SULFUR IN ASYMMETRIC SYNTHESIS

SERGE REIGNIER

Ph D

2002

Abstract

This thesis is divided into three chapters The first chapter is a review of the literature methods utilised to date in the synthesis of non-racemic chiral sulfoxides, including resolution, stereospecific nucleophilic substitution at sulfur, asymmetric oxidation and enzymatic methods Also, this first chapter introduces briefly the palladium-catalysed allylic nucleophilic substitution reaction, it covers the nature of different factors which can influence on the enantiomeric excess

The second section deals with our approaches to the synthesis of potentially chelating sulfoxides of high enantiomeric purity and their subsequent application, mainly in the process of palladium-catalysed allylic nucleophilic substitution reactions as chiral ligands, but also their application as chiral auxiliaries in the synthesis of chira α-hydroxy or α-amino ketones This second chapter also deals with the design of a new class of chiral amino-sulfides as ligand in the palladium-catalysed allylic nucleophilic substitution reaction

The most successful ligand synthesised enantiomerically pure *N*-(1,1-Dimethylethyl)-*N*-(1S,2S)-2-[(1,1-dimethylethyl)thio]-1-methyl-2-phenylethyl-*N*-methylamine was applied successfully to the palladium-catalysed allylic nucleophilic substitution reaction, furnishing the product in up to 89 % ee

The third part of this thesis deals with the experimental procedures undertaken in this work

Acknowledgments

This thesis and the work preceding it would not have been possible without the help and support of my mother and my brothers Laurent and Cyril, and I am deeply indebted to each of them

The contributions from my supervisor Professor Philip Page have been enormous. Phil has been generous in terms of advice given, in spirit, financially and in terms of friendship, above and beyond the call of duty and I am proud to say that I consider Phil to be a true friend

I could not possibly list all of the friends who made my stay in Loughborough such a fantastic three years They know who they all are, but a few need to be mentioned· Laura who had the brilliant idea to contact the university of Orsay (Paris) for the research of a PhD student Ritzy who spent so much time to correct my English without being too desperate about my English Eddy, for his short replies "Whaz that ?" which means " I didn't understand a word of what you said, Serge, your English is so s**t !!" Coco who everybody considered as a second mother, Pat for her effort to bring me in the right way. Special thanks to Sussie, Tim, and all past and present organic researchers

One particular thank to Jerry for taking t me to share his very wild knowledge and Salem for arguing about chemistry and having great discussions in the EHB

Of course, the drinkers lads, Kev, Rob, Dave, Ed, Fletch, Nigel for organizing pub crawls or pub tours to visit Lufbra and to make my stay as enjoyable as possible when I could manage to remember these such tours

None of the work in this thesis would have been possible without the often unappreciated work carried out by the various members of staff, technicians and secretaries and I would like to thank them all Special thanks go to Tim Smith who never banned me from using the NMR spectrometer even after I crashed it (more than once !!) So many people have contributed to this thesis in many ways that I am bound to have forgotten someone I apologise in advance!

Lastly, I must thank the University of Loughborough, and Philip Page for their generous financial support during my studies

Contents

Chapter 1

Sulfur in Asymmetric Synthesis:

1-A Routes to Non-racemic chiral sulfoxides·

1-A-1 Introduction

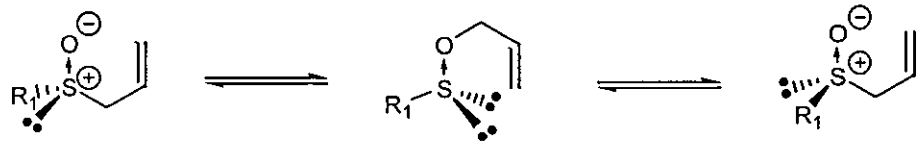
Over the last two decades, organosulfur compounds have been increasingly studied in organic synthesis In particular, sulfoxides have been widely used in organic processes[1] because of their ability to act as electrophiles as well as nucleophiles Furthermore, they have been employed as chiral auxiliaries in asymmetric transformations, especially in C-C bond formation reaction [2]

Because of these attractive chemical properties, many routes have been established for the synthesis of both racemic and non-racemic chiral sulfoxides [3]

The importance of sulfoxides in asymmetric synthesis is explained by the presence of 3 different groups at the sulfur with variable steric and/or electronic effects· a lone pair of electrons, the oxygen atom, and two aryl or alkyl groups The geometry of the sulfur is close to that of a tetrahedral carbon atom Pyramidal inversion at the sulfur centre is not observed at temperatures under 150 °C. (Scheme 1)[4]

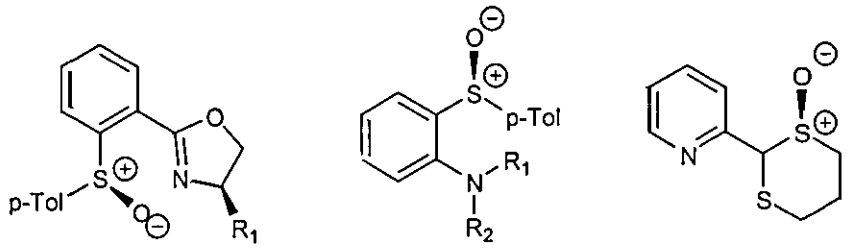
Scheme 1

Some exceptions are encountered such as allylic sulfoxides, which racemise through a [2,3]-sigmatropic shift at room temperature (Scheme 2)[5] Other racemisation conditions have also been observed, including exposure of sulfoxides to HCl in organic solvent, exposure to light (which is not a problem under the normal laboratory conditions), and exposure to organolithiums, although even strong bases do not usually racemise sulfoxides [6]



Scheme 2

Only recently, sulfoxides have roles for asymmetric syntheses other than the formation of covalent bonds They appeared, in 1993, when chiral non-racemic sulfoxides were used as ligands in a catalytic-metal transition process, namely, the palladium-catalysed allylic nucleophilic substitution reaction In the first two examples, the chiral asymmetric sulfoxide moiety was introduced by the Andersen procedure, the third example was synthesized by asymmetric oxidation (Fig 1)[7]



1 2 3

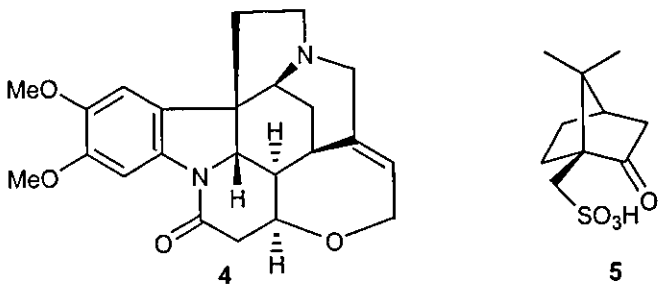
Fig 1

These successful applications of chiral non-racemic sulfoxides have driven research into efficient and relevant routes to enantiomerically pure or enriched sulfoxides, such as the Andersen process (cf 1-A-3) [7] There are very few applications of chiral sulfoxides in asymmetric synthesis where the sulfoxides have been synthesised by asymmetric sulfoxidation [8]

This introduction reports the various processes for access to enantiomerically pure or enriched sulfoxides Only the more useful, relevant and efficient processes are discussed and reported in the following order resolution of racemic sulfoxides, stereoselective nucleophilic substitution at the sulfur atom, asymmetric oxidation at sulfur and, finally, enzymatic processes and related methods used in the preparation of chiral sulfoxides

1-A-2 Resolution of sulfoxides

Harrison[9] described one of the first processes used for the resolution of chiral sulfoxide in 1926 These resolutions were achieved with sulfoxides containing an acid or a basic moiety by formation of diastereoisomeric salts with a chiral non-racemic base or acid, such as (-)-brucine (**4**) and (+)-camphorsulfonic acid (**5**) (Fig 2)



4 **5**

Fig 2

Fifteen years ago, Janczewski reported the resolution of sulfinylacetic acids by using a similar process [10]

The demand for stoichiometric amounts of chiral reagents does not make this process attractive as a route to non-racemic sulfoxides Poor enantiomeric excesses can be observed in some cases [11] Furthermore, this process cannot be applied to the resolution of sulfoxides containing non-basic or acid groups Because of these problems, more elegant and inventive methods have been established

An interesting process was reported, in 1979, by Pirkle[12] who used a chiral stationary phase for the chromatographic separation of enantiomeric sulfoxides This stationary phase was derived by attachment of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol to silica gel (Fig 3), and the separation was run as a chiral HPLC Efficient results were attributed to the presence of a hydroxyl group, the trifluoro group and a π-π donor-acceptor interaction Recently, Pirkle reported a chiral stationary phase,[13] for the separation of sulfoxides by hydrogen bonding between an N-H of the stationary phase and the oxygen atom of the sulfoxide

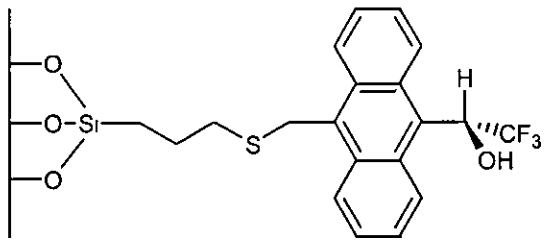
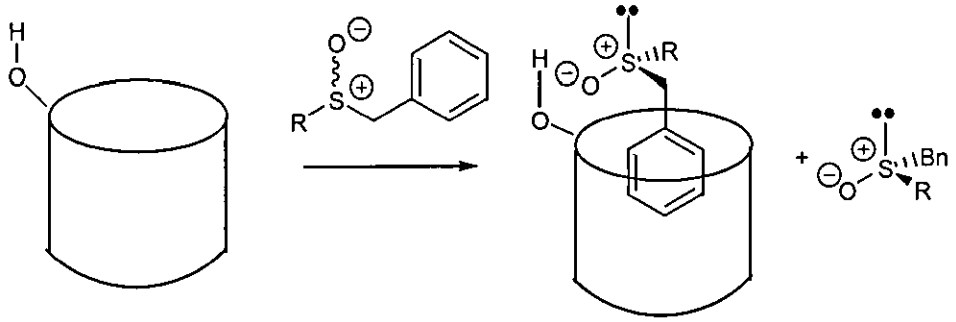


Fig 3

In a similar process,[14] β-cyclodextrin was used to separate phenyl or benzyl sulfoxides The chiral non-polar cavity of the cyclodextrin allows the insertion of one enantiomer of the sulfoxide (Scheme 3), while the sulfoxide moiety interacts with the external hydroxyl groups, leading to diastereoisomeric inclusions The results obtained are generally low, 9 1 % for the resolution of ethyl phenyl sulfoxide, but 68 2 % in the case of sulfinate esters such as isopropyl methyl sulfinate

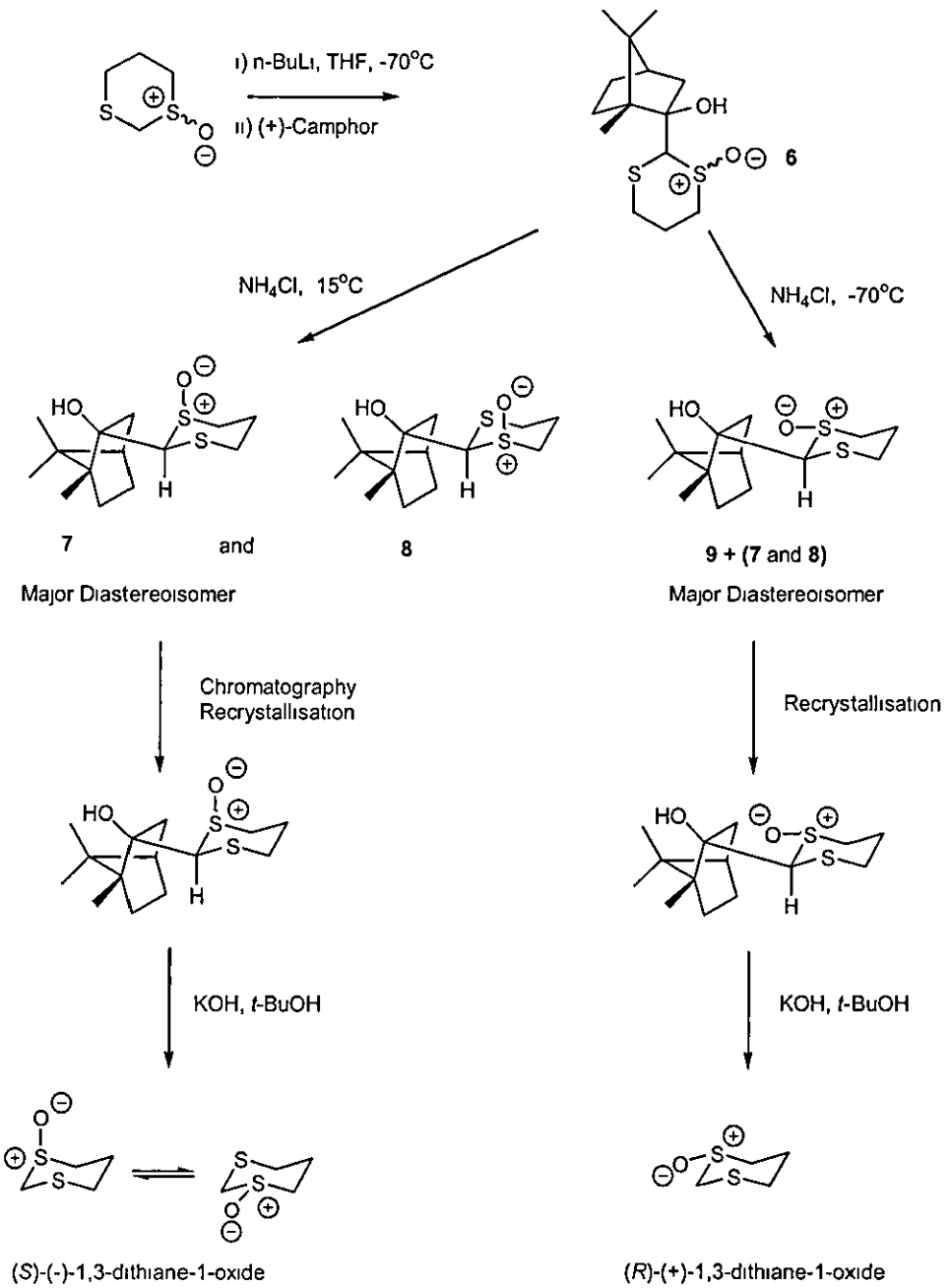


Scheme 3

In 1994, Kagan[15] observed an enantiomeric amplification for the flash column chromatography of (R)-methyl p-tolyl sulfoxide of 86 % ee The first fraction collected gives the product with 99 % ee whereas the last fraction yields the product with only 63 % ee. It has been suggested that a sulfoxide-sulfoxide interaction occurs and the column chromatography consists of the separation of "diastereoisomers"

All these processes depend on the existence of physical interactions However, Carey et al described an interesting synthesis of optically pure 1,3-dithiane-1-oxide using camphor as a

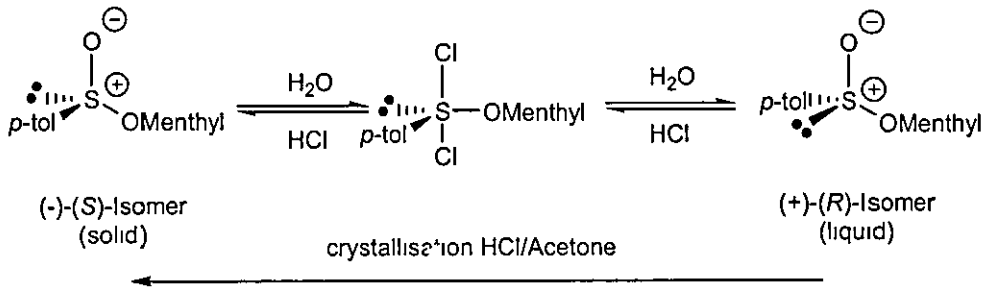
chiral auxiliary[16] (Scheme 4) The ratio of thermodynamic and kinetic intermediates could be controlled by variation of the temperature which lead to optically pure (*S*)-(-)-1,3-dithiane-1-oxide and (*R*)-(+)-1,3-dithiane-1-oxide in 3 5 % and 22 % yields respectively



Scheme 4

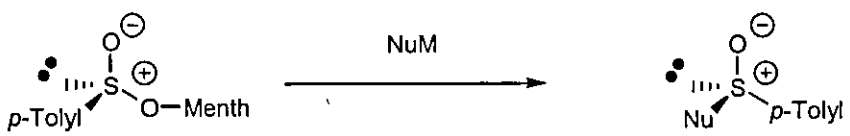
1-A-3 Nucleophilic substitution at sulfur

In 1962, Andersen[17] reported the use of optically pure (-)-(*S*)-menthol in the synthesis of chiral non-racemic *p*-tolyl alkyl sulfoxides The (-)-(*S*)-menthyl *p*-toluenesulfinate was isolated by recrystallisation of one diastereoisomer under interconversion conditions It is known that the use of HCl racemises sulfoxides in organic solvents With the advantage of having one diastereoisomer less soluble, it proved possible to prepare (-)-(*S*)-menthyl *p*-toluenesulfinate in almost quantitative yield (Scheme 5)



Scheme 5

The (-)-(*S*)-menthyl p-toluenesulfinate is then subjected to treatment with Grignard reagent to give sulfoxide with complete inversion at the sulfur atom This process is largely used for large scale preparation of optically pure sulfoxides but it is limited to p-tolyl sulfoxides and the range of available Grignard reagents (Scheme 6, table 1)

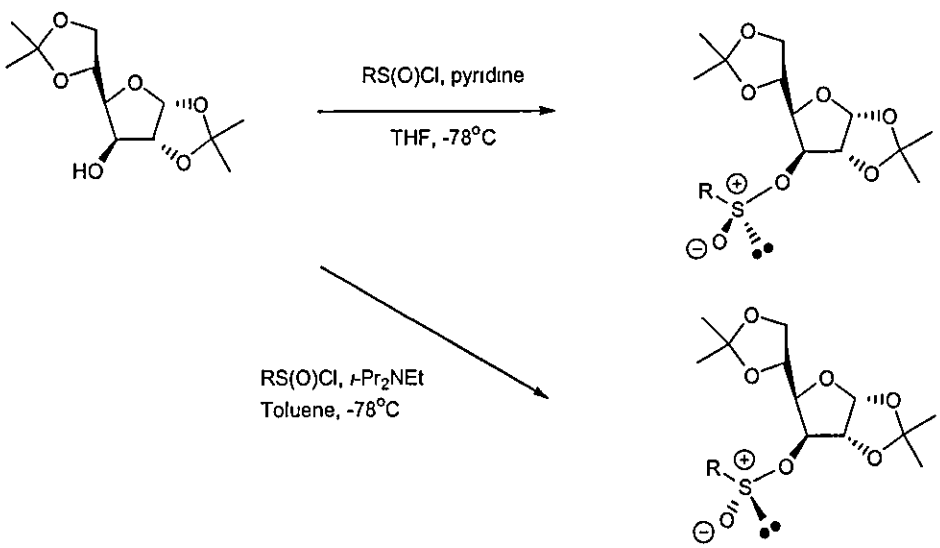


Scheme 6

Table 1

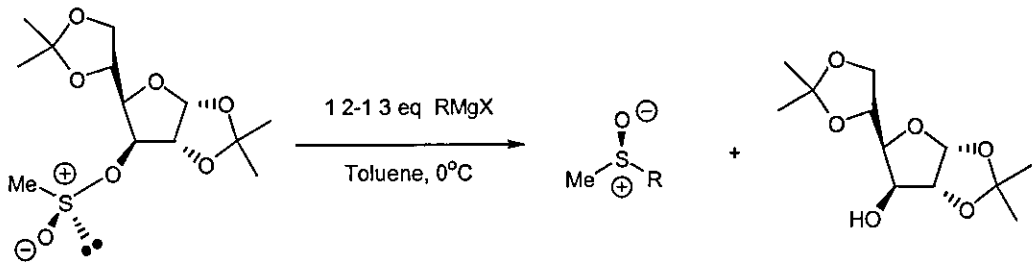
NuM / Solvent	Yield (%)	ee (%)
Me_2CuLi / Et_2O	55	85 1
MeMgBr / Et_2O	61	85 0
MeMgBr / PhH	82	89.5
EtMgBr / Et_2O	62	91 5
EtMgBr / PhH	92	97 5
PhMgBr / PhH	88	([α] = 20 0)
Ph_2CuLi / Et_2O	52	([α] = 20 0)

Alcudia[18] reported a similar process to the Andersen procedure in 1992 using (1,2 5,6-di-O-isopropylidene-α-D-glucofuranose) diacetone-D-glucose (DAG), which leads to both enantiomers of the sulfoxide The employment of the appropriate base-solvent system in the formation of the intermediate sulfenate from sulfinyl chlorides and DAG allows access to both diastereoisomers (Scheme 7)



Scheme 7

Subsequent treatment with Grignard reagents leads to optically pure sulfoxides The range of accessible sulfinyl chlorides and Grignard reagents only limits this process (Scheme 8, table 2)

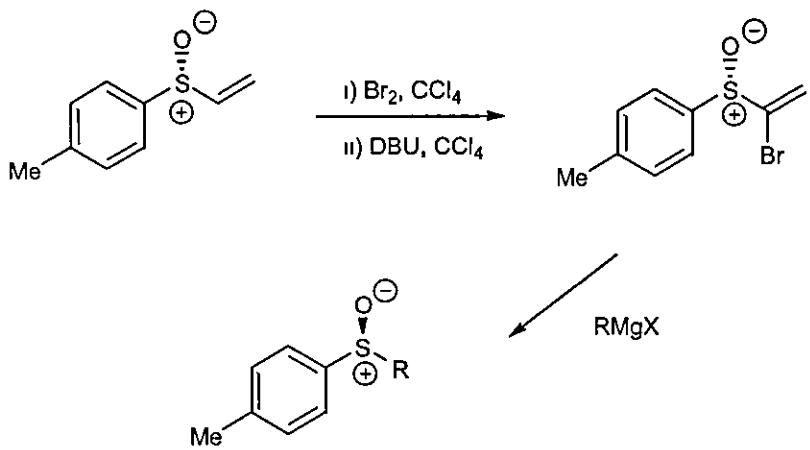


Scheme 8

Table 2

R	Yield (%)	ee (%)
p-Tol	84	100
Ph	78	100
Bn	83	100
n-Pr	66	100
t-Bu	62	100

Naso[19] has used optically pure chiral vinyl sulfoxides in displacement of a halovinyl group by subsequent bromination and Grignard addition, leading to sulfoxides with high optical purity. This process is dependent on the accessibility of the Grignard reagent used and the availability of the chiral vinyl sulfoxides (Scheme 9, table 3)

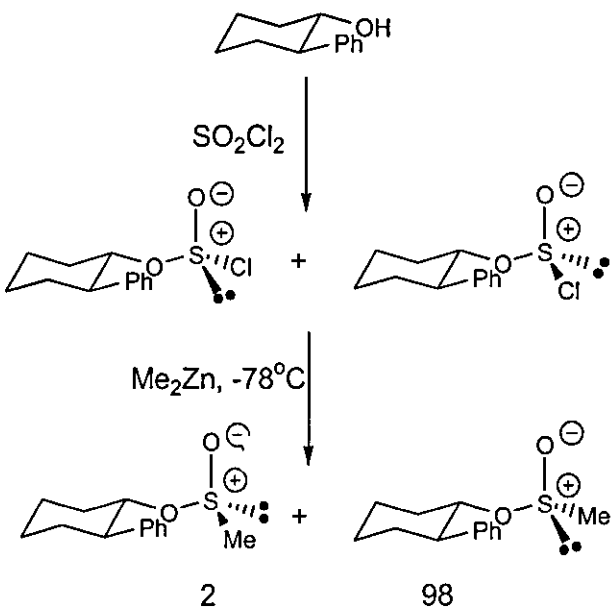


Scheme 9

Table 3

R	Yield (%)	ee (%)
Ph	77	100
n-Bu	81	99
n-Pr	78	100
i-Pr	86	100
Et	73	98

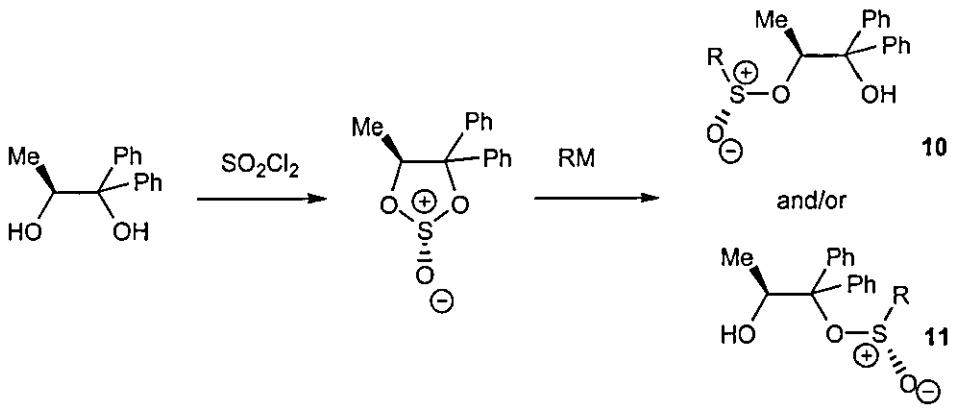
Whitesell[20] has reported the use of thionyl chloride as sulfur source in the formation of a chlorosulfinate ester, which can undergo reaction with alkylzincs to form alkylsulfinate esters. (Scheme 10)



Scheme 10

Kagan[21] has extended the use of sulfites which were developed by Mikoljczyk[22] who used a chiral amine in the asymmetric synthesis of t-butyl-alkanesulfinates in good yields and encouraging enantiomeric excesses Instead of chiral amines, Kagan has used chiral 1,2-diols for the preparation of optically pure cyclic sulfites which were subsequently treated with

organometallic reagents to afford 1,2-hydroxy sulfinates intermediates **10** and/or **11**. (scheme 11, table 4)



Scheme 11

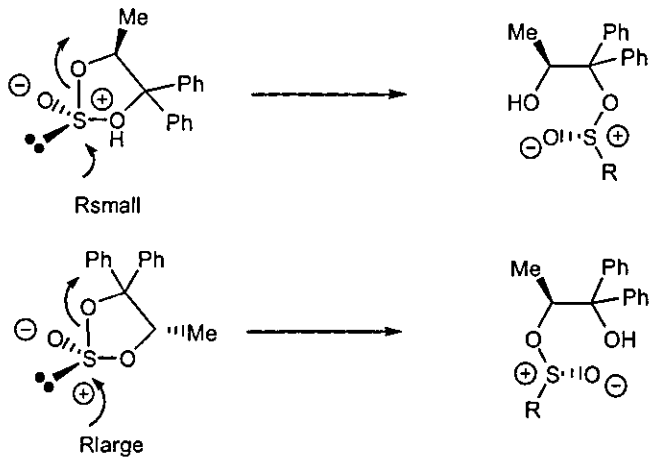
Table 4

RM	Product ratio **10 11**	Yield [a] (%)
MeLi	75 25	55
MeMgBr	80 20	70
EtMgBr	92 8	80
n-OctMgBr	95 5	60
t-BuMgBr	5 95	60
t-BuMgCl	10 90	70
BnMgCl	70 30	50
VinylMgCl	95 5	50
MesMgBr	12 88	70
PhMgBr	50 50	[b]

a) Isolated yield of major isomer, b) Separation failed

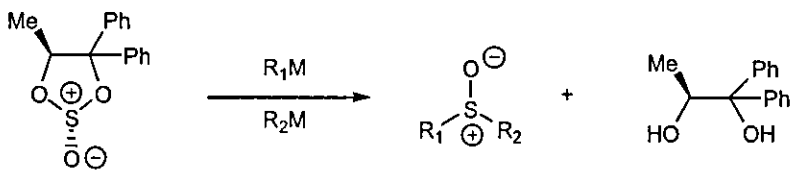
The regioselectivity of attack has been attributed to steric interactions between the bulky O-CPh_2 fragment and the incoming nucleophile in a trigonal bipyramidal transition state With a small nucleophile, the bulky O-CPh_2 fragment can lie in a preferred equatorial position with

concomitant attack at sulfur from an apical position In the case of large nucleophile, steric interactions between the incoming group and the two phenyl groups means adoption of an apical position for O-CPh_2 becomes favoured (Scheme 12)



Scheme 12

Subsequent treatment of the enantiomerically pure sulfinate esters with organometallic reagents leads to a wide range of sulfoxides with impressive enantioselectivities and coupled with a quantitative recovery of the chiral auxiliary make this an attractive route to access optically pure sulfoxides (Scheme 13, table 5)

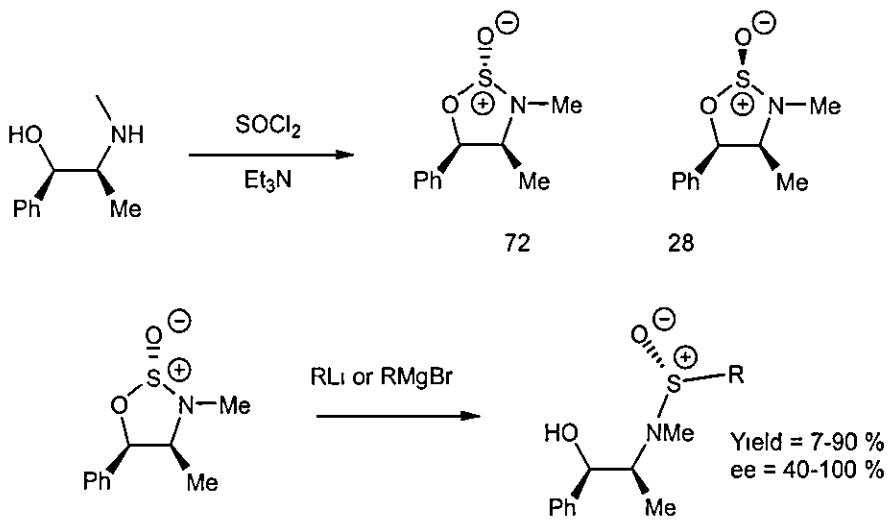


Scheme 13

Table 5

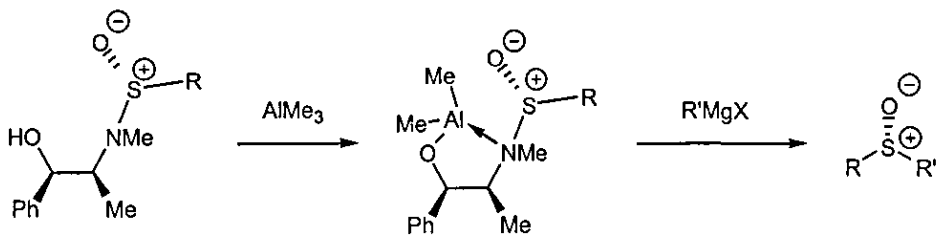
R_1	R_2	Config.	Ee (%)
t-Bu	Me	R	100
t-Bu	Ph	S	100
t-Bu	*n*-Bu	R	100
t-Bu	Vinyl	R	100
Mesityl	Me	R	100
Mesityl	Ph	R	100
Me	*n*-Oct	R	100
n-Oct	Me	S	100
Et	Bn	R	100
Bn	Et	S	100

Similar processes were reported by Wudl and Lee[23] using (-)-ephedrine in the formation of the sulfinamide intermediates, but partial racemisation was observed under these reaction conditions and several equivalents of the second Grignard reagent are required (Scheme 14)



Scheme 14

Later, Snyder[24] improved this process by introducing trimethylaluminium, which reduces to one equivalent the required quantity of the second Grignard reagent, and suppresses the racemisation process (Scheme 15, table 6)

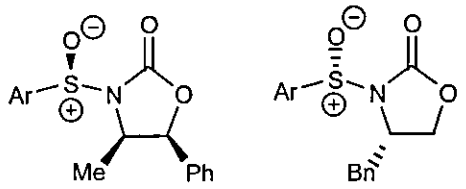


Scheme 15

Table 6

R	R'MgX	Yield (%)	ee (%)
Me	PhMgBr	71	>99
Me	*n*-BuMgCl	76	>99
Me	*t*-BuMgCl	63	>99
Vinyl	PhMgBr	75	>99
Allyl	PhMgBr	62	>99
i-Pr	PhMgBr	82	>99

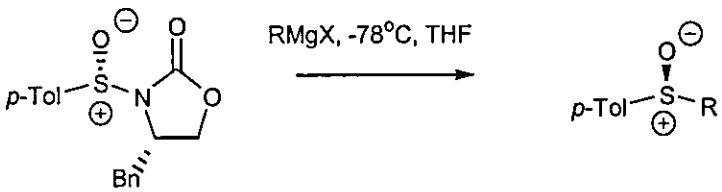
Evans and co-workers[25] have reported the use of oxazolidinones **12** and **13** derived from (-)-ephedrine and phenylalanine as chiral auxiliaries for a wide range of process These oxazolidinones were synthesized both by reaction of a sulfinyl chloride, leading to a 4 1 mixture of separable diastereoisomers, or by oxidation of the sulfenamide with *m*-CPBA, leading to a 1 2 mixture of diastereoisomers (Fig 4)



12 13

Fig 4

Subsequent treatment with Grignard reagents proceeds in excellent yield and with very high selectivities (Scheme 16, table 7)

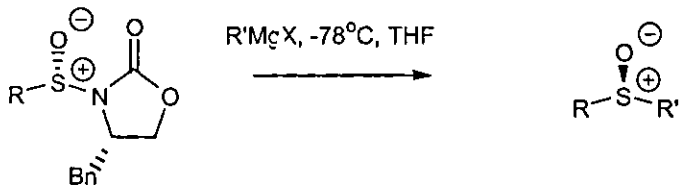


Scheme 16

Table 7

R	Yield (%)	ee(%)
Me	90	99
Et	90	98
i-Pr	91	97
t-Bu	88	97
Bn	86	99

In contrast to the Andersen procedure, the diastereoisomeric N-alkylsulfinyl precursors to dialkyl sulfoxides are readily separable, and therefore provide an excellent high yielding and highly selective route to dialkyl sulfoxides (scheme 17, table 8)

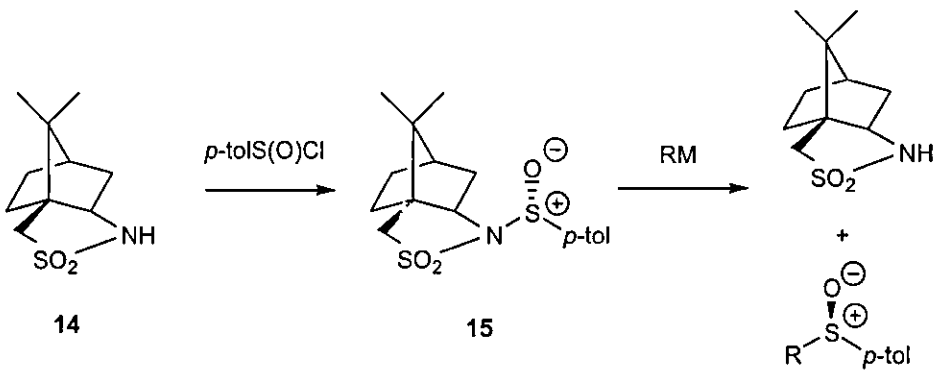


Scheme 17

Table 8

R	R'	Yield (%)	ee (%)
Me	Ph	87	90
Me	*t*-Bu	78	93
Me	Bn	82	91
Me	Octyl	78	100
t-Bu	Me	92	100
t-Bu	*n*-Bu	91	100

Recently, camphor sultam (**14**) has been reported in the formation of a sulfinylsulfonamides (**15**) by Oppolzer[26] Separation of the major diastereoisomer by recrystallisation and treatment with Grignard reagents furnished a variety of chiral sulfoxides in high yields and selectivities (Scheme 18, table 9)



14 **15**

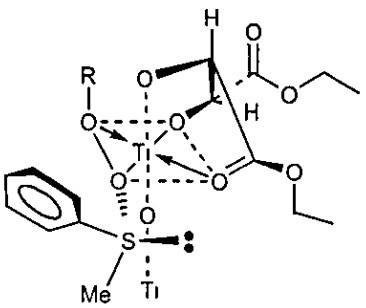
Scheme 18

Table 9

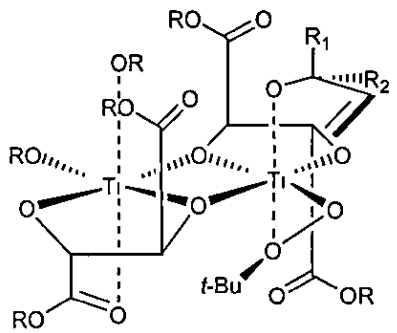
RM	Yield (%)	ee (%)	Sultam Yield (%)
MeMgBr	93	99	91
i-PrMgCl	92	99	91
n-BuMgCl	97	97	94
BnMgCl	91	>99	93
VinylMgCl	95	96	95
AllylMgCl	96	>99	98

1-A-4 Asymmetric oxidation of sulfides

In 1984, Kagan[27] and Modena[28] reported independently modifications of the Sharpless asymmetric epoxidation reaction conditions effective for the oxidation of sulfides First, sulfoxidation occurred in good yields but the sulfoxides appeared to be obtained in a racemic form Further studies by Kagan showed a need for one equivalent of water to reach high levels of asymmetric induction This feature was discovered accidentally when employing wet titanium tetraisopropyloxide[29] Kagan proposed a possible transition state (**TS1**) related to that of the asymmetric Sharpless epoxidation, which is a bimetallic transition state (**TS2**) (fig 5), but the main difference between these two transition states is that there is a covalent bond between the allylic alcohol substrate and the titanium metal in the Sharpless asymmetric epoxidation of allylic alcohols



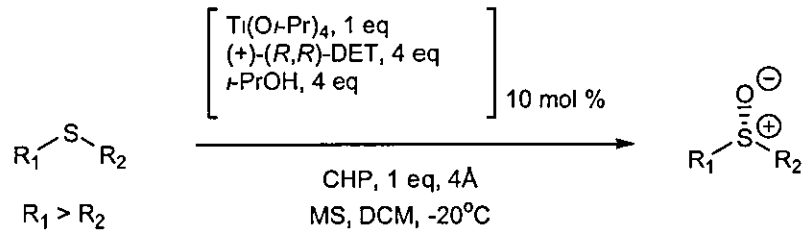
TS1 Modified Sharpless Asymmetric Oxidation of Sulfides



TS2 Sharpless Asymmetric Epoxidation of Allylic Alcohols

Fig 5

High similarities were found between the Sharpless asymmetric epoxidation process and its modified version Best enantioselectivities were obtained with the use of cumene hydroperoxide[30] instead of t-butyl hydroperoxide, but also the presence of molecular sieves has a great influence by a possible regulation of the amount of water in the reaction Kagan[31] described in 1996 an adapted catalytic system using isopropanol in place of water (Scheme 19, table 10)

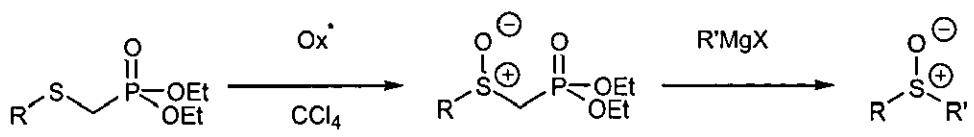


Scheme 19

Table 10

R_1	R_2	Yield (%)	ee (%)
Phenyl	Me	81	91 2 (R)
p-Tolyl	Me	77	95 6 (R)
p-Anisyl	Me	73	92 1 (R)
o-Anisyl	Me	72	89 3 (R)
p-NitroPhenyl	Me	51	75 0 (R)
Phenyl	Vinyl	58	55 4 (R)
p-Tolyl	Et	68	78 1 (R)
p-Tolyl	*n*-Bu	70	25 0 (R)
o-Anisyl	Ph	64	6 2 (R)
Benzyl	Me	72	90 3 (R)
n-Octyl	Me	69	70 7 (R)

This process has been widely employed in the synthesis of chiral sulfoxides by Naso[32] who studied the nature of the leaving group in nucleophilic substitution reactions on chiral sulfoxides induced by Grignard reagents (Scheme 20, table 11)



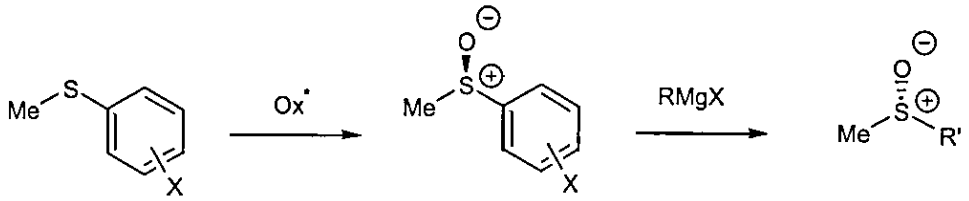
Ox• TBHP or CHP, Ti(O-Pr)4/(R)Binol/H2O

Scheme 20

Table 11

R	R'	Yield (%)	ee (%)
Me	*n*-Octyl	54	>98 (R)
Me	*n*-Decyl	46	>98 (R)
Me	*n*-Octadecyl	49	>98 (R)
Me	Cyclohexyl	50	>96 (R)
Me	*t*-Butyl	15	>98 (R)
Me	(E)-2-Styryl	43	>98 (R)
Et	*n*-Octyl	40	91 (R)
Et	*p*-Tolyl	36	91 (R)
Ph	Me	60	94 (S)
Ph	*p*-Tolyl	42	94 (R)

Naso[32] has shown as well that aryl groups can be good leaving group and be displaced by Grignard reagents (Scheme 21, table 12)



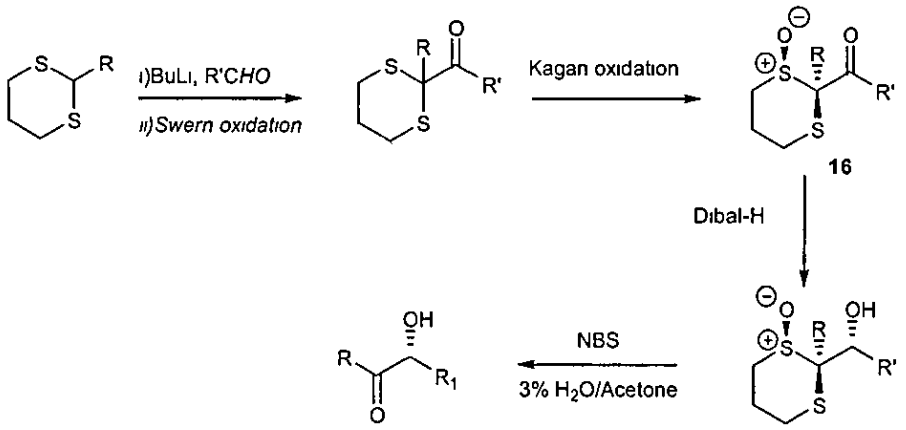
Ox• CHP, CH_2Cl_2, $Ti(O\text{-}Pr)_4$/(*R*,*R*)-DET/H_2O

Scheme 21

Table 12

X	Yield of sulfoxidation (%)	Ee (%)	R	Yield (%)	ee (%)
2-OMe	86	88 (R)	*n*-Decyl	40	86 (S)
3-OMe	70	93 (R)	''	56	91 (S)
4-OMe	72	92 (R)	''	24	92 (S)
2-Cl	94	80 (R)	*n*-Octyl	65	81 (S)
4-Cl	76	91 (R)	*n*-Decyl	73	89 (S)
2-Br	77	83 (R)	*n*-Octyl	68	85 (S)
3-Br	67	97 (R)	*n*-Decyl	81	96 (S)
4-Br	88	98 (R)	*n*-Octyl	84	>98 (S)
''	''	''	*n*-Tridecyl	74	''
''	''	''	*n*-Tetradecyl	90	''
''	''	''	*n*-Hexadecyl	77	''
''	''	''	Cyclohexyl	72	''

Page et al[33] have employed Sharpless modification sulfoxidation procedures for the synthesis of chiral 2-substituted-1,3-dithiane-1-oxide (Scheme 22, table 13) He has shown many applications of the 1,3-dithiane-1-oxide species as a chiral auxiliary in asymmetric synthesis, for example, in the preparation of chiral α-hydroxy ketones



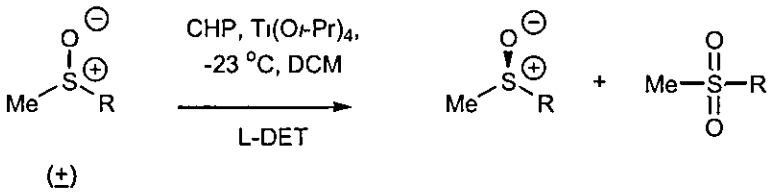
Scheme 22

Table 13

R	R'	Yield of **16** (%)	ee (%)
Ph	Me	anti 65	99
		syn 6	99
Ph	Et	anti 42	97
		syn 15	57
Me	Me	anti 47	78
		syn 43	82
Me	Ph	anti 58	86
		syn 0	-
Et	Me	anti 61	81
		syn 4	‡
Et	Et	anti 67	87
		syn 6	‡
Et	F	anti 60	90
		syn 6	‡
Et	Bn	anti 65	82
		syn 0	-
Et	Bn-CH_2	anti 61	81
		syn 2	81

‡ ee not determined

The modified Sharpless sulfoxidation process developed by Kagan has also been studied by Scettri & Lattanzi for the kinetic resolution of racemic sulfoxides[34] They investigated the nature of different hydroperoxides based on cumyl and furyl structures (Scheme 23, table 14 and Scheme 24, table 15)

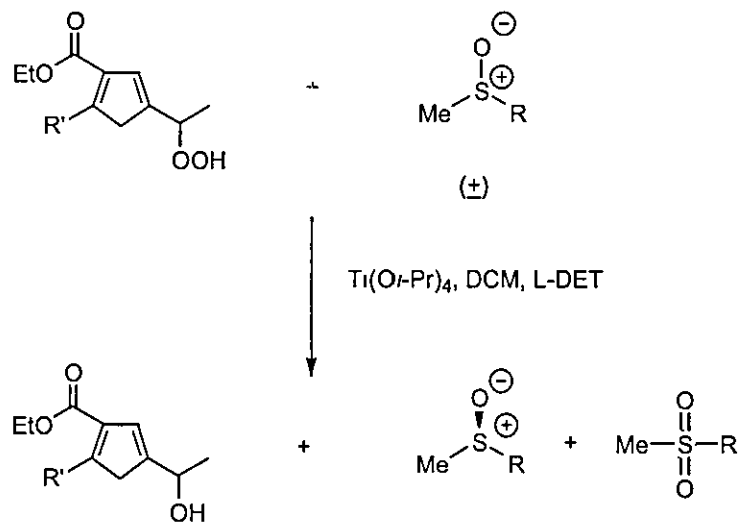


Scheme 23

Table 14

R	Yield (%)	ee (%)
p-Tolyl	40	83 (R)
Phenyl	39	87 (R)
p-Cl-Ph	31	94 (R)
Benzyl	31	9 (R)
p-Tolyl	75	13 (R)[a]

a) THP was employed



Scheme 24

Table 15

R	T (°C)	Yield [a] (%)	ee (%)
p-Tolyl	-23	38	>95 (R)
Phenyl	''	38	91 (R)
p-Cl-Ph	''	40	95 (R)
p-Tolyl	-15	49[b]	73 (S)
Phenyl	0	64[c]	40 (R)
p-Tolyl	0	48	81 (R)
p-Cl-Ph	''	38	76 (R)
Phenyl	''	38	83 (R)

a) All experiments were carried out with furylhydroperoxide R'=*i*-Pr unless notified, b) D-DET was employed,

c) In this experiment furylhydroperoxide R'=CH3 has been used

Another increasingly important method for asymmetric sulfoxidation is the employment of chiral imines or oxaziridines In 1977, Davis[35] reported for the first synthesis and uses of stable chiral camphor-derived sulfonyl oxaziridines (Fig 6 **17, 18, 19, 20**), which proved to be efficient in the synthesis of sulfoxides, but enantioselectivities were low

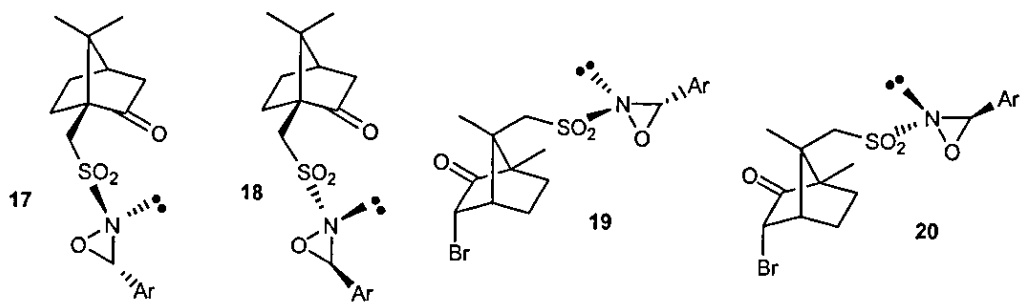
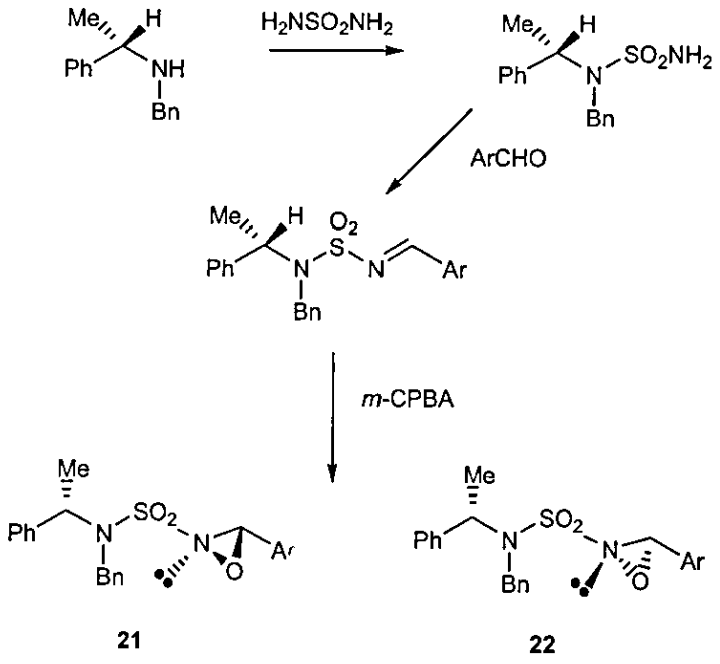


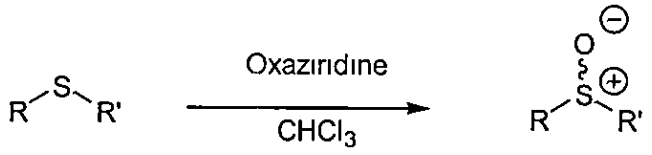
Fig 6

Davis[36] prepared sulfonyl oxaziridines (Scheme 25, **21** and **22**) from chiral secondary amine by conversion to the imine and oxidation to the two separable diastereoisomers of the oxaziridine by column chromatography in a mixture of 1 1



Scheme 25

Both of these oxazıridines wıth a varıety of aryl groups were used to oxıdıse several sulfides under a varıety of condıtıons to yıeld a large volume of data, a selectıon of whıch ıs reported here (Scheme 26, table 16)



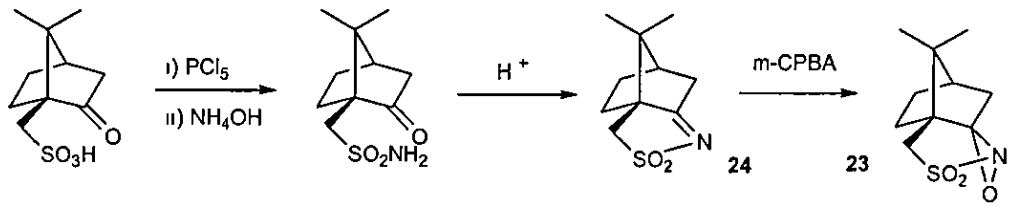
Scheme 26

Table 16

Oxazıridıne	Ar	Temp (°C)	Sulfoxide ee (%) / (Abs Conf)	
			i-Pr-S-*p*-Tol	9-Anthryl-S-Me
(*R*,*R*)-**22**	a	25	21 0 (R)	29 0 (R)
(*R*,*R*)-**22**	b	25	4 0 (R)	15 9 (R)
(*S*,*S*)-**21**	c	25	37 6 (S)	53 0 (S)
(*R*,*R*)-**22**	d	25	37 0 (R)	69 9 (R)
(*S*,*S*)-**21**	d	25	30 0 (S)	64 9 (S)
(*S*,*S*)-**21**	e	-42	52 2 (S)	77 4 (S)
(*S*,*S*)-**21**	e	-78	60 3 (S)	90 6 (S)

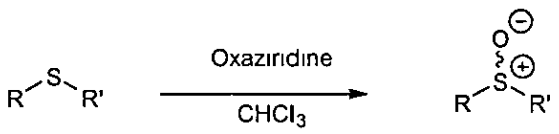
a = 3-NO_2-C_6H_4, b = 2-Cl-C_6H_4, c = 2-Cl-5-NO_2-C_6H_3,
d = 3,5-NO_2-C_6H_3, e = C_6F_5

It was only in 1988 that Davis[37] reported a synthesis of cyclic oxazıridines derived from camphor sulfonic acid These oxazıridines have the advantage that upon oxidation of the imine only one isomer of oxazıridine (**23**) is formed, which simplifies their purification (Scheme 27)



Scheme 27

The selectivity of the oxazıridine (**23**) in oxidation was also rationalised in terms of minimising steric interactions in a non-spiro transition state, although enantioselectivity was not high, except in the case of methyl 9-anthryl sulfide (Scheme 28, table 17) In addition, the reactivity of **23** was found to be about half that of **21** and **22** This lowering of activity was ascribed to increased steric bulk around the oxazıridine and the presence of electron donating groups which reduce the electrophilicity of the oxazıridine.

