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New Classes Of Ligands For Asymmetric Synthesis

A thesis presented by

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In Partial Fulfilment of the Requirement for the Award of

Doctor of Philosophy

Supervised by

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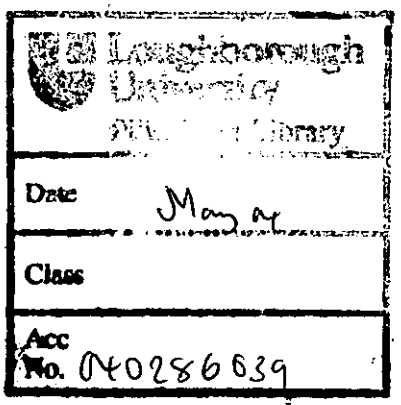
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Abstract

This thesis is divided into six chapters.

The first is a review of general asymmetric synthesis, and considers in detail the palladium cacalysed allylic substitution reaction, the 1,4-conjugate addition and the Heck reaction.

The second deals with our general synthetic approach to the chiral ligands. Here we synthesized a range of ligands derived from chiral amino alcohols condensed with aryl and aliphatic ketones. We also synthesized chiral sulfur imine and phosphorus imine ligands.

The third deals with applications of the ligands in the above reactions, and discusses the most successful ligands. In the palladium catalysed allylic displacement reaction, the sulfur imine ligands were the most successful ligands with ee of 96%. In the case of the 1,4 conjugate addition of diethylzinc to cyclic and acyclic enones, we were able to acheive excellent results using the phosphorus imine and the S_N ligands derived from pseudoephedrine and ketones, ee of >99% were obtained.

Chapter four deals with asymmetric sulfoxidation and the effect of electron donating and withdrawing groups on the sulfoxidation. Here we demonstrated the inductive influence of the substituent on the ee of the sulfoxide.

Chapter five deals with the conclusion.

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

Acknowledgement

I would like to thank my supervisor, Professor P C B Page, for his advice and constant help. I would also like to thank Professor Harry Heaney for his invaluable contribution and advice throughout.

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List of Abbreviations

Ac	acetyl
Ar	aryl
AIBN	azo*bis-iso*butyronitrile
ATP	adenosine 5'-triphosphate (and related compounds)
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bis-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	carbobenzyloxy
COD	cycloocta-1,5-diene
COSY	correlation spectroscopy
Cp	cyclopentadienyl ligand
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
DBA	(or dba as a ligand) dibenzylideneacetone

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
(+)-DET	(+)-(*R*,*R*)-diethyl tartrate
DIBAL	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcabodiimide
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
Et	ethyl
FAB	fast atom bombardment

Fc	ferrocene
Fmoc	fluoren-9-ylmethoxycarbonyl
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
HPLC	high-performance liquid chromatography
Hz	Hertz
IR	infrared
J	coupling constant in NMR spectroscopy
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Li(K)HMDS	lithium (potassium) hexamethyldisilazide
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MEM	(2-methoxyethoxy)methyl
Mes	2,4,6-trimethylphenyl (mesityl) (not methylsulfonyl)
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
Naph	Naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide

nOe	nuclear Overhauser enhancement effect/ nuclear Overhauser effect
Nu	nucleophile
PBN	*N-tert*-butyl-_-phenylnitrone(*N*-benzylidene-*tert*- butyl amine N-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
Ph	phenyl
PPTS	pyridinium toluene-*p*-sulfonate
Pr	propyl
Pri	*iso*propyl
PTSA	toluene-*p*-sulfonic acid
QSAR	quantitative structure activity relationship
RNA	ribonucleic acid
RT	room temperature
SPMB	(4-methoxyphenyl) methane thiol
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCNE	tetracyanoethylene
TCNQ	tetracyanoquinodimethane
TEMPO	tetramethylpiperidine-*N*-oxide

Tf	trifluoromethylsulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	tri*iso*propylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl *or* tetramethylsilane (can be used for either as long as no ambiguity results)
TPAP	tetrapropylammonium perruthenate
Tr	trityl
tris	tris(hydroxymethyl)aminomethane
Ts	toluene-p-sulfonyl
TTF	tetrathiafulvalene

CHAPTER 1

Introduction

1.1 INTRODUCTION

Biological systems in general, tend to recognise each member of a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. Thus one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer could be highly toxic. The sad case of thalidomide is a well-known example. It has been shown that only one enantiomer produces the desired activity and the other is totally inactive or toxic. Another example of this is L -DOPA.

The importance and practicality of asymmetric synthesis as a tool to obtain enantiomerically pure or enriched compounds is recognised by chemists in synthetic organic chemistry, medicinal chemistry, agricultural chemistry, natural product chemistry, pharmaceutical industries and agricultural industries. This prominence is due to the explosive development of new and more efficient methods during the last decade.

Among the types of asymmetric reaction, the most desirable and most challenging is catalytic asymmetric synthesis because one chiral molecule can create millions of chiral product molecules, just as enzymes do in biological systems. Among the significant achievements in asymmetric synthesis are asymmetric hydrogenation,[1,2] the Sharpless epoxidation,[3,4] and the transition-metal catalysed allylic displacement reaction.[5-7]

Transition metal catalysed allylic displacement

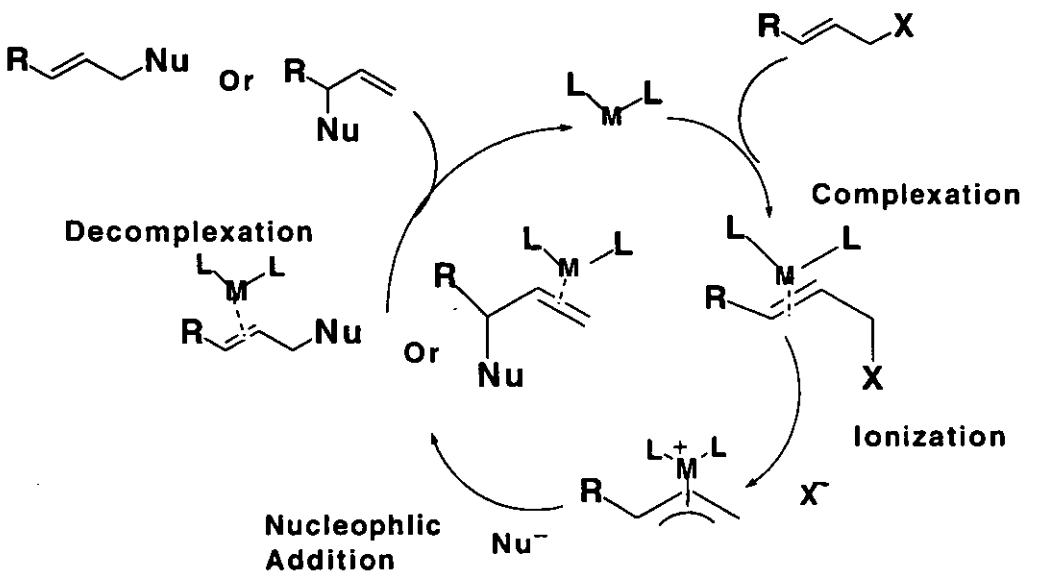
The transition metal catalysed allylic displacement reaction presents an advantage to form many different types of carbon-carbon and carbon-heteroatom bonds.[8-10]

The transition metal catalysed allylic displacement reactions have emerged as one of the more powerful tools for the controlled introduction of various chemical bonds into organic compounds (Scheme 1).

Scheme 1

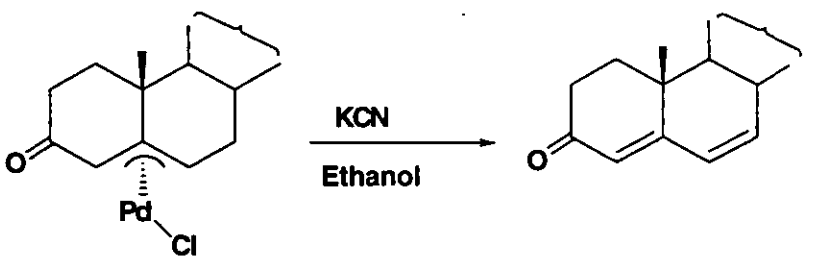
The reaction involves a (π–allyl) metal complex as a key intermediate, which can be exploited for various transformations with high chemo, regio and stereoselectivities.[11-13]

The mechanism of metal catalysed allylic displacement reaction is generally believed to involve the four fundamental steps shown in Scheme 2.

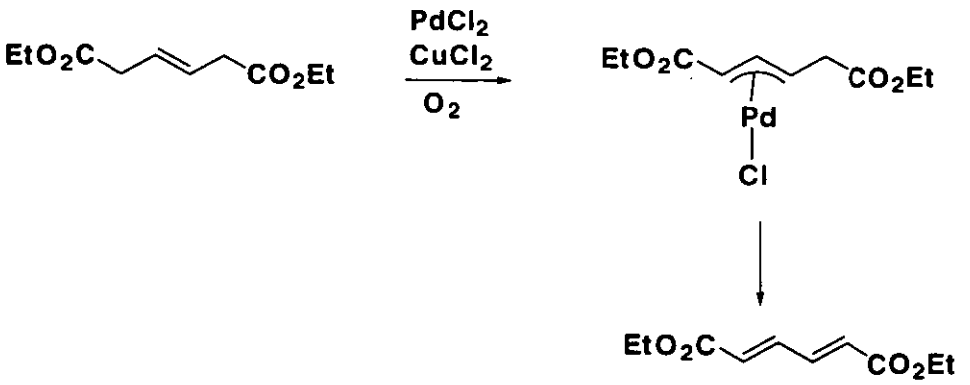


Scheme 2

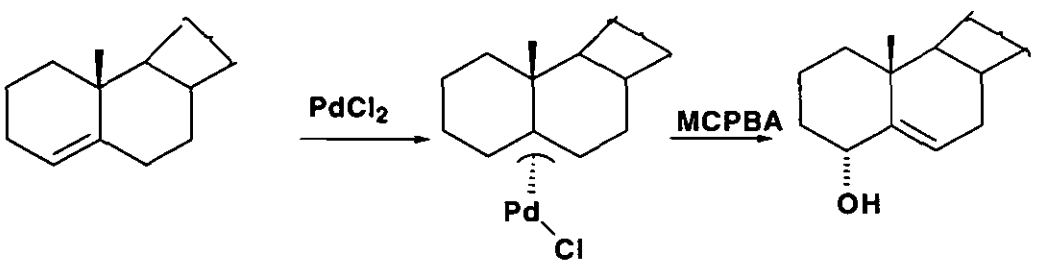
The key feature of the catalytic cycle is the intermediate (π-allyl) metal complex . Its generation and subsequent reaction represent the bond-breaking and making event in which the source of chiral induction can be derived. The π–allyl complex may undergo many useful transformations;for example the conjugated 4,6-dienone shown in Scheme 2.1 may be prepared from a steroidal enone *via* a π–allyl palladium complex.[14] Catalytic oxidative dehydrogenation of ethyl 3-butenedicarboxylate, Scheme 2.2, proceeds via a π–allyl palladium complex.[15] Oxidation of a π–allyl palladium complex with peracids produces allylic alcohols regioselectively with retention of configuration (Scheme 2.3).[16]



Scheme 2.1

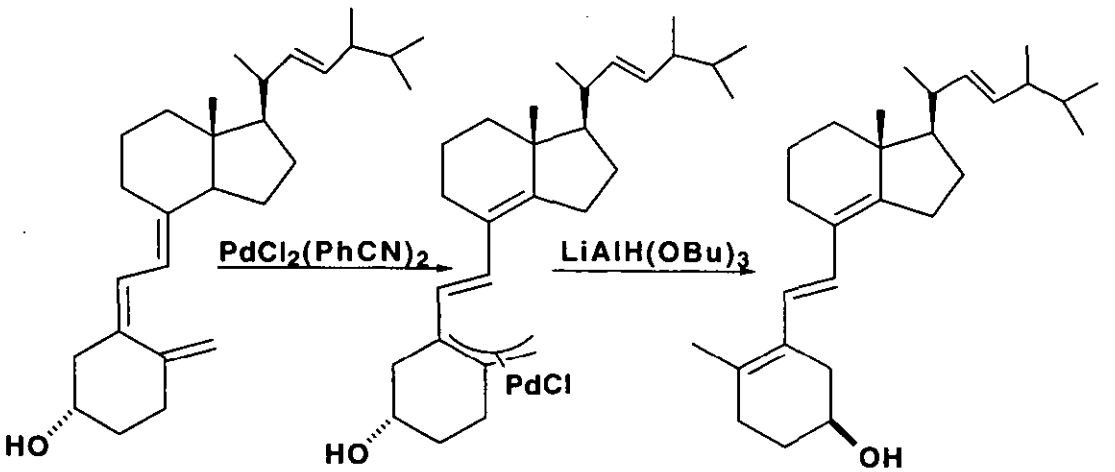


Scheme 2.2



Scheme 2.3

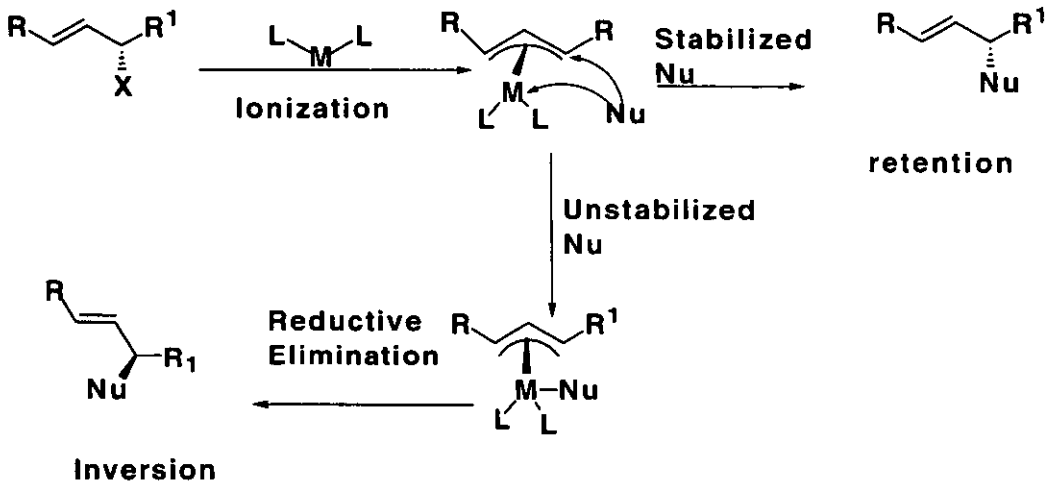
Isomerization of the double bond in vitamin D analogues such as calciferol occurs by an oxidation reduction sequence via π–allyl palladium complex (Scheme 2.4).[17]



Scheme 2.4

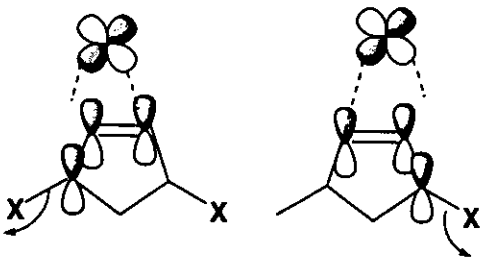
Depending on the structure of substrate every step may provide an opportunity for enantioselection with the exception of the decomplexation, which occurs after bond formation.

Although ionization proceeds with inversion of stereochemistry, regardless of the nucleophile, the addition of a nucleophile can involve two pathways in which the nature of the nucleophile leads to a different stereochemical outcome (Scheme 3).[18-20]

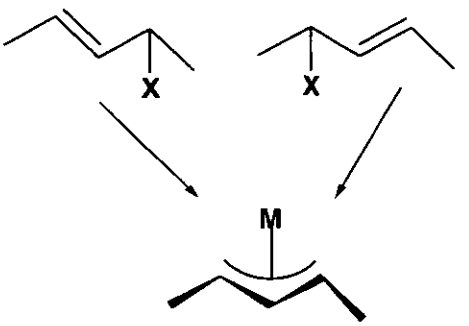


Scheme 3

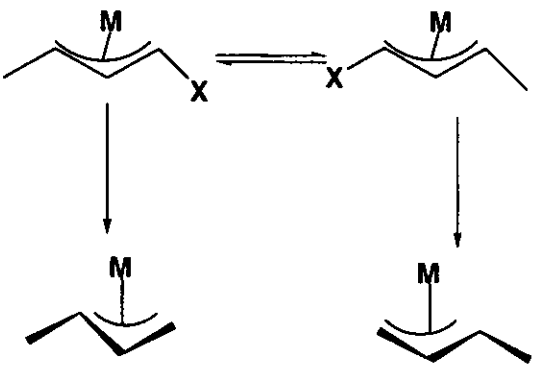
A unique feature of the transition metal catalysed allylic displacement is its ability to convert starting materials of various types, such as racemic, meso and achiral compounds, into optically pure material. Strategies which effect such transformations are derived from recognition of the stereochemical courses in each step of the catalytic cycle (Scheme 2), and analysis of symmetry elements in the substrate or intermediate. Scheme 4 summarizes potential sources of enantio-discrimination in transition-metal catalysed allylic displacement.



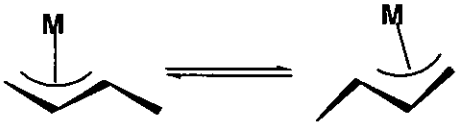
A:Enantiotopic leaving group



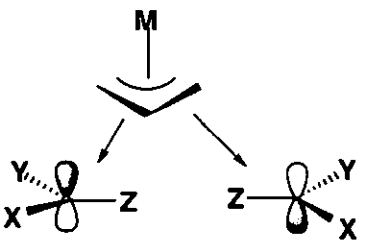
B: Enantiotopic Terminii of the allyl



D: Enantiotopic Faces of Olefin



C:Enantiotopic Faces Exchange



E: Enantiotopic Faces of Nucleophile

Scheme 4

The first strategy (A) involves discrimination between enantiotopic leaving groups, the transition metal catalyst can be made to choose deftly between the two leaving groups.[21]

The second strategy (B), involves two enantiomers of a racemic substrate converge into a meso π–allyl complex wherein preferential attack of the nucleophile at one of either allylic terminal leads to asymmetric induction.[22a]

If the η^3-allylic intermediate is not symmetrically 1,3-disubstituted, enantioselection will be dictated by which face of the allylic fragment is presented to the nucleophile. This is represented by(C).[22b]

The fourth strategy shown in (D), involves the transition metal testing both faces of the olefin, but only one face will lead to metal ionization,[23] this strategy only works if the olefin is not symmetrically distributed.

Enantioselectivity can also be achieved if the nucleophile is prochiral or is an equilibrating mixture of racemic nucleophiles. Here, enantioselectivity is achieved by enantioface discrimination of the nucleophile moiety (E).

Examples of chiral ligands used in allylic displacement are shown in Fig 1

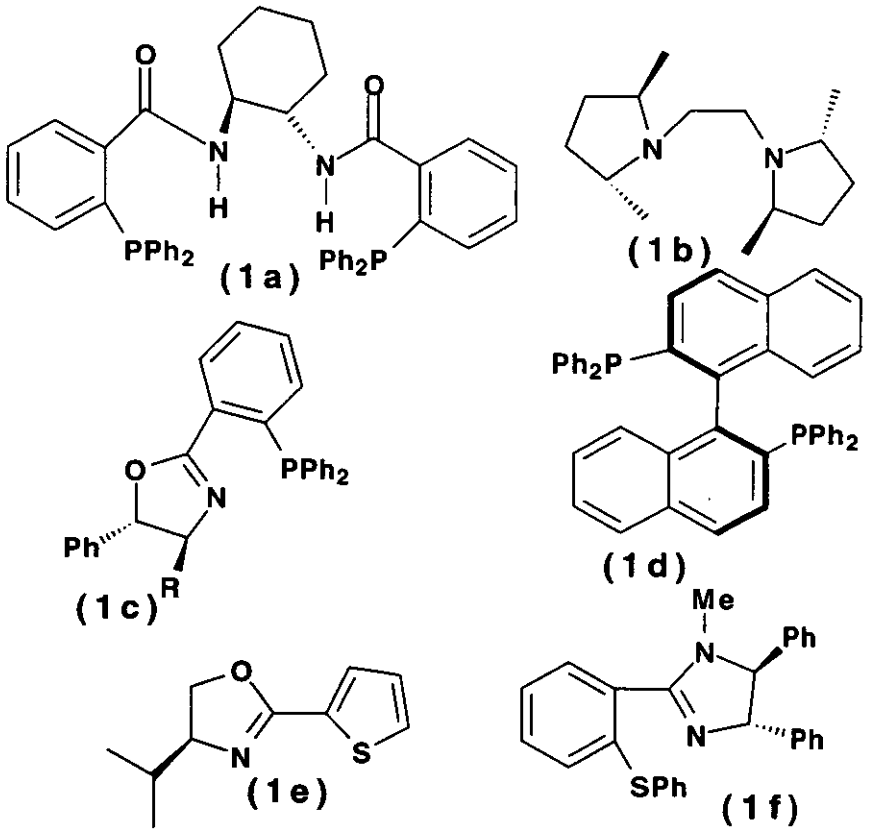
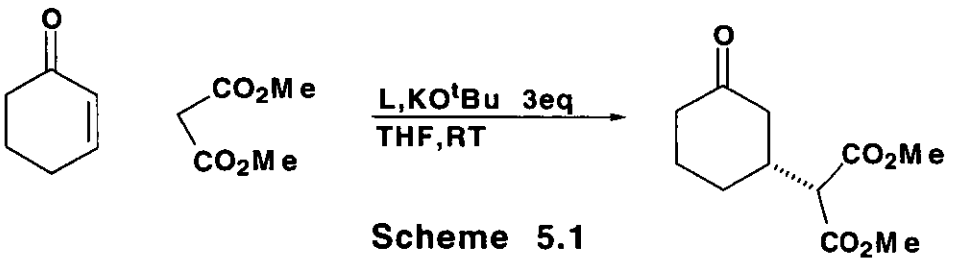


Fig 1

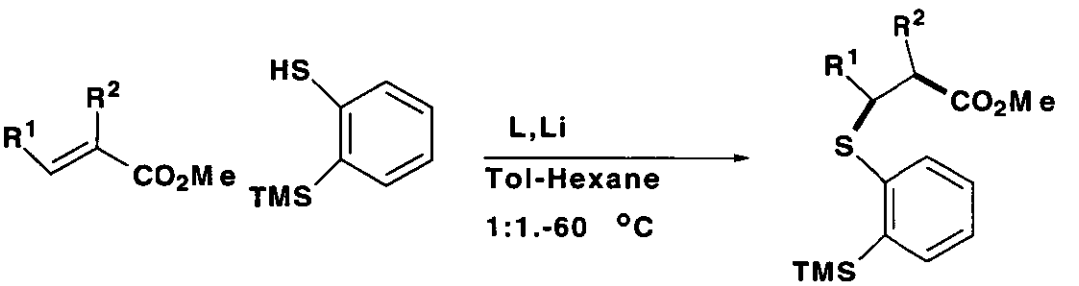
Zinc mediated conjugate addition

Another very important reaction is the Michael addition to α, β-unsaturated systems which is a fundamental process in organic chemistry, because it forms carbon-carbon (Scheme 5.1),[24] carbon-nitrogen (Scheme 5.2),[25] carbon-sulfur (Scheme 5.3)[26] or carbon-oxygen bonds at the β position of the carbonyl group and results in highly functionalized compounds with one or two asymmetric centres.



