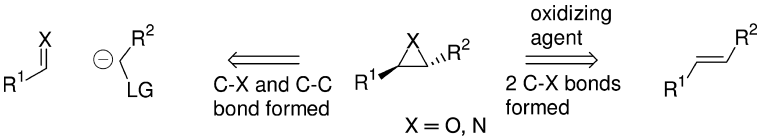
1
Asymmetric Synthesis of Epoxides and Aziridines from Aldehydes and Imines

Varinder K. Aggarwal, D. Michael Badine, and Vijayalakshmi A. Moorthie

1.1
Introduction

Epoxides and aziridines are strained three-membered heterocycles. Their synthetic utility lies in the fact that they can be ring-opened with a broad range of nucleophiles with high or often complete stereoselectivity and regioselectivity and that 1,2-difunctional ring-opened products represent common motifs in many organic molecules of interest. As a result of their importance in synthesis, the preparation of epoxides and aziridines has been of considerable interest and many methods have been developed to date. Most use alkenes as precursors, these subsequently being oxidized. An alternative and complementary approach utilizes aldehydes and imines. Advantages with this approach are: *i*) that potentially hazardous oxidizing agents are not required, and *ii*) that both C–X and C–C bonds are formed, rather than just C–X bonds (Scheme 1.1).



Scheme 1.1

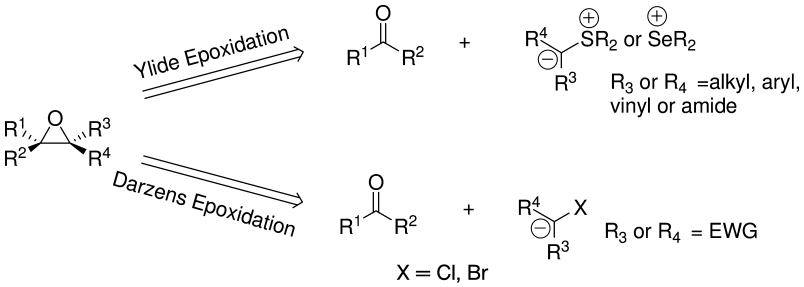
This review summarizes the best asymmetric methods for preparing epoxides and aziridines from aldehydes (or ketones) and imines.

1.2
Asymmetric Epoxidation of Carbonyl Compounds

There have been two general approaches to the direct asymmetric epoxidation of carbonyl-containing compounds (Scheme 1.2): ylide-mediated epoxidation for the construction of aryl and vinyl epoxides, and α-halo enolate epoxidation (Darzens reaction) for the construction of epoxy esters, acids, amides, and sulfones.

Aziridines and Epoxides in Organic Synthesis. Andrei K. Yudin

ISBN: 3-527-31213-7



Scheme 1.2

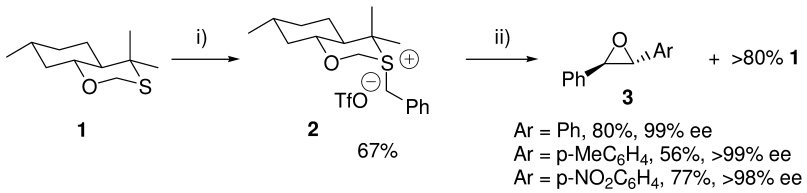
1.2.1
Aryl, Vinyl, and Alkyl Epoxides

1.2.1.1 Stoichiometric Ylide-mediated Epoxidation

Solladié-Cavallo's group used Eliel's oxathiane **1** (derived from pulegone) in asymmetric epoxidation (Scheme 1.3) [1]. This sulfide was initially benzylated to form a single diastereomer of the sulfonium salt **2**. Epoxidation was then carried out at low temperature with the aid of sodium hydride to furnish diaryl epoxides **3** with high enantioselectivities, and with recovery of the chiral sulfide **1**.

Using a phosphazene (EtP_2) base, they also synthesized aryl-vinyl epoxides **6a-c** (Table 1.1) [2]. The use of this base resulted in rapid ylide formation and efficient epoxidation reactions, although it is an expensive reagent. There is potential for cyclopropanation of the alkene when sulfur ylides are treated with α,β-unsaturated aldehydes, but the major products were the epoxides, and high selectivities could be achieved (Entries 1–4). Additionally, heteroaromatic aryl-epoxides could be prepared with high selectivities by this procedure (Entries 5 and 6) [3]. Although high selectivities have been achieved, it should be noted that only one of the two enantiomers of **1** is readily available.

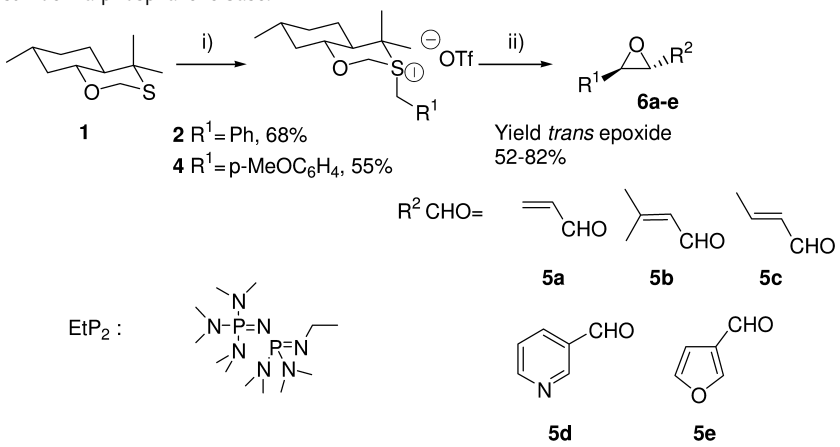
The Aggarwal group has used chiral sulfide **7**, derived from camphorsulfonyl chloride, in asymmetric epoxidation [4]. Firstly, they preformed the salt **8** from either the bromide or the alcohol, and then formed the ylide in the presence of a range of carbonyl compounds. This process proved effective for the synthesis of aryl-aryl, aryl-heteroaryl, aryl-alkyl, and aryl-vinyl epoxides (Table 1.2, Entries 1–5).



i) BnOH, Tf_2O, pyridine, CH_2Cl_2, -10 °C; ii) NaH, CH_2Cl_2, ArCHO, -40 °C, 24 - 48 h.

Scheme 1.3

Table 1.1 Synthesis of aryl-vinyl epoxides by use of chiral sulfide **1** a phosphazene base.



i) BnOH, Tf_2O, pyridine, CH_2Cl_2, -10 °C; ii) EtP_2, **5a-e** (R^2CHO), -78 °C, CH_2Cl_2.

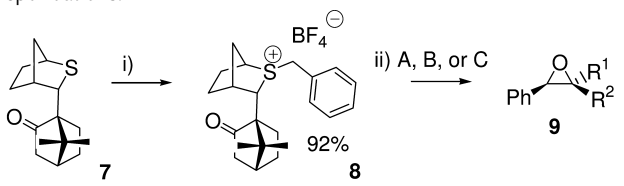
Entry	R^1 (ylide)	R^2CHO	Epoxide: epoxycyclop.: cyclop.	Epoxide *trans: cis*	Epoxide *ee trans* (*cis*) (%)
1	Ph	**5a**	77:11:12	100:0	97
2	*p*-$MeOC_6H_4$	**5a**	100:0:0	77:23	95 (98)
3	Ph	**5b**	100:0:0	97:3	100
4	Ph	**5c**	100:0:0	97:3	100
5	Ph	**5d**	–	100:0	96.8
6	Ph	**5e**	–	100:0	99.8

Until this work, the reactions between the benzyl sulfonium ylide and ketones to give trisubstituted epoxides had not previously been used in asymmetric sulfur ylide-mediated epoxidation. It was found that good selectivities were obtained with cyclic ketones (Entry 6), but lower diastereo- and enantioselectivities resulted with acyclic ketones (Entries 7 and 8), which still remain challenging substrates for sulfur ylide-mediated epoxidation. In addition they showed that aryl-vinyl epoxides could also be synthesized with the aid of α,β-unsaturated sulfonium salts **10a-b** (Scheme 1.4).

1.2.1.2 **Catalytic Ylide-mediated Epoxidation**

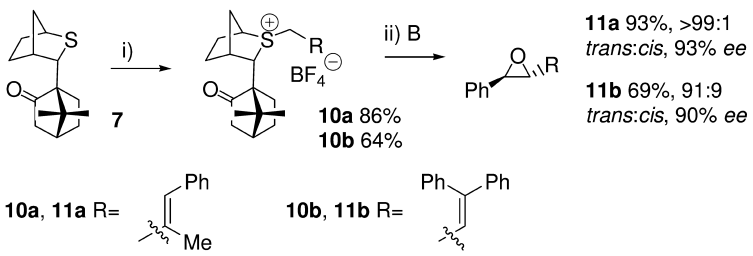
The first attempt at a catalytic asymmetric sulfur ylide epoxidation was by Furukawa's group [5]. The catalytic cycle was formed by initial alkylation of a sulfide (**14**), followed by deprotonation of the sulfonium salt **15** to form an ylide **16** and

Table 1.2 Application of the chiral sulfide **7** in asymmetric epoxidations.



i) BnBr, $AgBF_4$, CH_2Cl_2; ii) **A**: KOH, R^1R^2CO, MeCN:H_2O (9:1), rt ; **B**: EtP_2 R_1R_2CO, CH_2Cl_2, -78 °C; **C**: KHMDS, THF, -78 °C.

Entry	R^1COR^2	Method	Yield (%)	d. r. *trans* : *cis*	*ee* trans (%)
1	PhCOH	A	75	98:2	98
2	2-PyrCOH	B	88	98:2	99
3	C_4H_9COH	C	87	90:10	>99
4	CH_2=C(Me)COH	B	52	>99:1	95
5	(*E*)-MeCH=CH_2COH	B	90	>99:1	95
6	cyclohexanone	B	85	–	92
7	$MeCOC_6H_4$-p-NO_2	B	73	>1:99	71
8	MeCOPh	B	77	33:67	93 (50)

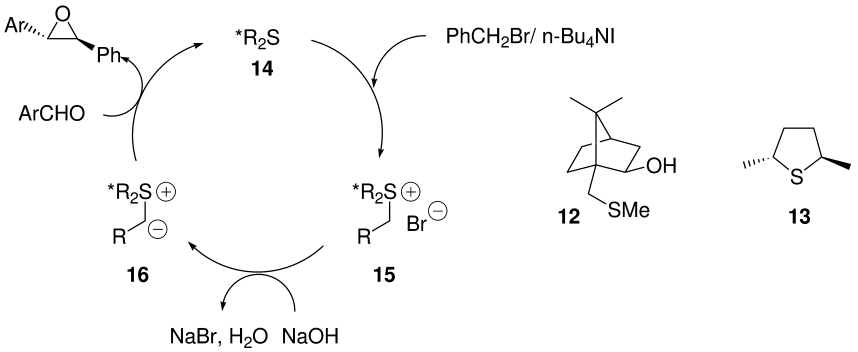


i) RCH_2OH, HBF_4, Et_2O; ii) **B**: EtP_2, PhCHO, CH_2Cl_2, -78 °C.

Scheme 1.4

subsequent reaction with an aldehyde to furnish the epoxide with return of the sulfide **12** (Scheme 1.5). However, only low yields and selectivities resulted when the camphor-derived sulfide **12** was employed. Metzner improved the selectivity of this process by using the C_2 symmetric sulfide **13** [6].

Although reactions required 2 days to reach completion in the presence of stoichiometric amounts of sulfide, they became impracticably long (28 days) when 10 % sulfide was employed, due to the slow alkylation step. The alkylation step was

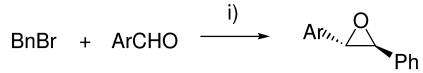


Scheme 1.5

accelerated upon addition of iodide salts, however, and the reaction times were reduced (Table 1.3). The yields and selectivities are lower than for the corresponding stoichiometric reactions (compare Entry 1 with 2, Entry 4 with 5, and Entry 6 with 7). The use of iodide salts proved to be incompatible with allylic halides, and so stoichiometric amounts of sulfide were required to achieve good yields with these substrates [7].