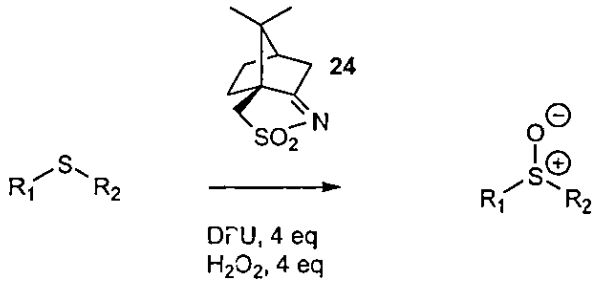


Scheme 28

Table 17

Oxazıridıne	R	R'	ee (%) / (Abs Conf)
(+)-**23**	*p*-Tolyl	*n*-Bu	2 9 (S)
(+)-**23**	*p*-Tolyl	*ı*-Pr	4 7 (S)
(-)-**23**	*p*-Tolyl	*n*-Bu	3 5 (R)
(-)-**23**	*p*-Tolyl	*ı*-Pr	5 3 (R)
(+)-**23**	9-Antrhyl	Me	72.7 (S)
(+)-**23**	9-Anthryl	*ı*-Pr	66 2 (S)
(-)-**23**	9-Anthryl	Me	77 5 (R)
(-)-**23**	9-Anthryl	*ı*-Pr	68 0 (R)

Page[38] recently published a new system for catalytic asymmetric oxidation using a modified Payne oxidation, which involves *in-situ* a highly reactive oxidant This catalytic process employed camphorsulfonylimines similar to those used by Davis The absolute configurations of the sulfoxide product were opposite when imine (**24**) and oxazirıdine (**23**) were employed (Scheme 29, table 18)



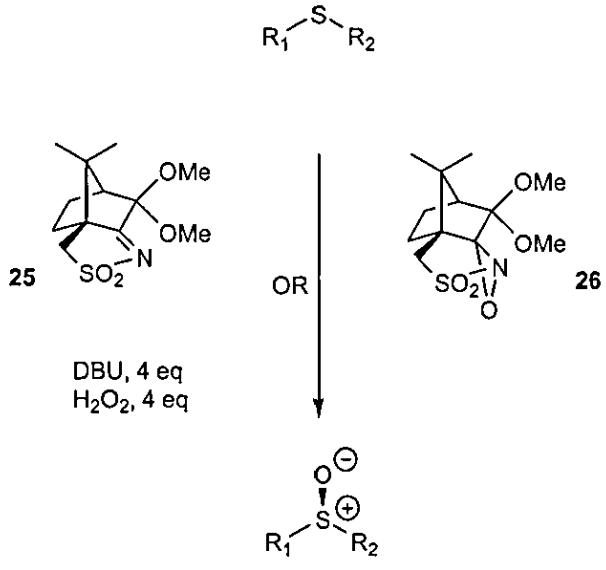
Scheme 29

Table 18

R1	R2	Yield (%)	ee (%)	Abs Conf
t-Bu	Me	83	42	R
Bn	Me	100	35	R
p-Tol	Me	100	20	R
t-Amyl	Me	87	26	-
2-Phenyl-1,3-dithiane		100	44[a]	S
2-Pivaloyl-1,3-dithiane		66	49[a]	S

a) *anti* isomer

After many investigations of the nature of the group at the α position of the imine, Page[39] reported in 1995, the application of 8,8-dimethoxycamphor sulfonyl imine (**25**) which improved reactivity and enantioselectivities In this case, the corresponding oxaziridine (**26**) gave similar results and selectivities, including the same absolute configuration at the sulfur atom, in contrast to the process using the unsubstitued imine (**24**) instead (Scheme 30, table 19)

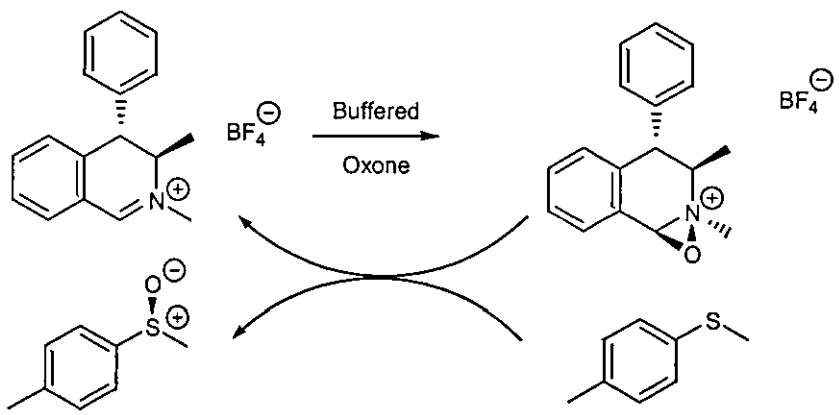


Scheme 30

Table 19

R_1	R_2	ee (%), (Yield (%))	
		Imine (**25**) / H_2O_2	Oxaziridine (**26**)
Me	*t*-Bu	86 *S* (100)	85 *S* (100)
Me	Bn	63 *S* (100)	49 *S* (100)
Me	*p*-Tol	60 *S* (96)	61 *S* (100)
Me	Cyclohexyl	66 (+) (100)	53 (+) (100)
2-Phenyl-1,3-dithiane		≥98 *S* (100) (anti)	98 *S* (100) (anti)
2-*t*-Butyl-1,3-dithiane		78 *R* (46) (anti)	83 *R* (68) (anti) 85 *R* (28) (syn)
1,3-dithiane		32 *R* (77)	36 *R* (96)

Recently, Lusinchi[40] published a promising process based on the use of a chiral iminium salt as catalyst for the oxidation of sulfides The positive charge on the nitrogen appeared to make the iminium salt more active than oxaziridines, perhaps due to their increased electrophilicity. This chiral iminium salt was treated in presence of buffered Oxone®, perhaps to give a very active oxaziridinium oxidant (Scheme 31, table 20) These oxaziridinium salts seem to oxidise sulfides species to sulfoxides very efficiently but with a lack of stereochemistry

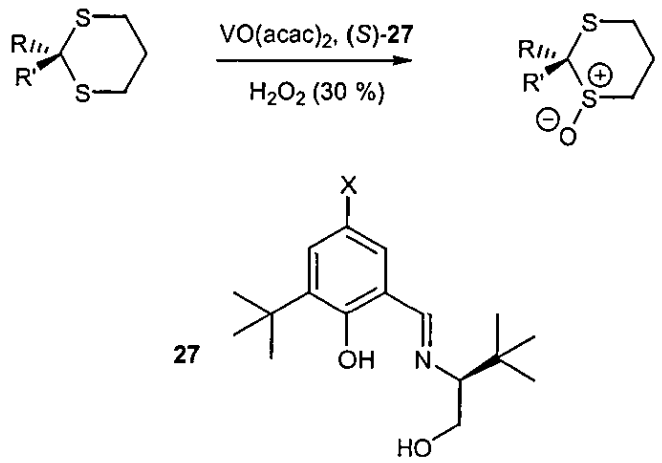


Scheme 31

Table 20

Solvent	Yields % (conversion)	ee % (abs Config)
CH_2Cl_2	60 (100)	35 (S)
C_6H_6	76 (100)	37 (S)
n-C_5H_{12}	93 (100)	37 (S)

In 1995, Bolm[41] reported the catalytic asymmetric sulfoxidation by a chiral vanadium complex of dithioacetals and dithioketals Many advantages were observed, including the use of 30 % aqueous H_2O_2 as terminal oxidant, the simplicity of the reaction conditions, its catalytic efficiency (0 01-1 mol% of catalyst), and the use of simple ligands (1 5 mol%), (e g **27**) derived from amino alcohol and salicylaldehydes (Scheme 32, table 21)



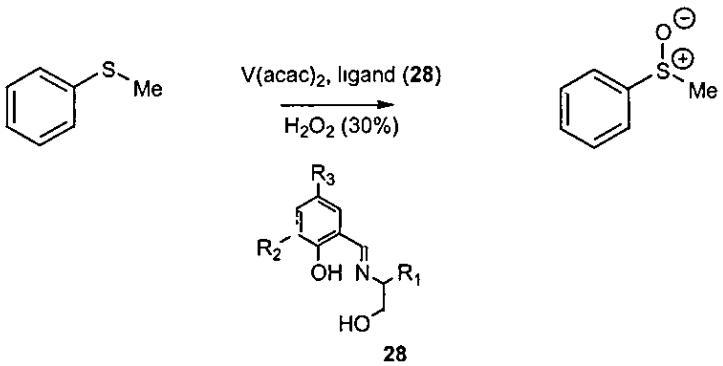
Scheme 32

Table 21. Asymmetric oxidation of dithioacetals and dithioketals to give sulfoxides catalysed by 1 mol% of $[VO(acac)_2]$ and 1 5 mol% of ligand (*S*)-**27** (X=*t*-Bu)

R	R'	Yield (%)	ee (%)	Optical rotation
Ph[a]	H	77	76	(-)
Ph	H	84	85	(-)
p-Tol	H	79	77	(-)
P-Cl-Ph	H	87	64	(-)
p-MeO-Ph	H	60	57	(-)
o-Br-Ph	H	81	64	(-)
o-NO_2-Ph	H	75	62	(+)
t-Bu	H	67	46	n d [b]
$C(CH_3)_3CH_2OH$	H	62	47	(+)
Ph	Me	44 (cis)	68	n d
		37 (trans)	12	(-)
o-Br-Ph	Me	57 (cis)	85	n d
		25 (trans)	15	n d

a) Ligand J (*S*) (X=NO_2) was used in this run, b) n d = not determined

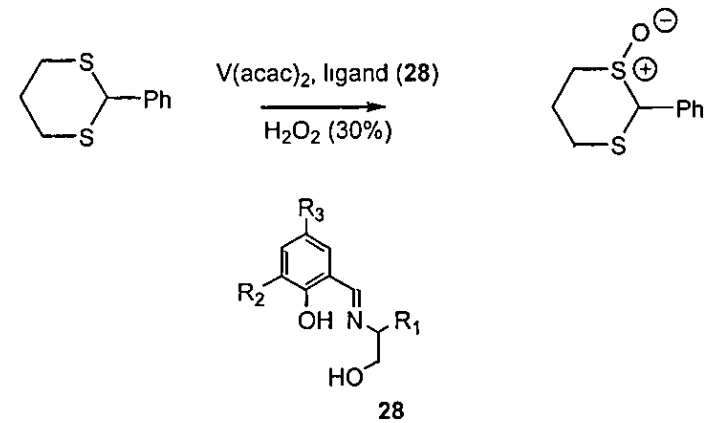
Recently, Skarzewski[42] published his research on this process for the optimisation of the different groups from the ligand and obtained optimum results with the ligand (**28**), and applied the catalytic process to aryl sulfides, 1,3-dithiane species, and bis(arylthio)alkanes, giving excellent ees (Scheme 33, table 22 and Scheme 34, table 23) Skarzewski confirmed the observation reported by Bolm that the chirality transfer occurred generating the same configuration at the sulfur atom as in the catalyst, i e (*S*)-sulfoxide was formed using the ligands derived from L-valinol, and (*R*)-sulfoxide was obtained with that of D-valinol



Scheme 33

Table 22

R_1	R_2	R_3	Yield (%)	ee (%)
t-Bu	*t*-Bu	NO_2	94	70
t-Bu	*t*-Bu	*t*-Bu	73	59
i-Pr	Ph	NO_2	90	75
t-Bu	Ph	NO_2	74	73
i-Pr	*t*-Bu	NO_2	64	69
Ph	Ph	NO_2	74	15
Ph	*t*-Bu	*t*-Bu	79	30
i-Pr	*t*-Bu	*t*-Bu	58	50



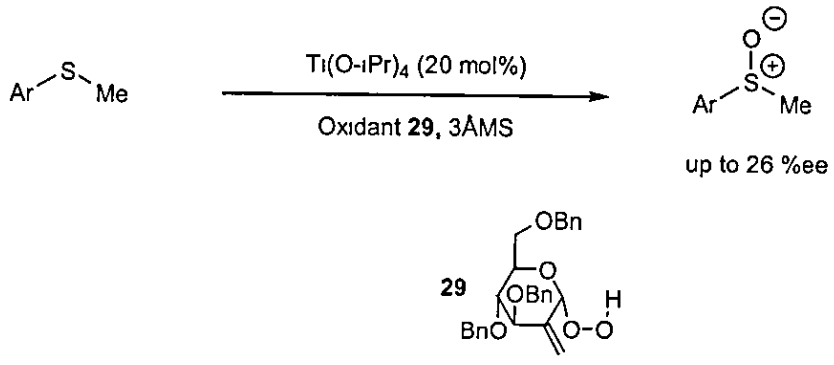
Scheme 34

Table 23

R_1	R_2	R_3	Yield (%)	ee (%)[a]
t-Bu	*t*-Bu	NO_2	77	76
t-Bu	*t*-Bu	*t*-Bu	84	85
i-Pr	Ph	NO_2	80	88
t-Bu	Ph	NO_2	88	71

a) only *trans* product observed

Optically pure sugar hydroperoxides have been shown by Hamann et al [43] to oxidise methyl aryl sulfides, in a similar process to the modified Sharpless sulfoxidation developed by Kagan, with up to 26 % ee (Scheme 35)

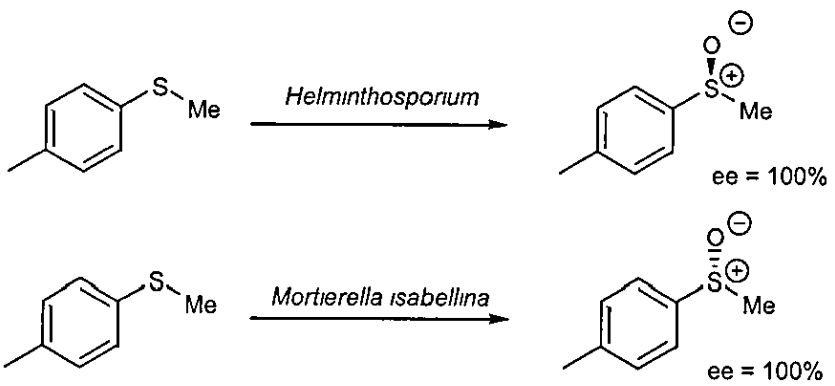


Scheme 35

1-A-5· Reactions involving the use of enzymes

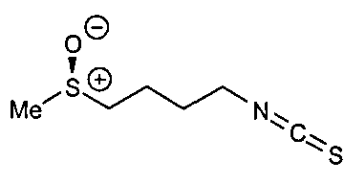
The biotransformation of sulfides to sulfoxides was first reported in 1954 by Wright[44] et al and was reviewed by Holland[45] in 1988 Generally, enzymatic processes can afford exceptional results with extremely high enantioselectivities, but have poor scope with regard to sulfide structure

Helminthosporium and *Mortiella isabellina* were reported in 1978 by Sin[46] to effect the sulfoxidation of p-tolyl methyl sulfide with high enantiomeric purity but of opposite absolute configurations (Scheme 36)



Scheme 36

The used of *Helminthosporium* has been extended to the oxidation of 4-substituted methyl benzyl sulfides with moderate to good yields and enantioselectivities [47] *Helminthosporium* has also been employed in the synthesis of the anticarcinogenic compound (*R*)-sulforaphane (Fig. 7, **30**) in 45 % yield and 93 % ee [48]

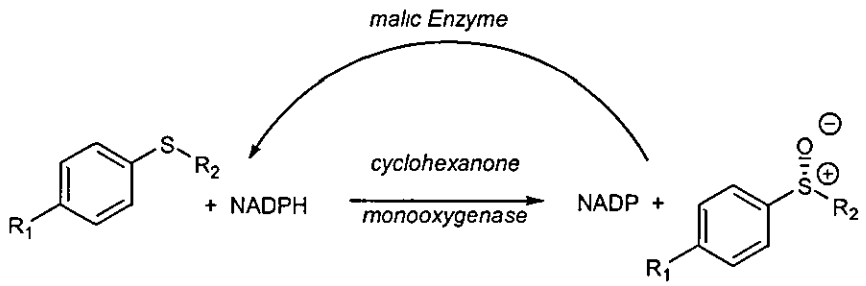


30

Fig 7

Colonna[49] reported the investigation of cyclohexanone monooxygenase (CMO) derived from *Acinetobacter* in the oxidation of a range of sulfides Colonna[50] extensively investigated the

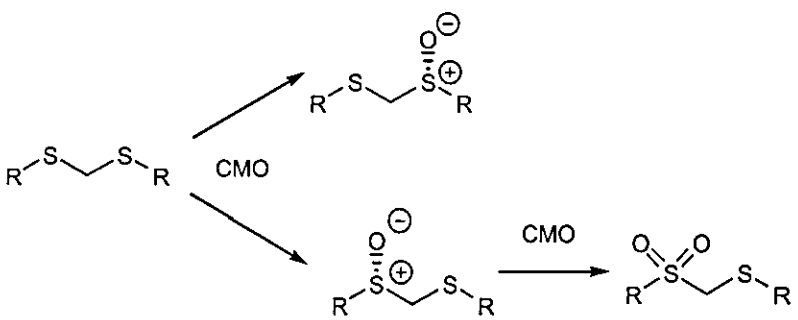
influence of sulfide structures on the obse ved enantioselectivity and also reported the action of CMO on the oxidation of dithioacetals, with excellent results (Scheme 37, table 24 and Scheme 38, table 25)



Scheme 37

Table 24

R_1	R_2	Yield (%)	ee (%)	Abs Conf
Ph	Me	88	99	R
o-Tol	Me	90	87	R
m-Tol	Me	90	40	R
p-Tol	Me	94	37	S
2-Pyridyl	Me	86	87	R
Ph	*i*-Pr	93	3	S
p-Tol	*i*-Pr	99	86	S
p-Tol	Et	89	89	S
p-F-Ph	Et	96	93	S

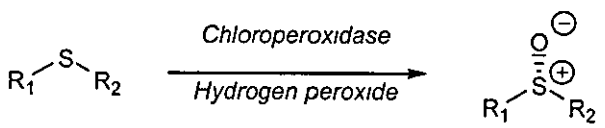


Scheme 38

Table 25

Sulfide	Yield (%)	ee (%)	sulfone Yield (%)
1,3-dithiane	81	≥98	19
1,3-dithiolane	94	≥98	6
Bis(methylthio)methane	92	≥98	8

Colonna[51] also reported the use of the enzyme chloroperoxidase (CPO), derived from *caldariomyces fumago*. This enzyme has also been applied by Wong[52] to the sulfoxidation of a variety of sulfides with similar results (Scheme 39, table 26)



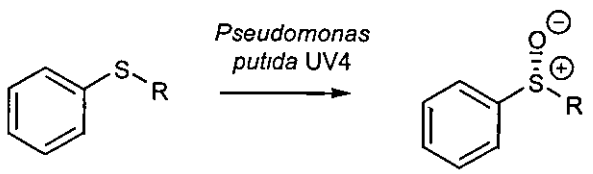
Scheme 39

Table 26

R_1	R_2	Yield (%)	ee (%)
Ph	Me	100	98
p-Tol	Me	98	91
o-Tol	Me	27	33
p-Tol	Et	50	68
p-Tol	Pr	53	5
Bn	Me	100	90
2-Pyridyl	Me	100	99
p-Cl-Ph	Me	77	90
o-Cl-Ph	Me	33	85
p-NO_2-Ph	Me	10	80

Recently, Dalton[53] has reported the use of strains of *Pseudomonas putida* for the oxidation of a variety of alkyl aryl and dialkyl sulfides with excellent selectivities but with extremely variable yields The UV4 strain was the most successful and gave the same sense of enantioselectivity in

all cases with regard to the phenyl group, although the configurational assignment is changed in some examples due to a change in priority of the non-phenyl substituents (Scheme 40, table 27)



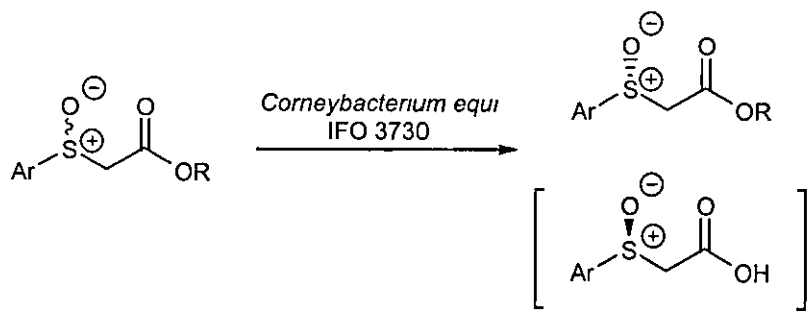
Scheme 40

Table 27

R	Yield (%)	ee (%)	Abs Conf.
Me	95	≥98	R
Et	64	≥98	R
n-Pr	5	≥98	R
n-Bu	7	97	R
i-Pr	27	97	R
t-Bu	2	62	R
o-Tol	1	86	S
p-Tol	1	≥98	S
Vinyl	38	≥98	S

Roberts[54] has reported the use of a strain of baker's yeast in the oxidation of methyl tolyl sulfide with good enantioselectivity (up to 92 % ee) The use of bovine serum albumin (BSA)[55] was reported in 1991 giving variable selectivities (up to 79 % ee) Also, the use of *Rhodococcus equi* has been published by Ohta[56] in a procedure involving the resolution of sulfinate esters In 1994, Schultz[57] reported the use of catalytic antibodies in the oxidation of sulfides in presence of sodium periodate

Enzymes have also been used in kinetic resolution of functionalised sulfoxides In 1986, Ohta[58] reported a selective hydrolysis of sulfinyl esters by using *Corneybacterium equi* IFO 3730 which afforded good levels of optical purity of the sulfinyl ester (up to 97 % ee) (Scheme 41)



Scheme 41

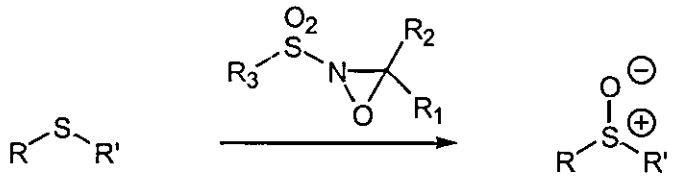
Burgess[59] reported similar results using Pseudomonas K10, with the advantage that the hydrolysed acid was also recovered with good optical purity for the sulfinyl ester and the hydrolysed sulfinyl acid, in >95 % ee and up to 94 % ee respectively

1-A-6 Conclusions

Since the first asymmetric sulfoxidation in the early 1960's, many procedures have been developed to access a wide range of chiral sulfoxides with various groups at the sulfur atom One of the most important developments in asymmetric sulfoxidation was introduced by Kagan and Modena (Scheme 42) by adaptation of the Sharpless asymmetric epoxidation conditions, to access mainly chiral aryl methyl sulfoxides with high enantiomeric excess Other sulfide types are less successful substrates

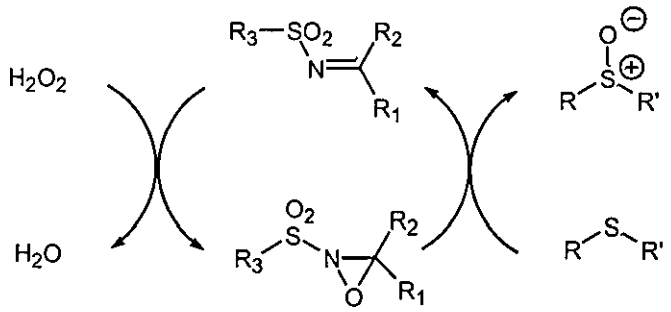
Scheme 42

Another efficient procedure was recently developed by Davis and subsequently by Page who have observed high enantiomeric purity with the use of chiral oxaziridines and related reagents generated *in situ* (Scheme 43)



Scheme 43

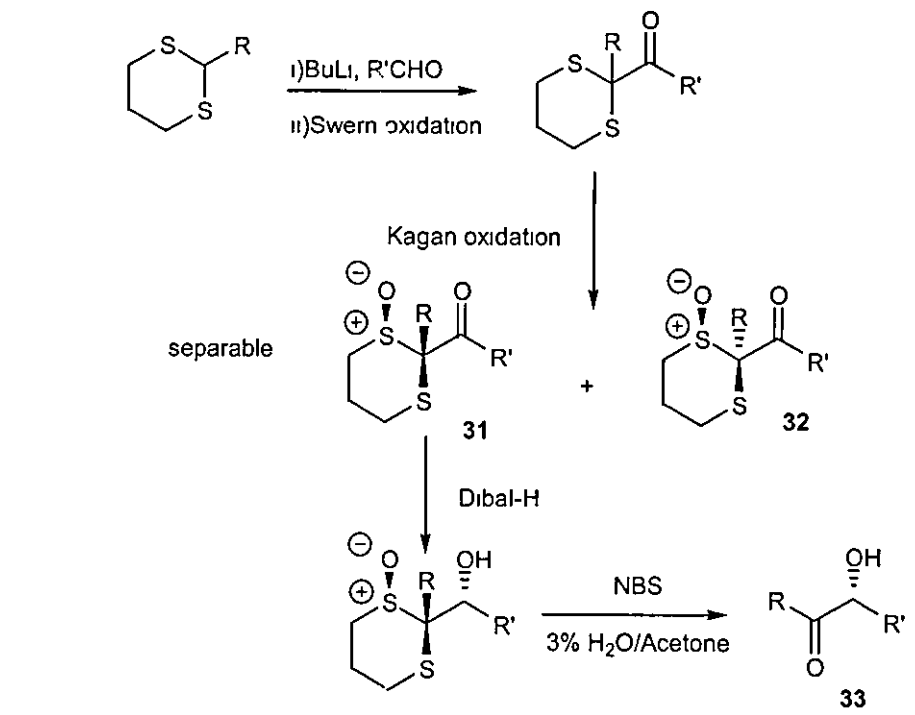
Furthermore, the modified Payne oxidation developed by Page (Scheme 44) using chiral sulfonyl imines for asymmetric sulfoxidation is used for the access of dialkyl sulfoxides with high ees



Scheme 44

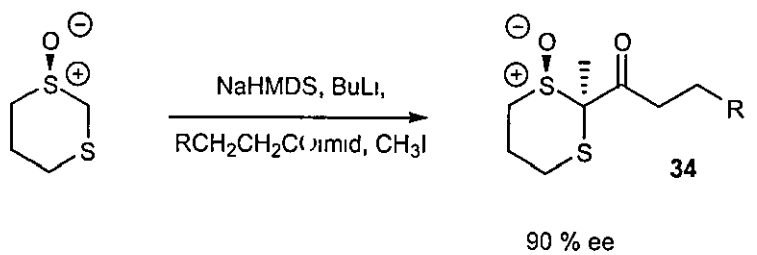
The development of these highly selective procedures has allowed the synthesis of chiral auxiliaries using the 1,3-dithiane-1-oxide moiety, which has been already introduced by Page (Scheme 45) for the enantioselective synthesis of α-hydroxy ketones For example, deprotonation of the 2-substitued-1,3-dithiane species, addition of the resulting anion to aldehyde, oxidation to the ketone, asymmetric sulfoxidation by modified Sharpless protocol allows isolation of the two separable diastereoisomers **31** and **32**, and subsequent stereoselective reduction of **31** followed by thioacetal hydrolysis affords the α-hydroxy ketone (**33**) with high optical purity

Page route



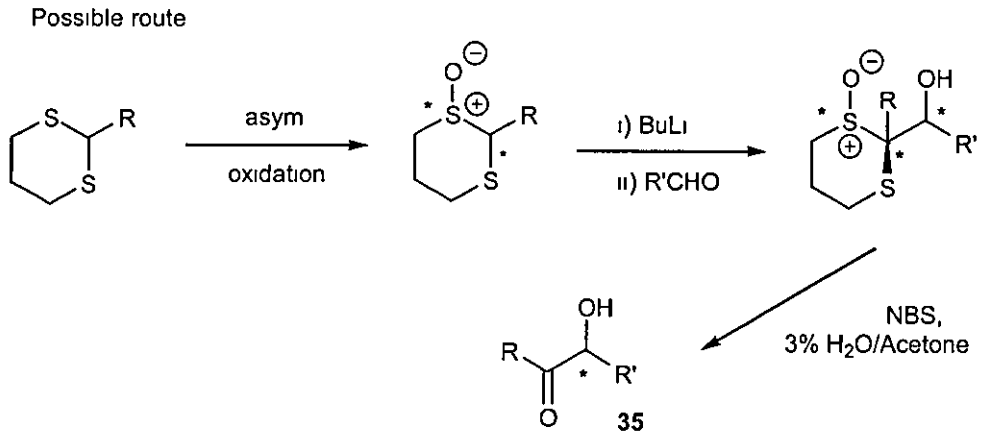
Scheme 45

Page[60] has also reported similar chemistry from optical pure 1,3-dithiane-1-oxide in one pot reactions, by reacting the 2-anion derived from chiral 1,3-dithiane-1-oxide with an appropriate acyl imidazole in the presence of additional base, and treatment of the enolate so generated with methyl iodide (Scheme 46) to afford the chiral keto-dithiane-oxide intermediate (**34**)



Scheme 46

The aim of this work is to extend this procedure to a wide range of 2-substituted-1,3-dithiane species, for the enantioselective synthesis of α-hydroxy aryl ketones (**35**) (scheme 47) using our standard procedure for the asymmetric sulfoxidation of the 1,3-dithiane species



Scheme 47

The advantage of such routes is the production of only one diastereoisomer instead of the chromatographic separation of a mixture of diastereoisomers required in the earlier scheme 45.

1-B: Allylic Nucleophilic Substitution Palladium-Catalysed Reaction·

1-B-1 Introduction

The synthesis of non-racemic enriched chiral compounds has increased the attention of many researchers over the last four decades Many synthetic approaches have been developed to afford high enantiomeric excess of the synthesized product, but the most efficient method developed so far is asymmetric catalysis, which requires a catalytic amount of chiral material to transmit the chiral information to a larger amount of substrate

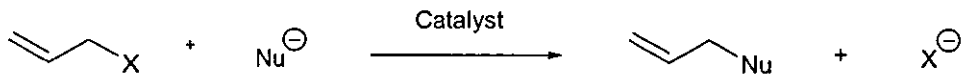
The process, which describes the formation of a chiral product, enriched in either enantiomer, from an achiral or a chiral racemic substrate, is called enantioselective synthesis [61]

The design of an enantioselective catalytic process would be advantageous to obtain high yields of enantiomerically pure products synthesized from a chiral racemic substrate The kinetic resolution cannot respond to such demand where optimal yields are only 50 % Furthermore, the challenge to convert both enantiomers of the substrate into a single enantiomer of the product can be achieved by a chiral catalyst, which reacts with either enantiomers of the substrate with possible loss of chiral information from the substrate

The transition metal-catalysed reactions respond to such demand and have been widely studied over the last two decades to control the regioselectivity as well as the stereoselectivity in the formation of organic molecules Asymmetric epoxidation,[62] dihydroxylation,[63] aminohydroxylation and the Heck[65] reactions of olefins, allylic alkylation reactions[64], etc are a few examples of transition metal-catalysed reactions

In 1977, Trost[66] reported the metal-catalysed allylic nucleophilic substitution reaction and its synthetic applications These have been widely demonstrated by a growing presence of reports in the literature Most of the enantioselective transition metal-catalysed processes involve transfer of

oxygen or molecular hydrogen, but the metal-catalysed allylic substitution reaction involves carbon-carbon as well as carbon-heteroatom bond formation (Scheme 48)

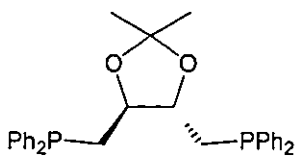


Scheme 48

Furthermore, the greatest advantage of the metal-catalysed allylic substitution reaction over the other enantioselective transition metal-catalysed reactions, is its ability to convert racemic substrate into only one enantiomer of the product The kinetic resolution processes, such as the hydrogenation of substituted β-ketoesters, are the only exceptions

The transition metal-catalysed allylic substitution reaction has been widely studied with different transition metals including nickel, palladium, platinum, rhodium, iron, ruthenium, molybdenum, and tungsten Various observations have been reported on the regioselectivities for unsymmetrically 1,3-disubstituted allyl substrates

Trost[66] reported, in 1977, the first enantioselective example of a palladium-catalysed allylic nucleophilic substitution reaction with the employment of DIOP (Fig 8) as chiral ligand



DIOP

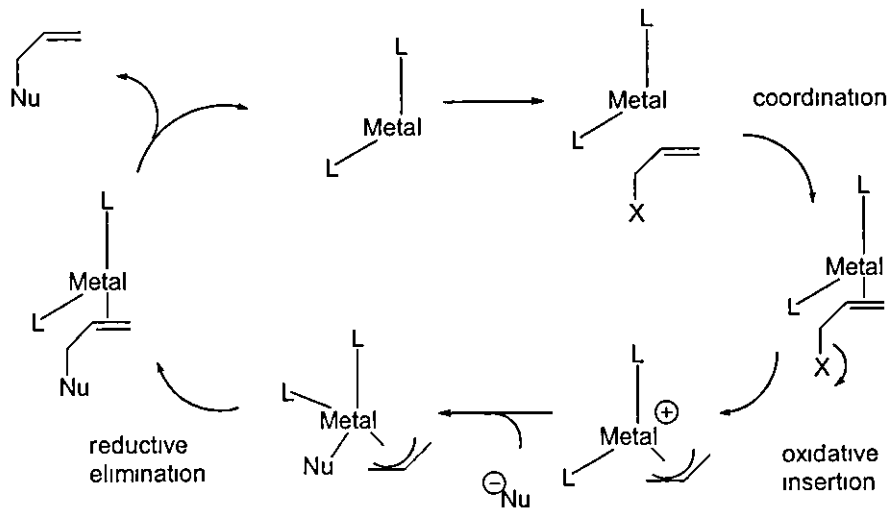
Fig 8

Since his pioneering research, a wide range of chiral ligands has been elaborated to access high level of regioselectivity and enantioselectivity for the catalytic process.

This introduction is limited to the metal-catalysed allylic nucleophilic substitution reactions It considers the role of each of the reac'ion components and their possible importance in enantioselective induction, treated in the following order nucleophiles, enantiodiscrimination in substrate-metal intermediates, transition metals and ligands

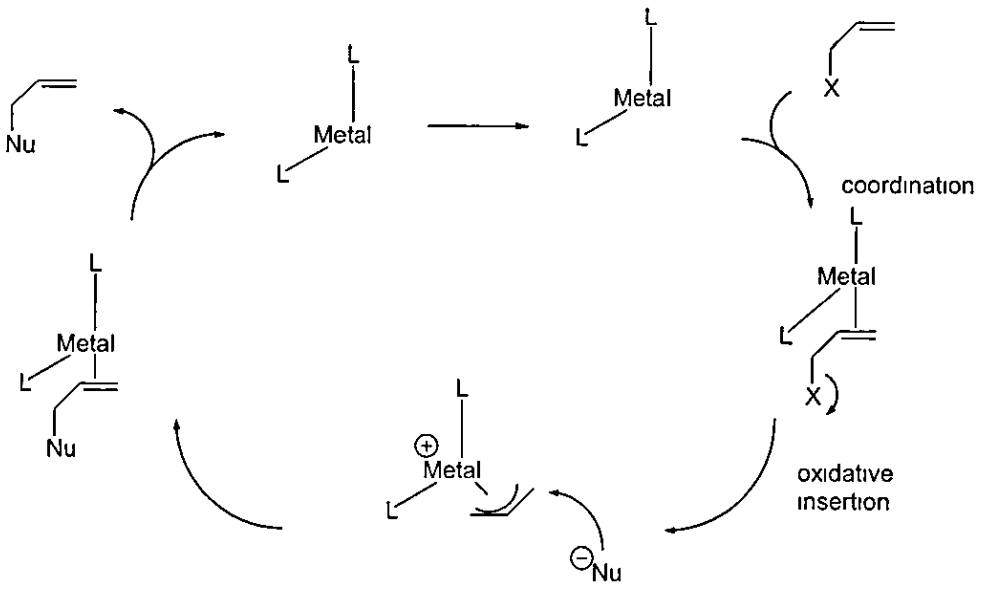
1-B-1-a Nucleophiles

There are two different types of palladium-catalysed allylic substitution depending upon the nature of nucleophiles, "hard" nucleophiles which have a p*K*a > 25 for the conjugate acids, are attached to the transition metal in the first step and undergo reductive elimination (Scheme 49) These nucleophiles have not been extensively studied because of the similarity of the reaction to organocopper chemistry



Scheme 49

The other type of nucleophiles, "soft" nucleophiles, has a p*K*a < 25 for the conjugate acids In this case, the dissociation and formation of bonds occur outside of the coordination sphere, i e , the nucleophile approaches the π allyl face opposite to the transition metal and its ligands (Scheme 50)


Nu
L
Metal
L
L
Metal
L
X
coordination
L
Metal
L
X
oxidative
insertion
Nu
L
Metal
L
Nu
L
Metal
L
Nu

Scheme 50

1-B-1-b Enantiodiscrimination in substrates-metal intermediates

The nature of the substrate also has great influence on the enantioselective induction during the substrate-palladium attachment step The effect has been shown to be an example of enantiofacial discrimination by Trost[64]

Many enantiodiscrimination processes have been reported One of these is "enantiofacial complexation and ionisation", where the transition metal must distinguish between two different faces of the olefin In these cases, ionisation from different enantiofaces of the olefin affords enantiomeric allyl complexes (Fig 9)

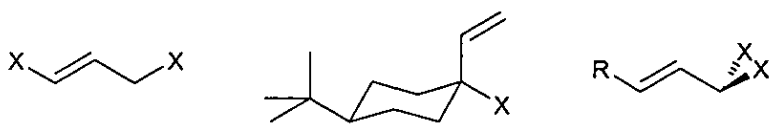
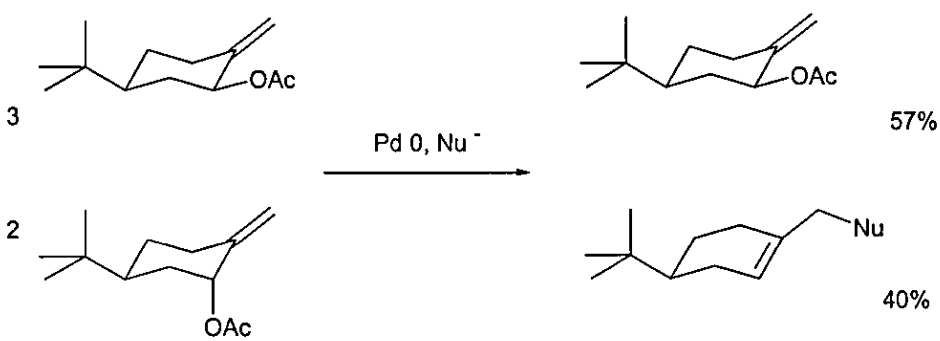


Fig 9

Another aspect of enantiodiscrimination is "ionisation of enantiotopic leaving group" A stereoelectronic effect occurs in the ionisation step in the palladium-catalysed reaction For example, Fiaud[67] observed different reaction rates in the ionisation of axial and equatorial leaving groups (Scheme 51)



Scheme 51

The axial acetate X underwent complete transformation to give the palladium-catalysed allylic nucleophilic substitution product while the equatorial isomer Y was recovered unchanged Fiaud[68] also reported similar behaviour in meso substrates with two enantiotopic leaving groups and described it as a "desymmetrisation process" (Fig 10)

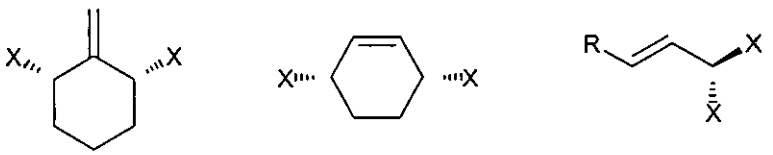
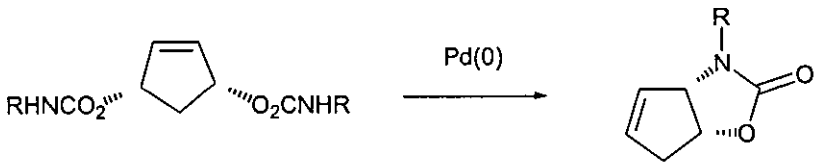


Fig 10

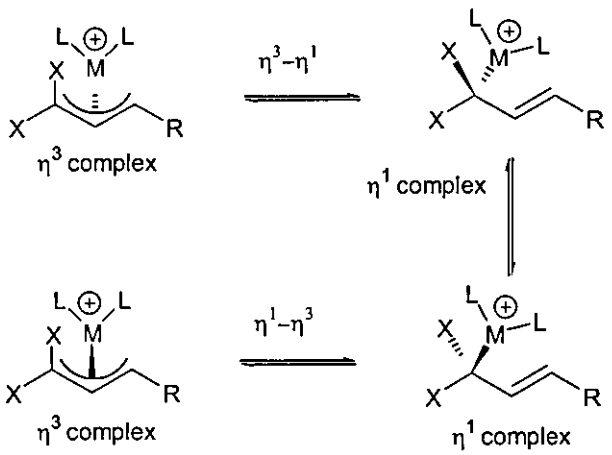
An intramolecular palladium-catalysed allylic nucleophilic substitution reaction has been reported by Trost[69] on an allyl dicarbamate substrate (Scheme 52)



Scheme 52

Another distinctive enantiodiscrimination effect is based on "enantioface exchange in η^3-allyl complexes" In the case of unsymmetrically 1,3-disubstituted allylic intermediates, the metal switches between enantiofaces of the allylic moiety, and isomerisation exchange process can be important for enantioselectivity if one face has less steric and/or electronic effects in detriment to the other

Two different isomerisation mechanisms were defined depending upon the substrate structure For substrates containing two identical substituents on one of the allyl termini, the "η^3-η^1-η^3" mechanism can occur (Scheme 53)



Scheme 53

This process may operate on the same time scale as other steps in the catalytic cycle Furthermore, stereochemical information gained in the ionisation step can be lost The figure 11 illustrates some substrates whose complexes may racemise under a η^3-η^1-η^3 process.

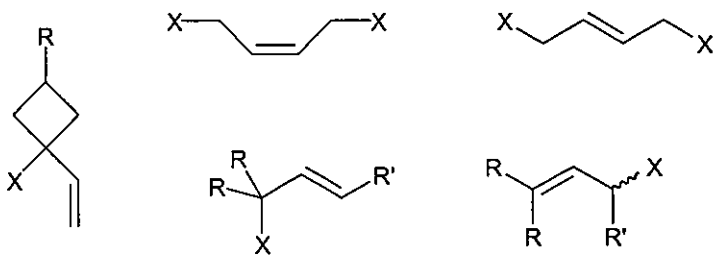
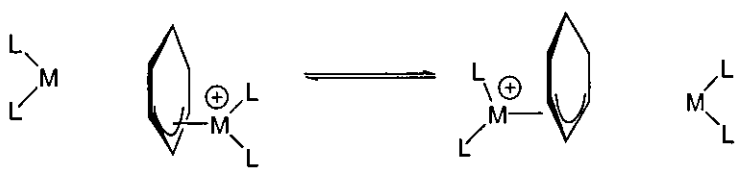


Fig 11

It appears that the rate of exchange for the η^3-η^1-η^3 process, is proportional to the concentration of palladium (0) in stoichiometric studies (Scheme 54) By mean, introversion occurs between a metal and a metal allyl complex.



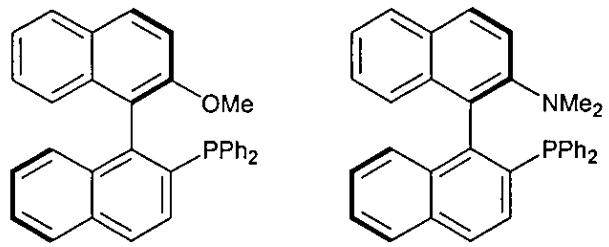
Scheme 54

Granberg[70] has shown that this isomerisation process (η^3-η^1-η^3) can be minimised by a reactive allylic substrate, a low concentration of palladium (0), bidentate ligands and use of halide ions Trost[71] has proposed the isolation of each of the palladium sites on solid supports which avoided the isomerisation process to take place

1-B-1-c Transition metals

Despite the η^3-η^1-η^3 isomerisation process, palladium metal can be considered as the most widely used transition metal in the allylic nucleophilic substitution reaction These reactions however show a lack of regioselectivity in the presence of unsymmetric substrates

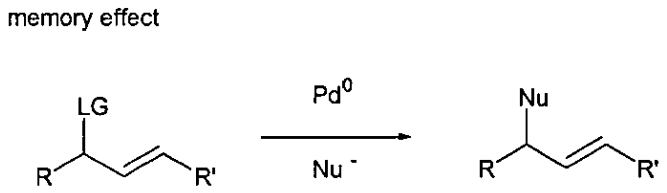
Meanwhile, good regioselectivities were obtained in ambiguous cases depending upon the choice of ligand or substrate which have an apparent role in the regioselectivity Hayashi[72] reported the application of MOP (**36**) (Fig 12) as a ligand with unsymmetric substrates in the palladium-catalysed allylic nucleophilic substitution reaction and observed a "memory effect" in his results



36 MOP **37** MAP

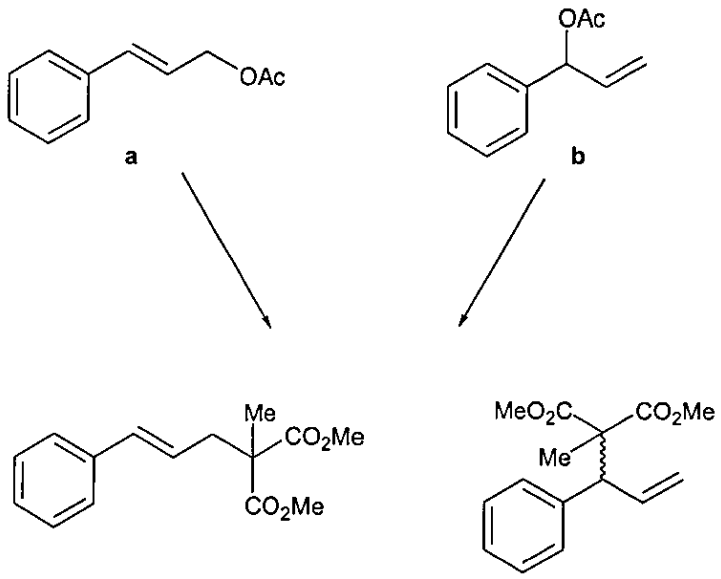
Fig 12

The meaning of 'memory effect' as introduced by Hayashi is that the incoming nucleophile becomes attached to the carbon of the allyl moiety where the leaving group was previously bonded (Scheme 55)



Scheme 55

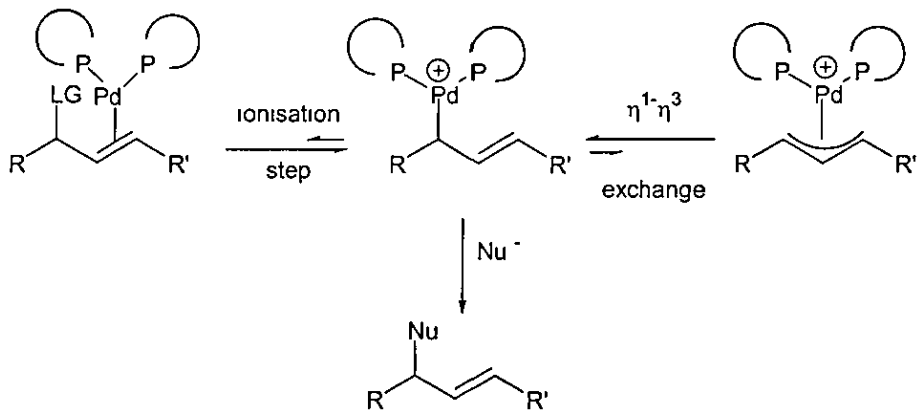
In contrast to these results using MOP, Vyskocil[73] observed a dramatic loss of this memory effect in the palladium-catalysed allylic alkylation reactions of unsymmetrical substrates when MAP (**37**) was employed as chiral ligand (Scheme 56)



MOP (Hayashi)	72 21	From acetate substrate **a**
	23 77	From acetate substrate **b**
MAP (Vyskocil)	>200 1	From acetate substrate **a**
	91 9	From acetate substrate **b**

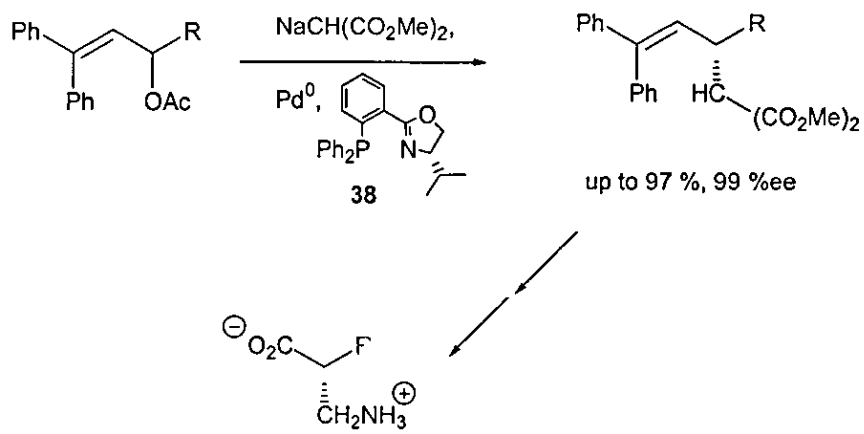
Scheme 56

The apparent differentiation in chemical behaviour between MOP and MAP is surprising but was explained by different modes of chelation to the transition metal Oxygen is generally not a good ligating group and in extreme cases, oxygen does not ligate to transition metals at all A metal complex intermediate with two monodentate molecules of MOP attached was proposed, and would decrease the η^3-η^1-η^3 exchange equilibrium after the substrate ionisation step In this case, the memory effect occurs after nucleophilic addition at the allyl moiety of the carbon bearing the metal complex (Scheme 57)



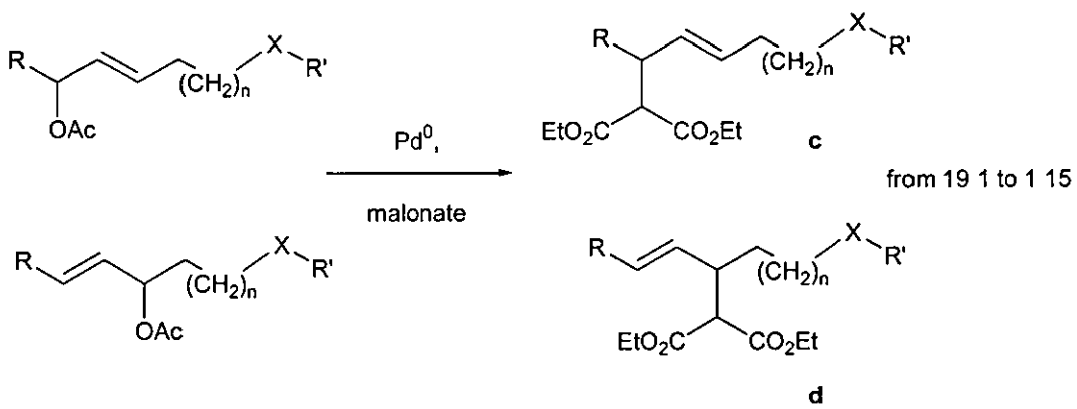
Scheme 57

Williams[74] also reported good regioselectivities using a hybrid N,O ligand (**38**) in this reaction in an application for the synthesis of β-amino-acids by using bulky groups on one side of the unsymmetric substrate to induce the approach of the nucleophile on the other (Scheme 58)



Scheme 58

One of the most inventive regioselective inductions with palladium was reported by Krafft[75] in 1998 who introduced a heteroatom directing group into the substrate (Scheme 59)



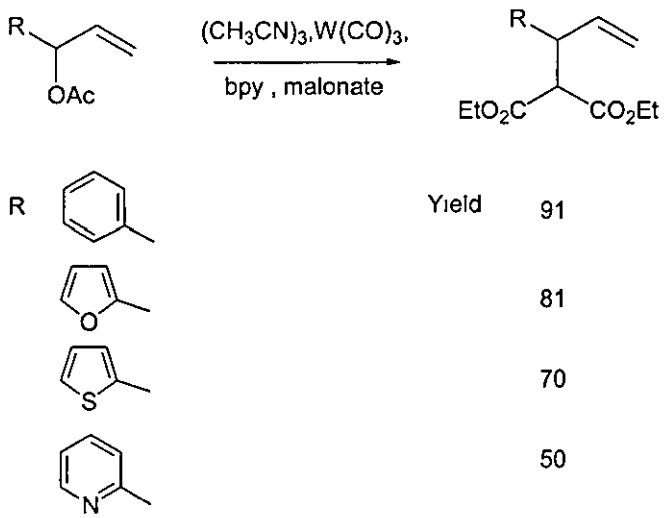
Scheme 59

The regioselective additions to allylic acetates, catalysed by palladium, can be achieved by incorporation of a thioether or tertiary amine into the substrate It was demonstrated, for the first time, that heteroatoms capable of coordinating to palladium can change or even reverse the expected regiochemical and stereochemical outcome Reactions with malonate anion proceed with high selectivity to provide the product substituted at the terminus of the allyl moiety proximal to the heteroatom, even if that position was more substituted

Although the elaboration of favourable interactions or in the choice of substrates, palladium metal failed in most of the cases to afford good regioselectivities with unsymmetric substrates

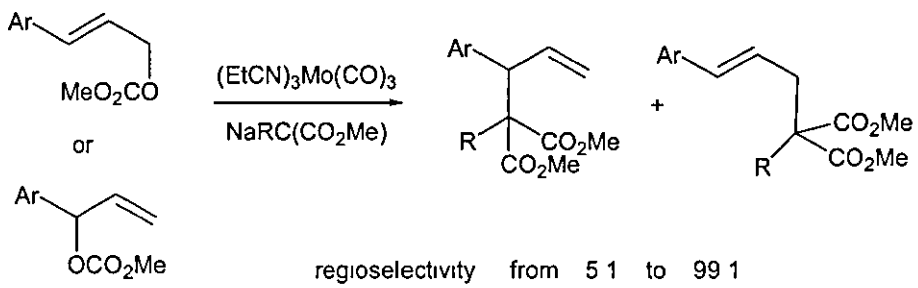
This lack of regioselectivity was solved by changing the steric and electronic demands of the metal template, and good to excellent regioselectivities were obtained with the use of tungsten, molybdenum, rhodium and platinum as described below

In 1983, Trost[76] reported a tungsten-catalysed allylic nucleophilic alkylation reaction for unsymmetric allyl substrates bearing one aromatic group (Aryl, pyridyl, furyl, thienyl) in the presence of bipyridine as ligand which facilitates the opening of a coordination site on the tungsten complex (Scheme 60)



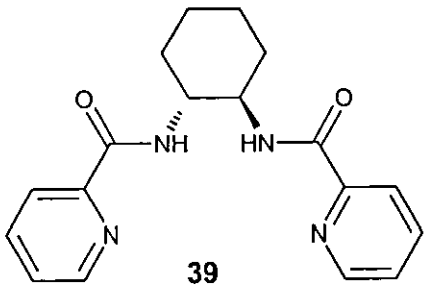
Scheme 60

Molybdenum also proved to be efficient in obtaining high regioselectivities for unsymmetric substrates. Trost[77] reported the asymmetric version of the molybdenum-catalysed allylic nucleophilic substitution reactions of unsymmetric substrates with, in most of the cases, excellent results (Scheme 61)



Scheme 61

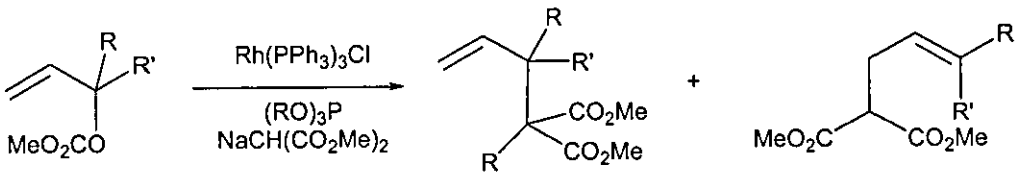
Very high enantioselectivities were achieved with the use of a bipyridine ligand (**39**) (fig 13) on the same aromatic substrates as already reported by Trost[78] with tungsten



39

Fig 13

Similar regioselectivities were reported by Evans[79] with the use of a modified Wilkinson's catalyst ($RhCl(PPh_3)_3$) as a transition metal binding site for the allylic nucleophilic substitution reactions of unsymmetric substrates (Scheme 62)



Yields up to 95 %
ratio up to 99 1

Scheme 62

Although excellent regioselectivities were obtained, this process was not carried out in an asymmetric version

Platinum[80] also gave good regioselectivities in the allylic nucleophilic substitution reaction for unsymmetric substrates but with a slightly lower regioselective induction (up to 15 1)

1-B-1-d Ligands

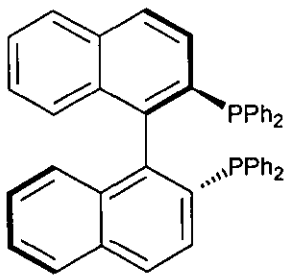
One of the most important methods for controlling enantioselectivity into transition metal-catalysed processes is by the incorporation of chiral ligands The two most important classes of chiral ligands are homobidentate ligands with C_{2h} symmetry and heterobidentate ligands

Homobidentate ligands with C_{2h} symmetry

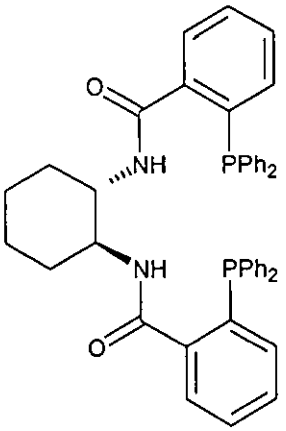
One of the first chiral ligands used in palladium-catalysed allylic nucleophilic substitution reactions was a P,P homobidentate ligand with C_{2h} symmetry developed by Noyori[81] (BINAP) (Fig. 14), but this gave very poor enantiomeric induction reported by Trost[82] despite his success in other metal-catalysed reactions

In 1992, Trost[69] reported the first successful P,P-homobidentate chiral ligand with C_{2h} symmetry derived from *trans*-1,2-diamino-cyclohexane (**40**) A "dome-type architecture" controls the stereochemistry of the reaction primarily by steric effects

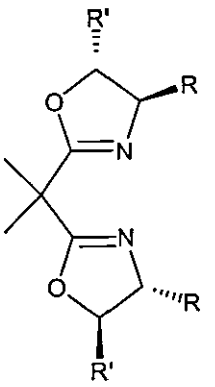
Excellent enantioselectivities were obtained with optically pure N,N C_{2h} symmetrical homobidentate bis-oxazolines (**41**) reported by Evans[83] Pfaltz [84] This last type of N,N C_{2h} symmetrical homobidentate bis-oxazoline ligands were widely applied to copper-catalysed reactions [85]



BINAP up to 34 % ee



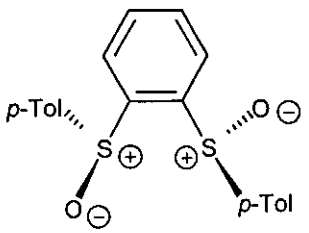
40 up to 96 % ee



41 up to 88 % ee

Fig 14

Shibasaki[86] has reported moderate results for the enantioselective palladium-catalysed allylic nucleophilic substitution reactions with S,S homobidentate C_{2h} symmetrical chiral bis-sulfoxide ligands (**42**)



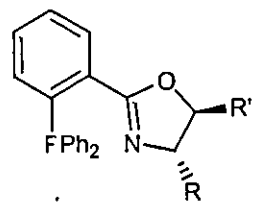
42 up to 64 % ee

Heterobidentate ligands

A conceptually different approach for enantioselective induction was based on the idea that a bidentate ligand with two electronically different ligating groups should encourage preferential attack at one of the two termini of the π-allyl complex owing to the *trans* effect of the acceptor

centre relayed through the metal These effects may be monitored by the ^{13}C shifts of the allylic complexes The lowest field allylic ^{13}C sh·fts were observed with complexes containing electron-withdrawing phosphite ligands (back-bon.'ing), the highest field allylic ^{13}C shifts are observed with tertiary amine ligands (pure σ donors) The stereoelectronic predictions of the *trans* effect are that bonds *trans* to phosphorus will be longer and weaker than bonds *trans* to nitrogen

Pfaltz,[87] Williams[88] and Helmchem[89] independently introduced P,N ligands (Fig 15, **43**) capable of chelating palladium between a traditionally arylated phosphorus atom and an imine-type nitrogen contained in an oxazoline ring

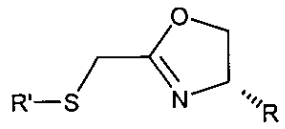


43 Up to 98 5 % ee

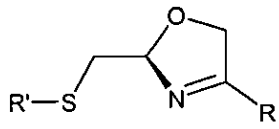
Fig 15

Many ligands have been reported following this highly successful P,N ligand (**43**) and many of them retained the oxazoline ring as the source of chirality and nitrogen for chelation to palladium The phosphorus atom has been moved within the structure or replaced by other heteroatoms (S, Se, O or N) [90, 91, 92]

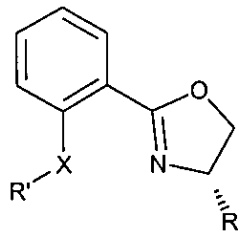
Williams[90] reported N,S oxazoline ligands (**44**, **45**, **46**) with good to excellent enantioselectivities Ikeda[91] reported diphenylphinooxaline ligands (**47**) with a chiral binaphthyl backbone for palladium-catalysed allylic alkylation with moderate selectivities



44 up to 76 % ee

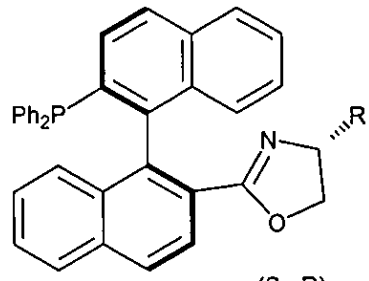


45 up to 88 % ee



X S, S(O), Se

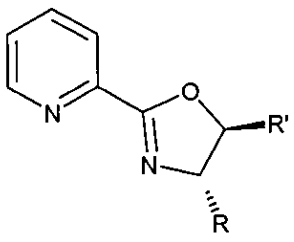
46 up to 92 % ee



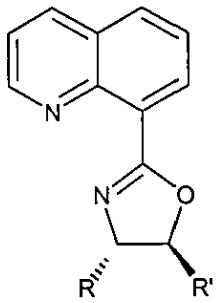
(S,aR)

47 up to 96 % ee

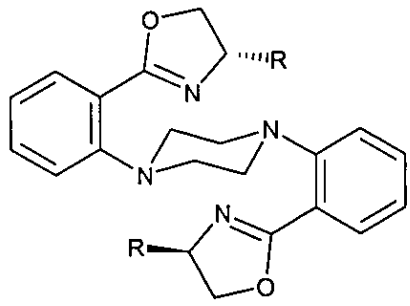
A very recent paper[92] reported the application of *N,N* oxazoline-pyridine (or quinoline) ligands (**48**, **49**) and *N,N* oxazoline-tertiary amine ligands (**50**) to the palladium-catalysed allylic alkylation reaction, but with poor enantioselective induction in most of the cases, which may be due to the similar electronic nature of the groups chelated to palladium



48 up to 25 % ee

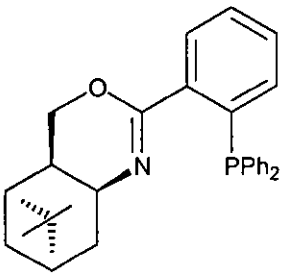


49 up to 69 % ee

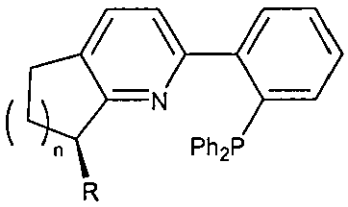


50 up to 17 % ee

A wide range of ligands containing a nitrogen atom contained in moieties other than an oxazoline has been reported These include P,N oxazine ligands (**51**) reported by Evans[93] with excellent enantioselectivities in palladium-catalysed allylic alkylation reaction, and P,N pyridine ligands (**52**) investigated by Ito[94] with very good enantiomeric excesses

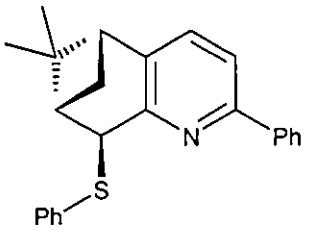


51 up to 95 % ee

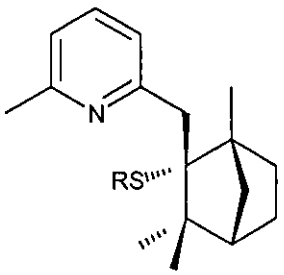


52 up to 98 % ee

Good to excellent enantioselective induction was observed with N,S ligands such as (+)-pinocarvone derived N,S pyridine-thioether (**53**) ligands reported by Chelucci[95] Kellogg[96] reported the same type of ligand derived from *S*-thiofenchone (**54**) as a chiral site source for asymmetric induction.