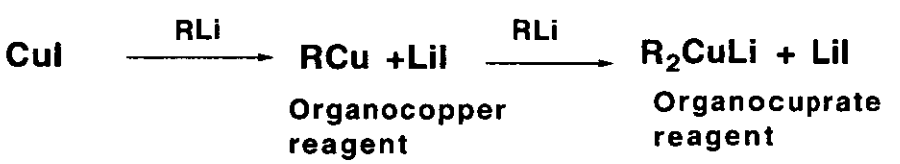
Scheme 5.1

Scheme 5.2



Scheme 5.3

The golden age of organocopper chemistry began in 1941 when Kharasch and Tawney[27] reported the 1,4 addition reaction of Grignard reagent to an α,β-unsaturated ketone in the presence of a small amount of Cu^{I} salt.[28] Gilman reported in 1952 that the addition of one equivalent of MeLi to a Cu(I) salt resulted in the formation of a yellow precipitate, which then afforded a colourless solution upon addition of another equivalent of MeLi (Scheme 5.4).[29]



Scheme 5.4

In 1966, Costa isolated a complex between phenylcopper (I) and magnesium, as well as crystals of lithium diphenyl cuprate (I) complex.[30]

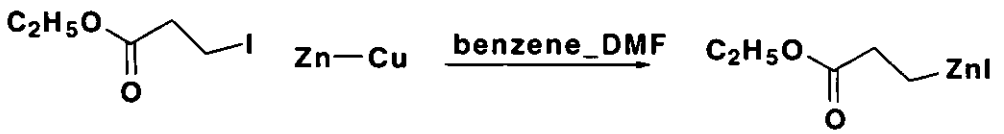
The organic chemistry of organocuprates started its rapid development in 1966, when House showed that the reactive species of conjugate addition is the lithium diorganocuprate (I) called a Gilman reagent.[31] Foundations for subsequent vigorous synthetic development were laid by Corey and Posner.[32]

Shortly after the opening of the Lewis acid era with the discovery of the Mukaiyama aldol reaction in 1973,[33] Yamamoto and Marayama's reports on the $RCuBF_3$ reagents[34] introduced the new concept of Lewis acid assistance in organocopper chemistry.[35] Although the identity of the $RCuBF_3$ moiety is still elusive,[36] BF_3 activation was applied to numerous synthetic work, as illustrated by a diastereoselective addition of a homoenolate species in the total synthesis of cortisone.[37]

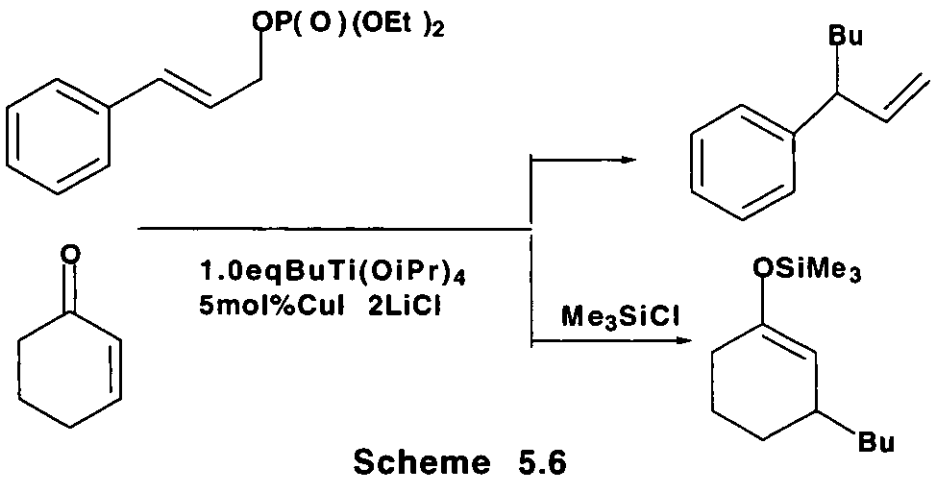
Since the initial discovery by Nakamura and Kuwajima in 1984,[38] Me_3SiCl has become a standard reagent for acceleration of conjugate addition. This effect was reported first for the copper-catalysed conjugate addition of the zinc homoenolate of propanoic acid ester, then for Grignard-based catalytic reagents[39,40] and stoichiometric lithium diorganocuprates.[41-45]

The zinc homoenolate started the chemistry of metal homoenolates.(Scheme 5.5).[46-48] The synthetic scope of such a nucleophile-bearing electrophile was further exploited by Tamaru, Yoshida, and co-workers first,[49] and then extensively by Knochel and others.[50-51] Dominated by lithium and magnesium-based systems until the mid 1980s, organocopper chemistry now routinely utilizes much milder organometallic nucleophiles such as organozinc, titanium,[52] zirconium,[53,54] and

aluminium reagents.[55] With the aid of proper activators, these mildly reactive reagents show selectivities unavailable with the conventional reagents, as illustrated in Scheme 5.6 for Me_3SiCl-dependent chemoselectivity.[56]



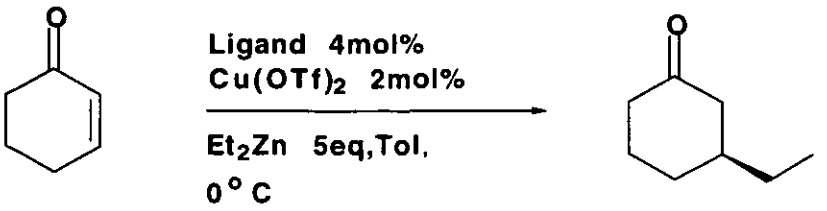
Scheme 5.5



Scheme 5.6

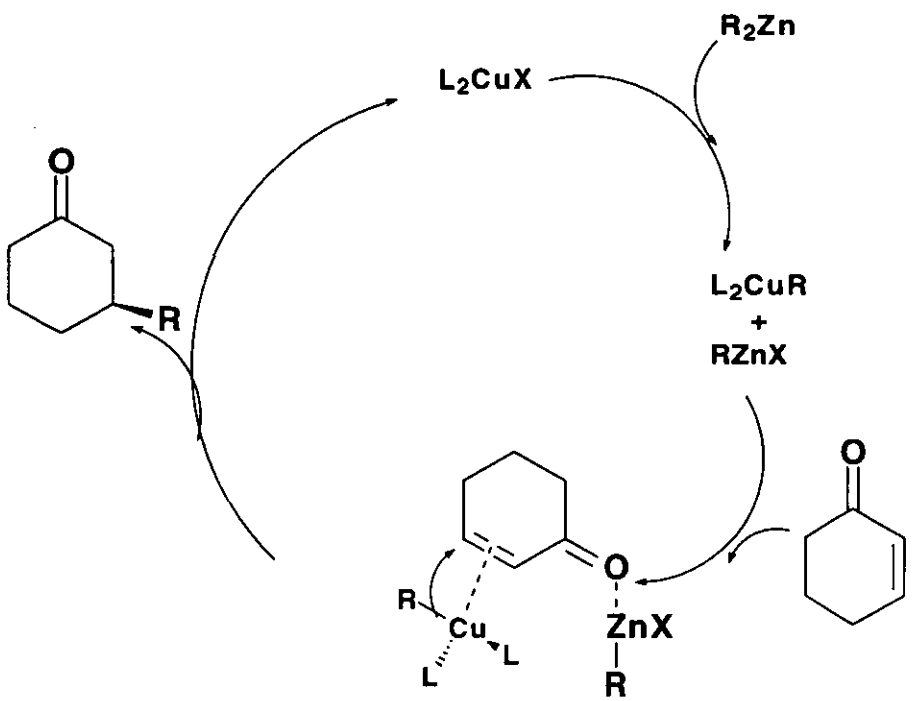
Organocopper chemistry is still rapidly expanding its synthetic scope. The scope of carbocupration, previously limited to acetylenes, has been extended to olefins.[57-59] Enantioselective conjugate addition[60] has become truly useful through the use of dialkylzinc, a cationic copper catalyst and a chiral ligand (Scheme 6).

In 1997 Feringa reported one of the most enantioselective conjugate addition to date of dialkylzinc reagents, catalysed by chiral copper phosphoramidite complexes.[61] The reaction is mediated by 2 mol % $Cu(OTf)_2$ and 4 mol % chiral ligand (Scheme 6), and he reported an ee of 92% when the reaction was carried at –35 *°C*.



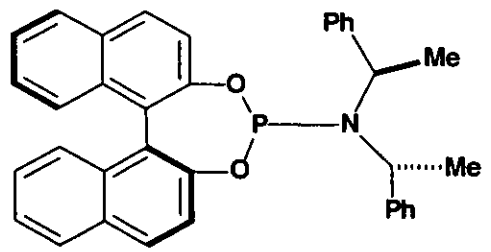
Scheme 6

A possible pathway for the 1,4-addition is shown in Scheme 7. This involves the transfer of an alkyl fragment from R_2Zn to the copper complex,[62] followed by π–complexation of the resulting copper alkyl species to the double bond of the enone and of the alkylzinc ion to the enone-carbonyl. Next, alkyl transfer to the β–position of the enone generates a zinc enolate, which upon protonation provides the 1,4-adduct.

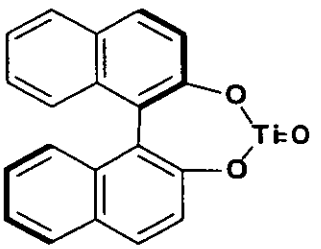


Scheme 7

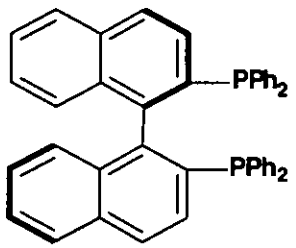
The presence of a ligand is fundamental, as without it the reaction is very slow and with many side products found. Some examples of chiral ligands used in this type of reaction are shown in Fig 2.



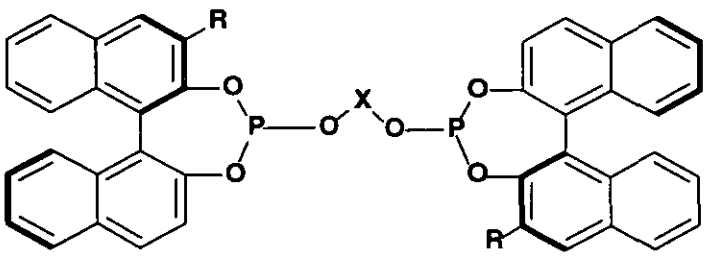
Feringa 1997
(2a)



Kobayashi 1994
(2b)



Alexakis 1997
(2c)

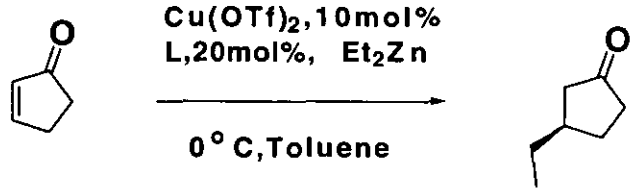


Ming 1999 X=binaphthyl
(2d)

Fig 2

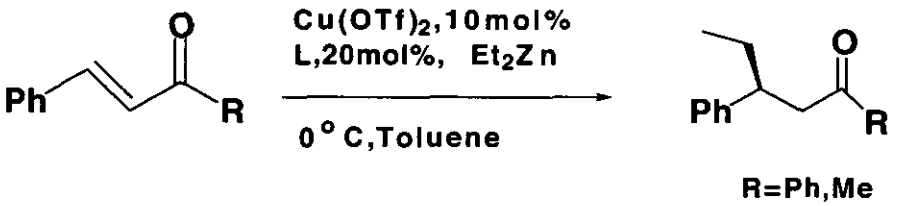
The asymmetric 1,4-addition of diethylzinc to cyclohex-2-enone (Scheme 6) has been well developed and is well understood, and using this methodology it has been possible to incorporate stereoselectively functionalized cyclohexane and larger rings in natural product synthesis.[63] In contrast, the asymmetric 1.4-conjugate addition to cyclopent-2-enone (Scheme 8) presents more of a challenge. The importance of the cyclopentane skeleton stems for example from its presence in postaglandins,[64] and alkaloids including dendrobine.[65] Recent reports by Chan,[66]

Pfaltz[67] and Hoveyda[68] give ees of up to 97% for the asymmetric 1,4-addition of diethylzinc to cyclopent-2-enone at –35 °C.



Scheme 8

Attempts by Pfaltz[67] to apply the asymmetric 1,4addition to acyclic enones (Scheme 9) showed little success with ees achieved of only up to 50% when the reactions were carried out at –35 °C.

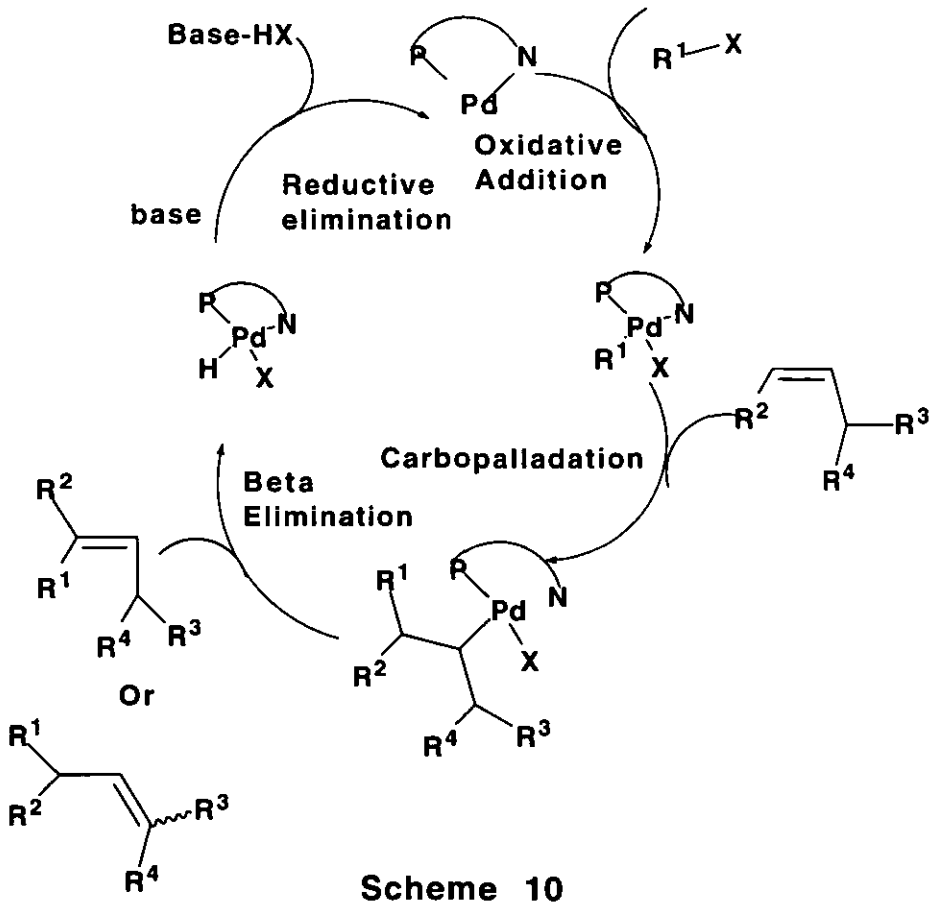


R=Ph,Me

Scheme 9

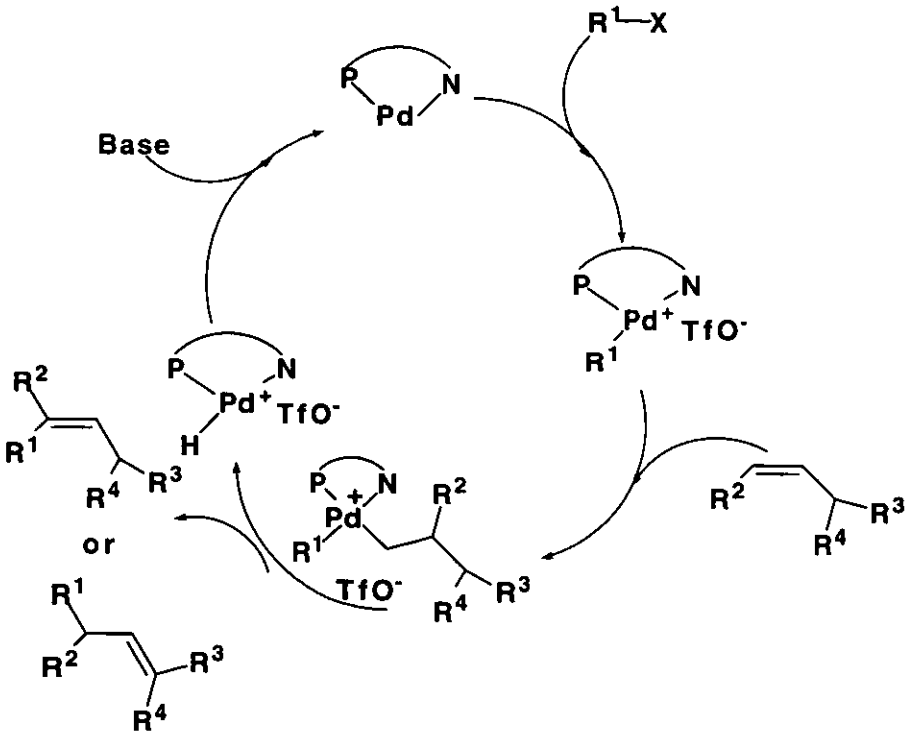
Heck reaction

In recent years there has been considerable interest in the use of the Heck-type arylation and alkenylation of olefins for constructing carbon skeletons of biologically important organic compounds.[69,70] Development of the asymmetric Heck reaction, where the carbon-carbon bond formation proceeds with high enantioselectivity, would provide new efficient routes to the optically active compounds. Pioneering work in this area by Shibasaki[71] and Overman[72] has opened the way for the asymmetric Heck reaction. The catalytic cycle, shown below in Scheme 10, is termed the neutral pathway, which is followed for unsaturated halide substrate.



Scheme 10

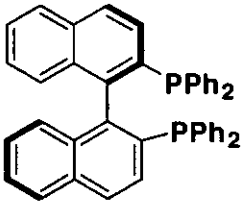
However, there is also a cationic pathway, which is shown below in Scheme 11 This pathway is followed by unsaturated triflate substrates, or for unsaturated halides in the presence of halide scavengers such as Ag (I) or Tl(I) salts.[73,74] The individual steps are similar to the neutral pathway, but the difference between the two mechanisms lies in the nature of palladium(II) intermediate, which is now cationic, and this difference has a marked effect on the reactivity and stereoselectivity.



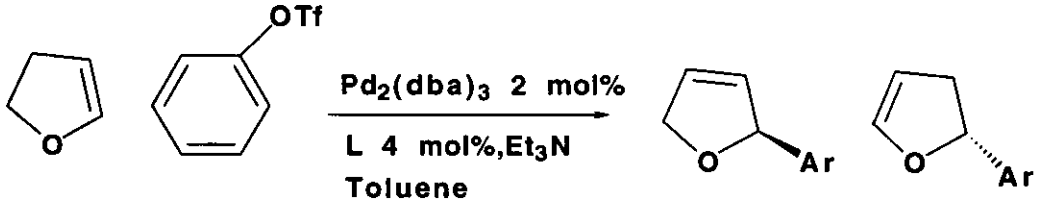
Scheme 11

The salient features of the cationic pathway shown in Scheme 11 were deduced by Cabri[75] and Hayashi.[76] Subsequent to oxidative addition, a vacant co-ordination site is generated by triflate dissociation or by halide abstraction by Ag(I); this vacant site facilitates double bond coordination to form the cationic intermediate which ultimately results in the formation of the Heck product.

The key feature of this reaction is the removal of an anionic ligand from the palladium coordination sphere, which allows the coordination of the alkene while the integrity of the chiral ligand is maintained. Ozawa[77] reported the application of the ligand (3) in the asymmetric Heck reaction (Scheme12), and published ees exceed 96%.

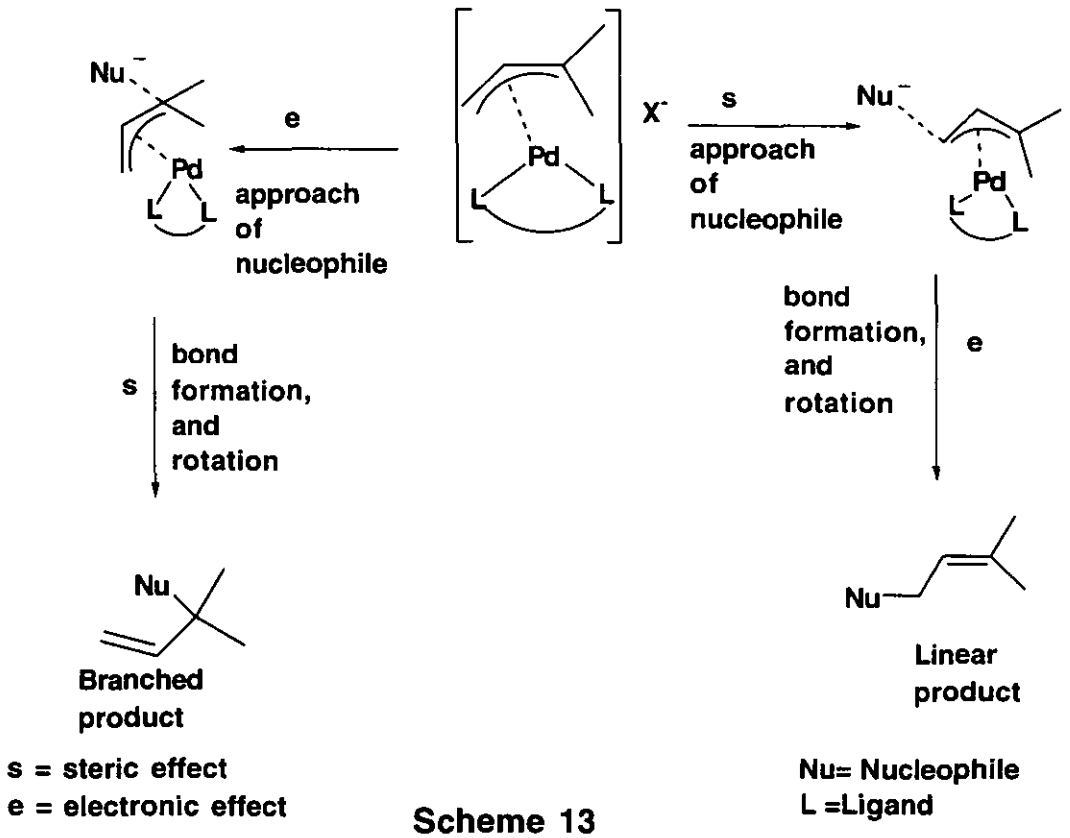


(3)



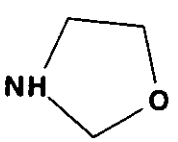
Scheme 12

A common feature of the ligands involved in the palladium catalysed allylic displacement reaction, 1,4-addition and the Heck reaction is that in most cases nitrogen appears as one of the ligating atoms. The need to balance the steric and electronic conditions in order to achieve the best results in the catalytic reaction[78] (Scheme 13) may dictate the need to introduce substituents at nitrogen. The usual method is the application of the Eschweiler-Clarke approach.[79] The reaction involves heating a primary or secondary amine with formaldehyde and formic acid to yield the tertiary amine. The hydride acceptor is the iminium ion, from condensation of the amine with formaldehyde. The resulting *N*-methyl amino alcohol core structures are found in several bioactive molecules.[80,81]



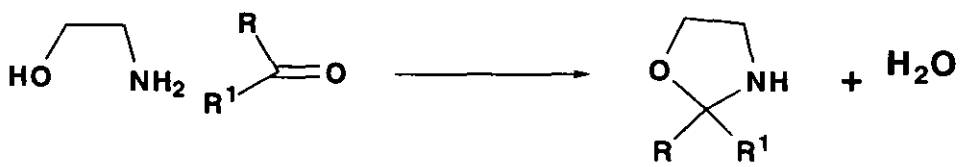
Scheme 13

α-Amino alcohols are important intermediates in many organic synthesis, but there are few methods to generate these compounds One method is to construct an oxazolidine ring, which is obtained by condensation of an amino alcohol and aldehyde or ketones, and then reductively cleave the ring to give the α-amino alcohol.[82] An alternative strategy for the synthesis of α-amino alcohols is through the synthesis of cyanohydrins derived from aldehydes or ketones followed by reduction using lithium aluminium hydride,[83] or by reduction of α-amino acids.

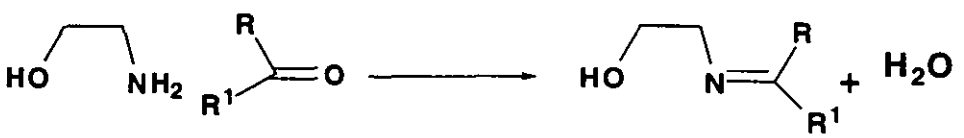


4

The oxazolidine ring system **4** has been studied extensively by Knorr and coworkers[83] who ascribed the cyclic structure to products which were obtained, e.g. from ethanolamine and aldehyde or ketones with loss of a molecule of water (Scheme 14), without taking into account the possibility that the condensation product might simply be the Schiff base (Scheme 15).



ha **Scheme 14**

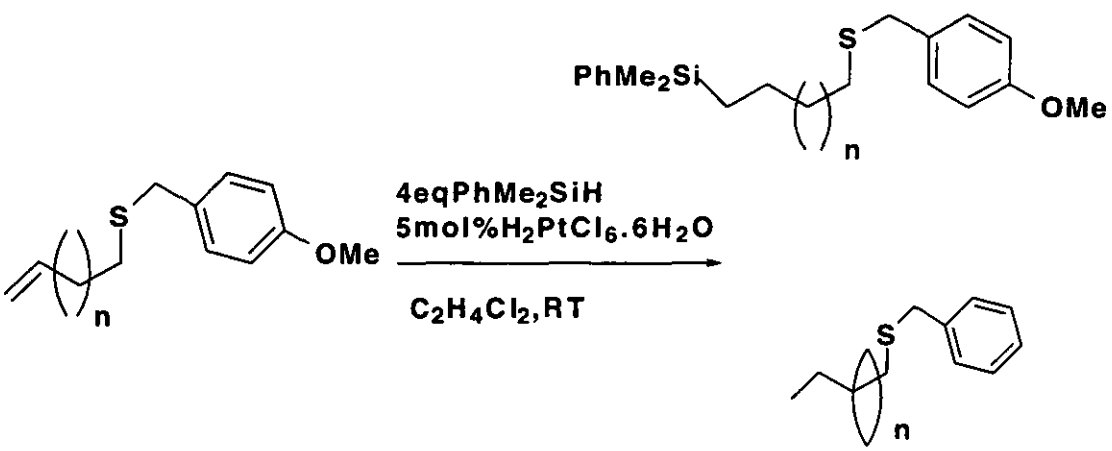


Scheme 15

In 1951 McCasland and Horswill[86], who were investigating some complex cases arrived at the conclusion that the product structures were not well-established. The formation of oxazolidines from aldehydes and simple aliphatic ketones has since been studied extensively.[87-90] However their formation from aromatic ketones has not been reported prior to our work.[91]

Since the first reports of π-allyl palladium catalysed allylic substitution,[92] and the subsequent reviews by Trost,[93] many examples of chiral ligands have been synthesized for application in this reaction, and here we report novel approaches to the synthesis of some ligands to be applied in this reaction. However, few attempts have been made to use thioethers. Thioethers are powerful ligands for transition metals, and the affinity of thioether groups for transition metals has been used to direct the outcome to stoichiometric reactions mediated by transition metals.[94]

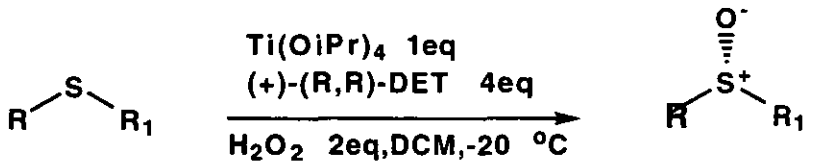
Recently, Krafft and co-workers have shown that the Pauson-Khand reaction gives excellent regiocontrol when a thioether is present in the substrate.[95] The most dramatic advance has been the demonstration that a sulfur atom in the substrate can exert an influence in the palladium-catalysed alkylation, dictating the regiochemistry of nucleophilic attack. [96] More recently, thioethers have proved to modify reactivity in the platinum-catalysed hydrosilyation of olefins (Scheme 16).[97] The importance of the thioether moiety was demonstrated in a competition experiment, in which homoallyl sulfide was mixed with octene and subjected to hydrosilylation at room temperature; only the thioether substrate underwent hydrosilylation. Hydrosilylation of octene fails under similar conditions, demonstrating that homoallylic thioether was accelerating an otherwise sluggish reaction.[97]



Scheme 16

The final class of ligand which we consider here are those containing sulfoxides. The synthesis of sulfoxides has been widely reviewed. The efficiency of the sulfoxde group in asymmetric synthesis is thought to be due to the presence of three different groups at the asymmetric centre; while nitrogen tends to be hindered by pyramidal inversion this is not the case with sulfur, where pyramidal inversion is not observed below 150 °C.[99]

Since the first reports of sulfoxidation by Belenovic[100] and Montanovi,[101] many authors have attempted asymmetric sulfoxidation with the modified Sharpless asymmetric epoxidation,[102] adopted independently by Kagan[103] and Modena[104] (Scheme 17).



Scheme 17

Kagan modified the Sharpless procedure by adding one equivalent of water, a poison in the epoxidation reaction, and increased the ratio of (+) DET to titanium isopropoxide to 2:1 (Scheme 18). Under these conditions, double bonds, amines, alcohols and phenols are not oxidized.

Davis reported the use of *N*-sulfonyl oxaziridines as sulfoxidation reagents.[105,106] Later, Davis reported the use of cyclic oxaziridines based upon camphor sulfonic acid,[107] and this was later modified by Page.[108] In oxaziridines the nitrogen is a stable chiral centre, and electron-releasing groups tend to stabilize oxaziridines, reducing their electrophilicity. In the camphor system, the sulfonyl group is electron-withdrawing, rendering these compounds highly electrophilic, a property exploited in their use for sulfur oxidation.[109]

To summarize, the aim of the work described in this thesis is to design ligands which show multipurpose usage in asymmetric synthesis. The main focus of our design is to synthesize ligands for the asymmetric palladium catalysed allylic substitution reaction, the asymmetric 1,4-addition of dialkylzinc to enones , and

the asymmetric Heck reaction. Additionally it was intended to investigate the efficiency of the Page sulfoxidation reagent in the presence of electron withdrawing groups (EWG) and electron donating groups (EDG) in the substrate molecules.

