide predominated from both methods.

The authors rationalised the differences between the two methods as shown in Scheme 2.[21] It is proposed that the diastereoselectivity is established in the initial reaction with Cl–X to give the intimate ion





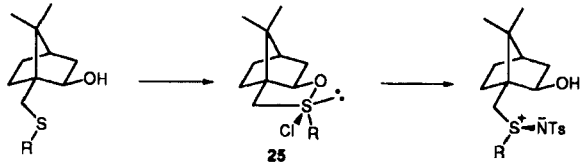
SCHEME 2

pair **20**. If this ion pair dissociates to give **21** nucleophilic displacement is predicted to proceed with the nucleophile and the leaving group in the axial positions of the trigonal–bipyramidal sulfurane intermediate **22** *leading to inversion*. Hence subsequent attack by either HO^- or $TsNH^-$ would be expected to proceed with inversion giving major diastereoisomers with the same absolute configuration at sulfur in both the sulfoxide and sulfimide case (i.e. homochiral products) (Swern's suggestion that there is a chloride-*t*-butoxide exchange when *t*-butyl hypochlorite is used[22] does not change this argument).

Ruff and Kucsman suggest that the anomalous chloramine-T case (TsNHCl is thought to be the reactive species) can be explained by the fact that the source of Cl^+ and the source of $TsNH^-$ are from the same molecule.[21] They propose that the lowest-energy route may well be rapid combination of the ion pair **20** to produce sulfurane **23** with the TsNH group in the *equatorial* position, elimination from **23** proceeding to sulfimide **24a** with *retention* of configuration (any pseudorotation of **23** would still leave an axial–equatorial relationship between nucleophile and leaving group, hence retention would still be observed).

From a synthetic point of view the diastereoselectivities from both methods were disappointing (around 20%). A better *de* (60%) was observed for the *o*-carboxyphenyl derivative using chloramine-T. This reaction is presumed to proceed with neighbouring group participation and the fact that *inversion* of configuration occurred supports this. That this kind of process can occur was demonstrated by the group of Koizumi, who isolated the unstable intermediates **25** from reaction of chiral hydroxybornyl sulfides using the hypochlorite method.

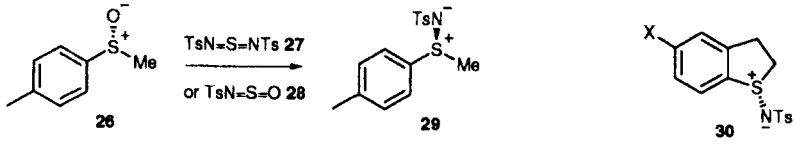
The absolute configuration of the product sulfimides was established by crystallography.[23]



3.2.2. *From Non-racemic Chiral-at-sulfur Compounds*

There are now a number of excellent methods for the preparation of enantiomerically pure sulfoxides.[7] Hence, an apparently simple approach to the preparation of enantiomerically pure sulfimides is conversion from the corresponding sulfoxides. However, the simplest methods for achieving this transformation, which generally involve an electrophilic activating agent such as triflic anhydride before addition of the nitrogen nucleophile,[1–6] are unfortunately not stereospecific. For example, enantiomerically pure methyl *p*-tolyl sulfoxide **26**, on reaction with phosphorus pentoxide and *p*-toluenesulfonamide, yielded the corresponding *N*-tosyl sulfimide of 68% enantiomeric purity, although this could be recrystallised to enantiomeric purity.[24]

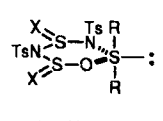
A number of activated nitrogen nucleophiles have been discovered, the reactions of which with sulfoxides are reported to be stereospecific. A classic series of papers from the Cram group describes three of these in detail.[24–26]



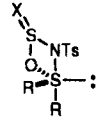
Reaction of enantiomerically pure sulfoxide **26** with *N*,*N*-ditosyl sulfur diimide **27** in pyridine led to sulfimide **29** of 96% enantiomeric purity and the use of *N*-sulfinyl-*p*-toluenesulfonamide **28** in pyridine gave a product of even higher purity. The disadvantage of these methods is that the two reagents **27** and **28** are difficult to handle and purify and that the procedure described by Cram must be followed precisely.

This second point is important, since it limits the generality of the procedure.[3] Nevertheless, a number of other enantiomerically enriched sulfimides, for example **30**, have been prepared in this manner.[25]

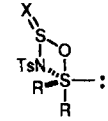
Both these reactions proceed with *inversion* of configuration. As mentioned above, this usually results from the nucleophile and the leaving group both being axial in the intermediate sulfurane. However, this is not consistent with the fact that the reaction is second order in **27** or **28** (i.e. two equivalents are involved in the rate determining step) but that only one equivalent of reagent is needed (i.e. one equivalent must be regenerated in the rate determining step). This led Cram to propose an unusual mechanism, proceeding via **31** in which both the nucleophile and the leaving group are equatorial.[24] In benzene this model is clearly not applicable, as *retention* of stereochemistry is observed.[25]



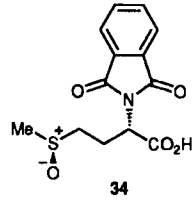
31, X = O, NTs



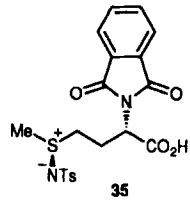
32, X = O, NTs



33, X = O, NTs



34



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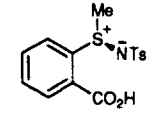


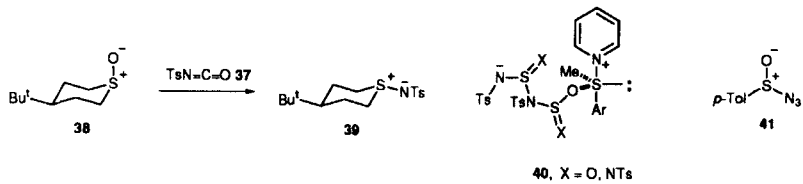
36

Indeed, both Christensen[27] and Cram[25] have proposed a four-membered transition state for the reaction in benzene with the nucleophile and the leaving group being either axial and equatorial **32** or equatorial and axial **33**, both of which predict retention of configuration. Christensen showed that this was also true for *tert*-butyl methyl sulfimide.[27]

There are also examples of sulfoxide to sulfimide conversions proceeding with retention of configuration *in pyridine*, but these invariably turn out to involve neighbouring group participation and the mechanism is probably a double inversion leading to apparent retention. Hence, the methionine derivative **34** was shown by the

Christensen group to give the homochiral sulfimide **35**[28] and another carboxy sulfimide **36** was also prepared from the homochiral sulfoxide analogue.[19,29]

In dichloromethane, the situation becomes even more complicated! Cram proposed that this was probably due to its ability to *partially* stabilise polar intermediates.[25] Hence, for practical purposes, either a nucleophilic solvent such as pyridine (which normally gives inversion) or a non-polar solvent such as benzene (for retention) should be used. The third TsN=X reagent to be considered is the isocyanate **37**, which was used, as well as TsNSO, by Johnson and Rigau to transform the *cis*-sulfoxide **38** into the *trans*-sulfimide **39**.[30] Cram's group later applied this reagent to enantiomerically enriched sulfoxide **26** and found that no reaction occurred in pyridine.[26] In acetonitrile the reaction did proceed, but was not stereospecific. However, on the addition of *tert*-butyl methyl sulfide, an essentially stereospecific reaction was observed. These observations are consistent with the comments on solvent above, acetonitrile giving a parallel result to dichloromethane and the sulfide perhaps playing the same mechanistic role as the pyridine. Indeed, Kwart and King proposed a solution to Cram's equatorial–equatorial dilemma (intermediate **31**), by proposing a mechanism including instead intermediate **40**.[31]



An alternative procedure employs *p*-toluenesulfinyl azide **41**. This reaction presumably involves a nitrene and is believed to pass through a four-membered intermediate which, as for TsNSO in benzene, must lead to the observed *retention* of configuration.[32] While this procedure appears to be quite general, it is not stereospecific and the reagent is not a convenient one.