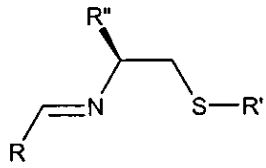
53 up to 83 % ee



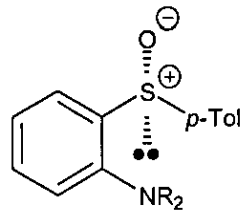
54 up to 98 % ee

In 1999, Anderson[97] reported the enantioselective palladium-catalysed allylic alkylation reaction using N,S imine-thioether ligands (**55**) derived from optically pure amino alcohols The steric environment around the palladium complex orients the nucleophilic attack opposite to the imine group, due to a tilted angle of 15 5° between the plane of the allyl group and the perpendicular of

the N-Pd-S plane In comparison, poor to moderate success were reported by Hiroi[98] for the application of N,S chiral β-amino sulfoxides ligands (**56**) in palladium catalysed allylic alkylations, where sulfoxide functionality is the sole chiral source



55 up to 96 % ee



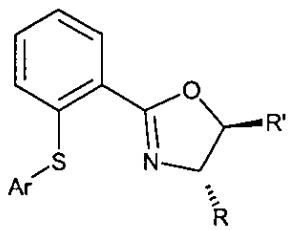
56 up to 38 % ee

1-B-2· Nitrogen (sp^3)-Sulfur and Nitrogen (sp^2)-sulfoxide as Ligands

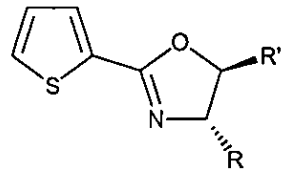
Over the last decade, many research groups have focused on the synthesis and uses of nitrogen-sulfur-based hybrid chiral ligands for the reason that N,S-chelates create additional possibilities compared to N,N and N,O-chelates, because the sulfur atom may become chiral when coordinated to the metal A new class of ligands is formed by oxidation of the sulfur atom In these cases, the sulfur atom itself is chiral and possesses different electronic and polarity characteristics.

This work has also stimulated interest in the coordination chemistry of chiral sulfinyl functionalities and extensive efforts have been devoted to the development of new chiral ligands bearing chiral organosulfur functionalities as sole chiral sources

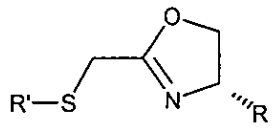
One of the most widely studied types of nitrogen-sulfur-based chiral ligand, incorporate a nitrogen sp^2 hybrid and a thioether functionalities (**57**, **58**, **44**, **45**) The most successful application of such ligands was reported by Williams[90] based on his previous observation of a N,P-phosphinooxazoline ligand (**43**) in palladium-catalysed allylic alkylation reactions



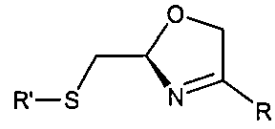
57 up to 92 % ee



58 up to 80 % ee

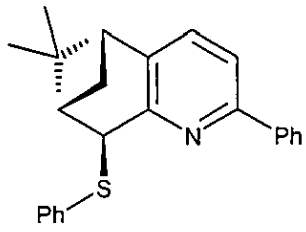


44 up to 76 % ee

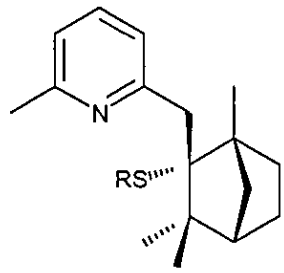


45 up to 88 % ee

Great successes were also reported by Chelucci[95] and Kelloggs[96] with their pyridine-based ligands containing (+)-pinocarvone (**59**) and *S*-thiofenchone (**60**) moieties.

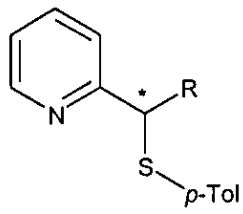


59 up to 83 % ee

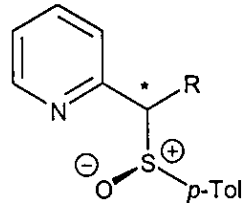


60 up to 98 % ee

Chelucci[99] also reported the application of simple pyridine-thioether ligands but with poor results The synthesis includes the introduction of the chirality by incorporation of a chiral sulfinyl group followed by separation of the diastereoisomers and subsequent reduction of the sulfoxide functionality to afford the pyridine-thioether ligand (**61**) The sulfoxide intermediates (**62**) were also tested as potential chiral ligands in palladium-catalysed allylic alkylation reactions and gave better, but still poor, results

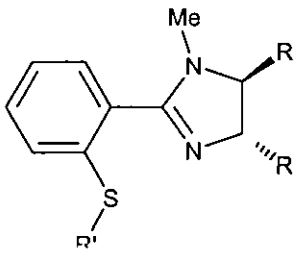


61 up to 34 % ee



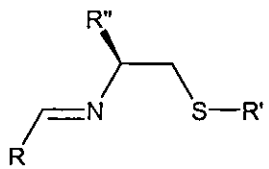
62 up to 20 % ee

An alternative sp^2 nitrogen moiety was reported by Morimoto[100] by using an imidazoline (**63**) ring instead of oxazoline The imidazoline ring was built by reacting a chiral diamine and an imidic ester The results obtained for the investigation of these ligands in palladium-catalysed allylic alkylation reaction were similar to those obtained for the oxazoline ligands

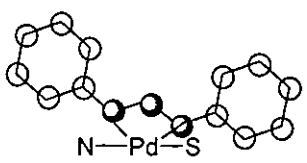


63 up to 96 % ee

Excellent results were also reported by Anderson[97] using an imine functionality (**64**) to provide one chelation site and using optically pure amino thioethers for the source of chirality Anderson believes that the steric influence of the chiral ligand predisposes the allyl group toward nucleophilic attacks opposite to the nitrogen The plane of the allyl ligand is tilted of 15 5° from the perpendicular to the N-Pd-S plane (**1**)

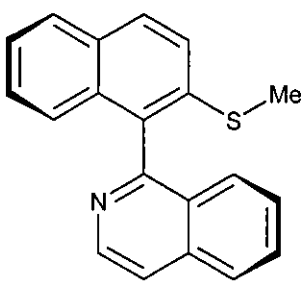


64 up to 96 % ee



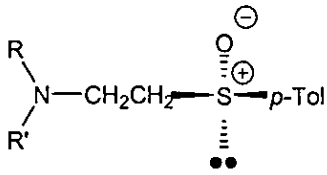
1

No such successes were obtained by Chelucci[101] who used a binaphthyl backbone type structure (**65**) as a source of chirality in the synthesis and investigated as ligand a thioether-naphthyl isoquinoline The very poor results observed may be explained by a lower energy gate for the racemisation of the naphthyl-isoquinoline core than for the BINAP analogue

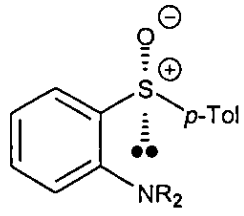


65 2 % ee

Another promising class of ligands containing a tertiary amine as a sp^3 nitrogen source was also investigated by Hiroi [98] An interesting feature of these ligands (**66, 67**) is that the sulfoxide moiety is the sole source of chirality They were synthesised from chiral (*R*)-*p*-tolyl vinyl sulfoxide or aromatic amine and (-)-menthyl (*S*)-*p*-toluenesulfinate

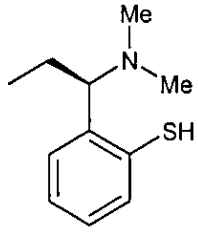


66 up to 33 % ee

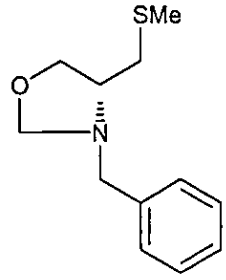


67 up to 38 % ee

Sp^3 nitrogen-thiol/thioether ligands have however encountered great success in catalytic asymmetric additions of diethylzinc or other zinc reagents to aldehydes Wipf[102] reported the application of amino thiol ligands (**68**) derived from α-ethylbenzylamine with excellent enantioselectivities. Amino-thioether ligands (**69**) derived from *R*-cysteine gave optically pure alcohols in the asymmetric addition of diethylzinc to aldehydes

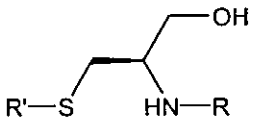


68 up to 99 % ee

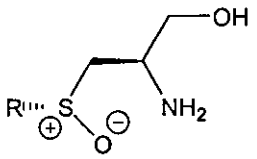


69 up to >99 % ee

Very recently, van Leeuwen[103] reported the iridium(I)-catalysed asymmetric hydrogen transfer in the reductions of ketones with chiral amino thioether (**70**) and amino sulfoxide ligands (**71**) derived from (*R*)-cysteine Poor enantioselectivities were obtained for the amino thioether series but good enantioselectivities were obtained for amino sulfoxide homologues

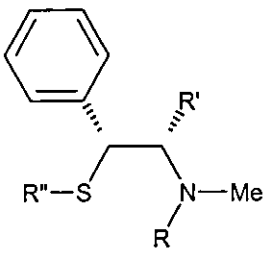


70 up to 19 % ee



71 up to 82 % ee

van Leeuwen also synthesised and investigated N,S-chelates (**72**) derived from (1*R*, 2*S*)-(nor)-ephedrine and (1*R* 2*S*)-2-aminodiphenylethanol using Mitsunobu reaction conditions to afford an aziridine intermediate which was stereoselectively ring opened with thiol nucleophiles Excellent enantioselectivities were obtained by optimisation of the reaction conditions

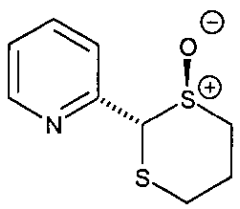


72 up to 82 % ee

1-B-3 Conclusion

Despite extensive efforts for the application of nitrogen-sulfur-based chiral ligands in metal-catalysed reactions, only a few successes have been reported, for example in the palladium-catalysed allylic nucleophilic substitution reaction, using sp2 nitrogen-thioether ligands This area is however still virgin ground for sp3 nitrogen-thioether and sp2 nitrogen-sulfoxide ligands.

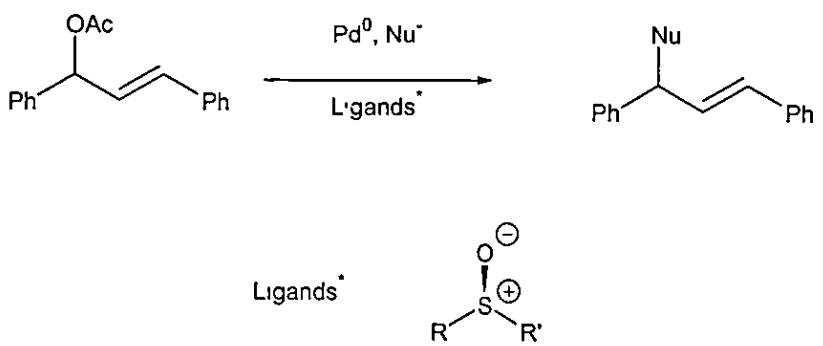
Only recently, the application of the 1,3-dithiane-1-oxide core as a ligand in metal-catalysed reactions has been investigated within our research group,[104] with moderate but promising success (fig 16)



up to 37 % ee in Pd-catalysed allylic nucleophilic substitution reaction

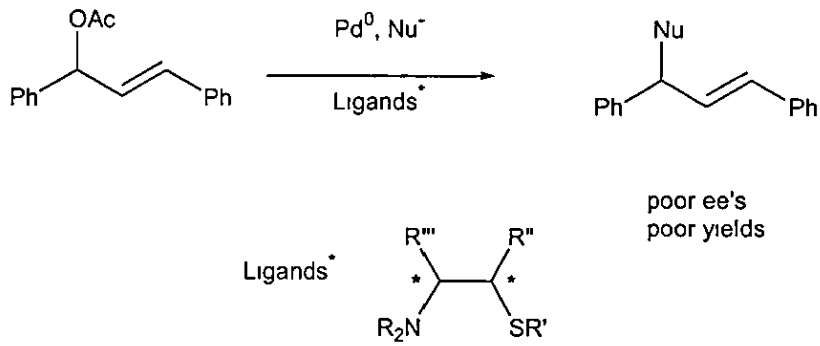
Fig 16

The aim of this present work was to synthesise and investigate non-racemic chiral hybrid-sulfoxide ligands in the palladium-catalysed allylic alkylation reaction where the sulfoxide moiety was the sole chiral source for the asymmetric induction (Scheme 63)



Scheme 63

A further aim was to promote the use of sp^3 nitrogen-thioether ligands which have never been successfully investigated in palladium-catalysed allylic alkylation reaction Anderson,[97] for example, dismissed tertiary amino-thioether ligands as inactive using standard reaction conditions (BSA + AcOK cat as base to generate the nucleophile) (Scheme 64)



Scheme 64

1-C References

(1) Solladie, G , Carreno, M C *in Organosulfur Chemistry-Synthetic Aspects*, Page, P C B , Ed. **1995**, p 1 , Carreno, M C *Chem Rev* **1995**, *95*, 1717 , Walker, A G *Tetrahedron Asymmetry* **1992**, *3*, 961 , Mikolajczyk, M , Drabowicz, J , Kielbasinski, P *in The Chemistry of Sulfones and Sulfoxides*, Patai, S., Ed **1988**, *Chapter 8*, p 233, John Wiley and Sons Ltd , Andersen, K K. *in The Chemistry of Sulfones and Sulfoxides*, Patai, S , Ed **1988**, *Chapter 3*, p 55, John Wiley and Sons Ltd , Barbachyn, M R , Johnson, C R *in Asymmetric Synthesis*, Morrison, J D , Ed **1983**, *vol 4*, p 227 , Solladie, G *in Asymmetric Synthesis*, Morrison, J D , Ed **1983**, *vol 2*, p 157 , Solladie, G *Synthesis* **1981**, 185

(2) Walker, A G *Tetrahedron Asymmetry* **1992**, *3*, 961

(3) Mata, E G *Phosphorus, Sulfur and Silicon* **1996**, 117, 231 ; Rayner, C M *Contempory Organic Synthesis* **1995**, *2*, 409 , Carreno, M C *Chem Rev* **1995**, *95*, 1717 , Mikolajczyk, M , Drabowicz, J , Kielbasinski, P *in The Chemistry of Sulfones and Sulfoxides*, Patai, S , Ed **1988**, *Chapter 8*, p 233, John Wiley and Sons Ltd , Andersen, K K *in The Chemistry of Sulfones and Sulfoxides*, Patai, S , Ed **1988**, *Chapter 3*, p 55, John Wiley and Sons Ltd.

(4) Rayner, D R , Gordon, A J , Mislow, K J *J Am Chem Soc* **1968**, *90*, 4954

(5) Tang, R , Mislow, K J *J Am Chem Soc* **1970**, *92*, 2100

(6) Andersen, K K *in The Chemistry of Sulfones and Sulfoxides*, Patai, S , Ed **1988**, *Chapter 3*, p 55, John Wiley and Sons Ltd

(7) von Matt, P., Pfaltz, A *Angew Chem , Int Ed Engl* **1993**, *32*, 566 , Sprinz, J , Helmchen, G *Tetrahedron lett* **1993**, 34, 1769 , Frost, C G , Williams, J M J. *Tetrahedron lett* **1993**, *34*, 2015 , Hiroi, K , Suzuki, Y *Heterocylces* **1997**, *46*, 77 , Andrew Lund Thesis

(8) Andrew Lund Thesis, **1999**, Loughborough University

(9) Harrison, P W B ,Kenyon, J , Phillips, H *J Am Chem Soc* **1926**, *48*, 2079

(10) Janczewski, M , Gos, L , Jurczak, J *Pol J Chem* **1984**, *58*, 749, and references cited therein

(11) Mikolajczyk, M , Midura, W ; Grzejszczak, S , Zatorski, A , Chefczynska, A *J Org Chem* **1978**, *43*, 473

(12) Pirkle, W H , House, D W *J Org Chem* **1979**, *44*, 1957

(13) Villani, C , Pirkle, W H *Tetrahedron Asymmetry* **1995**, *6*, 27

(14) Mikolajczyk, M , Drabowicz, J *J Am Chem Soc* **1978**, *100*, 2510

(15) Diter, P , Taudien, S, Samuel, O ; Kagan, H B *J Org Chem* **1994**, *59*, 370.

(16) Bryan, R F , Carey, F A , Dailey, O D , Maher, R J , Miller, R.W *J Org Chem* **1978**, *43*, 90

(17) Andersen, K K *Tetrhedon lett* **1962**, 93

(18) Llera, J M, Fernandez, I , Alcudia, F *Tetrahedron Lett* **1991**, *32*, 7299 , Llera, J M, Fernandez, I , Alcudia, F , Khiar, N *J Org Chem* **1992**, *67*, 6789

(19) Cardellicchio, C ; Fiandanese, V , Naso, F , Scilimati, A *Tetrahedron Lett* **1992**, *33*, 5121.

(20) Whitesell, J K, Wong, M S *J Org Chem* **1994**, *59*, 597

(21) Rebiere, F, Kagan, H B *Tetrahedron Lett* **1989**, *30*, 3659

(22) Mikolajczyk, M , Drabowski, J., Legedz, S *J Chem Soc , Chem Commun* **1985**, 1670

(23) Wudl, F , Lee, T B K *J Chem Soc , Chem Commun* **1972**, 61 , Wudl, F , Lee, T B K. *J Am Chem Soc* **1973**, *95*, 6349

(24) Benson, S C , Snyder, J K *Tetrahedron Lett* **1991**, *32*, 5885

(25) Evans, D A , Faul, M M , Colombo, L ; Bisaha, J J , Clardy, J , Cherry, D *J Am Chem Soc* **1992**, *114*, 5977.

(26) Oppolzer, W , Froelich, O ; Wiaux-Zamar, C , Bernardinelli, G. *Tetrahedron Lett* **1997**, *38*, 2825

(27) Pitchen, P , Kagan, H B *Tetrahedron Lett* **1984**, *25*, 1049

(28) Di Furia, S H , Modena, G , Seraglia, G *Synthesis* **1984**, 325.

(29) Pitchen, P , Kagan, H B , Deshmukh, M N , Dunach, E *J Am Chem Soc* **1984**, *106*, 8188 , *Phosphorus Sulfur*, H B Kagan, *27*, (**1986**), 127 , Baldenius, K ; Kagan, H B *Tetrahedron Asymmetry* **1990**, *1*, 597 , Kagan, H B , Rebiere, F. *Synlett* **1990**, 643

(30) Samuel, O , Zhao, S , Kagan, H B *Tetrahedron* **1987**, *43*, 5135

(31) Brunel, J M , Kagan, H B *Synlett* **1996**, 404

(32) Cardellicchio, C , Iacuone, A , Naso, F , Tortorella, P. *Tetrahedron lett* **1996**, *37*, 6017-6020 ; Cardellicchio, C , Fracchiolla, G , Naso, F , Tortorella, P. *Tetrahedron* **1999**, *55*, 525-532 , Capozzi, M A M , Cardellicchio, C , Fracchiolla, G, Naso, F , Tortorello, P *J Am Chem Soc*

1999, *121*, 4708-4709 , Capozzi, M A M , Cardellicchio, C , Naso, F , Tortorello, P *J Org Chem* **2000**, *65*, 2843-2846

(33) Page, P. C B ; Wilkes, R D , Namwindwa, E. S , Witty, M J *Tetrahedron lett* **1996**, *52*, 2125-2154, and references therein

(34) Scettri, A, Bonadies, F , Lattanzi, A , Senatore, A , Soriente, A. *Tetrahedron Asymmetry* **1996**, *7*, 657-658 , Lattanzi, A , Bonadies, F , Senatore, A, Soriente, A , Scettri, A *Tetrahedron Asymmetry* **1997**, *8*, 2473-2478

(35) Davis, F A , Nadir, U K , Kluger, E W *J Chem Soc , Chem Commun* **1977**, 25 , Davis, F A , Lamendoza, J , Nadir, U , Kluger, E W , Sedergan, J C.; Panunto, T W , Billmers, R , Jenkins, R , Turchi, I J , Watson, W H , Chen, J S , Kimura, M. *J Am Chem Soc* **1980**, *102*, 2000 , Davis, F A.; Jenkins, R H , Awad, S B , Stringer, O O , Watson, W H , Galloy, J *J Am Chem Soc* **1982**, *104*, 5412

(36) Davis, F A , McCauley, Jr J P , Chattopadhayay, S., Harakal, M E , Towson, J C ; Watson, W H , Tavanaeipour, I *J Am Chem Soc* **1987**, *109*, 3370

(37) Davis, F A , Towson, J C , Carroll, P J , Weismiller, M C , Lal, S. *J Am Chem Soc* **1988**, *110*, 8477 , Davis, F A , Weismiller, M C , Reddy, R T *J Am Chem Soc* **1989**, *111*, 5964 , Davis, F A , Reddy, T R , Han, W , Carroll, P J *J Am Chem Soc* **1992**, *114*, 1428

(38) Page, P C B , Heer, J P , Bethell, D , Collington, E W.; Andrews, D M *Tetrahedron Lett* **1994**, *35*, 9626

(39) Page, P C B , Heer, J.P ; Bethell, D , Collington, E W , Andrews, D.M *Tetrahedron Asymmetry* **1995**, *6*, 2911

(40) Hanquet, G , Lusinchi, X *Tetrahedron Lett* **1993**, *34*, 5299 , Bohe, L , Hanquet, L , Lusinchi, X. *Tetrahedron Lett* **1993**, *34*, 7271 , Bohe, L , Lusinchi, M , Lusinchi, X. *Tetrahedron* **1999**, 55, 155

(41) Bolm, C , Bienewald, F *Angew Chem* **1995**, *107*, 2883, *Angew Chem , Int Ed Engl* **1995**, *34*, 2640 , Bolm, C , Bienewald, F. *Synlett* **1998**, 1327

(42) Skarzewski, J , Ostrycharz, E , Siedlecka, R *Tetrahderon Asymmetry* **1999**, *10*, 3457-3461.

(43) Hamann, H J , Hoft, E , Mostowicz, D , Mishnev, A ; Urbanczyk-lipkowska, Z , Chmielewski, M *Tetrahedron* **1997**, *53*, 185

(44) Wright, L D , Cresson, E L , Valiant, J , Wolf, D E , Folkers, K. *J Am Chem Soc* **1954**, *76*, 4163.

(45) Holland, H L *Chem Rev* **1988**, *88*, 473

(46) Abushanab, E , Reed, D , Suzuki, F ; Sin, C J *Tetrahedron Lett* **1978**, *19*, 3415.

(47) Holland, H L , Brown, F M , Larsen, B G *Tetrahedron Asymmetry* **1994**, *5*, 1241 , Holland, H L , Brown, F M , Larsen, B G *Tetrahedron Asymmetry* **1995**, *6*, 1561.

(48) Holland, H L , Brown, F M , Larsen, B G *Tetrahedron Asymmetry* **1994**, *5*, 1129

(49) Carrea, G , Redigolo, B , Riva, S , Colonna, S , Gaggero, N , Battistel, E , Bianchi, D *Tetrahedron Asymmetry* **1992**, *3*, 1063

(50) Colonna, S , Gaggero, N , Bertinotti, A , Carrea, G , Pasta, P , Bernardi, A *J Chem Soc , Chem Commun* **1995**, 1123

(51) Colonna, S , Gaggero, N , Manfredı, A , Casella, L , Gulottı, M. *J Chem Soc , Chem Commun* **1988**, 1451 , Colonna, S , Gaggero, N , Casella, L , Carrea, G , Pasta, P *Tetrahedron· Asymmetry* **1992**, *3*, 95

(52) Fu, H , Kondo, H , Ichıkawa, Y , Look, G C , Wong, C *J Org Chem* **1992**, *57*, 7265

(53) Allen, C C R , Boyd, D R , Dalton, H , Sharma, N D , Haugley, S A , McMordıe, R A S , McMurray, B T , Sheldrake, G N , Sproule, K *J Chem Soc , Chem Commun* **1995**, 119

(54) Beecher, J , Brackenrıdge, I , Roberts, S M ; Tang, J , Wıllets, A J *J Chem Soc , Perkın Trans 1* **1995**, 1641 , Beecher, J , Brackenrıdge, I , Roberts, S M , Tang, J , Wıllets, A J. *Tetrahedron* **1995**, *51*, 13217.

(55) Colonna, S , Gaggero, N , Leone, M *Tetrahedron* **1991**, *47*, 8385

(56) Kawasakı, T , Watanabe, N , Sugaı, T , Ohta, H *Chem Lett* **1992**, 1611

(57) Hsıeh, L C , Stephans, J C , Schultz, P G *J Am Chem Soc* **1994**, *116*, 2167.

(58) Ohta, H , Kato, Y , Tsuchıhası, G *Chem Lett* **1986**, 217.

(59) Burgess, K , Henderson, I *Tetrahedron lett* **1989**, *30*, 3633 , Burgess, K , Henderson, I , Ho, K *J Org Chem* **1992**, *57*, 1290

(60) Page, P C B , Shuttleworth, S J , Schılling, M. B , Tapolczay, D J. *Tetrahedron lett* **1993**, *34*, 6947.

(61) For recent revıews on asymmetrıc catalysıs Consıglıo, G , Waymouth, R W *Chem Rev* **1989**, *89*, 257-276 , Blystone, S L *Chem Rev* **1989**, *89*, 1663-1679 , Sawamura, M , Ito, Y *Chem Rev* **1992**, *92*, 857-871 , Wılls, M *J Chem Soc , Perkın Trans 1* **1998**, 3101 , Tonks, L ;

Williams, J M J. *J Chem Soc, Perkin Trans 1* **1998**, 3637-3652 ; Haughton, L , Williams, J. M J *J Chem Soc, Perkin Trans 1* **1999**, 2645-2658

(62) Jacobsen, E N , Zhang, W , Muci, A R , Ecker, J. R *J Am Chem Soc* **1991**, *113*, 7063.

(63) Kolb, H C ; VanNieuwenhze, M S , Sharpless, K B *Chem Rev* **1994**, *94*, 2483

(64) Trost, B M , Van Vranken, D L *Chem Rev* **1996**, *96*, 395-422

(65) Ozawa, F , Kubo, A , Hayashi, T *J Am Chem Soc* **1991**, *113*, 1417 , Ozawa, F , Kubo, A , Hayashi, T J *Tetrahedron Lett* **1992**, *33*, 1485 , Sato, Y , Watanabe, S , Shibasaki, M. *Tetrahedron lett* **1992**, *33*, 2589 and 2593

(66) Trost, B M , Strege, P E *J Am Chem Soc* **1977**, *99*, 1650

(67) Fiaud, J C ; Aribi-Zouioueche, L *J Chem Soc, Chem Commun* **1986**, 390.

(68) Fiaud, J C , Legros, J Y. *J Org Chem* **1990**, *55*, 4840

(69) Trost, B M , Van Vranken, D L *Angew Chem, Int Ed Engl* **1992**, *31*, 228

(70) Granberg, K L , Backwall, J E *J Am Chem Soc* **1992**, *114*, 6858

(71) Trost, B M , Keinan, E. *J Am Chem Soc* **1978**, *100*, 7779

(72) Uozumi, Y , Hayashi, T *J. Am Chem Soc* **1991**, *113*, 9887 , Hayashi, T , Iwamura, H., Naito, M , Matsumoto, Y , Uozumi, Y *J Am Chem Soc* **1994**, *116*, 775 , Kitayama, K ; Uozumi, Y , Hayashi, T *J Chem Soc, Chem Commun* **1995**, 1533.

(73) Vyskocil, S , Smrcina, M ; Hanus, V , Polasek, M ; Kocovsky, P. *J Org Chem* **1998**, *63*, 7738-7748

(74) Bower, J F; Jummah, R ; Williams, A. C , Williams, J M J. *J Chem Soc, Perkin Trans 1* **1997**, 1411.

(75) Krafft, M E , Wilson, A M ; Fu, Z , Procter, M J , Dasse, O. A. *J Org Chem* **1998**, *63*, 1748-1749

(76) Trost, B M , Hung, M -H *J Am Chem Soc* **1983**, *105*, 7757-7759.

(77) Trost, B M , Hachiya, I *J Am Chem Soc* **1998**, *120*, 1104-1105

(78) Trost, B M , Van Vranken, D L , Bingel, C *J Am Chem Soc* **1992**, *114*, 9327

(79) Evans, A. P , Nelson, J D *Tetrahedron lett* **1998**, *39*, 1725-1728

(80) Blacker, J A , Clarke, M L , Loft, M S , Mahon, M F , Humphries, M. E , Williams, J M J *Chem Eur J* **2000**, *6*, 353

(81) Miyashita, A , Yasuda, A , Takaya, H , Toriumi, K ; Ito, T , Souchi, T., Noyori, R *J Am Chem Soc* **1980**, *102*, 7932 , Miyashita, A , Takaya, H , Souchi, T., Noyori, R *Tetrahedron* **1984**, *40*, 1245 , Takaya, H , Mashima, K , Koyano, K , Yagi, M , Kumobayashi, H , Taketomi, T., Akutagawa, S , Noyori, R *J Org Chem* **1986**, *51*, 629.

(82) Trost, B M , Murphy, D. J *Organometallics* **1985**, *4*, 1143

(83) Woerpel, K A ; Hinman, M M , Faul, M M , Evans, D A *J Am Chem Soc* **1991**, *113*, 726

(84) Pfaltz, A *Acc Chem Res* **1993**, *26*, 339

(85) Lowenthal, R E , Abiko, A , Masamune, S *Tetrhedron lett* **1990**, *31*, 6005-6008

(86) Tokunoh, R , Sodeoka, M ; Aoe, K -I ; Shibasaki, M *Tetrahedron lett* **1995**, *36*, 8035-8038

(87) von Matt, P , Pfaltz, A *Angew Chem , Int Ed Engl* **1993**, *32*, 566

(88) Dawson, G J , Frost, C. G , Williams, J M J , Coate, S. W. *Tetrahedron lett* **1993**, *34*, 3149

(89) Sprınz, J , Helmchen, G *Tetrahedron lett* **1993**, *34*, 1769

(90) Frost C. G , Wılhams, J M J *Tetrahedron lett* **1993**, *34*, 2015-2018 , Dawson, G J , Frost, C J ; Martın, C J , Wılhams, J M J *Tetrahedron lett* **1993**, *34*, 7793-7796 , Allen, J. V ; Wılhams, J M J. *Tetrahedron Asymmetry* **1994**, *5*, 277-282 , Allen, J V , Bower, J F , Wılhams, J M. J *Tetrahedron Asymmetry* **1994**, *5*, 1895-1898 ; Allen, J. V ; Coote, S J , Dawson, G J , Frost, C. J , Martın, C J , Wılhams, J M J. *J Chem Soc , Perkın Trans 1* **1994**, 2065

(91) Imaı, Y , Zhang, W ; Kıda, T , Nakatsujı, Y , Ikeda, I *Tetrahedron lett* **1998**, 4343-4346

(92) Canal, J M , Gomez, M ; Jımenez, F , Rocamora, M., Muller, G , Dunach, E , Franco, D ; Jımenez, A , Cano, F H. *Organometallıcs* **2000**, *19*, 966-978

(93) Evans, A. P ; Brandt, T A. *Tetrahedron lett* **1996**, *37*, 9143-9146

(94) Ito, K , Kashıwagı, R , Iwasakı, K , Katsukı, T *Synlett* **1999**, *10*, 1563-1566

(95) Chellucci, G , Cabras, A M *Tetrahedron Asymmetry* **1996**, *7*, 965-966.

(96) Konıng, B, Meetsma, A , Kelloggs, R M *J Org Chem* **1998**, *63*, 5533-5540.

(97) Adams, H , Andersen, J C , Cubbon, R , James, D S , Mathıas, J P *J Org Chem* **1999**, *64*, 8256-8262

(98) Hıroı, K , Suzukı, Y *Heterocylces* **1997**, *46*, 77 , Hıroı, K , Suzukı, Y , Abe, I ; Hasegawa, Y., Suzukı, K *Tetrahedron Asymmetry* **1998**, *9*, 3797-3817

(99) Chelucci, G , Berta, D , Saba, A *Tetrahedron* **1997**, *53*, 3843-3848

(100) Morımoto, T , Tachıbana, K , Achıwa, K *Synlett* **1997**, 783

(101) Chellucı, G , Bacchı, A , Fabbrı, D , Saba, A , Ulgheri, F *Tetrahedron Lett* **1999**, *40*, 553-556

(102) Wipf, P , Ribe, S *J Org Chem* **1998**, *63*, 6454-6455.

(103) Petra, D G I , Kamer, P C J , Spek, A L , Schoemaker, H E , van Leuween, P W N. M *J Org Chem* **2000**, *65*, 3010-3017

(104) Andrew Lund Thesis, **1999**, Loughborough University

Chapter 2

Results & Discussions:

2-A: Asymmetric Sulfoxidation:

2-A-1 Introduction

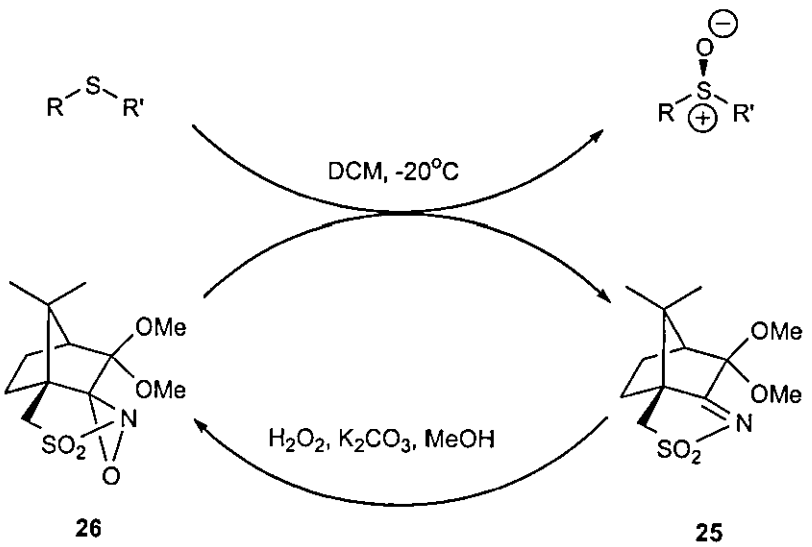
Optically active sulfoxides constitute a class of highly valuable chiral auxiliaries and reagents in asymmetric synthesis The most attractive method for their preparation is the enantioselective oxidation of the easily accessible prochiral sulfides

The first successful and commonly used chemical method of asymmetric sulfoxidation, modified Sharpless epoxidation system, was developed independently by Kagan[1] and Modena[2] Davis[3] introduced the employment of chiral oxaziridines also subsequently studied by Page [4]

These asymmetric sulfoxidation procedures allow accessing various chiral sulfoxides with high optical purity But, we were interested to promote 1,3-dithiane-1-oxide derivatives as chiral auxiliaries and limitations appeared for the choice of the procedure to oxidise enantioselectively 1,3-dithiane derivatives Apparently, the chiral oxaziridines developed by Page[5] afford generally better asymmetric sulfoxidation than other procedures for asymmetric sulfoxidation of some 1,3-dithiane derivatives

Furthermore, these chiral oxaziridines have been developed within our research group and we were aware how to deal for the syntheses of such chiral oxidising agents

Further reasons for using chiral oxaziridine oxidising agents for asymmetric sulfoxidation are the simple reaction conditions (dichloromethane, and -20 °C), work-up (aqueous solution of sodium sulfite, extraction with dichloromethane), and the almost quantitative recovery of the corresponding chiral imine (**25**) which can be converted to the oxaziridine (**26**) by oxidation with hydrogen peroxide and potassium carbonate (Scheme 1)



26 **25**

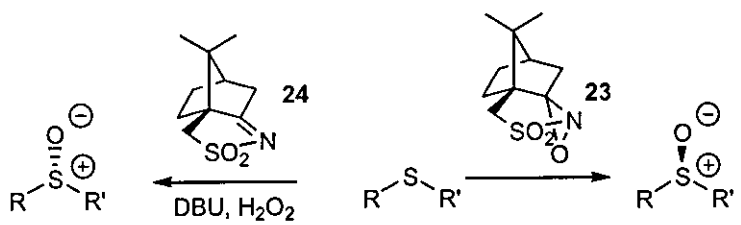
Scheme 1

The disadvantages for the other procedures are the use of an excess of DBU and hydrogen peroxide with the chiral sulfonyl imine (Payne-related procedure developed by Page), or careful control of the ratio $Ti(O\text{-}iPr)_4$, (+)-DET, and water for optimal enantioselectivities in the modified Sharpless procedure.

2-A-2 Oxazıridıne as chıral oxıdısıng agent

Oxazıridınes are versatile reagents that can be used ın hydroxylatıon of enolate, epoxıdatıon and sulfoxıdatıon A major advantage of these stoıchıometrıc reagents ıs that they can oxıdise substrates under neutral, aprotıc condıtıons.

Chıral oxazıridınes based on camphor skeleton have been wıdely studıed and optımised by Page[4,5] A range of these chıral oxazıridınes can be used for the preparatıon of varıous sulfoxıdes wıth varıable level of selectıvıtıes and asymmetrıc ınductıon followıng the nature of oxazıridıne used Wıth non-substıtuted chıral sulfonyl ımıne (**24**) or oxazıridıne (**23**), ıt ıs possıble to access both enantıomer of the sulfoxıdes (Scheme 2)[3]



Scheme 2

Many chıral sulfonyl ımınes (**24**, **73**, **74**, **25**, **75**) and oxazıridınes (**23**, **76**, **77**, **26**, **78**) have been synthesısed and successfully ınvestıgated as chıral oxıdısıng agents for sulfides (Fıg 1)[5]

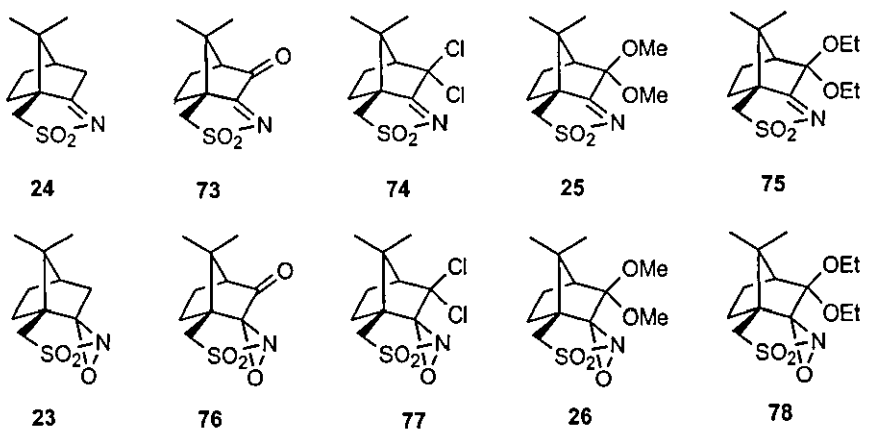
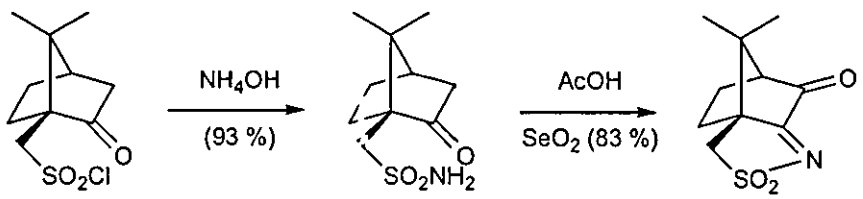


Fıg 1

We decided to opt for the use of [(3,3-dimethoxycamphoryl) sulfonyl)imine (**25**) as chiral oxidising agent, because it gave very high levels of asymmetric induction for the oxidation of various sulfides and it is easily synthesised from (+)-10-camphorsulfonyl chloride by standard reactions in four steps without requirement of chromatographic purification at any stage

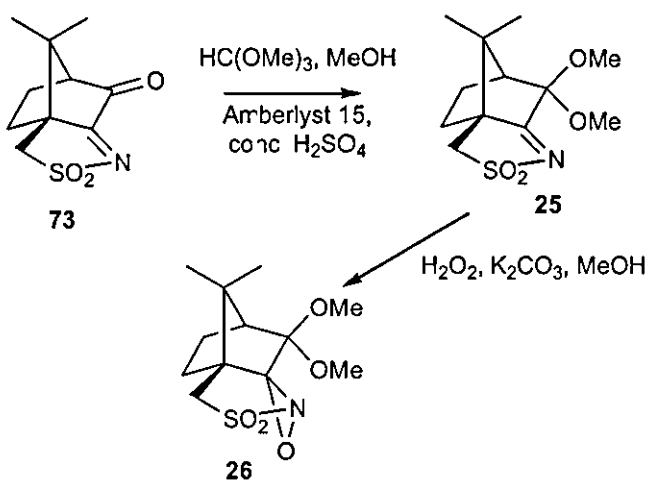
First, the (+)-10-camphorsulfonyl chloride (**79**) is converted to the corresponding sulfonyl imine (**73**) by treatment with ammonium hydroxide followed by condensation and oxidation of the crude sulfonamide (**80**) (Scheme 3)



79 **80** **73**

Scheme 3

The keto function of (-)-oxocamphorsulfonyl imine (**73**) was protected through treatment with trimethyl orthoformate under acid catalysis and subsequent oxidation with hydrogen peroxide and potassium carbonate afford the oxaziridine (**26**) (Scheme 4)



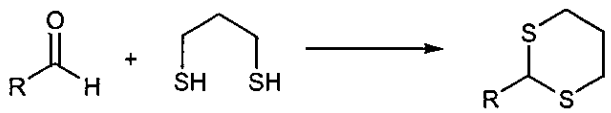
73 **25** **26**

Scheme 4

2-A-3 1,3-dithiane species

2-A-3-1 Synthesis

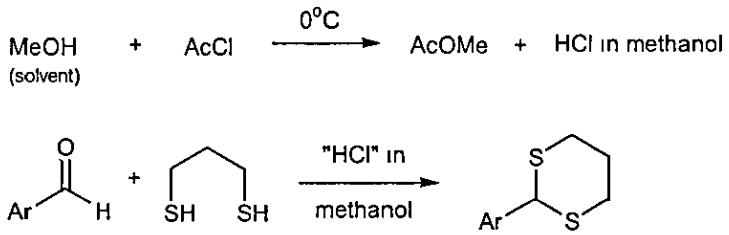
The synthesis of 1,3-dithiane derivatives is largely covered in the literature[6] by procedures involving dithioacetalisation of aldehydes with 1,3-propanedithiol The typical procedure is to reflux an equimolar mixture of aldehydes and 1,3-propanedithiol in presence of Lewis acid under Dean-Stark condition reaction (Scheme 5)



Scheme 5

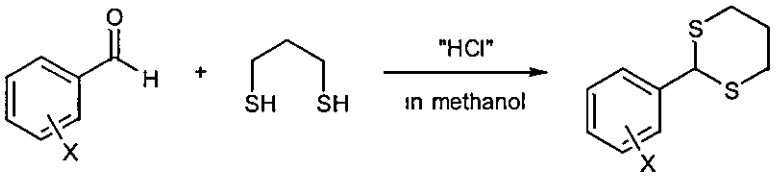
Many improvements have been developed to this process for the access to higher yields, shorter reaction times, cleaner reaction conditions and easier purification step of 1,3-dithiane derivatives

One of the most inventive improvements to this process has been reported by Graham[7] who generated hydrogen chloride *in situ* from methanol and acetyl chloride to catalyse the dithioacetalisation reaction (Scheme 6)



Scheme 6

The purification of the 1,3-dithiane derivatives from the reaction mixture was achieved by evaporation of the solvent reaction to dryness and recrystallisation from methanol of the crude mixture to afford the product in generally good yields We mad a series of 2-aryl-1,3-dithiane derivative using this methodology All elemental analyses were in agreement with the calculated values (Scheme 7, table 1)

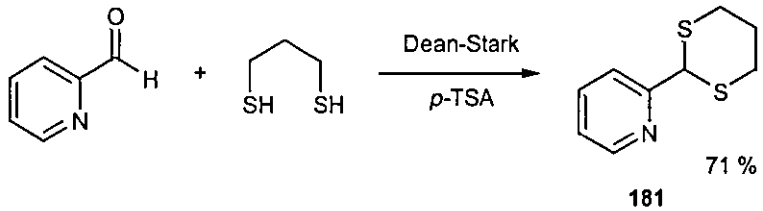


Scheme 7

Table 1

Entry	Compounds	X	Yields (%)
1	**81**	o-Br	74
2	**82**	o-NO2	82
3	**83**	o-F	69
4	**84**	p-Br	74
5	**85**	o-MeO	81
6	**86**	m-MeO	95
7	**87**	p-MeO	91

The inconvenience of this process is that it cannot be applied to aldehydes containing a basic sensitive group Therefore, the preparation of 2-pyridyl-1,3-dithiane (**181**) was performed under Dean-Stark reaction condition in presence of a catalytic amount of *p*-toluene sulfonic acid (*p*-TSA) to condense 1,3-propanedithiol and pyridine-2-carboxaldehyde (Scheme 8)[8]



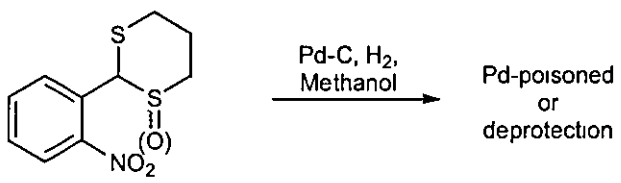
Scheme 8

We were also interested to synthesise 2-(2-aminophenyl)-1,3-dithiane as precursor of imine-sulfoxide ligands for application in asymmetric metal-catalysed reactions

The 2-aminobenzaldehyde is not commercially available for understandable reason, we decided to reduce the nitro group of either 2-(2-nitrophenyl)-1,3-dithiane and 2-(2-nitrophenyl)-1,3-dithiane-1-oxide (synthesised by oxidation of the corresponding 1,3-dithiane derivative with

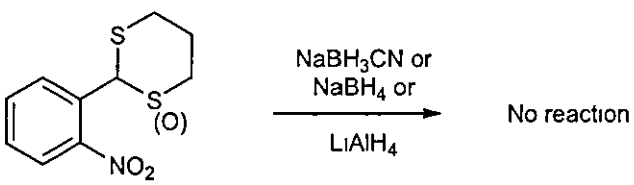
MMPP) by standard reduction processes with in mind to preserve the sensitive 1,3-dithiane moiety by careful choice of selective reducing agents

We first turned on the use of catalytic hydrogenation process with palladium on charcoal (Scheme 9) in methanol with hydrogen, but it appears that 1,3-dithiane moiety acted as a poison for palladium metal in the case of 2-(2-nitrophenyl)-1,3-dithiane, and a partial deprotection of the 1,3-dithiane-1-oxide ring was detected by the characteristic odour of thiols for reduction of 2-(2-nitrophenyl) -1,3-dithiane-1-oxide



Scheme 9

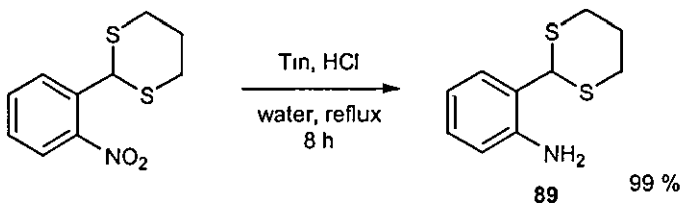
The use of hydride sources was investigated without any success for both 1,3-dithiane and 1,3-dithiane-1-oxide derivatives (Scheme 10)



Scheme 10

After these unsuccessful attempts to reduce the nitro moiety, we decided to use tin/HCl as reducing agent, without any great hope as 1,3-dithiane moiety is an acid sensitive group But, we were surprised upon analysing the reaction mixture to observe complete consumption of the nitro compound The 1,3-dithiane moiety was not cleaved and the amino derivative (**89**) was obtained

in almost quantitative yields Scaling up the reaction was less successful because under longer reaction time, hydrogenolysis of the 1,3-dithiane moiety started to occur and polymer formation was observed which complicated purification (Scheme 11)



89 99 %

Scheme 11

The purification step was achieved by filtration of the unreacted tin metal, and alkalination of the aqueous phase 2-(2-Aminophenyl)-1,3-dithiane (**89**) precipitated in the absence of organic solvent, but so did tin dihydroxide ($Sn(OH)_2$) affording inseparable phases even after addition of dichloromethane. By addition of excess sodium hydroxide solid, tin dihydroxide dissolved to give a highly water soluble complex, tin tetrahydroxide ($Sn(OH)_4^{2-}$) (Scheme 12), and the purification of the amino product was achieved without further difficulties

$$Sn(OH)_{2\,(sol)} + 2\,(Na^+ + OH^-)_{(aq)} \longrightarrow Sn(OH)_4^{2-}{}_{(aq)} + 2\,Na^+{}_{(aq)}$$

Scheme 12

The synthesis of 2-(2-methylenepyridyl)-1,3-dithiane (**90**) (Fig 2) was also investigated, given the potential application of its chiral 1,3-dithiane-1-oxide (**91**) derivative as ligand in metal-catalysed reaction Its similarity with the 2-pyridyl-1,3-dithiane-1-oxide (**88**) homologue already successfully used by us[8] as ligand in palladium-catalysed allylic alkylation, prompted its synthesis to help the clarification on the nature of the interaction between the ligand and the palladium complex

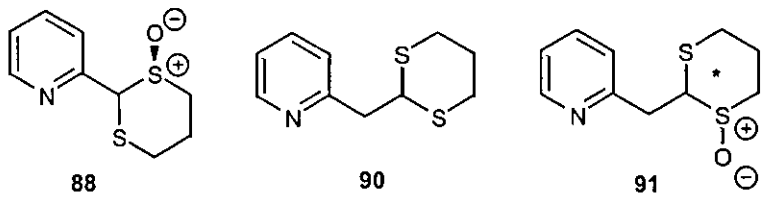
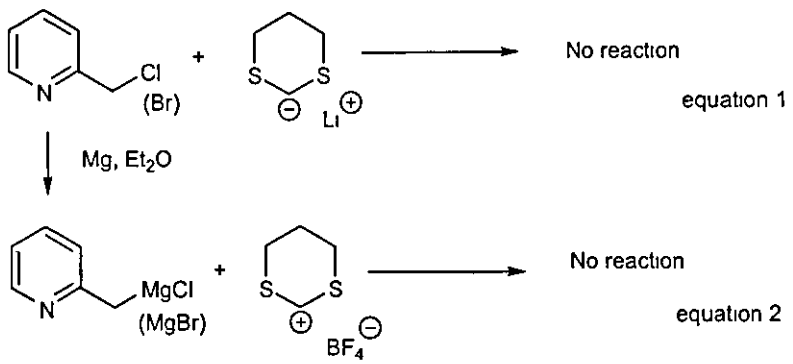


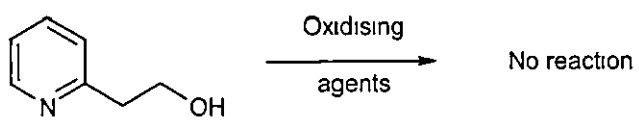
Fig 2

2-Pyridyl-acetaldehyde is not commercially available, and we decided to synthesise pyridyl-methylene-1,3-dithiane (**90**) by nucleophilic substitution reaction from 2-lithio-1,3-dithiane and 2-halomethyl pyridine Unfortunately, no formation of product was observed (Scheme 13, eq 1) Inversion of the polarity of the reagents was also unsuccessfully attempted by preparation of the Grignard reagent of 2-halomethyl pyridine and subsequent attack onto the isolated tetrafluoroborate salt of 1,3-dithiane (Scheme 13, eq 2)



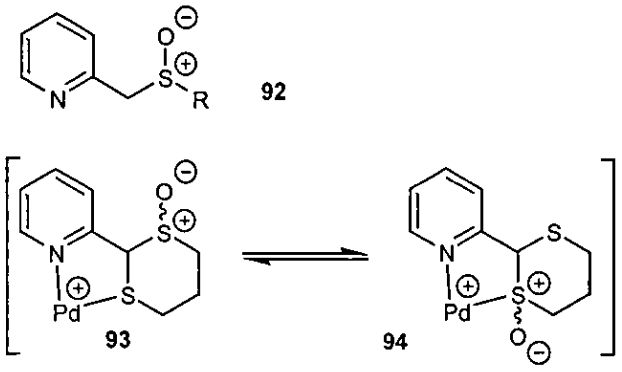
Scheme 13

Attempted oxidation of 2-pyridyl ethanol to the corresponding aldehyde was also fruitless using selenium dioxide, pyridinium chlorochromate, pyridinium dichlorochromate, TEMPO-BAIB, Swern oxidation process and manganese dioxide (Scheme 14)



Scheme 14

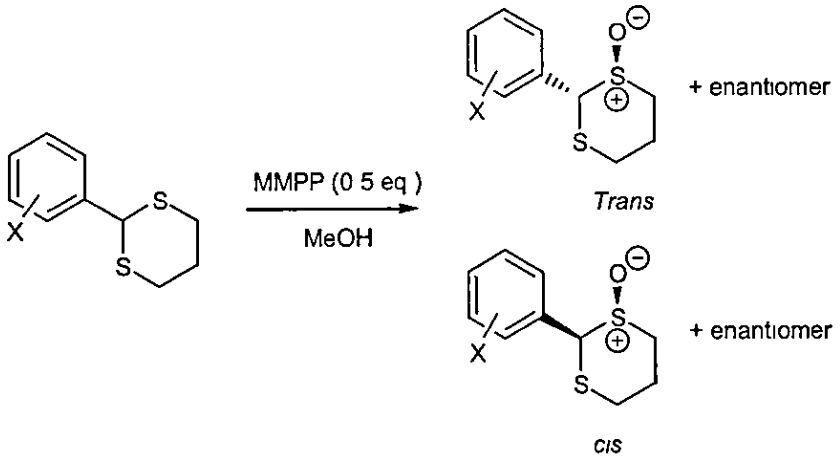
Given our difficulty to access this useful intermediate, we synthesised 2-(methylsulfoxide) pyridine-based ligands (**92**) which contained only pyridine (N sp2) and sulfoxide moiety Investigation of these compounds as ligands might shed lights on the possible competition of N (sp2)-thioether (**93**) and N (sp2)-sulfoxide (**94**) chelation with palladium complex (Scheme 15) (cf 2-A-4)



Scheme 15

2-A-3-2 Oxidation using chiral oxaziridine

With the 1,3-dithiane substrates in hand, racemic sulfoxidation was first carried out with magnesium monoperoxyphthalate (MMPP) on the 1,3-dithiane substrates to afford a mixture of *cis* and *trans* isomers with a major presence of the *trans* isomer (Scheme 16)



Scheme 16

After separation, a ^{1}H NMR spectrum was obtained in presence of an equimolar mixture of (±)-*trans* 1,3-dithiane-1-oxide substrate and (*R*)-(3,5-dinitrobenzoyl)-1-phenylethylamine (Fig 3, **95**)[9] as chiral shift reagent (instead of the usual Pirkle reagent (Fig 3, **96**)[10] which requires 10 molars equivalents), to check the possible determination of enantiomeric excesses (in case of asymmetric sulfoxidation) by splitting the singlet signal corresponding to the proton attached to the carbon between the thioether and the sulfoxide moiety

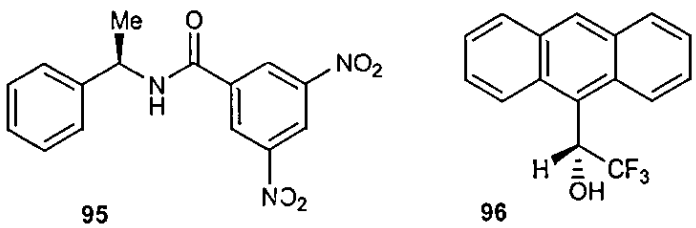
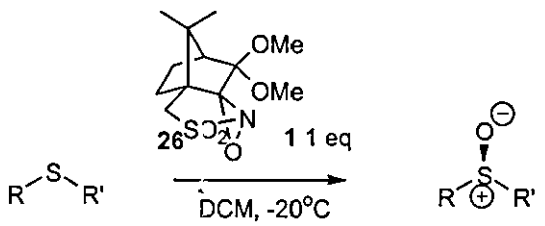


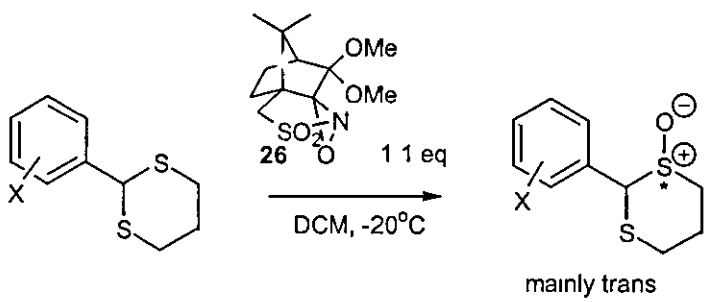
Fig. 3

After verifying that enantiomeric excess determination was possible by ^{1}H NMR spectroscopy, we carried out the asymmetric oxidation using the well-established procedure with the chiral oxaziridine oxidising agent (**1**) This procedure has been optimised by Page (Scheme 17)[5]