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CHAPTER 2
Ligand Design

LIGAND DESIGN

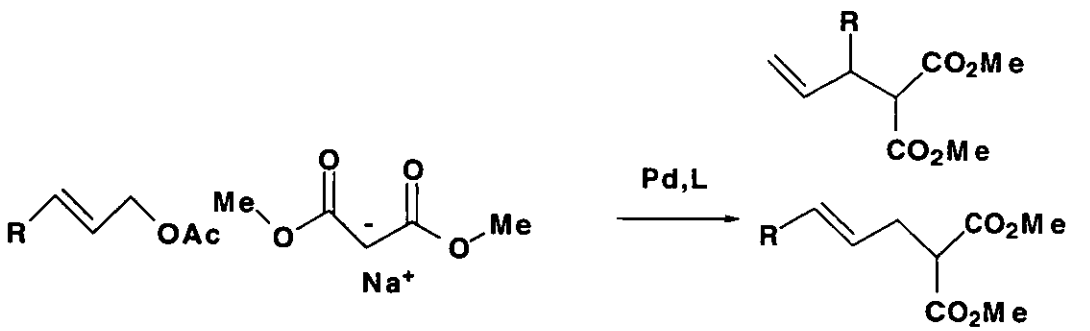
In attempting to design ligands, there are certain constraints which must be considered, these constraints often limit the scope or degree to which the ligands can function. Thus it is up to the designer to try and overcome those constraints. In designing ligands for complexing with transition metal the following constraints must be considered.

a) The metal: The metal to which the ligand is complexing has a great influence on the outcome. Some metals complex to the ligand and never release it, others do not complex at all. Ligands can also form inert and labile complexes.

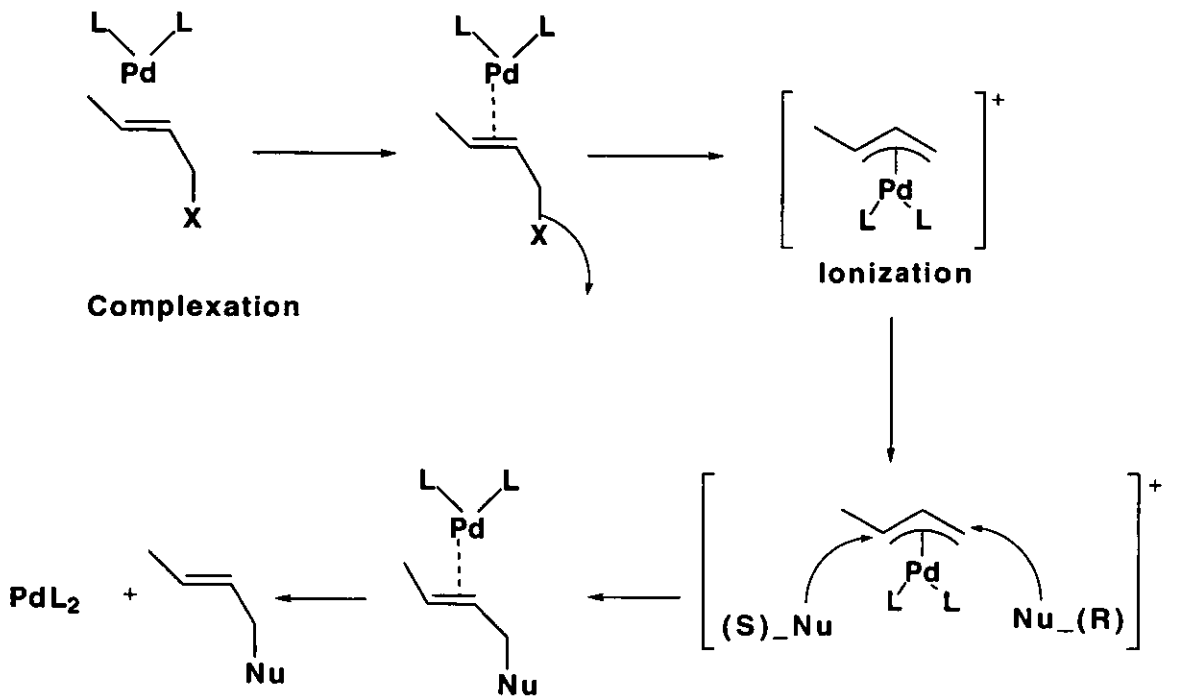
b) The nature of the ligand heteroatoms: The binding nature of the heteroatom again has fundamental importance, the ability or otherwise of a heteroatom to act as a Lewis base is very important if complexation is to occur. The Lewis basicity has a great influence on the stereoselectivity; for example, as has been well documented for the palladium catalysed alkylation, the nucleophile approaches *trans* to the better π accepting heteroatom.[1]

c) Type of reaction: Some ligands which are designed for alkylation might not be useful for epoxidation or other reactions and *vice versa*.

For the case of the allylic displacement reaction shown below in Scheme 18, the general catalytic cycle shown in Scheme 19,[1] must be considered in order to enable us to design a good ligand. The basic cycle consists of metal-olefin complexation, ionization, alkylation and decomplexation.



Scheme18

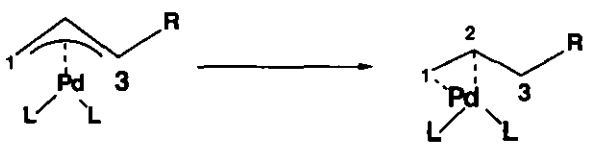


Scheme 19

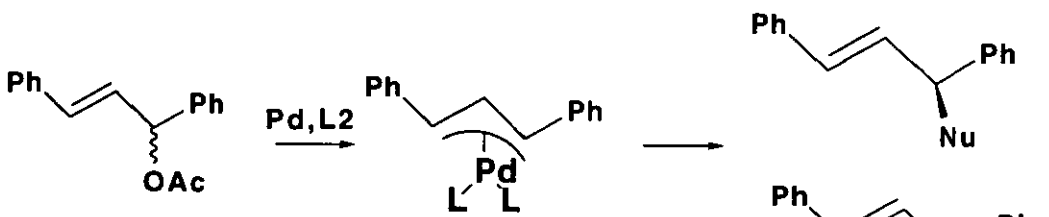
To achieve asymmetric induction, the asymmetric environment of the ligands must be felt on the opposite face of the π-allyl unit, where bond making and breaking are occurring. For complexes containing bidentate ligands, it has been suggested that

regioselectivity is determined by the bonding of the allyl moiety.[2] When the allyl group is substituted at one of its terminal positions, the symmetry of its bond to palladium is distorted. QSAR studies[1] have shown that the palladium-allyl bond is distorted from η^3 to η^1-η^2 (Scheme 20). The Pd-C_1 bond is shorter than the Pd-C_3, this distortion occurs if the allyl group is substituted at one terminus.

It appears that the malonate nucleophile (Scheme 18) attacks preferentially at the allylic carbon atom with the largest palladium-C distance.[3,4] To avoid this complication we opted for a symmetrically substituted olefin (Scheme 21), this allows the designed ligand to provide the required environment distortion; for example, this could be achieved by altering the bite angle. This is the angle which the ligand makes with the palladium (Figure 5).



Scheme 20



Scheme21

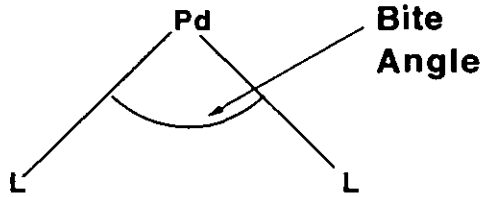
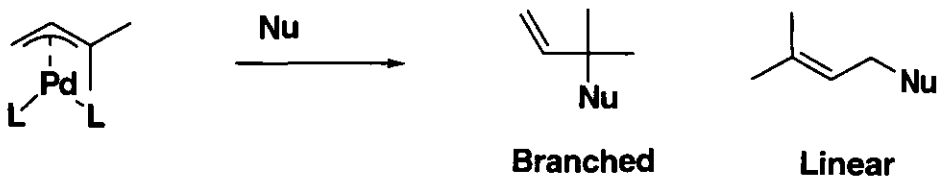


Fig 5

It has been shown that increasing the size of the bite angle enhances the regioselectivity towards the branched product (Scheme 22).

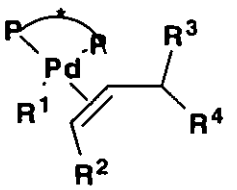


Scheme 22

Considering the Heck reaction (Schemes 10,11) the catalytic cycle reveals many differences from the allylic displacement reaction, here the key step which determines enantioselectivity is the association and insertion into the palladium-R^1 bond.

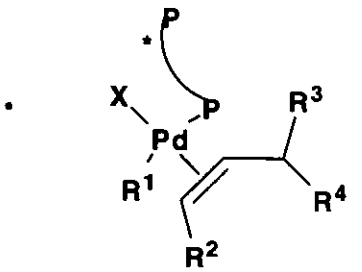
Moreover, here the two pathways shown result in different enantioselectivity. For example, the cationic pathway is regarded as being more stereoselective than the neutral pathway. This is due to the former involving a vacant site on the metal which gives a 16 electron species (Figure 6A below). In this case the integrity of the whole system is preserved, thus maximising the asymmetric induction, which results in better stereoselectivity, while in the neutral pathway dissociation of chiral ligand

(Figure 6B) in order to accommodate alkene insertion, tends to reduce enantioselectivity.



16e Species

A



Dissociation of 16e Species

B

Fig 6

In practice it has been possible to influence which pathway will be followed in a given Heck process either by adding silver salts to the reaction[5] or by adding excess halide anions to reactions using triflate, which results in nucleophilic displacement of triflate anion from the product of oxidative addition.[6]

Finally, the 1,4-conjugate addition catalytic cycle is as shown in Scheme 7 in the introduction (page 14).

Here again the asymmetric induction is achieved in a different manner from both of the above reactions. The assumption here is that the chiral ligands are located at opposite corners of the planar array of the metal atom to minimize unfavourable electronic and steric interactions (Figure 7).[7]

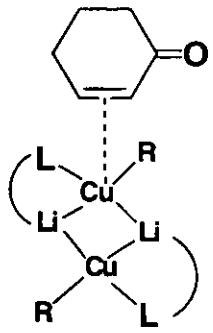
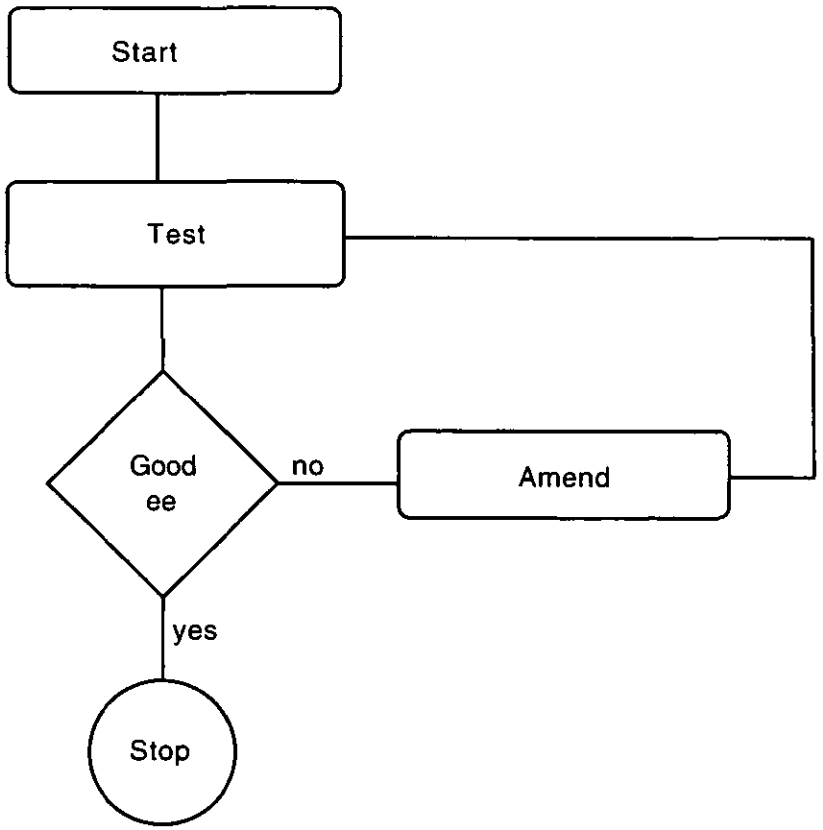


Fig 7

For chiral lithium organocuprates, one model of the conjugate addition reaction assumes that the cuprate reagent is a dimer with a planar array of metal atoms,[8] and that the chiral ligands are located at the diagonal corners of the planar array of metal atoms to minimize any unfavourable interaction. The observed enantioselectivities then depend upon a number of factors, including substrate structure, ligand stereochemistry, solvent, and the cuprate composition. For a model of the zinc-mediated reaction, see Scheme 51 page 97.

Our design strategy is shown below in Scheme 23.

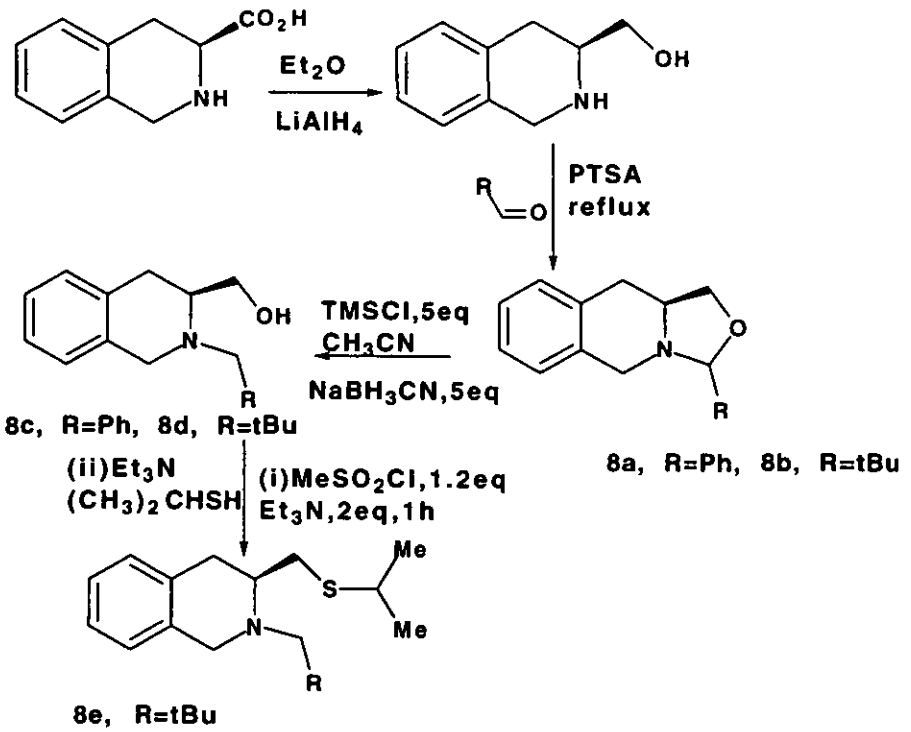


Scheme 23

Armed with this information we proceeded to design a number of ligands. Each class of ligands is considered in terms of their ligating atoms S,N, P,N, etc. Within each class the synthesis is considered and any new novel approaches are explained.

2.1 S,N LIGAND SYNTHESIS

The first attempt in this class of ligands started from the enantiomerically pure commercially available isoquinoline shown in Scheme 24.



Scheme 24

We were able to synthesize the ligand 8e by first reducing the acid using lithium aluminium hydride to give the alcohol. The alcohol was then refluxed with benzaldehyde or pivalaldehyde to give the oxazolidines 8a and 8b, the oxazolidines were then subjected to reductive cleavage to afford the corresponding amino alcohols 8c and 8d, which were then subjected to nucleophilic displacement by the isopropyl thiol after activation of the hydroxy groupn as the mesylate, prepared using methanesulfonyl chloride.

Only poor enantioselectivity was achieved when the ligands were tested in the palladium catalysed allylic displacement reaction of 1,3-diphenyl propyl-2-enyl acetate using dimethyl malonate as the nucleophile, as described in Chapter 3. The

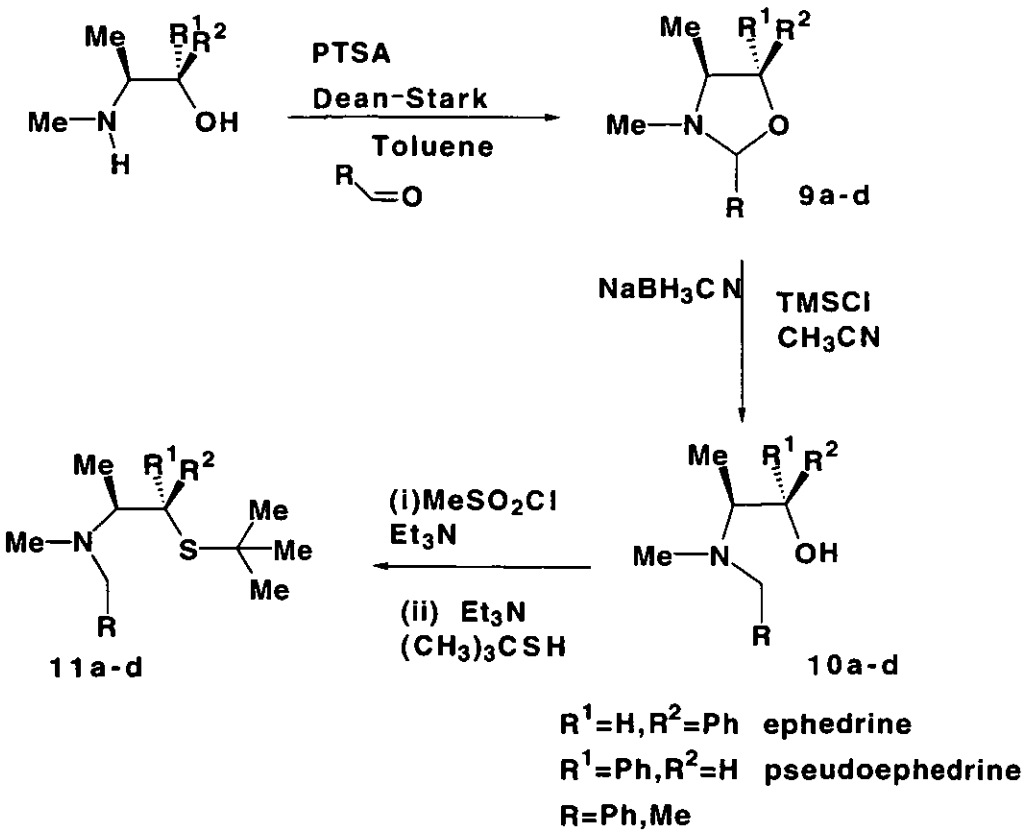
Table 1

Palladium Allylic Alkylation Reaction

R	Yield %	Ligand	ee %
Ph	78	8e	12
t-butyl	92	8d	23

Ephedrine and pseudoephedrine have been used as chiral auxiliaries in many asymmetric syntheses,[9, 10] and we decided to proceed with the design of our ligand using both as our chiral materials. It is essential when planning a design sequence to minimize the number of steps, in order to increase simplicity and to maximise efficiency.

Thioethers (sulfides) have been widely used as chiral ligands in many catalytic asymmetric reactions, for example for the palladium catalysed allylic displacement,[11] and we decided to attempt the synthesis of this type of ligand. The synthetic route is outlined in Scheme 25.



Scheme 25

This route involved formation of oxazolidines (9a-d) by condensing ephedrine or pseudoephedrine with the aldehyde in the presence of PTSA under Dean-Stark conditions to give the oxazolidines in 67-90% yield. Table 2 below shows the data for the oxazolidines.

Table 2

Oxazolidines from Aldehyde

Compound Number	R^1	R^2	R	Yield %
9a	Ph	H	Me	86
9b	Ph	H	Ph	65
9c	H	Ph	Me	89
9d	H	Ph	Ph	90

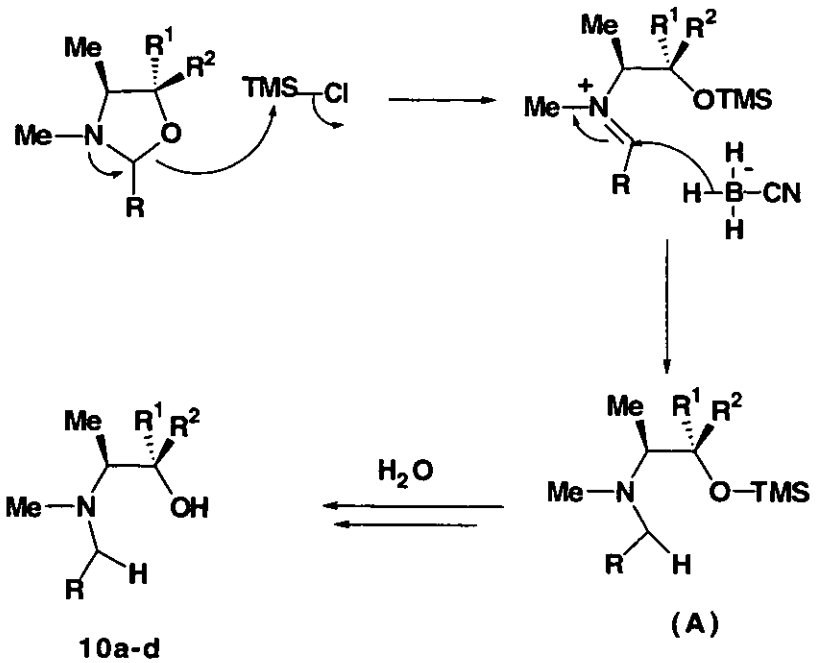
We then proceeded to ring open the oxazolidines (9a-d) to obtain the *N*-substituted amino alcohols (10a-d) (Scheme 26). These are usually synthesized by utilizing the Eschweiler-Clarke approach, whereby primary or secondary amines are condensed with formaldehyde followed by hydride transfer from formic acid to yield the N-substituted product. Our approach was to use $NaBH_3CN$/TMSCl in acetonitrile and to our delight we were able to ring open a variety of substrates.[12] The resulting ring opened structures (10a-d) are shown in Table 3 below. The detailed mechanism of this ring opening procedure is shown below in Scheme 26.

Table 3

Ring Opening of Oxazolidines Using TMSCl, $NaBH_3CN$

number	R^1	R^2	R	Yield %
10a	Ph	H	Me	98
10b	Ph	H	Ph	96
10c	H	Ph	Me	83
10d	H	Ph	Ph	93

Ring Opening Using
$TMSCl,NaBH_3CN$

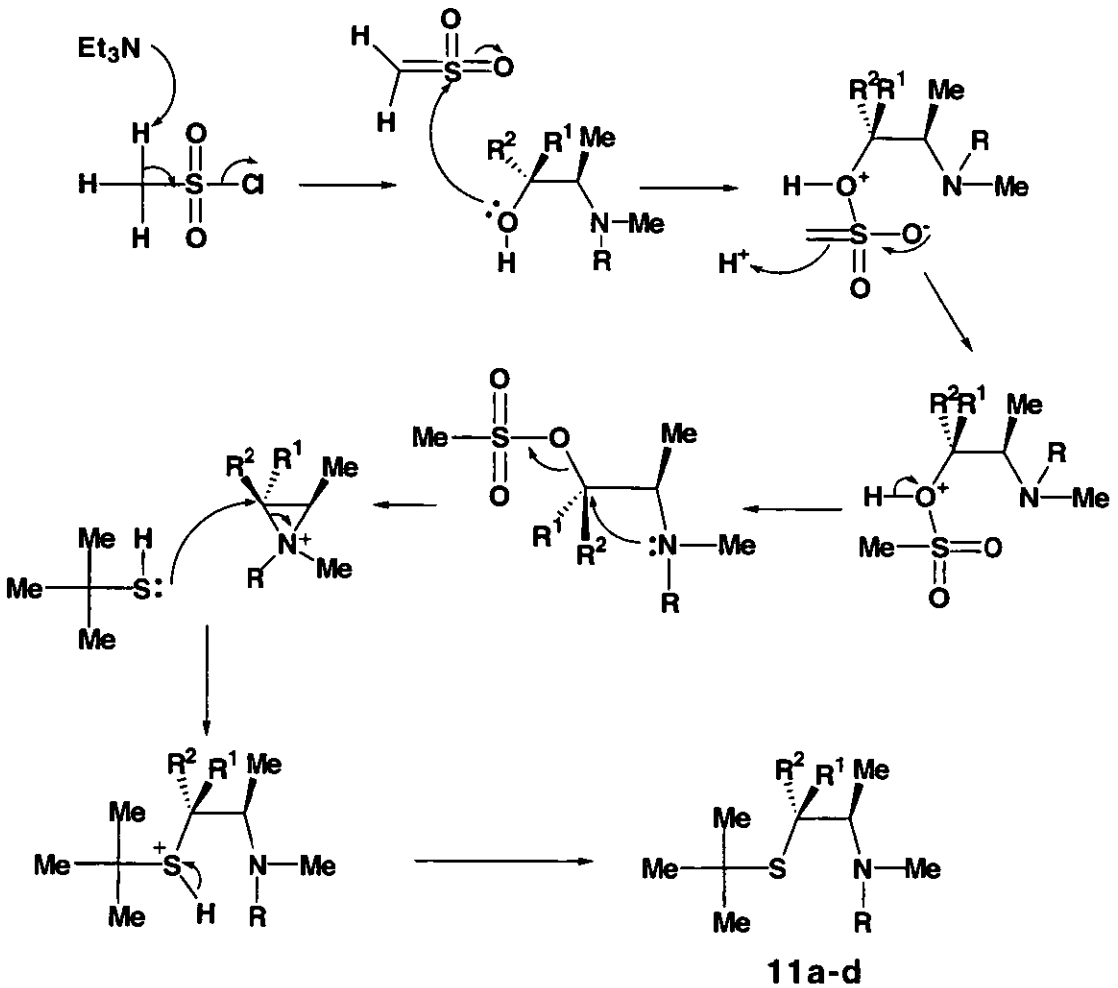


Scheme 26

The ring opening procedure presumably occurs by coordination of the oxygen atom of the oxazolidine to the TMSCl, resulting in iminium ion formation. Hydride ion is then transferred from $NaBH_3CN$ to yield the intermediate (A). Hydrolysis during work up of intermediate (A) yields the required amino alcohol (10a-d).

Having ring-opened the oxazolidines (9a-d) to obtain the *N*-substituted chiral amino alcohols (10a-d), we then proceeded to synthesize the thioethers (11a-d), by substituting the hydroxy groups with the mesylate and then displacing the mesylate with the thiol as outlined in Scheme 25 The mechanism of formation of the thioethers is outlined in Scheme 27 below. The mechanism involves a double inversion sequence at the reacting carbon atom.[13] This overall result has been proved by our group, by obtaining a single crystal X-ray structure which confirms the retention of configuration of the original amino alcohol.[76b] Table 4 shows the thioethers (11a-d) obtained. When tested in the palladium catalysed allylic

displacement (Chapter 3, page 80-81, tables 16 and 17), using 10 mol % of the ligands and 10 mol % of palladium, the outcome was an improvement in ee as compared to (8d-e).