Metzner et al. also prepared the selenium analogue **17** of their C_2 symmetric chiral sulfide and tested it in epoxidation reactions (Scheme 1.6) [8]. Although good enantioselectivities were observed, and a catalytic reaction was possible without the use of iodide salts, the low diastereoselectivities obtained prevent it from being synthetically useful.

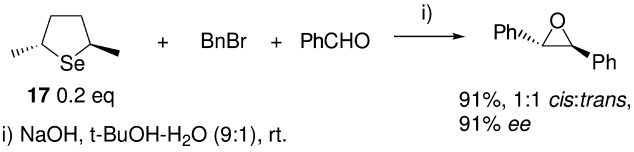
Table 1.3 Catalytic ylide-mediated epoxidations.



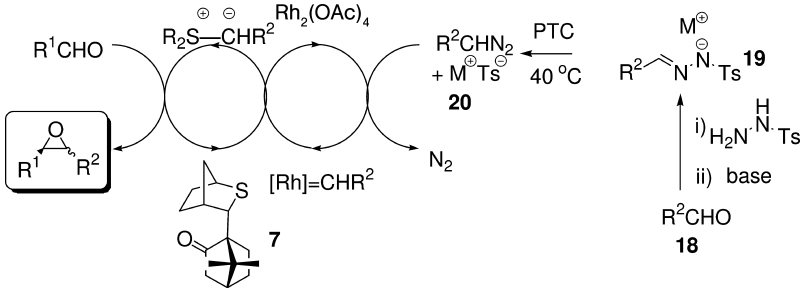
i) NaOH,n-Bu_4NI, **13**, t-BuOH-H_2O (9:1), rt.

Entry	Ar in ArCHO	Eq. 13	Time (days)	Yield (%)	d.r.	*ee* (%)
1	PhCHO	1[a]	1	92	93:7	88
2	PhCHO	0.1	4	82	93:7	85
3	*p*-ClC_6H_4	0.1	6	77	80	72
4	cinnamyl	1[a]	2	93	98:2	87
5	cinnamyl	0.1	6	60	89:11	69
6	2-thiophenyl	1[a]	4	90	91:9	89
7	2-thiophenyl	0.1	6	75	88:12	80

[a] Without *n*-Bu_4NI.



Scheme 1.6



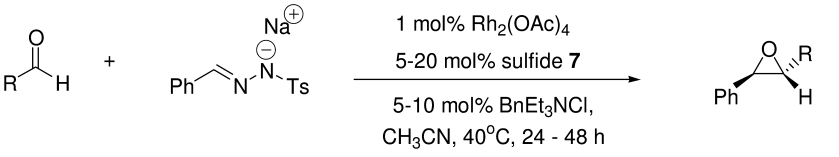
Scheme 1.7

Aggarwal and co-workers have developed a catalytic cycle for asymmetric epoxidation (Scheme 1.7) [9]. In this cycle, the sulfur ylide is generated through the reaction between chiral sulfide **7** and a metallocarbene. The metallocarbene is generated by the decomposition of a diazo compound **20**, which can in turn be generated *in situ* from the tosylhydrazone salt **19** by warming in the presence of phase-transfer catalyst (to aid passage of the insoluble salt **19** into the liquid phase). The tosylhydrazone salt can also be generated *in situ* from the corresponding aldehyde **18** and tosylhydrazine in the presence of base.

This process thus enables the coupling of two different aldehydes together to produce epoxides in high enantio- and diastereoselectivities. A range of aldehydes have been used in this process with phenyl tosylhydrazone salt **19** (Table 1.4) [10]. Good selectivities were observed with aromatic and heteroaromatic aldehydes (Entries 1 and 2). Pyridyl aldehydes proved to be incompatible with this process, presumably due to the presence of a nucleophilic nitrogen atom, which can compete with the sulfide for the metallocarbene to form a pyridinium ylide. Aliphatic aldehydes gave moderate yields and moderate to high diastereoselectivities (Entries 3 and 4). Hindered aliphatic aldehydes such as pivaldehyde were not successful substrates and did not yield any epoxide. Although some α,β-unsaturated aldehydes could be employed to give epoxides with high diastereo- and enantioselectivities, cinnamaldehyde was the only substrate also to give high yields (Entry 5). Sulfide loadings as low as 5 mol% could be used in many cases.

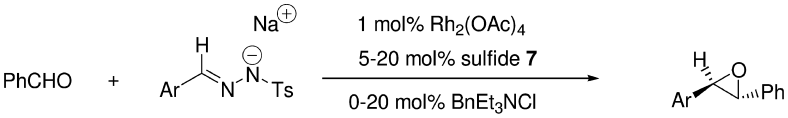
Benzaldehyde was also treated with a range of tosylhydrazone salts (Table 1.5). Good selectivities were generally observed with electron-rich aromatic salts (Entries 1–3), except in the furyl case (Entry 7). Low yields of epoxide occurred when a hindered substrate such as the mesityl tosylhydrazone salt was used.

Table 1.4 Tosylhydrazone salt **19** in catalytic asymmetric epoxidation.



Entry	Aldehyde	Sulfide equiv.	*t* (h)	Yield (%)	*trans*:*cis*	*ee trans* (*cis*) (%)
1	benzaldehyde	0.05	48	82	>98:2	94
2	3-furaldehyde	0.05	48	77	>98:2	92
3	valeraldehyde	0.2	48	46	75:25	89
4	cyclohexanecarboxaldehyde	0.05	48	58	88:12	90 (74)
5	*trans*-cinnamaldehyde	0.05	48	70	>98:2	87
6	3-methyl-2-butenal	0.2	24	21	>98:2	87

Table 1.5 Use of a range of tosylhydrazone salts in catalytic asymmetric epoxidation of benzaldehyde.



Entry	Ar	Solvent	t (°C)	(mol%) 7	Yield	*trans*:*cis*	*ee* (%) *trans* (*cis*)
1	*p*-MeC_6H_4	CH_3CN	40	5	74	95:5	93
2	*p*-$MeOC_6H_4$	CH_3CN	30	20	95	80:20	93
3	*o*-$MeOC_6H_4$	CH_3CN	30	5	70	>98:2	93
4	*p*-ClC_6H_4	CH_3CN	40	20	81	>98:2	93
5	*p*-$CO_2MeOC_6H_4$	CH_3CN	30	20	80	>98:2	73
6	*p*-$CO_2MeOC_6H_4$	CH_3CN/ H_2O (9:1)	30	20	>10	100:0	86
7	3-furyl	toluene	40	20	46	63:37	63 (31)

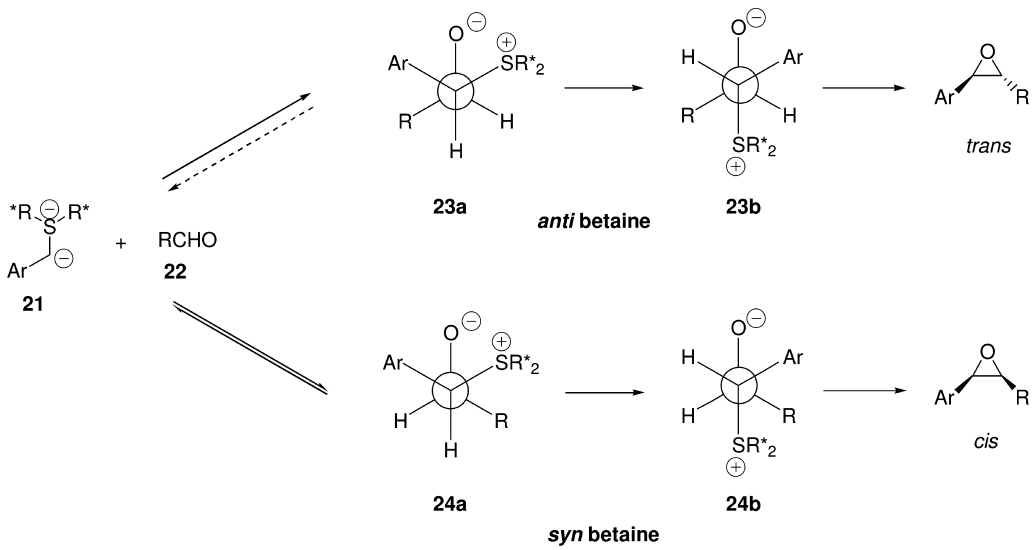
With electron-deficient aromatic substrates (Entries 4 and 5), high yields and selectivities were observed, but enantioselectivities were variable and solvent-dependent (compare Entry 6 with 7 and see Section 1.2.1.3 for further discussion). With α,β-unsaturated tosylhydrazone salts, selectivities and yields were lower. The scope of this process has been extensively mapped out, enabling the optimum disconnection for epoxidation to be chosen [10].

1.2.1.3 Discussion of Factors Affecting Diastereo- and Enantioselectivity

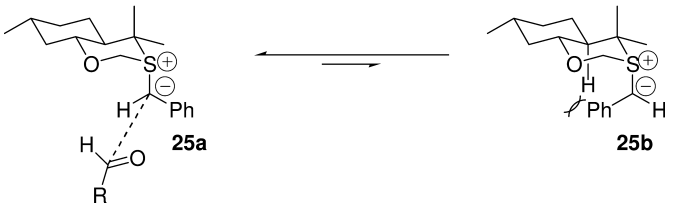
The high diastereoselectivities observed in aryl-stabilized sulfur ylide-mediated epoxidation can be understood by considering the intermediate betaines (Scheme 1.8). In reactions with benzaldehyde it was found that the *trans* epoxide was derived from the non-reversible formation of the *anti* betaine **23**, whilst the *cis* epoxide was generated by the reversible formation of the *syn* betaine **24** [11]. This productive non-reversible *anti* betaine formation and unproductive reversible *syn* betaine formation results in the overall high *trans* selectivities. Of course, the extent to which the intermediate betaines are reversible will depend upon the stability of the betaines, the stability of the starting aldehyde **22**, the stability of the starting ylide **21**, and the steric hindrance of the aldehyde/ylide [12, 13]. A less stabilized ylide will exhibit less reversible *syn* betaine formation and will result in a lower diastereoselectivity (compare Entry 1 with 2, Table 1.5; the less stabilized *p*-methoxybenzyl ylide gives a lower diastereoselectivity than the *p*-metylbenzyl ylide).

There are four main factors that affect the enantioselectivity of sulfur ylide-mediated reactions: *i*) the lone-pair selectivity of the sulfonium salt formation, *ii*) the conformation of the resulting ylide, *iii*) the face selectivity of the ylide, and *iv*) betaine reversibility.