Scheme 17

We applied the optimised reaction conditions to the oxidation of our 1,3-dithiane substrates using a slight excess of oxidising agent (**1**) to reach complete consumption of substrate within 24 hours. The 1,3-dithiane-1-oxide products were obtained exclusively as the *trans* isomers In most cases, the *cis* isomer was ever not detected or obtained in less than 5 % yield (Scheme 18)



Scheme 18

The enantiomeric excesses were determined by ^{1}H NMR spectroscopy of an equimolar mixture of 1,3-dithiane-1-oxide species and (*R*)-(3,5-dinitrobenzoyl)-1-phenylethylamine (**95**) as chiral shift reagent Comparison of the integration of the split signals gave the enantiomeric excesses

Yields and enantiomeric excesses for the asymmetric sulfoxidation of 1,3-dithiane substrates are summarised in table 2

Table 2

Entry	compounds	X	Yield (%)[a]	ee (%)
1	**97**	o-Br	90	56
2	**98**	o-NO_2	90	72
3	**99**	o-NH_2	98	92 (99)[b]
4	**100**	o-F	83	72
5	**101**	p-Br	99	96
6	**102**	o-MeO	97	84
7	**103**	m-MeO	84	96
8	**104**	p-MeO	95	>99[c]
9	**88**	pyridyl[d]	78	>99[c]

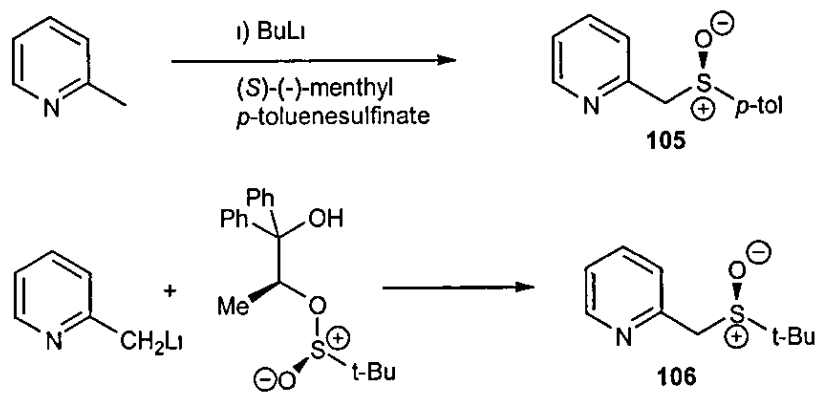
a) isolated yields , b) after recrystallisation , c) minor isomer not detected ,
d) substituted phenyl was replaced by pyridyl ring

Better asymmetric induction was obtained for substrates containing a substituent in the *para* position than for those with an *ortho* substituent (Entries 1 and 5, 6 and 8) The nature of the substituent was also decisive for excellent results electron donating groups (EDG) afford a higher enantiomeric excess (Entries 3, 7, 8) than do electron withdrawing groups (EWG) (Entry 2)

2-A-4: Sulfoxides containing pyridyl ring

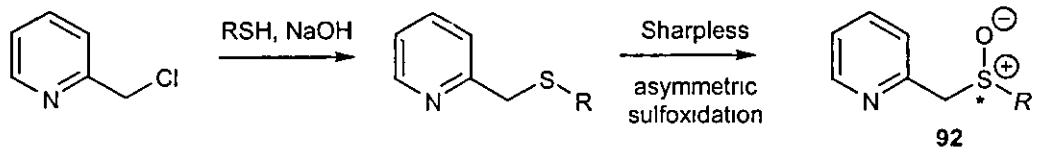
2-A-4-1 Synthesis of sulfides and asymmetric sulfoxidation

Kagan[11] has reported the synthesis of new optically active sulfoxides with chelating properties, but investigation of these sulfoxides in metal-catalysed reactions as ligands remains missing from the literature Anderson's method[12] was used to access optically pure (*R*)-(+)-2-(*p*-toluenesulfinylmethyl) pyridine (**105**) An analogous substitution process developed by Kagan[13] afforded optically pure (*R*)-(+)-2-(*t*-butylsulfinylmethyl) pyridine (**106**) (Scheme 19)



Scheme 19

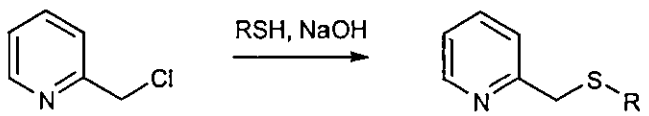
Kagan investigated an additional route to sulfoxides by asymmetric sulfoxidation using the modified Sharpless procedure[14] Pyridylmethyl sulfoxides (**92**) can be prepared by nucleophilic thiolate attack on 2-(chloromethyl)pyridine, but asymmetric sulfide oxidation turned out to proceed without satisfactory enantiomeric excess (Scheme 20)



Scheme 20

We decided to follow such procedure involving asymmetric oxidation of sulfides using our chiral oxaziridine oxidising agent in place of the modified Sharpless procedure

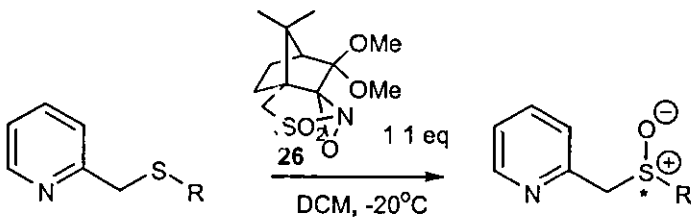
The synthesis of the 2-pyridylmethyl sulfoxides series was achieved first by nucleophilic displacement of the chloro atom by thiolate anion generated from thiol and sodium hydroxide in a bi-phasic solvent (Scheme 21)[15]



Entry	Compound	R	Yield (%)
1	**107**	Ph	96
2	**108**	Me	86
3	**109**	*t*-Bu	100

Scheme 21

Asymmetric oxidation was carried out with the chiral oxaziridine oxidising agent (**26**) to give, in general, better enantiomeric excess than the modified Sharpless procedure. The same configuration at the sulfur atom was obtained, determined by comparison of optical rotation, but remains unknown (Scheme 22)



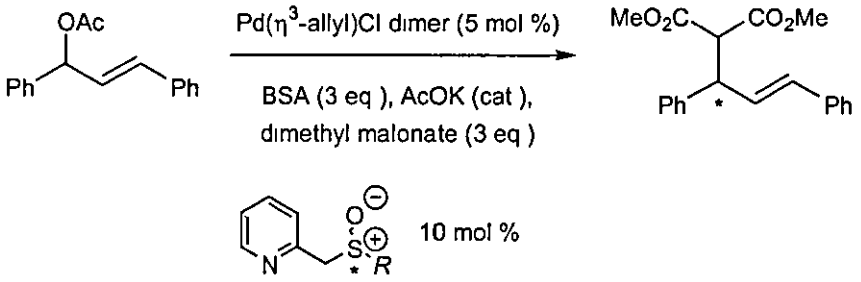
Entry	compound	R	yield (%)	ee (%)	Kagan' ee (%)[13]
1	**110**	Ph	78	17	-
2	**111**	Me	80	51	26
3	**112**	*t*-Bu	99	53	-

Scheme 22

2-A-4-2 Application of sulfo ..ides compounds containing pyridyl ring as ligands

Even with the moderate enantioselectivities achieved by asymmetric oxidation with chiral oxaziridine (**26**), we decided to investigate pyridylmethyl sulfoxides as ligands in the palladium-catalysed allylic nucleophilic substitution reaction[16] of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate anion as nucleophile generated using *N,O*-bis(trimethylsilyl)acetamide (BSA), a catalytic amount of potassium acetate and dimethyl malonate

These reaction conditions are commonly applied according to the literature[17] when potential ligands are investigated for the determination of their activities as asymmetric mediator. Palladium allyl chloride dimer was chosen as palladium source in tetrahydrofuran or dichloromethane solvent (Scheme 23, table 3)



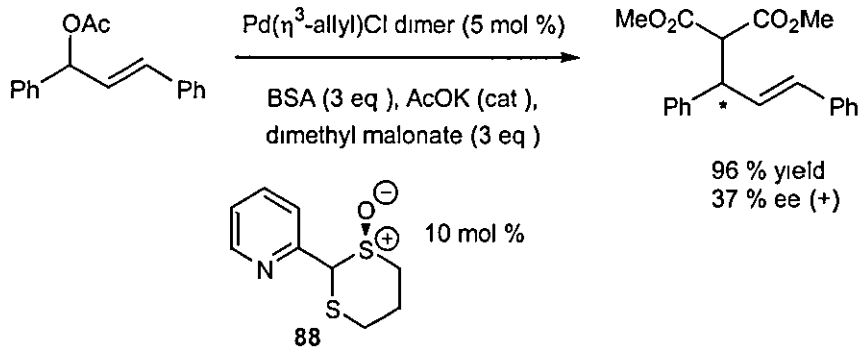
Scheme 23

Table 3

Entry	R	compound (ee's)	r t (h)	solvent	T	yield (%)	ee (%)	optical rotation
1	Me	**111** (51)	48	THF	RT	0		
2	Ph	**110** (17)	48	THF	RT	0		
3	*t*-Bu	**112** (53)	48	THF	RT	0		
4	*t*-Bu	**112**	48	THF	reflux	0		
5	*t*-Bu	**112**	70	DCM	RT	17	8	(-)
6	Me	**111**	48	DCM	RT	5	5	(-)
7	*t*-Bu	**112**	18	DCM	reflux	78	8	(-)

Dichloromethane seems to be the solvent of choice but reaction times were long. Only under reflux was a reasonable yield achieved (Entry 7), with almost no activity shown by sulfoxide ligands as asymmetric mediator (up to 8 % ee)

As mentioned above, *trans*-2-(*S*)-(2-pyridyl)-1,3-dithiane-1-(*S*)-oxide (**88**) has been previously employed as ligand in the same palladium reaction with excellent yield (96 %) and an enantiomeric excess up to 37 % of the (+) isomer. (Scheme 24)



Scheme 24

The synthesis of this ligand used the same asymmetric sulfoxidation process as the pyridylmethyl sulfoxide ligands, and we expected that same absolute stereochemistry should be obtained for our pyridylmethyl sulfoxides (**110, 111, 112**) The opposite sense of induction actually observed in palladium-catalysed reaction might be explained with different coordination sites with palladium (Fig. 4)

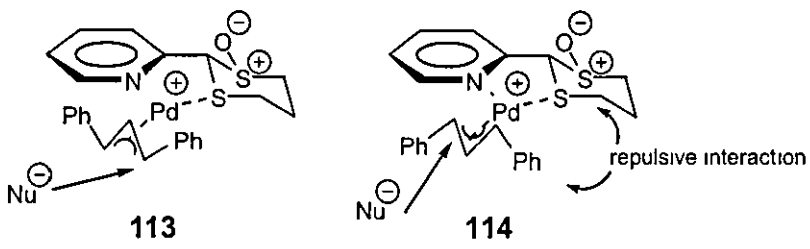
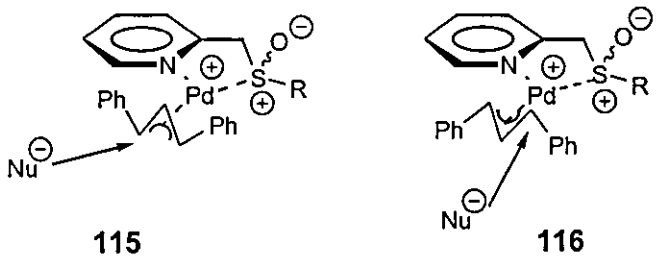


Fig 4

It is absolutely impossible to give a possible transition state by comparison of the ligand **88** and pyridylmethyl sulfoxide ligands (**110, 111, 112**) to explain the induction of chirality from the pyridylmethyl sulfoxide ligands (**110, 111, 112**), for several reasons The first reason is that the mode of chelation is different, i e chelation between S-Pd from the sulfide for the ligand **88** and S(O)-Pd from the pyridylmethyl sulfoxides (**110, 111, 112**) The other reason is that the asymmetric centre at the sulfoxide remains unknown and the spatial position of the R and phenyl group cannot be determined for the minimisation of the main repulsive interaction (Fig 5, **115, 116**)



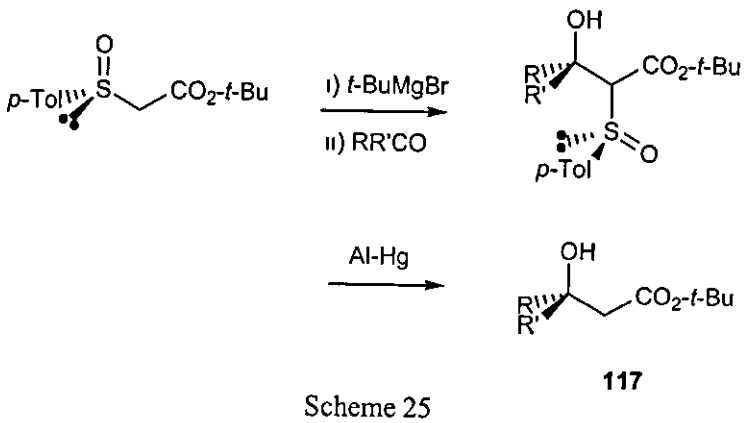
115 **116**

Fig 5

2-A-5 Possible application of chiral 1,3-dithiane-1-oxide species

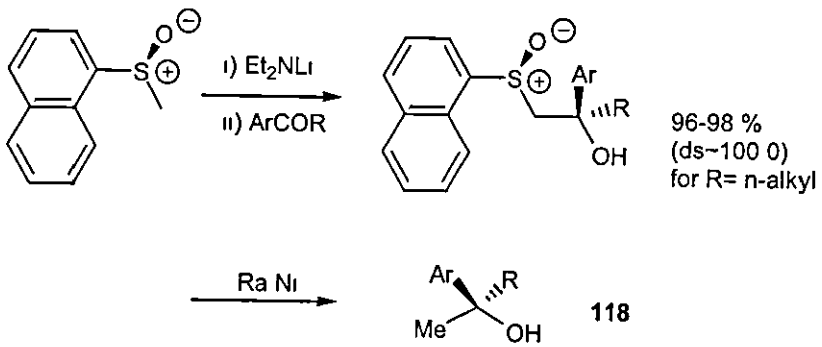
2-A-5-1. Chiral auxiliary

The application of chiral sulfoxides as asymmetric mediator was first reported by Solladié [18] Usually condensation of chiral esters with aldehydes results in low levels of asymmetric induction Incorporation of a chiral sulfoxide, however, as a chiral auxiliary affords for the synthesis of β-hydroxy acid (**117**), good chemical yields and enantioselectivities (Scheme 25)



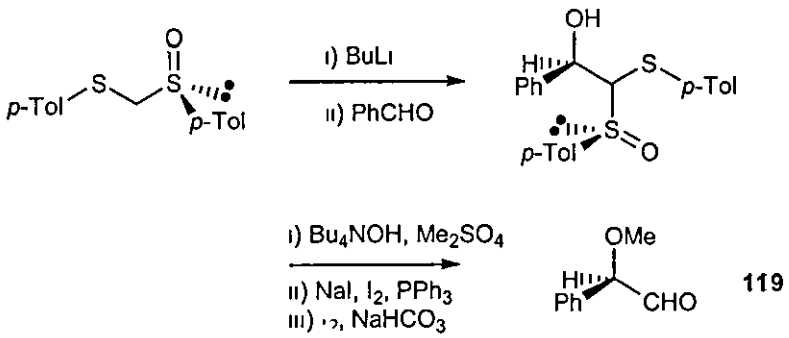
Scheme 25

Chiral sulfoxides have been reported[19] in the synthesis of chiral alcohol (**118**) by nucleophilic addition of chiral sulfoxide anion to aryl ketone with high selectivities (Scheme 26)



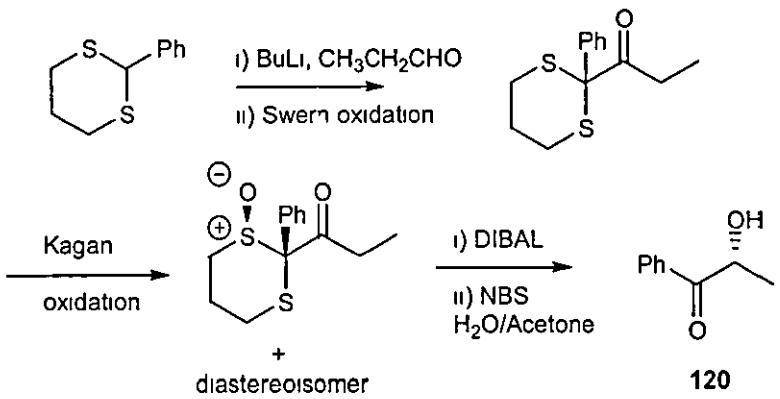
Scheme 26

An application of acyclic sulfide-sulfoxides as chiral auxiliaries has also been reported[20] for chiral homologation of aldehyde (**119**) (Scheme 27) with good to excellent enantioselectivities (≥ 70 % ee)



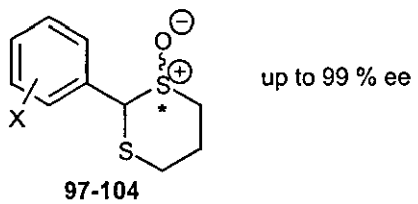
Scheme 27

Page[21] introduced the application of chiral 1,3-dithiane-1-oxide derivatives for the asymmetric synthesis of α-hydroxy ketone (**120**) The chiral sulfoxides are generated by a modified Sharpless asymmetric epoxidation process to yield a separable mixture of *trans* and *cis* diastereoisomers. (Scheme 28)



Scheme 28

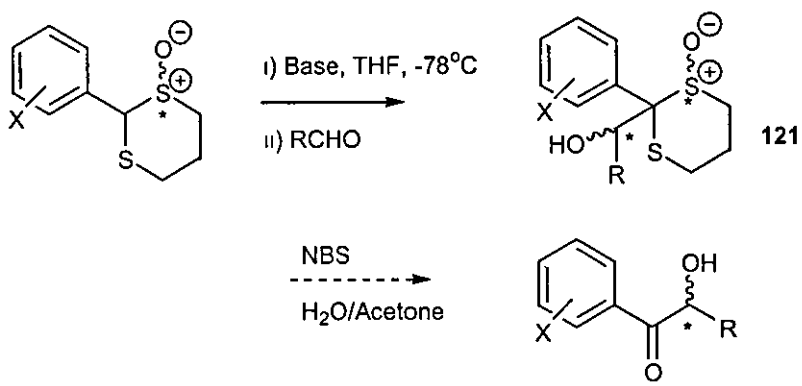
Many other asymmetric synthetic methodologies with chiral sulfoxides have been developed, for example in the synthesis of biologically active compounds [22] But, chiral 2-aryl-1,3-dithiane-1-oxide (Fig 6, **97-104**) have never been investigated as chiral auxiliaries



97-104

Fig 6

Their easy synthesis, with high chemical yields and enantioselectivities, prompted us to apply 2-aryl-1,3-dithiane-1-oxide as a chiral mediator in the synthesis of chiral α-hydroxy ketones (Scheme 29)



Scheme 29

Unfortunately, no formation of product was observed with any aldehydes or bases in the formation of the chiral anion intermediate (**121**) (Table 4)

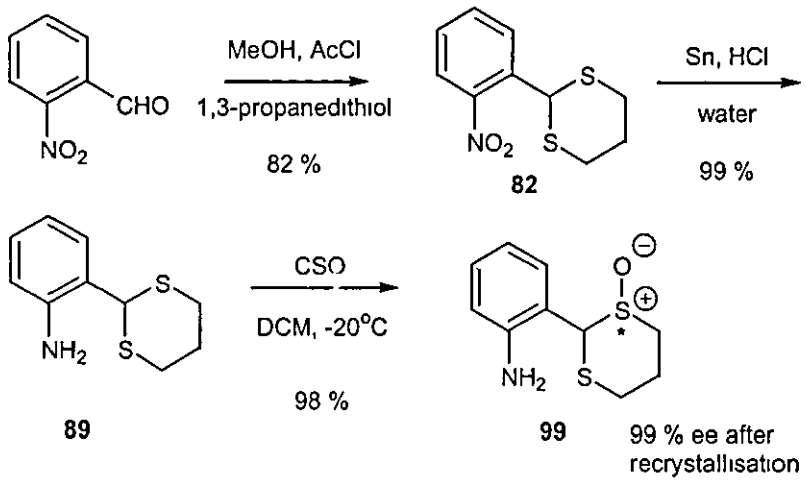
Table 4

Entry	X	R	T (°C)	Base	Yield (%)
1	*p*-OMe	Me	-78	*n*-BuLi	-
2	*p*-OMe	Me	-78	*t*-BuLi	-
3	*p*-OMe	Me	-78	LHMDS	-
4	*p*-OMe	Ph	-78	*n*-BuLi	-
5	*p*-OMe	Ph	-78	*t*-BuLi	-
6	*p*-OMe	Me	RT	MeLi	-

This lack of reactivity from the chiral an on might be explained partly by steric effects which prevent the approach of the electrophile Further, the low nucleophilicity of 2-anion of the 2-aryl-1,3-dithiane-1-oxide intermediate may prevent nucleophilic attack . The use of solvent having strong coordinating properties such as 1,4-dioxane was also investigated, with a smaller organic base (methyl lithium), in a mixture of tetrahydrofuran and 1,4-dioxane as solvent, at room temperature This experiment failed also

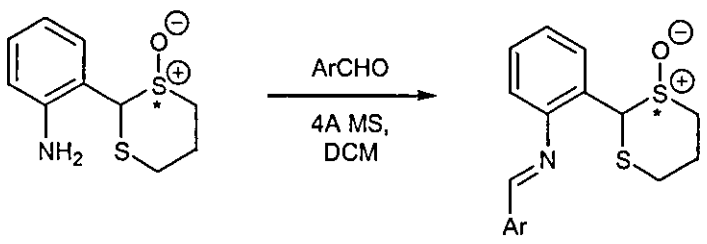
2-A-5-2 Application as ligands in palladium-catalysed allylic alkylation reaction

During our work on asymmetric sulfoxidation with chiral oxaziridine for the preparation of chiral 1,3-dithiane-1-oxide derivative to be investigated as potential asymmetric mediator, we were able to synthesise 2-(2-aminophenyl) 1,3-dithiane-1-oxide in good chemical yield and high enantioselectivity (Scheme 30)



Scheme 30

By simple condensation of this chiral aromatic amine with different aromatic aldehydes, we accessed potential imine-S(O) ligands, where the sulfoxide moiety is the sole source of chirality These chiral imine were synthesised in moderate yields with aromatic aldehydes containing different groups at different position (Scheme 31, table 5)

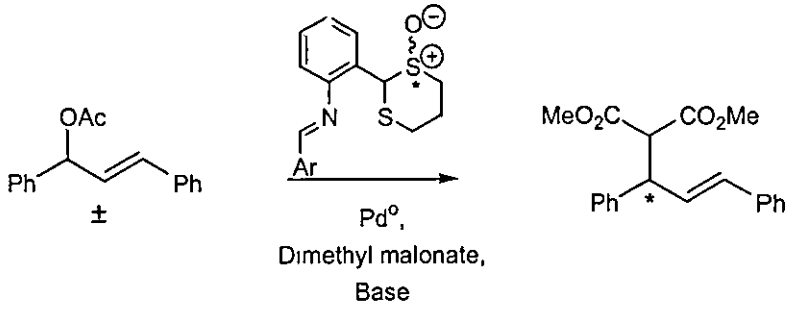


Scheme 31

Table 5

Entry	Compound	Ar	Yields (%)
1	**122**	Ph	71
2	**123**	*o*-NO_2Ph	50
3	**124**	*o*-MeOPh	53
4	**125**	*m*-MeOPh	50
5	**126**	*p*-MeOPh	34

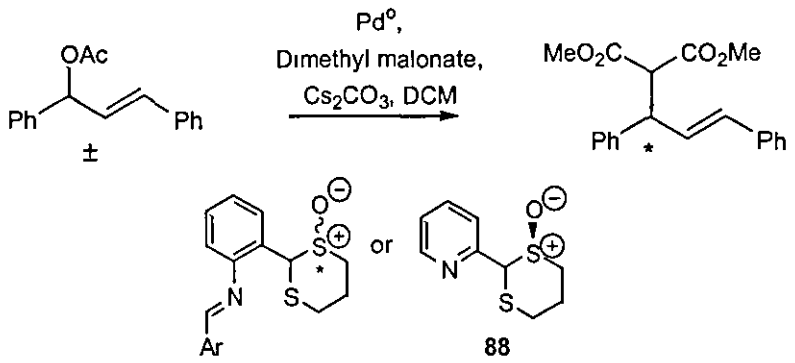
Only one diastereoisomer was isolated in each case, which we presumed to be the more stable E isomer NMR studies could not prove this due to the absence of suitable protons for NOE experiments For the reason of their instability under laboratory conditions (hydrolysis observed even under nitrogen atmosphere storage at -20 °C), we decided to investigate, straight after their purification, these chiral imine-S(O) compounds as potential chiral ligands in palladium-catalysed allylic nucleophilic substitution reaction (Scheme 32)



Scheme 32

We decided to apply the optimised reactions conditions for short reaction time (avoiding hydrolysis of the imine moiety) reported by Kocovski[23] who investigated different solvent reactions and the use of organic or inorganic bases to generate the nucleophile from dimethyl malonate Caesium carbonate in dichloromethane seem to be the best choice of reaction conditions, leading to short reaction time, good chemical yields and enantioselectivities in general

Furthermore, for future comparison with the previously successful chiral (*S*)-2-(2-pyridyl)-1,3-dithiane-1-oxide ligand (**88**), designed within our group, we had also to apply the same optimised reaction condition as for our chiral imine-S(O) ligands (Scheme 33, table 6)



Scheme 33

Table 6

Entry	compound	Ar	r t (h)	Yield (%)	ee (%)	Optical rotation
1	**123**	*o*-NO_2Ph	24	<10	22	(-)
2	**122**	Ph	24	37	25	(+)
3	**124**	*o*-MeOPh	4	>95	40	(+)
4	**125**	*m*-MeOPh	24	24	30	(+)
5	**126**	*p*-MeOPh	7	100	34	(+)
6	**88**	Ligand **88**	10	100	49	(+)

First, we observed even better asymmetr c induction for the 2-(2-pyridyl)-1,3-dithiane-1-oxide ligand (**88**) with the use of optimal reaction conditions, from 37 % ee with BSA-AcOK catalysis in dimethylformamide, to 49 % ee with caesium carbonate in dichloromethane leading to completion within 10 hours.

Furthermore, asymmetric induction and reactivity were dependent on the nature of the group contained in the aromatic imine-S(O) ligands. The electron withdrawing nitro group (entry 1)

caused the reaction to proceed very slowly, surprisingly, with opposite asymmetric induction This might be explained by formation of a metal complex intermediate between palladium metal and chiral ligand, where the two better b nding groups are attached to the palladium metal, by means, oxygen atom from the nitro group and sulfur from the thioether moiety Our knowledge in the nature of such chelation remains superficial however

Excellent reactivities were achieved with electron donating groups in the para and ortho positions in the ligand (entries 3 and 5) In particular, the ortho position gave a higher asymmetric induction in our imine-S(O) ligands, by possible chelation between oxygen-caesium-nucleophile helping to drive the approach of the nucleophile (Fig 7)

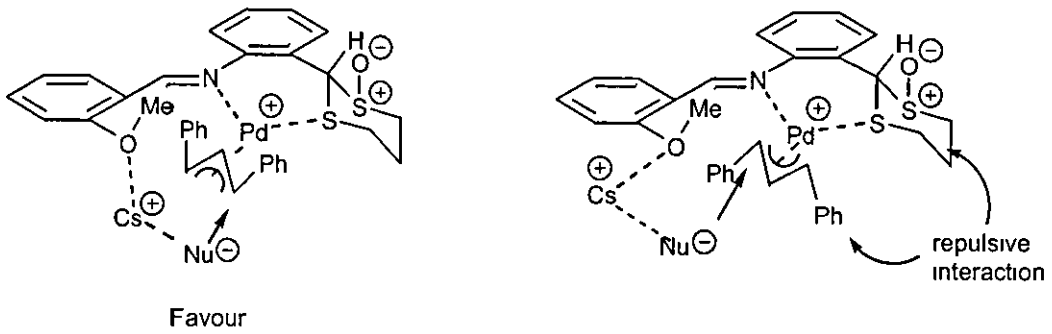
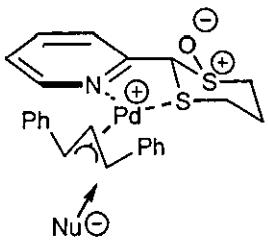
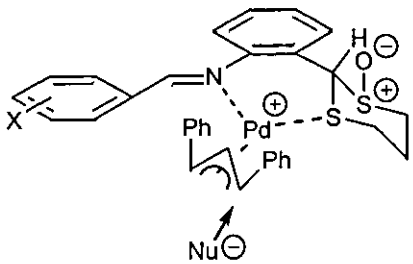


Fig 7

The formation of the chiral sulfoxide moiety was achieved with the same chiral oxidising agent (oxaziridine), so we expected the same absolute configuration at the sulfur atom bearing the oxygen A transition state (**127**), using 2-(2-pyridyl)-1,3-dithiane-1-oxide (**88**) as ligand, can be proposed to explain the higher asymmetric induction This transition state (**127**) should hold the chiral ligand, the palladium metal and the diphenyl allyl substrate in the close five membered ring for good asymmetric induction For the imine S(O) ligands (**122-126**), a six membered ring transition state (**128**) can be proposed. Therefore, the chiral centre, from the ligand, stands one carbon away from the diphenyl allyl substrate, leading to lower asymmetric induction



127

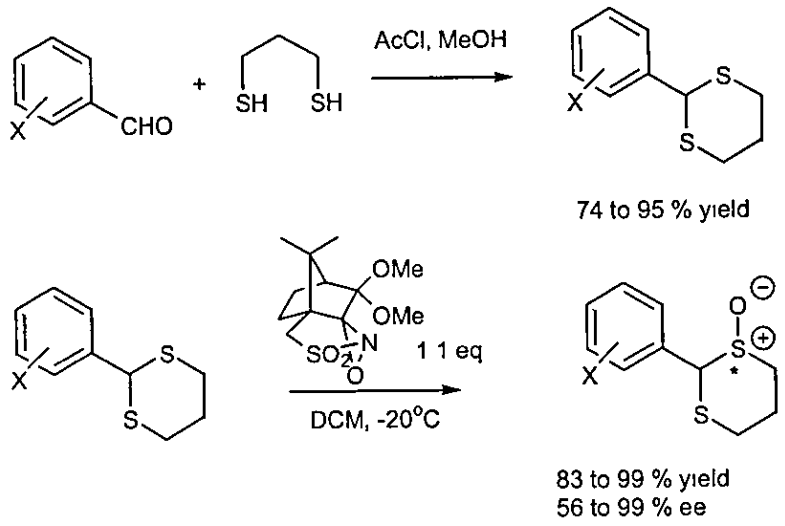


128

Fig 8

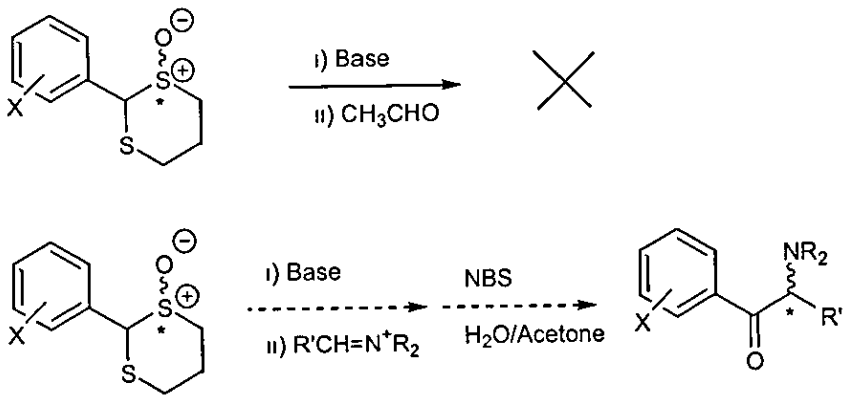
2-A-6 Conclusion

We have developed an easy route to access chiral 1,3-dithiane-1-oxide aryl derivatives by condensation reaction between an aldehyde and 1,3-propanedithiol under *in situ* generation of HCl in methanol, followed by asymmetric sulfoxidation with chiral oxaziridine leading to 1,3-dithiane-1-oxide aryl derivatives with good yields in the condensation reaction and excellent chemical yields with good to high enantioselectivities (Scheme 34) for asymmetric sulfoxidation with our chiral oxaziridine



Scheme 34

Unfortunately, the application of the optically pure 2-(4-methoxyphenyl)-1,3-dithiane-1-oxide as chiral mediator in the asymmetric preparation of α-hydroxy ketones was not successful, even in presence of strong coordinating solvent and small organic base The application of more electrophile substrates may be considered for asymmetric preparation of α-amino ketones. (Scheme 35)



Scheme 35

We have applied, with moderate success, chiral sulfoxides as ligands in palladium-catalysed allylic nucleophilic substitution reaction We hypothesise that our chiral oxidising agent **(26)** (oxaziridine used to synthesise these ligands) should oxidise, under same reaction conditions, 1,3-dithiane ring and mono sulfide in the same manner, so giving same absolute configuration at the sulfur atom It may be that in the palladium-catalysed allylic alkylation, the nucleophile attacks opposite to the sulfoxide moiety for pyridinylmethyl sulfoxide ligands **(110-112)**, and opposite to the nitrogen for 2-(2-pyridyl)-1,3-dithiane-1-oxide **(88)** and imine-S(O) ligands **(122-126)** (Fig 9)

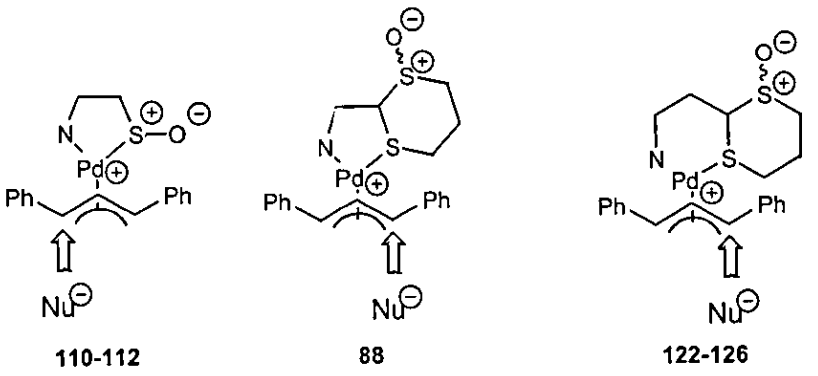


Fig 9

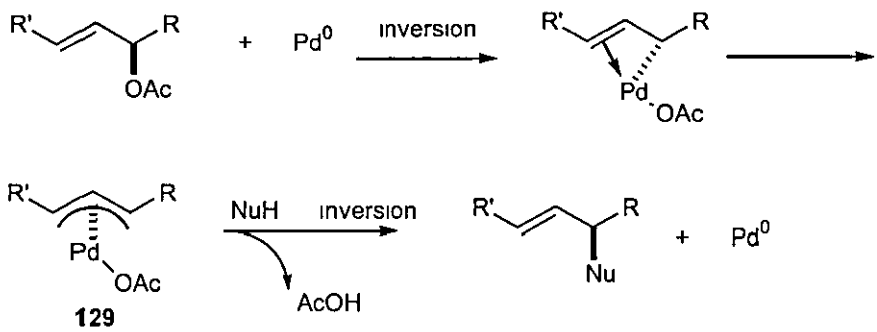
We attempted to react chiral 2-(2-aminophenyl)-1,3-dithiane-1-oxide with chiral (-)-menthyl chloroformate to obtain a suitable solid for X-ray spectrum to find out the configuration at the sulfur atom Unfortunately, the product was isolated as a liquid

2-B Amino-Sulfides in the Allylic Nucleophilic Substitution Palladium-Catalysed Reaction:

2-B-1· Introduction

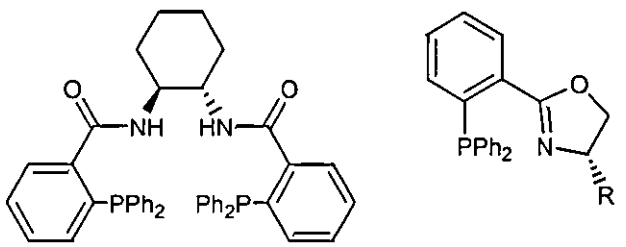
There are several features which make reactions involving palladium particularly useful and versatile amongst the many transition metals used for organic synthesis Most importantly, palladium offers many possibilities for carbon-carbon bond formation [24] The importance of carbon-carbon bond formation in organic synthesis needs no explanation, and no other transition metal offers such versatile methods for carbon-carbon bond formation as does palladium The tolerance of palladium reagents to many functional groups such as carbonyl and hydroxy groups is another important feature Palladium-catalysed reactions can be carried out without protection of these functional groups Although reactions involving palladium should be carried out carefully, palladium reagents and catalysts are often not very sensitive to oxygen and moisture, or even to acid

The most useful reactions of palladium are catalytic reactions, which can be carried out with only a small amount of an expensive palladium compound In particular, the formation of a π-allylpalladium complex (**129**) takes place by an oxidative addition of allylic compounds, mainly allylic esters, to palladium (0) The π-allylpalladium complex is a resonance form of σ-allylpalladium and a coordinated π-bond π-Allylpalladium complex formation involves inversion of stereochemistry, and attack of the soft carbon nucleophile on the π-allylpalladium complex is also an inversion of stereochemistry, resulting in overall retention of stereochemistry (scheme 36)



Scheme 36

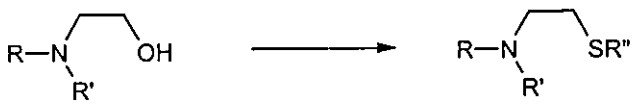
The possibility to incorporate chiral ligands onto the palladium catalyst makes this process highly useful for asymmetric carbon-carbon bond formation Since the first example of an enantioselective palladium-catalysed allylic nucleophilic substitution reaction,[25] a wide library of chiral ligands have been reported with different properties in their asymmetric induction, i e., C_{2h} symmetry of chiral homobidentate and chiral heterobidentate ligands Some of the most successful investigations of chiral ligands in the palladium-catalysed allylic nucleophilic substitutions involve the dome-type architecture homobidentate P-P ligand (Fig 9, **40**) reported by Trost[26] and the heterobidentate N-P ligand (Fig 10, **68**), investigated independently by Helmchen,[27] Pfaltz[28] and Williams [29]



40 **43**

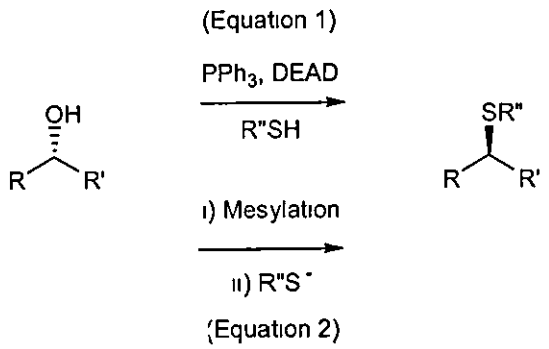
Fig 10

Good enantioselectivities have also been achieved with N,N bis-oxazoline,[30] oxazoline-sulfide,[31] imine-sulfide,[32] pyridine-sulfide,[33] amino-sulfoxide[34] ligands and many others Only one type of ligand remains absent for the palladium-catalysed allylic alkylation, namely tertiary amino sulfide ligands, which have been widely used in asymmetric additions of diethylzinc to aldehydes[35] with excellent results (>90 % ee in most cases) in enantioselective induction Access to optically pure amino-sulfide compounds can be carried out from commercially available amino-alcohols involving a nucleophilic substitution reaction of the derivatized alcohol group (Scheme 37)



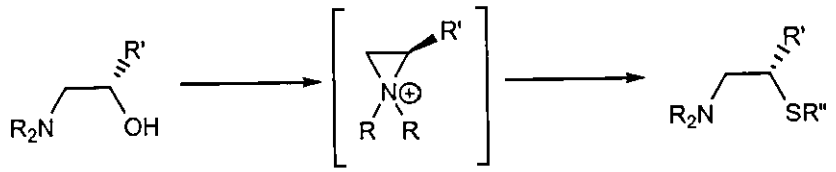
Scheme 37

At least two main processes can be achieved this transformation, the well-known Mitsunobu reaction (Scheme 38, equation 1),[36] and a two-step reaction which involves mesylation of the alcohol followed by a nucleophilic displacement reaction by the appropriate thiol (Scheme 38, equation 2) [37] Both processes give inversion of configuration at the carbon atom bonded to the alcohol



Scheme 38

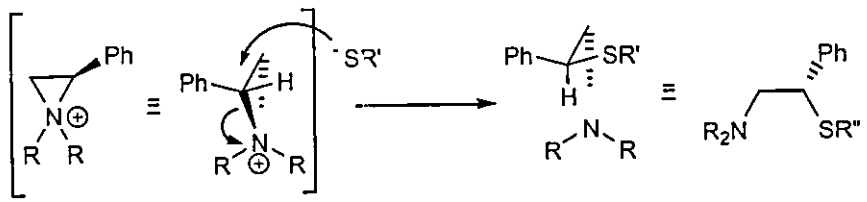
There is some precedent for the application[36,37] of such conditions to tertiary amino-alcohols resulting in a double inversion reaction where an aziridinium cation (**N**) is purported to be the reactive intermediate (Scheme 39)



N

Scheme 39

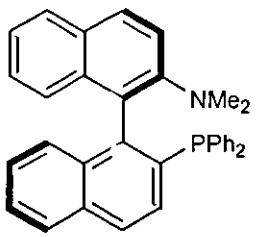
The ring opening step of the aziridinium cation intermediate occurs only in the presence of a phenyl group at one carbon centre and the nucleophile attacks on the opposite face of the nitrogen at the benzylic position (Scheme 40)



Scheme 40

2-B-1-1 Optimisation of the conditions for the palladium-catalysed reaction

In 1998, Vyskocil and Kocovsky[38] reported the investigation of 2-amino-2'-diphenylphosphino-1,1'-binaphthyl (Fig 11, **MAP**) in the palladium-catalysed allylic nucleophilic substitution reaction



MAP

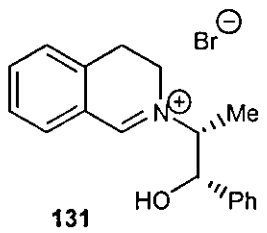
Fig 11

Different reaction conditions were applied to optimise the asymmetric induction from MAP to the diphenyl allyl substrate Reactions were carried out in tetrahydrofuran or dichloromethane, the nucleophile was generated by sodium hydride, bis-silyl acetamide in the presence of a catalytic amount of potassium acetate, or caesium carbonate Optimisation of the reaction conditions earlier reported by Trost[39] used dichloromethane as solvent and caesium carbonate to generate the nucleophile The influence of the metal/ligand ratio was also investigated (with the amount of palladium remaining constant a. 5 mol%), but practically no effect was observed The actual catalyst loading also proved to be unimportant (same ee for reactions run with 3, 5 and 10 mol% Pd)

2-B-2 First generation of ligands

2-B-2-1 Synthesis

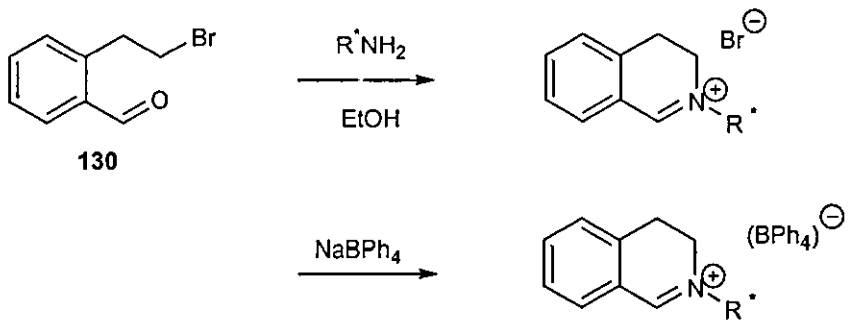
Another research program being investigated within our group focuses on the application of chiral iminium salts in asymmetric epoxidation of carbon-carbon double bonds [40] Many chiral iminium salts have been synthesised with different functionalities; one of the potential catalyst types consists of a norephedrine core with a free hydroxy group. (e g. **131**, Fig 12)



131

Fig 12

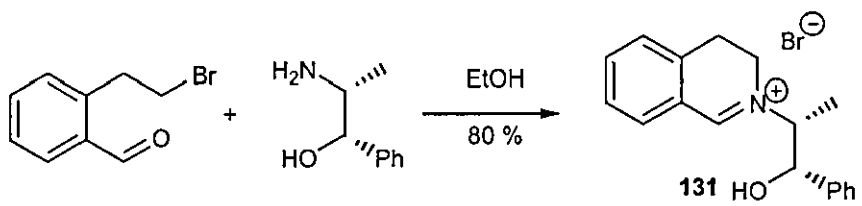
The synthetic procedure to access these chiral iminium salts was described by Rieche and Schimtz,[41] who reacted 2-bromoethyl-benzaldehyde **130** with many chiral amines (Scheme 41). By anion-exchange, it is possible to isolate the final iminium salt by recrystallisation from the crude reaction mixture The commonly used counter-anion is tetraphenyl borate



130

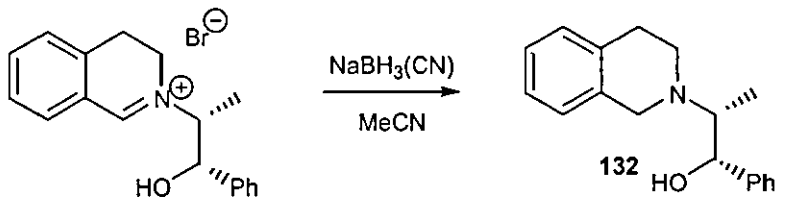
Scheme 41

In the case of norephedrine, the anion-exchange process was not required, the iminium salt could be isolated by filtration of the reaction m xture and recrystallised from acetonitrile to yield the bromide salt **131** (Scheme 42)



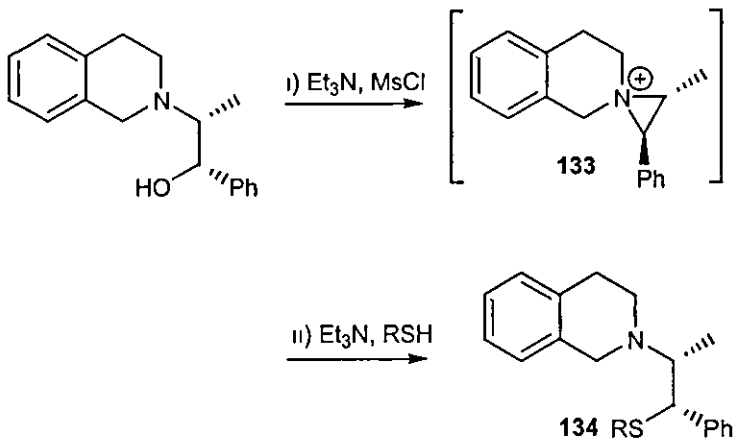
Scheme 42

Subsequent reduction with sodium cyanoborohydride afforded quantitatively the corresponding amino alcohol **132** (Scheme 43) These two steps, iminium salt formation and reduction to the amino alcohol, were carried out on a 20 gram scale.



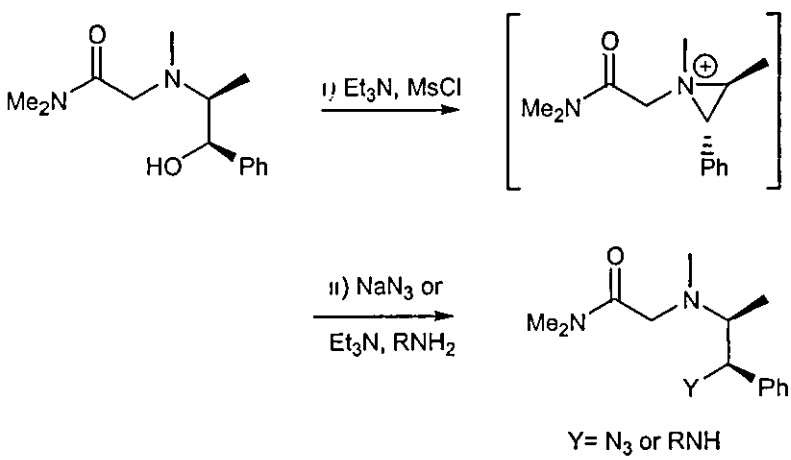
Scheme 43

The transformation of the amino alcohol into the corresponding amino sulfide **134** was performed with a double inversion reaction involving the formation of a mesylate intermediate, which, according to the literature,[36,37] undergoes intramolecular substitution by the nitrogen atom to give an aziridinium cation The ring opening reaction of this aziridinium species **133** occurred at the benzylic position by attack of a thiolate as nucleophile The original configuration at the sulfur-bearing carbon atom thus remains conserved overall (Scheme 44)



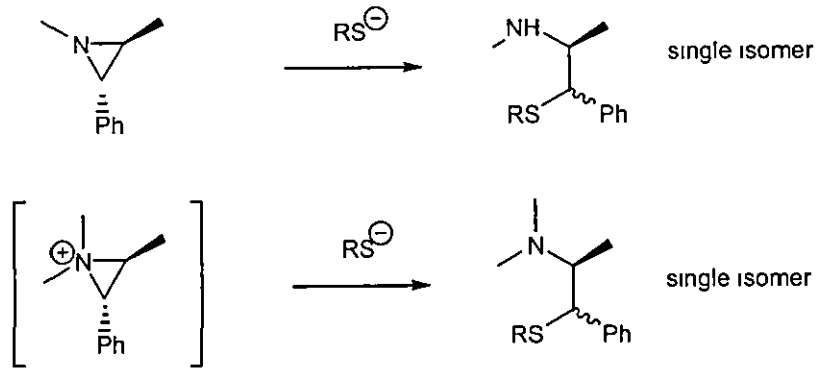
Scheme 44

Previous reports involved the synthesis of chiral diamines and triamines derived from ephedrine and pseudoephedrine employed amine or azide nucleophiles for the ring opening reactions of the aziridinium intermediate (Scheme 45) [37] X-ray analysis confirmed that the substitution reaction had proceeded regiospecifically and stereospecifically with retention of configuration



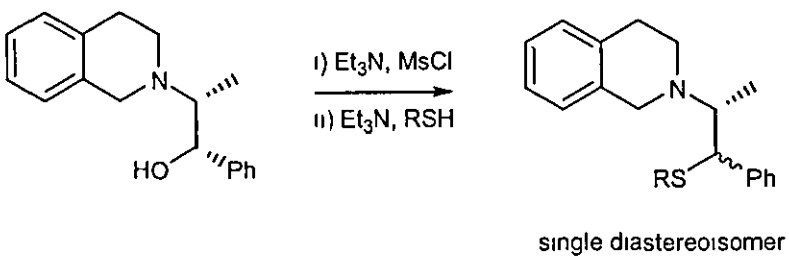
Scheme 45

This ring opening reaction was also performed by Kellogg[36] with thiolate anions on aziridines and aziridinium cations, but the double inversion reaction was determined by comparison of the coupling constants at the benzylic proton, as well as the observed optical rotations, the configuration was thus not verified rigorously (Scheme 46)



Scheme 46

The synthesis of our tetrahydroisoquinoline amino thioether derived from norephedrine occurred by performing the mesylation reaction with 1 2 equivalent of mesyl chloride in dichloromethane at 0 °C followed by addition of 3 equivalents of a thiolate anion for the ring opening reaction. Only one diastereoisomer was isolated in moderate chemical yields (Scheme 47, table 7)



Scheme 47

Table 7

Entry	compound	RSH	r t.	Yield (%)
1	**135**	PhSH	o/n	49
2	**136**	*p*-MeOPhSH	o/n	28
3	**137**	2-naphthylSH	o/n	57
4	**138**	MeSNa	o/n	64
5	**139**	iPrSH	o/n	60
6	**140**	tBuSH	o/n	68
7	**141**	TritylSH	o/n	57

We were able to recrystallise the *tert*-butyl sulfide derivative and an X-ray analysis confirmed that the configuration had been conserved (Fig 13)

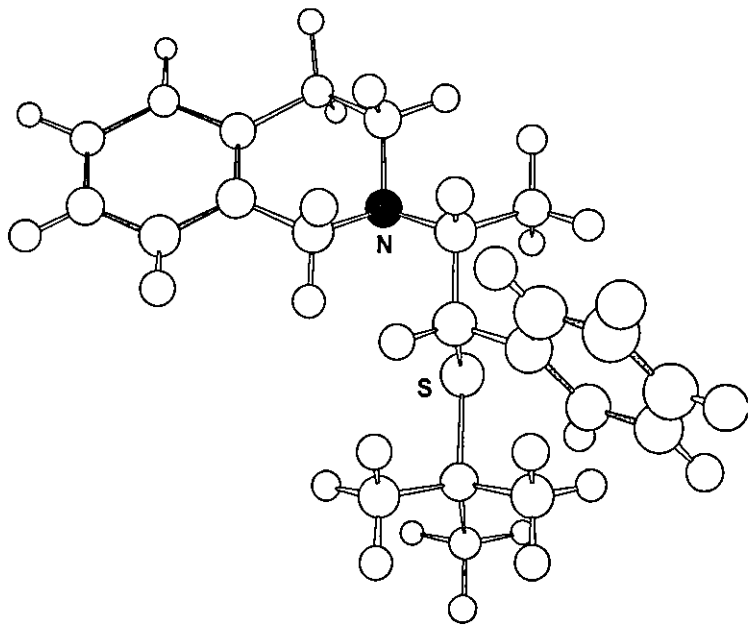
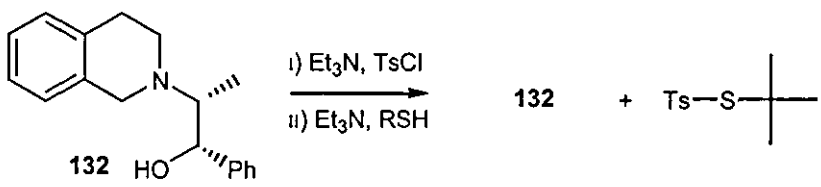


Fig 13

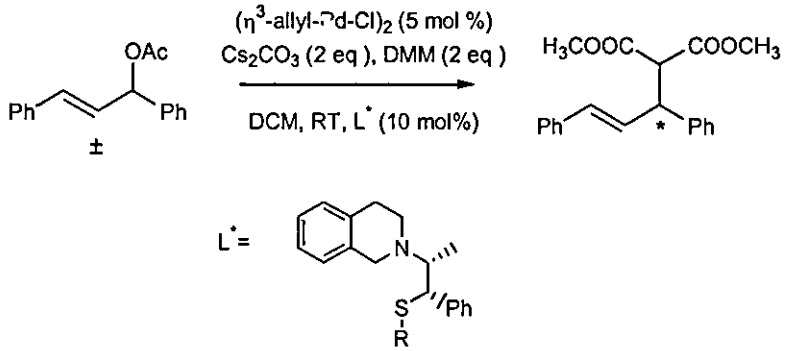
We decided to carry out the same reaction with tosyl chloride in place of mesyl chloride and *tert*-butyl thiolate as nucleophile to investigate whatever the tosylate group would give a double or single inversion reaction We were surprised to isolate the starting amino alcohol in quantitative yield along with tosyl *t*-butyl sulfide This observation proved that the tosylation does not occur, perhaps a tosyl salt between the amine moiety and the tosyl group was formed The subsequent addition of the *tert*-butyl thiolate anion merely reacted with the tosyl group. (Scheme 48)



Scheme 48

2-B-2-2 Application of amino sulfide ligands in the palladium-catalysed reaction

The investigation of these chiral amino sulfides as ligands in the palladium-catalysed allylic nucleophilic substitution reaction was carried out with the optimised reaction conditions reported by Vyskocil and Kocovsky[38] The palladium loading was generated using η^3-allyl chloride palladium dimer and maintained at 5 mol%, with 10 mol% of the chiral amino sulfides (Scheme 49) For simpler purification of the product, only 2 equivalents of caesium carbonate and dimethyl malonate were used Reactions proceeded to completion within a short period of time (approximately one hour), with complete consumption of the allyl acetate substrate The chemical and optical yields are reported in table 8



Scheme 49

Table 8

Entry	R	r.t. (h)	Yield (%)[a]	ee (%)[b]	Optical rotation / Absolute config
1	Ph (**135**)	1	92	11	(+)-(*R*)
2	*p*-MeOPh (**136**)	1	85	11	(+)-(*R*)
3	2-naphthyl (**137**)	1	70	6	(+)-(*R*)
4	Me (**138**)	1	95	15	(-)-(*S*)
5	*i*-Pr (**139**)	1	94	34	(+)-(*R*)
6	*t*-Bu (**140**)	1	90	72	(+)-(*R*)
7	Trityl (**141**)	24	3	8	(-)-(*S*)

a) isolated yields , b) determined by ^{1}H NMR in presence of Eu(hfc)$_3$

2-B-2-3 Interpretation of the asymmetric induction

It is unclear why the reactions are less enantioselective with aromatic substrates at the sulfur terminus However, with sterically more demanding aliphatic thioethers, the enantiomeric excesses increased up to 72 % (entry 6 for R= *t*-Bu) With the bulky trityl group, neither increased enantiomeric excess nor full consumption of the substrate was observed (Table 8, entry 7)

Our results suggest that it is mainly the steric rather than the electronic properties of the thioether moiety that are responsible for fast and highly enantioselective reactions These dramatic responses of enantioselectivity to reactions changes in the thioether terminus suggest that the orientation of the diphenyl allyl moiety may be directed by the steric interaction from the group at the sulfur terminus

Ligand effects in η^3-allyl-palladium complexes monitored by ^{13}C NMR spectroscopy in the literature,[42] suggest that the nucleophile probably attacks along the trajectory of the palladium-sulfur bond which is considered as the longer and weaker bond in contrast with the palladium-nitrogen bond (Fig 14)

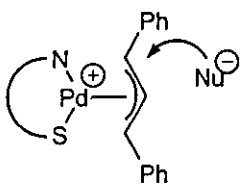


Fig 14

At least two transition states can be proposed to explain the enantioselective induction from the amino sulfide ligands to the substrate by minimised steric and/or electronic effects which may stabilise and destabilise the interaction between η3-allyl moiety and the palladium complex

Transition state **142** (Fig 15) appears to be the most favoured because the *t*-butyl group points away from the phenyl group labelled Ph^1, therefore the diphenyl allyl moiety has to be oriented as shown in **142** In contrast, repulsive interactions occur in the transition state **143** where the diphenyl allyl moiety is very close to the *t*-butyl group In the extreme case, the diphenyl allyl acetate substrate cannot approach the palladium complex.