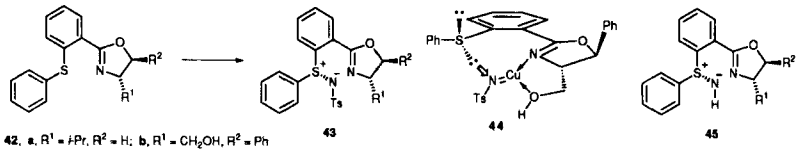
3.3. From Achiral Starting Materials

The preparation of enantiomerically enriched sulfimides from achiral starting materials requires some kind of asymmetric synthesis. This

could involve a chiral auxiliary or template (Section 3.3.1), a chiral reagent (Section 3.3.2) or a chiral catalyst (Section 3.3.3).

3.3.1. Use of a Chiral Auxiliary or Template

Very recently, Takada and Uemura reported the first steps in an auxiliary-based approach to asymmetric synthesis of chiral sulfimides.[33] Diaryl sulfides, such as **42a** and **42b**, bearing chiral auxiliaries, were subjected to nitrene transfer sulfimidation conditions (see Section 3.3.3).[34] Interestingly, the diastereoselectivities were much better (< 91% vs. < 40%) for the hydroxymethyl substituted compound **42b**. That this was not due to the phenyl group was demonstrated by making ethers of **42b**; the *de*'s were much lower. This led the authors to propose a nitrenoid intermediate **44** involving coordination from this hydroxy group.

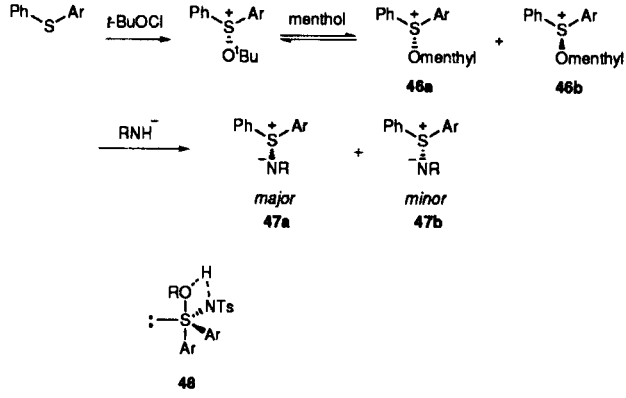


42, a, R^1 = *i*-Pr, R^2 = H; b, R^1 = CH_2OH, R^2 = Ph **43** **44** **45**

The product tosyl sulfimides **43** can be hydrolysed to the free sulfimide analogues **45** but it remains to be seen whether the auxiliary can be cleaved from any of these compounds to complete the asymmetric synthesis. Other applications of these products are described in Section 4.3.3.

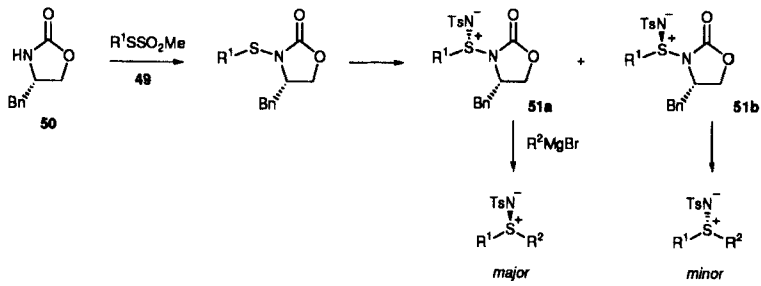
For many years the principal method for asymmetric synthesis of sulfimides was that developed by Oae, Furukawa and coworkers.[35] A range of *N*-sulfonyl, -acyl and -aryl *S*,*S*-diaryl sulfimides were prepared by a modification of the classic *tert*-butyl hypochlorite method. Before adding the amide nucleophile, menthol was added. Presumably, the menthol displaces the *tert*-butanol to form an equilibrium mixture of two diastereoisomeric oxysulfonium salts **46**, of which the major isomer **46a** was deduced to be R_S. Displacement by the amide nucleophile is thought to proceed stereospecifically with inversion to yield predominantly the *S* sulfimide, as determined by comparison of CD data with those of the analogous sulfoxides.[35] The *ee*'s for these reactions were not high (around 30%), but with *S*-*o*-methoxyphenyl substituted

compounds, recrystallisation to optical purity was practical. Importantly, enantiomerically pure material from this procedure can be used to seed saturated benzene solutions of the racemate, permitting crystallisation of enantiomerically pure **47a** (Ar = *o*-$MeOC_6H_4$, R = Ts) on a large scale.[36]



In a later paper, the same authors reported the apparently strange result that with strongly electron-withdrawing acyl groups on nitrogen (e.g. trifluoroacetyl), the sulfimide was formed with *retention* of configuration.[37] Having read Section 3.2, we should immediately expect a four-membered intermediate which forces the axial–equatorial relationship of entering and leaving groups. Indeed, Oae and Furukawa tentatively proposed the four-membered hydrogen bonded **48** intermediate in this case.

The Milan group has very recently published a method for the preparation of *S*-methyl *N*-tosyl sulfimides of high enantiomeric purity (Scheme 3).[38] Firstly, a sulfenyl sulfone **49** is used to attach the sulfenyl fragment to an oxazolidinone chiral template **50**. Reaction of the product with chloramine-T yields two diastereoisomeric sulfimidyl oxazolidinones **51a** and **51b** with poor diastereoselectivity, this being the main disadvantage of the procedure. After separation, the final step involves displacement of the chiral group by a Grignard reagent to produce the enantiomerically enriched sulfimide. A wide range of nucleophiles can be employed (Table I). Apart from one example of an *isopropyl* sulfimide, all the products are *S*-methyl sulfimides. However this is not a great drawback as non-racemic *S*-methyl sulfimides have



SCHEME 3

TABLE I Yields and *ee*'s for sulfimides in Scheme 3

Entry	R^1	R^2	*Yield*, %	*ee*, %
1	Me	Ph	91	94
2	Me	Ph	72	81
3	Me	*p*-Tol	89	87
4	Me	2-naphthyl	75	98
5	Me	Bn	86	84
6	Me	Vinyl	89	98
7	Me	cyclohexyl	85	98
8	Me	*i*-Pr	80	85
9	Me	*t*-Bu	0	—
10	*i*-Pr	Ph	39	96

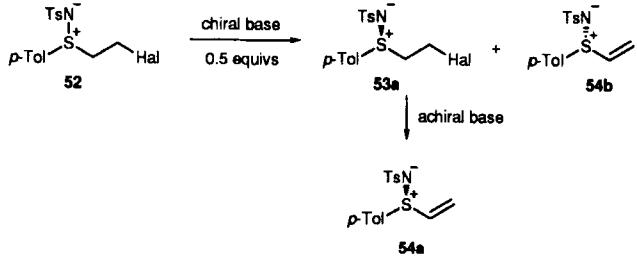
considerable potential in asymmetric synthesis (see Section 4.3.3) and are not yet accessible via Oae's method (above) or the asymmetric sulfimidation procedure (see Section 3.3.3).