11a-d

Scheme 27

Table 4

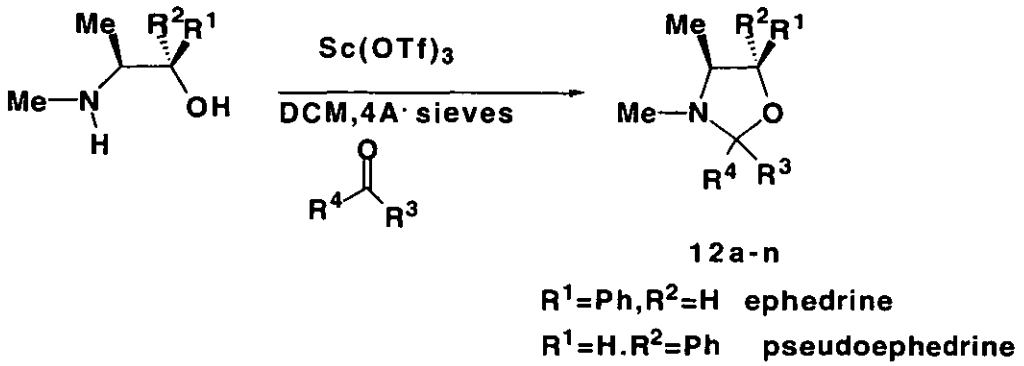
Chiral Sulfide Ligands from Aldehydes

Ligand	R^1	R^2	R	Yield %
11a	Ph	H	Me	65
11b	Ph	H	Ph	63
11c	H	Ph	Me	62
11d	H	Ph	Ph	69

We considered the possibility of using the same sequence of reactions, but instead of an aldehyde, to condense the chiral amino alcohol with aromatic and bulky aliphatic ketones. In doing so we are entering the realm of the unknown because many groups have tried to form oxazolidines from aromatic and bulky aliphatic ketones, but were not successful.[14]

Our original attempt to form the oxazolidines from aromatic ketones used the procedure outlined in Scheme 10, but instead of PTSA, we used $MgBr_2$, $AlCl_3$ and subsequently even camphor sulfonic acid, but in all cases we did not isolate the required oxazolidines.

We noted that scandium triflate has been used as a mild Lewis acid agent in radical cyclisation reactions,[15] in studies of the intramolecular reactions of *N*-acyliminium ions to synthesize the neuvamine skeleton,[16] and in a high yielding cascade sequence.[17] We decided to use this reagent as outlined in Scheme 28. Due to the importance of the ring closure reaction using ketones, a description of the experimental procedure is given here for clarity. 10 mol % of scandium (iii) triflate was added to a solution of 1.2 eq of the ketone in dry dichloromethane, then 1 eq of the ephedrine or pseudoephedrine was added, then 10 g of 4Å molecular sieves was added and the container was sealed and left standing for a period of 7-10 days. Fresh sieves were added four times during the course of the reaction; this was essential for the success of the reaction. The reaction was followed by carbon-13 NMR spectroscopy for the appearance of a peak at 97-110 ppm. When the required peak had been observed, the molecular sieves were removed by filtration and washed with dry dichloromethane (20 ml), the filtrate was stirred with 10-12g of sodium hydrogen carbonate for 2 hours and then removed by filtration. The filtrate was washed with water, dried over magnesium sulfate, and removal of the solvent yielded the oxazolidines (12a-n).



12a-n

R^1=Ph,R^2=H ephedrine

R^1=H.R^2=Ph pseudoephedrine

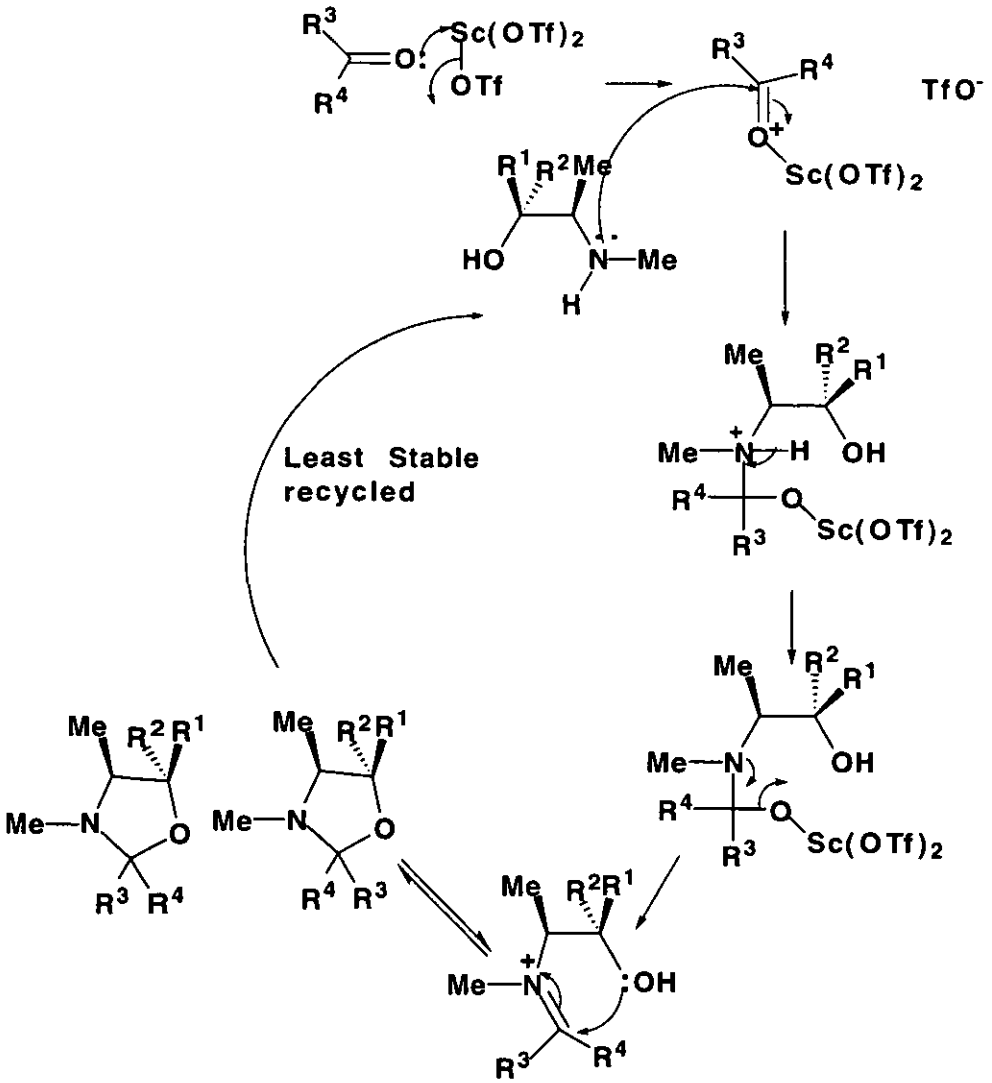
Scheme 28

Table 5 below shows the oxazolidines obtained together with yields and diastereisomeric ratios The diastereoisomeric ratios were measured using NMR spectroscopy. The proposed mechanism is shown below in Scheme 29.

Table 5

Formation of Oxazolidines from Ketones using Sc(III) Triflate

Compound Number	R^1	R^2	R^3	R^4	Ratio of Major/ Min	Yield %
12a	Ph	H	Ph	Me	13:1	76
12b	Ph	H	Ph	Et	5 : 3	65
12c	Ph	H	Furyl	2-Me	2 : 1	62
12d	Ph	H	Pyridyl	2-Me	3 : 2	61
12e	Ph	H	p-OMe Ph	Me	6 : 5	63
12f	Ph	H	Et	Me	7 : 1	77
12g	Ph	H	P_r^i	Me	16:1	81
12h	H	Ph	Ph	Me	15:1	74
12i	H	Ph	Ph	Et	7:1	73
12j	H	Ph	Furyl	2-Me	4 : 1	72
12k	H	Ph	Pyridyl	2-Me	7 : 1	74
12l	H	Ph	p-OMe Ph	Me	9 : 1	71
12m	H	Ph	Et	Me	12:1	88
12n	H	Ph	P_r^i	Me	only one observed	83



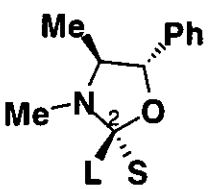
Scheme 29

We believe the reaction to be a thermodynamically controlled one. The diastereoselectivity of a thermodynamic controlled reaction is generally dictated by the difference in energy between the products. One will therefore expect an influence of external conditions on the equilibrium states. Indeed it has been documented that the equilibrium shows a dependency on concentration. Furthermore, Cope and Hancock[18] have shown that the product from ethanolamine and dipropyl ketone changes its refractive index upon standing for two months, the phenomenon is reversed by distillation of the product. Metzger[19] showed that when 2-ethyl-2 hexenal and 2-amino-3-methyl-3-butanol were condensed at elevated temperature,

there is a tendency for the Schiff base to be formed and no oxazolidines were observed.

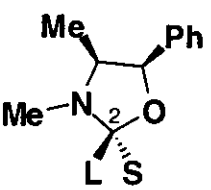
The presence of a Lewis acid such as scandium triflate increases the electrophilicity of the functionality to which it is complexed. In our system we believe that the Lewis acid complexes to the oxygen in the ketone. The diastereoselectivity observed relates to the structure of the substrate. The formation of one diastereoisomer is disfavoured because of the orientation of the large proximal group which raises the energy . The presence of scandium (iii) triflate seems to influence the process by favouring the equilibration between isomers.

Having synthesized the oxazolidines, we needed to know the stereochemistry at C2, and decided to carry out nuclear Overhauser enhancement (nOe) studies on oxazolidines derived from each series of ephedrine and pseudoephedrine. These are shown in Appendix 1. On the basis of the nOe data we were able to confirm the C2 configuration. These are shown in Figure 13.



(A)

Pseudoephedrine derivatives



(B)

Ephedrine derivatives

L=Large
S=Small

Fig 13

These results are of considerable interest. The pseudoephedrine configuration at C2 is as expected, that is, the large group is on the same side as the smaller ring methyl group. The result from the ephedrine series, where the large group (L) and the ring

phenyl are on the same side, is surprising. However, if we draw the envelope conformation as shown in Figure 14, in this case the large group (L) and the phenyl are both in pseudoequatorial positions and in doing so they minimize their interaction and result in the lowest energy conformation .

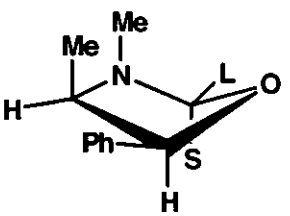
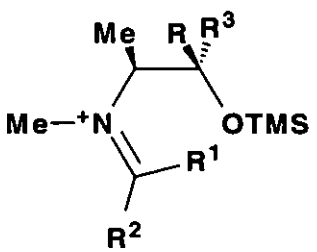
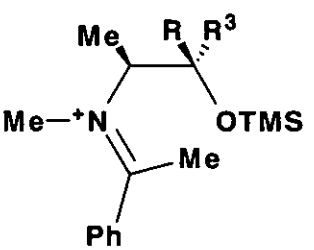


Fig 14

Having finally obtained the oxazolidines, we proceeded to investigate their ring opening using our method with $NaBH_3CN/TMSCl$.[12] However, to our disappointment the method did not work. This may be because the reductive cleavage using this sequence must proceed through the iminium ion intermediate, Figure 15.



A



B

R=Ph,R^3=H Ephedrine

R=H,R^3=Ph Pseudoepedrine

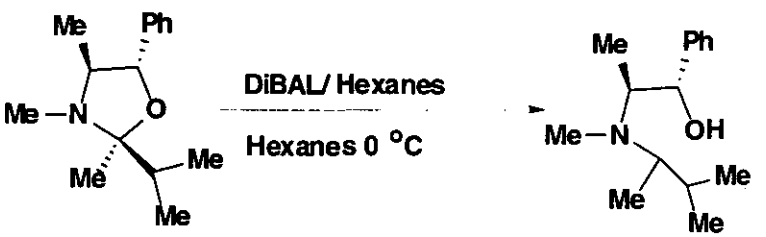
Fig 15

When R^1 is a methyl and R^2 is a hydrogen, or R^1 is a methyl and R^2 is a methyl, the reaction is successful, as is also the case when R^1 is a phenyl and R^2 is hydrogen. However, when R^1 is a phenyl and R^2 is a methyl, the reaction does not work. The explanation may be that in the three former cases the iminium ions are less stable

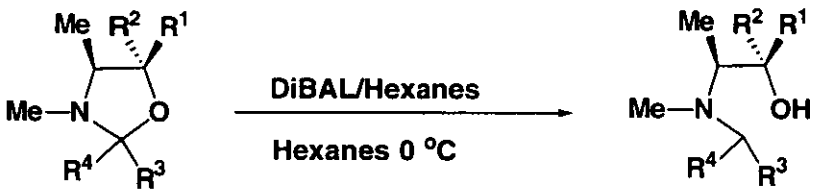
than in the latter case, because in the latter case where phenyl and methyl substituents are present, Figure 15B, these will stabilize the iminium ion to such an extent that the sodium cyanoborohydride is not able to induce reduction of the iminium intermediate. There is no precedent for reductive ring opening of this type of compound derived from ketones.

An alternative approach was thus needed to ring open this new class of oxazolidines.

We first investigated pyridine borane complex, however, this was unsuccessful. A recent report[20] has described the use of dibutylchlorotin - HMPA complexes, but again with the present substrates the reaction did not give the desired product. Polymethyl hydrosiloxane[21] has been used to reduce ketones but it also did not work in our case. More recently the reductive cleavage of C-N bond in cyclic amidines using DIBAL has been reported, [22] we therefore decided to use this reagent in hexanes or toluene solutions, and to our delight we were able to reduce a range of chiral oxazolidines to obtain a wide range of α-amino alcohols with high selectivities shown in Table 6 (Scheme 31). For the case of oxazolidine (12n) the reductive ring oprning resulted in the amino alcohol (16n) Scheme 30



Scheme 30



12a-n

16a-n

R^1=Ph,R^2=H ephedrine

R^1=H,R^2=Ph pseudoephedrine

Scheme 31

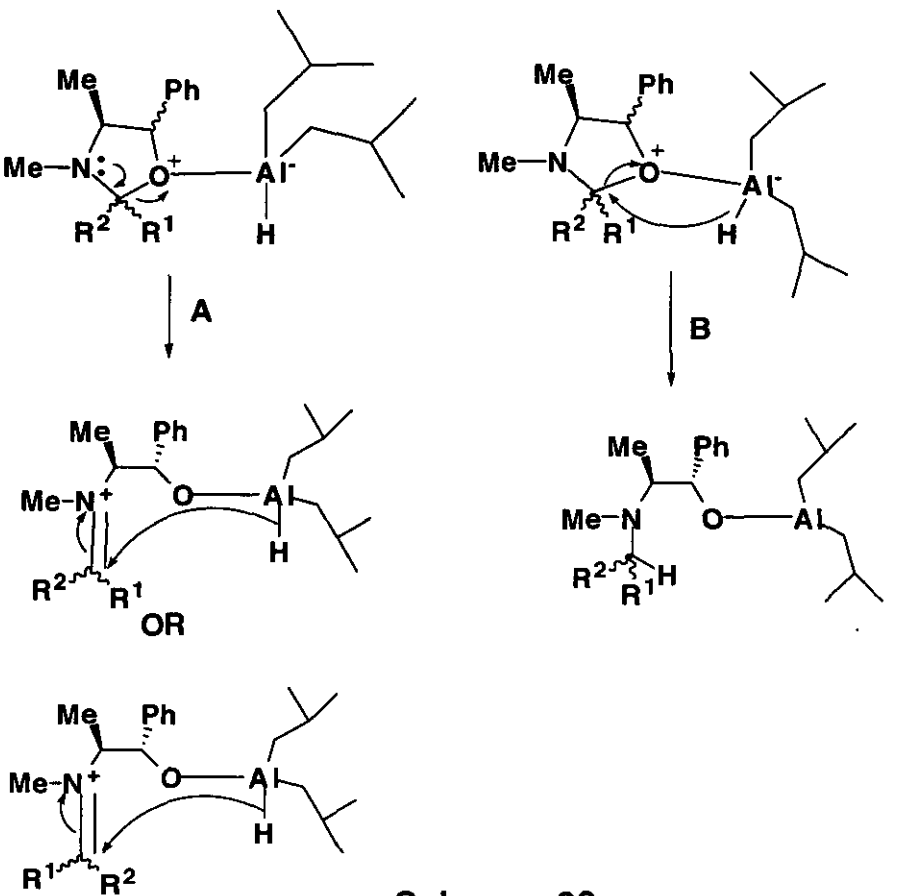
Table 6

Formation of aminoalcohols from Oxazolidines using DiBAL

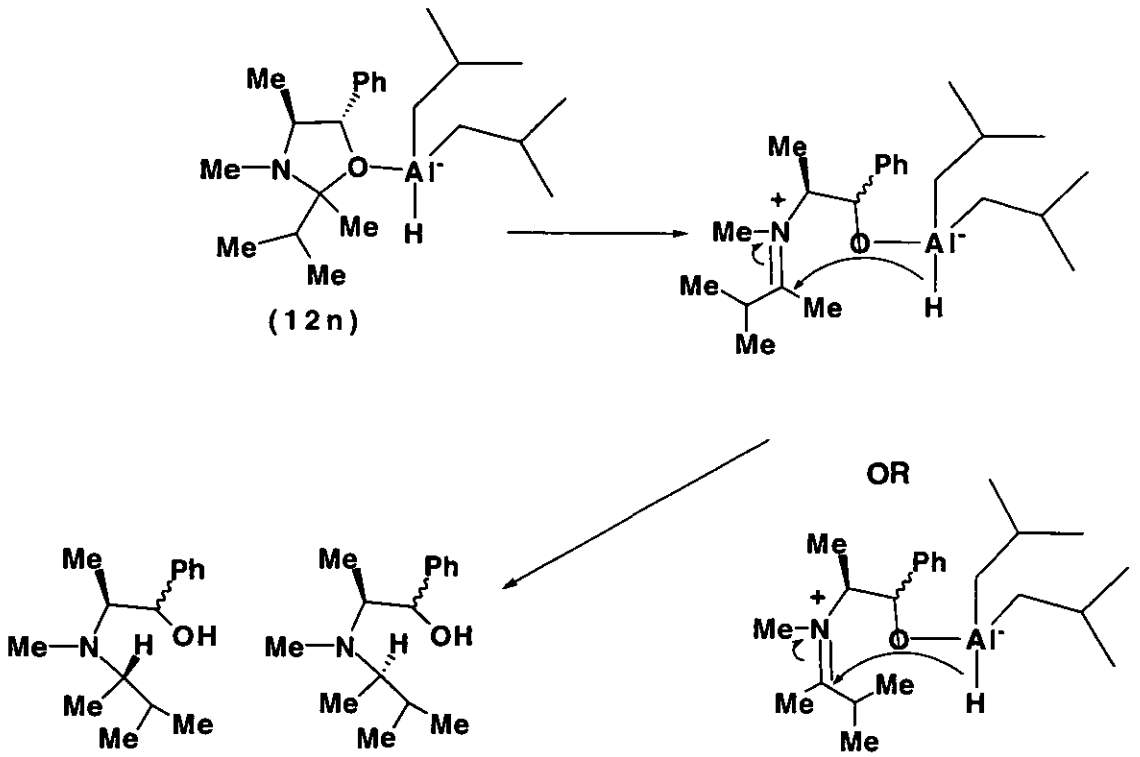
Compound Number	R^1	R^2	R^3	R^4	Ratio of Major /Min	Yield %
16a	Ph	H	Ph	Me	13: 1	85
16b	Ph	H	Ph	Et	5: 3	83
16c	Ph	H	Furyl	2-Me	7: 1	87
16d	Ph	H	Pyridyl	2-Me	3: 2	88
16e	Ph	H	p-OMe	Me	6: 5	71
16f	Ph	H	Et	Me	7: 1	79
16g	Ph	H	iPr	Me	6: 1	87
16h	H	Ph	Ph	Me	5: 1	82
16i	H	Ph	Ph	Et	7: 1	86
16j	H	Ph	Pyridyl	2-Me	4: 1	87
16k	H	Ph	Furyl	2-Me	7: 1	83
16l	H	Ph	p-OMe	Me	9: 1	81
16m	H	Ph	Et	Me	12: 1	89
16n	H	Ph	iP r	Me	only one	98

Since the application of DIBAL to the oxazolidines resulted in the required amino alcohols (6a-n), then the pathway may well be different from that using

$NaBH_3CN$/TMSCl. Also, the reaction in DIBAL is successful when the solvent is either hexanes or toluene, but not THF. This may indicate that the oxygen atom of the oxazolidine is coordinating with the aluminium atom, when hexane or toluene is used as solvent. However, when THF is the solvent, the THF coordinates to the aluminium, and the oxazolidine oxygen atom is presumably not sufficiently basic to coordinate with the aluminium atom and hence the reduction does not occur. This suggests that the coordination to aluminium is an important step in the ring opening process. A possible mechanism is suggested in Scheme 32.



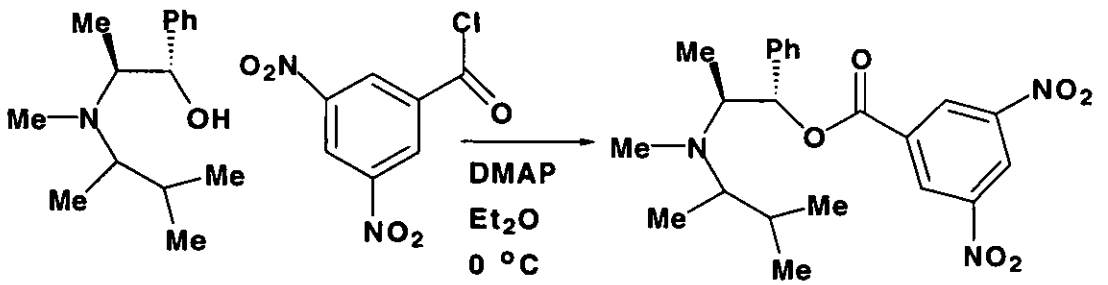
Scheme 32



Scheme 33

Two cases must be considered. In route A Scheme 32, the iminium ion is formed first, then the hydride is delivered. This will result in the formation of two iminium species which will give two different stereisomeric alcohols. For the case where R^3 and R^4 are methyl and isopropyl the two possible stereoisomers are shown in Scheme 33 above, but we only obtained one. In route B, reductive cleavage occurs by attack of hydride at C2 without formation of iminium ion. This mechanism would be expected to lead to higher stereoselectivities. The two pathways shown in scheme 32 above are likely to take place but we are not sure which is correct. The stereoselectivities obtained using DIBAL are shown in Table 6. These were determined by NMR spectroscopy. These results show that the pseudoephedrine derivatives give higher stereoselectivity than the ephedrine derivatives.

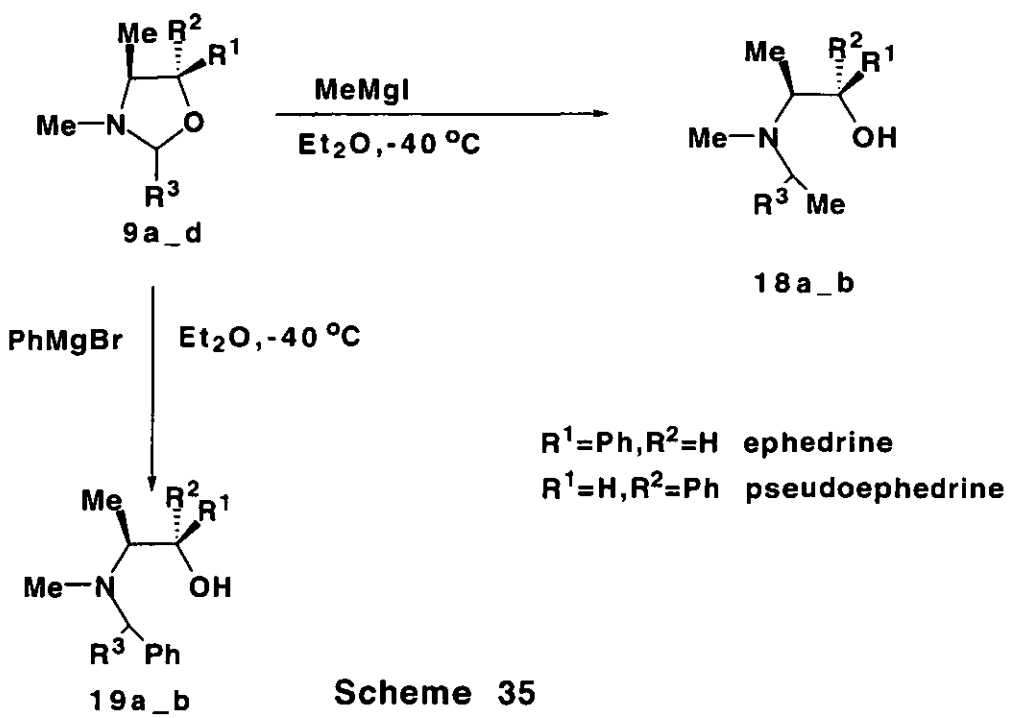
In order to make certain that the amino alcohol had been formed, we decided to synthesize a 3,5-dinitrobenzoate derivative, as shown in Scheme 34 below. We were hoping to obtain an X-ray crystal stucture, however to our disappointment, the compound (17) was an oil, Appendix 5 shows the relevant NMR and COSY 45 spectra of this compound.



(17)

Scheme 34

Having formed the chiral amino alcohol, we decided to compare our method with the traditional method of ring opening using Grignard reagents (Scheme 35). [26]

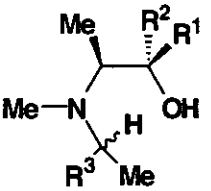


Scheme 35

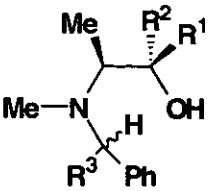
The results obtained from these reactions are shown in Table 7 below.

Table 7

Ring Opening of Oxazolidines using Grignard Reagent



18a-b



19a-b

Entry	Compound Number	R^1	R^2	R^3	Grignard Reagent	Ratio major/min	Yield (%)
1	18a	Ph	H	Ph	Me	13: 1	76
2	19a	Ph	H	Me	Ph	8: 1	62
3	18b	H	Ph	Ph	Me	3: 1	59
4	19b	H	Ph	Me	Ph	2: 1	69

As mentioned earlier, when using DIBAL to ring open the oxazolidines, the pseudoephedrine series were reduced more selectively. However, as the results in Table 7 show, when Grignard reagents are used to ring open the oxazolidines, the ephedrine derivatives gave the better stereoselectivities. This could be due to the possibility that when oxazolidines are opened with Grignard reagent, they do so through iminium ion formation,[26] while in our proposed mechanism the ring opening using DIBAL proceeds in a concerted fashion without going through the iminium ion. Moreover, when using methylmagnesium iodide as the Grignard reagent, we obtained better selectivity than with phenylmagnesium bromide agents. This is unexpected.

For the case where the oxazolidines were formed from benzaldehyde or acetaldehyde and ephedrine, the oxazolidines formed would be expected to adopt anenvelope

conformation, since this results in the lowest energy, with the larger groups pseudoequatorial. The Grignard reagent can then attack either the *si* or *re* faces of the iminium unit (figur20).