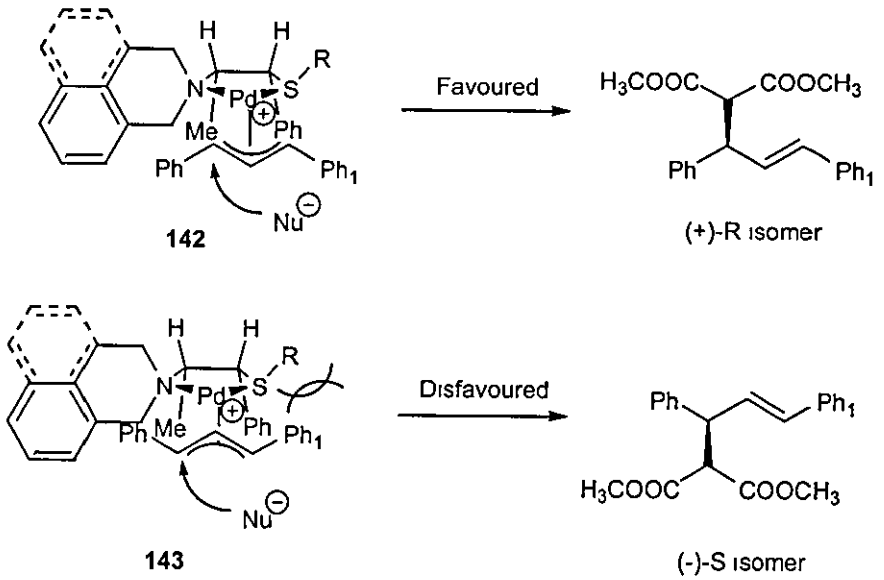


Fig 15

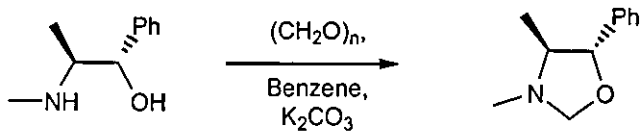
2-B-3 Second generation of ligands

2-B-3-1 Synthesis

The syntheses of our first generation of ligands allowed us to optimise and to familiarise ourselves with the double inversion reaction which takes place during their preparation Our study of their use in the palladium-catalysed allylic nucleophilic substitution reaction had permitted us to determine the best group at the sulfur terminus (*tert*-butyl).

The transition state established for the determination of the induction process could not clarify which of the two present chiral centres is the most important for asymmetric induction Therefore, we synthesised a second generation of ligands derived from optically pure (+)-(1 *S* ,2 *S*)-pseudoephedrine which also allowed us to optimise the group at the nitrogen atom

These syntheses involved three steps to afford the corresponding amino sulfide ligands with no racemisation at any stage In the first step, condensation reactions of the optically pure pseudoephedrine was carried out with aldehydes under various reaction conditions The condensation of pseudoephedrine with paraformaldehyde (Scheme 50) was performed in benzene under reflux in presence of potassium carbonate to afford the oxazoline product (**144**) in 98 % yield

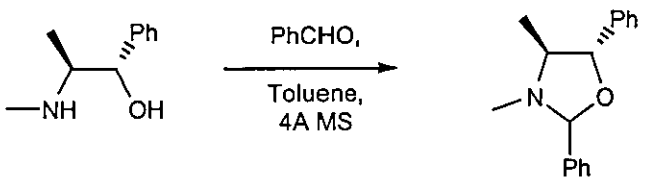


144

Scheme 50

For the condensation of benzaldehyde with pseudoephedrine, the reaction was performed with an equimolar mixture of aldehyde and amino alcohol over 4Å molecular sieves in toluene under reflux (Scheme 51) The employment of an equimolar mixture allowed us to avoid the distillation

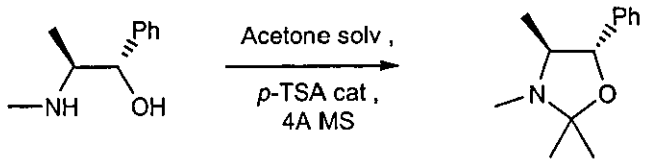
of the excess benzaldehyde, and a simple filtration afforded the oxazoline (**145**) in high purity after removal of the solvent in 95 % yield



145

Scheme 51

We also condensed pseudoephedrine with acetone, but the reaction had to be assisted by addition of a catalytic amount of a Brønsted acid (*p*-TSA) over 4Å molecular sieves under reflux in acetone used as solvent (Scheme 52) The acetone was easily removed because of its low boiling point After work-up, the oxazoline (**146**) was isolated in 99 % yield.

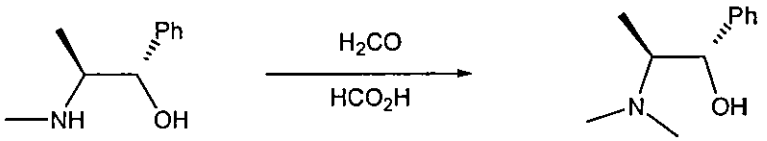


146

Scheme 52

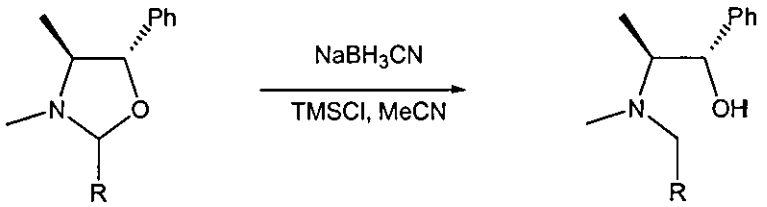
We investigated two possible ring opening reactions of these oxazolines, one of which has been developed within our group in collaboration with another research program The second reaction was the addition of a Grignard reagent to the oxazoline

The reductive cleavage of oxazoline was derived from the Eschweiler-Clarke procedure[43] (Scheme 53) and only allows the synthesis of N-methyl amine



Scheme 53

The known conversion of 2-alkyloxazolidines into enamines[44] by using chlorotrimethylsilane in the presence of Hunig's base, and the use of chlorotrimethylsilane and dichlorodimethyl-silane to generate iminium ions from aminol ethers,[45] suggested that a "one-pot" reductive ring opening reaction of aminol ether could be effected by using chlorotrimethylsilane in the presence of a source of hydride ions Following a number of trial experiments we found that reductive ring opening reactions could be carried out rapidly in high yields to give the corresponding alkylated amino alcohol, by adding 5 equivalents of chlorotrimethylsilane to a solution of the aminol ether and sodium cyanoborohydride (Scheme 54)[46]

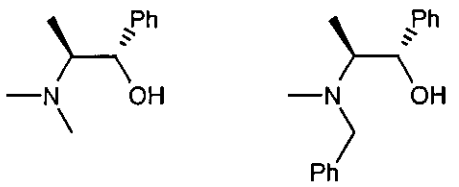


R= H or Ph

Scheme 54

We were faced with the problem of isomerisation in the purification step by the presence of partial silyl protected alcohol. Treatment of the crude mixture with potassium hydroxide in methanol resulted in isolation of the amino alcohol as a mixture of two diastereoisomers We assume that the silyloxy group acts as a leaving group and therefore the chiral information at the benzylic position is compromised Potassium carbonate has been employed to cleave silyl group, and no racemisation was observed in our case by treatment of the crude reaction mixture with potassium carbonate in methanol The N-methyl pseudoephedrine (Fig 16, **147**) and N-benzyl

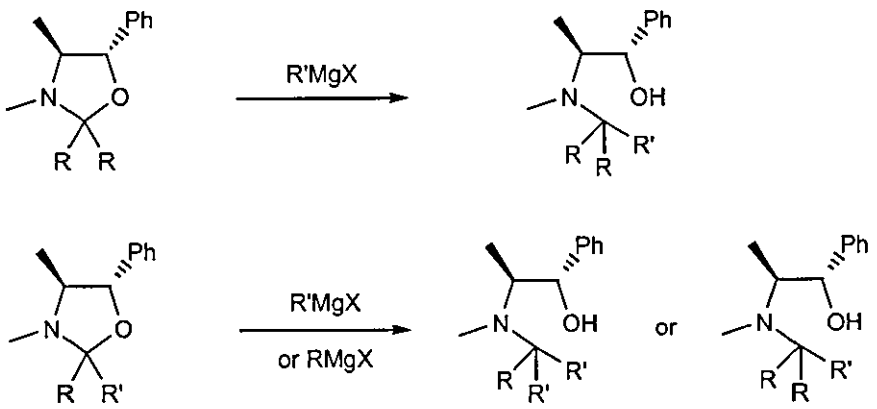
pseudoephedrine (**148**) were isolated in enantiomerically pure form in 97 and 95 % yields respectively



147 **148**

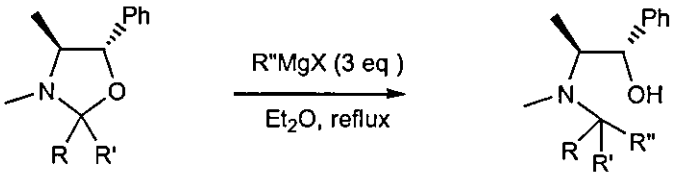
Fig 16

Treatment of oxazolines with Grignard reagents[47] was performed with the intention not to create a third chiral centre That is, if the 2 position on the oxazoline already has two identical groups, any Grignard reagent can be used On the other hand, if two different groups are at this position, only Grignard reagents having a group identical to that of one of those substituents was be used. (Scheme 55)



Scheme 55

The addition of Grignard reagents to oxazolines proceeded in excellent chemical yields with an excess of 3 equivalents of Grignard reagent under reflux in diethyl ether for half an hour (Scheme 56, table 9)

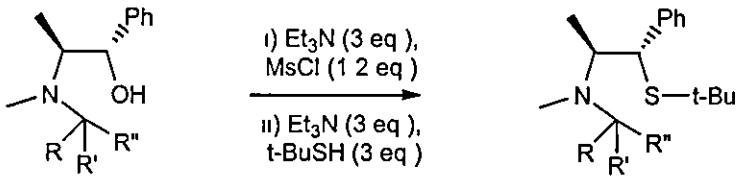


Scheme 56

Table 9

Entry	compound	R	R'	R"	Yields (%)
1	**149**	Me	Me	Me	95
2	**150**	Ph	H	Ph	99
3	**151**	Me	Me	Ph	98

With the tertiary amino alcohols in hand, the double inversion reactions were carried out with *tert*-butyl thiol to afford the corresponding amino sulfides (Scheme 57) in moderate to good yields (Table 10) The importance of the *tert*-butyl group has been discussed previously



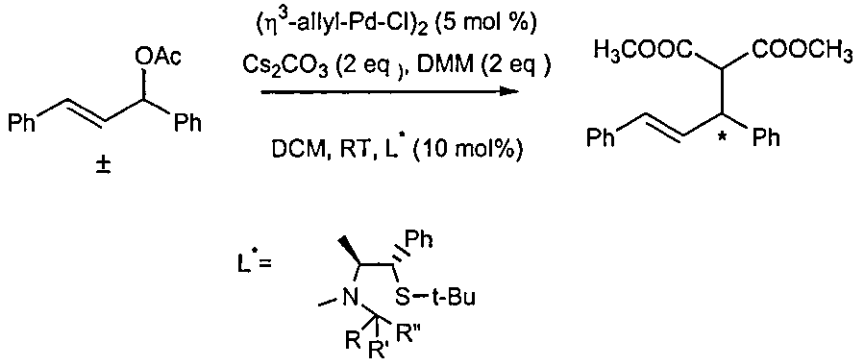
Scheme 57

Table 10

Entry	compound	R	R'	R"	Yield (%)
1	**152**	H	H	H	38
2	**153**	H	H	Ph	51
3	**154**	Me	Me	Me	71
4	**155**	Ph	H	Ph	68
5	**156**	Me	Me	Ph	47

2-B-3-2 Application of amino sulfide ligands in the palladium-catalysed reaction

A second generation of ligands was synthesised for the two reasons previously mentioned The most important reason was to determine the influence of each chiral centre on asymmetric induction The second reason was to optimise the nature of the group at the nitrogen atom The palladium-catalysed allylic nucleophilic substitution reactions were performed with the optimised reaction conditions reported by Vyskocil and Kocovski (Scheme 58, table 11)[38]



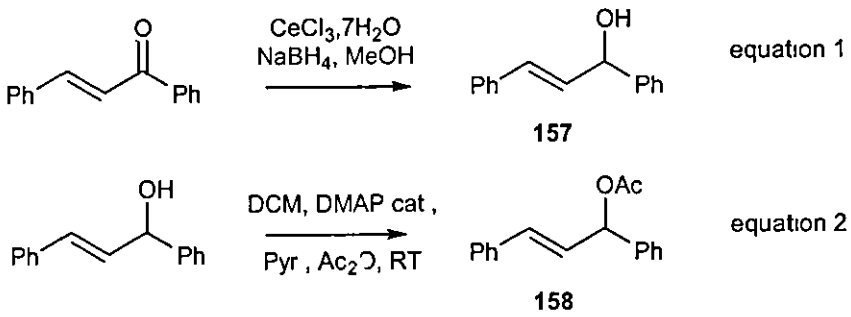
Scheme 58

Table 11

Entry	compounds	r t (h)	yield (%)	ee (%)	optical rotation / absolute config.
1	**152**	18	7	87	(-)-S
2	**154**	7	98	89	(-)-S
3	**155**	24	20	82	(-)-S
4	**156**	24	10	77	(-)-S
5	**153**	24	35	78	(-)-S

The chemical yields were variable and may have been dependent on the purity of the diphenyl allyl acetate **158** The synthesis of this allyl acetate was performed in two steps, a Luche

reduction of the chalcone affords the allyl hydroxy intermediate **157** (Scheme 59, equation 1) which was treated in dichloromethane in presence of 2 equivalents of pyridine, 1 2 equivalents of acetic anhydride and a catalytic amount of N,N-dimethylamino-pyridine (Scheme 59, equation 2) After complete consumption of the alcohol, the solvent was removed and the crude product was taken up in diethyl ether

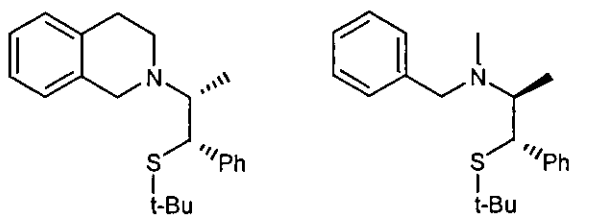


Scheme 59

The purification of the allyl acetate **158** was achieved by aqueous washing First, the ethered solution was washed with copper sulfate solution to remove the pyridine and the catalyst, followed by treatment with a solution of sodium carbonate to remove the acetic anhydride and acetic acid But such purification was not completely effective. Subsequent column chromatography and fractional distillation failed to provide a higher purity product

2-B-3-3· Interpretation of the asymmetric induction

Except for aliphatic groups (entries 1 and 2) the enantioselectivities observed do not seem to be dependent on the nature of the group at the nitrogen atom The bulky *tert*-butyl group gave rise to the enantioselective induction up to 89 % for the (-)-(*S*) product This absolute configuration of the product is opposite to that obtained with the first generation of ligands (Fig 17), and therefore we might postulate that the orientation of the diphenyl allyl moiety in the transition state is greatly affected by the methyl group

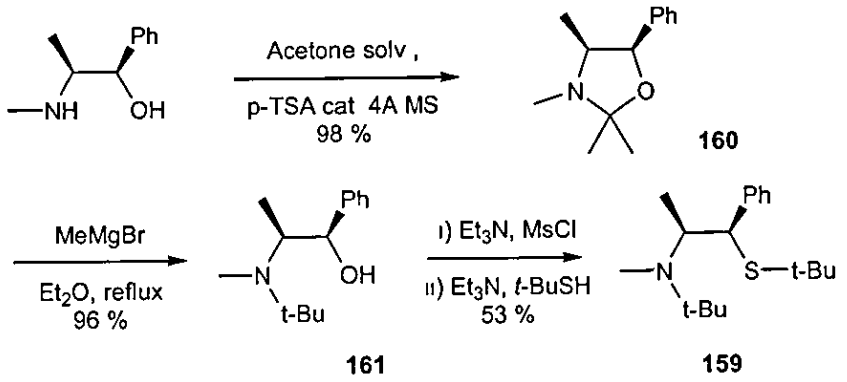


induces formation of the (+)-*R* isomer

induces formation of the (-)-*S* isomer

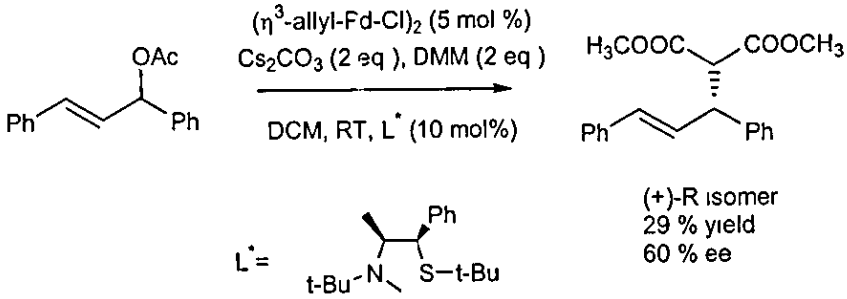
Fig 17

Such a postulate might be verified by the investigation of (-)-ephedrine derivative amino sulfides as ligands in the palladium-catalysed allylic nucleophilic substitution reaction as these have the opposite relative stereochemistry as the two asymmetric centres A synthesis was performed from (-)-ephedrine to obtain the diastereoisomer of the best ligand (**154**) from the second generation (Table 11, entry 2) A condensation reaction between (-)-ephedrine and acetone was performed by the same process as for the (+)-pseudoephedrine, a ring opening reaction was achieved by addition of methyl magnesium bromide, and finally, the double inversion reaction afforded the amino sulfide **159** (Scheme 60)



Scheme 60

Investigation of the palladium-catalysed allylic nucleophilic substitution reaction using the di-*tert*-butyl amino sulfide derived from ephedrine as ligand was carried out in dichloromethane and caesium carbonate (Scheme 61)



Scheme 61

The absolute configuration of the major product is in opposition with that expected from our mechanistic postulation The actual group which orients the spatial position of the diphenyl allyl moiety is thus not the methyl but the phenyl group In the first generation of ligand, such as (Fig 18, **140**), therefore, the most decisive group for asymmetric induction is perhaps the tetrahydroisoquinoline core The conformation of the six membered ring clearly has a great importance, but details remain unclear

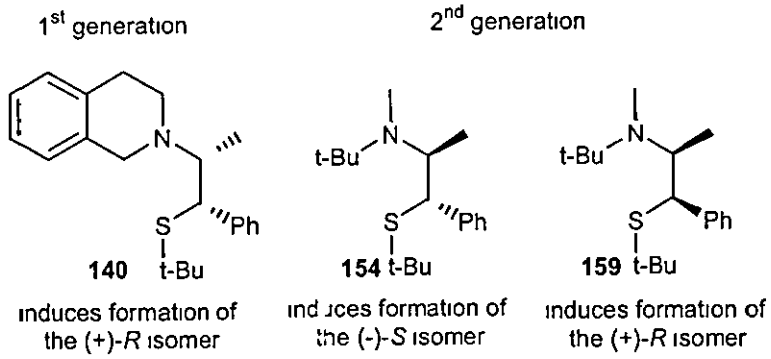


Fig 18

We were interested in further investigating the reason why the amino sulfide ligand derived from pseudoephedrine (**154**) gave opposite asymmetric induction and higher level of asymmetric induction than the amino sulfide ligand derived from ephedrine (**159**) in the palladium-catalysed allylic nucleophilic substitution reaction Two transition states **162** and **163** can be drawn for the pseudoephedrine derivative (**154**) (Fig 19 and 20)

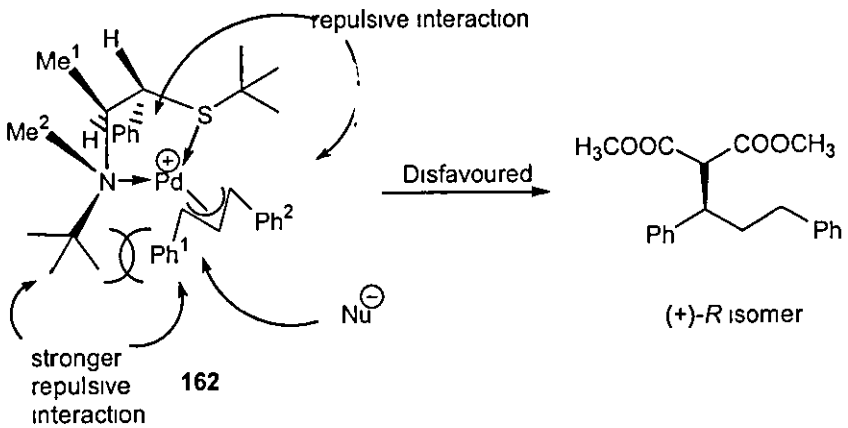


Fig 19

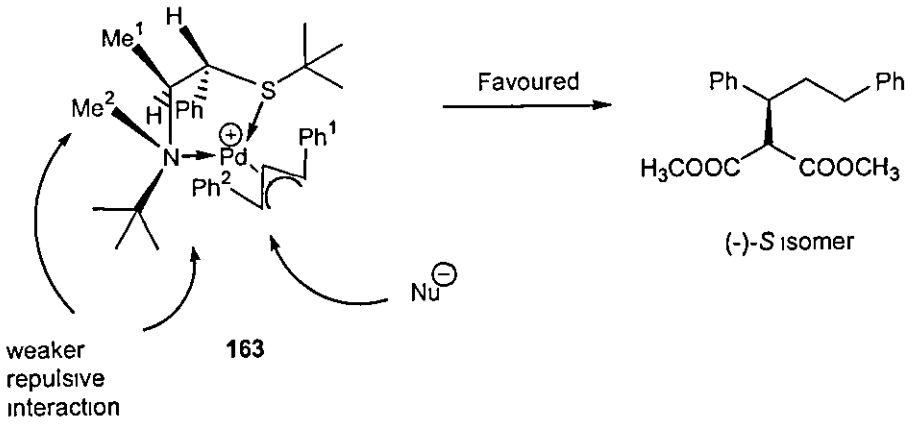


Fig 20

The orientation of the preferred palladium-ligand complex is determined by the relative sizes of the methyl group labelled Me^2 and the *tert*-butyl group at the nitrogen centre Thus, in the transition state **162,** a strong repulsive interaction between the tert-butyl group at the nitrogen and the phenyl labelled Ph^1 disfavours the spatial position of the diphenylallyl moiety Also, a interaction may occur in this transition state between the phenyl group from the ligand and the phenyl group labelled Ph^2 On the other hand, the transition state **163** adopts a spatial configuration for the diphenylallyl moiety where interactions are kept to the minimum and lead to the formation of the (-)-*S* isomer.

For the amino sulfide ligand derived from ephedrine (**159**), we may also similarly suggest two transition states **164** and **165** (Fig 21), where one palladium-ligand complex is preferred due to the same repulsive interactions with the *tert*-butyl group at the nitrogen and the methyl group labelled Me^2

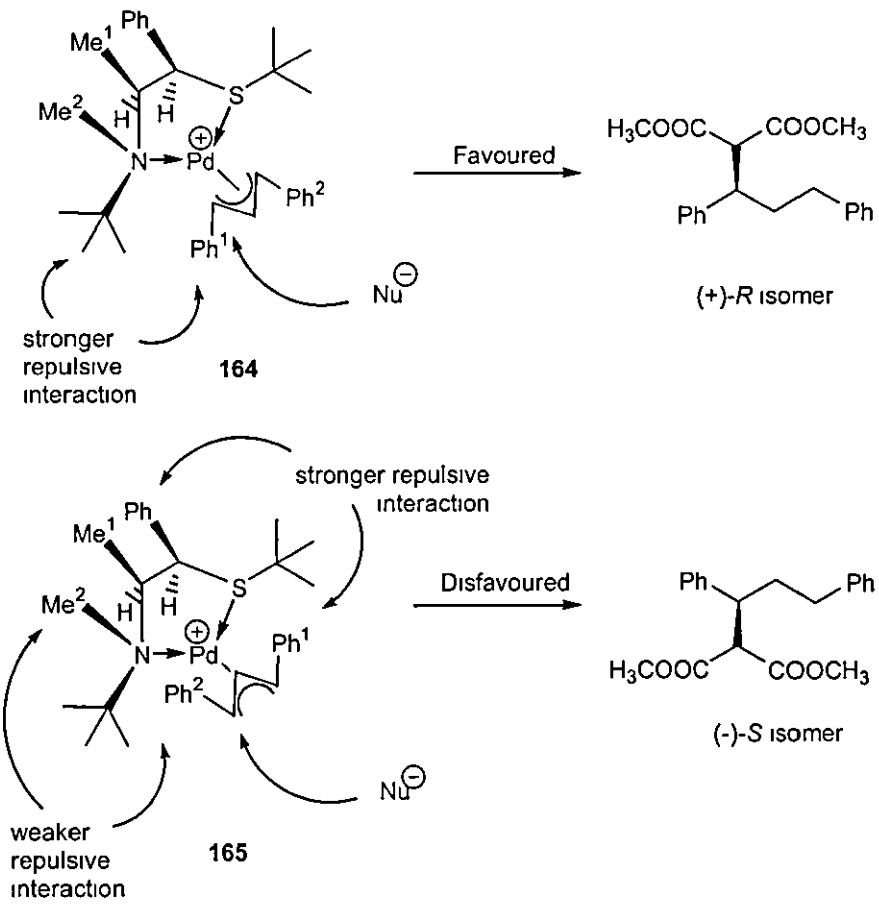


Fig 21

The preferred transition state **163** (for the pseudoephedrine derivative **154**) is preferred over the transition state **162** because both interactions with N-*t*-Bu and Phenyl groups on the ligand are avoided.

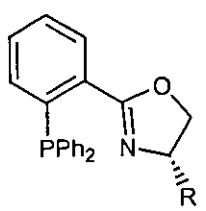
The transitions state **164** and **165** (for the ephedrine derivative **159**) cannot avoid both interactions In fact, the transition **164** is preferred over the transition state **165** because it avoids the interaction with the phenyl group on the ligand, which seems to be the most important

2-B-4 Third generation of ligands

2-B-4-1 Introduction

In our design of amino sulfide ligands, we have optimised the group at the sulfur terminus in the synthesis of our first generation of ligands Aryl and alkyl thiols have been used as nucleophiles for the displacement of the alcohol group in the double inversion reaction The second generation of ligands permitted us to investigate the best configuration between the methyl and phenyl at the chiral centres The *trans* configuration showed better asymmetric induction than the *cis* configuration

The next step in our design of amino sulfide ligands was to investigate the effect of a third chiral centre in the nitrogen substituent The chiral oxazolidine-diphenylphosphine ligand (Fig 22, **43**) reported independently by Helmchem,[27] P'altz,[28] and Williams[29] contains only one chiral centre outside the palladium-ligand ring complex.



43

Fig 22

The transition state used for the investigation of the asymmetric induction of this type of ligand has been widely studied to understand the high level of asymmetric induction observed In this case where nitrogen and phosphorus are used as chelating groups to the palladium, the nucleophile attacks along the trajectory of the palladium-phosphorus bond which is considered as the longer and the weaker bond Furthermore, the addition of the nucleophile creates a sp^3 carbon centre which causes the phenyl group to move closer to the chiral oxazolidine ring. The

formation of the most stable transition state is therefore directed by two matching interactions (Fig 23)

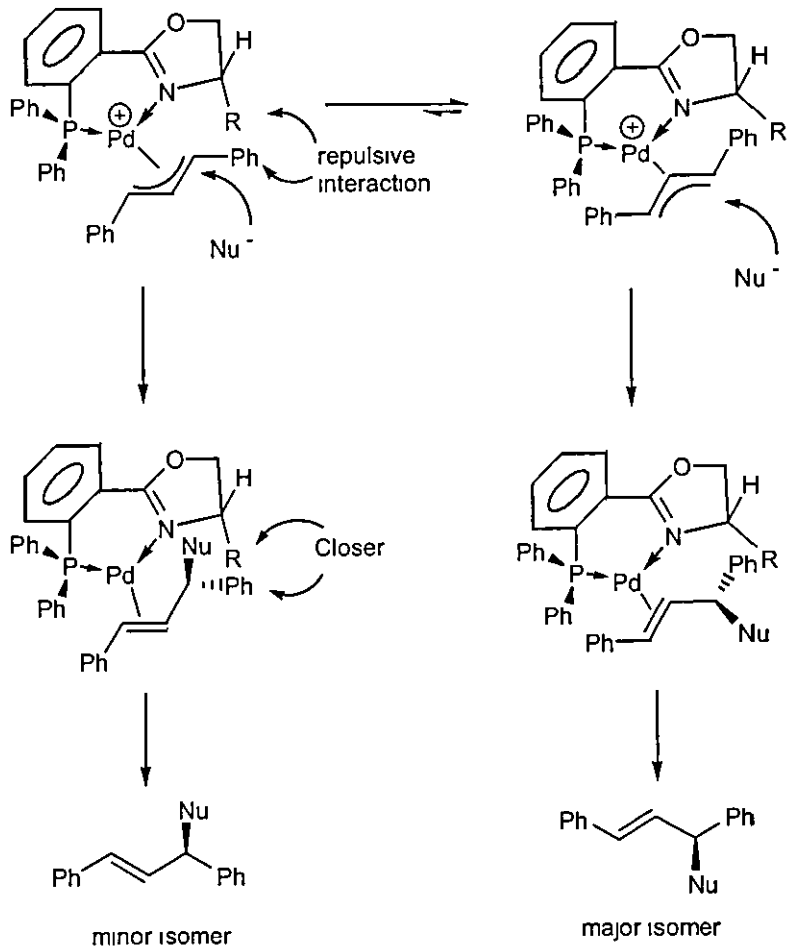
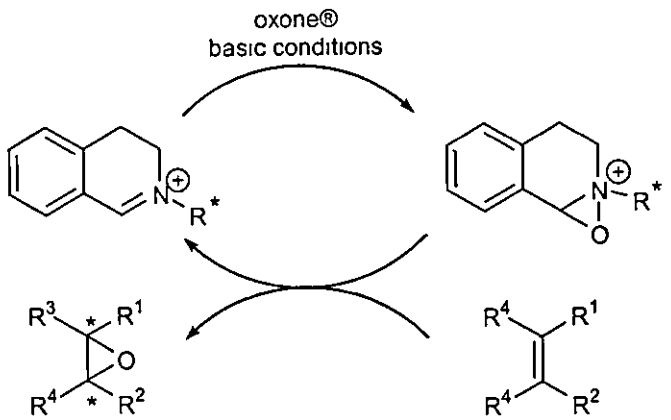


Fig 23

In the investigation of the first generation of ligands, the nucleophile is believed to attack along the axis of the palladium-sulfur bond and t[illegible]erefore approaches closer to the nitrogen side, but the absence of an external chiral centre prevents any increase of the instability of the less stable transition state during the formation of the sp^3 carbon (cf. 2-B-2-3, scheme, transition state **143**)

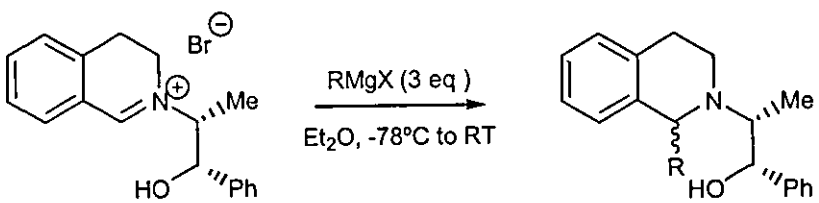
2-B-4-2· Synthesis

During the synthesis of the first generation of ligands, an iminium salt has been used as intermediate. Iminium salts have been applied as catalyst in asymmetric epoxidation of carbon-carbon double bonds [48] The positive charge makes them highly versatile electrophilic catalysts (Scheme 62)



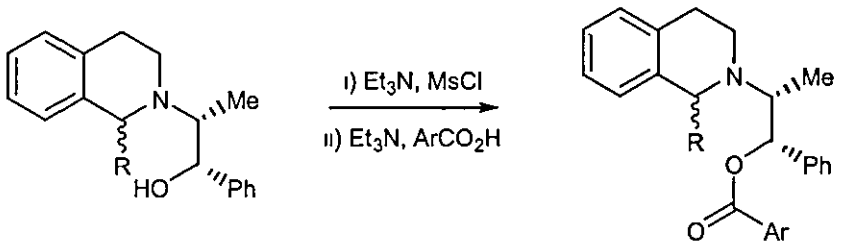
Scheme 62

Due to its electrophilic behaviour we decided to test the addition of several Grignard reagents[49] onto the iminium functionality to form the corresponding amino alcohols A mixture of diastereoisomers was obtained in the formation of a third chiral centre (Scheme 63)



Scheme 63

Determination of the stereochemistry generated was investigated by derivatisation of the alcohol with *p*-nitrobenzoic acid and 3,5-dinitrobenzoic acid to afford the crystalline amino esters **166** and **167** (Scheme 64)

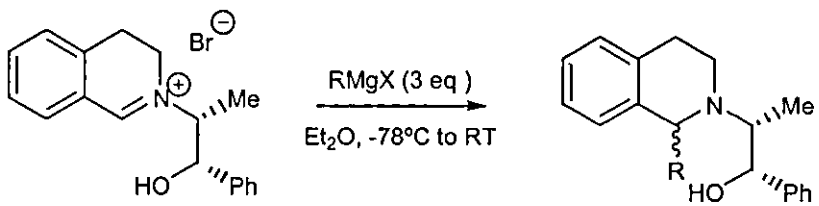


166 Ar = p-nitrophenyl
167 Ar = 3,5-dinitrophenyl

Scheme 64

Our double inversion reaction conditions were applied successfully for these derivatisations, but recrystallisation failed to give a suitable crystal for X-ray analysis

During the investigation of Grignard reagents addition onto the iminium salts, we observed different levels of asymmetric induction depending on the nature of the Grignard reagent and on the nature of the halide counterion (Scheme 65, table 12)



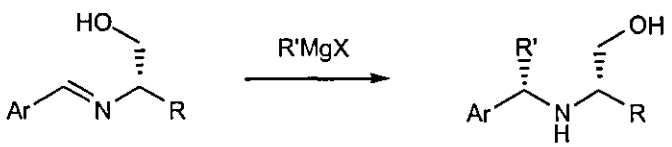
Scheme 65

Table 12

Entry	compound	RMg	X	Yield (%)	de ratio
1	**168**	PhMg	Br	99	10 1
2	**169**	MeMg	I	99	10 1
3	**169**	MeMg	Br	99	10 1
4	**169**	MeMg	Cl	99	1.1
5	**170**	EtMg	Br	99	4 2[a]
6	**171**	*i*-PrMg	I	99	[b]
7	**171**	*i*-PrMg	Br	99	[b]
8	**171**	*i*-PrMg	Cl	99	1 1

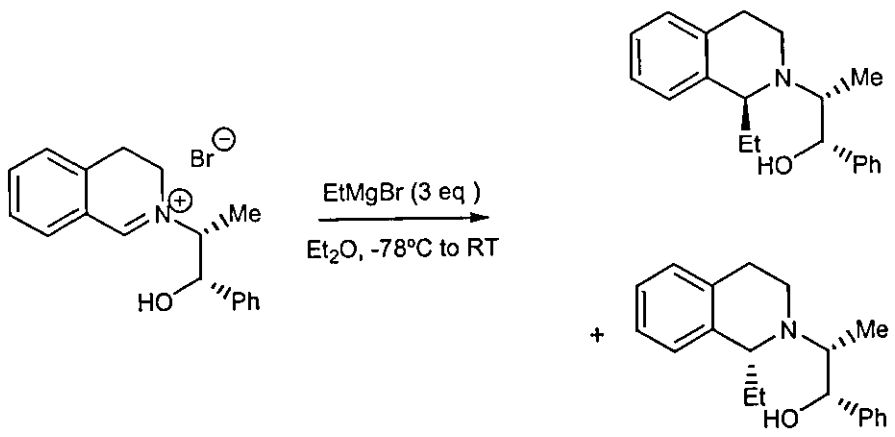
a) diastereoisomers separated in 20 and 40 % yields respectively, b) not determined

Bromide and iodide Grignard reagents gave good asymmetric induction for the formation of a third chiral centre in the asymmetric addition of Grignard reagents In contrast, the chloride equivalent afforded a 1·1 mixture of diastereoisomers It is difficult to interpret these observations, but presumably the Schlenk equilibrium is a factor Bloch[50] has previously reported that in addition of Grignard reagents to chiral imine-alcohols where slightly better asymmetric induction was observed for bromide and iodide (Scheme 66)



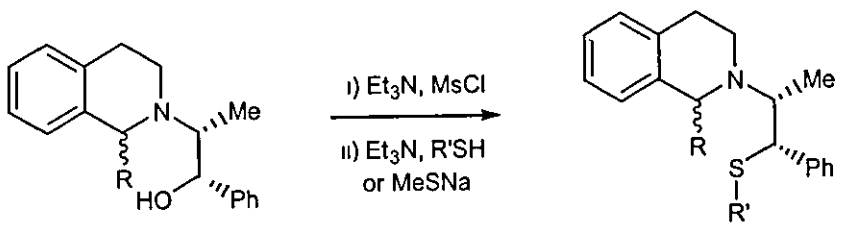
Scheme 66

The Grignard addition of ethyl magnesium bromide onto the iminium salt gave a separable mixture of diastereoisomers in 20 and 40 % yields respectively (Scheme 67) ^{1}H NMR spectroscopy could not tell which diastereoisomer is which We have labelled them **170 A** and **170 B** following the order of their Rf (**A** for higher Rf, **B** for smaller Rf) to differentiate them



Scheme 67

With good diastereoisomeric excesses (non separated) of the amino alcohols derived from norephedrine by Grignard addition to iminium salts, we proceeded with the synthesis of the third generation of ligands The conversion of the amino alcohols into the corresponding amino sulfides was achieved with the double inversion process previously described (Scheme 68)



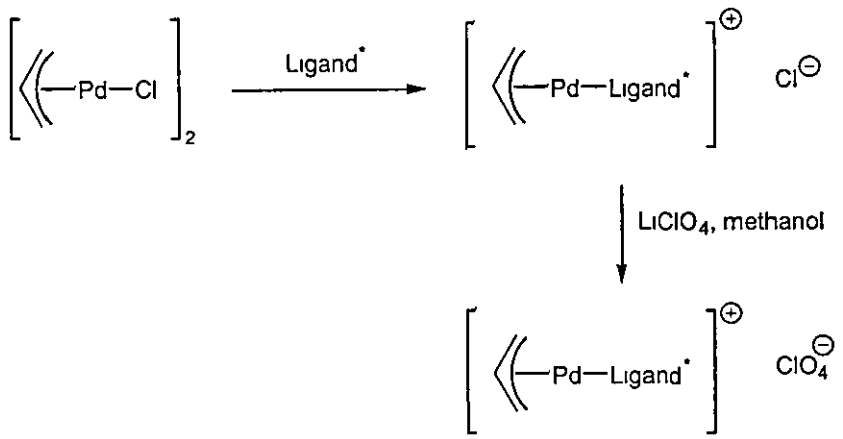
Scheme 68

In the second step of the double inversion process, we extended the range of other thiol reagents to methyl, isopropyl and *tert*-butyl groups (Table 13), in expectation of particular interactions between the third chiral centre of the amino sulfide ligands and the diphenyl allyl substrate in the palladium-catalysed allylic nucleophilic substitution reaction

Table 13

Entry	compound	R	R'	Yield (%)	ee (%)	de (%)
1	**172**	Me	Me	30	100	≈ 90
2	**173**	Me	*i*-Pr	81	100	≈ 90
3	**174**	Me	*t*-Bu	55	100	≈ 95
4	**175**	Ph	Me	61	100	≈ 90
5	**176**	Ph	*i*-Pr	56	100	≈ 90
6	**177**	Ph	*t*-Bu	60	100	≈ 95
7	**178-A**	Et	*t*-Bu	35	100	100
8	**178-B**	Et	*t*-Bu	51	100	100

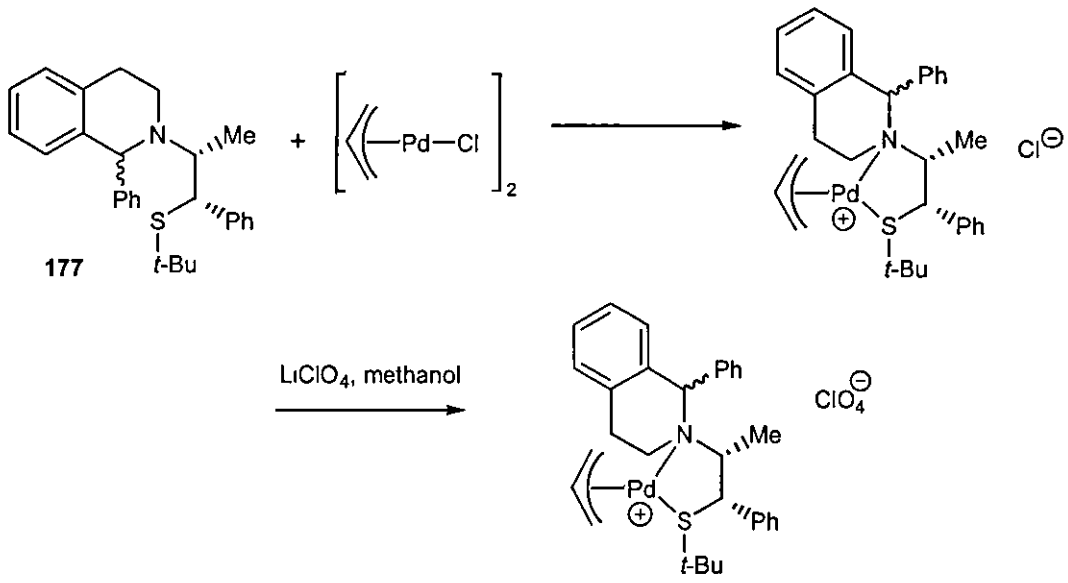
In 1999, Buono[51] reported the isolation of a palladium complex by reacting an equimolar mixture of η^3-allyl chloride palladium dimer and a bidentate ligand (Scheme 69) The exchange of the counter anion (chloride) by the appropriate salt allowed the solid palladium complex to be isolated and recrystallised for X-ray analysis



Scheme 69

We applied the same methodology to one (**177**) of our ligands of the third generation (Scheme 70), but recrystallisation of the crude powder obtained after anion exchange reaction with lithium

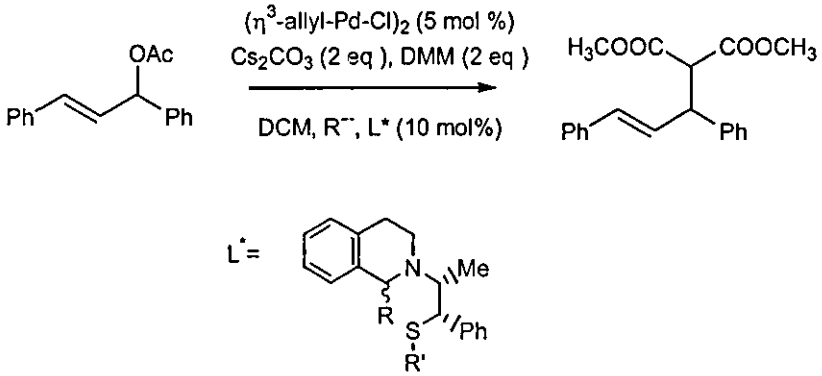
perchlorate has failed to produce a suitable crystal for X-ray analysis The configuration at the third chiral centre still remains unknown



Scheme 70

2-B-4-3 Application of amino sulfide ligands in the palladium-catalysed reaction

The third generation of ligands was synthesised to determine the possible effects of the insertion of a third chiral centre into the amino sulfide ligands, enabling us to review the transition state for the asymmetric induction in our first generation of ligands The palladium-catalysed allylic nucleophilic substitution reactions (Table 14) were performed with the optimised reaction conditions reported by Vyskocil and Kocovski (Scheme 71)[38]



Scheme 71

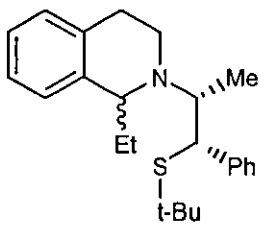
Table 14

Entry	compound	de (%) of L*	r t (h)	yield (%)	ee (%)	optical rotation
1	**175**	≈ 90	24	45	61	(-)-(*S*)
2	**176**	≈ 90	24	84	68	(-)-(*S*)
3	**177**	≈ 95	24	39	60	(-)-(*S*)
4	**172**	≈ 90	10	94	83	(-)-(*S*)
5	**173**	≈ 90	24	97	72	(-)-(*S*)
6	**174**	≈ 95	24	92	71	(-)-(*S*)
7	**178-A**	100	24	88	30	(-)-(*S*)
8	**178-B**	100	24	74	1	(-)-(*S*)
9[a]	**138**	100	1	95	15	(-)-(*S*)
10[a]	**139**	100	1	94	34	(+)-(*R*)
11[a]	**140**	100	1	90	72	(+)-(*R*)

a) From the first generation of ligands

The first piece of evidence which appears from these results is that the inclusion of the third chiral centre has reversed the sense of asymmetric induction in the palladium-catalysed allylic nucleophilic substitution reaction (entries 1-8) The modification of asymmetric induction from this third generation of ligands might be explained by steric interaction between the substituent at the new chiral centre and the diphenylallyl substrate

We have been able to synthesise in enantiomerically and diastereoisomerically pure form the ligands **178-A** and **178-B** (Fig 24), and investigated them independently in the palladium-catalysed allylic nucleophilic substitution reaction It seems that both diastereoisomers catalyse the reaction, but with very different asymmetric induction



minor isomer **178-A**

major isomer **178-B**

Fig 24

During the asymmetric addition of ethyl magnesium bromide onto the iminium salt, we have managed to separate the mixture of diastereoisomers After a double inversion reaction to convert the alcohol group into *tert*-butyl sulfide group, these ligands were investigated independently

The minor diastereoisomer **178-A** gave higher selectivity in asymmetric induction (Table 14, entry 7, 30 % ee) in the palladium-catalysed allylic alkylation reaction than the major diastereoisomer **178-B** (Table 14, entry 8, 1 % ee)

We have optimised the sulfide group for the first generation of ligands by increasing the repulsive interaction between the sulfide group and the phenyl group from the diphenyl allyl substrate (Entries 9-11) But in our third generation of ligands, we observed completely opposite

results The smaller the sulfide group is, the higher the level of asymmetric induction transmitted from the ligand to the diphenyl allyl substrate It seems that the presence of the third chiral centre has somehow obliged the diphenyl allyl substrate to adopt the alternative conformation in the palladium complex and therefore increase the repulsive interaction between the sulfide group and the phenyl group from the substrate Thus the smaller the sulfide group is, the smaller the repulsive interaction is

Unfortunately, the absolute configuration at the third chiral still remains unknown, therefore, we cannot propose any transition states to explain the asymmetric induction from our third generation of ligands to the diphenylallyl substrate But, we believe in this case that the decisive interaction occurs between the third chiral centre on the ligand and the phenyl group on the diphenylallyl substrate (Fig 25, transition state **179** and **180**)

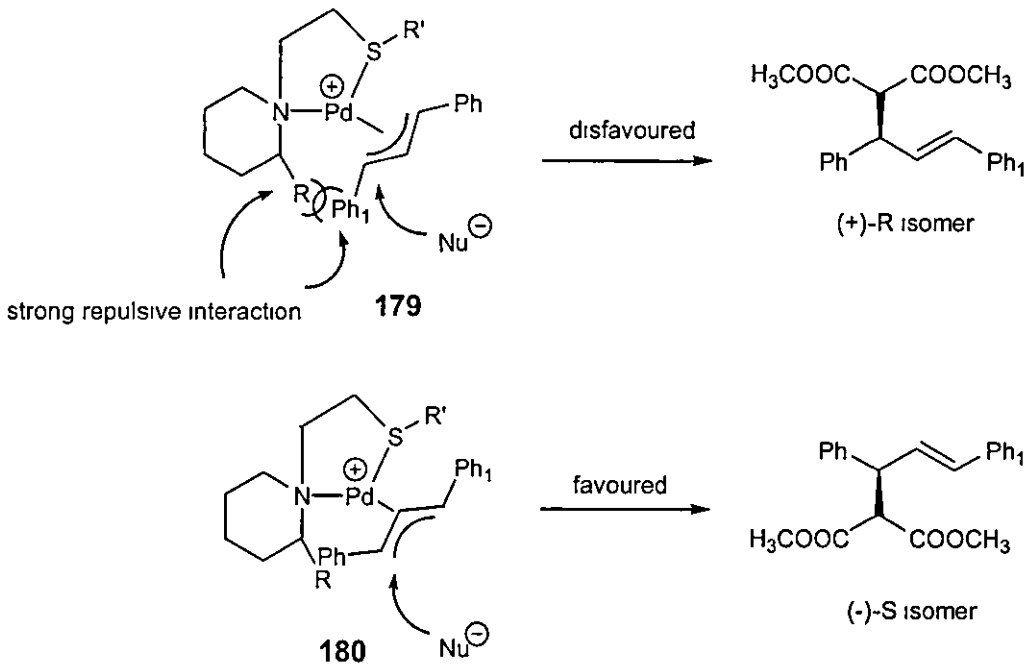
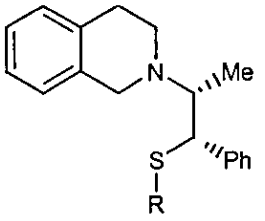


Fig. 25

2-B-5 Conclusions

We have positively demonstrated the asymmetric efficiency of chiral optically pure amino sulfides as ligands in the palladium-catalysed allylic nucleophilic substitution reaction

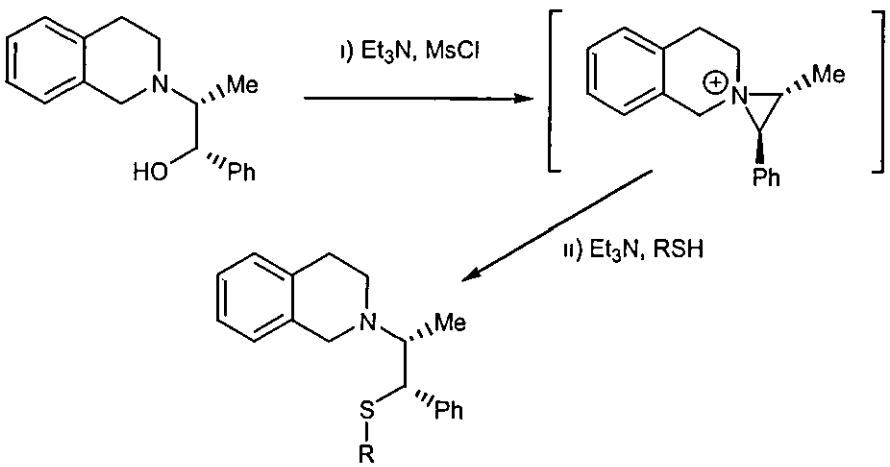
We developed a large-scale synthesis of amino alcohols derived from tetrahydroisoquinoline core for the access to our first generation of ligands (Fig 26) We have also optimised the nature of the sulfide group to obtain high asymmetric induction in the palladium-catalysed allylic alkylation.



up to 72 % ee for R= t-Bu

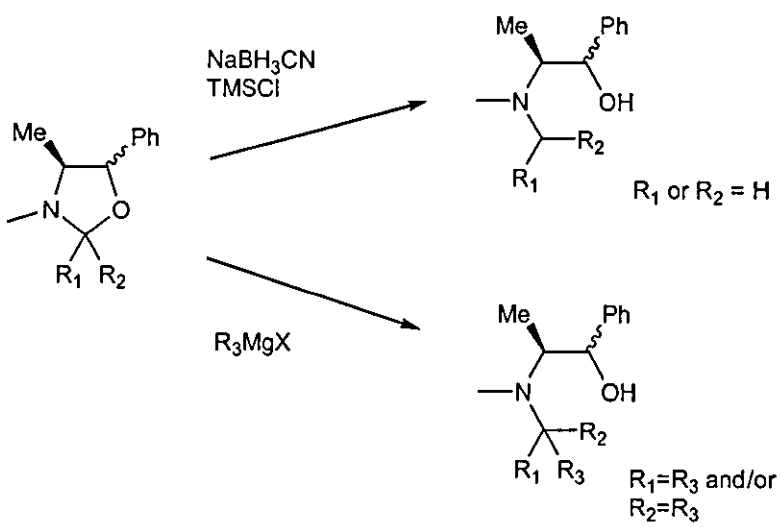
Fig 26

By X-ray analysis, the double inversion reaction has been proven to take place upon treatment of the amino alcohol with triethylamine and mesyl chloride, followed by displacement by the appropriate thiolate anion (Scheme 72) The aziridinium cation seems to be the reactive intermediate in this double inversion reaction



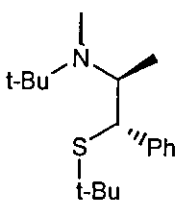
Scheme 72

We have turned our attention to find which of the two asymmetric centres has the most important effect in the asymmetric induction This second generation of ligands has been synthesised by the appropriate reactions for the cleavage of the oxazoline ring and has afforded a range of different groups on the nitrogen for the optimisation of this part of the ligands These cleavage reactions of the oxazoline ring were performed to avoid the formation of a third chiral centre in the nitrogen substituents (Scheme 73)

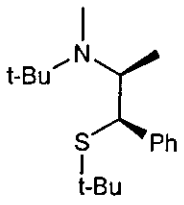


Scheme 73

By comparison of the results obtained for the application of the pseudoephedrine and ephedrine series as ligands in the palladium-catalysed allylic nucleophilic substitution reaction, it appears that the phenyl group induces the spatial conformation of the diphenylallyl substrate, and furthermore, the *trans* relative position of the two chiral centres in the transition state provides highest enantiomeric excesses (Fig 27)



induces formation of
the (-)-*S* isomer in 89 % ee

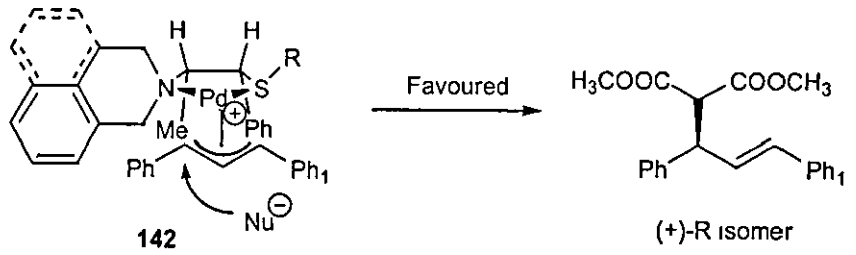


induces formation of
the (+)-*R* isomer in 60 % ee

Fig 27

The synthesis of the third generation of ligands has been achieved to observe the influence of a third chiral centre in the nitrogen substituent The closeness of the third chiral centre, the phenyl group from the substrate and the nucleophile have shown very interesting results The spatial conformation of the diphenyl allyl substrate has apparently switched to the opposite conformation defined for our first generation of ligands (Fig 28 and 29) The opposite enantiomer has been obtained with even higher asymmetric induction

First generation



142

(+)-R isomer

Fig 28

Third generation

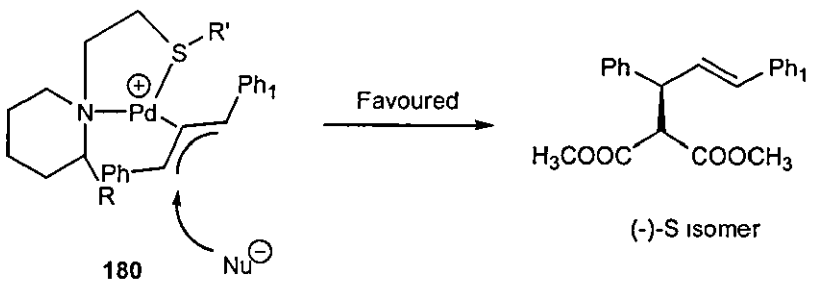
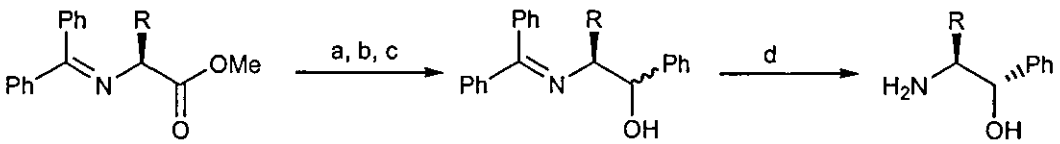


Fig 29

The importance of the phenyl group in our ligands has been demonstrated by access to high asymmetric induction in the palladium-catalysed allylic nucleophilic substitution reaction, but also during the double inversion reaction where the nucleophile attacks opposite to the nitrogen at the benzylic position Due to time constraint, the investigation of the nature of the second chiral centre which has been a methyl group afforded by pseudoephedrine, ephedrine and norephedrine was not possible Meanwhile, Polt has reported the synthesis of β-amino alcohols from amino ester with a chelation control via Schiff bases (Scheme 74) [52] These syntheses of amino alcohols with different groups other than methyl could provide ready access to new ligands for the investigation of the influence of the second chiral centre



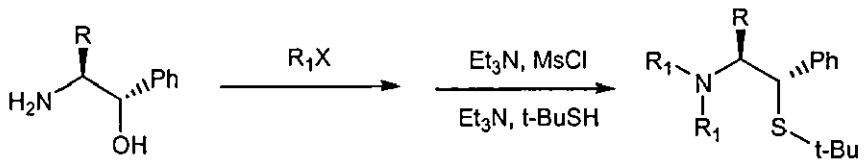
from 8 1 to 18 1 de

a) i-Bu_2Al-H / CH_2Cl_2 / - 78°C b) PhMgBr / Et_2O / -78°C -> 0°C
c) $NaHCO_3$ / H_2O d) H_3O^+

Scheme 74

The wide range of commercially available chiral amino esters could be useful for access to various amino alcohols, which could be converted into the corresponding amino sulfides by

dialkylation of the primary amine and double inversion reaction at the alcohol position (Scheme 75)



Scheme 75

The investigation of such ligands in the palladium-catalysed allylic nucleophilic substitution reaction would allow optimisation of the steric and electronic nature of this chiral centre

2-C: References

(1) Pıtchen, P , Kagan, H B *Tetrahedron Lett* **1984**, *25*, 1049

(2) Dı Furıa, S H , Modena, G., Seraglıa, G *Synthesıs* **1984**, 325

(3) Davıs, F A , Nadır, U K., Kluger, E W *J Chem Soc , Chem Commun* **1977**, 25 , Davıs, F A , Lamendoza, J , Nadır, U , Kluger, E W , Sedergan, J C ; Panunto, T W , Bıllmers, R ; Jenkıns, R , Turchı, I J , Watson, W H , Chen, J S , Kımura, M *J Am Chem Soc* **1980**, *102*, 2000 , Davıs, F A , Jenkıns, R H , Awad, S B , Strınger, O O , Watson, W.H , Galloy, J *J Am Chem Soc* **1982**, *104*, 5412 , Davıs, F A , McCauley, Jr J P , Chattopadhayay, S , Harakal, M E ; Towson, J C , Watson, W H ; Tavanaeıpou-, I *J. Am Chem Soc* **1987**, *109*, 3370 ; Davıs, F A , Towson, J C , Carroll, P J , Weısmıller, M C , Lal, S *J Am Chem Soc* **1988**, *110*, 8477 , Davıs, F A ; Weısmıller, M C , Reddy, R T. *J Am Chem Soc* **1989**, *111*, 5964 , Davıs, F A , Reddy, T R ; Han, W , Carroll, P.J *J Am Chem Soc* **1992**, *114*, 1428

(4) Page, P C B , Heer, J P ; Bethell, D , Collıngton, E W , Andrews, D M *Tetrahedron Lett* **1994**, *35*, 9626

(5) Page, P C B , Heer, J P , Bethell, D , Collıngton, E W , Andrews, D M *Tetrahedron Asymmetry* **1995**, *6*, 2911

(6) Soderquıst, J A ; Mıranda, E I *Tetrahedron lett* **1986**, *27*, 6305-6306 , Sato, T , Yoshıda, E ; Kobayashı, T , Otera, J , Nozakı, H *Tetrahedron lett* **1988**, *29*, 3971-3974 , Ku, B , Oh, D. Y. *Synthetıc Communıcatıons* **1989**, *19*, 433-438 , Tanı, H , Masumoto, K , Inamasu, T , Suzukı, H *Tetrahedron lett* **1991**, *32*, 2039-2042 , Kumar, P , Reddy, R S , Sıngh, A. P ; Pandey, B *Synthesıs* **1993**, *67* , Sato, T , Otera, J , Nozakı, H *J Org Chem* **1993**, *58*, 4971-4978 , Komatsu, N ; Uda, M , Suzukı, H. *Synlett* **1995**, 984 , Fırouzabadı, H , Iranpoor, N ; Karımı, B *Synthesıs* **1999**, *1*, 58-60 , Fırouzabadı, H , Iranpoor, N , Karımı, B *Synlett* **1999**, *3*, 319-320 , Graham, A E *Synthetıc Communıcatıons* **1999**, *29*, 697-703 , Patrocınıo, A F , Correa, I R , Moran, P J S *J Chem Soc , Perkın Trans 1* **1999**, 3133-3137 , Fırouzabadı, H , Karımı, B ,

Eslami, S *Tetrahedron lett* **1999**, 4055-4058 , Tietze, L F , Weigand, B , Wulff, C *Synthesis* **2000**, *1*, 69-71

(7) Graham, A E *Synthetic Communications* **1999**, *29*, 697-703

(8) Andrew Lund Thesis, **1999**, Loughborough University

(9) Deshmukh, M , Dunach, E , Juge, S , Kagan, H B *Tetrahedron lett* **1984**, *25*, 3467

(10) Pirkle, W H , House, D W *J Org Chem* **1979**, *44*, 1957

(11) Baldenius, K -U , Kagan, H B *Tetrahedron Asymmetry* **1990**, *1*, 597-610

(12) Andersen, K K *Tetrahedron Lett* **1962**, 93 , Andersen, K K , Gaffield, W ; Papanikolaou, N E , Foley, J W , Prekins, R I *J Am Chem Soc* **1964**, *86*, 5637

(13) Rebiere, F , Kagan, H B *Tetrahedron lett* **1989**, *30*, 3659

(14) Kagan, H B *Phosphorous Sulfur* **1986**, *27*, 127

(15) Holland, H L , Turner, C. D , Andreana, P R , Nguyen, D *Can J Chem* **1999**, *77(4)*, 463-471 , Canovese, L , Visentin, F., Uguagliati, P ; Chessa, G , Lucchini, V , Bandoli, G *Inorg Chim Acta* **1998**, *275-276(1,2)*, 385-394 , Canovese, L , Visentin, F ; Uguagliati, P , Chessa, G , Pesce, A *J Organomet Chem* **1998**, *566(1-2)*, 61-71

(16) Trost, B M ; Strege, P E *J Am Chem Soc* **1977**, *99*, 1650

(17) Longmire, J. M ; Wang, B , Zhang, X. *Tetrahedron lett* **2000**, *41*, 5435-5439 , Okuyama, Y , Nakano, H , Hongo, H *Tetrahedron Asymmetry* **2000**, *11*, 1193-1198 , Adams, H ; Anderson, J C , Cubbon, R , James, D S , Mathias, J P *J Org Chem* **1999**, *64*, 8256-8262 ; Yonehara, K , Hashizume, T., Mori, K , Ohe, K , Uemura, S. *J Org Chem* **1999**, *64*, 9374-9380 , Chelucci, G , Pinna, G A ; Saba, A *Tetrahedron Asymmetry* **1998**, *9*, 531-534 ; Longmire, J M , Zhang, X. *Tetrahedron lett* **1997**, *38*, 1725-1728 , Sprinz, J , Kiefer, M , Helmchen, G ; Reggelin, M , Huttner, G , Walter, O , Zsolnai, L *Tetrahedron lett* **1994**, *35*, 1523-1526.