3.3.2. Use of a Chiral Reagent

It was reported in 1981 that chiral vinyl sulfimides could be obtained in enantiomerically enriched form by a kinetic resolution procedure using readily available enantiomerically pure bases as chiral reagents.[39] β-Halo sulfimides **52** were treated with 0.5 equivalents of the chiral base which induced elimination of HHal, this occurring preferentially from one enantiomer. The product vinyl sulfimides **54b** were of up to 50% *ee* and the unreacted halo compounds **53a** were of up to 73% *ee*. Unreacted **53a** could be converted to the enantiomeric vinyl sulfimides **54a** by reaction with an achiral base.

Quinidine was the most effective chiral base and the chlorides the best substrates. Strangely the sense of asymmetric induction changed on

switching from chloro or bromo to fluoro. The authors point out that a *syn* rather than *anti* elimination in the fluoro case would explain this result. As with any kinetic resolution procedure, low yields and purification problems are inherent.



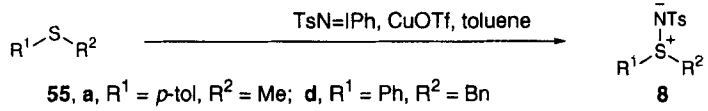
As nitrogen transfer from an oxaziridine to a sulfide has recently been demonstrated[40] and as oxaziridines are highly successful chiral oxidising agents[41] it is possible that chiral oxaziridines could find a role in asymmetric synthesis of sulfimides, but this remains to be realised.

3.3.3. Use of a Chiral Catalyst

The group of Uemura was the first to communicate a catalytic asymmetric synthesis of sulfimides.[42] The method, which was developed independently by the groups of Uemura and of Taylor but published jointly,[34] is closely related to the asymmetric aziridination procedure reported by Evans.[43] Interestingly the Jacobsen asymmetric aziridination conditions[44] are not effective for asymmetric sulfimidation.

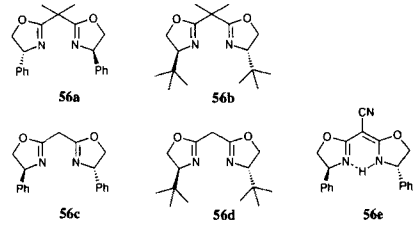
Using TsN = IPh as the reagent and 5–10 mol-% of the catalyst derived from copper(I) triflate (CuOTf) and a bis(oxazoline) ligand **56**, the reactions proceeded smoothly to give the expected sulfimides in 56–80% yield. As can be seen in Table II, asymmetric induction occurred, but the nature of the sulfide **55**, the solvent and the chiral ligand **56** all had significant effects on the enantioselectivity. Asymmetric induction was poor in acetonitrile with all of the bis(oxazoline) ligands (less than 22% *ee*), but the change of the solvent from acetonitrile to toluene led to good enantioselectivities. The highest *ee*'s were observed with **55d** (65% *ee*) using **56a** as the chiral ligand in toluene (entry 2). As to the effectiveness of ligands, **56a** gave the best result

TABLE II Asymmetric sulfimidation: effect at ligands and solvent



55, **a**, R^1 = *p*-tol, R^2 = Me; **d**, R^1 = Ph, R^2 = Bn — **8**

Entry	*Substrate*	*Chiral ligand*	*Solvent*	*Product*	*ee*, %
1	**55a**	**56a**	Toluene	**8a**	16
2	**55d**	**56a**	Toluene	**8d**	65
3	**55d**	**56b**	Toluene	**8d**	34
4	**55d**	**56c**	Toluene	**8d**	< 5
5	**55d**	**56d**	Toluene	**8d**	< 5
6	**55d**	**56e**	Toluene	**8d**	55
7	**55d**	**56a**	MeCN	**8d**	12



followed by **56e** and then **56b**, **56c** and **56d** (entries 2, 6, 3, 4 and 5) in the imidation of **55d** with TsN=IPh in toluene.

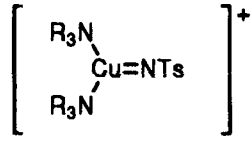
The optimum conditions for asymmetric sulfimidation were judged to be copper(I) triflate with chiral ligand **56a** in toluene at 25 °C for 48 h. Interestingly, using these conditions, a higher enantioselectivity was generally obtained in the cases of diaryl sulfides than those of alkyl aryl sulfides and dialkyl sulfides (Table III). The highest enantioselectivity (71% *ee*) was obtained with the sulfide **55h**. The absolute configuration of the product (+)-methyl *p*-tolyl sulfimide **8a** was assigned as *R*.[34] All other sulfimides were (+), but their configuration is not known.

Regarding the different ligands **56a** to **56e**, all of C_2 symmetry, which were employed, it is interesting to compare the very similar **56a** and **56c** and also **56b** and **56d**. In all cases, the *gem*-dimethyl compounds **56a** and **56b** gave higher *ee*'s than their methylene analogues. Considering this *gem*-dimethyl effect alongside the observation that two large groups are required for high *ee* led to the following hypothesis. If, by analogy with

TABLE III Asymmetric sulfimidation with ligand **56a** in toluene

Entry	*Substrate*	R^1	R^2	*Product*	*Yield*, %	*ee*, %
1	**55a**	Tol	Me	**8a**	82	13
2	**55b**	Ph	Me	**8b**	78	<10
3	**55c**	Ph	*i*-Pr	**8c**	44	23
4	**55d**	Ph	Bn	**8d**	78	64
5	**55e**	4-MeOC $_6H_4$	Bn	**8e**	72	<10
6	**55f**	2-$NO_2C_6H_4$	Bn	**8f**	54	<10
7	**55g**	Ph	4-$NO_2C_6H_4CH_2$	**8g**	37	25
8	**55h**	1-naphthyl	Bn	**8h**	75	71
9	**55i**	$PhCH_2CH_2$	Bn	**8j**	63	22
10	**55k**	Et	Me	**8k**	36	<10
11	**55l**	EtO_2CCH_2	Me	**8l**	41	<10
12	**55m**	Bn	Me	**8m**	70	15

Jacobsen's work[45] the reaction proceeds *via* intermediates **57**, to gain maximum asymmetric induction it is important that the sulfide approaches the complex in such a way that its substituents interact with the substituents on the oxazolidine (phenyl or *tert*-butyl). The bulky *gem*-dimethyl moiety in **56a** and **56b** will help to direct the sulfide into such an orientation and this directing effect will be most marked with sulfides bearing two bulky substituents.



57

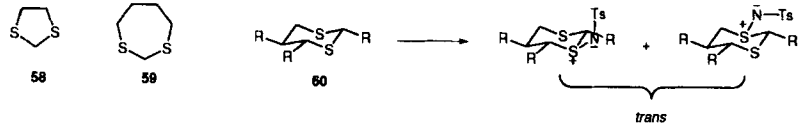
This hypothesis is not consistent with the 55% *ee* observed for the sulfimidation of benzyl phenyl sulfide with **56e**, which does not have a *gem*-dimethyl bridging group. An explanation more consistent with this result is that the approach of the sulfide to the nitrene complex may be favoured from the side where a $\pi-\pi$ interaction between the aryl group of the substrate and the phenyl group of chiral ligand **56a** can occur. Although this model is not consistent with all the observations either, the authors showed that it does predict the observed *R* configuration for **8a**.