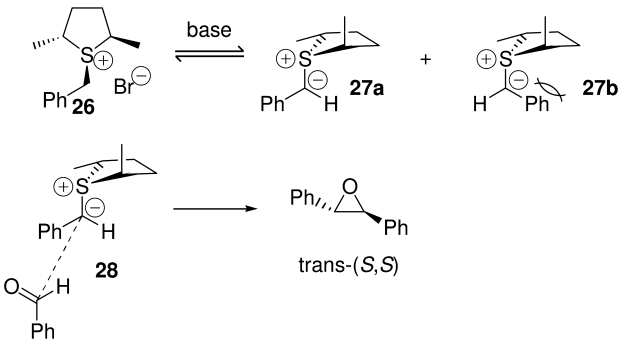
To control the first factor, one of the two lone pairs of the sulfide must be blocked such that a single diastereomer is produced upon alkylation. For C_2 symmetric sulfides this is not an issue, as a single diastereomer is necessarily formed upon alkylation. To control the second factor, steric interactions can be used to favor one of the two possible conformations of the ylide (these are generally accepted to be the two conformers in which the electron lone pairs on sulfur and carbon are orthogonal) [14]. The third factor can be controlled by sterically hinder-



Scheme 1.8



Scheme 1.9



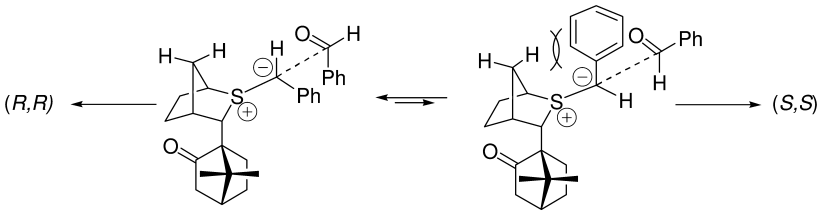
Scheme 1.10

ing one face of the ylide, thus restricting the approach of the aldehyde to it. By considering these first three factors, the high selectivities observed with the sulfides previously discussed can be broadly explained:

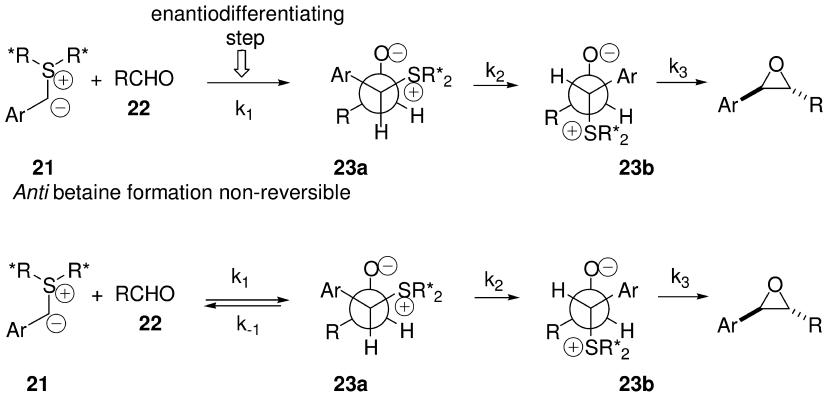
For oxathiane **1**, lone pair selectivity is controlled by steric interactions of the *gem*-dimethyl group and an anomeric effect, which renders the equatorial lone pair less nucleophilic than the axial lone pair. Of the resulting ylide conformations, **25a** will be strongly preferred and will react on the more open *Re* face, since the *Si* face is blocked by the *gem*-dimethyl group (Scheme 1.9) [3, 15].

The C_2 symmetry of sulfide **13** means that a single diastereomer is formed upon alkylation (Scheme 1.10). Attack from the *Si* face of the ylide is preferred as the *Re* face is shielded by the methyl group *cis* to the benzylidene group (**28**). Metzner postulates that this methyl group also controls the conformation of the ylide, as a steric clash in **27b** renders **27a** more favorable [16]. However, computational studies by Goodman revealed that **27a** was not particularly favored over **27b**, but it was substantially more reactive, thus providing the high enantioselectivity observed [17].

In the case of sulfide **7** the bulky camphoryl moiety blocks one of the lone pairs on the sulfide, resulting in a single diastereomer upon alkylation. One of the conformations (**29b**) is rendered less favorable by non-bonded interactions such that conformation **29a** is favored, resulting in the observed major isomer (Scheme 1.11). The face selectivity is also controlled by the camphoryl group, which blocks the *Re* face of the ylide.



Scheme 1.11



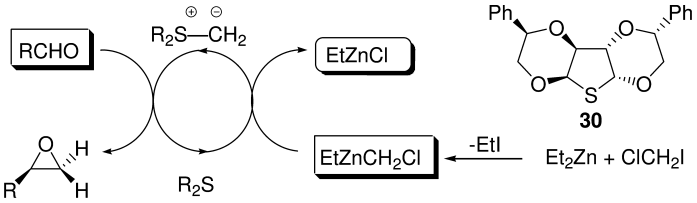
Scheme 1.12

The fourth factor becomes an issue when *anti* betaine formation is reversible or partially reversible. This can occur with more hindered or more stable ylides. In these cases the enantiodifferentiating step becomes either the bond rotation or the ring-closure step (Scheme 1.12), and as a result the observed enantioselectivities are generally lower (Entry 5, Table 1.5; the electron-deficient aromatic ylide gives lower enantioselectivity). However the use of protic solvents (Entry 6, Table 1.5) or lithium salts has been shown to reduce reversibility in betaine formation and can result in increased enantioselectivities in these cases [13]. Although protic solvents give low yields and so are not practically useful, lithium salts do not suffer this drawback.[18]

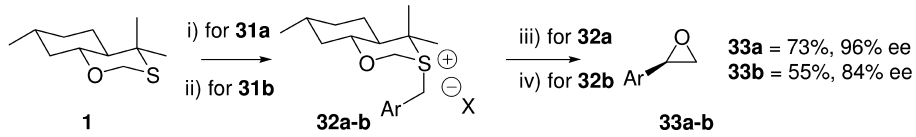
The diastereo- and enantioselectivity are clearly dependent on a number of factors, including the reaction conditions, sulfide structure, and nature of the ylide.

1.2.2 Terminal Epoxides

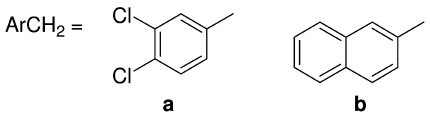
One class of particularly challenging targets for asymmetric epoxidation is that of terminal epoxides. Aggarwal and co-workers found that zinc carbenoids generated



Scheme 1.13



i) $ArCH_2OH$ (**31a**), Tf_2O, pyridine, CH_2Cl_2, -10 °C; ii) $AgBF_4$, $MeNO_2$, $ArCH_2I$ (**31b**); iii) NaH, THF, $(CH_2O)_n$, -40 °C, 5h; iv) NaH, DMF, $(CH_2O)_n$, -40 °C, 24 h.



Scheme 1.14

from Et_2Zn and $ClCH_2I$ could efficiently transfer a methylidene group to a sulfide, and, in the presence of aldehydes, produce epoxides in good yield (Scheme 1.13) [19, 20].

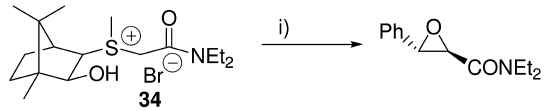
Unfortunately, the highest enantioselectivity so far obtained for the synthesis of styrene oxide by this route is only 57% *ee* with Goodman's sulfide **30** [21]. Thus methylidene transfer is not yet an effective strategy for the synthesis of terminal epoxides.

Another way to disconnect a terminal epoxide is to add a functionalized ylide to paraformaldehyde. This was the route explored by Solladié-Cavallo, who treated two aromatic ylides with paraformaldehyde at low temperatures and obtained good selectivities (Scheme 1.14) [22]. It would thus appear that this is the best ylide-mediated route to terminal aromatic epoxides to date.

1.2.3
Epoxy Esters, Amides, Acids, Ketones, and Sulfones

1.2.3.1 Sulfur Ylide-mediated Epoxidation

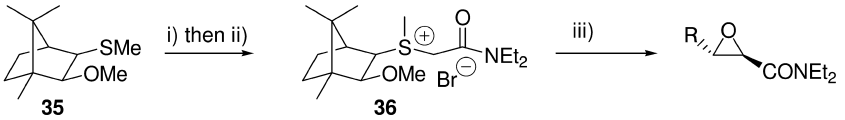
In general sulfur ylide-mediated epoxidation cannot be used to form an epoxide with an adjacent anion-stabilizing group such as an ester, as the requisite ylide is too stable and does not react with aldehydes [23]. With the less strongly electron-withdrawing amide group, however, the sulfur ylide possesses sufficient reactivity for epoxidation. The first example of an asymmetric version of this reaction was by



i) KOH, MeCN, PhCHO, rt. 61%, 71.5% ee

Scheme 1.15

Table 1.6 Use of the sulfonium salt **36** in low-temperature epoxidations.



i) $BrCH_2CONEt_2$; ii) recrystallisation; iii) KOH, EtOH, RCHO, -50 °C.

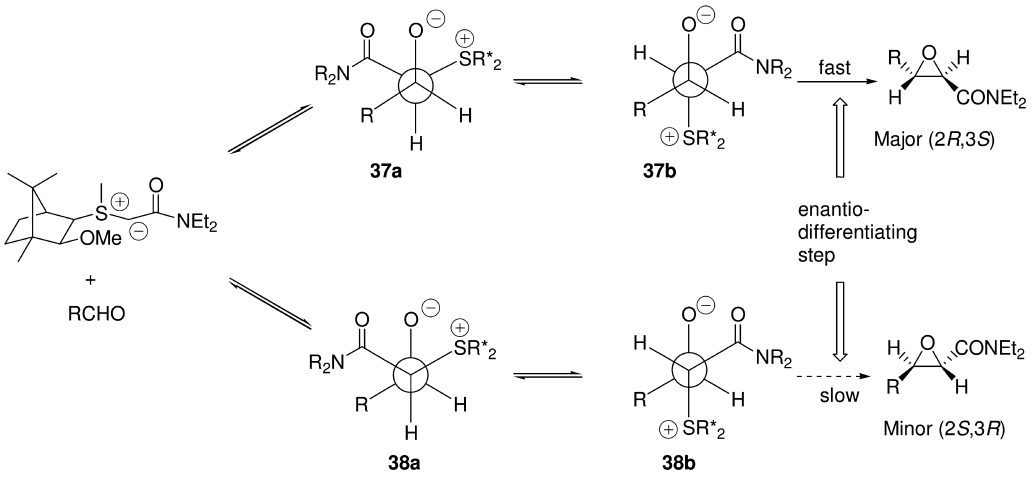
Entry	R	Yield (%)	*ee* (%)
1	Ph	93	97
2	*p*-ClC_6H_4	87	99
3	*p*-MeC_6H_4	88	98
4	3-pyridyl	87	95
5[a]	dodecyl	84	63
6[b]	*t*-butyl	87	93

[a] –30 °C. [b] –20 °C.

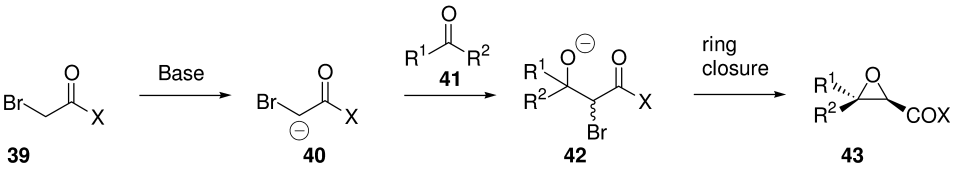
Dai and co-workers, who used sulfonium salt **34** in epoxidation reactions to give glycidic amides (Scheme 1.15) [23].

Improved selectivities were achieved by the Aggarwal group, who used sulfonium salt **36** (Table 1.6), with the same parent structure, in low-temperature epoxidation reactions [24]. In most cases complete diastereocontrol was accompanied by high enantioselectivities; aromatic and heteroaromatic aldehydes were excellent substrates (Entries 1–4). Aliphatic aldehydes gave variable results: mono- and trisubstituted aldehydes gave moderate to high enantioselectivities (Entries 5 and 6), whilst secondary aliphatic aldehydes gave very low enantioselectivities. Although tertiary amides are difficult to hydrolyze, they can be cleanly converted to ketones by treatment with organolithiums.

As the formation of betaines from amide-stabilized ylides is known to be reversible (in contrast with aryl- or semistabilized ylides, which can exhibit irreversible *anti* betaine formation; see Section 1.2.1.3), the enantiodifferentiating step cannot be the C–C bond-forming step. B3LYP calculations of the individual steps along the reaction pathway have shown that in this instance ring-closure has the highest barrier and is most likely to be the enantiodifferentiating step of the reaction (Scheme 1.16) [25].