(18) Mioskowski, C , Solladié, G *J Chem Soc , Chem Commun* **1977**, 162 , *Tetrahedron* **1980**, *36*, 227

(19) Sakuraba, H , Ushiki, S *Tetrahedron lett* **1990**, *31*, 1985

(20) Colombo, L , Gunnari, C ; Scolastico, C , Guanti, G , Narisano, E *J Chem Soc , Chem commun* **1979**, 591

(21) Page, P. C B , Purdie, M , Lathbury, D *Tetrahedron Lett* **1996**, *37(49)*, 8929-8932.

(22) Carreno, M C *Chem Rev* **1995**, *95*, 1717

(23) Vyskocil, S , Smrcina, M , Hanus, V , Polasek, M , Kocovsky, P *J Org Chem* **1998**, *63*, 7738-7748

(24) Consiglio, G , Waymouth, R M *Chem Rev* **1989**, *89*, 257-276 , Blystone, S L *Chem Rev* **1989**, *89*, 1665-1679 , Trost, B M ; Van Vranken, D L *Chem Rev* **1996**, *96*, 395-422 , Tonks, L , Williams, J M J *J Chem Soc , Perkin Trans 1* **1998**, 3637-3652 , Haughton, L ; Williams, J. M J *J Chem Soc , Perkin Trans 1* **1999**, 2645-2658

(25) Trost, B M , Strege, P E *J Am Chem Soc* **1977**, *99*, 1649-1651

(26) Trost, B M , Van Vranken, D L *Angew Chem , Int Ed Engl* **1992**, *31*, 228

(27) Sprinz, J , Helmchen, G *Tetrahedron lett* **1993**, *34*, 1769

(28) von Matt, P , Pfaltz, A *Angew Chem , Int Ed Engl* **1993**, *32*, 566

(29) Dawson, G J , Frost, C G , Williams, J M J , Coate, S. W *Tetrahedron lett* **1993**, *34*, 3149.

(30) Woerpel, K A , Hinman, M M , Faul, M M ; Evans, D A. *J Am Chem Soc* **1991**, *113*, 726

(31) Frost, C , Williams, J M J. *Tetrahedron Lett* **1993**, *34*, 2015

(32) Adams, H , Anderson, J C , Cubbon, R , James, D S , Mathias, J P *J Org Chem* **1999**, *64*, 8256-8262

(33) Chelucci, G , Cabras, M A *Tetrahedron Asymmetry* **1996**, *7*, 965-966 , Chelucci, G , Berta, D , Saba, A *Tetrahedron* **1997**, *53*, 3843-3848

(34) Hiroi, K , Suzuki, Y *Heterocycles* **1997**, *46*, 77-81 , Hiroi, K , Suzuki, Y ; Abe, I , Hasegawa, Y ; Suzuki, K *Tetrahedron Asymmetry* **1998**, *9*, 3797-3817

(35) Wipf, P ; Ribe, S *J Org Chem* **1998**, *63*, 6454-6455 , Braga, A. L ; Appelt, H R , Schneider, P H , Silveira, C C , Wessjohann, L A. *Tetrahedron Asymmetry* **1999**, *10*, 1733-1738

(36) Poelert, M. A ; Hof, R P , Peper, N C M W ; Kellogg, R M *Heterocycles* **1994**, *37*, 461-475 , Poelert, M A , Hulshof, L A ; Kellogg, R M *Recueil des Travaux Chimiques des Pays-Bas* **1994**, *113*, 355-364 , Poelert, M A , Hulshof, L A , Kellogg, R M *Recueil des Travaux Chimiques des Pays-Bas* **1994**, *113*, 365-368

(37) Dieter, R. K , Deo, N , Lagu, B , Diete , J W *J Org Chem* **1992**, *57*, 1663-1671

(38) Vyskocil, S , Smrcina, M , Hanus, V , Polasek, M , Kocovsky, P *J Org Chem* **1998**, *63*, 7738

(39) Trost, B M , Krueger, A C , Bunt, R C , Zambrano, J *J Am Chem Soc* **1996**, *118*, 6520.

(40) Page, P C B , Rassias, G A , Bethell, D , Schilling, M B *J Org Chem* **1998**, *63*, 2774 , Page, P C B , Heer, J P , Rassias, G A , Bethell, D *Reactivity* **1999**, 14

(41) Rieche, A , Schimtz, E *Chem Ber* **1959**, *89*, 125

(42) Akermark, B , Krakenberger, B , Hansson, S , Vitagliano, A *Organometallics* **1987**, *6*, 620-628 ; Cesarotti, E , Grassi, M , Prati, L , Demartin, F *J Chem Soc , Dalton Traans* **1991**, 2073-2082

(43) Eschweiler, W *Chem Ber* **1905**, *38*, 880 , Clarke, H T , Gillespie, H B , Weishaus, S Z *J Am Chem Soc* **1933**, *55*, 4571 , Icke, R N , Moore, M L *Org Reactions* **1945**, *5*, 31 , Wisegarver, B B , Alles, G A *Org Syn , Coll Vol 3*, **1955**, 723

(44) Ito, Y , Sawamura, M , Kominami, K , Saegusa, T *Tetrahedron Lett* **1985**, *26*, 5303.

(45) Heaney, H , Papageorgiou, G ; Wilkins, R F *Tetrahedron* **1995**, *51*, 10737 , Heaney, H ; Papageorgiou, G *Tetrahedron* **1996**, *52*, 3473 , Heaney, H , Papageorgiou, G , Wilkins, R F. *Tetrahedron* **1997**, *53*, 2495 , Heaney, H , Papageorgiou, G , Wilkins, R F *Tetrahedron* **1997**, *53*, 14381.

(46) Page, P C B , Heaney, H , Rassias, G A ; Reignier, S , Sampler, E P , Talib, S *Synlett* **2000**, *1*, 104-106

(47) Goodson, L H , Christopher, H *J Am Chem Soc* **1950**, *72*, 358 , Senkus, M *ibid* , **1945**, *62*, 1515

(48) Hanquet, G , Lusinchi, X *Tetrahedron Lett* **1993**, *34*, 5299 , Bohe, L , Hanquet, L , Lusinchi, X *Tetrahedron Lett* **1993**, *34*, 7271

(49) Neelakantan, L *J Org Chem* **1971**, *36*, 2256-2260

(50) Bloch, R *Chem Rev* **1998**, *98*, 1407

(51) Brunel, J M , Constantieux, T , Buono, G *J Org Chem* **1999**, *64*, 8940

(52) Polt, R , Peterson, M A *Tetrahedron Lett* **1990**, *31*, 4985

Chapter 3

Experimental Part:

3 1 General experimental procedures

Commercially available reagents were used as supplied, without further purification, unless otherwise stated Air and moisture sensitive compounds were stored in a desiccator over self indicating silica pellets, under a nitrogen atmosphere

Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh) and hand bellows to apply pressure to the column Thin layer chromatography (TLC) was carried out on glass or aluminium plates coated with silica gel layer of 0 25 mm thickness, containing fluorescer Compounds on this material were visualised by UV radiation at wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid, (acidified with concentrated sulfuric acid), followed by charring where appropriate

Light petroleum ether (b p 40-60 °C), was distilled from calcium chloride prior to use Ethyl acetate was distilled over calcium sulphate or chloride Dichloromethane was distilled over calcium hydride Tetrahydrofuran (THF) was distilled under nitrogen atmosphere from the sodium/benzophenone ketyl radical or from lithium aluminium hydride Triethylamine and diisopropylethylamine were stored over potassium hydroxide pellets.

Highly air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240 °C These were allowed to cool in a desiccator over self indicating silica pellets The reactions were carried out under a slight positive static pressure of nitrogen

Microanalyses were performed on a Perkin Elmer Elemental Analyser 2400 CHN Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at l=589 nm, corresponding to the sodium line (D) The solvents used for these measurements were of spectrophotometric grade The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of the solvent used Melting points were carried out on a Electrothermal-IA 9100 and are uncorrected.

Fourier transformed infrared absorption spectra were recorded on a Perkin Elmer FT-IR spectrometer Paragon 2001 instrument in the range of 4000-600 cm^{-1}. Solid samples were run as thin films of their solution in dichloromethane Liquid samples were run neat on sodium chloride discs Mass spectra were recorded on Cra os MS-80 or Jeol-SX102 instruments using electron impact (EI), ionisation technique

Proton nuclear magnetic resonance spectra, were recorded on Bruker AC 250 and Bruker DPX 400 operating at 250 13 and 400 13 MHz respectively The experiments were conducted in deuteriated solvents with tetramethylsilane as the internal standard Multiplicities were recorded as broad signals (br s), singlets (s), doublets (d), triplets (t), quartets (q), quintets (quint), heptets (hept), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), doublet of double doublets (ddd), and multiplets (m)

Carbon-13 nuclear magnetic resonance spectra were recorded on Bruker AC 250 and Bruker DPX 400 instruments operating at 62 86 and 100 62 MHz respectively Normally the ^{13}C NMR spectrum for each compound was recorded in the same deuteriated solvent as that used for the ^{1}H NMR spectrum, unless otherwise stated Tetramethylsilane was used as the internal standard DEPT was recorded on a Bruker AC 250 and Bruker DPX 400

Enantiomeric excesses were determined by either proton nuclear magnetic resonance, (^{1}H NMR), or by Chiral High Performance Liquid Chromatography, (Chiral HPLC).

The proton nuclear magnetic resonance spectra were recorded in deuteriated chloroform on Bruker AC 250 NMR instruments, operating at 250 13 MHz, in the presence of *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [(+)-Eu(hfc)$_3$], or (*R*)-(3,5-dinitrobenzoyl)-1-phenylethylamine as the chiral shift reagent, and tetramethylsilane as the internal standard Between 20 and 40 mol% of the chiral europium shift reagent was used for the determination of the enantiomeric excess of 1,3-Diphenyl-1-(2-dimethylmalonyl)prop-2-ene In no case, however, did the total mass of the chiral shift reagent used in each of the ^{1}H NMR

experiments exceed 10 mg due to the paramagnetic properties of europium(III), which may compromise data through line broadening

The chiral columns used for the determination of enantiomeric excesses (ee), of non-racemic mixtures of chiral compounds by chiral HPLC, were Chiracel OD or Chiracel OJ on a TSP Thermo-Separating-Products Spectra Series P200 instrument, with a TSP Spectra Series UV100 ultra-violet absorption detector and a Cromojet Integrator For 1,3-Diphenyl-1-(2-dimethylmalonyl)prop-2-ene, the solvent system used was hexane/isopropanol (95 5), operating at a flow rate of 0 50 mL per minute, (pump pressure equivalent to 80-135 psi), with the UV detector set at 254 nm Both solvents used for these measurements (hexane and isopropanol), were of HPLC grade

3-2: Individual experimental procedures

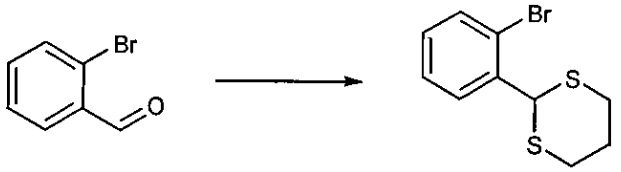
2-Pyridyl-1,3-dithiane (181):[1]

A solution of equimolar of 2-pyridinecarboxaldehyde (2 00 g, 18 7 mmol) and 1,3-propanedithiol (1 88 ml, 18 7 mmol) in toluene in presence of a catalytic amount of *p*-toluene sulfonic acid, was heated to reflux for 24 hour After cooling the reaction mixture, the solvent was removed and a careful column chromatography on silica gel was carried on the crude mixture to yield the title compound (2 59 g, 71 %) as a colourless oil IR ν_{max} cm^{-1} 3047, 3006, 2931, 2898, 1667, 1585, 1568, 1469, 1431, 1277, 1172, 993, 750 δ_H (250 MHz, $CDCl_3$) 1 90-2 10 (1H, m), 2 12-2 30 (1H, m), 2 90-3 20 (4H, m), 5 36 (1H, s), 7 18-7 25 (1H, m, C*H* pyr), 7 45-7 50 (1H, m, C*H* pyr), 7 65-7 73 (1H, m, C*H* at pyr), 8 56-8 60 (1H, m, C*H* pyr) δ_C ($CDCl_3$, 62 MHz) 24 94, 31 14, 52 66, 121 8, 122 7, 136 6, 149 8, 157 4

General procedure for the condensation of ´,3-propanedithiol and substituted benzaldehydes

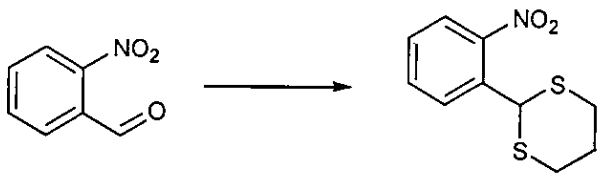
Acetyl chloride (5 ml) was added to methanol (50 ml) at 0°C After 5 minutes the ice-bath was removed and aryl aldehyde was added followed by 1,3-propanedithiol Then the reaction was left to stir overnight at room temperature The solvents were removed under reduced pressure and the crude mixture was recrystallised in methanol to yield the titled compound

2-(2-Bromophenyl)-1,3-dithiane (81):



See above 2-Bomobenzaldehyde (1 06 ml, 9 08 mmol), 1,3-propanedithiol (1 ml, 9 95 mmol, 1 1 eq), to yield 1 86 g of the titled compound as a colourless crystalline solid (74 %) m p 100-101°C IR ν_{max} cm^{-1} 3070, 2897, 1466, 1419, 1276, 1176, 1021, 745, 668 δ_H (400 MHz, $CDCl_3$) 1 94 (1H, ddt, *J* 14, 12 5, 3 Hz), 2 19 (1H, ddt, *J* 14, 4.3, 2 5 Hz), 2 92 (2H, ddd, *J* 14, 12 5, 4 3 Hz), 3 12 (2H, ddd, *J* 14, 3, 2 5 Hz), 5 60 (H, s), 7 14 (1H, ddd, *J* 8, 7 4, 1.7 Hz), 7 33 (1H, ddd, *J* 7 8, 7 4, 1 3 Hz), 7 54 (1H, dd, *J* 8, 1 3 Hz), 7 68 (1H, dd, *J* 7 8, 1 7 Hz) δ_C (100 MHz, $CDCl_3$) 25 14 (CH_2), 32 29 (2x CH_2), 50 74 (CH), 123 01 (CH ar.), 125 87 (d, *J* 59 Hz, C ar), 128 11 (Ch ar), 129 76 (CH ar), 132 94 (CH ar), 138 27 (C ar) Elemental analysis. found C, 43 55; H, 3 94, $C_{10}H_{11}BrS_2$ requires C, 43 64, H, 4 03, Br, 29 03, S, 23 30

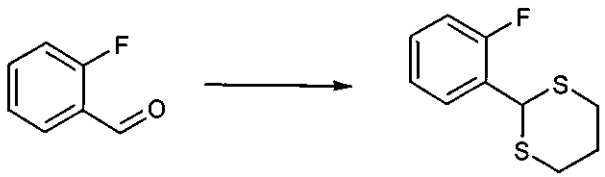
2-(2-Nitrophenyl)-1,3-dithiane (82):[2]



See above· 2-Nitrobenzaldehyde (2 00 g,, 13 23 mmol), 1,3-propanedithiol (1 46 ml, 14 53 mmol, 1 1 eq), to yield 2 63 g of titled compound as an orange crystalline solid (82%) m p 121-123 °C. IR ν_{max} cm^{-1} 3074, 2904, 2890, 1520 (NO_2), 1423, 1352, 1274, 1250, 1173, 721. δ_H (400 MHz, $CDCl_3$) 1 95 (1H, m), 2 20 (1H, m), 2 93 (2H, m), 3 13 (2H, m), 5 89 (1H, s), 7 44 (1H, ddd, J 1 5, 7.5, 8 2 Hz), 7 62 (1H, dt, *J* 1 5, 7 5 Hz), 7 88 (2H, m) δ_C (100 MHz, $CDCl_3$) 25 00 (CH_2), 32 25 (2x CH_2), 45 95 (CH), 124.72 (CH ar.), 129 08 (CH ar), 130 73 (CH ar), 133 43

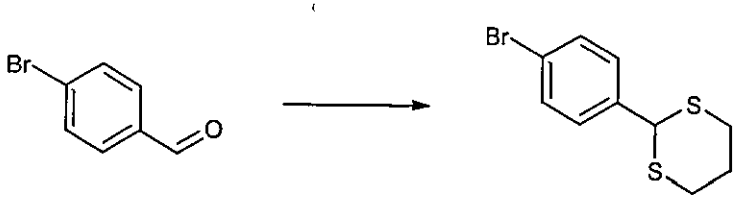
(CH ar), 133 47 (C ar), 147 72 (C ar) Exact mass calcd for $C_{10}H_{11}NO_2S_2$ 241 02312; found 241.02312. Elemental analysis found C, 49 70, H, 4 53, N, 5 75, $C_{10}H_{11}NO_2S_2$ requires C, 49 77, H, 4 59, N, 5 80, O, 13 26, S, 26 57

2-(2-Fluorophenyl)-1,3-dithiane (83):[3]



See above 2-Fluorobenzaldehyde (2 00 ml, 18 98 mmol), 1,3-propanedithiol (1 91 ml, 19 01 mmol, 1 1 eq), to yield 2 80 g of titled compound as a colourless crystalline solid (69%) m p 77-79 °C IR ν_{max} cm^{-1} 2900, 1487, 1275, 1232, 1089, 757. δ_H (400 MHz, $CDCl_3$) 1 95 (1H, m), 2 18 (1H, m), 2 92 (2H, m), 3 13 (2H, m), 5 55 (1H, s), 7 05 (1H, ddd, *J* 1 25, 8 08, 9.8 Hz), 7 15 (1H, dt, *J* 1 27, 7 52 Hz), 7 27 (1H, m), 7 62 (1H, dt, *J* 1 85, 7 5 Hz) δ_C (100 MHz, $CDCl_3$) 25 08 (CH_2), 32 18 (2x CH_2), 43 08 (CH, *J* 4 Hz), 115 49 (CH ar , *J* 22 2 Hz), 124 64 (CH ar , *J* 3 7 Hz), 126 29 (C ar , *J* 14 24 Hz), 129 56 (CH ar , *J* 2 8 Hz), 129 87 (CH ar , *J* 8 4 Hz), 158 91 (CF ar , *J* 248 1 Hz) Exact mass calcd for $C_{10}H_{11}FS_2$ 214 02862, found 214 02834 Elemental analysis found C, 55 85, H, 5 10, $C_{10}H_{11}FS_2$ requires C, 56 04, H, 5 17, F, 8 86; S, 29 92

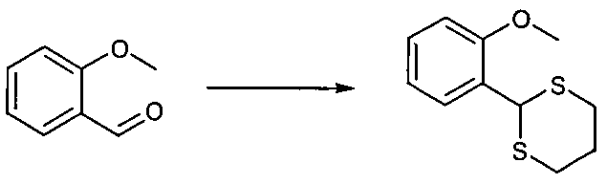
2-(4-Bromophenyl)-1,3-dithiane (84):[4]



See above. 4-Bromobenzaldehyde (2 00 g, 10 81 mmol), 1,3-propanedithiol (1 20 ml, 11 94 mmol, 1 1 eq) to yield 2 203 g of the titled compound as a colourless crystalline solid (74 %) m p 98-99°C (Lit 92-94°C) IR ν_{max} cm^{-1} 3058, 2951, 2931, 2896, 1588, 1484, 1398, 1274,

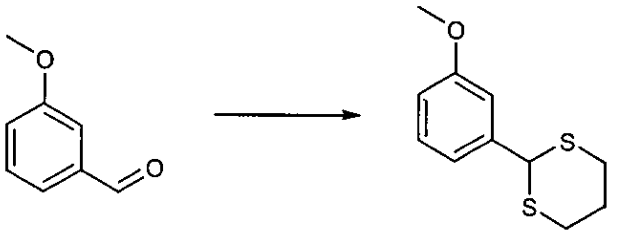
1070, 1007, 760 δ_H ($CDCl_3$, 400 MHz) 1 90 (1H, m), 2 16 (1H, m), 2 90 (2H, dddd, 1, 3 1, 4 5, 13 8 Hz), 3 04 (2H, dddd, *J* 1, 2 5, 12 3, 14 6 Hz), 5 11 (1H, s), 7 35 (2H, d, *J* 8 6 Hz), 7 48 (2H, d, *J* 8 6 Hz) δ_C ($CDCl_3$, 62 MHz) 24 96 (CH_2), 31 95 (2*CH_2), 50 60 (CH), 122 22, 129 43 (CH ar), 131 80 (CH ar), 138 06 Elemental analysis· found C, 43 57, H, 3 89, $C_{10}H_{11}BrS_2$ requires C, 43 64, H, 4 03, Br, 29 03, S, 23 30

2(-2-Methoxyphenyl)-1,3-dithiane (85):[4]



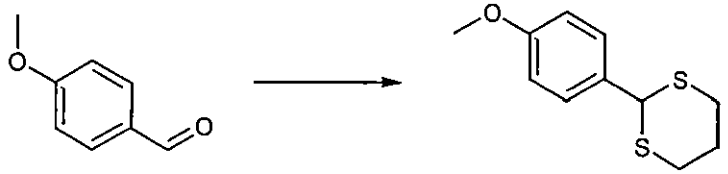
See above Ortho-anisaldehyde (2 00 g, 14 69 mmol), 1,3-propanedithiol (1 62 ml, 16 12 mmol, 1 1 eq) to yield 2 686 g of the titled compound as a colourless crystalline solid (81 %) m p 130-132°C IR ν_{max} cm^{-1} 3060, 3029, 2994, 2897, 2834, 1596, 1491, 1244, 1096, 1022, 757 δ_H ($CDCl_3$, 400 MHz) 1 93 (1H, dtt, *J* 3, 12 6, 14 1 Hz), 2 16 (1H, dtt, *J* 2 5, 4 3, 14 1 Hz), 2 88 (2H, ddd, *J* 3, 4 2, 14 5 Hz), 3 11 (2H, dt, *J* 2 5, 12 6 Hz), 3 07 (3H, s), 5 71 (1H, s), 6 86 (1H, dd, *J* 1, 8 3 Hz), 6 96 (1H, dt, *J* 1 1, 7 5 Hz), 7 25 (1H, dt, *J* 1 8, 7 4, 8 3 Hz), 7 58 (1H, dd, *J* 1 8, 7 6 Hz) δ_C ($CDCl_3$, 62 MHz) 25 35 (CH_2), 32 42, 43 64, 55 73 (CH), 110 69 (CH ar), 120.98 (CH ar.), 127 24, 129.10 (CH ar), 129 32 (CH ar), 155 35 Exact mass calcd for $C_{11}H_{14}OS_2$ 226 04861, found 226 04892. Elemental analysis found C, 58 21, H, 6 11, $C_{11}H_{14}OS_2$ requires C, 58 37; H, 6 23, O, 7 07, S, 28 33

2(-3-Methoxyphenyl)-1,3-dithiane (86):[4]



See above Meta-anisaldehyde (1 79 ml, 14 69 mmol), 1,3-propanedithiol (1 62 ml, 16 12 mmol, 1 1 eq) to yield 3 165 g of the titled compound as a colourless crystalline solid (95 %) m p 62-64°C IR ν_{max} cm^{-1} 3052, 3000, 2936, 2896, 2832, 1582, 1498, 1464, 1452, 1431, 1421, 1315, 1298, 1275, 1243, 1146, 1047, 871, 761, 694 δ_H ($CDCl_3$, 400 MHz) 1 94 (1H, dtt, *J* 3 1, 12 3, 14.1 Hz), 2 17 (1H, dtt, *J* 2 5, 4 4, 14 1 Hz), 2 91 (2H, ddd, *J* 3, 4 3, 14 5 Hz), 3 06 (2H, dddd, *J* 1, 2 5, 12 4, 13 5 Hz), 3 81 (3H, s), 5 15 (,H, s), 6 84 (1H, ddd, *J* 1, 2 6, 8 3 Hz), 7 04 (2H, m), 7 25 (1H, m). δ_C ($CDCl_3$, 62 MHz) 25 17 (CH_2), 32.13 (CH_2), 51 58 (CH_2), 55 28 (CH_3), 113 03 (CH ar), 114 37 (CH ar), 120 03 (CH ar), 129 68 (CH ar), 140 48, 159 75 Exact mass calcd for $C_{11}H_{14}OS_2$ 226 04861, found 226 04881 Elemental analysis found C, 58 21, H, 6 14, $C_{11}H_{14}OS_2$ requires C, 58 37, H, 6 23, O, 7 07, S, 28 33

2(-4-Methoxyphenyl)-1,3-dithiane (87):[2]



See above Para-anisaldehyde (1 79 ml, 14 69 mmol), 1,3-propanedithiol (1 62 ml, 16 12 mmol, 1 1 eq) to yield 3 044 g of the titled compound as a colourless crystalline solid (91 %) m p 118-120°C IR ν_{max} cm^{-1} 3030, 3005, 2960, 2936, 2902, 2834, 1608, 1508, 1249, 1179, 1030, 776, 757, 675 δ_H ($CDCl_3$, 400 MHz) 1 90 (1H, dtt, *J* 2 8, 12, 14 Hz), 2.14 (1H, dhept, *J* 1 5, 14 4 Hz), 2 89 (2H, dt, *J* 4 4, 14 4 Hz), 3 03 (2H, dm, *J* 2 4 Hz), 3 78 (3H, s), 5 13 (1H, s), 6 85 (2H, d, *J* 9 Hz), 7 38 (2H, d, *J* 9 Hz) δC ($CDCl_3$, 100 MHz) 25 03 (CH2), 32 13 (CH2), 50 69, 55 23, 114 03 (CH ar), 128 87 (CH ar), 131 26, 159 52 Exact mass calcd for $C_{11}H_{14}OS_2$ 226 04861, found 226 04892 Elemental analysis· found C, 58 20, H, 6 08, $C_{11}H_{14}OS_2$ requires C, 58 37, H, 6 23, O, 7 07, S, 28 33

2-(2-Aminophenyl)-1,3-dithiane (89):[5]

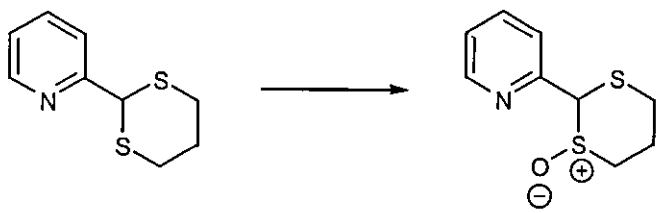
To a suspension of 2-(2-nitrophenyl)-1,3-dithiane (4 00 g, 16 58 mmol) and tin (5 g, 46 34 mmol, 2 8 eq) in water (40 ml) was added hydrochloric acid concentrated (15. ml), then the reaction mixture was heated with a water bath until disappearance of the starting material (i e · clear solution), then the reaction was cooled down to room temperature, filtrate by suction, basified with a solution of sodium hydroxide until alkaline pH Then sodium hydroxide was added until disappearance of the precipitated, the mixture was transferred to a separating funnel and extraction was carried out with dichloromethane The combined organic layer were dried over sodium sulfate and the solvent was removed to yield 3 44 g of the titled compound as a orange-red crystalline solid (99 %) m p 121-123 °C IR ν_{max} cm^{-1} 3432, 3342, 1622, 1490, 1273, 751 δ_H (400 MHz, $CDCl_3$) 1 83-2 02 (1H, m), 2 11-2 24 (1H, m), 2 86-2 97 (2H, m), 3 02-3 16 (2H, m), 4 16 (2H, broad, NH_2), 5 29 (1H, s), 6 66-6 71 (1H, m), 6 73-6 81 (1H, m), 7 07-7 16 (1H, m), 7 28-7 34 (1H, m), δ_C (100 MHz, $CDCl_3$) 25 31 (CH_2), 32.02 (2x CH_2), 48 68 (CH), 117 01 (CH ar), 119 06 (CH ar), 123 09 (CH ar), 128 54 (CH ar), 129 27 (CH ar), 144 39 (CH ar) Exact mass calcd for $C_{10}H_{13}NS_2$ 211 04894, found 211 04903 Elemental analysis found C, 56 74, H, 6 16, N, 6 51, $C_{10}H_{13}NS_2$ requires C, 56 83, H, 6 20, N, 6 63, S, 30 34

General procedure for the asymmetric sulfoxidation of 1,3-dithiane species

To a solution of 2-aryl-1,3-dithiane (≈ 500 mg) in dichloromethane (20 ml) at -20°C, was added 8,8-(dimethoxycamphor)sulfonyl oxaziridine (1 1 eq) The reaction was left to stir at -20°C for 48 hours, then a saturated solution of sodium sulfite was added to quench the reaction Brine and dichloromethane were added and the phases separated The aqueous layer was washed twice with

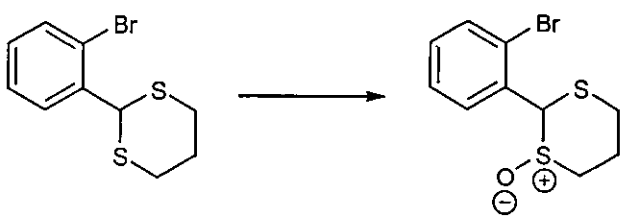
dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure The crude product was purified by flash column chromatography over silica gel to yield the titled compound

2-Pyridyl-1,3-dithiane-1-oxide (89):[1]



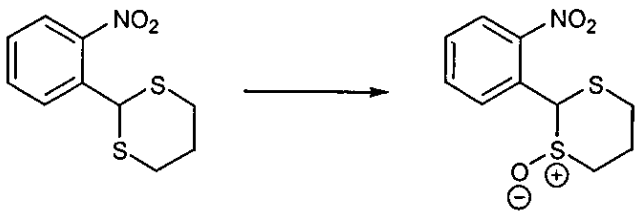
See Above 2-pyridyl-1,3-dithiane (500 mg, 2 54 mmol), 8,8-(dimethoxycamphor)sulfonyl oxaziridine (806 mg, 2 79 mmol, 1 1 eq), to yield 421 6 mg of the titled compound as a colourless crystalline solid (78 %, >99 % ee) m p 132-134°C. IR ν_{max} cm^{-1} (CH_2Cl_2 solution) 3050, 1469, 1274, 1040 δ_H ($CDCl_3$, 400 MHz) 2 30-2 45 (1H, m), 2 50-2 61 (1H, m), 2 70-3 00 (3H, m), 3 52-3 70 (1H, m), 4 76 (1H, s), 7 26-7 31 (1H, m, C*H* pyr.), 7 45-7 48 (1H, m, C*H* pyr), 7 70-7 75 (1H, m, C*H* pyr), 8 66-8 68 (1H, m, C*H* pyr) δ_C ($CDCl_3$, 62 MHz) 29 49, 30 99, 54 82, 71 38, 124 00, 124 92, 137 12, 150 53, 152 90 $[\alpha]_D^{20}$= 110° (c=1 002, $CHCl_3$) Exact mass calcd for $C_9H_{11}NOS_2$ 213 02821, found 213 02850 Elemental analysis· found C, 50 48, H, 5 13, N, 6 44, $C_9H_{11}NOS_2$ requires C, 50 68, H, 5 20, N, 6 57, O, 7 50, S, 30 66.

2-(2-Bromophenyl)-1,3-dithiane-1-oxide (97):[6]



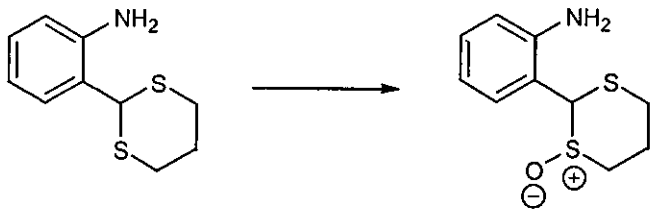
See above 2-(2-Bromophenyl)-1,3-dithiane (1 52 g, 5 51 mmol) and 8,8-(dimethoxycamphor)sulfonyl oxaziridine (' 75 g, 6 05 mmol, 1 1 eq) to yield 1.45 g of the titled compound as a colourless crystalline solid (90%, 56 % ee) m p 154-156°C IR ν_{max} cm^{-1} 3055, 1471, 1422, 1269, 1030 (S-O), 753, 669 δ_H ($CDCl_3$, 250 MHz) 2 52 (3H, m), 2 93 (2H, m), 3 62 (1H, dm, *J* 13 Hz), 5 28 (1H, s), 7 21 (1H, ddd, J 1 7, 7 4, 8 Hz), 7 39 (1H, ddd, *J* 1 3, 7.5, 7 5 Hz), 7 53 (1H, dd, *J* 1 7, 7.5 Hz), 7 64 (1H, dd, *J* 1 3, 8 Hz) δ_C ($CDCl_3$, 62 MHz) 29 78 (CH_2), 31 72 (CH_2), 54 85 (CH_2), 67 87 (CH), 125 53 (C ar), 128 36 (CH ar.), 129 27 (CH ar), 130 35 (CH ar), 133 07 (C ar) 133 46 (CH ar) $[\alpha]_D^{20}$= 66° (c=0 992, $CHCl_3$) Elemental analysis· found C, 41 10, H, 3 75, $C_{10}H_{11}BrOS_2$ requires C, 41 24, H, 3 81, Br, 27 44, O, 5 49, S, 22 02

2-(2-Nitrophenyl)-1,3-dithiane-1-oxide (98):[6]



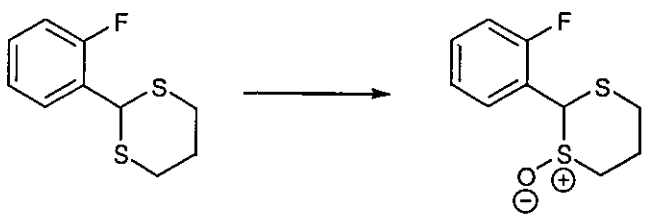
See above 2-(2-Nitrophenyl)-1,3-dithiane (1 29 g, 5 35 mmol) and 8,8-dimethoxycamphor)sulfonyl oxaziridine (1 70 g, 5 89 mmol, 1 1 eq), 1 24 g of the titled compound as a orange crystalline solid (90 %, 72 % ee) m p 161-163°C IR ν_{max} cm^{-1} 3068, 2905, 1520, 1426, 1349, 1037 (S-O), 781, 752, 712 δ_H ($CDCl_3$, 250 MHz), 2 70 (5H, m), 3 60 (1H, dm, *J* 13 Hz), 5 68 (1H, s), 7 53 (1H, m), 7 70 (2H, m), 8 03 (1H, dm, *J* 8 Hz) δ_C ($CDCl_3$, 62 MHz) 29 74 (CH_2), 31 60 (CH_2), 55 00 (CH_2), 63 54 (CH), 125 46 (CH ar), 128 37 (C ar), 129 69 (CH ar), 129 78 (CH ar), 133 85 (CH ar), 149.54 (C ar) $[\alpha]_D^{20}$= -80° (c=1 002, $CHCl_3$) Exact mass calcd for $C_{10}H_{11}NO_3S_2$ 257 01804, found 257 01807. Elemental analysis: found C, 46 76, H, 4 23, N, 5 37, $C_{10}H_{11}NO_3S_2$ requires C, 46 68, H, 4 31, N, 5 44, O, 18 65, S, 24 92

2-(2-Aminophenyl)-1,3-dithiane-1-oxide (99):



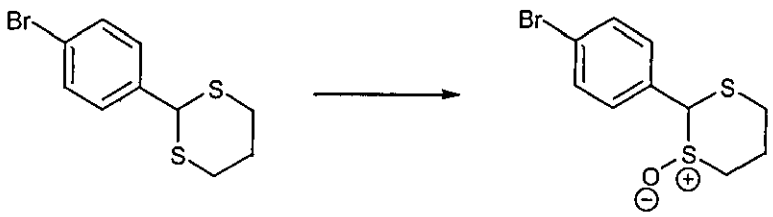
See above 2-(2-Aminophenyl)-1,3-dithiane (500 mg, 2 37 mmol) and 8,8-dimethoxycamphor)sulfonyl oxaziridine (752 mg, 2 60 mmol, 1 1 eq), 531.1 mg of the titled compound as a orange-red crystalline solid (98 %, 92 % ee, 99 % ee after recrystallisation) m p 143-144°C IR ν_{max} cm^{-1} 3436, 3347, 3237, 1646, 1026, 752 δ_H (250 MHz, $CDCl_3$), 2 22-2 43 (1H, m), 2.46-2 59 (1H, m), 2 66-2 77 (1H, m), 2 78-2 94 (2H, m), 3 54-3 65 (1H, m), 3 70-4 30 (2H, broad, NH_2), 5 07 (1H, s), 6 73-6 79 (1H, dd, *J* 7 9, 1 Hz), 6 81-6 89 (1H, ddd, *J* 7 7, 7 5, 1 Hz), 7 11-7 18 (1H, ddd, *J* 7 9, 7 5, 1 5 Hz), 7 19-7 24 (1H, dd, *J* 7 7, 1 5 Hz) δ_C (100 MHz, $CDCl_3$) 29 57 (CH_2), 31 13 (CH_2), 55 13 (CH_2), 63 85 (CH), 117 71 (CH ar), 119 77 (CH ar), 120 09 (CH ar), 128 04 (CH ar), 129 70 (CH ar), 146 67 (CH ar) $[\alpha]_D^{20}$= -171° (c=1.014, $CHCl_3$) Exact mass calcd for $C_{10}H_{13}NOS_2$ 227 04386, found 227 04410 Elemental analysis found C, 52 76, H, 5.73; N, 5 93, $C_{10}H_{13}NOS_2$ required C, 52 83, H, 5 76, N, 6 16, O, 7 04, S, 28.20

2-(2-Fluorophenyl)-1,3-dithiane-1-oxide (100):



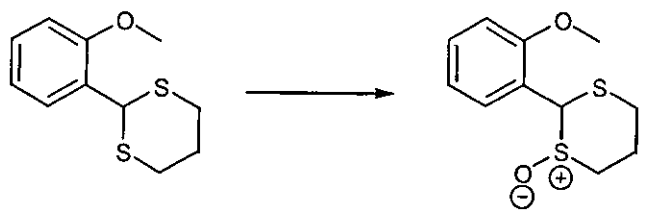
See above 2-(2-Fluorophenyl)-1,3-dithiane (500 mg, 2 33 mmol) and 8,8-dimethoxycamphor)sulfonyl oxazirıdine (741 mg, 2 56 mmol, 1.1 eq), 448 6 mg of the titled compound as a colourless crystalline solid (83 %, 72 % ee) m p 145-146°C IR ν_{max} cm^{-1} 3054, 2912, 1585, 1490, 1233, 1040 (S-O), 759 δ_H ($CDCl_3$, 250 MHz), 2 54 (3H, m), 2 89 (2H, m), 3 60 (1H, dm, *J* 12 7 Hz), 5 03 (1H, s), 7 11 (1H, ddd, *J* 1 3, 8 2, 9 6 Hz), 7 21 (1H, ddd, *J* 1 3, 7 5, 7.5 Hz), 7 35 (1H, m), 7 46 (1H, ddd, *J* 1 9, 7 5, 7 5 Hz) δ_C ($CDCl_3$, 100 MHz) 29 64 (CH_2), 31 48 (CH_2), 54 85 (CH_2), 61 64 (CH), 115 97 (CH ar , *J* 21 66 Hz), 120 88 (C ar , *J* 14 27 Hz), 124 96 (CH ar , *J* 3 91 Hz), 129 08 (CH ar , *J* 2 46 Hz), 130 75 (CH ar., *J* 8 36 Hz), 160 78 (CF ar , *J* 249 56 Hz) $[\alpha]_D^{20}$= 113° (c=1 008, $CHCl_3$) Exact mass calcd for $C_{10}H_{11}FOS_2$ 230 02354; found 230 02307 Elemental analysis found C, 51 96, H, 4 74, $C_{10}H_{11}FOS_2$ required C, 52.15, H, 4 81, F, 8 25, O, 6 95, S, 27 84.

2(-4-Bromophenyl)-1,3-dithiane-1-oxide (101):



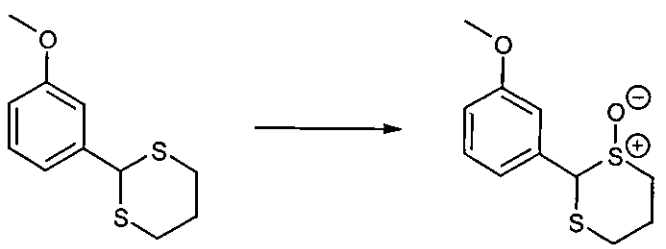
See above 2-(4-Bromophenyl)-1,3-dithiane (199 4 mg, 0 724 mmol) and 8,8-dimethoxycamphor)sulfonyl oxazirıdine (230 mg, 0 796 mmol, 1 1 eq), 218 9 mg of the titled compound as a colourless crystalline solid (99 %, 96 % ee) m p 181-183°C IR ν_{max} cm^{-1} 2908, 1487, 1426, 1402, 1270, 1072, 1040, 1010, 852, 823, 762 δ_H($CDCl_3$, 400 MHz) 2 36 (1H, m), 2 53 (1H, m), 2 72 (2H, m), 2 88 (1H, ddd, *J* 2 8, 12 4, 14 4 Hz), 3 56 (1H, dm, *J* 12 8 Hz), 4 51 (1H, s), 7 29 (2H, d, *J* 8 8 Hz), 7 53 (2H, d, *J* 8 8 Hz) δ_C ($CDCl_3$, 100 MHz) 29 78 (CH_2), 31 69 (CH_2S), 55 10 ($CH_2S(O)$), 69 35 (CH), 123 88 (C ar), 130 57 (CH ar), 132 53 (CH ar), 132 63 (C ar) $[\alpha]_D^{20}$= 115° (c=1 064, $CHCl_3$) Elemental analysis· found C, 41 23, H, 3.78, $C_{10}H_{11}BrOS_2$ requires C, 41 24, H, 3 81, Bi, 27 44, O, 5 49, S, 22 02

2(-2-Methoxyphenyl)-1,3-dithiane-1-oxide (102):



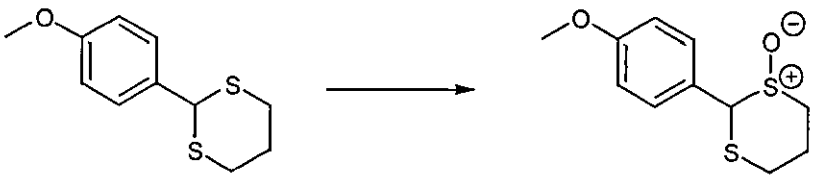
See above· 2-(2-methoxyphenyl)-1,3-d'thıane (199 3 mg, 0 882 mmol) and 8,8-dımethoxycamphor)sulfonyl oxazırıdıne (230 mg, 0 969 mmol, 1.1 eq), 207 9 mg of the tıtled compound as a colourless crystallıne solıd (97 %, 84 % ee) m p 170-172°C IR ν_{max} cm^{-1} 3029, 2998, 1596, 1492, 1462, 1428, 1311, 1289, 1246, 1098, 1023, 763 δ_H ($CDCl_3$, 400 MHz) 2 31 (1H, m), 2 47 (1H, dm, *J* 15 2 Hz), 2 58 (1H, dm, *J* 12 4 Hz), 2 78 (1H, dt, *J* 3.2, 13 2 Hz), 2 87 (1H, ddd, *J* 2 8, 12 4, 14 4 Hz), 3 52 (1H, dm, *J* 12 8 Hz), 3 85 (3H, s), 5 26 (1H, s), 6 91 (1H, d, *J* 8 4 Hz), 6 99 (1H, dt, *J* 0 8, 7 2 Hz), 7 28 (1H, dm, *J* 1 6 Hz), 7 41 (1H, dd, *J* 1 6, 7 6 Hz) δ_C ($CDCl_3$, 100 MHz) 29 51 (CH_2), 31 44 (CH_2), 54 61 (CH_2), 55 68 (CH_3), 61 64 (CH), 111 18 (CH ar), 121 04 (CH ar), 121 74 (C ar), 128 61 (CH ar), 130 02 (CH ar), 157 47 (C ar) $[\alpha]_D^{20}$= 113° (c=1 048, $CHCl_3$) Exact mass calcd for $C_{11}H_{14}O_2S_2$ 242 04352, found 242 04340 Elemental analysıs found C, 54 54; H, 5 75, $C_{11}H_{14}O_2S_2$ requıres C, 54 52, H, 5 82, O, 13.20, S, 26 46

2(-3-Methoxyphenyl)-1,3-dıthiane-1-oxide (103):



See above 2-(3-methoxyphenyl)-1,3-dithiane (201 mg, 0 889 mmol) and 8,8-dimethoxycamphor)sulfonyl oxaziridine (283 mg, 0 979 mmol, 1 1 eq), 181 7 mg of the titled compound as a colourless crystalline solid (84 %, 96 % ee) m p 150-152°C IR ν_{max} cm^{-1} 3031, 2987, 1598, 1490, 1270, 1151, 1037 δ_H ($CDCl_3$, 400 MHz) 2 31 (1H, tm, *J* 3 2 Hz), 2 46 (1H, dm, *J* 15 2 Hz), 2 62 (1H, ddd, *J* 1 2, 3 6, 14 Hz), 2 73 (1H, dt, *J* 2 8, 13 2), 2 83 (1H, ddd, *J* 2.4, 12, 14 Hz), 3 52 (1H, dm, *J* 12 8 Hz), 3.79 (3H, s), 4 53 (1H, s), 6 89 (1H, ddd, *J* 1 2, 2 8, 8 4 Hz), 6 95 (1H, dd, *J* 2, 2 4 Hz), 7 01 (1H, dm, *J* 7 6 Hz), 7 29 (1H, t, *J* 8 Hz) δ_C ($CDCl_3$, 100 MHz) 29 93 (CH_2), 31 82 (CH_2), 55 19 (CH_2), 55 71 (CH_3), 70 06 (CH), 114 55 (CH ar.), 115.57 (CH ar), 121 49 (CH ar), 130 58 (CH ar), 135 24 (C ar), 160 42 (C ar) $[\alpha]_D^{20}$= 125° (c=1 058, $CHCl_3$) Exact mass calcd for $C_{11}H_{14}O_2S_2$ 242 04352, found 242 04351 Elemental analysis found C, 54 49, H, 5 75, $C_{11}H_{14}O_2S_2$ requires C, 54 52, H, 5 82, O, 13 20, S, 26 46

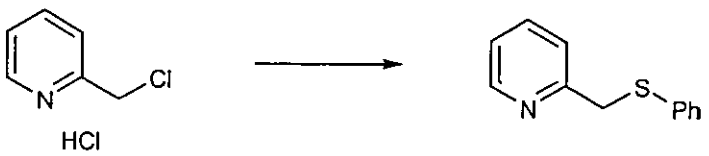
2(-4-Methoxyphenyl)-1,3-dithiane-1-oxide (104):[7]



See above 2-(4-methoxyphenyl)-1,3-dithiane (202 mg, 0 894 mmol) and 8,8-dimethoxycamphor)sulfonyl oxaziridine (284 mg, 0 983 mmol, 1 1 eq), 205 1 mg of the titled compound as a colourless crystalline solid (95 %, >99 % ee) m p 183-184°C (Lit 166°C) IR ν_{max} cm^{-1} 3028, 2908, 2838, 1609, 1512, 1460, 1442, 1304, 1258, 1177, 1108, 1025, 847, 757 δ_H ($CDCl_3$, 400 MHz) 2 34 (1H, tm, *J* 2 4 Hz), 2 50 (1H, dm, *J* 14 8 Hz), 2 69 (2H, m), 2 86 (1H, ddd, *J* 2 4, 12 8, 14 4 Hz), 3 64 (1H, dm, *J* 12 8 Hz), 3 79 (3H, s), 4 50 (1H, s), 6 91 (2H, d, *J* 8 6 Hz), 7 33 (2H, d, *J* 8 6 Hz) δ_C ($CDCl_3$, 100 MHz) 29 48 (CH_2), 31 48 (CH_2), 54.71 (CH_2), 55 25 (CH_3), 69 10 (CH), 114 54 (CH ar.), 125 19 (C ar), 129 87 (CH ar), 160 32 (C ar) $[\alpha]_D^{20}$= 142° (c=0 990, $CHCl_3$) Exact mass calcd for $C_{11}H_{14}O_2S_2$ 242 04352, found 242.04340.