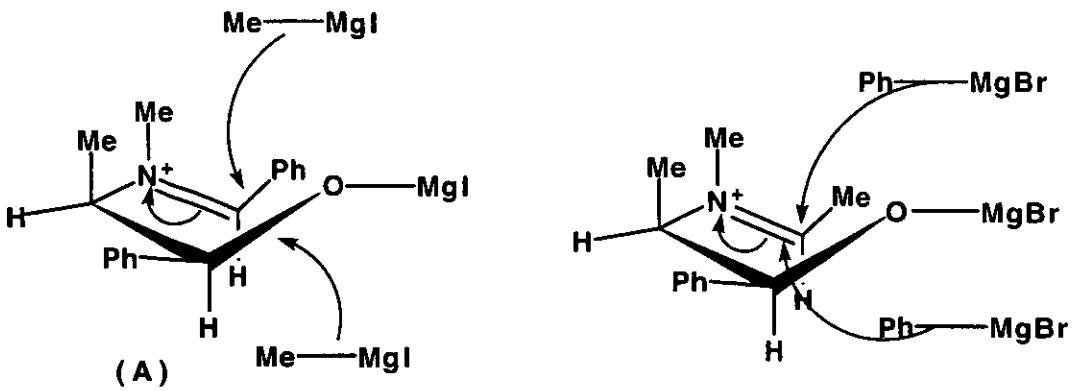


Fig 20

In the case of oxazolidines formed from benzaldehyde, acetaldehyde and pseudoephedrine, attack by the Grignard reagents occurs via iminium ions shown in Figure 21.

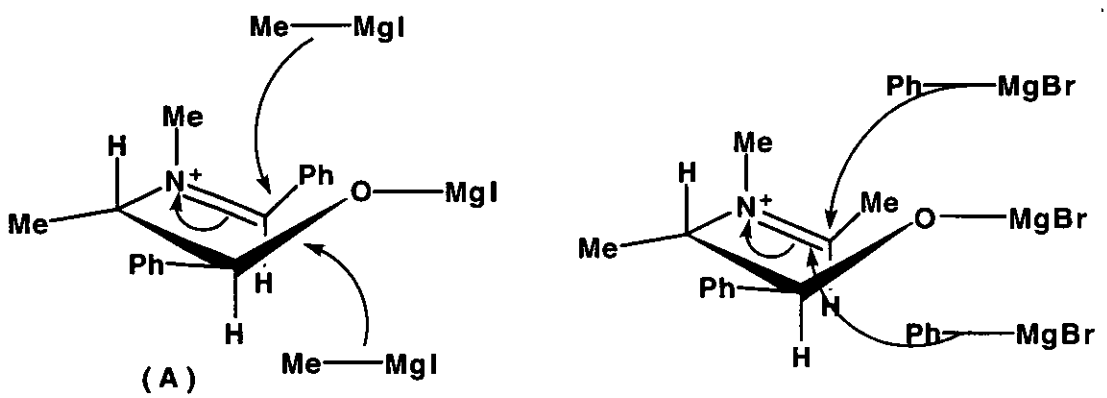
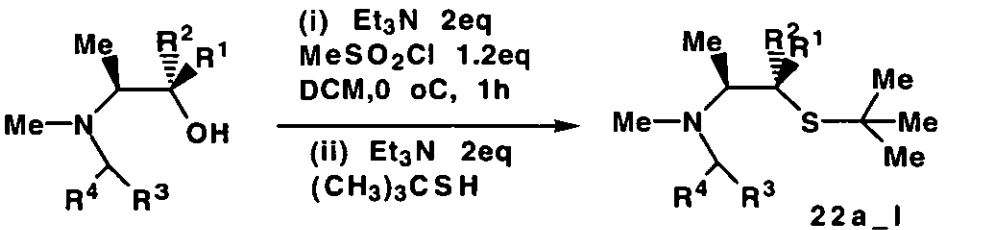


Fig 21

Attack by Grignard reagent could again occur at either the *si* or *re* faces of the iminium unit (Table 7).

Having formed the chiral amino alcohols, the next step in the synthesis was to proceed and synthesize the thioethers (Scheme 36).



16a_n

22a_l

R^1=Ph,R^2=H ephedrine

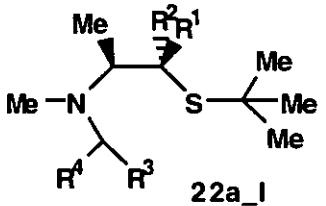
R^1=H,R^2=Ph pseudoephedrine

Scheme 36

This was achieved by displacing the hydroxyl group with the mesylate followed by nucleophilic attack by the thiol substrate to yield thioethers (22a-l), Table 8 below. Thioethers obtained through this procedure retain the configuration of the alcohol from which they were derived by a process of double inversion, (Scheme 27).[23]

Table 8

Chiral Sulfide Ligands derived from Ketones



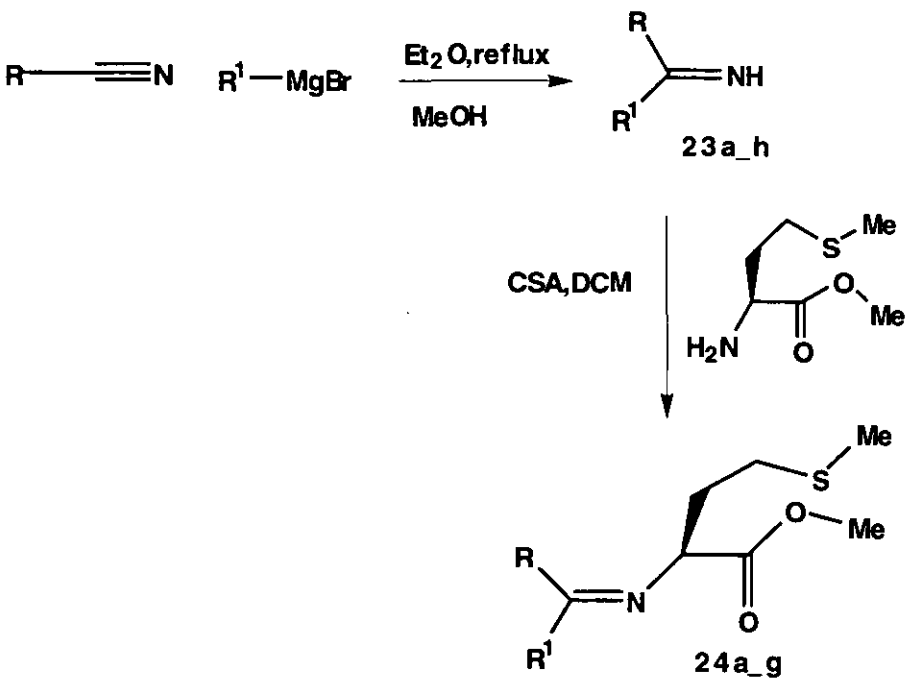
22a_l

Compound Number	R^1	R^2	R^3	R^4	Yield %
22a	Ph	H	Ph	Me	65
22b	Ph	H	Ph	Et	61
22c	Ph	H	Furyl	2-Me	55
22d	Ph	H	Pyridyl	2-Me	45
22e	Ph	H	^{i}Pr	Me	76
22f	Ph	H	Et	Me	78
22g	H	Ph	Ph	Me	71
22h	H	Ph	Ph	Et	74
22i	H	Ph	Furyl	2-Me	61
22j	H	Ph	Pyridyl	2-Me	55
22k	H	Ph	^{i}Pr	Me	88
22l	H	Ph	Et	Me	91

On testing these ligands in the palladium catalysed allylic reaction of 1,3 diphenyl propyl-2-enyl acetate, see Chapter 3, an improvement in ee was observed over ligands (8a-b) and (11a-d).

Anderson used imine-derived ligands to achieve some respectable results in the palladium catalysed allylic displacement reaction,[24] and Fiore used pyridine -derived ligands, also to give respectable ees in the same reaction.[25] Therefore we

decided to investigate this approach and to synthesize a number of imine ligands (SchemeÜ37).



Scheme 37

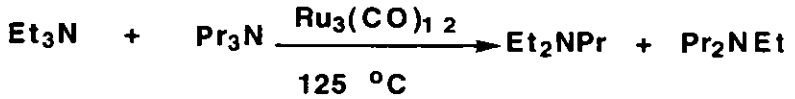
The imines were prepared by refluxing the nitrile, typically 1 eq, with the required Grignard reagent (2.5 eq) in dry ether for 2 h, or until the nitrile had fully reacted. The reaction mixture was then allowed to cool and placed in a cool bath at Ò15 ∞C and 20 eq of dry methanol was added. The solid precipitate was filtered off and washed with (3 × 30 ml) dry methanol. The methanol was evaporated to dryness to yield the imine (23a-h) (Table 9).

Table 9
Imine from Nitrile

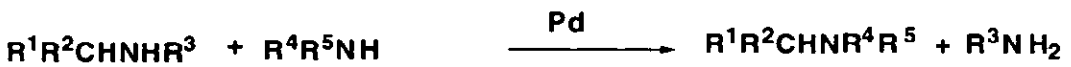
23a_h

Compound Number	*R*	R^1	Yield %
23a	Me	Ph	82
23b	Propyl	Ph	85
23c	Et	Ph	89
23d	Bu	Ph	83
23e	Ph	Ph	95
23f	P_r^j	Ph	88
23g	1-Naph	1-Naph	72
23h	2-Naph	2-Naph	65

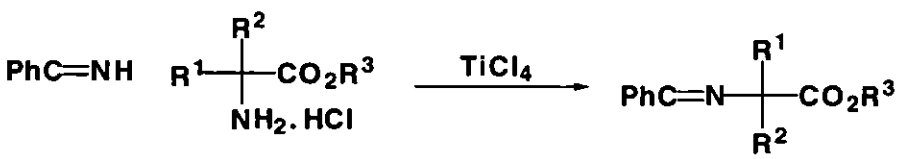
The required imine ligands were obtained by imine exchange. A recent report[27] describes transalkylation using the homogeneous catalysts $Ru_3(CO)_{12}$, $Rh_6(CO)_{16}$ to afford the tertiary amines (Scheme 38). Imine exchange,[28] where Pd black is used as catalyst in the presence of an amine to afford the exchange (Scheme 39) has also been reported. However we opted to use the O'Donnell protocol (Scheme 40),[29] but instead of the Lewis acid ($TiCl_4$) we used the protic acid camphor sulfonic acid (CSA). A suggested mechanism is shown in scheme 41. The imine exchange was carried out by stirring a mixture of 1:1 of the imine (23a-h) and the amine (Scheme 37) in DCM in the presence of 10 mol % of CSA overnight, and then the crude product was purified to yield the imine ligand (24a-g) in 81-95% yields, (Table 10).



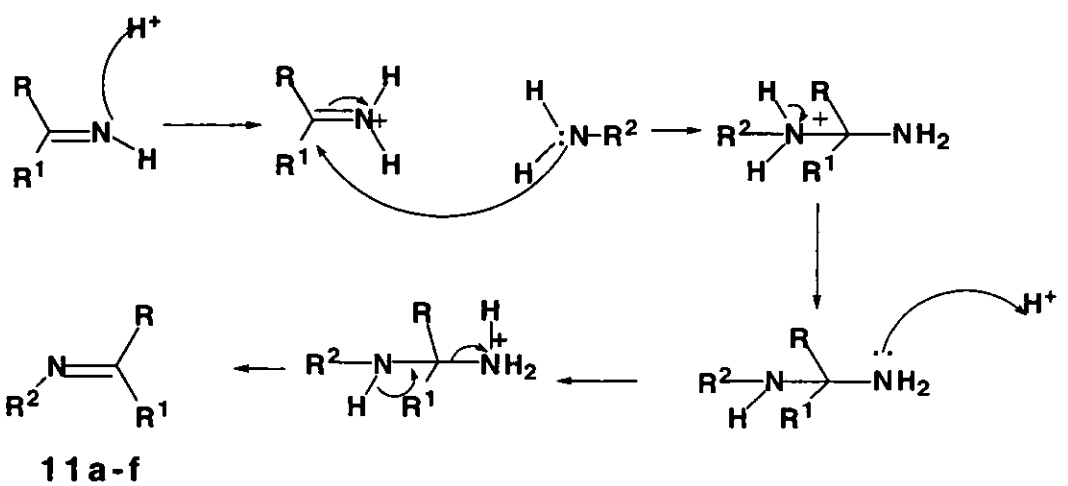
Scheme 38



Scheme39

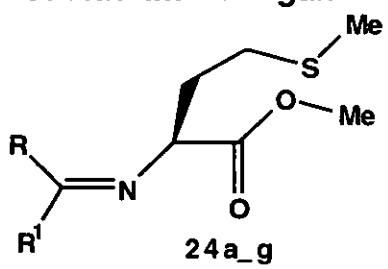


Scheme 40



Scheme 41

Table 10
Sulfur Imine Ligands



24a_g

Compound Number	*R*	R^1	Yield %
24a	Me	Ph	95
24b	Propyl	Ph	92
24c	P_r^i	Ph	96
24d	Ph	Ph	96
24f	1-Naph	1-Naph	81
24g	2-Naph	2-Naph	81

On testing these ligands in the Pd catalysed allylic displacement of 1,3-diphenyl propyl-2-enyl acetate, a dramatic improvement of ees was observed of up to 96%. An X-ray structure of one of the imine ligands is shown in Appendix 2 and is represented in Figure 25.

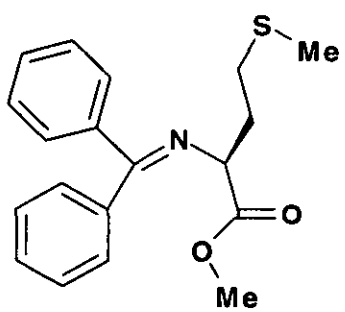


Fig 25

For the cases where the imine was not symmetrical, we needed to know the stereochemistry of the ligand and we resorted to the use of nOe spectroscopy.

Appendix 3 shows the results for the case of isopropyl, phenyl, and indicates that for this unsymmetrical imine, the isopropyl group is on the same side as the carbon-nitrogen bond (Figure 26).

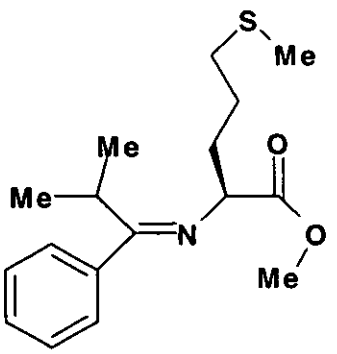
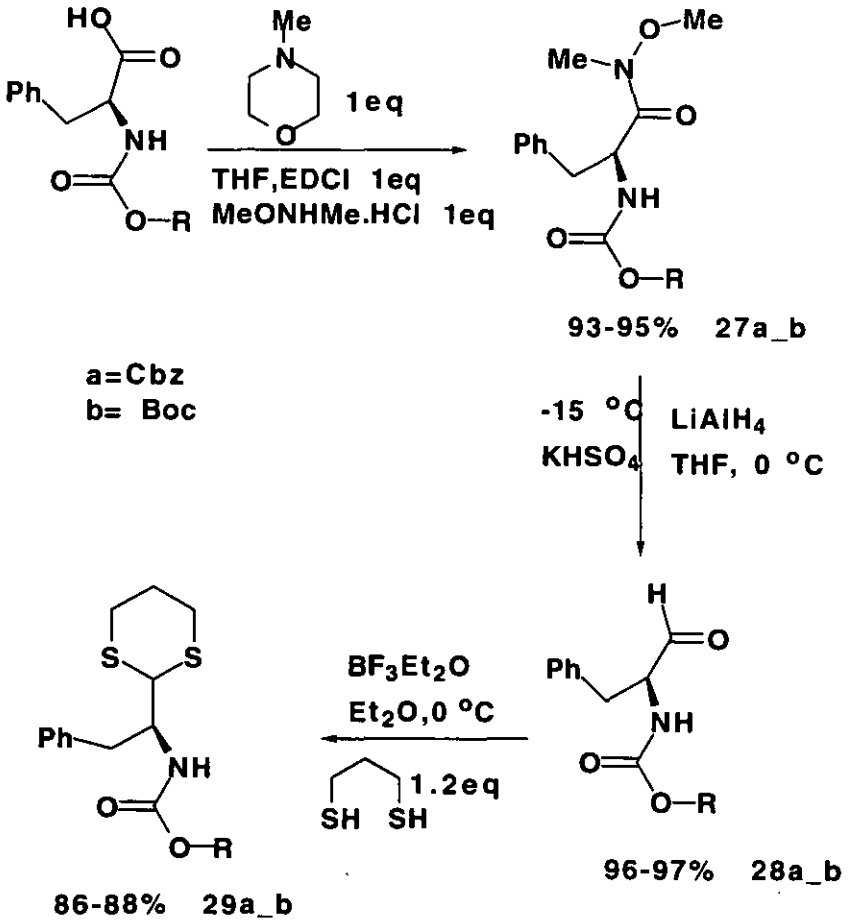


Fig 26

This stereochemistry may affect the conformations of the palladium complexes with the ligands, and so help to determine enantioselectivity in the palladium catalysed allylic displacement reactions.

From the pattern of ees observed in the palladium catalysed allylic displacement, we noted that substitution on nitrogen improved enantioselectivity, an observation also noted by Feringa,[30] and we decided to explore this effect by choosing ligands with the only structural variation being at nitrogen. Scheme 42 shows the ligands (29a-b) derived from L-phenylalnine.



Scheme 42

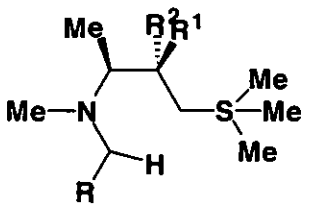
The nitrogen group is either Cbz or BOC substituted. Typically, a solution of the Cbz, or BOC substituted L-phenylalnine was stirred in THF, 1 eq of N-methyl morpholine and 1Üeq of N, O-dimethyl hydroxylamine hydrochloride were added and the solution was a stirred for 30 minutes. 1 eq of EDCI was added portion-wise over a 1 hour period, the THF was evaporated and the crude product was purified by chromotography to yield the Weinreb amides (27a-b) in ca 95% yield. The Weinreb amides (27a-b) were reduced to the aldehydes with lithium aluminium hydride at 0 ^{o}C . The mixture was quenched with potassium hydrogen sufate, worked up, and purified by chromatography to give the aldehydes in 96-97% yield.

The aldehydes (28a-b) were treated with propane-1-,3-dithiol in the presence

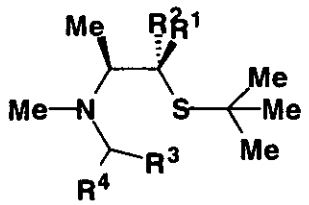
of $BF_3.Et_2O$ and the resulting products purified by chromatography yield the ligands (29a-b) in 86-88% yield.

On testing these ligands in the palladium catalysed allylic displacement reaction of 1,3-diphenyl propyl-2-enyl acetate using dimethyl malonate as the nucleophile, a dramatic improvement in enantioselectivity occurred from changing the substituent at nitrogen from Cbz (17% ee) to Boc (44% ee).

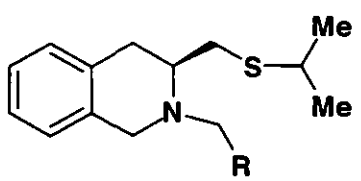
So far, we have concentrated on the design of S,N ligands. Figure 30 shows the S,N bidentate ligands which we designed , the uses of which in asymmetric reactions are discussed below,



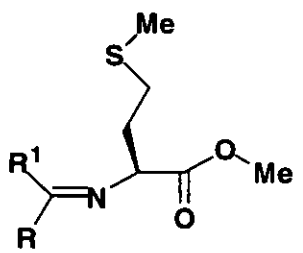
11a-d
R=Me,Ph



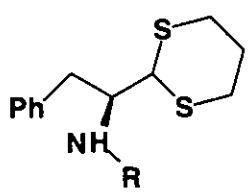
R^3=Me
R^4=Ph,iPr,Furyl,Pyridyl,Et



8d-e
R=Ph,tBut



24a_f
R^1=Ph,1-Naph,2-Naph
R=Ph,Me,Et,Prop,iPr
1-Naph,2-Naph

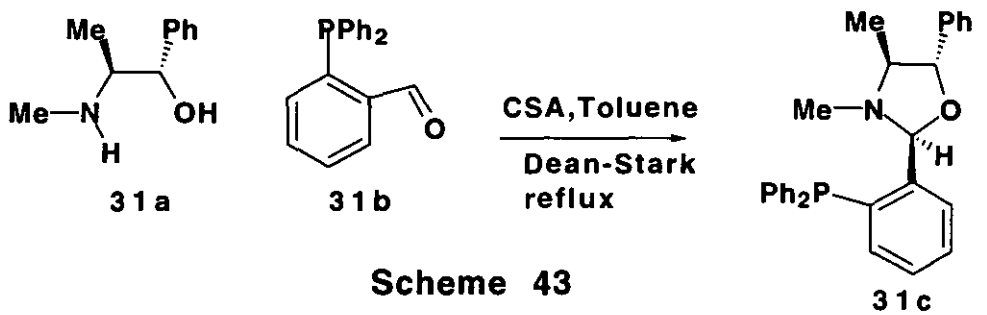


29a-b
R=Cbz,Boc

Fig 30

P-N LIGANDS

Phosphorus and nitrogen have different π-accepting properties, with phosphorus being the better π-acceptor than nitrogen,[30] thus in the palladium catalysed allylic displacement reaction, nucleophile will attack from the direction *trans* to the better π-acceptor phosphorus atom in the transition state. Also, Morimoto[31] has reported some excellent results in the application of P-N imine ligands in the 1,4 addition of diethylzinc to cyclic and acyclic enones. We decided to design a series of P-N ligating ligands. The starting point was the P-N compound (31c) derived from the phosphine benzaldehyde (31b) and pseudoephedrine (31a) (Scheme 43).

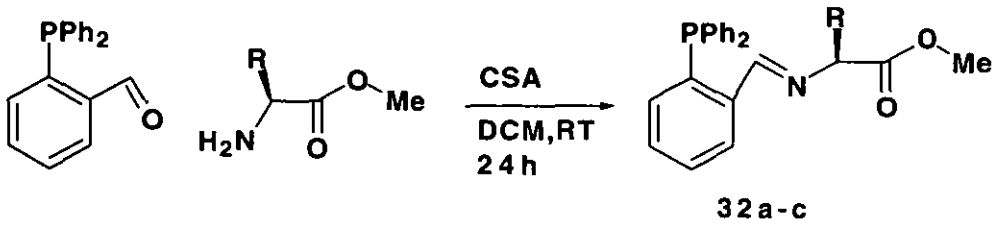


31a 31b 31c

Scheme 43

When tested in the palladium catalysed allylic displacement reaction, this ligand gave a respectable enantiomeric excess of 78%. An X-ray crystal structure of this ligand is shown in Appendix 4.

Based on our previous results obtained from the sulfur imine ligands, and from results obtained by Morimoto,[31] we decided to proceed and design phosphorus imine ligands and prepared the three ligands (32a-c) shown in Scheme 44 (Table 11), by condensation of the three aminoesters with 2-(diphenylphosphinyl) benzaldehyde.

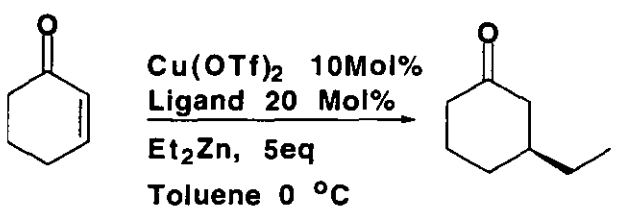


Scheme 44

Table 11
Phosphorus Imine Ligands

Compound Number	R	Yield %
32a	^{i}Pr	87
32b	Ph	79
32c	$(C_6H_4OH)CH_2$	65

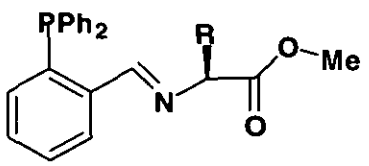
These ligands did not perform well in the palladium catalysed allylic displacement reaction. However, in the copper-catalysed 1,4 addition of diethylzinc to cyclohexenone (Scheme 45) the ligands gave ees of up to 96%. It is perhaps no surprise that ligands which do very well in one reaction may do badly in others. Thus once a ligand is prepared it pays to test it in more than one field of catalysis.



Scheme 45

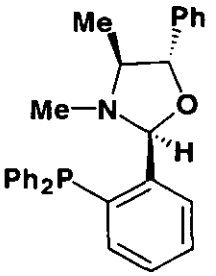
Figure 33 below shows the P-N ligands which we designed and prepared. The testing

of these ligands is described in the subsequent chapters.



32a-c

R=Ph, ^{i}Pr,(4-HOC$_6$H$_4$)CH$_2$



31c

Fig 33

The ligands in Figs. 30 and 33 were tested in three types of catalytic asymmetric reactions:

the palladium catalysed allylic displacement using 1,3-diphenylprop-2-enyl acetate and dimethyl malonate as a nucleophile;

the asymmetric copper- catalysed 1,4-addition of diethylzinc to cyclic and acyclic enones;

the asymmetric Heck cross coupling reaction.

CHAPTER 3

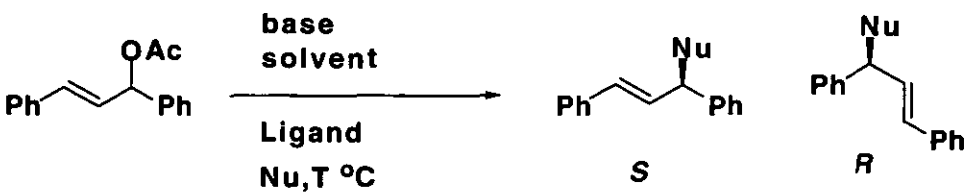
Testing the Ligands; "The Moment of Truth"

TESTING THE LIGANDS; "The MOMENT OF TRUTH"

In this chapter is reported the tests on our ligands which were synthesized as described in the previous chapter. This chapter is divided into three independent sections. Section one deals with the palladium catalysed allylic displacement reaction, section two deals with the 1,4-addition of diethylzinc, and finally section three deals with the asymmetric Heck reaction.

3.1 PALLADIUM CATALYSED ALLYLIC DISPLACEMENT

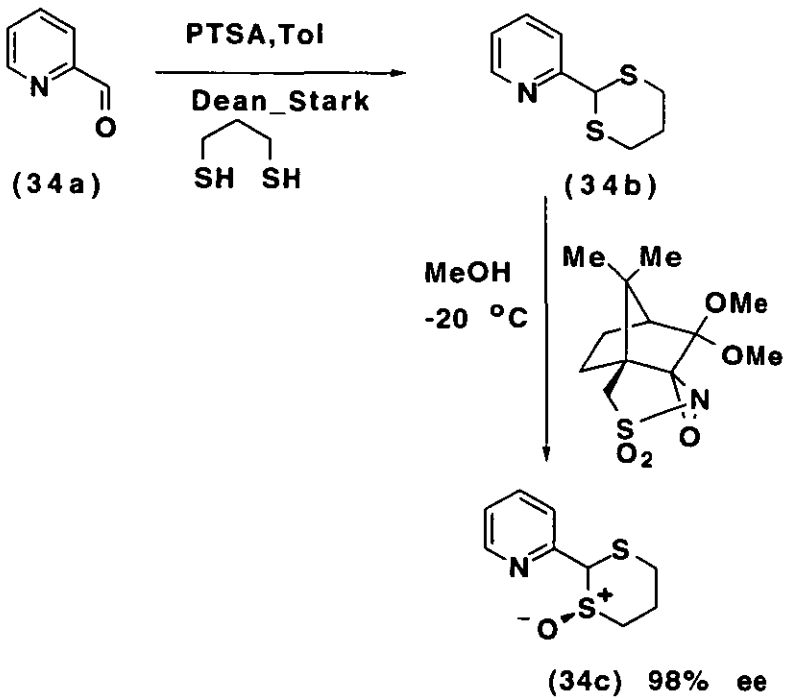
The palladium catalysed displacement reaction represented in Scheme 46 is a classic test of new ligands for asymmetric catalysis.