The group of Taylor has recently shown how chloramine-T can be exploited as a nitrene source, even though it usually undergoes ionic reactions with sulfides and other substrates.[46] However, the *ee*'s with

chloramine T in the asymmetric sulfimidation reaction were *much lower in all cases*.[34] The hypothesis that the sodium chloride by-product was responsible for this effect was tested by repeating the TsN=IPh reactions in the presence of 5 mol-% sodium chloride. The yields and reaction times were very similar to those for the salt-free reactions, but there was a drastic decrease in *ee* (e.g. 64% to < 10% for benzyl phenyl sulfide **55d**).

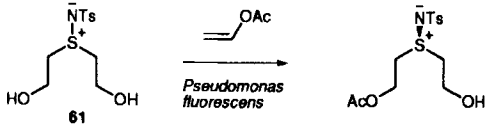
Copper(I) catalysed sulfimidation occurs in a very wide range of solvents. However, acetonitrile is the solvent of choice for racemic sulfimidations with TsN=IPh,[34] but is detrimental to asymmetric sulfimidations, where toluene is preferred. The simplest explanation for these phenomena is that for efficient copper-nitrenoid formation additional nitrogen ligands are required.[46] In the racemic reactions this role is fulfilled by acetonitrile, whereas in the asymmetric reactions it is the chiral ligand which is coordinated to copper. In the latter case, any acetonitrile present will compete for the ligand sites on copper, leading to lower *ee*'s.

Very recently, the asymmetric sulfimidation reaction has been extended by the Uemura group to cyclic dithioacetals.[47] With the five-membered 1,3-dithiolane **58**, low yields and *ee*'s were found and with the seven-membered 1,3-dithiepane **59** no reaction occurred, but with 1,3-dithianes **60**, yields were good.



With unsubstituted 1,3-dithiane the enantioselectivities were rather low, but interesting results were obtained for 2-, 4- and 5-substituted analogues. In these cases high diastereoselectivities, in favour of the *trans* products, were reported and the enantioselectivities improved. The best *ee* was observed for the 2-methyl compound and, unexpectedly, increasing the size of the 2-substituent led to lower *ee*'s. However, the authors pointed out that subtle conformational effects complicate rationalisation of stereoselectivities with these substrates.

It should be noted that a closely related catalytic asymmetric selenimidation procedure has recently been discovered. Again, the highest *ee*'s were observed for selenides with two large, aryl-type substituents, but the enantioselectivities are much lower than with the sulfur analogues.[48]



Finally, one example of an enantioselective synthesis of a sulfimide using a biocatalyst has recently been discovered.[49] The achiral sulfimide **61** was selectively acylated, using *Pseudomonas fluorescens* as catalyst, in 80% *ee*. The product could be crystallised to high enantiomeric purity.

3.4. Conclusion to Section 3

For the preparation of large amounts of enantiomerically pure sulfimides, resolutions (Section 3.1) and the Oae/Furukawa seeding method (Section 3.3.1) are the most practical, the latter being confined to diaryl sulfimides. There is still no experimentally simple method for the conversion of non-racemic sulfoxides to the corresponding sulfimides, hence the Milan oxazolidinone method (Section 3.3.1) provides a welcome, but untested, new route to small amounts of enantiomerically pure methyl sulfimides. The asymmetric sulfimidation reaction (Section 3.3.3) has the potential to deliver a wide range of non-racemic sulfimides cheaply on a reasonable scale, but further optimisation is required.

4. STEREOSELECTIVE SYNTHESIS USING SULFIMIDES

4.1. Stereospecific Reactions

Two classes of stereospecific reaction will be considered: stereospecific transformation to other chiral-at-sulfur compounds (Section 4.1.1); stereospecific electrocyclic reactions (Section 4.2.2).

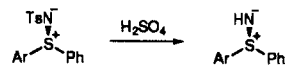
4.1.1. Preparation of Other Chiral-at-sulfur Compounds

One of the potentially very useful characteristics of chiral sulfimides is that they are readily converted to (i) other chiral sulfimides, (ii) chiral sulfoxides and (iii) chiral sulfoximides (sulfoximines).

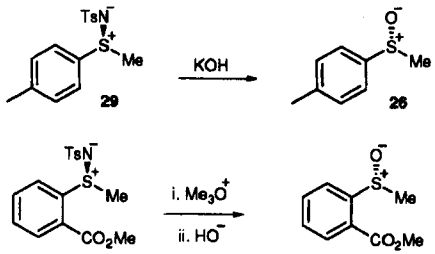
The group of Oae reported that non-racemic chiral *N*-tosyl diaryl sulfimides could be hydrolysed to the corresponding "free" sulfimides using concentrated sulfuric acid, with no loss of configurational integrity (Scheme 4).[35] A very recent example of this reaction, from the Uemura group, was mentioned in Section 3.3.1. The non-racemic free sulfimides are versatile chiral intermediates, since they are readily acylated or alkylated to yield a range of other non-racemic sulfimides.[35]

Hydrolysis of sulfimides does not generally proceed to the free sulfimide, however, but to the corresponding sulfoxide. With acidic conditions this usually leads to some or total loss of configuration.[24] Stereospecific acid hydrolysis with apparent *retention* of configuration, presumably due to neighbouring group participation from the carboxylate, can occur.[21] Stereospecific hydrolysis can be achieved under basic conditions. For example, Cram's group used methanolic potassium hydroxide to achieve clean inversion in the hydrolysis of **29** to **26**.[24] A perhaps more reliable two-step method of achieving the same transformation was reported by the group of Johnson[30] and was demonstrated to be useful for non-racemic chiral sulfimides by Bohman and Allenmark (Scheme 5).[29]

Oxidation of sulfimides to sulfoximides (sulfoximines) has routinely been achieved using peroxides, peracids or potassium permanganate.[1–6] The reaction is widely believed to proceed with *retention* of configuration in all cases. For example, Kresze's group oxidised resolved sulfimide **17a** (see Section 3.1),[50] Cram's group showed

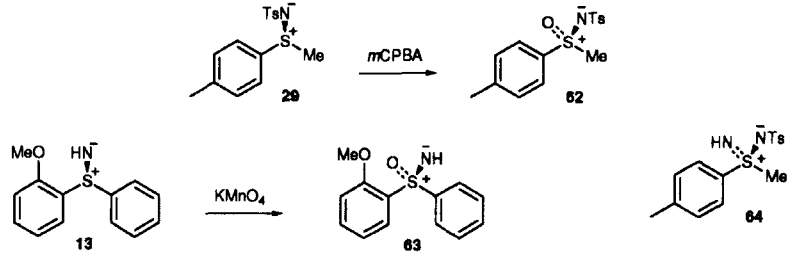


SCHEME 4



SCHEME 5

that sulfimide **29** was oxidised stereospecifically to sulfoximide **62** by *m*-chloroperbenzoic acid[24] and Oae's group used permanganate to stereospecifically oxidise a free sulfimide **13** to the corresponding free sulfoximide **63**.[35] More recently, the Milan group have demonstrated that dimethyldioxirane is a complementary *electrophilic* oxidising agent for sulfimides.[51] Once again, using non-racemic material, it was shown that the reaction is stereospecific with retention of configuration.

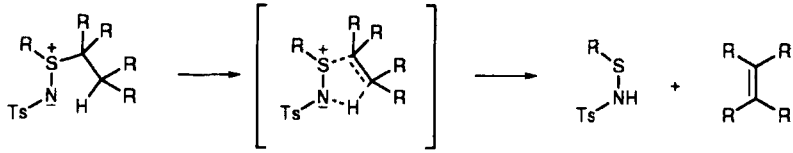


There is one example of conversion of a free sulfimide to a non-racemic sulfodiimide **64**.[20]

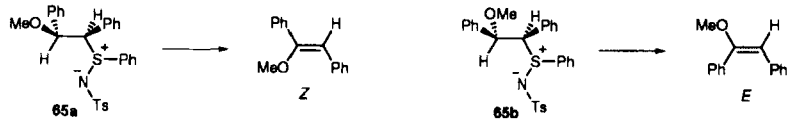
4.1.2. Electrocyclic Reactions

Two different classes of electrocyclic reactions of sulfimides have synthetic utility, *syn*-eliminations and [2,3] sigmatropic rearrangements.