Scheme 1.16



Scheme 1.17

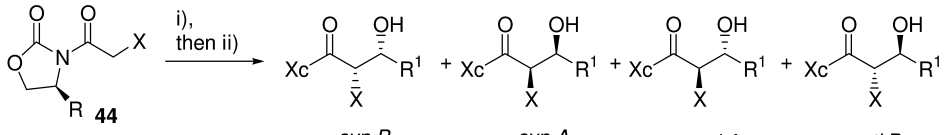
1.2.3.2 **Darzens Reaction**

Epoxides bearing electron-withdrawing groups have been most commonly synthesized by the Darzens reaction. The Darzens reaction involves the initial addition of an α-halo enolate **40** to the carbonyl compound **41**, followed by ring-closure of the alkoxide **42** (Scheme 1.17). Several approaches for inducing asymmetry into this reaction – the use of chiral auxiliaries, reagents, or catalysts – have emerged.

1.2.3.3 **Darzens Reactions in the Presence of Chiral Auxiliaries**

Although chiral auxiliaries have been attached to aldehydes for asymmetric Darzens reactions [26, 27], the most commonly employed point of attachment for a chiral auxiliary is adjacent to the carbonyl to be enolized. Indeed, many groups have investigated this strategy, and a variety of chiral auxiliaries have been employed. As the initial step of the Darzens reaction is an α-halogen aldol condensation, it is perhaps unsurprising that existing asymmetric aldol chemistry should have been exploited and adapted to the Darzens reaction. Prigden's group investigated the use of 2-oxazolidinones developed by Evans (Table 1.7) [28, 29], treating a variety of metal enolates (tin(II), tin(IV), zinc, lithium, titanium, and boron) with both aliphatic and aromatic aldehydes. The best results by far were obtained with

Table 1.7 2-Oxazolidinones as chiral auxiliaries in Darzens reactions.



X_c = chiral auxiliary

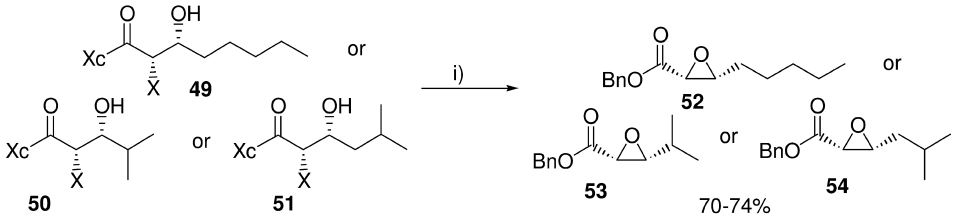
i) enolate formation; ii) R^1CHO.

Entry	R^1	X	R (X_c)	M[a]	Yield (%)	d.r. *syn*:*anti*	Enantioselectivity *syn* B:A	Enantioselectivity *anti* A:B
1	*n*-C_5H_{11}	Cl	*i*-Pr	B	62	>50:1	>50:1	–
2	*i*-$PrCH_2$	Cl	*i*-Pr	B	55	>50:1	>50:1	–
3	*i*-Pr	Cl	*i*-Pr	B	52	>50:1	>50:1	–
4	Ph	Cl	*i*-Pr	B[b]	68	>99:0	>99:0	–
5	Ph	F	*i*-Pr	Sn^{IV}	50	<0:99	–	94:5
6	Ph	Br	*i*-Pr	Sn^{II}	67	85:15	79:6	6:9
7	*o*-$NO_2C_6H_4$	Br	Ph	Sn^{II}	44	0:100	–	0:100
8	*o*-$MeOC_6H_4$	Br	Ph	Sn^{II}	65	21:79	0:21	0:79
9	*o*-*t*-BuC_6H_4	Br	Ph	Sn^{II}	58	0:100	–	0:100

[a] B refers to $B(n\text{-}Bu)_2$, Sn^{IV} refers to $Sn(n\text{-}Bu)_3$, Sn^{II} refers to $Sn(OSO_2CF_3)$. [b] B refers to BEt_3.

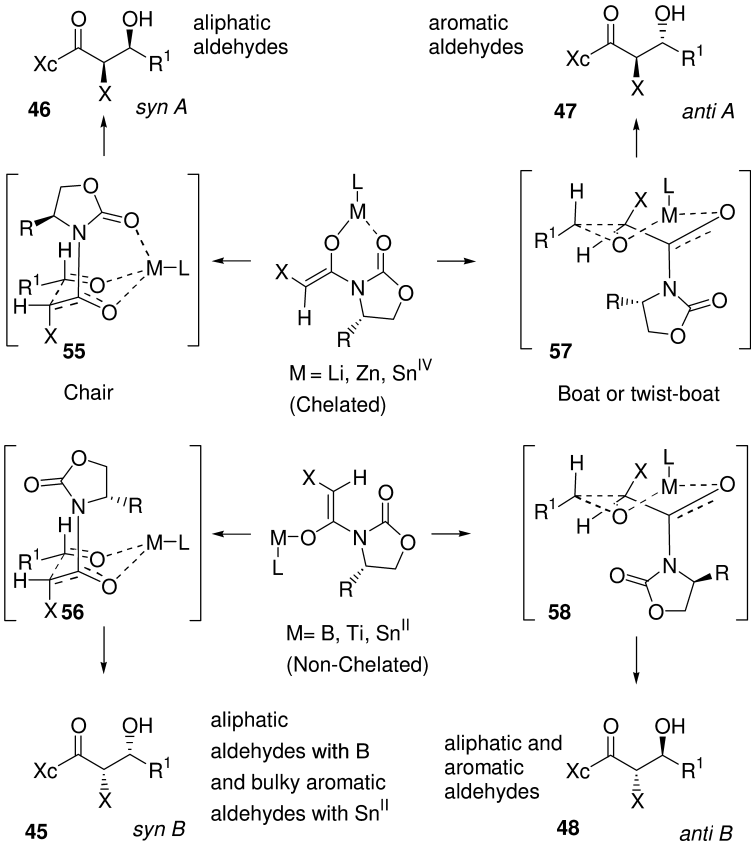
the use of boron enolates, which furnished the *syn* adducts with very high diastereo- and enantioselectivities (Entries 1–4).

Through the use of a tin(IV) enolate with benzaldehyde it was possible to generate the *anti* A diastereomer **47** with high selectivity (Entry 5). With tin(II) enolates a highly substituent-dependent outcome was observed. Low selectivities resulted with *para*-substituted aromatic aldehydes, but good selectivities were observed for *ortho*-substituted aromatic aldehydes (Entries 7–9). Simultaneous re-



i) BnOLi, THF, -78 to -20 °C. X_c = chiral auxiliary

Scheme 1.18



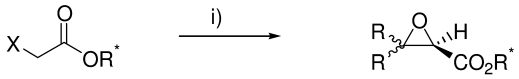
Scheme 1.19

moval of the auxiliaries and ring-closure cleanly furnished the corresponding epoxy esters without epimerization (Scheme 1.18).

The results were interpreted by considering enolates with tin (IV), zinc, or lithium counter-ions to react via three-point chair transition states **55** with aliphatic aldehydes to give predominantly the *syn* A adducts **46**, whilst tin (II), boron, and titanium enolates reacted via non-coordinated chair transition states **56** with aliphatic aldehydes to give the opposite *syn* B adducts **45** (Scheme 1.19). Aromatic aldehydes reacted with tin (IV), zinc, or lithium enolates through chelated twist-boat transition states **57** to give the *anti* A halohydrins **47**, whilst boron and titanium enolates still reacted via the nonchelated chair-like transition states to give the *syn* B **45**. The tin (II) enolate exhibited borderline selectivities. It reacted with aromatic aldehydes to give the *syn* B diastereomer **45** as with boron and titanium enolates, but with *ortho*-substituted aromatic aldehydes, an *anti* B (**48**) selectivity was observed, indicating that a twist-boat transition state **58** was being favored.

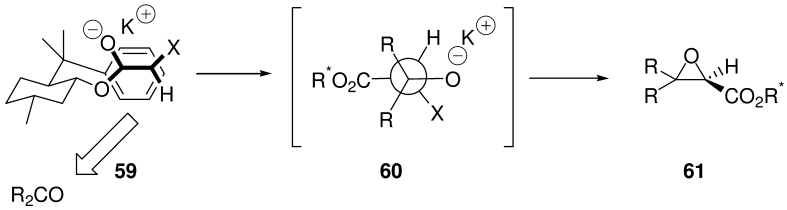
Thus, by varying the enolate counter-cation and the aldehyde, it was possible to

Table 1.8 Use of 8-phenylmenthyl esters to induce asymmetry in the Darzens reaction.



i) R_2CO, t-BuOK, CH_2Cl_2, -78-0°C. R* = (-)-8-phenylmenthyl.

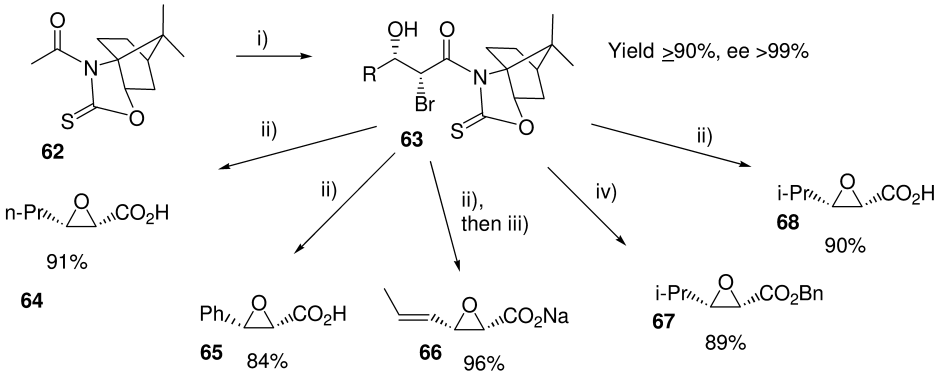
Entry	R_2CO	X	Yield (%)	*cis*:*trans*	de (*cis*) %	de (*trans*) %
1	acetophenone	Br	56	5.6:1	>95	21
2	propiophenone	Br	43	4.2:1	>95	>95
3	cyclohexanone	Cl	45	–	96	
4	acetone	Cl	64	–	87	
5	benzophenone	Cl	45	–	77	
6	benzaldehyde	Cl	90	2.8:1.0	38	33



Scheme 1.20

access a range of halo-aldol adducts, which could also be cyclized to the required epoxy esters without epimerization (Scheme 1.18).

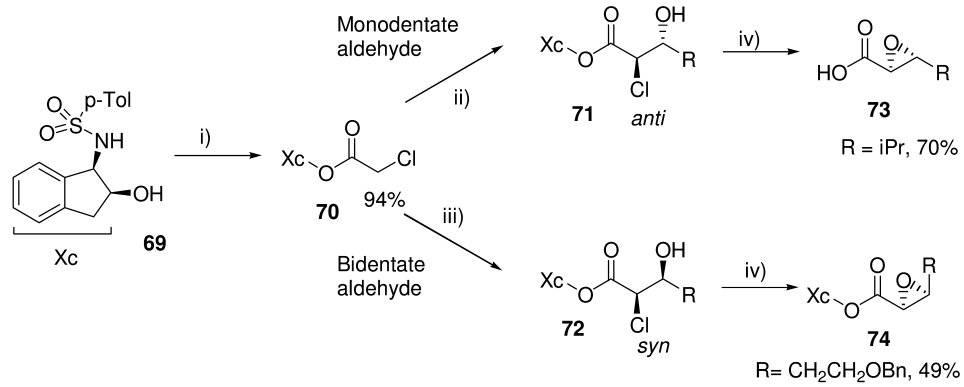
Ohkata [30, 31] and co-workers have employed an 8-phenylmenthyl ester to induce asymmetry in the Darzens reaction (Table 1.8). Moderate to high diaster-



i) $TiCl_4$, DIPEA; then Br_2, DIPEA, RCHO, -78°C; ii) CH_3CN/H_2O, NEt_3; then MeOH, K_2CO_3; iii) Na_2CO_3, CH_3CN/H_2O iv) DMAP, B_nOH ; then KF, LiF, n-Bu_4NHSO_4, CH_2Cl_2.