Scheme 46

The reaction is influenced by many factors, such as the solvent, bases, nucleophile, substrate, temperature and time. Thus there is a need to find the best or optimum conditions for each ligand type for a fixed substrate and nucleophile.

To do this we opted to use the ligand (34c) shown in Scheme 47 below, and opted to use dimethylmalonate as the nucleophile and 1,3- diphenylprop-2-enyl acetate as the substrate.



Scheme 47

The ligand was synthesized by reacting 1.2 eq of propane-1,3 -dithiol with 1 eq of the pyridine aldehyde (34a) in the presence of 10 mol % of PTSA under Dean-Stark conditions, to yield the dithiane (34b), this was then oxidized using the Davis oxaziridine to yield the sulphoxide in 88% yield and 98% ee (Scheme 47). The ee was determined using chiral HPLC.

Having prepared this ligand, we decided to use it in the palladium catalysed displacement reaction shown in Scheme 46.

To start with, we varied the solvent and kept the other variables constant. The results are shown in Table 12, and indicate that the use of CH_2Cl_2 (DCM) as solvent gave the best enantiomeric excess. This was not surprising since CH_2Cl_2 has no coordinating affinity to palladium while the other solvents do, thus those solvents which have affinity to coordinate to palladium will compete with the catalyst, and

since the solvent is used in excess, they may saturate the palladium sites and thus lower ees will result.[32a]

Table 12

Effect of Solvent in the Palladium Catalysed Allylic Displacement Reaction

Solvent	Reaction Temperature	Reaction Time	Yield %	ee %
THF	RT	24 hr	80	35
Et_2O	RT	24 hr	76	23
DCM	RT	24 hr	95	41
CH_3CN	RT	24 hr	93	35
DMF	RT	24 hr	72	21

Next we decided to look at the effect of different bases using CH_2Cl_2 as the solvent and keeping temperature and time constant. The results are shown in Table 13 and indicate that the use of NaH or Cs_2CO_3 as bases results in the best ees. Although there was not much difference between NaH and Cs_2CO_3, we decided on Cs_2CO_3 due to the handling difficulties associated with the use of NaH.

Table 13

Effect of Base Palladium Catalysed Allylic Displacement Reaction

Solvent	Reaction Temperature	Reaction Time	Base	Yield %	ee %
DCM	RT	24 hr	NaH	87	63
DCM	RT	24 hr	BSA	68	32
DCM	RT	24 hr	DBU	75	35
DCM	RT	24 hr	Cs_2CO_3	92	56

The effect of temperature on the ees is well known,[32b] so we wished also to investigate the effect of this parameter on the ees in our case. The results are

shown in Table 14 and indicate that in agreement with published work, the effect of temperature on ee is small.[32b]

Table 14

Effect of Temperatures on Palladium Catalysed Allylic Displacement

Solvent	Reaction Temperature	Reaction Time	Base	Yield %	ee %
DCM	RT	24 hr	Cs_2CO_3	87	46
DCM	0	24 hr	Cs_2CO_3	83	55
DCM	−10	24 hr	Cs_2CO_3	80	55
DCM	−20	24 hr	Cs_2CO_3	74	59
DCM	10	24 hr	Cs_2CO_3	79	53
DCM	Reflux	24 hr	Cs_2CO_3	65	44

The ees only varied by less than 2% in going from −20 °C to 0 °C.

Finally, we investigated the influence of time on the ee. As shown in Table 15, time has no influence on the ee, but influences the chemical yield.

Table 15

Effect of Time on the Palladium Catalysed Allylic Displacement

Solvent	Reaction Temperature	Reaction Time	Base	Yield %	ee %
DCM	RT	6 hr	Cs_2CO_3	42	55
DCM	RT	12 hr	Cs_2CO_3	61	52
DCM	RT	24 hr	Cs_2CO_3	85	53
DCM	RT	36 hr	Cs_2CO_3	93	54

Thus from these experiments we were able to fix our conditions listed below.

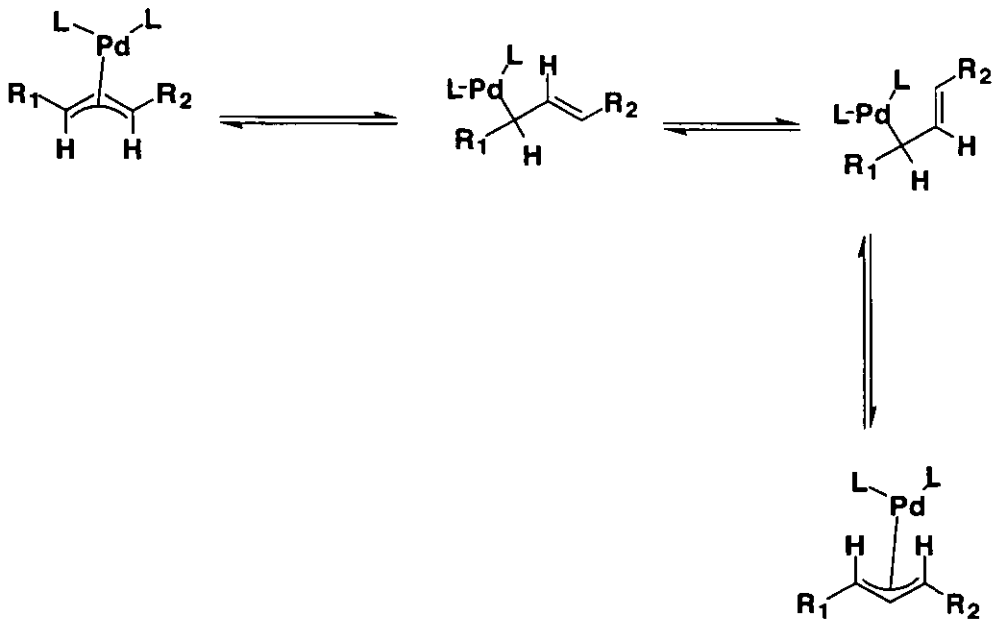
Temperature	0 °C
Base	Cs_2CO_3
Solvent	CH_2Cl_2 (dichloromethane)
Time	24 hours (complete conversion)
Pd source	allyl palladium chloride dimer
Nucleophile	dimethylmalonate
Substrate	1,3-diphenyl prop-1-enyl acetate

It is important to discuss the stereochemical outcomes of the palladium catalysed allylic displacement reaction. The π -allyl metal complexes exist in dynamic equilibrium under typical displacement reaction conditions (Scheme 48).[33] The choice of ligand (L) may result in a preference for one configuration, due to steric and/or electronic considerations.[34]

W- Conformation **M- Conformation**

Scheme 48

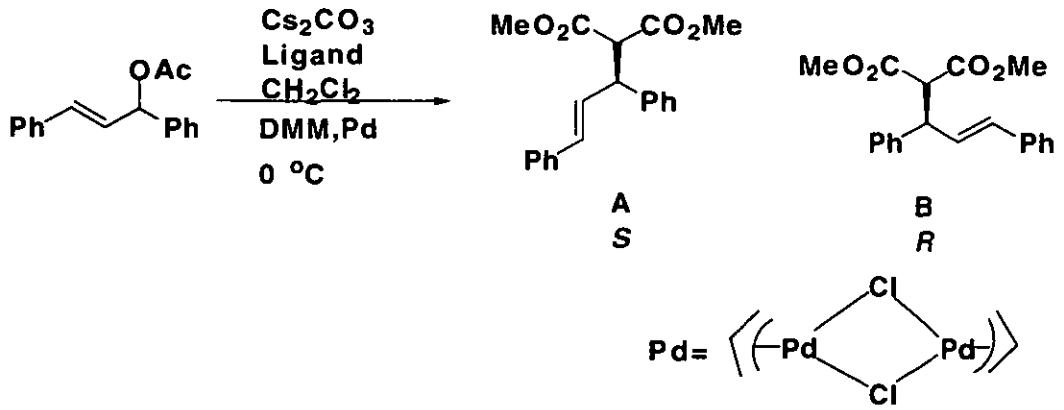
The isomeric forms are able to equilibrate by π-σ-π mechanism (Scheme 49).[1]



Scheme 49

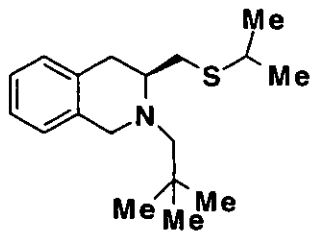
Akermark, Vitagliano and co-workers[35,36] demonstrated that the presence of a π–acceptor in the ligand is of fundamental importance for controlling selectivity, and enhancing reactivity. The π–acceptor properties may be thought of as withdrawing electron density from the metal, which in turn increases the positive change character of the allyl unit, rendering it more susceptible to nucleophilic attack. Furthermore, it has been observed that π–acceptor properties of the ligand are relayed predominantly in a *trans* manner across the complex.[33]

Once we had established those conditions, we proceeded to test our ligands under these conditions using racemic 1,3-diphenyl-1-en-3-yl acetate and dimethyl malonate as nucleophile (Scheme 50).

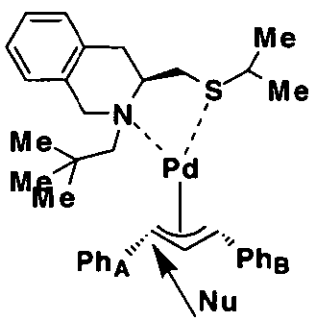


Scheme 50

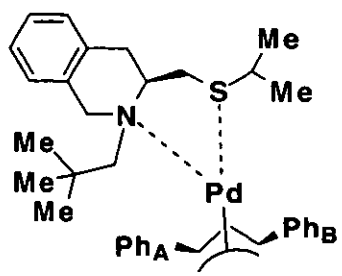
Our first ligand to be tested (8e) gave the *S* product in 55% yield with an ee of 23%. The attacking nucleophile is expected to approach the complex *trans* to the sulfur atom, which is the better π–acceptor,[37,38] but may be hindered in its approach by the large group on the nitrogen. Figure 35 shows the two possible conformations of the π-allyl complex obtained. Attack by the nucleophile *trans* to the better π-acceptor in conformation A will give *S* configuration. This conformation presumably allows the minimization of interactions between the phenyl groups of the substrate and the isopropyl and t-butyl groups of the complex.[34]



(8a)



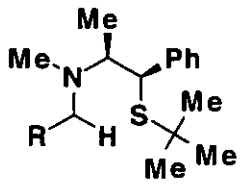
(A) M-Conformation



(B) W-Conformation

Fig 35

As indicated in our synthetic strategy (Scheme 24) in the previous chapter, our next set of ligands were derived from commercial chiral ephedrine and pseudoephedrine by condensation with aldehydes. The first set of ephedrine derived ligands (11a-b) is shown in Figure 36 below and the corresponding results of the palladium catalysed allylic displacement are shown in Table 16.



R=Me,11a
R=Ph, 11b

Fig 36

Table 16

Palladium Catalysed Displacement Reaction

Entry	Compound Number	R	Yield %	ee %	Configuration
1	11a	Me	78	47	*S*
2	11b	Ph	83	54	*S*

The results show some improvement in ee compared with the previous ligand (8a). This may be because approach of the nucleophile is not as congested as that for ligand 8a. Again the absolute configuration of the product may be explained by attack of the nucleophile trans to the better p-acceptor, the sulfur atom, at conformation A shown in Figure 37. Conformation A is preferred because Ph_B avoids the phenyl group of the ligand.

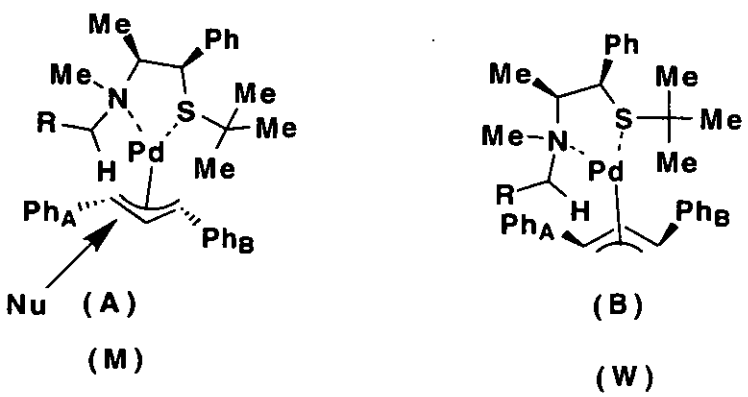
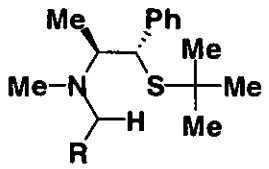


Fig 37

For the pseudoephedrine derivatives (11c-d), Figure 38, results of the palladium catalysed displacement reaction are shown in Table 17 below.



11c_d

R=Me,11c
R=Ph, 11d

Fig 38

Table 17

Palladium Catalysed Allylic Displacement

Entry	Compound Number	R	Yield%	ee%	Configuration
1	11c	Me	85	56	*R*
2	11d	Ph	88	64	*R*

As the results indicat, there is some improvement, and the configuration of the major product is now R. This change is presumably due to the pseudoephedrine skeleton which has opposite relative configuration to ephedrine at the one of the asymmetric centres (the phenyl group). Figure 39 shows the two possible conformations of the allyl moiety. Transition state A may be prefered as it minimizes interaction between Ph_A and the phenyl group of the pseudoephedrine backbone.

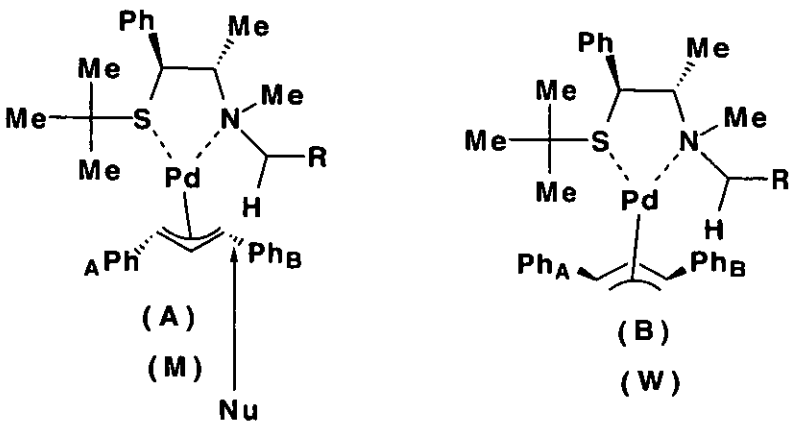
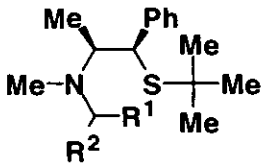


Fig 39

Presumably the higher selectivity obtained by the ligands where R=Ph than the case R=Me is due to the detailed conformation of the reactive transition state.

Our next series of ligands was derived from ephedrine and pseudoephedrine condensed with several ketones.

The ephedrine derivatives (22a-f) (Figure 40) were tested in the palladium catalysed allylic displacement reaction, and the results are shown in Table 18 below.



22a-f

Fig 40

Table 18

Palladium Catalysed Allylic Displacement Reaction

Entry	Compound Number	R^1	R^2	Yield %	ee %	Configuration
1	22a	Ph	Me	82	52	*S*
2	22b	Ph	Et	86	44	*S*
3	22c	Furyl	2-Me	85	25	*S*
4	22d	pyridyl	2-Me	70	38	*S*
5	22e	Pr^i	Me	88	56	*S*
6	22f	Et	Me	83	54	*S*

As indicated in Table 18, the product absolute configuration obtained is *S*, as obtained from ligand (11a-b) also derived from ephedrine , and this confirmed that substituent changes had no effect on the overall transition state conformation. Attack by the nucleophile *trans* to sulfur atom would result in the required *S* configuration through transition state conformation A shown in Figure 41. Again conformation A may be preferred to B because interaction is avoided between Ph_B and the ephedrine phenyl group.

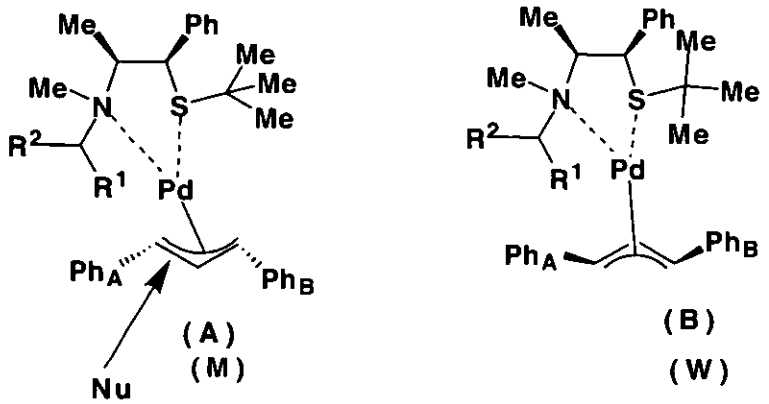
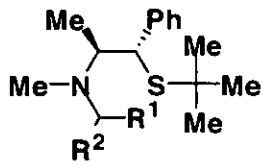


Fig 41

The corresponding series of ligands derived from pseudoephedrine (22g-l) (Figure 42) were next used in the palladium catalysed allylic displacement, and the results are shown in Table 19



22g-l

Fig 42

Table 19

Palladium Catalysed Allylic Displacement Reaction

Entry	Compound Number	R^1	R^2	Yield %	ee %	Configuration
1	10g	Ph	Me	92	68	*R*
2	10h	Ph	Et	94	61	*R*
3	10i	Furyl	2-Me	76	45	*R*
4	10j	pyridyl	2-Me	78	51	*R*
5	10k	Pr^i	Me	93	78	*R*
6	10l	Et	Me	92	64	*R*

Table 19 shows that the configuration obtained is R, which is again opposite to that of the ephedrine case, the explanation for this outcome is by considering the proposed transition state conformations shown in Figure 43. Again Figure A may be the preferred conformation because Ph_A avoids the phenyl group of the ligand, while in Figure 43B Ph_A may interact with the ligand phenyl group.

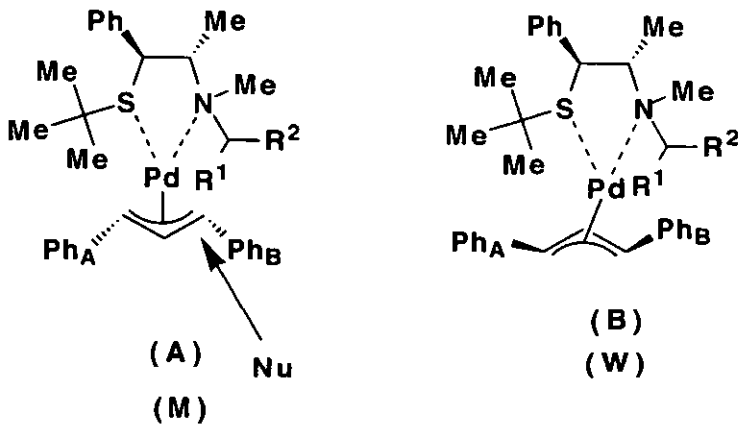


Fig 43

Although the backbone substituents of the ephedrine and pseudoephedrine skeletons are far away from the Pd atom, they may also exert indirect influence by forcing the substituent on the binding hetroatom to be organized in such away as to minimize steric ineractions. In the ephedrine case the backbone substituents are both pointing up as drawn in figure 44A, thus this will force the substituents on sulfur and nitrogen to point down in order to minimize steric interactions. However, for pseudoephedrine the backbone substiuents are opposite, the phenyl pointing down while the methyl points up. This may have the effect of forcing the substituent on sulfur to point up while the larger substituent on nitrogen points down (figure 4B); the situation is however less clear.

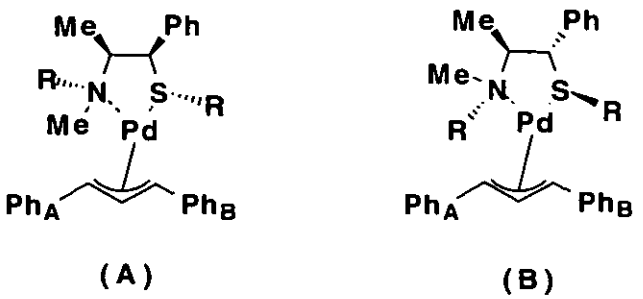
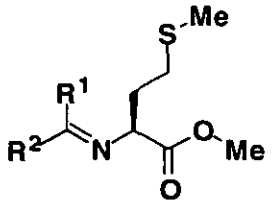


Fig 44

We next investigated the sulfur imine ligands (24a-f) (Figure 45). These ligands were derived from L-methonine and the corresponding imine by the application of the O'Donnell protocol.[29] The results of the use of these ligands in the palladium catalysed allylic displacement reaction are shown in Table 20 below.



24a-f

Fig 45

Table 20

Palladium Catalysed Allylic Displacement Reaction

Entry	Compound Number	R^1	R^2	Yield %	ee %	Configuration
1	24a	Me	Ph	91	56	*R*
2	24b	Propyl	Ph	90	53	*R*
3	24c	P_r^i	Ph	93	60	*R*
4	24d	Ph	Ph	94	96	*R*
5	24e	1-Naph	1Naph	78	82	*R*
6	24f	2-Naph	2Naph	78	83	*R*

One of these ligands gave exceptionally good ees, and the absolute configuration obtained in the product was (R) in each case.

The reacting conformation is presumed to be that shown in Figure 46A, because again Ph_A avoids the ester group; the second conformation (Figure 46B) is disfavoured because Ph_Awould interact with the ester and perhaps with substituents R^1 and R^2. The imines, as mentioned in Chapter 2, have the Z geometry where the groups are different. Attack *trans* to imine in the conformation shown (Figure 46A) would result in the (R) configuration of the product.

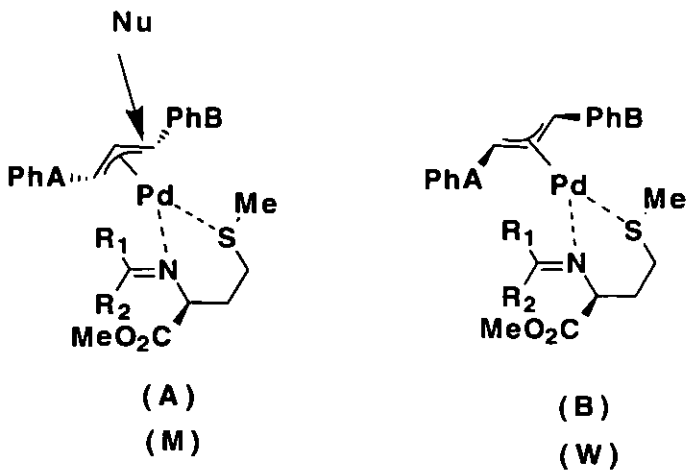


Fig 46

In this ligand system we believe that the imine group is the better π–acceptor as thioethers are considered to be poorer π–acceptors. Also we believe the unsaturated nitrogen atom may offer greater stabilization to low oxidation state electron-rich metals, such as palladium.[43]

Very good ees, up to 96%, resulted from use of the aromatic imine, ie. R^1, R^2 = Ph (Figure 47) (entries (4-6), Table 20). However, if one of R^1 or R^2 is aliphatic this resulted in lower ees (entries (1, 2), Table 20), and indeed the longer the linear chain, the lower the ee, because presumably as the linear chain becomes large, steric interactions increase, and binding to palladium weakens. Low ee results.

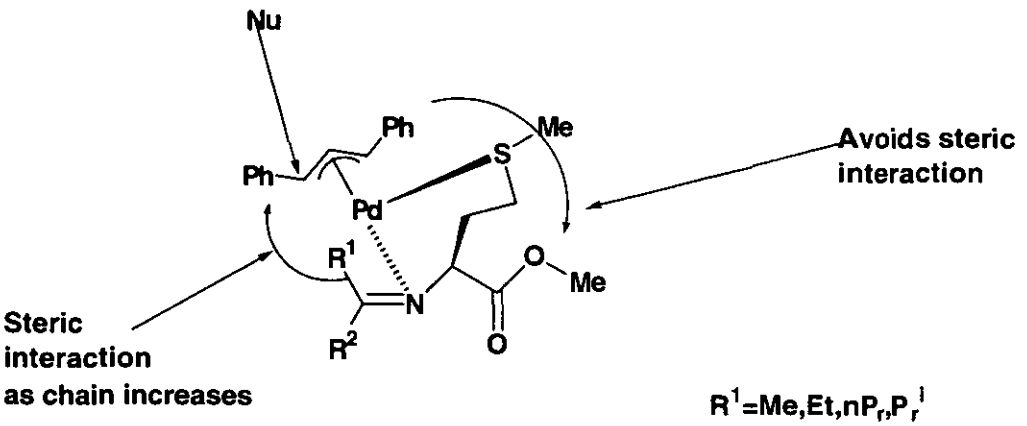
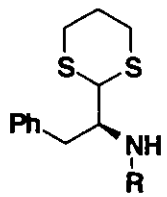


Fig 47

Naphthyl derivatives (entries (5, 6) Table 20) gave poorer ees than the diphenyl ligand 24d (entry 4), perhaps due to poorer binding to Pd.

So far in the palladium catalysed allylic displacement reaction, we have used N-S ligating ligands (11a-d), (22a-l) and (24a-g). Before starting to consider the phosphorus-nitrogen ligands (31c) and (32a-c) it is worthwhile taking a look at the ligands (29a-b) (Figure 48, Table 21) and to try to offer an explanation for the observed result that when the nitrogen is BOC substituted a better ee results than when it is Cbz substituted.



29a-b R=BOC,CbZ

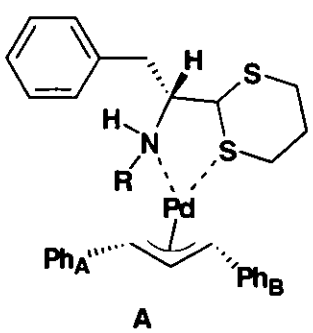
Fig 48

Table 21

Palladium Catalysed Allylic Displacement Reaction

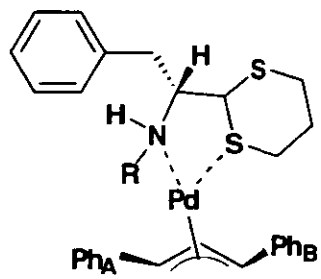
Ligand	*R*	Yield %	ee %	Configuration
29a	BOC	88	44	*S*
29b	Cbz	52	17	*S*

The possible conformers are shown in Figure 49.



A

M-Conformation



B

W-Conformation

R=BOC,Cbz

Fig49

For both cases where R=BOC, Cbz the conformation A is preferred because in this conformation Ph_A does not interact with the BOC group or Cbz group. Attack of the nucleophile *trans* to sulfur will then result in the observed *S* configuration of the

product, while in conformation B there is interaction between Ph_A and the BOC or Cbz groups.

Also this conformation explains why in the case of BOC substituted derivative (entry 1) a better ee was observed than in the case of the Cbz substituted derivative (entry 2). In the former a larger steric interaction between Ph_A and the BOC group than occurs in the latter between Ph_A and the Cbz group reinforces the preference for conformation A.