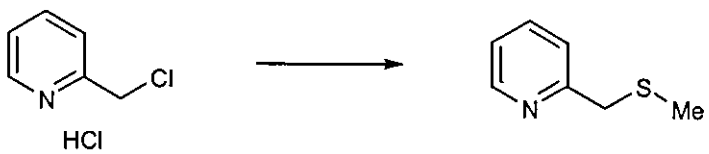
Elemental analysis found C, 54 44, H, 5 77, $C_{11}H_{14}O_2S_2$ requires C, 54 52, H, 5 82, O, 13 20, S, 26 46

2-[(Phenylthio)methyl]pyridine (107):[8]



To a solution of 2-(chloromethyl)pyridine hydrochloride (3 00 g, 18 3 mmol) in water was added neat thiophenol (2 4 g, 21 8 mmol, 1 2 eq) followed by 22 ml of a 3 M sodium hydroxide solution The reaction was left under stirring overnight at room temperature, then the reaction mixture was extracted with dichloromethane (3x100 ml). The combined organic layers were dried over magnesium sulfate and the solvent was removed and the crude product was purified by column chromatography over silica gel to yield the titled compound as a yellow oil (3 75 g, 61 %) IR ν_{max} cm^{-1} 3030, 1571 δ_H ($CDCl_3$, 250 MHz) 4 27 (2H, s, CH_2), 7.10-7 36 (7H, m, Ar and Pyr), 7 60 (1H, td, *J* 7 6, 2 3 Hz), 8 52-8 56 (1H, m)

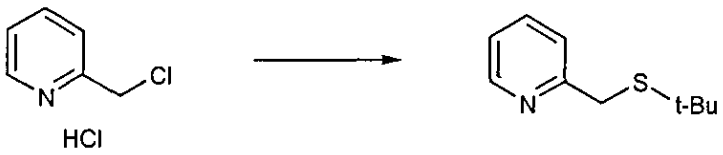
2-[(Methylthio)methyl]pyridine (108):[8]



To a solution of 2-(chloromethyl)pyridine hydrochloride (3 00 g, 18 3 mmol) in ethanol (50 ml) was added thiourea (1 39 g, 18 3 mmol) and the reaction mixture was refluxed for 1 5 hour. After cooling down the solution the solid was filtered and treated with a 3 M aqueous solution of sodium hydroxide The mixture was heated to 60 °C for 20 minutes then after cooling, a solution of iodomethane in dichloromethane was added The reaction was left overnight at room

temperature The reaction mixture was extracted with dichloromethane, the combined organic layers were dried over magnesium sulfate and the solvent was removed and the crude product was purified by column chromatography over silica gel to yield the titled compound as a light yellow oil (1 42 g, 56 %) IR ν_{max} cm^{-1} 30270, 1569 δ_H ($CDCl_3$, 250 MHz) 2 07 (3H, s, CH_3), 3 81 (2H, s, CH_2), 7.17 (1H, ddd, *J* 7 5, 4 9, 1 1 Hz), 7 37 (1H, dt, 8 8, 1 Hz), 7.66 (1H, td, *J* 7 6, 1 8 Hz), 8 54 (1H, m)

2-[(1,1-Dimethylethyl)thio]methylpyridine (109):[8]



To a solution of 2-(chloromethyl)pyridine hydrochloride (3 00 g, 18 3 mmol) in water was added sodium 2-methyl-propane-2-thiolate (2 05 g, 18 3 mmol, 1 0 eq) followed by 50 ml of a 3 M sodium hydroxide solution The reaction was left under stirring overnight at room temperature, then the reaction mixture was extracted with dichloromethane (3x100 ml) The combined organic layers were dried over magnesium sulfate and the solvent was removed and the crude product was purified by column chromatography over silica gel to yield the titled compound as a yellow oil (1 92 g, 58 %) IR ν_{max} cm^{-1} 3033, 1578 δ_H ($CDCl_3$, 250 MHz) 1.34 (9H, s, *t*-Bu), 3 93 (2H, s, CH_2), 7 13 (1H, ddd, *J* 7.5, 5, 1 1), 7 42 (1H, dt, *J* 7 9, 1 1 Hz), 7 63 (1H, td, *J* 7 7, 1 9 Hz), 8 52 (1H, ddd, *J* 5, 1 9, 1 Hz)

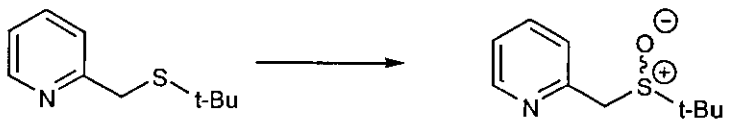
2-[(Phenylsulfinyl)methyl]pyridine (110):

To a solution of sulfide (519 3 mg, 2 58 mmol) in dichloromethane (20 ml) at -20°C, was added 8,8-(dimethoxycamphor)sulfonyl oxaziridine (0 750 mg, 2 59 mmol, 1 05 eq) The reaction was left to stir at -20°C for 48 hours, then a saturated solution of sodium sulfite was added to quench the reaction Brine and dichloromethane were added and the phases separated The aqueous layer was washed twice with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure The crude product was purified by flash column chromatography over silica gel to yield the titled compound as a thick oil (0 440 mg 78 %) IR ν_{max} cm^{-1} 3035, 1572, 1051. δ_H ($CDCl_3$, 250 MHz) 4.17 (1H, d, *J* 12 6 Hz), 4 24 (1H,d, *J* 12 6 Hz), 7 16-7 26 (2H, m), 7 44-7 55 (5H, m), 7 64 (1H, td, *J* 7 7, 1 8 Hz), 8 54 (1H, ddd, *J* 4 8, 1 8, 1 Hz)

2-[(Methylsulfinyl)methyl]pyridine (111):

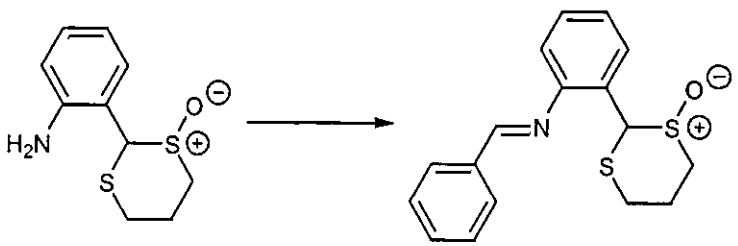
To a solution of sulfide (510 mg, 3 67 mmol) in dichloromethane (20 ml) at -20°C, was added 8,8-(dimethoxycamphor)sulfonyl oxaziridine (1 100 g, 3 81 mmol, 1.1 eq) The reaction was left to stir at -20°C for 48 hours, then a saturated solution of sodium sulfite was added to quench the reaction Brine and dichloromethane were added and the phases separated The aqueous layer was washed twice with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure The crude product was purified by flash column chromatography over silica gel to yield the titled compound as a thick oil (0 280 mg 49 %) IR ν_{max} cm^{-1} 3032, 1567, 1042 δ_H ($CDCl_3$, 250 MHz) 2 58 (3H, s, Me), 4.12 (1H, d, *J* 12 7 Hz), 4 20 (1H, d, *J* 12 7 Hz), 7 29 (1H, ddd, *J* 7 7, 5, 1.3 Hz), 7 38 (1H, dt, *J* 7 9, 1 2 Hz), 7 73 (1H, td, *J* 7 6, 1 8 Hz), 8 62 (1H, ddd, *J* 4 9, 1 7, 1Hz)

2-[(1,1-Dimethylethyl)sulfinyl]methylpyridine (112):



To a solution of sulfide (880 8 mg, 4 86 mmol) in dichloromethane (20 ml) at -20°C, was added 8,8-(dimethoxycamphor)sulfonyl oxaziridine (1 550 g, 5.36 mmol, 1 1 eq) The reaction was left to stir at -20°C for 48 hours, then a saturated solution of sodium sulfite was added to quench the reaction Brine and dichloromethane were added and the phases separated The aqueous layer was washed twice with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure The crude product was purified by flash column chromatography over silica gel to yield the titled compound as a thick oil (852 5 mg 89 %) IR ν_{max} cm^{-1} 3029, 1578, 1062 δ_H ($CDCl_3$, 250 MHz) 1 34 (9H, s, t-Bu), 3 78 (1H, d, *J* 12 6 Hz), 4 07 (1H,d, *J* 12 6 Hz), 7 25 (1H, ddd, *J* 7 6, 4 9, 1 2 Hz), 7 43 (1H, d, *J* 7 8 Hz), 7 69 (1H, td, *J* 7 6, 1 8 Hz), 8 58-8 63 (1H, m)

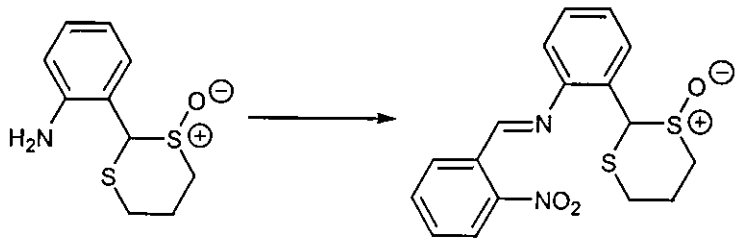
2-(2-[(E)-1-Phenylmethylidene]aminophenyl-1,3-dithiane-1-oxide (122):



A solution of 2-(2-Aminophenyl)-1,3-dithiane-1-oxide (331 4 mg, 1 46 mmol), benzaldehyde (154 6 mg, 1 46 mmol) and magnesium sulfate in dichloromethane was stirred for 48 hours at room temperature The reaction mixture was filtered and the solvent was removed The crude product was purified by column chromatography over neutral alumina to yield 329 4 mg of the titled compound (71 %) as a colourless oil IR ν_{max} cm^{-1} 3058, 2980, 2908, 1732, 1700, 1629, 1041, 766, 734, 693 δ_H ($CDCl_3$, 250 MHz) 2 50 (3H, m), 2 84 (2H, m), 3 55 (1H, dm, *J* 12 6

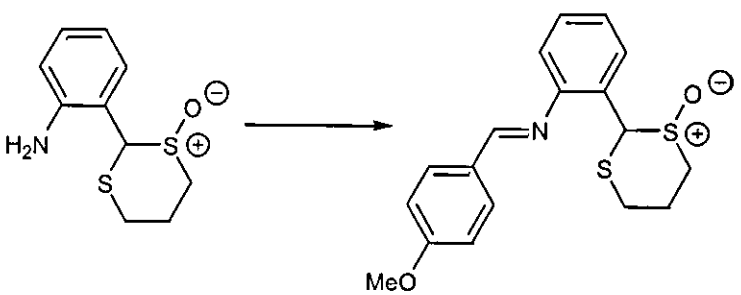
Hz), 5 43 (1H, s), 7 05 (1H, dd, *J* 1 6, 7 5 Hz), 7 33 (2H, m), 7 50 (4H, m), 7.94 (2H, m), 8 46 (1H, s) δ_C ($CDCl_3$, 62 MHz) 30 01, 31 89, 55 02, 64 80, 116 12, 120 34, 121 03, 127 88, 128 48, 128 65, 129 98, 139 90, 146 67, 161.75 $[\alpha]_D^{20}$= + 80 ° (c= 1 002, $CHCl_3$)

2-(-2[(E)-1-(2-Nitrophenyl)methylidene]aminophenyl)-1,3-dithiane-1-oxide (123):



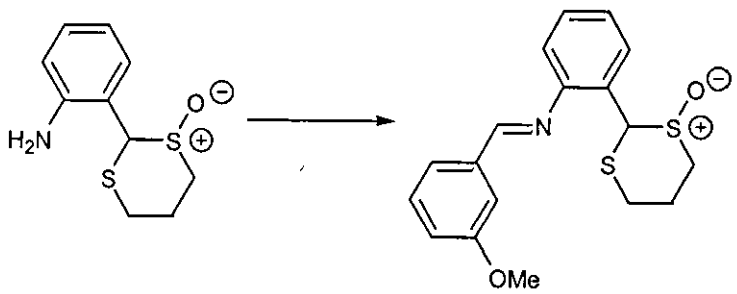
See above 2-(2-Aminophenyl)-1,3-dithiane-1-oxide (200 2 mg, 0 88 mmol), 4-nitrobenzaldehyde (133 1 mg, 0 88 mmol), magnesium sulfate to yield 140 4 mg of the titled compound (50 %) as an orange oil IR ν_{max} cm^{-1} 3060, 3023, 2986, 1693, 1548, 1335, 1046, 965, 743, 700 δ_H ($CDCl_3$, 250 MHz) 2 50 (3H, m), 2 91 (2H, m), 3 57 (1H, dm, *J* 12 6 Hz), 5 46 (1H, s), 7 20 (1H, dd, *J* 1 7, 7 8 Hz), 7 38 (2H, m), 7 54 (1H, dd, *J* 1 6, 7 4 Hz), 7 64 (1H, dt, *J* 1 6, 8 1 Hz), 7 75 (1H, dt, *J* 1 4, 7 6 Hz), 8 01 (1H, dd, *J* 1 3, 8 0 Hz), 8 27 (1H, dd, *J* 1 5, 7 7 Hz), 8 90 (1H, s) δ_C ($CDCl_3$, 100 MHz) 29 86, 31 65, 53 44, 54 97, 118 67, 124 42, 127 80, 128 26, 128 60, 130 19, 130 48, 130 73, 131 34, 133 25, 149 28, 150 06, 156 80 $[\alpha]_D^{20}$= + 117 ° (c= 0 99, $CHCl_3$)

2-[2-((E)-1-[4-(Methyloxy)phenyl]methylideneamino)phenyl]-1,3-dithiane-1-oxide (126):



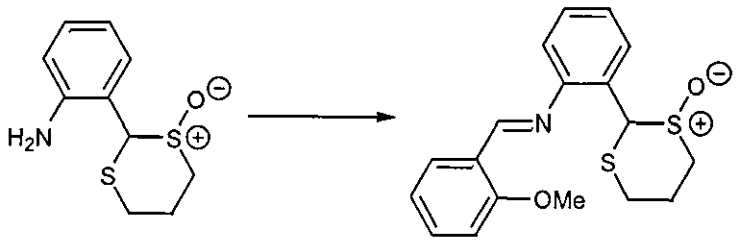
See above 2-(2-Aminophenyl)-1,3-dithiane-1-oxide (250 mg, 1 10 mmol), p-anisaldehyde (150 mg, 1 10 mmol) to yield 130 4 mg of the titled compound (34 %) as a colourless oil IR ν_{max} cm^{-1} 3059, 3026, 2996, 1699, 1568, 1345, 1035 760, 699 δ_H ($CDCl_3$, 400 MHz) 2 33 (1H, m), 2 50 (1H, m), 2 60 (1H, m), 2 75 (2H, m), 3 50 (1H, dm, *J* 12 4 Hz), 5 43 (1H, s), 7 00 (3H, m), 7 26 (1H, m), 7 33 (1H, m), 7 49 (1H, d, *J* 8 Hz), 7 89 (2H, d, *J* 8 Hz), 8 37 (1H, s) δ_C ($CDCl_3$, 100 MHz) 29 90, 31 79, 54 93, 55 46, 64 24, 114 17, 118 68, 126 30, 127 33, 128 35, 129 35, 130 01, 130 69, 151 60, 160 69, 162 45 $[\alpha]_D^{20}$= + 70° (c= 0 974, $CHCl_3$)

2-[2-((E)-1-[3-(Methyloxy)phenyl]methylideneamino)phenyl]-1,3-dithiane-1-oxide (125):



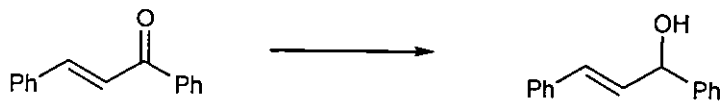
See above 2-(2-Aminophenyl)-1,3-dithiane-1-oxide (250 mg, 1 10 mmol), m-anisaldehyde (150 mg, 1 10 mmol) to yield 191 8 mg of the titled compound (50 %) as a colourless oil IR ν_{max} cm^{-1} 3025, 2983, 2896, 1690, 1340, 1042, 966, 700 δ_H ($CDCl_3$, 400 MHz) 2 30 (1H, m), 2 45 (1H, m), 2 58 (1H, dm, *J* 14 Hz), 2 72 (1H, dt, *J* 2 8, 13 2 Hz), 2 82 (1H, ddd, *J* 2 8, 12 4, 14 8 Hz), 3 50 (1H, d, m, *J* 12 4 Hz), 3 86 (3H, s, OMe), 5 38 (1H, s), 7 04 (2H, m), 7 27 (1H, m), 7 34 (2H, m), 7 48 (3H, m), 8 40 (1H, s) δ_C ($CDCl_3$, 100 MHz) 14 19, 29 85, 31 73, 54 98, 55 43, 112 99, 117 92, 118 61, 121 41, 126 65, 127 45, 128 42, 129 74, 130 00, 137 61, 151 22, 159 94, 161 36 $[\alpha]_D^{20}$= + 72° (c= 0 488, $CHCl_3$)

2-[2-((E)-1-[2-(Methyloxy)phenyl]methylideneamino)phenyl]-1,3-dithiane-1-oxide (124):



See above 2-(2-Aminophenyl)-1,3-dithiane-1-oxide (250 mg, 1 10 mmol), o-anisaldehyde (150 mg, 1 10 mmol) to yield 202 8 mg of the titled compound (53 %) as a colourless oil IR ν_{max} cm^{-1} 3060, 2993, 1694, 1598, 1039, 753, 700 δ_H ($CDCl_3$, 400 MHz) 2 48 (3H, m), 2.81 (2H, m), 3 54 (1H, dm, *J* 12 7 Hz), 3 87 (3H, s, OMe), 5 48 (1H, s), 6 94 (1H, d, *J* 8 4 Hz), 7 06 (2H, m), 7 40 (4H, m), 8 23 (1H, dd, *J* 1 7, 7.7 Hz), 8 91 (1H, s) δ_C ($CDCl_3$, 62 MHz) 30 20, 32 08, 55 19, 55 86, 64 50, 111 47, 119 12, 121 00, 125 01, 126 72, 127 91, 128 12, 128 52, 130 26, 133.20, 152 09, 157 40, 159 97 $[\alpha]_D^{20}$= + 83° (c= 0 998, $CHCl_3$)

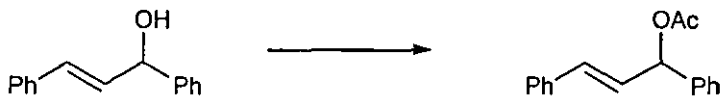
(E)-1,3-Diphenyl-3-hydroxy-prop-1-ene (157):[9]



To a stirred solution of chalcone (5 00 g, 24 00 mmol) and cerium chloride heptahydrate (9 90 g, 26 60 mmol, 1 1 eq) in methanol (50 ml), at 0 °C, was added sodium borohydride (1 00 g, 26 60 mmol, 1 1 eq) The reaction mixture was allowed to reach the room temperature and left under stirring for 3 hours The solvent was removed and the resulting gum was extracted with dichloromethane (three times) The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield an oily solid which was recrystallised from hexane to yield 4 80 g of the titled compound (95 %) as a white wool m p 52-54 °C (Lit 55-56°C) IR ν_{max} cm^{-1} 3350, 3027, 1494, 1450, 966 δ_H ($CDCl_3$, 400 MHz) 2 60 (1H, br s), 5 39 (1H, d, *J* 6 4 Hz),

6 39 (1H, dd, *J* 6 4, 15 8 Hz), 6 70 (1H, d, *J* 15 8 Hz), 7 35 (10H, m, Ar). δ_C ($CDCl_3$, 100 MHz) 78 60, 125 80, 126 10, 126 60, 127 20, 128 00, 129 80, 130 90, 136 10, 140 80, 141 00 Elemental analysis found C, 85 59, H, 6 73, $C_{15}H_{14}O$ requires C, 85 68, H, 6 71, O, 7 61

1,3-Diphenylprop-2-en-1-yl acetate (158):[10]



To a solution of alcohol (0 500 g, 2 38 mmol) in dichloromethane was added pyridine (0 40 ml, 4 76 mmol, 2 eq), followed by a catalytic amount of 4-dimethylamino-pyridine and acetic anhydride (0 27 ml, 2 88 mmol, 1 2 eq) The reaction was monitored by TLC (petroleum ether-diethyl ether, 2·1) until completion The reaction mixture was concentrated, taken in diethyl ether and washed with an aqueous solution of copper (II) sulfate (three times), and a saturated solution of sodium carbonate (twice) The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to yield the titled compound quantitatively as a colourless oil IR ν_{max} cm^{-1} 3030, 1737, 1495, 1370, 1236 δ_H ($CDCl_3$, 250 MHz) 2 13 (3H, s), 6 34 (1H, dd, *J* 7, 16 Hz), 6 45 (1H, d, *J* 7 Hz), 6 63 (1H, d, *J* 16 Hz), 7 30 (10H, m, Ar) δ_C ($CDCl_3$, 62 MHz) 21 31, 76 16, 126 8, 127 1, 127 6, 127 9, 128 1, 128 2, 128 5, 128 6, 128 8, 132 6, 136 2, 139 3, 170

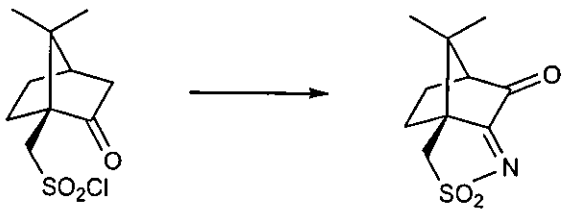
Palladium-catalysed allylic nucleophilic substitution reaction: 1,3-Diphenyl-1-(2-dimethylmalonyl)prop-2-ene:[11]

General procedure for the allylic nucleophilic substitution palladium-catalysed reaction ·

To a solution of allyl chloride palladium dimer (5 mg, 0 0137 mmol, 5 mol%) in dichloromethane (0 5 ml) was added an enantiomerically pure ligand (0 0273 mmol, 10 mol%) and the reaction

was left under stirring at room temperature for 15 minutes Then a solution of allyl acetate substrate (140 mg, 0 555 mmol) in dichloromethane (1 ml) was added The reaction was left for another 15 minutes Then a solution of dimethyl malonate (147 mg, 1 111 mmol, 2 eq) in dichloromethane (2 ml) was added followed by caesium carbonate (362 mg, 1 111 mmol, 2 eq) and the reaction was monitored for the first 2 hours. In the case of no total consumption of the allyl acetate substrate, the reaction was left under stirring for 24/48 hours. Then water was added and the phases were separated The aqueous layer was washed twice with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to yield the crude product which was purified by column chromatography over silica-gel with petroleum ether-ethyl acetate (95 5) to yield the titled compound as a colourless solid m p 120-122 °C IR ν_{max} cm^{-1} 3031, 2955, 1755, 1436 δ_H ($CDCl_3$, 250 MHz), 3 51 (3H, s, Me), 3 70 (3H, s, Me), 3 92 (1H, d, *J* 11 Hz), 4 22 (1H, dd, *J* 8, 11 Hz), 6 27 (1H, dd, *J* 8, 15 Hz), 6 44 (1H, d, *J* 15 Hz), 7 25 (10H, m, Ar) δ_C ($CDCl_3$, 62 MHz) 49 09, 52 30, 52 47, 57 53, 126 2, 127 0, 127 4, 127 7, 128 3, 128 5, 129 0, 131.7, 136 6, 140 0, 167 6, 168 0, Elemental analysis· found C, 73 94, H, 6 21, $C_{20}H_{20}O_4$ requires C, 74 06, H, 6 21, O, 19 73

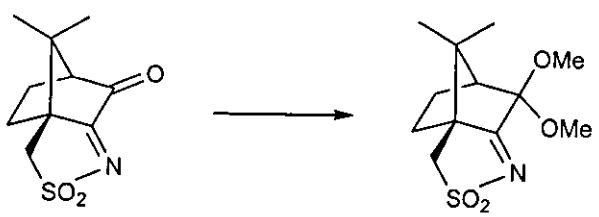
(-)-(Oxocamphorsulfonyl)imine (73):[12]



Reagent grade ammonium hydroxide (360 ml) was cooled to 0 °C A solution of (+)-10-camphorsulfonyl chloride (40 0 g, 159 mmol) in dichloromethane (400 ml) was added dropwise, over thirty minutes, to the rapidly stirring ammonium hydroxide solution using a pressure equalised dropping funnel The reaction mixture was left stirring at 0 °C for a further 2 hours, transferred to a separating funnel and the phases were separated and the aqueous layer washed twice with dichloromethane The combined organic layers were dried over magnesium sulfate,

filtered and concentrated *in vacuo* to yield the crude (+)-(1S)-10-camphorsulfonamide The (+)-(1S)-10-camphorsulfonamide was sufficiently pure to use for the subsequent preparation of (-)-(oxocamphorsulfonyl)imine The crude (+)-(1S)-10-camphorsulfonamide (11 5 g, 53 7 mmol) was added to a 1 litre flask containing selenium dioxide (8 50 g, 77 0 mmol, 1 4 eq), and acetic acid (400 ml) The reaction was heated under reflux for 20 hours, after which time, precipitated selenium was removed by filtration Water (500 ml) and dichloromethane (250 ml) were added to the filtrate The layers were separated and the aqueous layer was washed with dichloromethane (twice 250 ml) The combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed to yield the crude product which was recrystallised from chloroform to furnish 10 65 g of the titled compound (87 %) as a pale yellow crystals. m p. 196-198°C (Lit 190-191°C) IR ν_{max} cm^{-1} 1758, 1653, 1339, 1173, 1164 δ_H ($CDCl_3$, 400 MHz) 0 99 (3H, s, Me), 1 17 (3H, s, Me), 1 95 (2H, m), 2 30 (2H, m), 2 75 (1H, *J* 5 Hz), 3 22 (1H, d, *J* 14 Hz), 3 45 (1H, d, *J* 14 Hz) δ_C ($CDCl_3$, 100 MHz) 18 35, 20 14, 22 26, 27 95, 44 63, 50 05, 59 03, 62 75, 181 5, 197.7 $[\alpha]_D^{20}$= - 179° (c=1 000, $CHCl_3$)

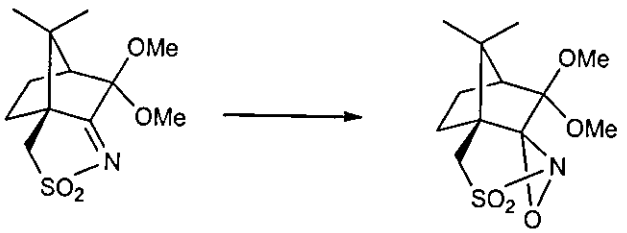
(+)-[(8,8-Dimethyloxycamphoryl)sulfonyl]imine (25):[13]



A solution of (-)-oxocamphorsulfonyl imine (2 27 g, 10 0 mmol) and Amberlyst® 15 ion exchange resin (0 500 g) in trimethyl orthoformate (25 0 ml), methanol (5 0 ml) and concentrated sulfuric acid (0 500 ml) were heated to reflux overnight The cooled solution was filtered, water added (20 ml) and the mixture extracted with dichloromethane (3x30 ml) The combined organic layers were washed with water (30 ml), dried over magnesium sulfate, filtered and the solvent was removed to yield the crude product which was recrystallised in absolute ethanol to yield 2 35 g of the titled compound (95 %) as a white solid m p 189-190 (Lit 186-187°C) °C IR ν_{max} cm^{-1}

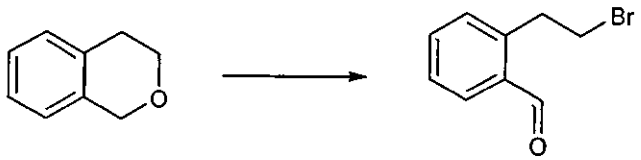
(nujol) 1653, 1332, 1161 δ_H ($CDCl_3$, 400 MHz) 1 00 (3H, s, Me), 1 09 (3H, s, Me), 2 10 (5H, m), 2 97 (1H, d, *J* 12 0 Hz), 3.16 (1H, d, *J* 12 0 Hz), 3 36 (3H, s, OMe), 3 47 (3H, s, OMe) δ_C ($CDCl_3$, 100 MHz) 20 46, 20 53, 20 63, 29 25, 46 01, 48 89, 50 33, 50 55, 52 07, 64 27, 103 00, 188 73 $[\alpha]_D^{20}$= - 111° (c=1 000, $CHCl_3$) (Lit –7 3°, c=3 4g/100ml, $CHCl_3$ and 4°, c=1g/100ml, acetone)

(+)-[(8,8-Dimethyloxycamphoryl)sulfonyl]oxaziridine (26):[14]



Potassium carbonate (2 00 g, 14 5 mmol) was rapidly stirred in a solution of methanol (20 ml) at room temperature Commercial hydrogen peroxide (3 32 ml, 29 3 mmol, 4 0 eq) was added followed by (+)-[(8,8-dimethyloxycamphoryl)sulfonyl]imine (2 00 g, 7 32 mmol) The reaction mixture was stirred overnight and partitioned between saturated brine solution (50 ml) and dichloromethane (100 ml) The organic layer was separated and the aqueous phase washed with dichloromethane (2x50 ml) The combined organic layers were quickly washed with a cold saturated solution of sodium sulfite (10 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* (water bath temperature below 35 °C) to yield 1 75 g of the titled compound (82 %) as a white crystalline solid, m p 188-190°C (Lit 189°C) IR ν_{max} cm^{-1} 1367, 1345, 1165. δ_H ($CDCl_3$, 400 MHz) 1 06 (3H, s, Me), 1 32 (3H, s, Me), 2 15 (5H, m), 3 08 (1H, d, *J* 12 Hz), 3 29 (1H, d, *J* 12 Hz), 3 27 (3H, s, OMe), 3 34 (3H, s, OMe) δ_C ($CDCl_3$, 100 MHz) 20 45, 21 62, 28 07, 29 31, 45 11, 47 42, 50 50, 50 78, 52 88, 54 57, 97 59, 102 77 $[\alpha]_D^{20}$= + 88° (c=2 000, $CHCl_3$) (Lit 91 3°, c=3 39g/100ml, $CHCl_3$)

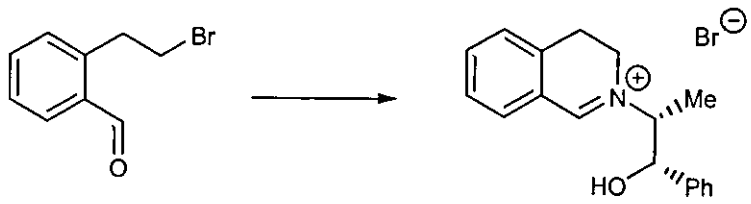
2-(2-Bromoethyl)-benzene-1-carbaldehyde (130):[15]



To an ice cooled solution of isochroman (50 g, 0 37 mol), in carbon tetrachloride (200 ml), in a 500 ml flask fitted with a reflux condenser, molecular bromine (60 g, 0 37 mol), is added slowly down the condenser over a period of 5 minutes with stirring After the vigorous reaction subsides, (*ca* 5 minutes), the cooling bath is removed and the dark brown solution is refluxed until the reaction mixture becomes pale yellow, and liberation of the white HBr smoke ceases, (indicative of complete consumption of bromine, *ca* 1 hour) The solution is the allowed to attain ambient temperature and the solvent is removed under reduced pressure To the yellow oil obtained, (1-bromo-isochroman), 75 ml of 48% hydrobromic acid (aqueous) is added and the reaction mixture is refluxed, (dark green-blue) After approximately 10 -15 minutes the solution is allowed to cool and extracted with diethyl ether (4x50 ml) (Care The solution must be at room temperature or below prior to extraction with ether, first ether extract may be the lower layer as it is very concentrated with organic material) The organic extracts are washed with water (2x30 ml), then with dilute sodium bicarbonate solution and dried over magnesium sulfate Evaporation of the solvent under reduced pressure furnished 67 5 g (65% yield) of the crude 2-(2-bromoethyl) benzaldehyde as an orange oil approximately 85-90% pure Analytically pure samples may be obtained by distillation under reduced pressure, *ca* 150°C 0 5 mbar (Lit. 82-83°C 0 1 mmHg, 100°C 0 7 mmHg), chromatography is not recommended The crude material which does not decompose when stored in a flask in the presence of light and air, was used for subsequent reactions unless stated otherwise IR ν_{max} cm^{-1} (neat) 2742, 1697, 1600, 1575, 1260, 1193, 755 δ_H ($CDCl_3$, 400 MHz) 3 54-3 63 (4 H, m), 7 33 (1 H, d, *J* 7 96 Hz), 7 48 (1 H, t, *J* 7 50 Hz), 7 54 (1 H, t, *J* 7 94 Hz), 7 80 (1 H, d, *J* 7 56 Hz), 10 14 (1 H, s, CHO) δ_C ($CDCl_3$, 62 MHz) 33 17 (CH_2), 36.70 (CH_2), 128 10 (CH ar), 132 51 (CH ar), 134 14 (CH ar) 134 33 (C ar), 134 88

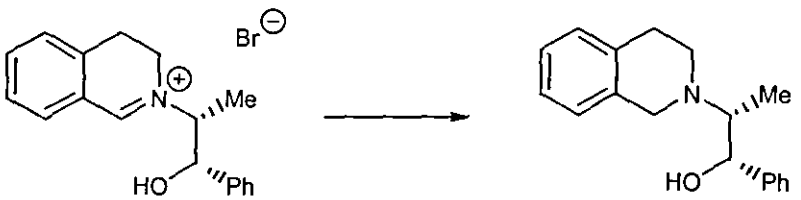
(CH ar), 140 95 (C ar), 193 33 (CH, HC=O). Exact mass calcd for C_9H_9BrO 211 98373, found 211 98370

(1S,2R)-2-(3,4-Dihydroisoquinolinium-2-yl)-1-phenylpropanol-1-ol bromide (131):



A solution of norephedrine (2 00 g, 13 2 mmol) in ethanol (4 ml) was added dropwise via a stoppered, pressure equalising, dropping funnel, to an ice cooled, one-neck flask, containing 2-(2-bromoethyl)-benzaldehyde, (5 63 g, 26 4 mmol, 2 equivalents) neat The reaction mixture was allowed to reach the room temperature after completed addition and was left under stirring for 1 hour Then the reaction mixture was left at room temperature without stirring The precipitated iminium salt was collected into a buchner funnel and washed with ethanol, ether and finally acetonitrile to yield 2 90 g of pure iminium salt (63 %) as a white solid, m p 227-229°C (decomp) IR ν_{max} cm^{-1} (nujol) 3557, 1649, 1600, 1570 δ_H ($CDCl_3$+*d*-6-DMSO, 400 MHz) 1 36 (3H, d, *J* 6 8 Hz), 3 27 (2H, m), 4 27 (2H, m), 4 85 (1H, m), 5 22 (1H, s, OH), 6 16 (1H, d, *J* 4 Hz), 7 30 (1H, m, Ar), 7 37 (2H, m, Ar), 7 50 (4H, m, Ar), 7 79 (1H, m, Ar), 8 00 (1H, d, *J* 8 Hz), 9 37 (1H, s) δ_C ($CDCl_3$+*d*-6-DMSO, 62 MHz) 11 46, 24 93, 48 43, 70 62, 71 49, 124 96, 126 10, 127 60, 128 01, 128 14, 133 86, 136 89, 137 46, 140 41, 165.75 $[\alpha]^{20}_D$= -9° (c=1 026, H_2O) Elemental analysis found C, 62 01, H, 5 79, N, 3 99, $C_{18}H_{20}BrNO$ requires C, 62 44, H, 5 82, Br, 23 08, N, 4 05, O, 4 62

(1S,2R)-1-Phenyl-2-(1,2,3,4-tetrahydroisoquinolin-2-yl)propan-1-ol(132):



To a suspension of the iminium salt (3 79 g, 10 95 mmol) in acetonitrile (20 ml) was added a aqueous solution of hydrobromic acid (48 %, 1 85 ml, 1 eq) then sodium cyanoborohydride solid was added by portions (0 625 g, 4 33 mmol, 1 5 eq) The precipitate gradually disappeared but after 10-20 minutes a white precipitate started to crash out The reaction mixture was left under stirring at room temperature for on hour The solvent was removed and the crude solid was taken in dichloromethane and aqueous potassium carbonate solution The phase were separated and the aqueous layer was extracted four times with dichloromethane The combined organic layer were dried over sodium sulfate, filtered and the solvent was removed to yield 2 75 g of the amino alcohol as a white solid (94 %) m p 111-113°C IR ν_{max} cm^{-1} 3200, 3064, 2917, 2802, 1602, 1492, 1450, 1380, 1164, 1130, 1096, 998, 740, 704 δ_H ($CDCl_3$, 400 MHz) 0 96 (3H, d, *J* 7 Hz), 2 86 (5H, m), 3 84 (2H, AB system, *J* 15 Hz), 4 23 (1H, br, OH), 4 96 (1H, d, *J* 3 7 Hz), 7 25 (9H, m, Ar) δ_C ($CDCl_3$, 100 MHz) 10 11 (CH_3), 29 50 (CH_2), 47 56 (CH_2), 53.81 (CH_2), 63 85 (CH), 72 62 (CH), 125 67 (CH ar), 125 99 (CH ar), 126 20 (CH ar), 126 64 (CH ar), 126 94 (CH ar), 128 00 (CH ar), 128 66 (CH ar). 134.58 (C ar), 135 08 (C ar), 142 02 (C ar) $[\alpha]^{20}_D$= 0 59 ° (c=2 03, $CHCl_3$) Exact mass calcd for $C_{18}H_{21}NO$ 267 16231, found 267 16185 Elemental analysis found C, 80 12, H, 7 8, N, 5 28, $C_{18}H_{21}NO$ requires C, 80 86, H, 7 92, N, 5 24, O, 5 98

General procedure for the conversion of amino alcohols into amino sulfides (double inversion).

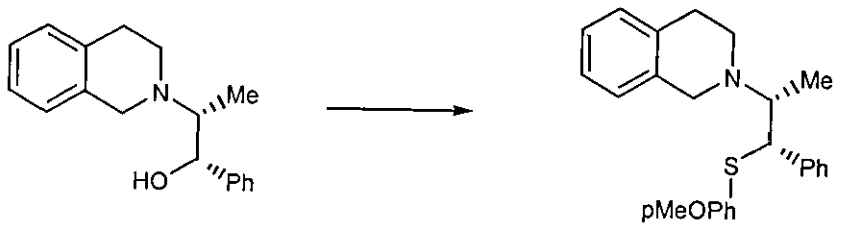
To a solution of amino alcohol (1 eq) in dichloromethane was added at 0°C triethylamine (3 eq) After 10 minutes, methanesulfonyl chloride(1 2 eq) was added and the reaction was left under stirring for 1 hour Triethylamine (3 eq) was added followed by the appropriate thiol (3 eq) The

ice bath was removed and the reaction was left under stirring at room temperature overnight. A solution of potassium carbonate was added and the phases were separated The aqueous layer was washed with dichloromethane The combined organic layers were dried over sodium sulfate and the solvent was removed The crude mixture was purified by column chromatography over silica gel with Petroleum Ether-dichloromethane to yield the corresponding amino sulfide

2-[(1R,2S)-1-Methyl-2-phenyl-2-(phenylthio)ethyl]-1,2,3,4-tetrahydroisoquinoline (135):

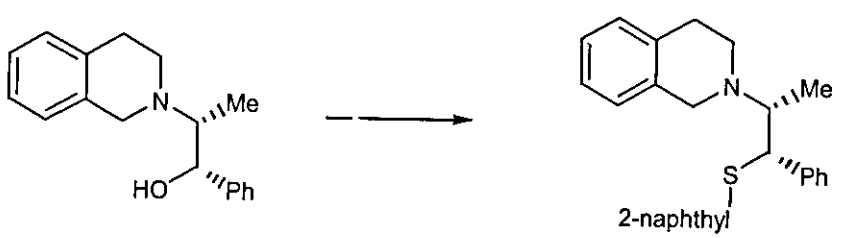
See above: Amino alcohol (1 01 g, 3 78 mmol), dichloromethane (10 ml), triethylamine (1 58 ml, 11 35 mmol, 3 eq), methanesulfonyl chloride (0 35 ml, 4 54 mmol, 1 2 eq), triethylamine (1 58 ml, 11 35 mmol), thiophenol (1 16 ml, 11 35 mmol, 3 eq) to yield 0 674 g of the titled compound as a orange oil (50 %) IR ν_{max} cm^{-1} 3060, 3023, 2916, 2799, 1583, 1493, 1480, 1450, 1381, 1154, 1136, 740, 694 δ_H ($CDCl_3$, 400 MHz) 1 33 (3H, d, *J* 6 7 Hz), 2 74 (4H, m), 3 29 (1H, quint , *J* 7 Hz), 3 78 (2H, AB system, *J* 14 8 Hz), 4 36 (1H, d, *J* 7 Hz), 7 14 (14H, m, ar.) δ_C ($CDCl_3$, 100 MHz) 12 41 (CH_3), 29 75 (CH_2), 46 01 (CH_2), 52 49 (CH_2), 58 26 (CH), 63 52 (CH), 125 32 (CH ar), 125 69 (CH ar), 126 43 (CH ar), 126 56 (CH ar), 126 65 (CH ar), 127 89 (CH ar), 128 50 (CH ar), 128 58 (CH ar),128 62 (CH ar), 134 93 (C ar.), 135 51 (C ar), 135 64 (C ar), 141 65 (C ar) Exact mass calculated for $C_{24}H_{25}NS$ 359 17077, found 359 17012 $[\alpha]^{20}_D$= 145 ° (c=1 036, $CHCl_3$)

2-((1R,2S)-1-Methyl-2-[(methyloxy)phenyl]thio-2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (136):



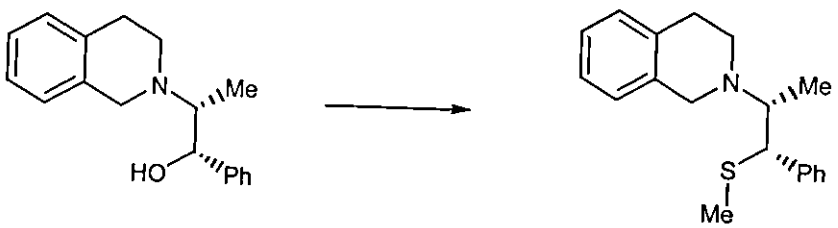
See above Amino alcohol (1 00 g, 3 74 mmol), triethylamine (1 57 ml, 11 24 mmol, 3 eq), methanesulfonyl chloride (0 35 ml, 4 49 mmol, 1 2 eq), triethylamine (1 57 ml, 11 24 mmol), *p*-methoxy-thiophenol (1 38 ml, 11 24 mmol, 3 eq) to yield 0 409 g of the titled compound as a orange oil (28 %) IR ν_{max} cm^{-1} 3061, 2912, 2834, 1592, 1493, 1285, 1246, 1172, 1031, 827, 742, 699 δ_H ($CDCl_3$, 400 MHz) 1 36 (3H, d, *J* 6 7 Hz), 2 70 (4H, m), 3 28 (1H, quint , *J* 6 7 Hz), 3 73 (3H, s, OMe), 3 74 (2H, AB system, *J* 14 3 Hz), 4 14 (1H, d, *J* 7 6 Hz), 6 67 (2H, m, ar), 7 09 (11H, m, ar) δ_C ($CDCl_3$, 100 MHz) 12 43 (CH_3), 29 85 (CH_2), 45 75 (CH_2), 52 19 (CH_2), 55 22, 59 92, 62 80, 114 17 (CH ar), 125 27 (CH ar), 125 43 (C ar), 125 61 (CH ar), 126 43 (CH ar), 127 73 (CH ar), 128 58 (CH ar), 127 73 (CH ar), 128 62 (CH ar), 135 03 (C ar), 135 31 (CH ar), 135 65 (C ar), 141 94 (C ar.), 159 31 (C ar) Exact mass calcd for $C_{24}H_{27}NOS$ 389 18134, found 389 18018, $[\alpha]^{20}_D$= 170 ° (c=1 040, $CHCl_3$).

2-[(1R,2S)-1-Methyl-2-(naphthalen-2-ylthio)-2-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (137):



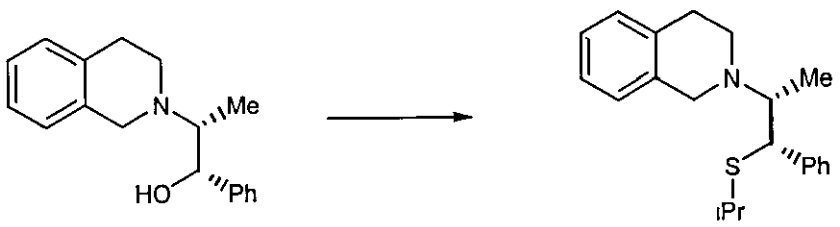
See above Amino alcohol (1 00 g, 3 74 mmol), triethylamine (1 57 ml, 11.24 mmol, 3 eq), methanesulfonyl chloride (0 35 ml, 4 49 mmol, 1 2 eq), triethylamine (1 57 ml, 11 24 mmol), 2-thionaphthol (1 80 g, 11 24 mmol, 3 eq) to yield 0 881 g of the titled compound as a orange oil (57 %) IR ν_{max} cm^{-1} 3054, 2918, 2800, 1646, 1586, 1498, 1451, 1381, 1267, 1133, 814, 741, 700 δ_H ($CDCl_3$, 400 MHz) 1 37 (3H, d, *J* 6 7 Hz), 2.75 (4H, m), 3.33 (1H, quint , *J* 6 9 Hz), 3 80 (2H, AB system, *J* 14 8 Hz), 4 47 (1H, d, *J* 6 7 Hz), 7 33 (16H, m, ar) δ_C ($CDCl_3$, 100 MHz) 12 48 (CH_3), 29 77 (CH_2), 46 06 (CH_2), 52 57 (CH_2), 58 23, (CH), 63 54 (CH), 125 33 (CH ar), 125 70 (CH ar), 125 75 (CH ar), 126 22 (CH ar), 126 44 (CH ar), 126 74 (CH ar), 127 24 (CH ar), 127 56 (CH ar),127 95 (CH ar), 128 00 (CH ar), 128 54 (CH ar), 128 63 (CH ar), 129 15 (CH ar), 129 88 (CH ar), 131 99, 133 17, 133 56, 134 95, 135 55, 141 56 Exact mass calcd for $C_{28}H_{27}NS$ 409 18642, found 409 18690 $[\alpha]^{20}_D$= 180 ° (c=1 084, $CHCl_3$)

2-[(1R,2S)-1-Methyl-2-(methylthio)-2-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (138):



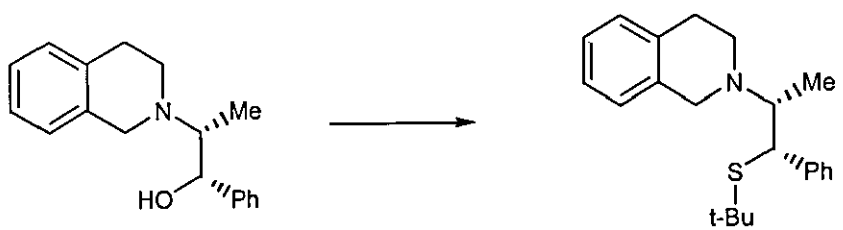
See above Amino alcohol (1 00 g, 3 74 mmol), triethylamine (1 57 ml, 11 24 mmol, 3 eq), methanesulfonyl chloride (0 35 ml, 4 49 mmol, 1 2 eq), triethylamine (1 57 ml, 11 24 mmol), sodium methanethiolate (0 78 g, 11 24 mmol, 3 eq) to yield 0 714 g of the titled compound as a orange oil (64 %) m p 56-58°C IR ν_{max} cm^{-1} 3062, 3023, 2969, 2914, 2800, 1599, 1493, 1451, 1380, 1270, 1139, 936, 740, 699 δ_H ($CDCl_3$, 250 MHz) 1 29 (3H, d, *J* 6 7 Hz), 1 82 (3H, s, SMe), 2 60 (3H, m), 2 82 (1H, m), 3 20 (1H, dq, *J* 6 7, 8 1 Hz), 3 74 (2H, AB system, *J* 14 8 Hz), 3 90 (1H, d, *J* 8 1 Hz),7 11 (9H, m, ar) δ_C ($CDCl_3$, 100 MHz) 12 55, 14 88, 30 18, 45 94, 52 38, 56 47, 63 45, 125 55, 125 88, 126 67, 126 87, 128 26, 128 75, 128 87, 135 21, 135 86, 141 90 Exact mass calcd for $C_{19}H_{21}NS$ 297 15512, found 297 15453 $[\alpha]^{20}_D$= 80 ° (c=0 998, $CHCl_3$)

2-(1R,2S)-1-Methyl-2-[(1-methylethyl)thio]-2-phenylethyl-1,2,3,4-tetrahydroisoquinoline (139):



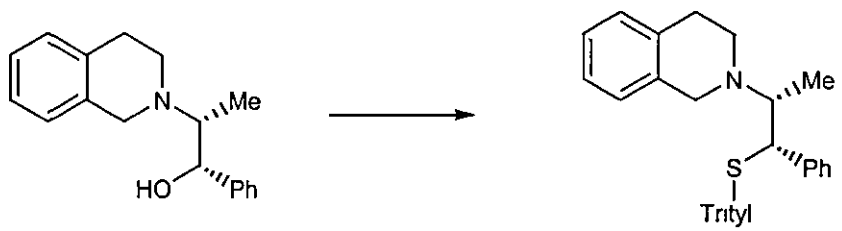
See above. Amino alcohol (1 02 g, 3 82 mmol), triethylamine (1 60 ml, 11 46 mmol, 3 eq.), methanesulfonyl chloride (0 36 ml, 4 58 mmol, 1 2 eq), triethylamine (1 60 ml, 11 46 mmol), propane-2-thiol (1 06 ml, 11 46 mmol, 3 eq) to yield 0 735 g of the titled compound as a orange oil (60 %) IR ν_{max} cm^{-1} 3061, 3023, 2962, 2922, 2800, 1650, 1600, 1492, 1451, 1380, 1154, 741, 699 δ_H ($CDCl_3$, 400 MHz) 1 10 (3H, d, *J* 6 8 Hz), 1.23 (3H, d, *J* 6 5 Hz), 1 26 (3H, d, *J* 6 7 Hz), 2 48 (1H, hept , *J* 6 6 Hz), 2 62 (3H, m), 2 36 (1H, m), 3 15 (1H, quint , *J* 6 7 Hz), 3 75 (2H, AB system, *J* 14 8 Hz), 4 08 (1H, d, *J* 7 4 Hz), 7 23 (9H, m, ar). δ_C ($CDCl_3$, 100 MHz) 12 37 (CH_3), 23 09 (CH_3), 23 67 (CH_3), 29 86 (CH_2), 34 12 (CH), 45 75 (CH_2), 52 28 (CH_2), 53 01 (CH), 125 27 (CH ar), 125 61 (CH ar), 126 42 (CH ar), 126 50 (CH ar), 127 96 (CH ar), 128 63 (CH ar), 128 77 (CH ar), 135 05 (C ar), 135 73 (C ar), 142 68 (CH ar) Exact mass calcd for $C_{20}H_{27}NS$ 325 18642; found 325 18633 $[\alpha]^{20}_D$= 113 ° (c=1 016, $CHCl_3$)

2-(1R,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-1,2,3,4-tetrahydroisoquinoline (140):



See above Amino alcohol (2 22 g, 8 31 mmol), triethylamine (3 50 ml, 24 94 mmol, 3 eq), methanesulfonyl chloride (0 77 ml, 9 98 mmol, 1 2 eq), triethylamine (3 50 ml, 24 94 mmol), 2-methyl-propane-2-thiol (2 81 ml, 24 94 mmol, 3 eq) to yield 1 928 g of the titled compound as a colourless solid after recrystallisation in methanol (68 %) m p 86-88°C IR ν_{max} cm^{-1} 3061, 3022, 2960, 2921, 2798, 1599, 1492, 1450, 1380, 1363, 1159, 1134, 936, 740, 699. δ_H ($CDCl_3$, 250 MHz) 1 18 (9H, s, tBu), 1 25 (3H, d, *J* 6 8 Hz), 2 67 (3H, m), 3 00 (2H, m), 3 81 (2H, AB system, *J* 15 Hz), 4 07 (1H, d, *J* 6 3 Hz), 7 20 (9H, m) δ_C $CDCl_3$, 62 MHz) 12 28, 30 10, 31 84, 43 88, 46 12, 52 21, 53.12, 64 93, 125 47, 125 83, 126 41, 126 65, 128 02, 128 77, 128 85, 135 29, 136 02, 145 06 Exact mass calcd for $C_{22}H_{29}NS$ 339 20207, found 339 20179 $[\alpha]^{20}_D$= 114 ° (c=1 028, $CHCl_3$) Elemental analysis found C, 77 46, H, 8 56, N, 4 08, $C_{22}H_{29}NS$ requires C, 77 82, H, 8 61, N 4.13, S, 9 44.

2-(1R,2S)-1-Methyl-2-phenyl-2-[(triphenylmethyl)thio]ethyl-1,2,3,4-tetrahydroisoquinoline (141):



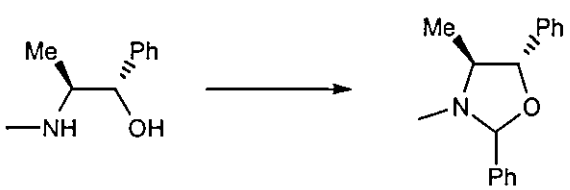
See above Amino alcohol (1 02 g, 3 82 mmol), triethylamine (1 60 ml, 11 46 mmol, 3 eq), methanesulfonyl chloride (0 36 ml, 4 58 mmol), triethylamine (1 60 ml, 11 46 mmol), triphenyl methane mercaptan (3 17 g, 11 46 mmol) to yield 1 15 g of the titled compound as a orange solid (57 %) m p 84-86°C. IR ν_{max} cm^{-1} 3057, 3026, 2924, 2799, 1646, 1598, 1491, 1446, 1382, 1266, 1134, 1034, 739, 699 δ_H ($CDCl_3$, 400 MHz) 0 88 (3H, d, *J* 6 9 Hz), 2 40 (4H, m), 2 83 (1H, quint , *J* 6 7 Hz), 3 21 (1H, d, *J* 5 8 Hz), 3 55 (2H, s), 7 12 (24H, m, ar) δ_C ($CDCl_3$, 100 MHz) 12 20 (CH_3), 29 64 (CH_2), 46 08 (CH_2), 53 85 (CH_2), 55 78 (CH), 64 17 (CH), 68 58 (C), 125 16, 125 55, 126 07, 126 38, 127 31, 127 52, 127 83, 128 55, 129 23, 130 01, 135 22, 136 04,

142 22, 144 94 Exact mass calcd for $C_{38}H_{35}NS$ 525 24902, found 525 24832 Elemental analysis found C, 82 17, H, 6 46, N, 2 37, $C_{38}H_{35}NS$ requires C, 84 53, H, 6 71, N, 2 66, S, 6 10 $[\alpha]^{20}_{D}$= 192 ° (c=1 000, $CHCl_3$)

(4S,5S)-3,4-Dimethyl-5-phenyl-1,3-oxazolane (144):[17]

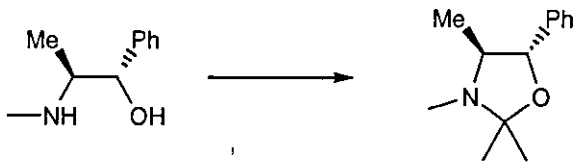
A solution of (1S,2S)-pseudoephedrine (2 00 g, 12 12 mmol), paraformaldehyde (0 400 g, 13 32 mmol, 1.1 eq) and potassium carbonate (1 83 g, 13 24 mmol, 1 1 eq) in benzene was heated to reflux for 8 hour The reaction mixture was cooled down and diethyl ether and water were added. The phases were separated and the aqueous layer was washed twice with diethyl ether The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed to yield 2 11 g of the titled compound as a colourless oil (98 %) IR ν_{max} cm^{-1} 3087, 3062, 3032, 2970, 2874, 2789, 1604, 1494, 1453, 1378, 1230, 1051, 1001, 753, 700 δ_H ($CDCl_3$, 400 MHz) 1 18 (3H, d, *J* 6 3 Hz), 2 38 (3H, s, NMe), 2 45 (1H, dq, *J* 6 3, 8 3 Hz), 4 31 (1H, d, *J* 3.4 Hz), 4 48 (1H, d, *J* 8 3 Hz), 4.76 (1H, d, *J* 3 4 Hz), 7 30 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 14 52, 37.20, 68 25, 86 11, 88 96 (CH_2), 126 23 (CH ar), 127.79 (CH ar), 128 44 (CH ar), 140 70 (C ar) Exact mass calcd for $C_{11}H_{15}NO$ 177.11536, found 177 11551 $[\alpha]^{D}_{20}$= 38° (c=1 016, $CHCl_3$) (Lit 50 8°, c=0 56, solvent unspecified)

(4S,5S)-3,4-Dimethyl-2,5-diphenyl-1,3-oxazolane (145):[18]



A equimolar solution of (1S,2S)-pseudoephedrine (2 00 g, 12.12 mmol) and benzaldehyde (1 23 ml, 12 12 mmol) in toluene and in presence of 4Å molecular sieves was heated to reflux overnight The reaction mixture was the cooled down and the mixture was filtered The solvent was removed to yield 2 95 g of the titled compound as a white solid in good purity (96 %) Aqueous washing or column chromatography have been unsuccessfully used to purified the oxazolidine m p 69-71°C. IR ν_{max} cm^{-1} (solution in dichloromethane) 3089, 3068, 3034, 2974, 2799, 1604, 1493, 1460, 1376, 1306, 1231, 1192, 1042, 1024, 1012 δ_H ($CDCl_3$, 400 MHz) 1 23 (3H, d, *J* 6 Hz), 2 21 (3H, s, NMe), 2 54 (1H, dq, *J* 6, 8 8 Hz), 4 78 (1H, d, *J* 8 8 Hz), 4 95 (1H, s), 7 39 (10H, m, ar) δ_C ($CDCl_3$, 62 MHz) 14 32, 35 13 68 80, 86 50, 99 58, 126 63 (CH ar), 127 85 (CH ar), 127 97 (CH ar), 128 31 (CH ar), 129 00 (CH ar), 139 45 (C ar), 140.39 (C ar) Exact mass calcd for $C_{17}H_{19}NO$ 253 14666, found 253 14609 $[\alpha]^D_{20}$= 49° (c=1 008, $CHCl_3$) Elemental analysis found C, 80 29, H, 7 52, N, 5.46, $C_{17}H_{19}NO$ requires C, 80 60, H, 7 56, N, 5 53, O, 6 32

(4S,5S)-2,2,3,4-Tetramethyl-5-phenyl-1,3-oxazolane (146):[20]



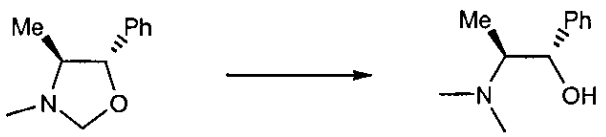
A solution of pseudoephedrine (4 00 g, 24 24 mmol) in acetone with a catalytic amount of para-toluene sulfonic acid and 4Å molecular sieves was heated to reflux overnight The reaction mixture was then cooled down The solvent was removed and the crude mixture was taken in diethyl ether. The organic layer was washed with a solution of potassium carbonate, dried over sodium sulfate, filtered and the solvent was removed to yield 4 93 g of the titled compound (99 %) as a colourless oil IR ν_{max} cm^{-1} 3087, 3063, 3030, 2974, 2869, 2795, 1604, 1495, 1452, 1375, 1257, 1214, 1043, 943, 856, 755, 699 δ_H ($CDCl_3$, 400 MHz) 1 09 (3H, d, *J* 6 Hz), 1 34 (3H, s), 1 43 (3H, s), 2 29 (3H, s, NMe), 2 56 (1H, dq, *J* 6, 8 8 Hz), 4 46 (1H, d, *J* 8 8 Hz), 7 32 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 14 53, 21 61, 27 69, 32 82, 65 12, 84 95, 95 28, 126 66 (CH ar),

127 81 (CH ar), 128 29 (CH ar), 139 91 (C ar) Exact mass calcd for $C_{13}H_{17}NO$ 205 14666, found 205 14656 $[\alpha]^{D}_{20} = 36^{\circ}$ (c= 1 022, $CHCl_3$)

General procedure for the ring opening reaction with TMSCl and NaBH3CN.

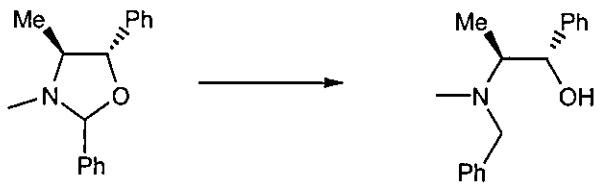
To a solution of oxazolidine (1 eq) in acetonitrile at 0°C was added sodium cyanoborohydride (5 eq) and trimethyl silyl chloride (5 eq) was slowly added to the reaction mixture After complete addition, the reaction was allowed to reach room temperature and left under stirring for 2 hours The solvent was removed and the crude mixture was taken in methanol and potassium carbonate was added The reaction was left at room temperature under stirring overnight Water was added and the aqueous layer was extracted with dichloromethane (4 times) The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed to yield the amino alcohol

(1S,2S)-2-(Dimethylamino)-1-phenylpropan-1-ol (147):[20]



See above. Oxazolidine (1 855 g, 10 48 mmol), sodium cyanoborohydride (3 30 g, 52 41 mmol, 5 eq), trimethyl silyl chloride (6 65 ml, 52 41 mmol, 5 eq) to yield 1 82 g of the titled compound (97 %) IR ν_{max} cm^{-1} 3322, 3064, 3032, 2974, 2944, 2876, 2835, 1456, 1104, 1037, 1025, 702 δ_H ($CDCl_3$, 250 MHz) 0 89 (3H, d, *J* 6 7 Hz), 2 55 (6H, s), 3 00 (1H, dq, *J* 6 7, 10 Hz), 4 33 (1H, d, *J* 10 Hz), 5 76 (1H, br, OH), 7 43 (5H, m, Ph) δ_C ($CDCl_3$, 62 MHz) 6 58, 40 16, 66 13, 75 13, 127 57, 127 88, 128 40, 142 23 Exact mass calcd for $C_{11}H_{17}NO$ 179 13101, found 179 13104 $[\alpha]^{D}_{20} = 40^{\circ}$ (c= 1 088, $CHCl_3$)

(1S,2S)-2-[Methyl(phenylmethyl)amino]-1-phenylpropan-1-ol (148):[21]

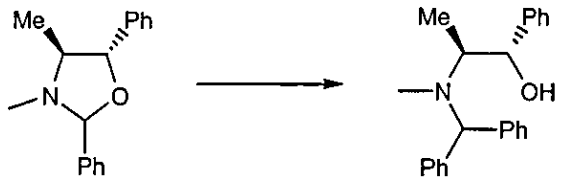


See above Oxazolidine (1 00 g, 3 95 mmol), sodium cyanoborohydride (0 50 g, 7 91 mmol, 2 eq) and trimethyl silyl chloride (1 ml, 7 91 mmol, 2 eq) to yield 0 95 g of the titled compound (95 %) as a white solid m p 42-44°C IR ν_{max} cm^{-1} 3356, 3085, 3062, 3029, 2970, 2801, 1602, 1494, 1453, 1401, 1373, 1343, 1321, 1206, 1131, 1090, 1026, 947, 757, 737, 700 δ_H ($CDCl_3$, 400 MHz) 0 79 (3H, d, *J* 6 4 Hz), 2 22 (3H, s, NMe), 2 74 (1H, dq, *J* 6 4, 9 6 Hz), 3 48 (1H, d, *J* 13 Hz), 3.73 (1H, d, *J* 13 Hz), 4 30 (1H, d, *J* 9 6 Hz), 5 20 (1H, br, OH), 7 30 (10H, m, ar) δ_C ($CDCl_3$, 100 MHz) 7 31, 35 72, 58 28 (CH_2), 64 87, 74 81, 127.31 (CH ar), 127 39 (CH ar), 127.71 (CH ar), 128 22 (CH ar), 128 48 (CH ar), 128 94 (CH ar), 138 69 (C ar), 142 02 (C ar) $[\alpha]^D_{20}$ = 124° (c= 1 004, $CHCl_3$), Elemental analysis found C, 79 85, H, 8 16, N, 5 42, $C_{17}H_{21}NO$ requires C, 79 96, H, 8 29, N, 5 49, O, 6 27.