In a series of papers, the group of Oae and Furukawa reported kinetic results and kinetic isotope effects which were consistent with the β-elimination reaction of sulfimides being a unimolecular concerted process (Scheme 6).[52] They proceeded to show that the process was



SCHEME 6



stereospecific by preparing the diastereoisomeric sulfimides **65a** and **65b** (each of a single but unknown configuration at sulfur).[53] On thermolysis at 80 °C compounds **65** gave exclusively *syn* elimination products, namely the *Z* and *E* alkenes, respectively. The small amount of *E* contaminant in the *Z* product was accounted for by epimerisation at sulfur and the kinetic data for racemisation discussed in Section 2.2 are consistent with this. In a later publication, the same group proved that even some examples of β-elimination which at first sight appeared good candidates to be exceptions to the above rule exhibited substituent, kinetic isotope and solvent effects which are entirely consistent with the concerted *syn* mechanism.[54] The data approach ideal for the E_i mechanism when there is a substituent which acidifies the β-hydrogen.[55]

Hence, β-elimination from sulfimides, which occurs with a range of *N*-sulfonyl, -alkoxycarbonyl and -acyl analogues,[3] should be considered as a useful tool for stereoselective synthesis. The rates of the reactions and diastereoselectivities are in general higher than for the corresponding sulfoxides.[3]

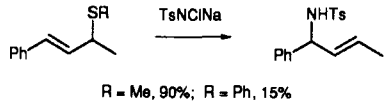
Allylic sulfimides have long been known to rapidly isomerise "with inversion" (Scheme 7);[56] this reaction was first classified as a [2,3] sigmatropic rearrangement by Baldwin and coworkers in 1968.[57] Since then, a number of further studies of the reaction have been reported, including the analogous rearrangement of free sulfimides.[58] The fact that similar results are observed when "nitrenes" react with allylic sulfides is good evidence for the existence of the proposed allyl sulfimide intermediate.[59]

Given the extremely facile preparation and one-pot rearrangement of allylic sulfimides, there are a great deal of potential applications in synthesis, although the stereospecificity of this rearrangement has not been proved.[60] Indeed, in 1992, the reaction was used by a group from SmithKline Beecham in the preparation of enantiomerically enriched tabtoxinine β-lactam, a potent irreversible inhibitor of glutamine synthase.[60] Cleverly, this group realised that a chiral allyl sulfide is a masked chiral amino acid.

SCHEME 7

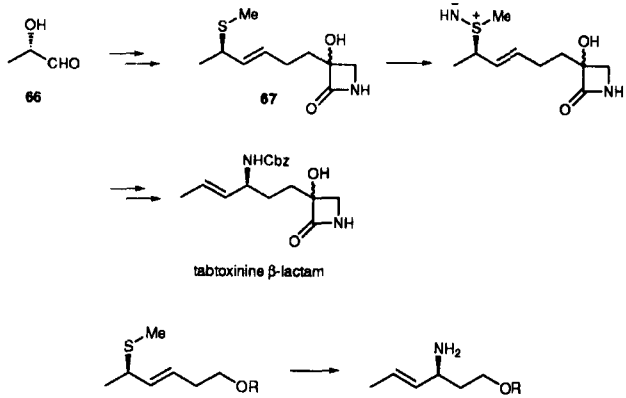
In model studies this group found that *methyl* sulfides were particularly good substrates for the reaction (Scheme 8); this group is lost during the synthesis so its nature is not otherwise important. Hence, enantiomerically pure lactaldehyde **66** was converted to methyl sulfide **67**. On treatment with *O*-(mesitylenesulfonyl)hydroxylamine (MSH), which produces a "free" sulfimide,[58] the [2,3] sigmatropic rearrangement proceeded as expected and the unstable amine product was protected *in situ*. Importantly a mixture of stereoisomers resulted (85% *de* in favour of the desired product). This suggested that the rearrangement may not in fact be stereospecific and, indeed, a model reaction (Scheme 9) gave a similar result, proceeding in around 80% *ee*. However, nothing is known about the diastereoselectivity of the sulfimidation, which makes analysis difficult.

The scope of the allylic rearrangement of sulfimides has been further extended by the introduction, by the group of Uemura,[34,42] of a catalytic asymmetric version. Using the same copper catalyst and nitrene source as in the catalytic asymmetric sulfimidation reaction (Section 3.3.3), non-racemic allylic sulfimides were generated *in situ*



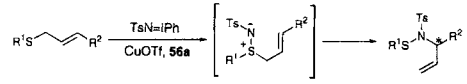
R = Me, 90%; R = Ph, 15%

SCHEME 8

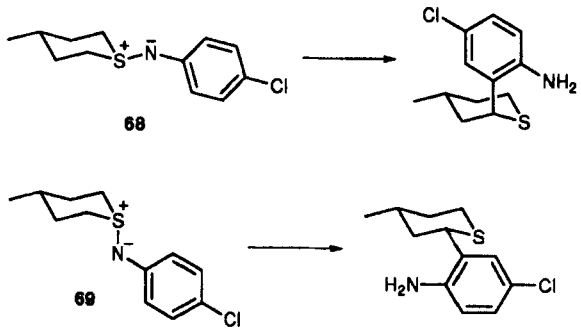


SCHEME 9

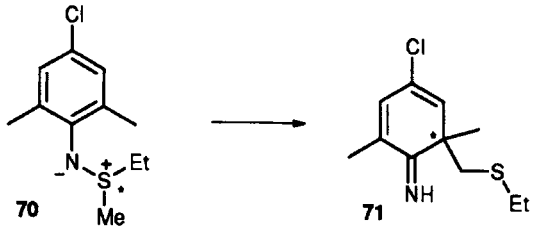
TABLE IV Catalytic asymmetric imidation of allylic sulfides



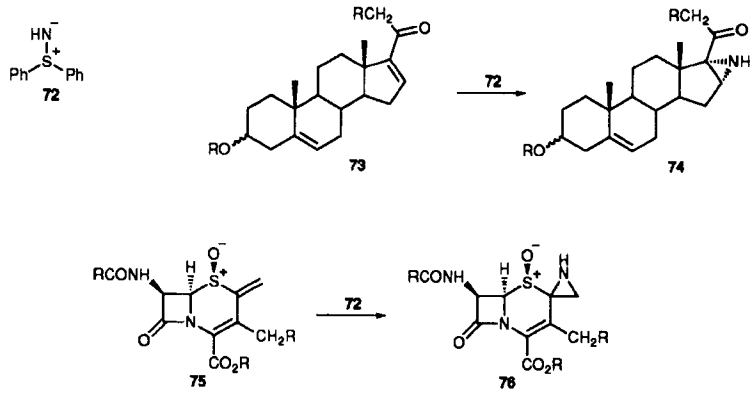
Entry	R^1	R^2	*Yield*, %	*ee*, %
1	Ph	Ph	40	27
2	2-$NO_2C_6H_4$	Ph	37	43
3	1-naphthyl	Ph	80	58
4	Ph	Me	30	25
5	1-naphthyl	Me	35	50



SCHEME 10



which rearranged to the corresponding allyl sulfenamides in 25–58% *ee* (Table IV). As with the asymmetric sulfimidation reaction, the best results were obtained with two aryl or with aryl alkyl substituents. Clearly some optimisation is required, but this reaction, which converts readily available achiral allylic sulfides into non-racemic masked amines, has great potential.