Next is considered the phosphorus-nitrogen ligand (Figure 50, ligand 31c). In the test palladium catalysed allylic displacement reaction this ligand provided a 92% yield and an ee of 78%. The configuration obtained in the product is the R; the possible transition state conformations are indicated in Figure 50. Conformation A must be preferred because it gives rise to the observed enantiomer of the product. It is however difficult to predict the conformation of the ligand-metal complex, particularly around the five-membered ring.

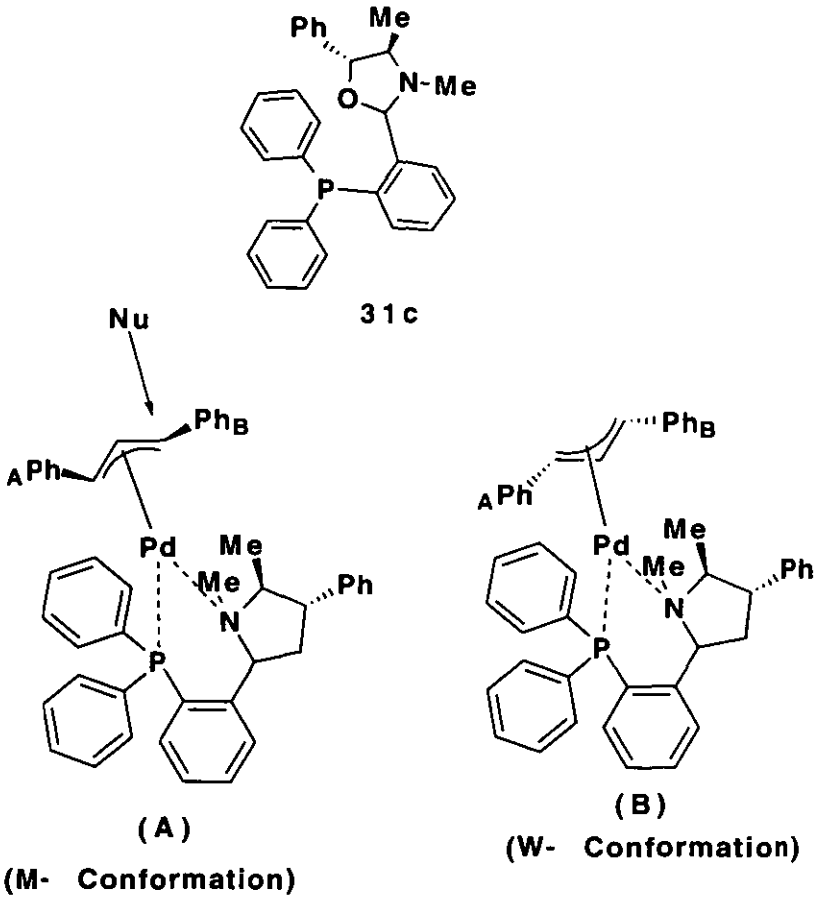
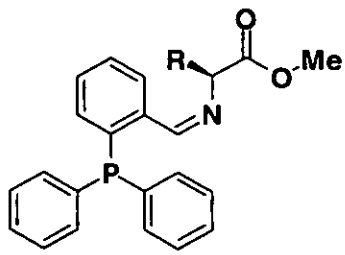


Fig 50

A similar phosphorus oxazolidine ligand has been reported by Svensson .[39]

The next set of phosphorus-nitrogen ligands (32a-c) which were tested are shown in Figure 51, and the results of the palladium catalysed allylic displacement are shown in Table 22.



32a-c

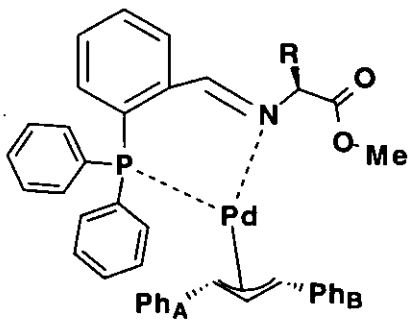
Fig 51

Table 22

Palladium Catalysed Allylic Displacement

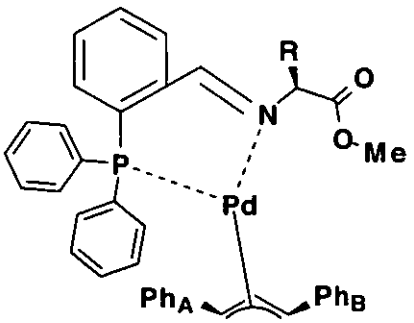
Compound Number	Entry	*R*	ee %	Yield %	Configuration
32a	1	Ph	61	82	*S*
32b	2	P_r^i	55	75	*S*
32c	3	p-(OH) C_6H_4 CH_2	67	82	*S*

The *S* configuration is obtained by attack of the nucleophile *trans* to phosphorus which is the better π–acceptor.[40] Figure 52 below shows the two possible square planar conformations Figure 52B must represent the favoured arrangement as it is this transition state which gives rise to the S enantiomer of the product. The prefered orientation of the nitrogen substituent cannot easily be predicted. The diagrams shown are not intended to imply any particular conformation of this substituent.



(A)

(M- Conformation)



(B)

(W- Conformation)

Fig 52

Table 22 shows that the ees are very similar for all of the ligands, perhaps due to the similar sizes of the R group. However, an interesting outcome, entry 3, showed an improved ee when a hydroxyl group (OH) is present. This group is electron-donating and thus may help to transfer electron density via the aromatic ring to the N-atom thus enhancing the binding to palladium.[40,41] Moreover, steric influence of the large $-CH_2Ph(OH)$ unit, may play a part, presumably Ph_A avoids this unit, dictating the exact preferred conformation.

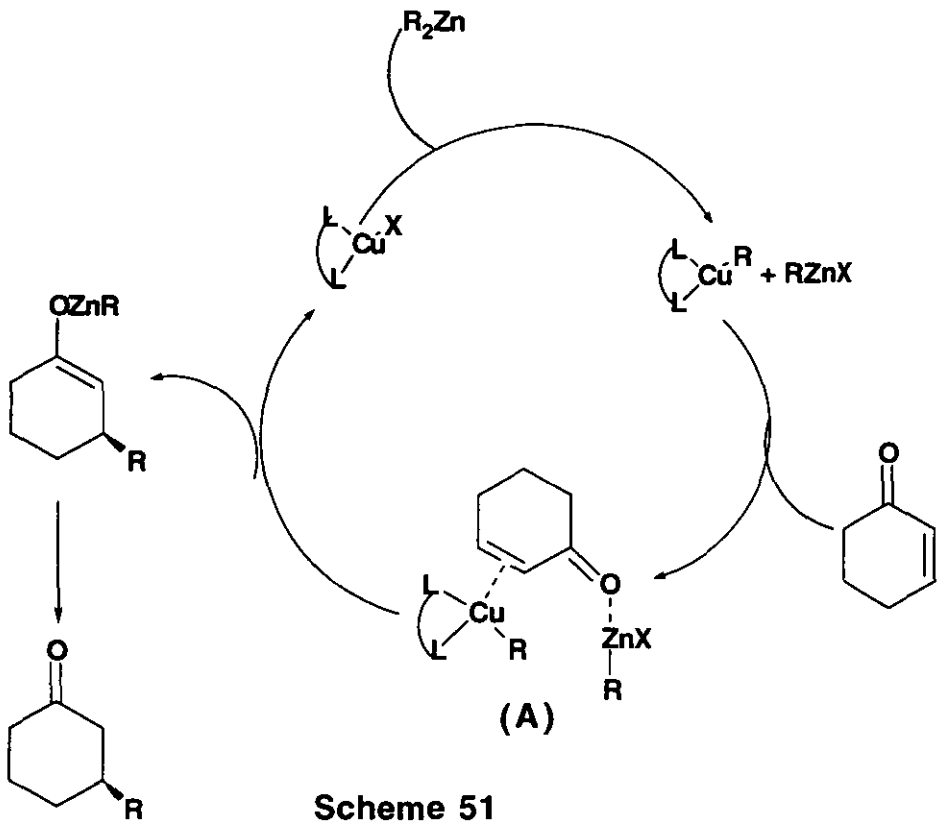
The ability of an element to act as good π-acceptor depends on whether the element has a vacant site to accomodate an electron. Second row elements have available to them the d orbital, this is not the case for first row elements. However, first row elements like nirogen can be made to be good π-acceptors if the hybridization is changed from sp^3 to sp^2, because then the donated electron can be accomodated in π^* orbital. Thus the general accepted hierarchy is sp^2 (N)>S>sp^3 (N).

Having screened our ligands using the palladium -catalysed displacement reaction, we decided to screen some of our ligands in the copper-catalysed conjugate addition of diethylzinc to enones, discussed in section 3.2 below.

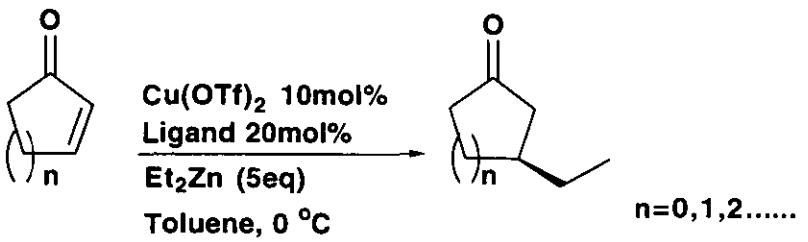
For this our first choice was to investigate the phosphorus-nitrogen ligands shown above in Figure 51, since hybrid ligands are often used in this type of reaction.[42]

3.2 1,4- Conjugate Addition to Enones with Diethyl Zinc

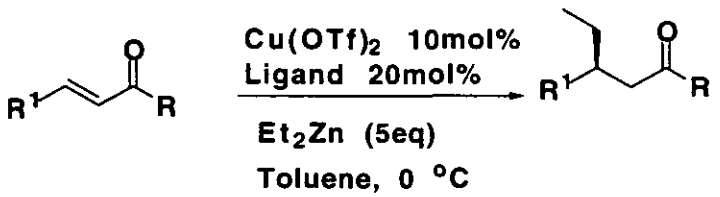
The 1,4- addition to enones is a fundamental process in organic chemistry as mentioned in the introduction. The accepted mechanism for the copper-catalysed 1,4-addition of diethylzinc to 2-cyclohexenone is shown in Scheme 51. The mechanism shows a transition state represented by (A). Recent investigations of this reaction were reported by Feringa[44], Alexakis,[45] and Schinner.[46] For cyclic enones the reaction is represented in Scheme 52, and for acyclic enones is represented in Scheme 53.



Scheme 51

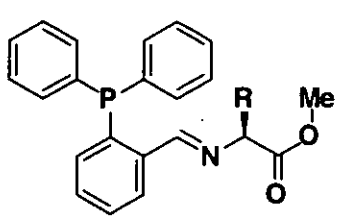


Scheme 52



Scheme 53

As mentioned at the end of Section 3.1 we decided to investigate our P,N phosphorus imine ligands (32a-c) (Figure 53) because others have used P,N hybrid ligands for this reaction.[47] A typical procedure for the catalytic addition reaction is as follows. A solution of $Cu(OTf)_2$ and ligand (32a-c) in toluene was stirred under a N_2 atmosphere at room temperature for 1 hour. The flask was placed in an ice-bath. Diethylzinc and a solution of enonewere added sequentially. After stirring for 3 hours the mixture was poured into 1M HCl solution and was extracted with ethyl acetate.



(32a-c)

Fig 53

The organic layer was washed with brine and dried over $MgSO_4$. After the solvent was evaporated the colourless oil obtained was purified by column chromatography (hexane/ethylacetate 9:1). The ees and yields obtained are shown in Tables 23-26 inclusive. The highest ee obtained for cyclopentenone (table 24, entry 3) was a pleasing 88% and this compares well with the published results by Knoble.[48b]

Table 23
Asymmetric Conjugate Addition of Et_2Zn

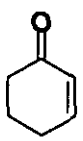
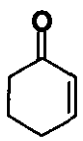
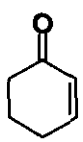
Entry	R	Enone	Temperature (°C)	Yield %	ee %	$[\alpha]_D$	Configuration
1	Ph		0	79	78	+44	*R*
2	Pr^i		0	81	58	+33	*R*
3	$p(OH)C_6H_4CH_2$		0	75	> 99	+58	*R*

Table 24
Asymmetric Conjugate Addition of Et_2Zn

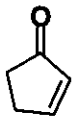
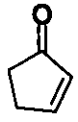
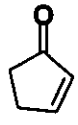
Entry	R	Enone	Temperature (°C)	Yield %	ee %	$[\alpha]_D$	Configuration
1	Ph		0	80	66	+51	*R*
2	Pr^i		0	65	35	+28	*R*
3	p-(OH)$C_6H_4CH_2$		0	55	88	+88	R

Table 25
Asymmetric Conjugate Addition of Et_2Zn

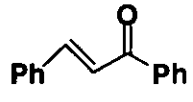
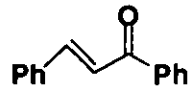
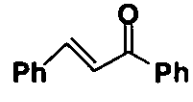
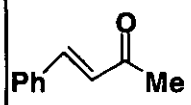
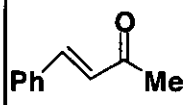
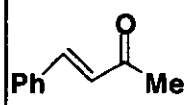
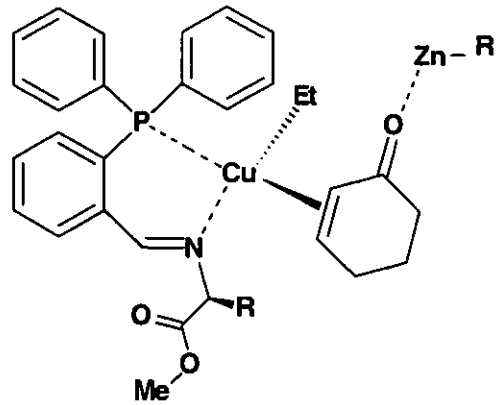
Entry	R	Enone	Temperature (°C)	Yield %	ee %	$[\alpha]_D$	Configuration
1	Ph		0	60	36	+27	*R*
2	Pr^i		0	51	17	+13	*R*
3	p_(OH)$C_6H_4CH_2$		0	78	65	+44	R

Table 26

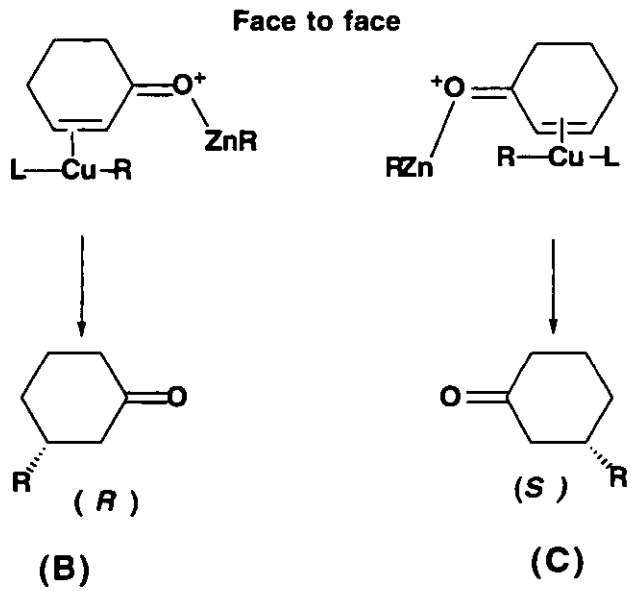
Asymmetric Conjugate Addition of Et_2Zn

Entry	R	Enone	Temperature (°C)	Yield %	ee %	$[\alpha]_D$	Configuration
1	Ph		0	55	31	+33	*R*
2	Pr^i		0	32	9	+11	*R*
3	p-(OH) C_6H_4 CH_2		0	82	44	+46	*R*

In every case the absolute configuration in the product obtained was *R*, suggesting a common transition state stereochemistry. Schinner[46] and Morimoto[48] suggested that a possible intermediate is that shown below in Figure 54A. Using this and the observation of Dieter,[49] Figure 54B (*S*) and (*R*) configurations could be explained. In our case the presence for the (*R*) configuration is due to enone zinc complex avoiding the bulky *R* group and the ester group on the ligand (Figure 54A).



(A)

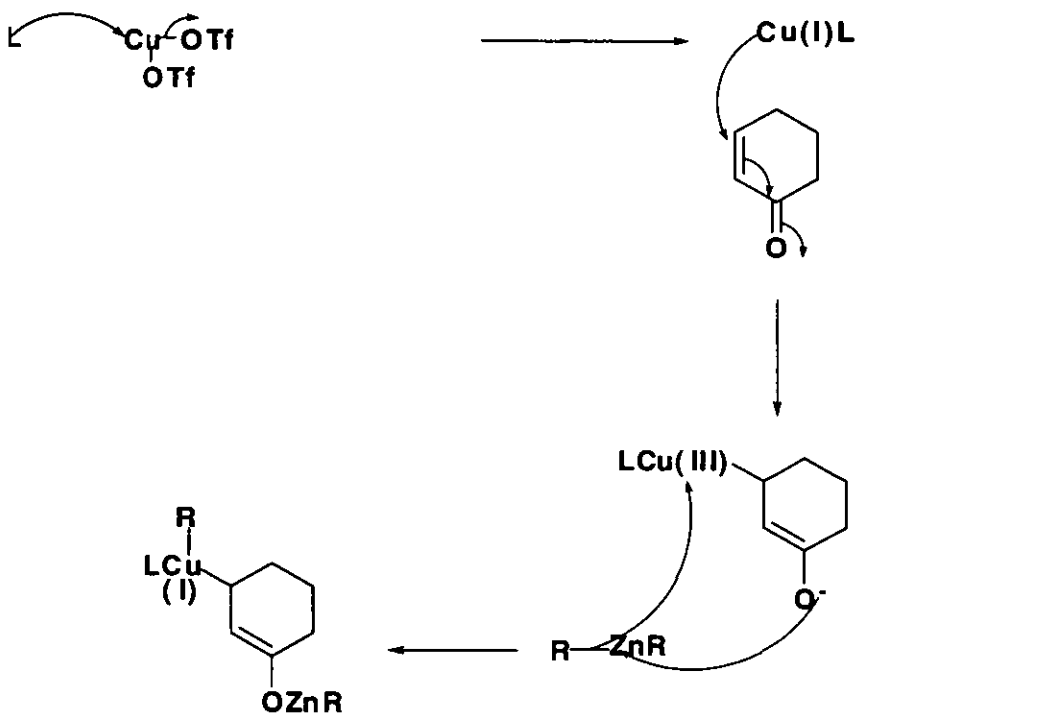


(B) (C)

Fig 54

A proposed mechanism for the transfer of alkyl group from R_2Zn to the Cu(II) ligand complex is given in Scheme 54 The mechanism is based on observation and kinetic studies by Kraus[54] and Nakamura[55] suggesting that a Cu(III) species is present. This species could be obtained by electron transfer from the ligand to form a Cu(I) ligand complex, this then attacks the enone which results in formation

form a Cu(I) ligand complex, this then attacks the enone which results in formation of a Cu(III) ligand enone complex (Scheme 54); this intermediate then attacks the R_2Zn to result in the transfer of an R group and results in reduction of the Cu(III) ligand complex, to a RCu(I) ligand complex, which on work up yields either the (*R*) or (*S*) enantiomer of the product depending on which face is coordinated, according to Dieter.[49a] The geometry of the copper dimer is believed to be distorted-square-planar.[49b]



Scheme 54

In each case, entry 3 (ligand (32c)) gave the best ee in this series. This may be because the presence of (OH) in the para position donates electron density and enhances the binding of the ligand to the metal, moreover the increase in electron density may have a direct effect on the concentration of the enone-cuprate complex.[50]

A lack of this effect may be the cause of the isopropyl derivative ligand (32b) giving low ees in this reaction.

Another effect which requires explanation is the difference in stereoselectivity seen between the cyclohexen-1-one and the cyclopentenone substrates. The much higher ees obtained for cyclohexenone presumably results from its much greater rigidity compared with cyclopentenone.

Having obtained such impressive results, we decided to investigate the effect of temperature on our best ligand (32c) to see if we could improve the yield, while keeping the ee value high. Table 27 shows the results for the conjugate addition to cyclohexen-1-one using our ligand 32c.

Table 27

Conjugate Addition to Cyclohexen-1-one with Ligand 32c

Entry	Temperature (°C)	Yield %	ee %
1	−10	75	> 99
2	−20	70	> 99
3	−35	65	> 99
4	10	86	81
5	30	88	44

We then repeated the same sequence of reactions to cyclopenten-1-one; the results are shown in Table 28.

Table 28

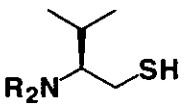
Conjugate Addition to Cyclopenten- 1- one with Ligand 32c

Entry	Temperature (°C)	Yield %	ee %
1	−10	50	91
2	−20	48	92
3	−35	47	92
4	10	66	69
5	30	70	48

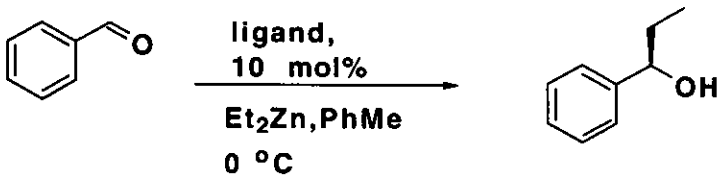
These results compare very well with those of Degrado[51] who obtained impressive ees of 98% for both the cyclohexen-1-one and cyclopenten-1-one substrates.

These results in Tables (27) and (28) indicate that the yield and ees are divergent quantities, thus for this type of reaction one needs to sacrifice the least important of either ee or yield and in this case the ee is the important entity.

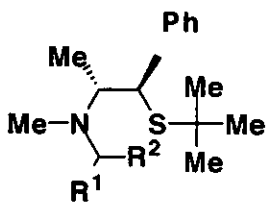
A recent report[52] on the use of thiol ligands in the addition of diethylzinc to aryl aldehydes (Scheme 55) describes impressive ees, and we decided to employ our thioether ligands (22g-l), Figure 55, in the 1,4 addition to cyclohexen-1-one, Scheme 53. Table 29 shows the results obtained.



Ligand



Scheme 55



22g-l

Fig 55

Table 29
Asymmetric Conjugate Addition to Cyclohexen-1-one using Ligands (22g-l)

Entry	R^1	R^2	Yield %	ee %	$[\alpha]_D$	Configuration
1	Pr^i	Me	75	> 99	+65	*R*
2	furyl	Me	42	66	+49	*R*
3	pyridyl	Me	62	62	+43	*R*
4	Ph	Me	66	> 99	+63	*R*

These results are again very impressive given the fact that thioethers have never been employed as ligands in this type of reaction. A possible transition state model

is shown in Figure 56. The very good ees provided by ligands, 22a, 22k (entries (1) and (4), Table 29), are perhaps due to bulk at nitrogen.[53]

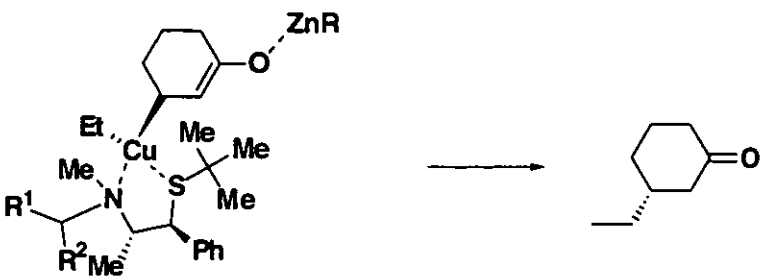


Fig 56

In the case of the pyridyl derivative ligand (22i) (entry 3,62% ee), we were disappointed with the outcome. However, Morimoto reported a similar ee of 52% when his ligand (Figure 57) was used in the asymmetric conjugate addition to cyclohexen-1-one (Scheme 52).[53] The explanation could be that in this case we have two possible transition states shown in Figure 58 below.

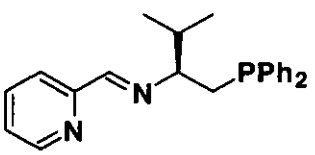


Fig 57

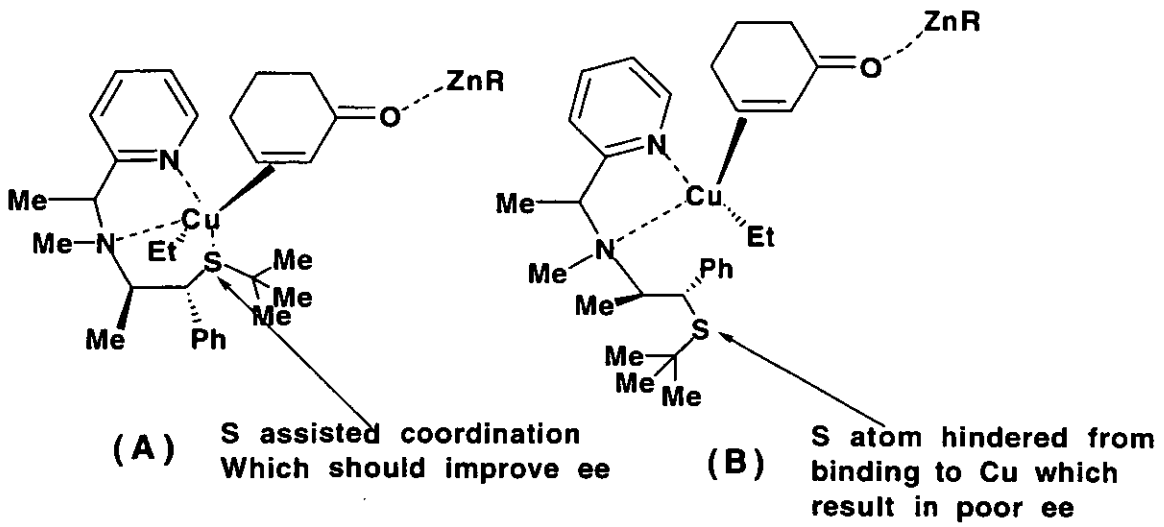


Fig 58

In the case of transition state model A, the face to face approach of the enone to the copper ligand complex is unhindered and the Cu binds to all three atoms, similarly to Morimoto.[53] Thus this results in stable binding and consequently good ee. The second possibility (Figure 58B), where binding of the sulfur atom is hindered by the t-Bu group , could result in an unfavourable ee. In our case it may be that the complex adopts conformation B (Figure 58).

Further, for the case of the furyl derivatives ligand (22j) (entry 2, 66% ee), again two possible transition state models are possible (Figure 59), each resulting in a different product configuration, similar to the pyridyl derivatives. Here, in the case of 59A, the approach of the enone is unhindered the Cu again binds to all three atoms similar to the Morimoto case and this should result in a product with good ees. However, in Figure 59B the sulfur atom is prevented from binding to the Cu; this may result in an unfavourable ees.