Scheme 1.21

Table 1.9 Scope of the indanyl-derived auxiliary **69**.



i) $ClCH_2COCl$, pyridine; CH_2Cl_2, 0 °C; ii) $TiCl_4$, iPr_2NEt, then RCHO,$TiCl_4$, MeCN or NMP, CH_2Cl_2, -78 °C, 2h; iii) $TiCl_4$, iPr_2NEt, then RCHO $TiCl_4$ CH_2Cl_2, -78 °C, 2h; iv) K_2CO_3, MeOH; v) K_2CO_3, (aq), DMF.

Entry	Aldehyde (RCHO)	Yield (%) (71 + 72)	*anti* 71: *syn* 72
1	*i*-BuCHO	90[a]	99:1
2	BuCHO	70[a]	96:4
3	PhCHO	47,[a] 62[b]	96:4
4	PhCHO	64	10:90
5	$BnOCH_2CHO$	86	1:99
6	$BnOCH_2CH_2CHO$	79	4:96
7	(*R*)-BnOCH-(Me)CHO	94	1:99
8	(*S*)-BnOCH-(Me)CHO	82	99:1
9	(±)-BnOCH-(Me)CHO	95[c]	5:95

[a] NMP (2.2 equiv.) used as additive. [b] MeCN (2.2 equiv.) used as additive. [c] 2 equiv. of aldehyde used, 30 min reaction time.

eoselectivities resulted from its reaction with ketones to furnish trisubstituted aliphatic and aromatic epoxy esters, but only low selectivities resulted in its reaction with benzaldehyde.

The high enantioselectivity observed was interpreted in terms of the face selectivity of the (*Z*)-enolate **59** (Scheme 1.20). The phenyl moiety is thought to stabilize the enolate through a π-π interaction and effectively shield its *Re* face such that the incoming ketone approaches preferentially from the *Si* face.

Yan's group has used the camphor-based chiral thioamide **62** in asymmetric Darzens reactions (Scheme 1.21) [32]. The addition of the titanium enolate of **62** to

a range of aldehydes resulted in the formation of essentially single diastereomers of halo alcohols **63**. Treatment of these with aqueous potassium carbonate resulted in the formation of the corresponding aryl (**65**), alkyl (**64** and **68**), and vinyl (**66**) epoxy acids without epimerization. If the thioamide adduct was instead treated with DMAP and benzyl alcohol, followed by KF and LiF in the presence of *n*-$Bu_4N^+HSO_4^-$, the epoxy ester **67** was formed [33]. In all cases the *cis* epoxide predominated; the selectivity was thus complementary to sulfur ylide chemistry, which almost always favors the *trans* epoxide.

Ghosh and co-workers have recently used the indanyl-derived auxiliary **69** (Table 1.9) in titanium enolate condensations with a range of aldehydes [34]. Of the four possible diastereomers, only the *anti* **71** and *syn* **72** were produced (the alternative *anti* and *syn* diastereomers were not detected by ^1H or ^{13}C NMR). The use of monodentate aliphatic aldehydes resulted in the formation of *anti* diastereomers **71** with high selectivities with the aid of acetonitrile or *N*-methylpyrrolidinone (NMP) as an additive (Entries 1 and 2). The use of bidentate aldehydes resulted in high *syn* diastereoselectivities without requiring the use of an additive (Entries 5 and 6). Interestingly, benzaldehyde exhibited *anti* selectivity in the presence of an additive (Entry 3), but *syn* selectivity in its absence (Entry 4). Additionally, a double asymmetric induction using (2*R*)- and (2*S*)-benzyloxypropionaldehyde was attempted (Entries 7 and 8). In the matched case ((2*R*)-), only the *syn* diastereomer **72** was produced, but in the mismatched case ((2*S*)-) the *anti* diastereomer **71** was obtained instead. It was thus possible to perform a kinetic resolution on two equivalents of racemic aldehyde (Entry 9) and to obtain the *syn* diastereomer **72** (through reaction of matched (2*R*)-aldehyde) with high selectivity. The (2*S*)-aldehyde was isolated in 40% yield and in 98.7% *ee*. Treatment of the halo-aldol adducts with potassium carbonate in DMF resulted in the formation of the epoxides (**74**). Simultaneous epoxide formation and removal of the auxiliary could be effected by treating the adducts with potassium carbonate in methanol to give the epoxy acids (**73**).

1.2.3.4 **Darzens Reactions with Chiral Reagents**

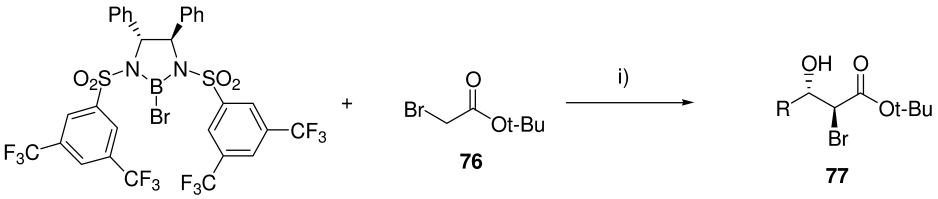
Clearly it is advantageous to be able to use achiral starting materials and a chiral reagent to induce an asymmetric reaction, thus obviating the need to attach and remove a chiral auxiliary and permitting the recovery and reuse of the chiral reagent.

Corey used a chiral bromoborane **75** (1.1 equiv.) to promote the addition of *tert*-butyl bromoacetate (**76**) to aromatic, aliphatic, and α,β-unsaturated aldehydes to give the halo alcohols **77** with high enantio- and diastereoselectivities (Table 1.10) [35].

Additionally, the sulfonamide precursor to **75** could be recovered and recycled to regenerate the bromoborane **75** [36]. The resulting aldols could then be cyclized to the epoxy esters by treatment with potassium *tert*-butoxide (Scheme 1.22).

A valine-based chiral oxazaborolidinone **80** (generated *in situ* from Ts-L-Val and $BH_3 \cdot THF$) was used by Kiyooka and co-workers [37] to catalyse the reaction be-

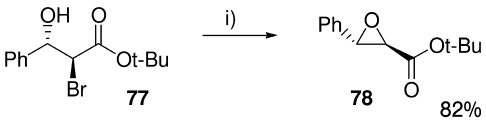
Table 1.10 Chiral reagent **75** in asymmetric Darzens reactions.



75 (1 equiv.)

i) Et_3N, -78 °C, 1:2 toluene/hexane; then RCHO, -78 °C.

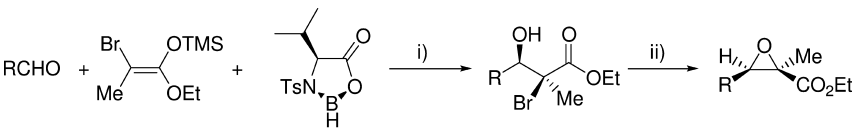
Entry	R of RCHO	Yield (%)	*anti*:*syn*	*ee* (%)
1	Ph	94	91:1	98
2	(*E*)-PhCH=CH	96	99:1	98
3	$PhCH_2CH_2$	72	95:5	91
4	cyclohexyl	65	98:2	91



i) KOt-Bu, t-BuOH.

Scheme 1.22

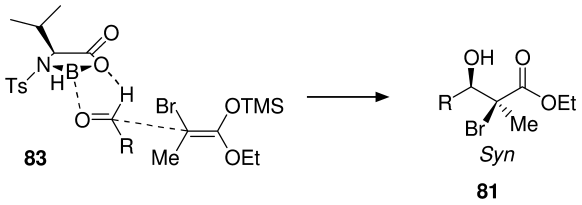
Table 1.11 Chiral induction through the use of the valine-based **80**.



79 **80** (1 equiv.) **81** **82**

i) CH_2Cl_2, -78 °C, 15 h; ii) NaOEt, EtOH, rt, 2 h.

Entry	R of RCHO	Yield 81	*syn* % : *anti*	% *ee* (*syn*)	Yield 82 (%)
1	Ph	82	7:1	95	87
2	*i*-Pr	68	16:1	97	74
3	$PhCH_2CH_2$	80	9:1	96	81
4	*n*-Pr	85	10:1	98	78
5	$TBSOCH_2CH_2$	87	15:1	95	93



Scheme 1.23

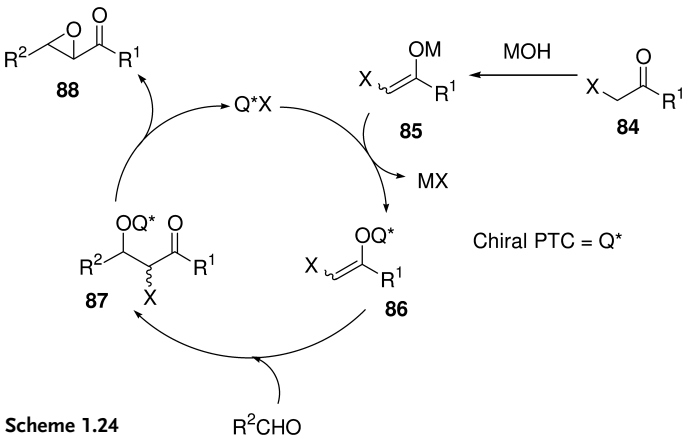
tween β-bromo-β-methylketene silyl acetal **79** and a range of aldehydes (Table 1.11). Good diastereoselectivities and excellent enantioselectivities resulted in the formation of the halo alcohols **81**, which could be converted into the trisubstituted aryl or alkyl methyl epoxy esters **82** by treatment with sodium ethoxide.

A transition state assembly as depicted in Scheme 1.23 was proposed in order to interpret the observed selectivity. Electronic effects are thought to be operative, as the methyl and bromo substituents in transition state **83** are sterically similar.

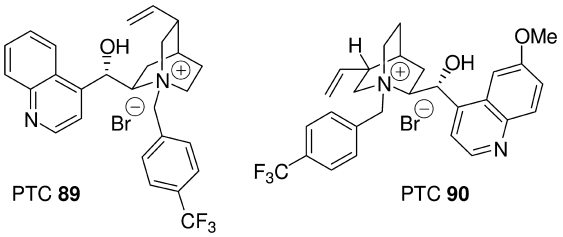
1.2.3.5 **Darzens Reactions with Chiral Catalysts**

Of course, the most practical and synthetically elegant approach to the asymmetric Darzens reaction would be to use a sub-stoichiometric amount of a chiral catalyst. The most notable approach has been the use of chiral phase-transfer catalysts. By rendering the intermediate enolate **86** (Scheme 1.24) soluble in the reaction solvent, the phase-transfer catalyst can effectively provide the enolate with a chiral environment in which to react with carbonyl compounds.

Early work on the use of chiral phase-transfer catalysis in asymmetric Darzens reactions was conducted independently by the groups of Wynberg [38] and Colonna [39], but the observed asymmetric induction was low. More recently Toké's group has used catalytic chiral aza crown ethers in Darzens reactions [40–42], but again only low to moderate enantioselectivities resulted.



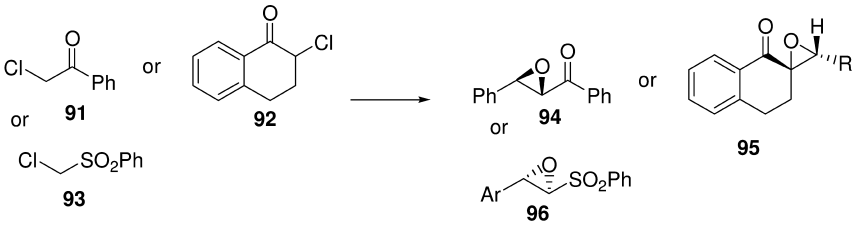
Scheme 1.24



Scheme 1.25

Arai and co-workers have used chiral ammonium salts **89** and **90** (Scheme 1.25) derived from cinchona alkaloids as phase-transfer catalysts for asymmetric Darzens reactions (Table 1.12). They obtained moderate enantioselectivities for the addition of cyclic **92** (Entries 4–6) [43] and acyclic **91** (Entries 1–3) chloroketones [44] to a range of alkyl and aromatic aldehydes [45] and also obtained moderate selectivities on treatment of chlorosulfone **93** with aromatic aldehydes (Entries 7–9) [46, 47]. Treatment of chlorosulfone **93** with ketones resulted in low enantioselectivities.