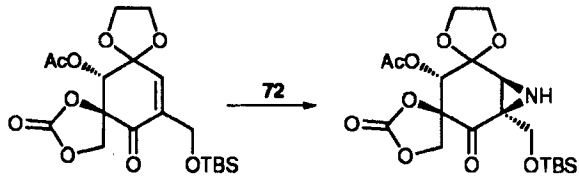


One other kind of sigmatropic rearrangement of sulfimides which is well known is the Sommelet–Hauser-like rearrangement of some *N*-aryl sulfimides.[1 6] This reaction was shown by the group of Klaus to be stereospecific.[61,62] For example, the equatorial sulfimide **68** gave only the axial product and vice versa with the axial isomer **69** (Scheme 10).[61] Also, the non-racemic sulfimide **70** led to the chiral product **71** which was determined to be optically active.[3] However, this interesting reaction has yet to find applications in stereoselective synthesis.

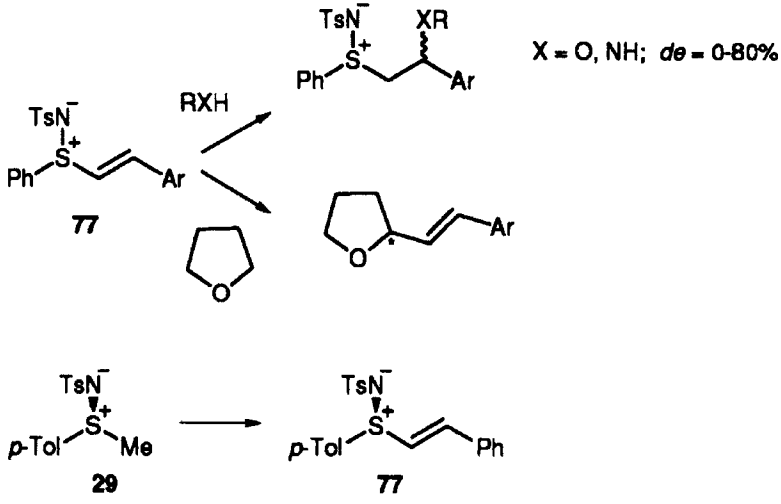
4.2. Diastereoselective Reactions

In developments of earlier reports, various groups have described the use of the "free" sulfimide **72** to aziridinate conjugated alkenes. Hence steroid **73** was transformed into aziridine **74**,[63] the cephalosporin **75** was converted to the spiro aziridine **76** (the configuration of the product was not given)[64] and the Nicolaou group used the reaction in Scheme 11 in an attempted total synthesis of esperamicinone.[65] In all three cases, the diastereoselectivity appears to be very high, essentially yielding just one isomer of the product. An enantioselective version of this reaction is described in Section 4.3.

Additions to chiral vinyl sulfimides have been investigated by the group of Taylor. Simple 1,4-additions of alcohols and amines to alkenes **77** proceeded with some diastereoselectivity.[66] However, very large excesses of nucleophile were needed for good yields, which limits the utility of this reaction.

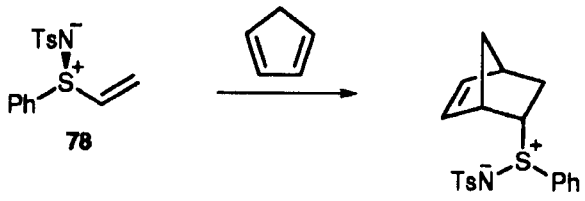


SCHEME 11



Clark and Taylor have shown that radicals also add to sulfimides **77**, but in these reactions the sulfimidyl group is eliminated.[67] It is not yet known if this addition is stereoselective, though in principle using enantiomerically enriched **77** could lead to non-racemic products. This could be tested, since Taylor's group has found that the synthesis of vinyl sulfimide **77** from non-racemic **29** proceeds without loss of configuration.[66]

Cycloadditions to vinyl sulfimides are also possible. Hence, the reaction of **78** with cyclopentadiene catalysed by Et_2AlCl proceeded with 74% *endo* selectivity.[66] Furthermore, one *endo* diastereoisomer was favoured over the other with a *de* of 88%, but the relative stereochemistry around the carbon–sulfur bond in the major product has not yet been determined.

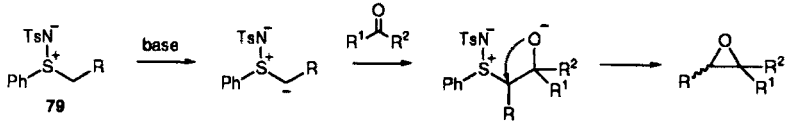


Sulfimidyl-stabilised carbanions have a great deal of potential in stereoselective synthesis (see Section 2.3 for discussion of the structure of these carbanions). The groups of Tamura and of Johnson showed in the 1970s that sulfimides **79** could be deprotonated and reacted with carbonyl compounds to yield epoxides (Scheme 12).[68,69]

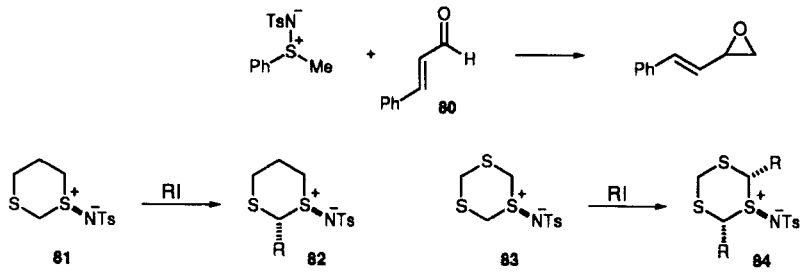
When R is not H, the products are 1,2-disubstituted epoxides with two centres of chirality. The Tamura group demonstrated that good diastereoselectivity was possible. With sodium hydride in DMSO *de*'s of up to 50% were observed in favour of the *cis* product. Intriguingly, on using sodium hydride in THF; much higher *de*'s were observed (around 80% for a large range of R groups) with the *trans* product predominating. Although the Johnson group's conditions, namely butyllithium in THF, led to higher yields, the diastereoselectivities were inferior.

Johnson showed that the additions of the sulfimidyl-stabilised carbanions were essentially irreversible, since reaction with the α,β-unsaturated aldehyde **80** yielded the epoxide rather than the thermodynamically favoured cyclopropane product (which is observed with sulfoximides but not sulfonium ylides).[69] Sulfimides **79** with R = H also led to epoxides, but clearly no stereoselectivity was possible, though these results paved the way for enantioselective epoxide synthesis (see Section 4.3). One example of a reaction with an imine to yield an aziridine was also reported.

Given the success of dithiane mono- and dioxides as auxiliaries for asymmetric synthesis,[70] the group of Taylor investigated the



SCHEME 12

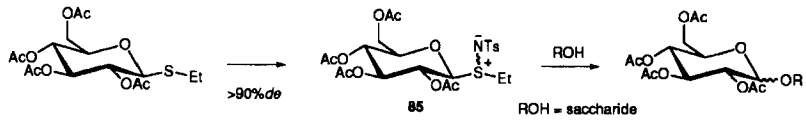


corresponding chemistry of the sulfimides **81** and **83**.[71] Racemic material was used to determine the scope of the chemistry and the diastereoselectivities of the reactions.