General procedure for the ring opening reaction with a Grignard reagent.

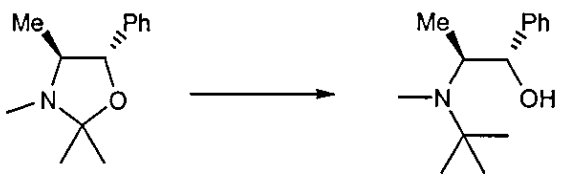
To a solution of oxazolidine (1 eq) in diethyl ether at 0°C was slowly added a solution of Grignard reagent (3 eq) in diethyl ether, the reaction was then heated to reflux for 30 minutes To the cooled solution was carefully added water (30 ml) The phases were separated and the aqueous layer was washed twice with diethyl ether The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed to yield the amino alcohol

(1S,2S)-2-[(Diphenylmethyl)(methyl)amino]-1-phenylpropan-1-ol (150):



See above Oxazolidine (1 50 g, 5 93 mmol), phenyl magnesium bromide (5 93 ml, C 3 0 M, 3 eq) to yield 1 94 g of the titled compound (99 %) as a white solid m p 25-27 °C IR ν_{max} cm^{-1} 3341, 3084, 3062, 3028, 2970, 1596, 1492, 1452, 1217, 1021, 756, 702 δ_H ($CDCl_3$, 250 MHz) 0 70 (3H, d, *J* 6 6 Hz), 2 20 (3H, s, NMe), 2 93 (1H, dq, *J* 6 6, 9 7 Hz), 4.33 (1H, d, *J* 9 7 Hz), 4 59 (1H, s), 5.39 (1H, br, OH), 7.35 (15H, m, ar) δ_C ($CDCl_3$, 250 MHz) 7.29, 33 07, 60 11, 73 94, 75 40, 127 52, 127 64, 127 67, 127 88, 127 94, 128 18, 128 45, 129 03, 129 11, 142 27, 142 32, 143 17 Exact mass calcd for $C_{23}H_{25}NO$ 331 19360, found 331 19372 $[\alpha]^D_{20}$ = 111° (c= 1 114, $CHCl_3$) Elemental analysis. found C, 80 93, H, 7 48, N, 3 90, $C_{23}H_{25}NO$ requires C, 83 35, H, 7 60, N, 4 23, O, 4 83

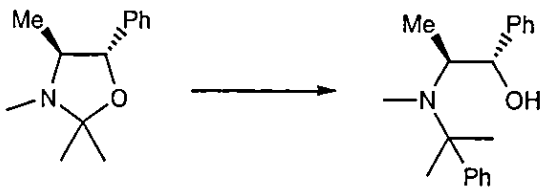
(1S,2S)-2-[(1,1-Dimethylethyl)(methyl)amino]-1-phenylpropan-1-ol (149):



See above Oxazolidine (1 00 g, 4 88 mmol), methyl magnesium bromide (4 90 ml, C 3 0 M, 3 eq) to yield 1 01 g of the titled compound (95 %) as a colourless solid m p 47 °C IR ν_{max} cm^{-1} 3267, 3086, 3063, 3029, 2974, 2874, 1604, 1454, 1392, 1214, 1140, 1049, 923, 758, 700 δ_H ($CDCl_3$, 400 MHz) 0 85 (3H, d, *J* 6 8 Hz), 1 17 (9H, s, tBu), 2 24 (3H, s, NMe), 2 98 (1H, dq, *J* 6 8, 9 2 Hz), 4 04 (1H, d, *J* 9 2 Hz), 5 35 (1H, br, OH), 7 30 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz)

12 16, 27 75, 27 82 (tBu), 54 92, 58 21, 74 41, 127 41 (CH ar), 127 46 (CH ar), 128 16 (CH ar.), 143 13 (C ar) $[\alpha]^{D}_{20}$ = 74° (c= 1 028, $CHCl_3$) Elemental analysis found C, 75 64, H, 10 57, N, 6 37, $C_{14}H_{23}NO$ requires C, 75 97, H, 10 47, N, 6 33, O, 7 23

(1S,2S)-2-[Methyl(1-methyl-1-phenylethyl)amino]-1-phenylpropan-1-ol (151):



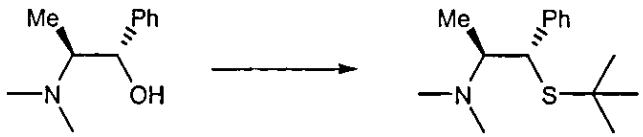
See above Oxazolidine (1 00 g, 4 88 mmol), phenyl magnesium bromide (4 90 ml, C 3 0 M, 3 eq) to yield 1 36 g of the titled compound (98 %) as a thick oil IR ν_{max} cm^{-1} 3285, 3086, 3060, 3031, 2977, 2876, 1605, 1594, 1494, 1474, 1448, 1375, 1269, 1134, 764, 700 δ_H ($CDCl_3$, 250 MHz) 0 78 (3H, d, *J* 6 6 Hz), 1 54 (3H, s), 1 55 (3H, s), 2 17 (3H, s, NMe), 2 95 (1H, dq, *J* 6 6, 9 2 Hz), 4 06 (1H, d, *J* 9 2 Hz), 7 30 (10H, m, ar) δ_C ($CDCl_3$, 62 MHz) 12 21, 25 76, 26 03, 28 14, 58 13, 60 44, 74 81, 126 32 (CH ar), 126 74 (CH ar), 127 37 (CH ar), 127 46 (CH ar), 128 09 (CH ar), 128.26 (CH ar.), 142 73 (C ar), 147 22 (C ar) $[\alpha]^{D}_{20}$ = 86° (c= 0 998, $CHCl_3$)

N,N-Dimethyl-N-(1S,2S)-1-[(1-methylethyl)thio]-2-phenylethylamine:

See general procedure for the conversion of amino alcohols into amino sulfides Amino alcohol (0 592 g, 3 31 mmol), triethylamine (1 38 ml, 9 92 mmol, 3 eq), methanesulfonyl chloride (0 31 ml, 3 97 mmol, 1 2 eq), triethylamine (1 38 ml, 9.92 mmol), propane-2-thiol (0 92 ml, 9 92 mmol, 3 eq) to yield 0 390 g of the titled compound as a orange oil (50 %) IR ν_{max} cm^{-1} 3082, 3060, 3025, 2965, 2863, 2820, 2777, 1598, 1452, 1363, 1126, 739, 700 δ_H ($CDCl_3$, 400 MHz) 0 68 (3H, d, *J* 6 4 Hz), 1 05 (3H, d, *J* 6 4 Hz), 1 16 (3H, d, *J* 6 4 Hz), 2 22 (1H, hept , *J* 6 4 Hz),

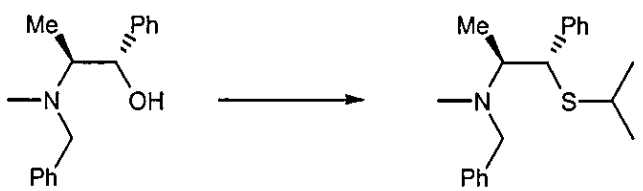
2 30 (6H, s, NMe2), 2 96 (1H, dq, *J* 6 4, 10 4 Hz), 3 86 (1H, d, *J* 10 4 Hz), 7.30 (5H, m, ar.) δ_C ($CDCl_3$, 100 MHz) 8 51, 22 59, 23 59, 32 50, 39 97 (NMe_2), 54 05, 63 89, 126 98 (CH ar.), 128 37 (CH ar), 128 81 (CH ar), 141 66 (C ar) Exact mass calcd for $C_{14}H_{23}NS$ 237 15512, found 237 15539 $[\alpha]^D_{20} = 254^\circ$ (c= 1 054, $CHCl_3$)

N-(1S,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-N,N-dimethylamine (152):



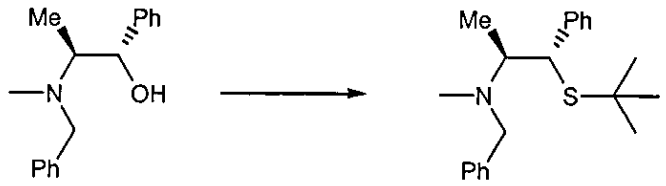
See above Amino alcohol (0 908 g, 5 07 mmol), triethylamine (2 10 ml, 15 22 mmol, 3 eq), methanesulfonyl chloride (0 47 ml, 6 09 mmol, 1 2 eq), triethylamine (2 10 ml, 15 22 mmol), 2-methyl-propane-2-thiol (1 72 ml, 15 22 mmol, 3 eq) to yield 0 482 g of the titled compound as a yellow solid (38 %) m p 44 °C. IR ν_{max} cm^{-1} 3082, 3061, 3025, 2966, 2822, 2778, 1599, 1453, 1363, 1161, 1118, 912 δ_H ($CDCl_3$, 400 MHz) 0 71 (3H, d, *J* 6 8 Hz), 1 10 (9H, s, tBu), 2 28 (6H, s, NMe_2), 2 90 (1H, dq, *J* 6 8, 9 6 Hz), 3 92 (1H, d, *J* 9 6 Hz), 7.30 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 8 83, 31 45 (tBu), 40 32, 43 03 (C tBu), 52 73, 64 24, 126 73 (CH ar), 128 10 (CH ar.), 129 14 (CH ar), 143 81 (C ar) Exact mass calcd for $C_{15}H_{25}NS$ 251 17077, found 251 17111 $[\alpha]^D_{20} = 154^\circ$ (c= 0 996, $CHCl_3$) Elementa' analysis found C, 70 33, H, 9 99, N, 6 30, $C_{15}H_{25}NS$ requires C, 71 66, H, 10 02, N, 5 57, S, 12 75

N-Methyl-N-(1S,2S)-1-methyl-2-[(1-methylethyl)thio]-2-phenylethyl-N-phenylmethylamine :



See above Amino alcohol (0 726 g, 2 85 mmol), triethylamine (1 20 ml, 8 54 mmol, 3 eq), methanesulfonyl chloride (0 26 ml, 3 42 mmol, 1 2 eq), triethylamine (1 20 ml, 8 54 mmol), propane-2-thiol (0 80 ml, 8.54 mmol) to yield 0 550 g of the titled compound as a orange oil (62 %) IR ν_{max} cm^{-1} 3083, 3061, 3025, 2965, 2791, 1599, 1493, 1451, 1365, 1154, 1127, 735, 699. δ_H ($CDCl_3$, 250 MHz) 0 77 (3H, d, *J* 6 4 Hz), 1 07 (3H, d, *J* 6 4 Hz), 1 15 (3H, d, *J* 6 4 Hz), 2 22 (3H, s, NMe), 2 21 (1H, hept , *J* 6 4 Hz), 3 10 (1H, dq, *J* 6 4, 10 4 Hz), 3 49 (1H, d, *J* 13 2 Hz), 3 76 (1H, d, *J* 13 2 Hz), 3 99 (1H, d, *J* 10 4 Hz), 7 30 (10H, m, ar) δ_C ($CDCl_3$, 100 MHz) 9 85, 22 63, 23 61, 32 64, 35 96, 54 50, 58 21, 62 90, 126 74 (CH ar), 126 94 (CH ar), 128 17 (CH ar), 128 34 (CH ar), 128 78 (CH ar), 128 94 (CH ar.), 139 95 (C ar), 141 85 (C ar) Exact mass calcd for $C_{20}H_{27}NS$ 313 18642, found 313 18649 $[\alpha]^D_{20} = 218°$ (c= 1 02, $CHCl_3$)

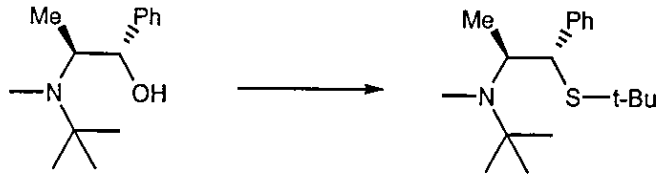
N-(1S,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-N-methyl-N-phenylmethylamine (153):



See above Amino alcohol (1 44 g, 5 65 mmol), triethylamine (2 36 ml, 16 94 mmol, 3 eq), methanesulfonyl chloride (0 52 ml, 6 78 mmol, 1 2 eq), triethylamine (2 36 ml, 16 94 mmol), 2-methyl-propane-2-thiol (1 91 ml, 16 94 mmol, 3 eq) to yield 0 942 g of the titled compound as a white solid (51 %) m p 43 °C. IR ν_{max} cm^{-1} 3061, 3026, 2963, 2939, 1598, 1488, 1453, 1371, 1197, 1171, 1147, 865, 737, 700 δ_H ($CDCl_3$, 400 MHz) 0 83 (3H, d, *J* 6 4 Hz), 1.11 (9H, s, tBu), 2 18 (3H, s, NMe), 3 06 (1H, dq, *J* 9 2, 6 4 Hz), 3 44 (1H, d, *J* 13 6 Hz), 3 74 (1H, d, *J* 13 6 Hz), 4 02 (1H, d, *J* 9 2 Hz), 7 35 (10H, m, Ar) δ_C ($CDCl_3$, 100 MHz) 10 31, 31 45, 36 99, 37 29, 53 23, 58 14, 63 06, 126 68, 128 06, 128 13, 128 83, 129 20, 140 19, 144 00 Exact mass calcd

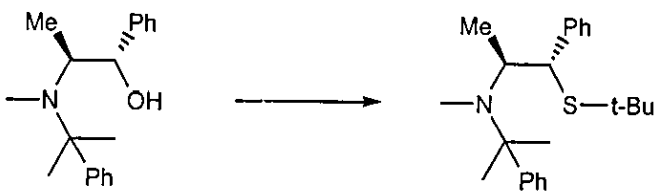
for $C_{21}H_{29}NS$ 327 20207, found 327 20241 $[\alpha]^{D}_{20}$ = 119° (c= 0 99, $CHCl_3$) Elemental analysis found C, 77 03, H, 8 78, N, 4 18, $C_{21}H_{29}NS$ requires C, 77 01, H, 8 92, N, 4 28, S, 9 79

N-(1,1-Dimethylethyl)-N-(1S,2S)-2-[(1,1-dimethylethyl)thio]-1-methyl-2-phenylethyl-N-methylamine (154):



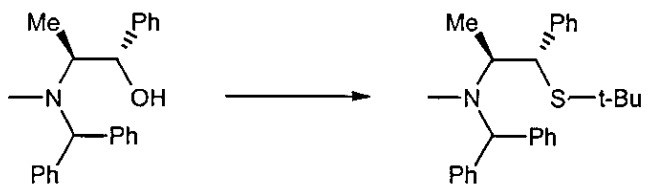
See above Amino alcohol (400 mg, 1 81 mmol), triethylamine (0 76 ml, 5 43 mmol, 3 eq), methanesulfonyl chloride (0 17 ml, 2 17 mmol, 1 2 eq), triethylamine (0 76 ml, 5 43 mmol), 2-methyl-propane-2-thiol (0 61 ml, 5 43 mmol, 3 eq) to yield 0 3766 g of the titled compound as a orange oil (71 %) IR ν_{max} cm^{-1} 3081, 3059, 3026, 2968, 2788, 1599, 1492, 1472, 1450, 1363, 1154, 700 δ_H ($CDCl_3$, 400 MHz) 0 92 (3H, d, *J* 6 8 Hz), 1 06 (9H, s, tBu), 1 14 (9H, s, tBu), 1 76 (3H, s, NMe), 3 43 (1H, dq, *J* 6 4, 6 8 Hz), 3 82 (1H, d, *J* 6 4 Hz), 7 30 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 13 67, 27 27 (tBu), 29 37, 31 46 (tBu), 43 07, 54 60 (C tBu), 55.10, 56 59, 84 52 (C tBu), 126 20 (CH ar), 127 45 (CH ar), 129 73 (CH ar), 155 45 (C ar) Exact mass calcd for $C_{18}H_{31}NS$ 293 21772, found 293 21784 $[\alpha]^{D}_{20}$ = 119° (c= 1 006, $CHCl_3$)

N-(1S,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-N-methyl-N-(1-methyl-1-phenylethyl)amine (156):



See above Amino alcohol (1 23 g, 4 35 mmol), triethylamine (1 82 ml, 13 04 mmol, 3 eq), methanesulfonyl chloride (0 40 ml, 5 22 mmol, 1 2 eq), triethylamine (1 82 ml, 13 04 mmol), 2-methyl-propane-2-thiol (1 47 ml, 13 04 mmol, 3 eq) to yield 0 7236 g of the titled compound as a yellow solid (47 %) m p 57-59°C IR ν_{max} cm^{-1} 3082, 3059, 2971, 2896, 2787, 1600, 1492, 1449, 1376, 1364, 1267, 1161, 1135, 1075, 1030, 1008, 950, 763, 703 δ_H ($CDCl_3$, 400 MHz) 0 96 (3H, d, *J* 6 8 Hz), 0 96 (9H, s, tBu), 1 33 (3H, s), 1 38 (3H, s), 1 62 (3H, s, NMe), 3 28 (1H, dq, *J* 5 6, 6 8 Hz), 3 72 (1H, d, *J* 5 6 Hz), 7 19 (2H, m, ar), 7 26 (2H, m, ar), 7 33 (2H, m, ar.), 7 44 (2H, m, ar), 7 66 (2H, m, ar) δ_C ($CDCl_3$, 100 MHz) 12 96, 23 15, 27 34, 29 66, 31 24 (tBu), 43 29 (C tBu), 53 71, 57 39, 61 07, 126 13 (CH ar), 126 28 (CH ar), 126 75 (CH ar), 127 55 (CH ar), 127 90 (CH ar), 129 71 (CH ar), 143 18 (C ar), 150 01 (C ar) Exact mass calcd for $C_{23}H_{27}NS$ 355 23337, found 355 23289 $[\alpha]^D_{20}$ = 24° (c= 0 994, $CHCl_3$), Elemental analysis found C, 77 88, H, 9 40, N, 3 89, $C_{23}H_{27}NS$ requires C, 77 69, H, 9 35, N, 3 94, S, 9 02

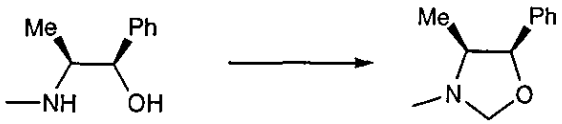
N-(1S,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-N-diphenylmethyl-N-methylamine (155):



See above. Amino alcohol (1 00 g, 3 02 mmol), triethylamine (1 26 ml, 9 06 mmol, 3 eq), methanesulfonyl chloride (0 28 ml, 3 63 mmol, 1 2 eq), triethylamine (1 26 ml, 9 06 mmol), 2-methyl-propane-2-thiol (1 02 ml, 9 06 mmol, 3 eq) to yield 0 8235 g of the titled compound as a yellow solid (68 %) m p 93-95° IR ν_{max} cm^{-1} 3081, 3060, 3025, 2961, 1598, 1491, 1452, 1363, 1160, 1025, 739, 700 δ_H ($CDCl_3$, 400 MHz) 0 73 (3H, d, *J* 6 4 Hz), 1 10 (9H, s, tBu), 2 09 (3H, s, NMe), 3 18 (1H, dq, *J* 6 4, 8 8 Hz), 3 96 (1H, d, *J* 8 8 Hz), 4 59 (1H, s), 7 30 (15H, m, ar) δ_C ($CDCl_3$, 100 MHz) 9 73, 31 48 (tBu), 33 05, 42 79, 54 22, 58 47, 74 17, 126 50 (CH ar), 126 61 (CH ar.), 126 78 (CH ar.), 127 94 (CH ar), 128 00 (CH ar), 128 33 (CH ar), 128 38 (CH ar),

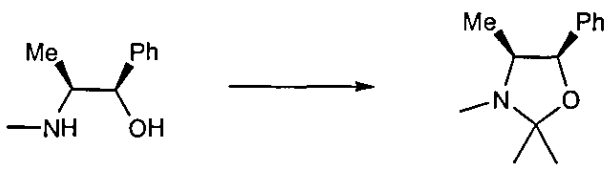
128 42 (CH ar), 129 20 (CH ar), 143 29 (C ar), 144 48 (C ar), 144.54 (C ar) Exact mass calcd for $C_{27}H_{33}NS$ 403 23337, found 403 23292 $[\alpha]^{D}_{20}$ = 148° (c= 0 982, $CHCl_3$) Elemental analysis. found C, 79 08, H, 7 97, N, 3 24, $C_{27}H_{33}NS$ requires C, 80 35, H, 8 24, N, 3 47, S, 7 94

(4S,5R)-3,4-Dimethyl-5-phenyl-1,3-oxazolane:[17]



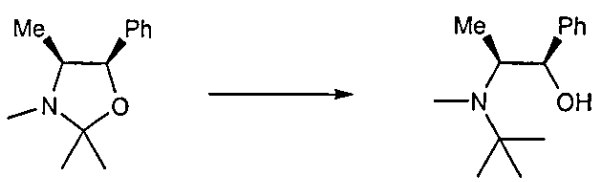
A solution of ephedrine (2 00 g, 12 12 mmol), paraformaldehyde (0 400 g, 13 32 mmol, 1 1 eq) and potassium carbonate (1 83 g, 13 24 mmol, 1 1 eq) in benzene was heated to reflux for 8 hour The reaction mixture was cooled down and diethyl ether and water were added The phases were separated and the aqueous layer was washed twice with diethyl ether The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed to yield 1 96 g of the titled compound (92 %) as a colourless oil IR ν_{max} cm^{-1} 3087, 3063, 3030, 2976, 2786, 1604, 1455, 1377, 1228, 1065, 753, 700 δ_H ($CDCl_3$, 400 MHz) 0 67 (3H, d, *J* 6 6 Hz), 2.37 (3H, s, NMe), 2 88 (1H, dq, *J* 6 6, 7 2 Hz), 4 06 (1H, d, *J* 3 2 Hz), 4 86 (1H, d, *J* 3.2 Hz), 5 09 (1H, d, *J* 7 2 Hz), 7 30 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 14 34, 37 80, 63 49, 82 01, 88 30 (CH_2), 126 96 (CH ar), 127 35 (CH ar), 127 97 (CH ar), 139 98 (C ar) Exact mass calcd for $C_{11}H_{17}NO$ 177 11536, found 177 11534 $[\alpha]^{D}_{20}$ = 18° (c= 1 07, $CHCl_3$) (Lit 5 6°, c=0 36, solvent unspecified)

(4S,5R)-2,2,3,4-Tetramethyl-5-phenyl-1,3-oxazolane (160):[19]



A solution of ephedrine (4 00 g, 24 24 mmol) in acetone with a catalytic amount of camphor sulfonyl acid and 4Å molecular sieves was heated to reflux overnight The reaction mixture was then cooled down The solvent was removed and the crude mixture was taken in diethyl ether. The organic layer was washed with a solution of potassium carbonate, dried over sodium sulfate, filtered and the solvent was removed to yield 4 90 g of the titled compound (98 %) as a white solid m p 47-48°C IR ν_{max} cm^{-1} 3064, 3027, 2976, 2895, 2843, 2796, 1496, 1458, 1364, 1322, 1267, 1223, 1208, 1170, 1083, 1046, 1031, 1026, 699 δ_H ($CDCl_3$, 400 MHz) 0 63 (3H, d, *J* 6 4 Hz), 1 21 (3H, s), 1 51 (3H, s), 2 26 (3H, s, NMe), 3 14 (1H, dq, *J* 6 4, 8 Hz), 5 02 (1H, d, *J* 8Hz), 7 28 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 15 44, 18 27, 26 63, 33 49, 60 51, 80 80, 95 08, 127.35 (CH ar), 127 64 (CH ar), 127.79 (CH ar), 140 42 (C ar) Exact mass calcd for $C_{13}H_{19}NO$ 205 14666, found 205.14656 $[\alpha]^D_{20}$ = 43° (c= 1 098, $CHCl_3$) Elemental analysis· found C, 76.17, H, 9 21, N, 6 74, $C_{13}H_{19}NO$ requires C, 76 06, H, 9 33, N, 6 82, O, 7 79

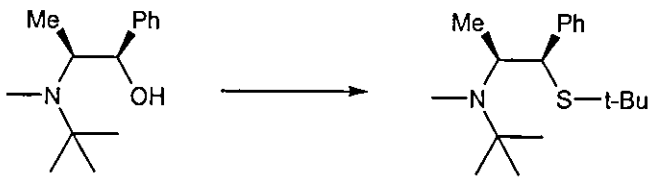
(1R,2S)-2-[(1,1-Dimethylethyl)(methyl)amino]-1-phenylpropan-1-ol (161):



To a solution of oxazolidine (2 00 g, 9 76 mmol) in diethyl ether at 0°C was slowly added a solution of methyl magnesium bromide (9 30 ml, C 3 M, 3 eq) in diethyl ether, the reaction was then heated to reflux for 30 minutes To the cooled solution was carefully added water (30 ml) The phases were separated and the aqueous layer was washed twice with diethyl ether The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed to yield 2 07 g the titled compound (96 %) as an oil IR ν_{max} cm^{-1} 3426, 3085, 3061, 3027, 2973, 1493, 1472, 1451, 1390, 1364, 1222, 1039, 1027, 748, 701 δ_H ($CDCl_3$, 250 MHz) 0 95 (3H, d, *J* 6 9 Hz), 1 08 (9H, s), 1 96 (3H, s, NMe), 3 39 (1H, dq, *J* 6 9, 5 8 Hz), 4 29 (1H, br, OH), 4 48 (1H, d, *J* 5 8 Hz), 7 29 (5H, m, ar.) δ_C ($CDCl_3$, 100 MHz) 13 21, 27.27 (tBu), 30 99, 54 95,

55 32, 74 97, 126 79 (CH ar), 126 88 (CH ar), 127 54 (CH ar), 142 83 (C ar) $[\alpha]^{D}_{20}$ = 0 8° (c= 0 99, $CHCl_3$)

N-(1,1-Dimethylethyl)-N-(1S,2R)-2-[(1,1-dimethylethyl)thio]-1-methyl-2-phenylethyl-N-methylamine (159):



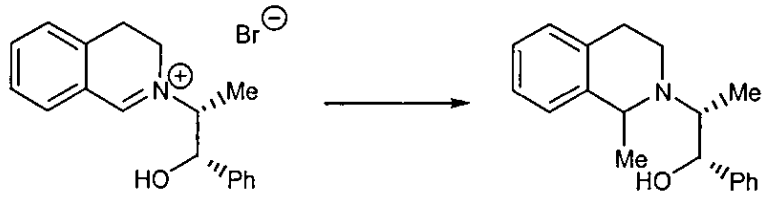
To a solution of amino alcohol (1 828 g, 8 27 mmol) in dichloromethane (20 ml) was added at 0°C triethylamine (3 50 ml, 24 82 mmol, 3 eq) After 10 minutes, methanesulfonyl chloride (0 70 ml, 9 93 mmol, 1 2 eq) was added and the reaction mixture was left under stirring for 1 hour. Triethylamine (3 50 ml, 24 82 mmol) was added followed by 2-methyl-propane-2-thiol (2 80 ml, 24 82 mmol, 3 eq). The ice bath was removed and the reaction was left under stirring at room temperature overnight A solution of potassium carbonate was added and the phases were separated The aqueous layer was washed with dichloromethane. The combined organic layer were dried over sodium sulfate and the solvent was removed The crude mixture was purified by recrystallisation with methanol to yield 1 29 g of the titled compound as a orange solid (53 %) m p 39-41°C IR ν_{max} cm^{-1} 3060, 3024, 2970, 1450, 1388, 1364, 1231, 1160, 1132, 744, 698 δ_H ($CDCl_3$, 400 MHz) 0 82 (9H, s, tBu), 1 17 (9H, s, tBu), 1 20 (3H, d, *J* 6 8 Hz), 2 18 (3H, s, NMe), 3 23 (1H, dq, *J* 6 8, 8 Hz), 3 73 (1H, d, *J* 8 Hz), 7 23 (5H, m, ar) δ_C ($CDCl_3$, 100 MHz) 15.30, 27 36 (tBu), 28 75, 31 48 (tBu), 43 34, 54 21, 55 05, 56 43, 125 72 (CH ar), 127 19 (CH ar), 128 89 (CH ar), 145 86 (C ar) $[\alpha]^{D}_{20}$ = -126° (c= 1 012, $CHCl_3$) Elemental analysis found C, 73 45, H, 10.70, N, 4 73, $C_{18}H_{31}NS$ requires C, 73 66, H, 10 65, N, 4.77, S, 10.92

General procedure for Grignard reagent addition to the iminium salt

To a suspension of the iminium salt (1 eq) in diethyl ether at room temperature was added drop wise a solution of Grignard reagent (3 eq) When the precipitate has disappeared the reaction

mixture was heated to reflux for 30 minutes To the cooled reaction was carefully added water to quench the excess of Grignard reagent The phases were separated and the aqueous layer was washed twice with diethyl ether The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed to yield the amino alcohol as a mixture of diastereoisomers

(1S,2R)-2-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-1-phenylpropan-1-ol (169):



See above Iminium salt (1 50 g, 4 34 mmol), methyl magnesium bromide (C= 3 0 M, 4 34 ml, 13 0 mmol, 3 eq) to yield 1 21 g of the titled compound (99 %) as an oil in 10-1 mixture of diastereoisomer IR ν_{max} cm^{-1} 3417, 306C, 3024, 2971, 2913, 2832, 1603, 1492, 1450, 1383, 1370, 1194, 1138, 1097, 1073, 1038, 756, ~02 δ_H ($CDCl_3$, 400 MHz)

Major diastereoisomer· 0 94 (3H, d, *J* 6 9 Hz), 1 36 (3H, d, *J* 6 7 Hz), 2 80 (4H, m), 3 22 (1H, dq, *J* 4 4, 6 9 Hz), 4 06 (1H, q, *J* 6 7 Hz), 4 71 (1H, d, *J* 4 4 Hz), 7 25 (9H, m, ar),

Minor diastereoisomer 0 96 (3H, d, *J* 6 9 Hz), 1 38 (3H, d, *J* 6 6 Hz), 2 80 (4H, m), 3 28 (1H, m), 4 17 (1H, m), 4 99 (1H, d, *J* 4 1 Hz), 7 25 (9H, m, ar.)

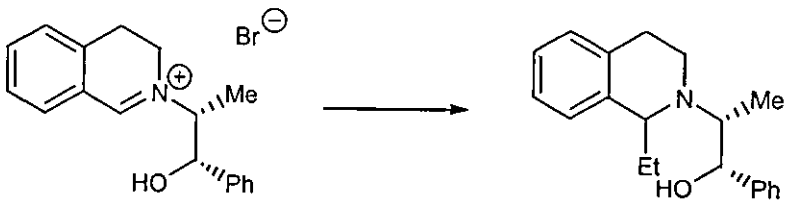
δ_C ($CDCl_3$, 100 MHz)

Major diastereoisomer 13 41, 19 78, 28 36, 39 54, 56 82, 60 70, 66 23, 125 99, 126 45, 126 55, 127 37, 127 51, 128 20, 129 36, 134 57, 141 20, 142 23,

Minor diastereoisomer not detectable

$[\alpha]^{D}_{20} = 21^{\circ}$ (c=0 986, $CHCl_3$)

(1S,2R)-2-(1-Ethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-1-phenylpropan-1-ol (170):



See above Iminium salt (3 00 g, 8 67 mmol) and a solution of ethyl magnesium bromide (C= 3 0 M, 8 70 ml, 26 0 mmol, 3 eq) to yield after careful column chromatography two separated diastereoisomers, 0 500 g and 1 03 g of the titled compound (60 %) as orange oils diastereoisomerically pur

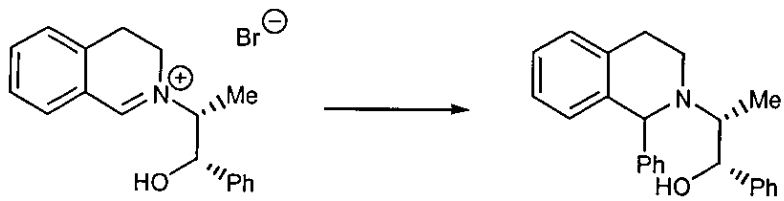
First diastereoisomer (20% yield) **A**.

IR ν_{max} cm^{-1} 3427, 3062, 3025, 2963, 2932, 2871, 1492, 1451, 1383, 909, 735, 701 δ_H ($CDCl_3$, 250 MHz) 0 90 (3H, d, *J* 6 7 Hz), 0 93 (3H, t, *J* 7 4 Hz), 1 77 (2H, m), 2 57 (1H, dt, *J* 4 2, 16 6 Hz), 2 79 (1H, m), 3 25 (3H, m), 3.73 (1H, br, OH), 3 93 (1H, t, *J* 6 5 Hz), 4 97 (1H, d, *J* 3 9 Hz), 7 21 (9H, m, Ar) δ_C ($CDCl_3$, 62 MHz) 11 04, 26 06, 29 70, 40 15, 60 22, 60 61, 72 52, 125 82, 126 00, 126 18, 126 94, 128 17, 128 21, 129 01, 142 12 $[\alpha]^D_{20}$ = - 32 ° (c= 1 024, $CHCl_3$)

Second diastereoisomer (40%) **B**

IR ν_{max} cm^{-1} 3425, 3061, 3024, 2965, 2930, 2870, 1491, 1450, 1382, 1244, 1196, 910, 735, 701 δ_H ($CDCl_3$, 250 MHz) 0 74 (3H, d, *J* 7 Hz), 1 05 (3H, t, *J* 7 4 Hz), 1 76 (2H, m), 2 59 (1H, m), 3 19 (5H, m), 3 74 (1H, m), 5 02 (1H, d, *J* 3 5 Hz) δ_C ($CDCl_3$, 62 MHz) 12 08, 12 26, 24 09, 29 90, 39 57, 58 96, 59 88, 72 34, 125 78, 125 99, 126 36, 126 96, 127 65, 128 20, 129.32, 134 28, 139 62, 142 08 $[\alpha]^D_{20}$ = -1 ° (c= 0 986, $CHCl_3$)

(1S,2R)-1-Phenyl-2-(1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-yl)propan-1-ol (168):



See above Iminium salt (3 05 g, 8 82 mmol) and phenyl magnesium bromide (c= 3 0 M, 8 80 ml, 26 4 mmol, 3 eq) to yield 2 96 g of the titled compound (99 %) as an oil in 10 1 mixture of diastereoisomer IR ν_{max} cm^{-1} 3423, 3060, 3024, 2980, 2923, 2830, 1601, 1492, 1451, 1382, 1038, 744, 701 δ_H ($CDCl_3$, 250 MHz)

Major diastereoisomer 0 70 (3H, d, *J* 6 9 Hz), 2 95 (5H, m), 3 45 (1H, br, OH), 4 96 (1H, d, *J* 3 7 Hz), 5 09 (1H, s), 7 10 (14H, m, Ar),

Minor diastereoisomer· 1 09 (3H, d, *J* 6 9 Hz), 2 95 (5H, m), 3 45 (1H, br, OH), 4 60 (1H, d, *J* 3 9 Hz), 4 84 (1H, s), 7 10 (14H, m, Ar)

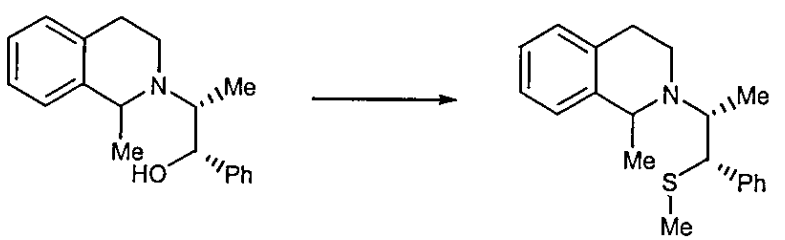
δ_C ($CDCl_3$, 62 MHz)

Major diastereoisomer 12 01, 28 26, 40 25, 59 58, 65 35, 72 65, 125 94, 126 09, 126 53, 127.17, 127 40, 128 20, 128 39, 129 00, 129 06, 129 64, 135 19, 137.74, 142 67, 143 76,

Minor diastereoisomer not detectable

Exact mass calcd for $C_{24}H_{25}NO$ 343 19361. found 343 19290 $[\alpha]^{D}_{20}$ = + 44° (c= 1 012, $CHCl_3$).

1-Methyl-2-[(1R,2S)-1-methyl-2-(methylthio)-2-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (172):



See general procedure for the conversion of amino alcohols into amino sulfides Amino alcohol (0 6522 g, 2 32 mmol), triethylamine (0 97 ml, 6 96 mmol, 3 eq), methanesulfonyl chloride (0 22 ml, 2 79 mmol, 1 2 eq), triethylamine (0 97 ml, 6 96 mmol, 3 eq), sodium methanethiolate (0 490 g, 6 96 mmol, 3 eq) to yield 0 2122 g of the titled compound (30 %) as an orange oil in a 10 1 mixture of diastereoisomer IR ν_{max} cm^{-1} 3059, 3022, 2968, 2913, 2826, 1599, 1490, 1450, 1380, 1367, 1138, 756, 733, 700 δ_H ($CDCl_3$, 250 MHz)·

Major diastereoisomer 1 22 (3H, d, *J* 6 8 Hz), 1 24 (3H, d, *J* 6 6 Hz), 1 81, (3H, s, SMe), 2 73 (4H, m), 3 34 (1H, m), 3 79 (1H, d, *J* 6 5 Hz), 3 90 (1H, q, *J* 6 7 Hz), 7 12 (9H, m, Ar);

Minor diastereoisomer 1 07 (3H, d, *J* 6 5 Hz), 1 26 (3H, *J* 6 Hz), 1 85 (3H, s, SMe), 2.73 (4H, m), 3 31 (1H, m), 3 82 (1H, d, *J* 5 1 Hz), 3 87 (1H, q, *J* 6 7 Hz), 7 12 (9H, m, Ar)

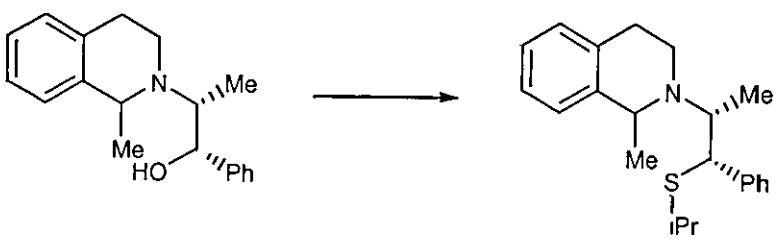
δ_C ($CDCl_3$, 62 MHz)

Major diastereoisomer 15 13, 16 44, 20 33, 29 44, 39 90, 56 48, 59 07, 61 30, 125 58, 125 79, 126 96, 127 17, 128 13, 129 04, 129 16, 135 17, 141 62, 141 83,

Minor diastereoisomer· 12 10, 15 30, 23 35, 30 40, 41 39, 55 24, 57.50, 58 90, 125 45, 125 85, 126 70, 127 35, 127 95, 128 50, 129 90, 136 05, 141 20, 142 15;

Exact mass calcd for $C_{20}H_{25}NS$ 311 17077, found 311 17008 $[\alpha]^{D}_{20}$ = + 150° (c= 0 98, $CHCl_3$)

1-Methyl-2-(1R,2S)-1-methyl-2-[(1-methylethyl)thio]-2-phenylethyl-1,2,3,4-tetrahydroisoquinoline (173):



See above Amino alcohol (0 7265 g, 2 59 mmol), triethylamine (1.08 ml, 7 76 mmol, 3 eq), methanesulfonyl chloride (0 25 ml, 3 10 mmol, 1 2 eq), triethylamine (1 08 ml, 7 76 mmol), 2-propanethiol (0 72 ml, 7 76 mmol, 3 eq) to yield 0 713 g of the titled compound (81 %) as an

orange oil in a 10 1 mixture of diastereoisomers IR ν_{max} cm^{-1} 3060, 3022, 2967, 2923, 2865, 2910, 1600, 1491, 1450, 1380, 1365, 1154, 1137, 756, 734, 700 δ_H ($CDCl_3$, 250 MHz)

Major diastereoisomer 0 86 (3H, d, *J* 6 5 Hz), 1 07 (3H, d, *J* 6 9 Hz), 1 22 (6H, 2d, *J* 6 7, 6 9 Hz), 2 52 (3H, m), 2 87 (2H, m), 3 32 (1H, hept , *J* 6 9 Hz), 3 91 (2H, m), 7 15 (9H, m, Ar),

Minor diastereoisomer (only detectable) 1 03 (3H, d, *J* 6 8 Hz), 3 99 (1H, d, *J* 9 5 Hz)

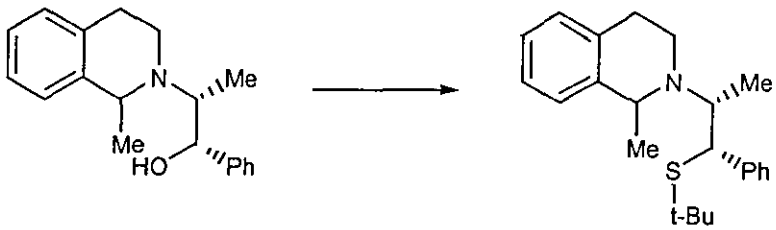
δ_C ($CDCl_3$, 62 MHz)

Major diastereoisomer· 16 34, 19.99, 23.47, 23.96, 34 43, 39 71, 55 79, 56 54, 61 63, 125 41, 125 65, 126 74, 127 12, 127 92, 128 93, 129 10, 135 15, 141 84, 142.33,

Minor diastereoisomer not detectable

Exact mass calcd for $C_{22}H_{29}NS$ 339 20207, found 339 20311. $[\alpha]^D_{20}$ = + 165° (c= 1 012, $CHCl_3$)

2-(1R,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (174):



See above. Amino alcohol (0 728 g, 2 59 mmol), triethylamine (1 08 ml, 7.77 mmol, 3 eq), methanesulfonyl chloride (0 25 ml, 3 11 mmol, 1 2 eq), triethylamine (1 08 ml, 7 77 mmol), 2-methyl-2-propanethiol (0 88 ml, 7 77 mmol, 3 eq) to yield 0 502 g the titled compound (55 %) as an orange oil in a 20 1 mixture of diastereoisomers IR ν_{max} cm^{-1} 3059, 3020, 2966, 2921, 1600, 1490, 1449, 1380, 1364, 1162, 1136, 1114, 1074, 1038, 909, 756, 733, 701 δ_H ($CDCl_3$, 250 MHz)

Major diastereoisomer 1 14 (9H, s, tBu), 1 16 (3H, d, *J* 6 5 Hz), 1 25 (3H, d, *J* 6 7 Hz), 2 50 (2H, m), 2 87 (2H, m), 3 32 (1H, dq, *J* 4 9, 7 Hz), 3 86 (1H, d, *J* 4 9 Hz), 4 02 (1H, q, *J* 6 7 Hz), 7 35 (9H, m, Ar.),

Minor diastereoisomer (only detectable) 4 12 (1H, q, *J* 6 9 Hz).

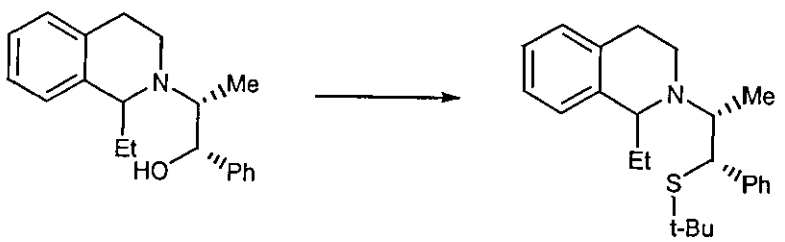
δ_C ($CDCl_3$, 62 MHz)

Major diastereoisomer· 16 07, 19 41, 29 34, 31 82, 39 48, 43 41, 55 05, 57 12, 62 60, 125 35, 125 65, 126 51, 127 15, 127 72, 128 96, 129 31, 135 16, 141 98, 144 00,

Minor diastereoisomer· not detectable

Exact mass calcd for $C_{23}H_{31}NS$ 353 21772, found 353 21686 $[\alpha]^{D}_{20}$ = + 166° (c= 0 984, $CHCl_3$)

2-(1R,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-1-ethyl-1,2,3,4-tetrahydroisoquinoline (178):



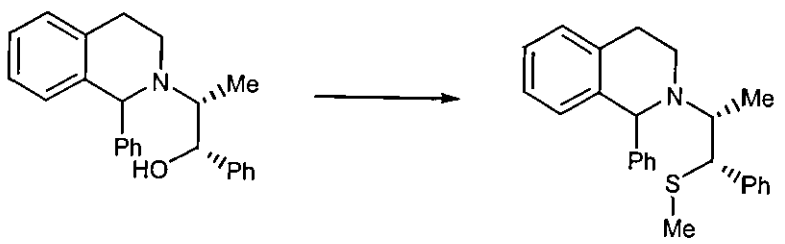
See above

Diastereoisomer **A** Amino alcohol (0492 g, 1 67 mmol), triethylamine (0 70 ml, 5 00 mmol, 3 eq), methanesulfonyl chloride (0 16 ml, 2 00 mmol, 1 2 eq), triethylamine (0 70 ml, 5 00 mmol), 2-methyl-2-propanethiol (0 56 ml, 5 00 mmol, 3 eq) to yield 0 212 g of the titled compound (35 %) as an orange oil IR ν_{max} cm^{-1} 3060, 3024, 2961, 2927, 1648, 1492, 1451, 1364, 1158, 742, 700 δ_H ($CDCl_3$, 250 MHz) -0 07 (3H, t, *J* 7 2 Hz), 1 20 (9H, s, tBu), 1 29 (3H, d, *J* 6 5 Hz), 1 41 (1H, m), 1 59 (1H, m), 2 53 (3H, m), 3 09 (2H, m), 3 85 (1H, t, *J* 3 7 Hz), 3 94 (1H, d, *J* 9 5 Hz), 7 20 (9H, m, Ar) δ_C ($CDCl_3$, 62 MHz) 7 09, 12 63, 28 52, 30 21, 31 79, 40 86, 43 95, 53 07, 60 66, 60 77, 125 21, 125 73, 126 17, 127 06, 127 89, 128 56, 137 69, 139 20, 145 77 $[\alpha]^{D}_{20}$ = + 120° (c= 1 03, $CHCl_3$)

Diastereoisomer **B**· Amino alcohol (1 02 g, 3 46 mmol), triethylamine (1 50 ml, 10 37 mmol, 3 eq), methanesulfonyl chloride (0 33 ml, 4 15 mmol, 1 2 eq), triethylamine (1 50 ml, 10 37 mmol), 2-methyl-2-propanethiol (1 18 ml, 10 37 mmol, 3 eq) to yield 0 645 g of the titled compound (51 %) as an orange oil IR ν_{max} cm^{-1} 3060, 3022, 2961, 2928, 1599, 1491, 1450, 1364, 1162, 739, 701 δ_H ($CDCl_3$, 250 MHz) 0 81 (3H, t, *J* 7 2 Hz), 1 12 (9H, s, tBu), 1 16 (3H, d, *J* 7 0 Hz), 1 69 (2H, m), 2 56 (1H, m), 2 85 (2H, m), 3 24 (2H, m), 3 75 (1H, t, *J* 5 8 Hz), 4 04

(1H, d, *J* 4 6 Hz), 7 20 (9H, m, Ar) δ_C ($CDCl_3$, 62 MHz) 10 97, 15 95, 28 41, 28 91, 31 83, 41 87, 43 57, 53 01, 60 81, 62 17, 125 29, 125 64, 126 41, 127 26, 127 99, 128 77, 129 04, 136 14, 140 47, 145 07 $[\alpha]^D_{20}$ = + 83° (c= 1 016, $CHCl_3$)

2-[(1R,2S)-1-Methyl-2-(methylthio)-2-phenylethyl]-1-phenyl-1,2,3,4-tetrahydroisoquinoline (175):



See above Amino (0 512 g, 1 49 mmol), triethylamine (0 63 ml, 4 48 mmol, 3 eq), methanesulfonyl chloride (0 14 ml, 1 79 mmol, 1 2 eq), triethylamine (0 63 ml, 4 48 mmol), sodium methanethiolate (0 314 g, 4 48 mmol, 3 eq) to yield 0 338 g of the titled compound (61 %) as an orange oil in a 10 1 mixture of diastereoisomers IR ν_{max} cm^{-1} 3060, 3024, 2969, 2915, 2827, 1599, 1491, 1451, 1377, 1154, 1132, 1033, 909, 741, 700 δ_H ($CDCl_3$, 400 MHz)

Major isomer· 1 04 (3H, d, *J* 6 8 Hz), 1 75 (3H, s, SMe), 2 85 (3H, m), 3 28 (2H, m), 3 95 (1H, d, *J* 7 4 Hz), 4 62 (1H, s), 7 00 (14H, m, Ar),

Minor isomer (only detectable) 1 27 (3H, d, *J* 6 6 Hz), 1 73 (3H, s, SMe), 3 75 (1H, d, *J* 10 4 Hz), 4 72 (1H, s)

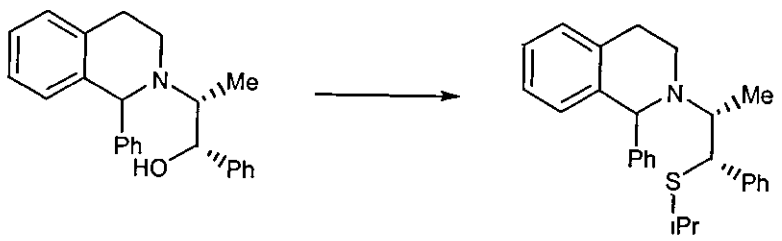
δ_C ($CDCl_3$, 100 MHz)·

Major diastereoisomer 14 86, 16 69, 30 90, 41 22, 55 54, 59 32, 65 98, 125 65, 125 69, 127 09, 127 19, 128 35, 128 38, 128 63, 128 88, 129 08, 129 42, 135 25, 139 41, 142 31, 145 06,

Minor diastereoisomer not detectable

Exact mass calcd for $C_{25}H_{27}NS$ 373.18642, found 373 18562 $[\alpha]^D_{20}$ = + 160° (c= 1 042, $CHCl_3$)

2-(1R,2S)-1-Methyl-2-[(1-methylethyl)thio]-2-phenylethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (176):



See above. Amino alcohol (0 490 g, 1 43 mmol), triethylamine (0 60 ml, 4 29 mmol, 3 eq), methanesulfonyl chloride (0 13 ml, 1 71 mmol, 1 2 eq), triethylamine (0 60 ml, 4 29 mmol), 2-propanethiol (0 40 ml, 4 29 mmol, 3 eq) to yield 0 332 g of the titled compound (56 %) as an orange oil in a 10 1 mixture of diastereoisomers IR ν_{max} cm^{-1} 3060, 3023, 2967, 2923, 2865, 1599, 1491, 1451, 1379, 1154, 910, 736, 701 δ_H ($CDCl_3$, 250 MHz)

Major diastereoisomer 1 01 (3H, d, *J* 6 7 Hz), 1 04 (3H, d, *J* 6 95 Hz), 1 19 (3H, d, *J* 6 7 Hz), 2 38 (1H, hept, *J* 6 7 Hz), 2 80 (2H, m), 3 24 (2H, m), 4 15 (1H, d, *J* 6 5 Hz), 4 66 (1H, s), 7 10 (14H, m, Ar);

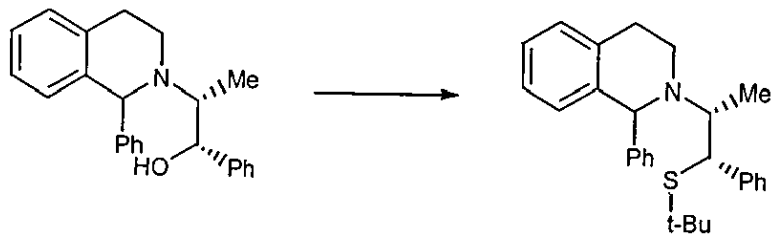
Minor diastereoisomer (only detectable) 1 00 (3H, d, *J* 6 9 Hz), 1.25 (3H, d, *J* 6 5 Hz), 2 69 (2H, m), 3 91 (1H, d, *J* 10 4 Hz), 4 71 (1H, s)

δ_C ($CDCl_3$, 62 MHz)·

Major diastereoisomer· 16 42, 23 32, 23 93, 30 94, 34 20, 41 37, 52 12, 59 65, 66 12, 125 60, 125 66, 126 89, 127 17, 128 27, 128 33, 128 62, 128 88, 128 96, 129 43, 135 32, 139 48, 143 06, 144 97,

Minor diastereoisomer (only detectable) 23 20, 30 25, 34 30, 42 05, 53 90, 57 70, 66 40 Exact mass calcd for $C_{27}H_{31}NS$ 401 21772, found 401 21636 $[\alpha]^D_{20} = +235°$ (c= 0 986, $CHCl_3$)

2-(1R,2S)-2-[(1,1-Dimethylethyl)thio]-1-methyl-2-phenylethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (177):



See above Amino alcohol (0 500 g, 1 46 mmol), triethylamine (0 61 ml, 4 37 mmol, 3 eq), methanesulfonyl chloride (0 14 ml, 1 75 mmol, 1 2 eq), triethylamine (0 61 ml, 4 37 mmol), 2-methyl-2-propanethiol (0 50 ml, 4 37 mmol, 3 eq) to yield 0 366 g of the titled compound (60 %) as an orange oil in a 20 1 mixture of diastereoisomers IR ν_{max} cm^{-1} 3060, 3023, 2966, 2922, 2828, 1599, 1491, 1451, 1363, 1216, 1160, 1130, 1029, 745, 701. δ_H ($CDCl_3$, 250 MHz).

Major diastereoisomer· 0 94 (3H, d, *J* 6 9 Hz), 1 15 (9H, s, tBu), 2 82 (3H, m), 3 23 (2H, m), 4 12 (1H, d, *J* 5 5 Hz), 4 87 (1H, s), 7 10 (14H, m, Ar),

Minor diastereoisomer (only detectable) 1 14 (9H, s, tBu), 3 81 (1H, d, *J* 9.7 Hz), 4 70 (1H, s)

δ_C ($CDCl_3$, 62 MHz)

Major diastereoisomer 15 58, 30 86, 31 88, 41 31, 43 90, 51 15, 60 56, 66 38, 125 54, 125 69, 126 48, 127 17, 127 98, 128 31, 128 63, 128 91, 129 46, 135 49, 139 49, 144 76, 145 13,

Minor diastereoisomer not detectable

Exact mass calcd for $C_{28}H_{33}NS$ 415 23337, found 415 23303 $[\alpha]^{D}_{20}$ = + 182° (c= 0 968, $CHCl_3$)

3-1: References

1 Andrew Lund's thesis, **1999** Loughborough University

2 Jnaneshwara, G K , Barhate, N B , Sudalai, A , Deshpande, V H.; Wakharkar, R. D , Gajare, A S , Shingare, M S , Sukumar, R *J Chem Soc , Perkin Trans 1*, **1998**, *5*, 965-968

3 Page, P C B ; Graham, A E , Park, B K *Tetrahedron*, **1992**, *48*(35), 7265-74

4 Firouzabadi, H , Iranpoor, N , Hazarkhani, H *J Org Chem* , **2001**, *66*(22), 7527-7529

5 Tzeng, Yih Ling, Yang, Ping Fan, Mei, Nai Wen, Yuan, Tien Min, Yu, Chun Chi, Luh, Tien Yau *J Org Chem* , **1991**, *56*(18), 5289-93

6 Bolm, C , Bieniewski, F *Syn Lett* , **1998**, *12*, 1327-1328

7 Stahl et al , Angew Chem , **1979**, *91*, 179

8 Holland, H L , Turner, C D , Andreana, P R , Nguyen, D *Can J Chem* , **1999**, *77*(4), 463-471, Canovese, L , Visentin, F , Uguagliati, P , Chessa, G , Lucchini, V , Bandoli, G *Inorg Chim Actal*, **1998**, *275-276*(1,2), 385-394, Canovese, L , Visentin, F ; Uguagliati, P , Chessa, G , Pesce, A *J Organomet Chem* , **1998**, *566*(1-2), 61-71.

9 Neumann,H , Seebach,D *Chem Ber*, **1978**, *111*, 2785-2812

10 Auburn, P R , Mackenzie, P B ; Bosnich, B *J Amer Chem Soc* , **1985**, *107*, 2033-2046

11 Nettekoven, U , Widhalm, M , Kamer, P C J ; Leeuwen, P W N M van *Tetrahedron Asymmetry*, **1997**, *8*, 3185-3188

12 Davis, F A , Kumar, A l, Chen, Bang-Chi *J Org Chem* , **1991**, *56*, 3, 1143-1145

13 Davis, F A ; Chen, Bang-Chi *Tetrahedron Lett* , **1990**, *31*, 47, 6823-6826, Verfuerth, U , Herrmann, R. *J Chem Soc Perkin Trans 1*, **1990**, *11*, 2919-2928

14 Davis, F A , Kumar, A , Chen, Bang-Chi *J Org Chem* , **1991**, *56*, 3, 1143-1145; Davis, F A , Chen, Bang-Chi *Tetrahedron Lett* , **1990**, *31*, 47, 6823-6826

15 Rieche, Schmitz *Chem Ber* , **1956**, *89*, 1254-1261, Schmitz *Chem Ber* , **1958**, *91*, 1133-1138

16. Page, P C B , Rassias, G A , Barros, D , Ardakani, A ; Buckley, B , Bethell, D , Smith, T A D , Slawin, A M Z *J Org Chem* , **2001**, *66*(21), 6926-6931

17. Khruscheva, N S , Loim, N M , Sokolov, V I , Makhaev, V D. *J Chem Soc , Perkin Trans 1*, **1997**, (*16*), 2425-2427

18 Santiesteban, F., Grimaldo, C , Contreras, R , Wrackmeyer, B *J Chem Soc , Chem Commun* , **1983**, (*24*), 1486-7

19 Grue-Soerensen, G , Spenser, I D *Can J Chem* , **1989**, *67*(6), 998-1009.

20. Miyano, S , Lu, L D L ; Viti, S M , Sharpless, K B *J Org Chem* , **1983**, *48*(20), 3608-11.

21 Kametani, T ; Kigasawa, K , Hiiragi, M , Wagatsuma, N ; Kohagizawa, T , Inoue, H *Heterocycles*, **1980**, *14*(6), 775-8