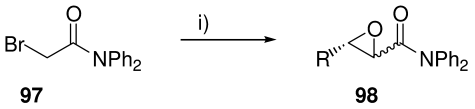
Table 1.12 Cinchona alkaloid-derived phase-transfer catalysts for asymmetric Darzens reactions.



Entry	R^2CHO	Halide	Method	Yield	*ee* (%)
1	*i*-PrCHO	**91**	I	80	53
2	EtCHO	**91**	I	32	79
3	PhCHO	**91**	I	43	42
4	*i*-PrCHO	**92**	II	99	69
5	*t*-$BuCH_2CHO$	**92**	II	86	86
6	PhCHO	**92**	II	67	59
7	PhCHO	**93**	III	85	69
8	*p*-MeC_6H_4CHO	**93**	III	84	78
9	*p*-BrC_6H_4CHO	**93**	III	80	64

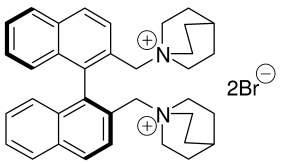
Method I: PTC **89** (10 mol%), $LiOH \cdot H_2O$, *n*-Bu_2O, 4 °C, 60–117 h;
Method II: PTC **90** (10 mol%), $LiOH \cdot H_2O$, *n*-Bu_2O, rt, 43–84 h;
Method III: PTC **90** (10 mol%), KOH, toluene, rt, 1 h.

Table 1.13 BINOL-derived phase-transfer catalysts for asymmetric Darzens reactions.



97 **98**

i) PTC **91** (2 mol%), $RbOH{\cdot}H_2O$, CH_2Cl_2, rt, 6.5-24 h.



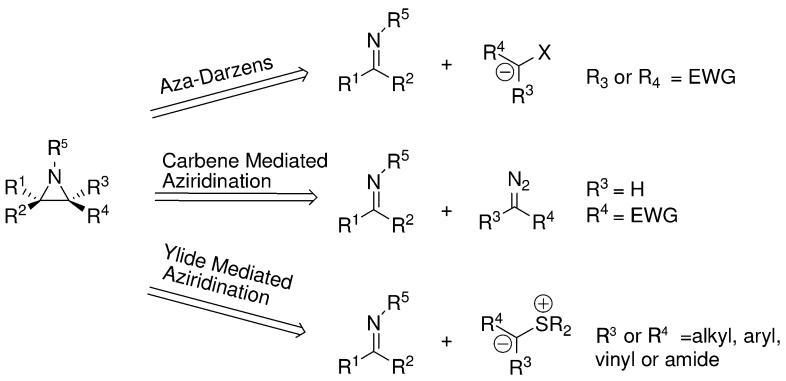
PTC **99**

Entry	RCHO	Yield (%)	*cis:trans*	*ee cis* (%)	*ee trans* (%)
1	PhCHO	81	2.3:1	58	63
2	*m*-BrC_6H_4CHO	93	2.4:1	51	60
3	*p*-$MeOC_6H_4CHO$	quant.	2.2:1	57	67

More recently, the same group has used a simpler and more easily prepared chiral ammonium phase-transfer catalyst **99** derived from BINOL in asymmetric Darzens reactions with α-halo amides **97** to generate glycidic tertiary amides **98** (Table 1.13). Unfortunately the selectivities were only moderate to low [48]. As mentioned in Section 1.2.3.1, tertiary amides can be converted to ketones.

1.3
Asymmetric Aziridination of Imines

Asymmetric transformation of imines into chiral aziridines remains less well developed than the analogous transformation of aldehydes into epoxides [49, 50, 51]. The reported methods can be divided into three conceptual categories involving



Scheme 1.26

reactions of imines with: *i*) α-halo enolates (aza-Darzens), *ii*) carbenes, or *iii*) ylides (Scheme 1.26). Categories *i*) and *ii*) are employed to prepare aziridines bearing electron-withdrawing groups such as esters or amides. Category *iii*), the ylide methodology, on the other hand, provides a route to aryl, alkyl, vinyl, and terminal aziridines, as well as ester- or amide-substituted aziridines. The most common method of asymmetric induction reported has been with the aid of chiral auxiliaries. There have been attempts at reagent-controlled induction, which has been most successful in the sulfur ylide methodology. However there exist only two examples of asymmetric catalysis: a sulfur ylide-mediated aziridination by Aggarwal and a Lewis acid-catalyzed diazoacetate decomposition by Wulff.

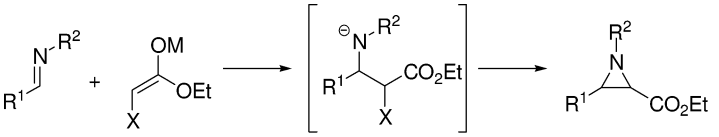
1.3.1
Aziridines Bearing Electron-withdrawing Groups: Esters and Amides

1.3.1.1 Aza-Darzens Route

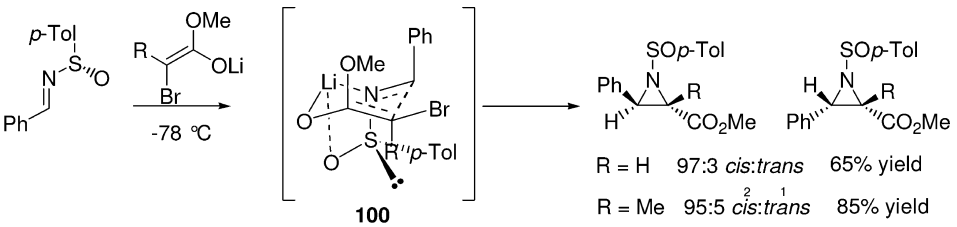
The aza-Darzens reaction is analogous to the Darzens synthesis of epoxides (see Section 1.2.3.2) but employs imines in the place of aldehydes (Scheme 1.27).

Davis has employed the enantiopure sulfinimine *N*-(benzylidene)-*p*-toluenesulfinimine in reactions with α-halo ester enolates to obtain aziridine-2-carboxylates in good yields and with high diastereoselectivities (Scheme 1.28) [52]. The selectivities are consistent with a six-membered chair-like transition state **100**, containing a four-membered metallocycle. It is assumed that the enolate of the unsubstituted α-bromoacetate has the *E* geometry resulting in the *cis* aziridine, while the enolate of the substituted α-bronoacetate adopts the *Z*-geometry resulting in the *trans* aziridine.

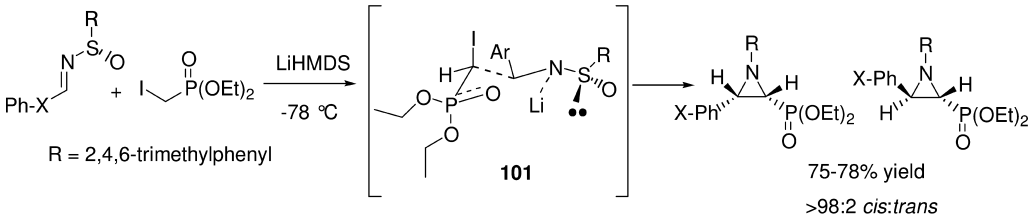
Davis has also employed a similar procedure for the synthesis of aziridine-2-phosphonoates, involving the addition of *N*-(2,4,6-trimethylphenylsulfinyl)imine to anions of diethyl α-halomethyl phosphonates (Scheme 1.29) [53, 54]. Aziridines



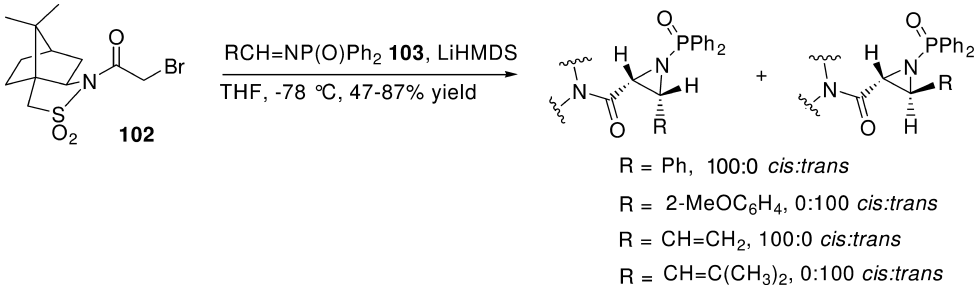
Scheme 1.27



Scheme 1.28



Scheme 1.29



Scheme 1.30

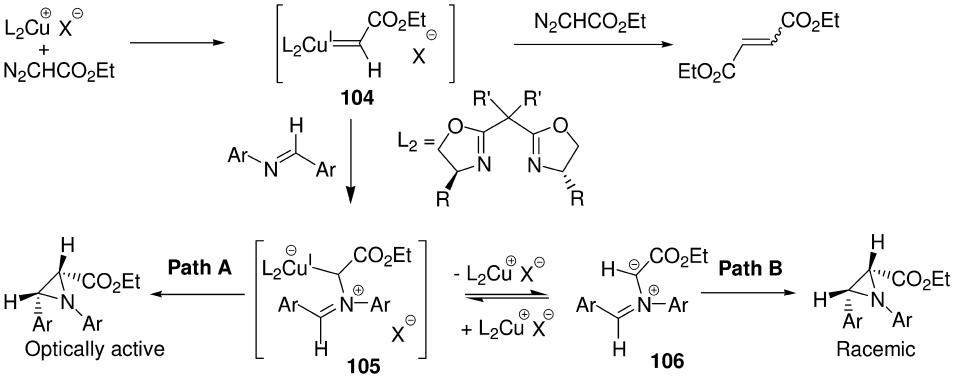
were obtained as single *cis* diastereomers (>98:2) in 75–78% isolated yields. The high selectivity is believed to arise from two types of steric interaction in the transition state. Attack by the anion at the C=N bond opposite the bulky sulfinyl group is highly favored and, secondly, the iodo group needs to occupy the axial position in the transition state **101**, as it would then have fewer steric interactions with the ethoxy phosphonate groups.

The substrate scope is limited, as electron-withdrawing groups (X = *p*-NO_2 or *p*-CF_3) on the aromatic substituent are not tolerated. However, this route does provide valuable intermediates to unnatural α-amino phosphonic acid analogues and the sulfimine can readily be oxidized to the corresponding sulfonamide, thereby providing an activated aziridine for further manipulation, or it can easily be removed by treatment with a Grignard reagent.

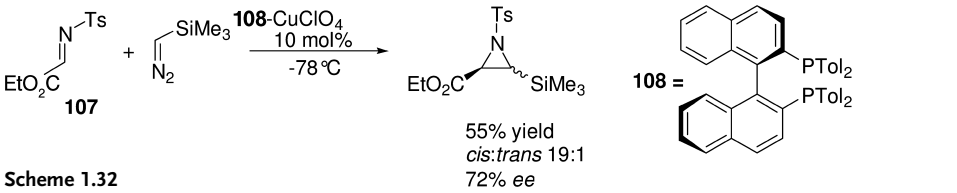
An alternative approach is to have the chiral auxiliary on the enolate. Sweeney has reported the addition of bromoacyl sultam **102** to phosphonyl imines **103**, which afforded the *cis*- or *trans*-aziridines with high levels of diastereoselectivity depending on the imine substituent (Scheme 1.30) [55].