The sodium salt of the dithiane imide **81** was successfully alkylated by alkyl iodides in DMF. The reactions were reasonably diastereoselective, the *anti* products **82** predominating in all cases. However, alkylation of **81** was successful only under these conditions. With other bases (alkyllithiums, LDA or NaHMDS), solvents, or alkyl halides (chlorides or bromides) the reactions failed. More importantly, **81** did not react cleanly with prochiral electrophiles such as aldehydes or ketones, nor with esters or bifunctional alkyl iodides ICH_2Z ($Z = COCl$, CO_2H, $SiMe_3$). In all these cases complex mixtures of products were observed, except with sterically demanding bases, when the starting material was recovered unchanged.

It was proposed that the unidentified by-products were due to elimination reactions leading to fragmentation of the heterocycle or to nucleophilic interception of the anion of **81**. The trithiane imide **83** was thus employed. Since it has no β-protons, at least the first of these pathways is blocked. Indeed, reactions of the sodium salt of trithiane imide **83** with sodium hydride and alkyl iodides appeared to proceed much more cleanly. However, the product mixture contained mainly the dialkylated *meso* compounds **84**, which result from alkylation at both acidic α-sites, which are of no use in asymmetric synthesis. The expected *anti*, *anti* relative stereochemistry of **84** ($R = Me$) was confirmed by a single crystal X-ray diffraction study.[72]

Some very recent work has shown that sulfimides have potential in stereoselective oligosaccharide synthesis. Rollin's group treated readily available thioglycosides with chloramine-T to obtain the sulfimides **85**.[73] For many of these reactions, almost complete diastereoselection



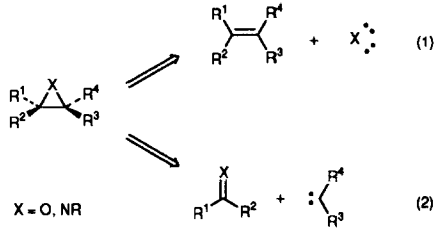
resulted. Reaction of **85** with various donors led to disaccharides in excellent yields. Interestingly, the ratio of α to β product was dependent on the solvent. Hence, ether and dichloromethane exhibit an α preference with 0–60% *de* whereas in acetonitrile the β product is preferred (10–60% *de*).

4.3. Enantioselective Reactions

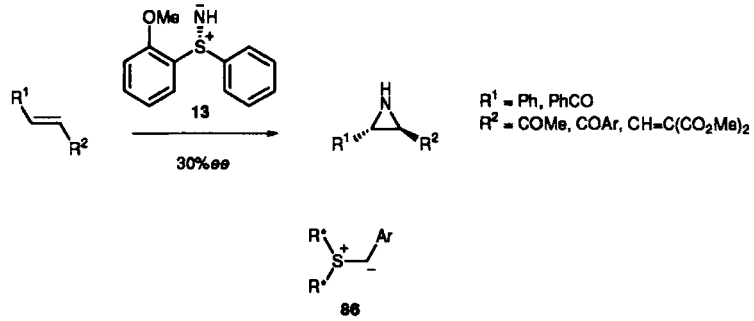
Asymmetric synthesis of epoxides and aziridines continues to attract a great deal of attention. The enantioselective methods can be classified retrosynthetically into two very different classes. Disconnections both to an alkene or to a carbon–heteroatom double bond and an alkylidene fragment are conceivable (Scheme 13). The synthetic procedures corresponding to disconnection (1) are known as asymmetric epoxidations and asymmetric aziridinations and, especially in the case of epoxidation, a great deal of progress has been made in achieving high enantioselectivities for a wide range of substrates.[74] The process corresponding to the disconnection (2) could be described as an "asymmetric alkylidene transfer" reaction.

In fact, free sulfimides can be used to achieve asymmetric aziridinations. Reaction of enantiomerically pure **13**, prepared as described in Section 3.3.2, with a number of conjugated alkenes gave 50–96% yields of aziridines in around 30% *ee*.[36]

Asymmetric alkylidene transfer reactions are, in principle, more synthetically attractive than asymmetric epoxidations for the synthesis



SCHEME 13

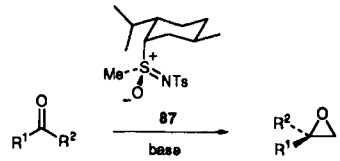


of non-racemic epoxides since both the relative and absolute configurations are established in one step. This is not a trivial point, since the synthesis of alkenes of defined configuration for enantioselective epoxidation is not always straightforward.[75] Dai and Aggarwal, whose groups have both reported important advances in catalytic asymmetric alkylidene transfer, using ylides of chiral sulfides **86** have recently reviewed the area.[7]

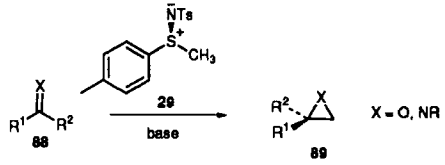
Despite the successes described above, the symmetric synthesis of monosubstituted and 2,2-disubstituted epoxides remains very challenging.[76] Typically, asymmetric epoxidations give low *ee*'s for these targets. Although Solladié-Cavallo has reported excellent enantioselectivities for asymmetric alkylidene transfer to formaldehyde,[77] this method has the drawback that a different chiral sulfonium ylide must be prepared for each given target, reducing the generality of the method.

A more promising approach would appear to be asymmetric methylidene transfer to carbonyl compounds, but *ee*'s with methylidene sulfides have improved little since Trost's original report of 0% *ee* for the process in 1973![78] Sulfoximides have been used as asymmetric methylidene transfer agents, yielding epoxides with moderate *ee*'s. Chiral sulfoximide-stabilised anions were first employed by Johnson in 1973.[79] More recently, analogues derived from neomenthol and from camphor were studied by the group of Soman.[80] The best results were observed with the sulfoximide **87** which reacted with aromatic aldehydes and ketones in 56–86% *ee* (Scheme 14).

Asymmetric synthesis of aziridines by alkylidene transfer was first reported by Aggarwal's group in 1996, with very high *ee*'s for *trans* 2,3-diaryl products.[81] Dai and coworkers have also made a recent



SCHEME 14



SCHEME 15

important contribution to this area.[82] However, we are aware of only one report of asymmetric methylidene transfer to imines.[79] Johnson reported the synthesis of 1,2-diphenylaziridine using a chiral sulfoximide in around 25% *ee*.

The purpose of this preamble is to highlight the significance of the fact that the sulfimide **29** (prepared as described in Section 3.2.2 from commercially available (*R*)-methyl *p*-tolyl sulfoxide) can be used as an asymmetric methylidenation reagent.[83] Before attempting the asymmetric methylidene transfer reactions Taylor's group reinvestigated the work from the groups of Tamura and of Johnson (Section 4.2).[68,69] Sodium hydride in THF was reported to give reasonable yields and high diastereoselectivities, but Taylor's group found that the yields were rather variable. However, when inverse addition was used the reaction only failed with the highly conjugated or sterically hindered examples **88f** and **88g** (Table V). Likewise, with DMSO as solvent good yields of aziridines were obtained.

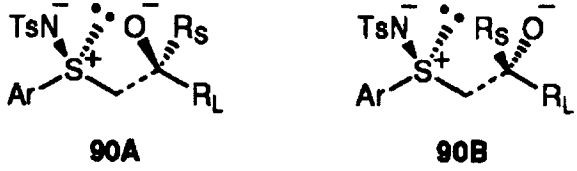
The *ee*'s for asymmetric methylidene transfer, as discussed above, are usually very low. Hence, the enantioselectivities using sulfimide **29** and a representative range of carbonyl compounds and imines (Scheme 15) listed in Table V are significant, though somewhat inferior to those of the Soman group using sulfoximides.[80] Since, with both the sulfimide and sulfoximide reagents, the chirality of the sulfur reagents is lost, the

TABLE V Reaction conditions, yields and *ee*'s for epoxides and aziridines **89**

89	R^1	R^2	X	T/°C	t/h	*Yield* (%)	*ee* (%)	$[\alpha]_D$ (589 nm)
a	Ph	H	O	−5	24	63	70	+31° (26 °C, benzene)
b	Ph	Me	O	20	160	60	45	+31° (26 °C, acetone)
c	Cyclohexyl	H	O	20	160	62	a	+37° (26 °C, acetone)
d	$PhCH_2CH_2$	Me	O	66	140	64	21	+8.3° (29 °C, acetone)
e	(*E*)-PhCH=CH	H	O	20	90	62	42	+11° (29 °C, acetone)
f	(*E*)-PhCH=CH	Ph	O	—	—	0	—	—
g	*t*-Bu	Me	O	—	—	0	—	—
h	Ph	H	NPh	25	12	79	38	−20° (26 °C, acetone)
j	Ph	H	$NC_6H_4Cl_4$	25	8	73	18	−23° (26 °C, acetone)

[a] *ee* not determined.

fact that **29** is synthetically much more accessible is important. One difference between the reactions of sulfimide- and sulfoximide-stabilised anions is that, as described in Section 4.2, sulfimide additions to enones are irreversible and always give the kinetically favoured epoxide product; with aryl sulfoximides the thermodynamically more stable cyclopropane product is found.[69] Hence, sulfimides appear to be the reagents of choice for targets such as **89e**. The *ee*'s of the aziridine products are lower, though the yields are higher. Nevertheless, the enantioselectivities do compare favourably with the one previous example of asymmetric methylidene transfer to an imine.[79]

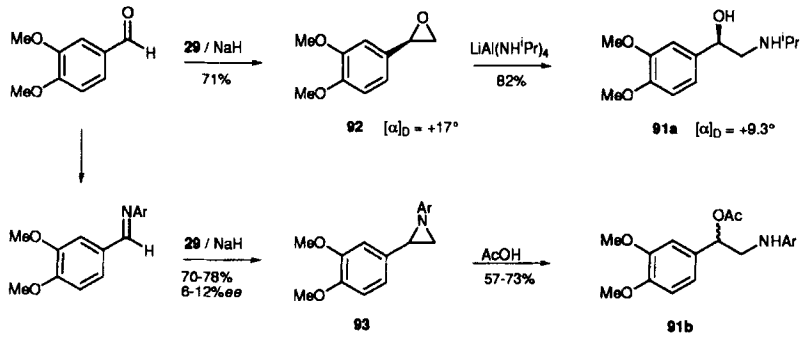


90A **90B**

R_S = small group, R_L = large group

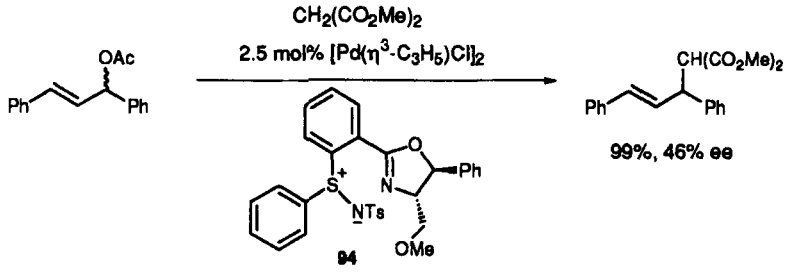
The predictable sense of the asymmetric induction for the epoxides was rationalised by means of an open-chain model, similar to one proposed by Pearson for the reaction of a sulfoximide analogue,[84] which is appropriate in the case of a sodium counterion. The model assumes that the largest groups in both the sulfimide and the carbonyl component will prefer an *anti*periplanar relationship with respect

to the newly forming chain, i.e. Ar *anti*periplanar to the forming carbon–carbon bond and R_L *anti*periplanar to the CH_2–S bond. This assumption generates two transition states **90A** and **90B**. It is proposed that the unfavourable electrostatic interaction between the highly negatively charged oxygen and nitrogen centres in **A** will lead to a preference for **B** in all cases. Increasing the size of the small group R_S will raise the energy of **B** more than the energy of **A**, as in **B** there are unfavourable steric interactions between R_S and TsN. The model thus predicts that (*S*)-sulfimide **29** will lead to (*R*)-epoxide **89** and that the enantiomeric excess will increase as the size of group R_S decreases, as observed.



Finally, the authors demonstrated the synthetic utility of their approach by preparing the more highly-functionalised targets **91**, which are analogues of β-adrenoreceptor agonists. Proceeding via the epoxide intermediate **92** and employing Solladié-Cavallo's regioselective epoxide-opening method,[85] they were able to synthesise enantiomerically enriched **91a**, but the *ee* was not reported. An alternative path was to proceed via the aziridine **93**. With *N*-aryl imines, good yields of aziridines **93b,c** resulted, though *ee*'s were very low. Unsurprisingly, the regioselective conversion of **93** to the targets **91b** using acetic acid led to racemic products.

Sulfimides have not yet found many applications as chiral catalysts. However, the enantiomerically pure sulfimide **94** (see Section 3.2) has been used as a chiral ligand for palladium in an asymmetric allylic substitution reaction. The reaction proceeded in high yield with an *ee* of 46%.[33]



4.4 Conclusion to Section 4

There are a number of stereospecific reactions of sulfimides which deserve more attention in synthesis: the facile stereospecific conversion to sulfoximides could be more widely used to prepare non-racemic sulfoximides; the stereospecific *syn* elimination procedure should find more applications in alkene synthesis and the [2,3] sigmatropic rearrangement of allylic sulfimides, which can be carried out enantioselectively, merits further investigation.

Aziridination by free diaryl sulfimides has been demonstrated to be useful synthetically when good diastereoselectivity is required, although enantioselectivities are less interesting. The diastereoselectivities and enantioselectivities for the synthesis of epoxides and aziridines by alkylidene transfer to carbonyl compounds and imines require optimisation, but these reactions could be synthetically very useful.

Other diastereoselective reactions monitored by sulfimides have produced somewhat disappointing results, with the exception of one promising example of a Diels–Alder reaction and the important new method for oligosaccharide synthesis.

5. CONCLUSION

Sulfimide-mediated stereoselective synthesis is currently an area offering exciting opportunities. As outlined in Section 3, obtaining enantiomerically enriched sulfimides is no longer difficult, although there is plenty of scope for developing new methods and optimising the current ones.

Sulfimides clearly have potential in stereoselective synthesis. Stereospecific oxidation to sulfoximides, *syn* elimination reactions and [2,3] sigmatropic rearrangements offer reliable relays of stereochemical information and deserve more widespread applications in synthesis, as does the highly diastereoselective aziridination of conjugated alkenes with diphenyl sulfimide. The use of sulfimides in oligosaccharide synthesis may also prove to be important.

Finally, the potential of sulfimides in enantioselective reactions ("asymmetric synthesis") remains to be realised. Given the very small number of contributions in this area, the results so far are promising. Interesting enantioselective syntheses of epoxides and aziridines and an asymmetric version of the allyl sulfimide rearrangement have been reported and it has been demonstrated that a sulfimide can act as a chiral ligand.

It is not immediately apparent why sulfimides have attracted less attention than other classes of chiral sulfur compounds in the last two decades. This review will have achieved its goal if it encourages its readers to redress the balance!

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