1.3.1.2 Reactions between Imines and Carbenes

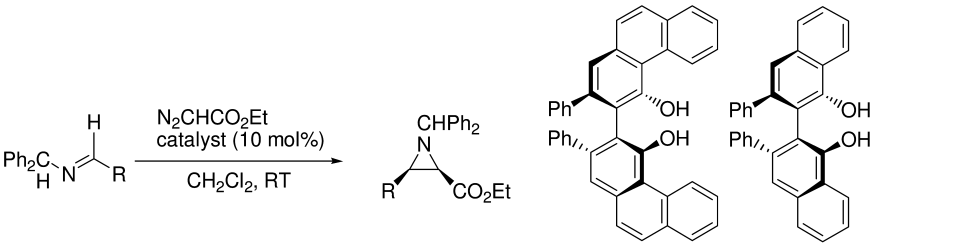
Synthesis of aziridines by treatment of carbenes with imines was reported by Jacobsen [56]. A metallocarbene **104** derived from ethyl diazoacetate and copper fluorophosphate was treated with N-arylaldimines to form aziridines with reasonable diastereoselectivities (>10:1 in favor of *cis*) but with low enantioselectivities (about 44% *ee*). This was shown to result from a competitive achiral reaction path-



Scheme 1.31



Scheme 1.32



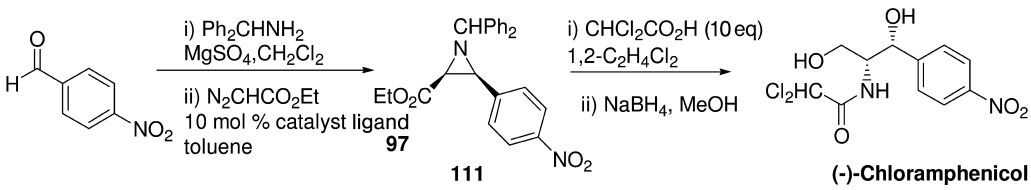
Scheme 1.33

way (Scheme 1.31). Path A goes through the chiral metal species **105**, yielding non-racemic aziridine, whereas path B goes through a planar azomethine ylide **106**, yielding the racemic aziridine. The reaction showed limited scope, as it was quite sensitive to the electronic properties of the imine.

Jørgensen has recently reported similar enantioselective reactions between *N*-tosylimines **107** and trimethylsilyldiazomethane (TMSD) catalyzed by chiral Lewis acid complexes (Scheme 1.32) [57, 53]. The *cis*-aziridine could be obtained in 72% *ee* with use of a BINAP-copper(I) catalyst, but when a bisoxazoline-copper(I) complex was used the corresponding *trans* isomer was formed in 69% *ee* but with very poor diastereoselectivity.

Table 1.14 Wulff's asymmetric aziridination synthesis.

Entry	R	Catalyst ligand	Yield of *cis*-aziridines (%)	*ee* of *cis*-aziridine (%)	*cis*:*trans* aziridine
1	Ph	**109**	77	95	>50:1
2	Ph	**110**	85	96	>50:1
3	*p*-BrC_6H_4	**109**	91	98	>50:1
4	*o*-MeC_6H_4	**109**	69	94	40:1
5	3,4-$(OAc)_2C_6H_3$	**110**	85	96	>50:1
6	1-naphthyl	**109**	87	92	>50:1
7	2-furyl	**110**	55	93	>50:1
8	*n*-Pr	**110**	60	90	>50:1
9	*t*-Bu	**110**	77	97	>50:1
10	*c*-C_6H_{11}	**109**	74	94	38:1

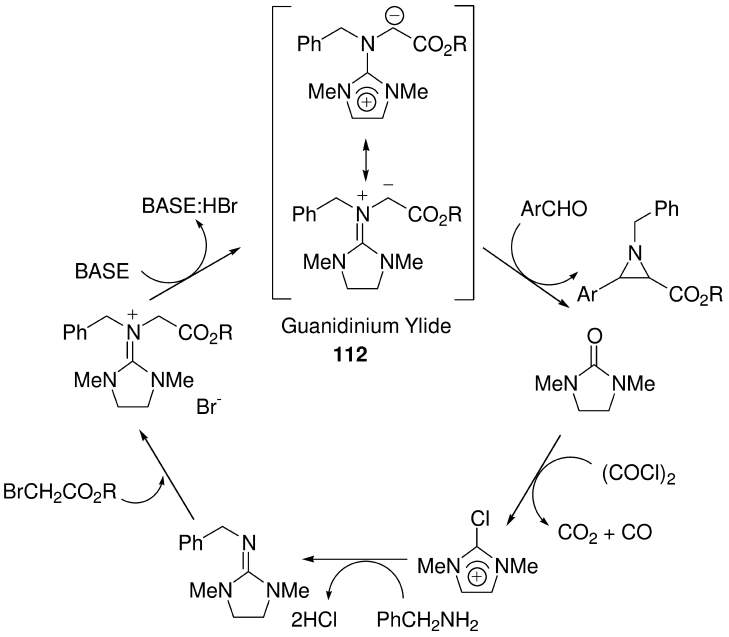


Scheme 1.34

The most successful approach in this reaction category has been the use of chiral boron Lewis acid catalysts, in the addition of ethyl diazoacetate to imines reported by Wulff (Scheme 1.33) [59–60].

Catalysts prepared either from VAPOL (**109**) or from VANOL (**110**) ligands and triphenylborate were found to catalyze the asymmetric aziridination efficiently. Good to high yields, excellent enantioselectivities, and *cis* diastereoselectivities were observed with all the reported substrates, which included aromatic, heteroaromatic and aliphatic imines (Table 1.14).

This is by far the most versatile route to the synthesis of ester-substituted aziridines, especially as the benzhydryl group can easily be cleaved by hydrogenolysis. Wulff has applied this methodology to a short asymmetric synthesis of the antibiotic (–)-chloramphenicol in four steps from *p*-nitrobenzaldehyde (Scheme 1.34) [61]. In this case it was found that treatment of the aziridine **111** with excess dichloroacetic acid gave the hydroxy acetamide directly, so no separate deprotection step was required.



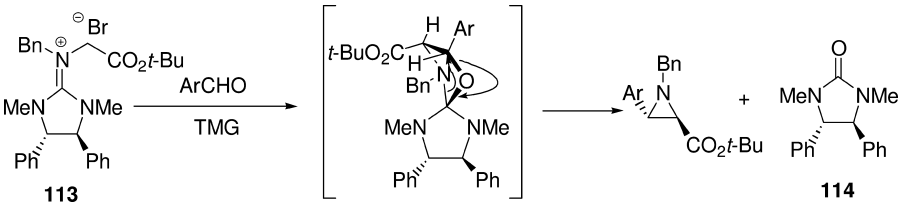
Scheme 1.35

1.3.1.3 Aziridines by Guanidinium Ylide Chemistry

A novel guanidinium ylide-mediated procedure has recently been reported by Ishikawa [62]. Though not an imine transformation, it does employ an imine precursor in the form of an aldehyde. Guanidinium ylides react with aldehydes to form aziridines (Scheme 1.35). The mechanism for the formation of the aziridine is believed to involve [3+2] cycloaddition between the guanidinium ylide **112** and the aldehyde, followed by stereospecific extrusion of the urea with concomitant aziridine formation.

Table 1.15 Chiral guanidylium ylides for asymmetric synthesis of aziridines.

Entry	Ar	Yield of *trans*-aziridines (%)	*ee* of *trans*-aziridine (%)	*trans*:*cis* aziridine
1	3-[(1-Boc)indolyl]	70	95	92:8
2	2-[(1-Boc)indolyl]	87	76	91:9
3	3,4-OCH_2OPh	82	97	93:7
4	C_6H_6	31	77	34:66
5	*p*-ClC_6H_4	35	59	41:59



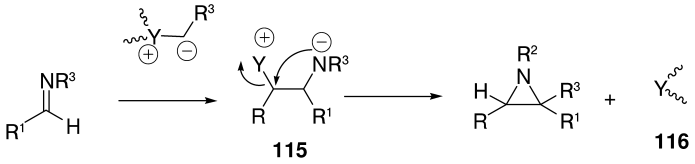
113 114

Scheme 1.36

This reaction was found to be applicable to aryl, heteroaryl, and α,β-unsaturated aldehydes, providing aziridine-2-carboxylates, sometimes with high *trans* diastereoselectivity. Excellent enantioselectivity was observed with use of a chiral guanidinium ylide (Scheme 1.36), but simple phenyl substituents on the aldehyde gave poor yields (Table 1.15). The enantioselectivity is controlled by the facial selectivity in the [3+2] cycloaddition (Scheme 1.36). The other product of the reaction was the chiral urea **113**, which could be recovered in high yield and reconverted into the guanidinium salt **114**. Guanidinium ylide chemistry provides a complementary methodology to sulfur ylide chemistry, which currently dominates non-metal-mediated asymmetric aziridination.

1.3.2
Aziridines Bearing Alkyl, Aryl, Propargyl, and Vinyl Groups

The usual route to aziridines bearing alkyl, aryl, propargyl, and vinyl groups, as well as to terminal aziridines, is through reactions between ylides and imines. The reaction between an ylide and an imine forms a betaine **115**, which ring-closes to form an aziridine through elimination of the heteroatom-containing leaving group originating from the ylide (Scheme 1.37). The heteroatom-containing group **116** derived from the ylide can thus be recovered and reused. The main class of ylides used in asymmetric aziridination reaction are sulfur ylides.

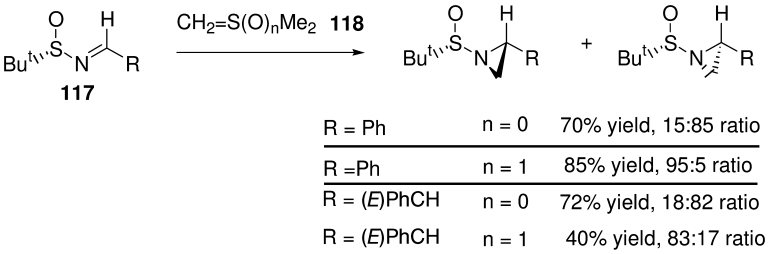


115 116

Scheme 1.37

1.3.2.1 Aryl, Vinyl, and Alkyl Aziridines: Stoichiometric Asymmetric Ylide-mediated Aziridination

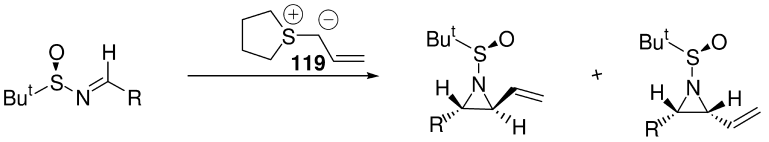
Ruano has reported substrate-controlled asymmetric ylide aziridination by treatment of enantiopure sulfinyl imines **117** with dimethyloxosulfonium methylide **118** to form terminal aziridines [63]. The chiral *tert*-butylsulfinyl group was shown



Scheme 1.38

to be the chiral auxiliary of choice, allowing the synthesis of aziridines in high yields and with good diastereoselectivities (Scheme 1.38).

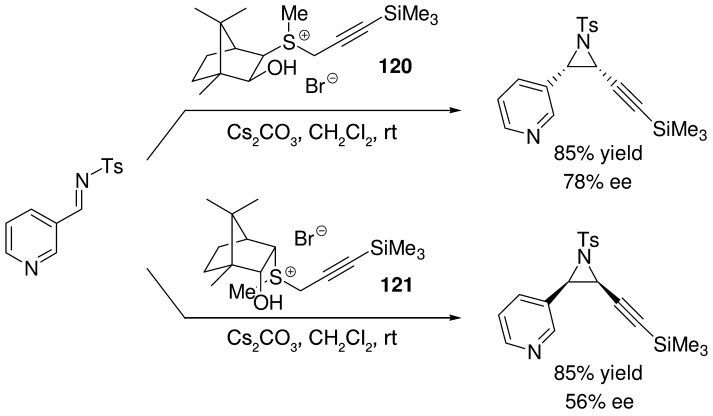
The sense of asymmetric induction could be tuned in two ways: firstly through the chirality of the sufinyl group, and secondly through the use of dimethyloxosulfonium methylide ($n = 1$) or of dimethylsulfonium methylide ($n = 0$), which was found to provide aziridines with opposite diastereoselectivity. This was interpreted by assuming the process to be under thermodynamic control in the former



Scheme 1.39

Table 1.16 Chiral *tert*-butylsulfinylimines in asymmetric aziridine synthesis.

Entry	R	Yield of *trans* aziridines (%)	*trans*:*cis* aziridine
1	Ph	68	71:29
2	*p*-$OMeC_6H_4$	76	82:18
3	*p*-$NO_2C_6H_4$	74	59:41
4	1-naphthyl	64	80:20
5	ethyl	44	80:20
6	cyclopropyl	61	72:28
7	cyclohexyl	78	83:17
8	2-furyl	55	67:33
9	2-piperidine	54	88:12



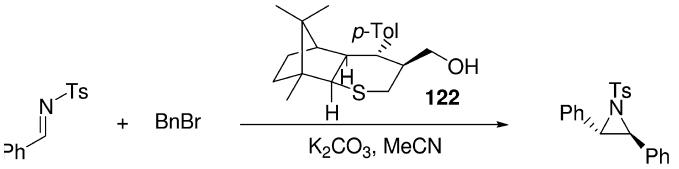
Scheme 1.40

case and under kinetic control in the latter case. When the reaction is under kinetic control the diastereoselectivity is determined in the attack of the ylide on the imine, whereas under thermodynamic control it is dependent on the relative stabilities of intermediate betaines and their relative rates of ring-closure.

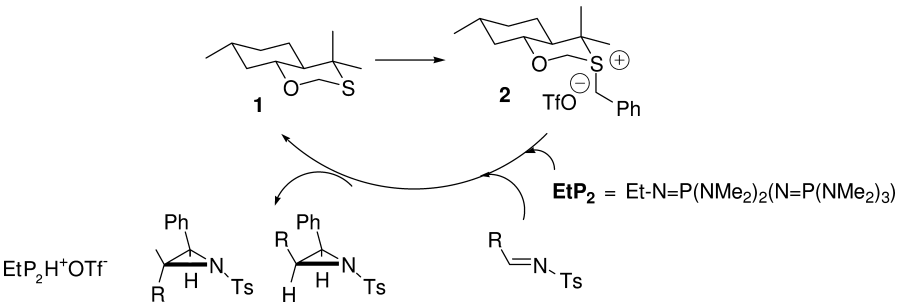
Stockman has reported the preparation of alkyl-, aryl-, and vinyl-disubstituted aziridines with good diastereoselectivities and in good yields through treatment of *tert*-butylsulfinylimines with the ylide **119**, derived from *S*-allyl tetrahydrothiophenium bromide (Scheme 1.39) [64]. A range of substrates were tolerated, including heterocyclic, aromatic, and aliphatic substrates (Table 1.16).

Dai has also studied the synthesis of chiral vinyl aziridines through reactions between allylic ylides and *N*-tosyl imines [65], but did not examine an asymmetric variant because of the low diastereoselectivities. In contrast, propargyl-substituted ylides, generated *in situ* from the corresponding sulfonium salts in the presence of Cs_2CO_3 as the base, were found to afford aziridines in high yields and with exclusive *cis* diastereoselectivity (Scheme 1.40). When the camphor-derived chiral sulfonium salt **120** was employed, variable enantioselectivity (depending on substrate) was obtained, but with complete *cis* diastereoselection, whereas use of the diastereoisomeric sulfonium salt **121** resulted in opposite asymmetric induction. Aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldimines and ketimines could all be employed with high diastereoselectivity, and the chiral sulfide precursors of the sulfonium salts could usually be recovered in high yield. The enantioselectivities varied considerably (40–85% *ee*), however, depending on the substrate.

Saito has recently reported high yields and enantioselectivities in aziridine synthesis through reactions between aryl- or vinyl-substituted *N*-sulfonyl imines and aryl bromides in the presence of base and mediated by a chiral sulfide **122** (Scheme 1.41) [66]. Aryl substituents with electron-withdrawing and -donating groups gave modest *trans*:*cis* selectivities (around 3:1) with high enantioselectiv-



Scheme 1.41



Scheme 1.42

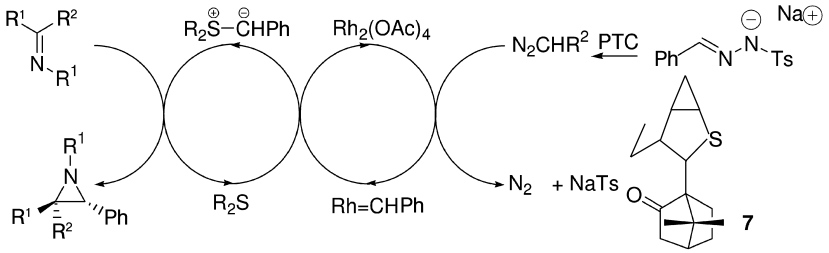
ities (85–99% *ee*). Vinyl-substituted imines gave similar enantioselectivities, but the diastereoselectivities were much lower.

Solladié-Cavallo has recently reported a two-step asymmetric synthesis of disubstituted *N*-tosylaziridines from (R,R,R,S_s)-(–)-sulfonium salt **2** (derived from Eliel's oxathiane; see Section 1.2.1.1) and *N*-tosyl imines with use of phosphazine base (EtP_2) to generate the ylide (Scheme 1.42) [67]. Although the diastereoselectivity was highly substrate-dependent, the enantioselectivities obtained were very high (98.7–99.9%). The chiral auxiliary, although used in stoichiometric quantities, could be isolated and reused, but the practicality and scope of this procedure is limited by the use of the strong – as well as expensive and sensitive – phosphazene base.

1.3.2.2 Aryl, Vinyl, and Alkyl Aziridines: Catalytic Asymmetric Ylide-mediated Aziridination

Of course, the key limitation of the ylide-mediated methods discussed so far is the use of stoichiometric amounts of the chiral reagent. Building on their success with catalytic asymmetric ylide-mediated epoxidation (see Section 1.2.1.2), Aggarwal and co-workers have reported an aza version that provides a highly efficient catalytic asymmetric synthesis of *trans*-aziridines from imines and diazo compounds or the corresponding tosylhydrazone salts (Scheme 1.43) [68–70].

A range of electron-withdrawing groups on the nitrogen – *N*-P(O)Ph_2, *N*-tosyl, and *N*-SES, for example – were tolerated. Imines derived from aromatic, heteroaromatic, unsaturated, and even aliphatic aldehydes and ketones were employed



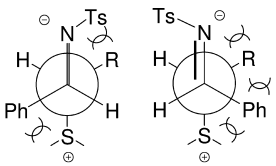
Scheme 1.43

Table 1.17 Catalytic asymmetric ylide-mediated aziridination.

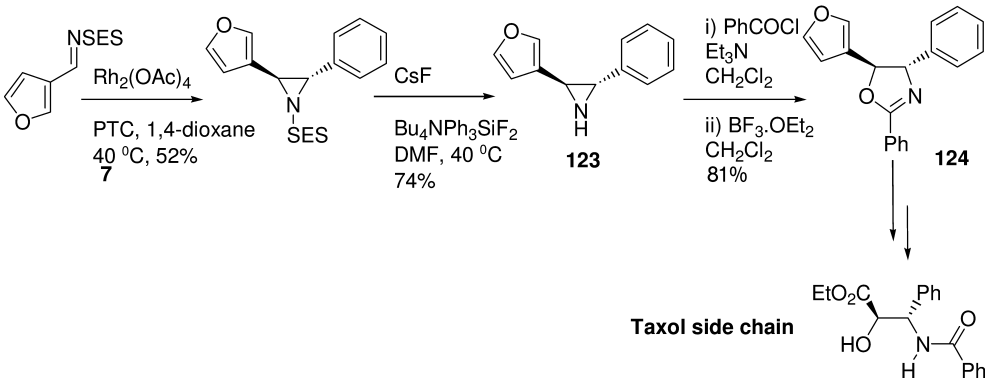
Entry	R^1	R^2	R^3	Yield of *trans* aziridines (%)	*trans*:*cis* aziridine	*ee* (%) *trans*	*cis*
1	*p*-ClC_6H_4	H	TcBoc	56	6:1	94	90
2	*p*-ClC_6H_4	H	SES	82	2:1	98	81
3	C_6H_{11}	H	SES	50	2.5:1	98	89
4	*t*-Bu	H	Ts	53	2:1	73	95
5	(*E*)-PhCH=CH	H	SES	59	8:1	94	–
6	*p*-$MeOC_6H_4$	H	SES	60	2.5:1	92	78
7	3-furyl	H	Ts	72	8:1	95	–
8	Ph	Ph	$SO_2C_8H_7$	50	–	84	–

and good yields were obtained (Table 1.17). High enantioselectivities were obtained in all cases, but diastereoselectivities were dependent both on the nitrogen activating group and on the imine substituent, with carbamate groups giving better diastereoselectivities than the corresponding sulfonyl groups.

The variation of the diastereoselectivity with groups on the nitrogen can be explained by the model shown in Scheme 1.44. Large bulky groups on the nitrogen will increase the congestion in transition state **A**, resulting in reduced *trans* selectivity. However, small groups (e.g., alkoxycarbonyl) will be accommodated in this transition state more easily, resulting in increased amounts of the *trans* isomer. The high enantioselectivity observed is interpreted as in the epoxidation case



A **B** **Scheme 1.44**



Scheme 1.45

(see Section 1.2.1.3), with the key difference being that the betaine formation is non-reversible [70], resulting in higher enantioselectivities and lower diastereoselectivities in general for aziridination than for epoxidation.

The main features of this process are: *i*) high convergency, *ii*) high enantioselectivity, *iii*) catalytic use of chiral sulfide and its quantitative reisolation, *iv*) ready availability of both enantiomers of the sulfide, and *v*) an efficient and user-friendly process. This methodology has been applied to construct the taxol side chain with a high degree of enantioselectivity via a *trans*-aziridine, followed by stereospecific rearrangement of the *trans*-benzoylaziridine **123** into the *trans*-oxazoline **124** (Scheme 1.45) [71].

1.4 Summary and Outlook

Two catalytic asymmetric sulfur ylide-mediated epoxidation processes have been developed. The method involving the reaction between a chiral sulfide and an alkyl halide and base in the presence of an aldehyde is generally limited to the synthesis of stilbene oxide derivatives. The method involving the reaction between a chiral sulfide and a diazo precursor in the presence of a PTC, metal catalyst, and aldehyde shows broader scope. Aromatic, heteroaromatic (but not pyridyl), aliphatic, and unsaturated aldehydes have been employed, together with a range of aromatic and heteroaromatic diazo precursors. Certain aldehydes and diazo precursors give rather low yields of epoxides, but in these cases an asymmetric stoichiometric process can be employed instead. The combined catalytic and stoichiometric processes allow access to a very broad range of epoxides, including glycidic amides and α,β-unsaturated epoxides, aziridines, and cyclopropanes, in many instances with control over both relative and absolute stereochemistry. This broad substrate scope of the process now allows the sulfur ylide disconnection to be applied with confidence in total synthesis. The synthesis of glycidic esters by a Darzens-type reac-

tion remains challenging. Although stoichiometric processes employing chiral reagents or chiral auxiliaries have delivered high selectivity, no useful catalytic process has yet emerged.

Aziridination remains less well developed than epoxidation. Nevertheless, high selectivity in imine aziridination has been achieved through the use of chiral sulfinimines as auxiliaries. Highly successful catalytic asymmetric aziridination reactions employing either sulfur ylides or diazo esters and chiral Lewis acids have been developed, although their scope and potential applications in synthesis have yet to be established.

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