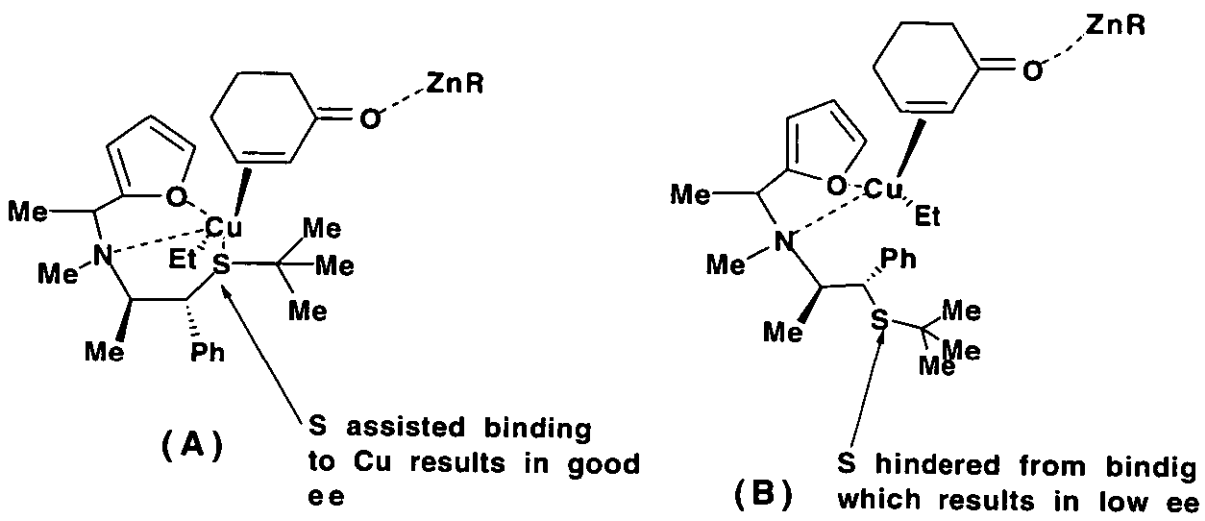
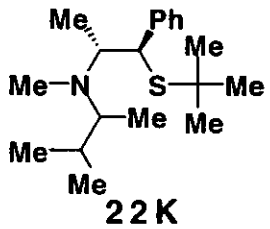


Fig59

Once we were able to screen the thioether ligands, we decided to use the methyl isopropyl ligand (22k) (Figure 60) with other enones, as shown in Table 30.

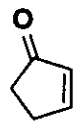
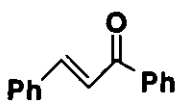
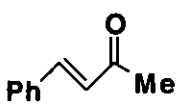


22K

Fig 60

Table 30

Conjugate Addition to Enones at 0 °C

Entry	Enone	Configuration	Yield %	ee %
1	Cyclopenten-1-one 	*R*	72	88
2	Chalcone 	*R*	46	> 99
3	Benzalacetone 	*R*	42	> 99

The results were very encouraging because to date no one has yet utilized these types of ligands in this kind of reaction. The absolute configuration of the product obtained was the (*R*) configuration. Again in order to explain the absolute configuration the possible transition state models may be examined. Figure 61A is presumably the

preferred conformation as this will result in the least steric interaction between the enone and the substituent on nitrogen, while Figure 61B will result in interaction between the enone and the substituent on nitrogen. The (*R*) configuration would then result from facial approach as reported by Dieter[49] through transition state model A.

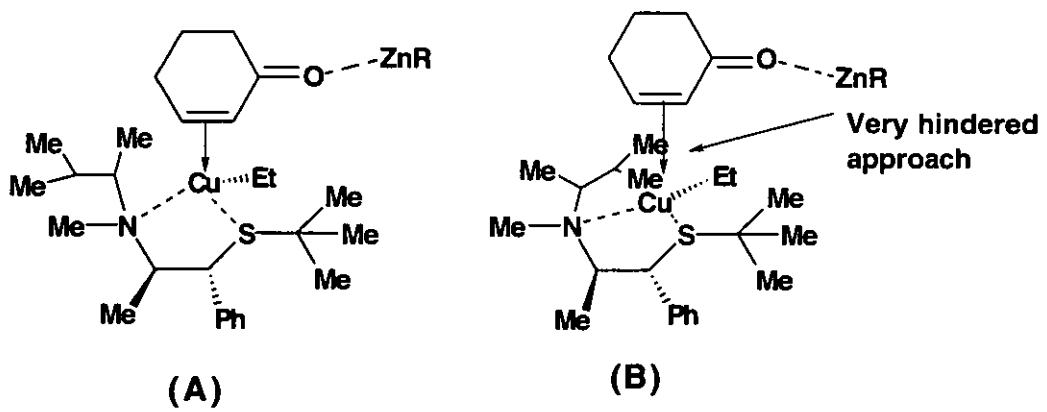


Fig 61

Having obtained these encouraging results, we wondered what effect the catalyst loading would have on the ee, in the conjugate addition (Scheme 53). We varied the ratio of ligand to copper triflate, and we repeated the conjugate addition to cyclohexen-1-one (Table 31), again using our ligand (22k), the methyl isopropyl derivative.

Table 31

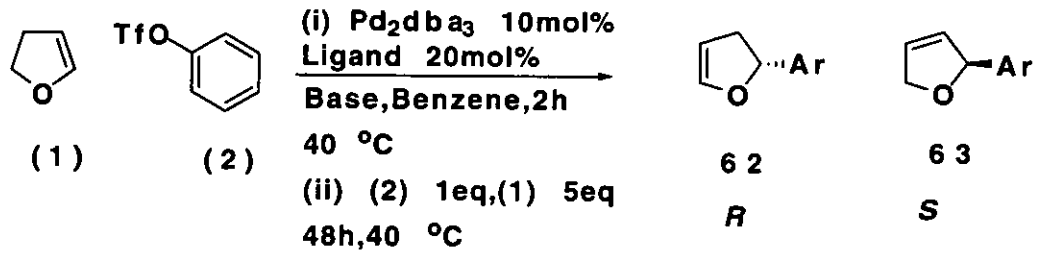
Asymmetric Conjugate Addition to Cyclohexen-1-one using Ligand (22k) and Varying the Loading

Entry	Loading	Time (hours)	Solvent	Temperature (°C)	Yield %	ee %
1	2.5 : 1	4	Toluene	0	82	> 99
2	3 : 1	4	Toluene	0	86	> 99
3	4 : 1	4	Toluene	0	88	> 99
4	4.5 : 1	4	Toluene	0	88	> 99
5	5 : 1	4	Toluene	0	88	> 99
6	5.5 : 1	4	Toluene	0	88	> 99

It can be seen from Table 31 that increasing the loading (ratio of ligand to $Cu(OTf)_2$) has no effect on the ee, but does increase the yield. This suggests that there is an optimum ratio of ligand/$Cu(OTf)_2$ needed, which is around 2.5/1 in this case.

3.3 The Asymmetric Heck Reaction

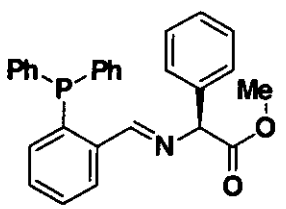
As is mentioned earlier in the Introduction, there has been considerable interest in the use of the Heck type arylation of olefins for constructing carbon skeletons of biological important organic compounds.[56,57] The asymmetric version, where the carbon-carbon bond formation proceeds with high enantioselectivity, has been demonstrated,[58] where BINAP is used as the chiral ligand. This is represented in Scheme 55 for the reaction of dihydrofuran with phenyl triflate.



(1) (2) 62 R 63 S

Scheme 55

Due to the conflicting reports on the use of base,[58,59] we decided to carry out our own optimization experiment using our phosphorus imine ligand (32b)(Figure 64). The ligand was chosen due to its ready availability.



32b

Fig 64

Because of time constraints we decided to use the most popular bases as shown in Table 32, and use the procedure shown in Scheme 55 as the test reaction.

Table 32

Optimization of Asymmetric Heck Reaction with Ligand 32b

Entry	Base	Time (hours)	Conversion	Ratio (S)63 /(R)62	ee % [a]	
					*(S)*63	*(R)*62
1	$(iPr)_2NEt$	48	100	4 : 1	60	42
2	Et_3N	48	100	6 : 1	66	47
3	pyridine	48	100	100	-	39
4	proton sponge	48	100	4 : 1	60	46

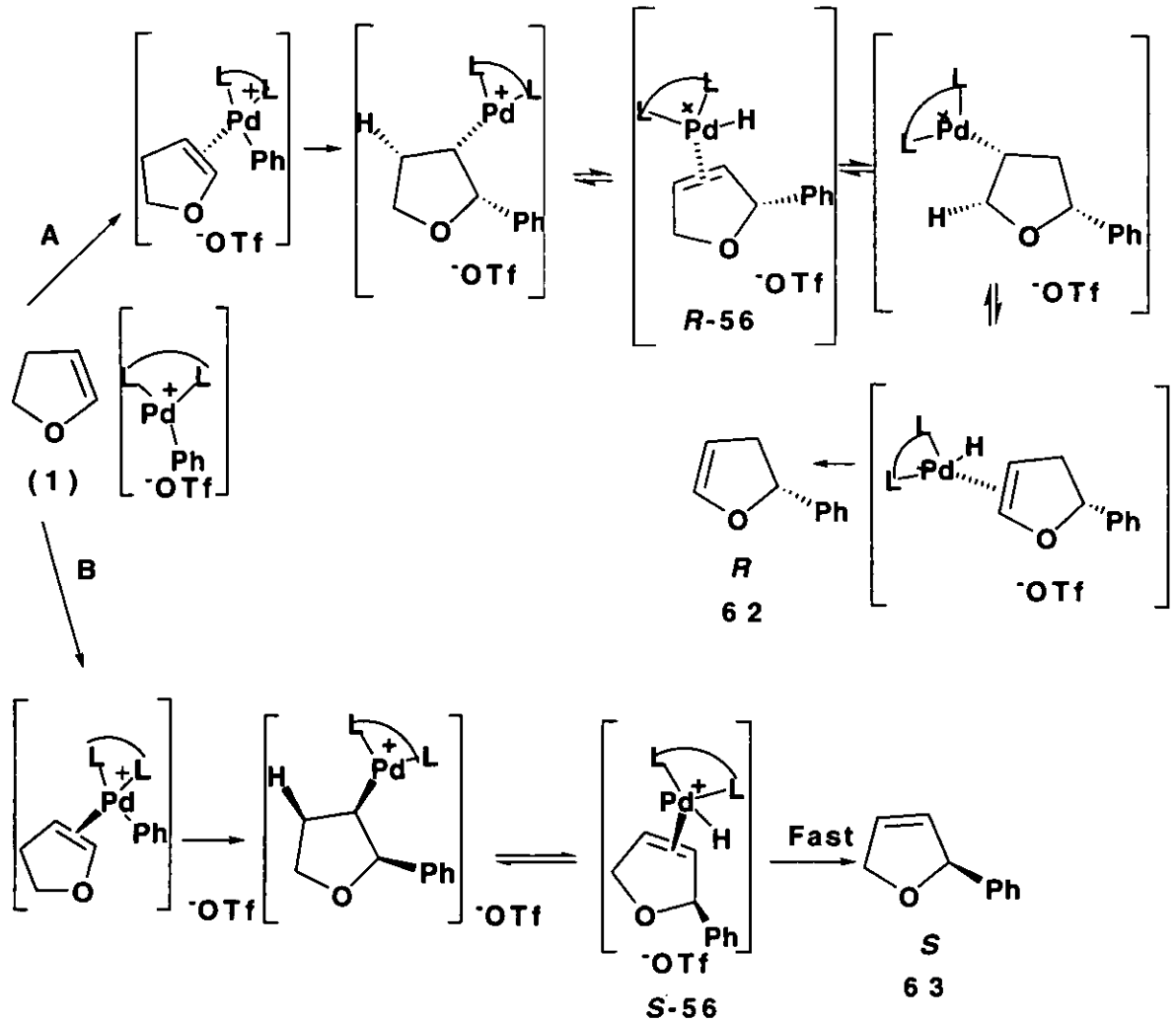
a Absolute configurations were determined by comparision of optical rotations with literature values.

The results in Table 32 indicate that the base of choice is triethylamine. However, other reports contradict our findings and indicate that the use of proton sponge gives better results.[58] A recent report on the use of bases in the asymmetric Heck reaction agrees with our findings and supports triethylamine as the preferred base.[59]

The racemate of each of the products had to be prepared in order to confirm the ee analysis. This was carried out as reported by R Larock.[61] Racemic (63) was prepared by heating together bromobenzene , dihydrofuran , $Pd(OAc)_2$, Ph_3P and silver carbonate in acetonitrile at 80 °C. Removal of the solvent and column chromatography in 70/30 petroleum ether/ ethyl acetate gave the product in 53% yield. Racemic (62) was prepared by stirring together at room temperature bromobenzene, dihydrofuran, $Pd(OAc)_2$, Ph_3P, nBu_4NCl, and Et_3N, in benzene. Removal of solvent and column chromatography gave the product in 66% yield.

A striking feature of the asymmetric Heck reaction shown in Scheme 55 is that the two

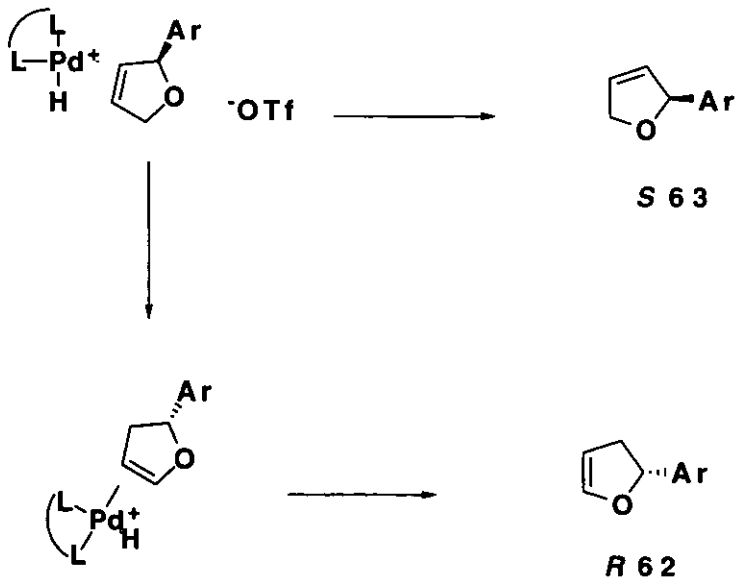
products (62a) and (63a) have not only opposite absolute configuration, but also a different double bond position. The rationale proposed by many authors[60-64] is shown in Scheme 56; it is hypothesized that the addition of the catalytic complex to either face of the substrate can take place, ultimately producing the complexes (*R*) 56 and (*S*) 56, but in the case of the latter, unfavourable steric factors caused by the ligand induce an immediate dissociation of the Pd species producing the minor product (63) (Scheme 56). However for (*R*) 56, another reinsertion of the alkene into Pd-H bond followed by a second β-hydride elimination occurs to produce the more themodynamically stable product (62). The overall effect is s kinetic resolution of (*R*) and (*S*)-56, effectively enhancing the facial selectivity in the initial steps of pathways A and B (Scheme 56).



Scheme 56

Ozawa reported that when he used (*R*) BINAP and proton sponge as the base then the favoured product was (*R)* 62 (Scheme 55), and the above explanation gives a credible explanation.

However, in our case the preference was for (63). One explanation for the difference in the product distribution is that the olefin-bond complex (Scheme 57) formed after migratory insertion and β–elimination is more prone to dissociate to give the (*S*) isomer (63) in the phosphorus-nitrogen catalyst system than in the phosphorus-phosphorus system, where as mentioned earlier (Scheme 56) a reverse β–elimination followed by β– elimination and dissociation occurs to give (*R*) (62)

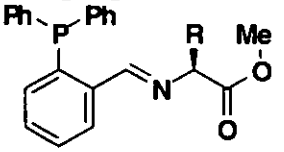


Scheme 57

Having obtained reasonable results we decided to investigate the use of all of our phosphorus imine ligands (32a-c) (Figure 33) in this reaction (Scheme 55) using Et_3N as base. Table 33 below shows the results, which are similar for all three ligands, giving (63) as the major product in resonable ees.

Table 33

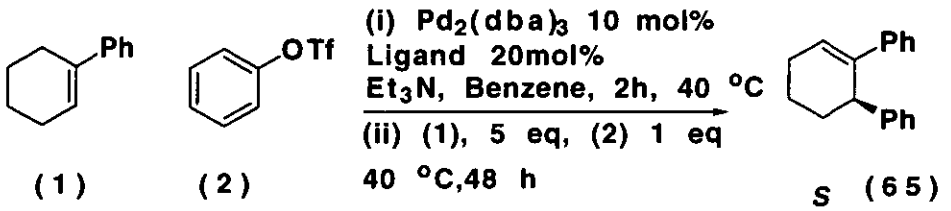
Results of Asymmetric Heck Reaction using Ligands 32a -c



32a_c

Compoound Number	R	Time (h)	Conversion	Ratio (S) 63 / (R) 62	ee %	
					*(S)*63	*(R)*62
32a	P_r^i	48	100	5 : 1	70	50
32b	Ph	48	100	60 : 1	66	47
32c	p-(OH)Bn	48	100	6 : 1	67	45

Having obtained resonable results using the dihydrofuran as substrate, we then proceded to investigate the Heck reaction using the alkene shown in scheme 58 below.



(1) (2) S (65)

Scheme 58

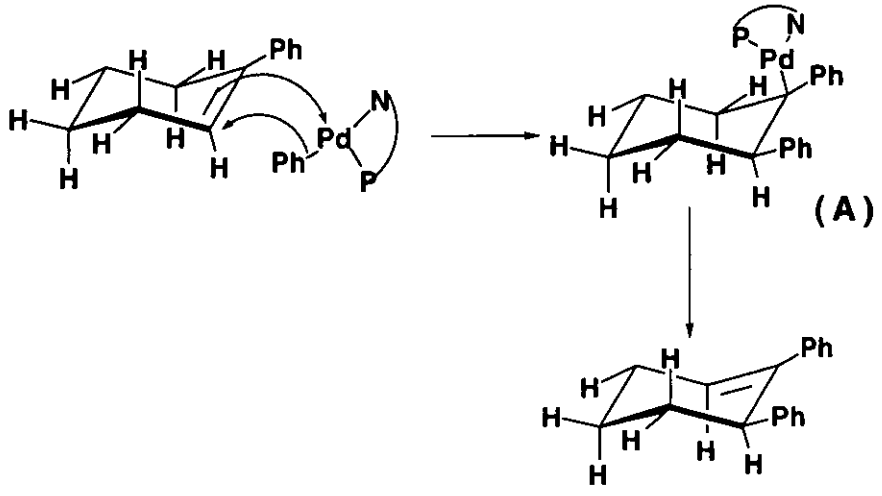
To our delight we were able to achieve ees of up to 97% and chemical yields of up to 80% using our phosphorus imine ligands (32a-c) (Table 34).

Table 34

Asymmetric Heck Reaction
using Ligands 32a -c, Scheme 58

Entry	*R*	Time (h)	Conversion	Configuration	ee %
1	P_r^i	48	100	*S*	87
2	Ph	48	100	*S*	92
3	p-(OH) C_6H_4 CH_2	48	100	*S*	97

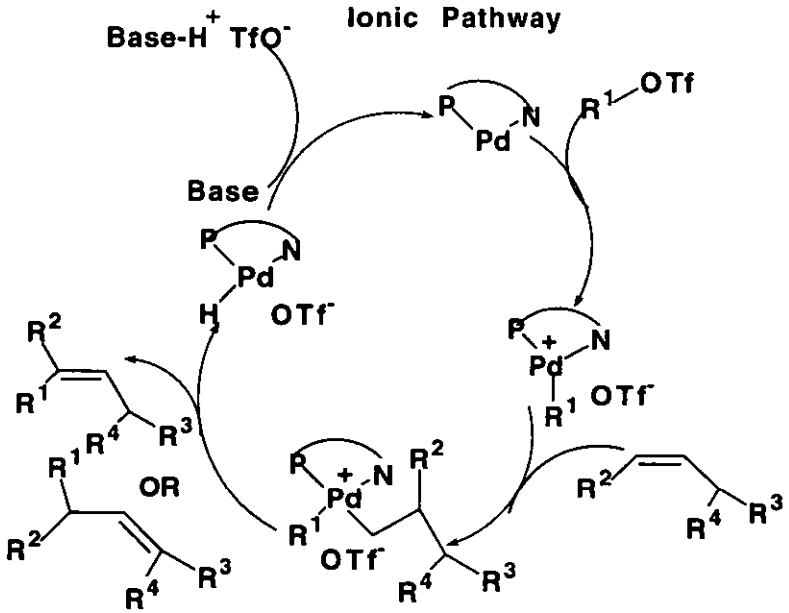
The absolute configuration of the major enantiomer obtained was (*S*). The double bond migration could be explained by looking at Scheme 59. The Pd ligand complex after *syn*-addition to the alkene takes up the conformation A shown; (Scheme 59). This then undergoes syn β–hydride elimination to yield product (65) (Scheme 58). [65]



Scheme 59

The excellent ees produced by this set of ligands, especially entry (3), may throw some light on the possible factors that govern enantioselectivity. The key step is the

association of the alkene and carbopalladation of the alkene. Since we obtained such high ees, the reaction most probably proceeds by an ionic pathway (Scheme 11) below, because according to Shibasaki this route will lead to high ees since the integrity of the ligand-palladium complex is not violated, while the neutral pathway (Scheme 10) will result in dissociation of the ligand-palladium complex in order to accommodate the alkene, and this generally leads to low ee.[62]



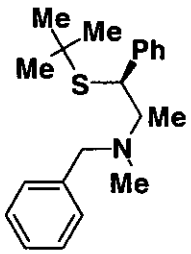
Scheme 11

Apart from the mechanistic pathway, other factors which play an important role are the nature of the olefins, with electron-rich olefins favouring the ionic pathway.[63]

Solvents have been varied, with ionic solvents having an improved effect on the enantioselectivity and yield.[64]

Thioethers had not been used as ligands in the asymmetric Heck reaction before the

investigation reported here. We therefore decided to apply our first generation thioether ligand (11d) (Figure 66) to the asymmetric Heck reaction (Scheme 58).



(11d)

Fig 66

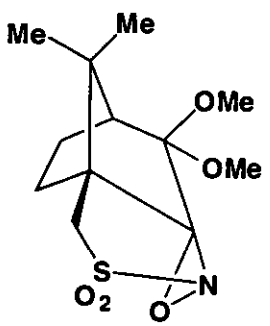
To our delight we obtained an ee of 77% and a yield of 72%. The absolute configuration obtained in the product was (*S*).

CHAPTER 4

Substituent effect on the enantioselective oxidation of sulfides to sulfoxides

As mentioned in the Introduction, chiral sulfoxides are an important class of compounds that find increasing use as chiral auxiliaries in asymmetric synthesis.[66]

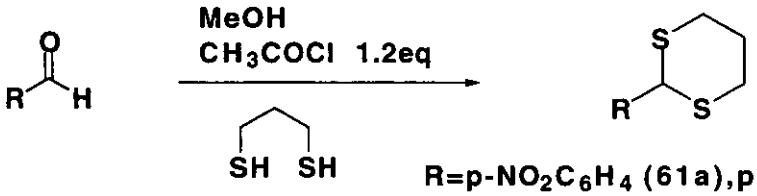
There are various approaches to enantiomerically pure sulfoxides; they include the modified Sharpless process reported by Kagan[67] and Modena,[68] the use of Davis oxaziridines,[69] and Page's modified procedure.[70] Our aim in the work described in this chapter was to use the Page modified procedure with the Davis oxaziridine (Figure 67) to investigate the effect of substituent groups in the sulfide substrate on the enantiomeric purity of the products of oxidation in certain classes of sulfide.



(+)-((8,8-dimethoxycamphoryl) sulfonyl) oxaziridine

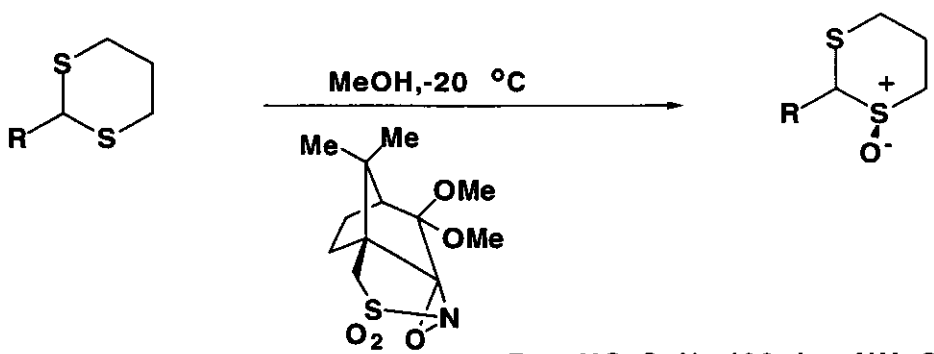
Fig 67

To do this we decided to proceed as shown in Scheme 61 to form amino- and nitro-phenyl substituted 1,3-dithianes, and then to carry out the sulfoxidation as shown in Scheme 62



R=p-$NO_2C_6H_4$ (61a),p-$NH_2C_6H_4$ (61b),Ph(61c), H (61d)
R=m-$NO_2C_6H_4$ (61e),m-$NH_2C_6H_4$ (61f)

Scheme 61



R=p-$NO_2C_6H_4$ (62a),p-$NH_2C_6H_4$ (62b),Ph (62c), H (62d)
R=m-$NO_2C_6H_4$ (62e),p-$NH_2C_6H_4$ (62f)

Scheme 62

The results of the asymmetric sulfoxidation are shown in Table 35.

Table 35

Sulfoxidation of 4- substituted 2- phenyl- 1,3- dithianes

Entry	Compound	*R*	Yield %	ee %	Configuration
1	62a	p-$NO_2C_6H_4$	87	92	*R*
2	62b	p -$NH_2C_6H_4$	92	95	*R*
3	62c	Ph	98	98	*R*
4	62d	H	95	36	*R*

We next investigated the effect of changing the position of the substituent group on the ees. We prepared the *meta*-substitued substrate using similar chemistry (Scheme 61), and proceded to oxidize it as shown in (Scheme 62); the results are shown in table 36.

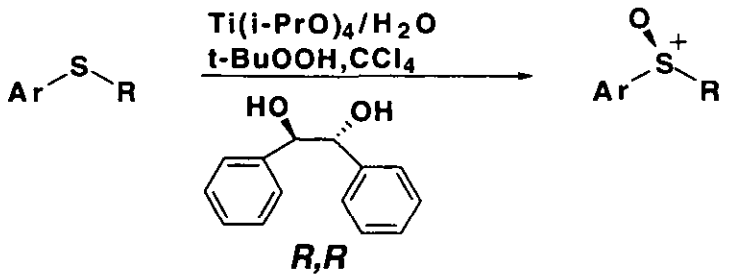
Table 36

Sulfoxidation of 2- substituted- 2- phenyl 1,3- dithianes

Entry	Compound	R	Yield %	ee %	Configuration
1	62e	m -$NO_2C_6H_4$	92	59	*R*
2	62f	m- $NH_2C_6H_4$	94	69	*R*
3	62c	Ph	98	98	*R*
4	62d	H	95	36	*R*

These results agree with the published work of Donnoli, that the introduction of a *meta* substituent eg (Br, NO_2) group to a phenyl will result in a lowering of ee due

to the inductive influence of this group. However, in Donnoli's case they utilized $Ti(O^iP_r)_4$ and t-butyl hydroperoxide as the oxidant (Scheme 63).



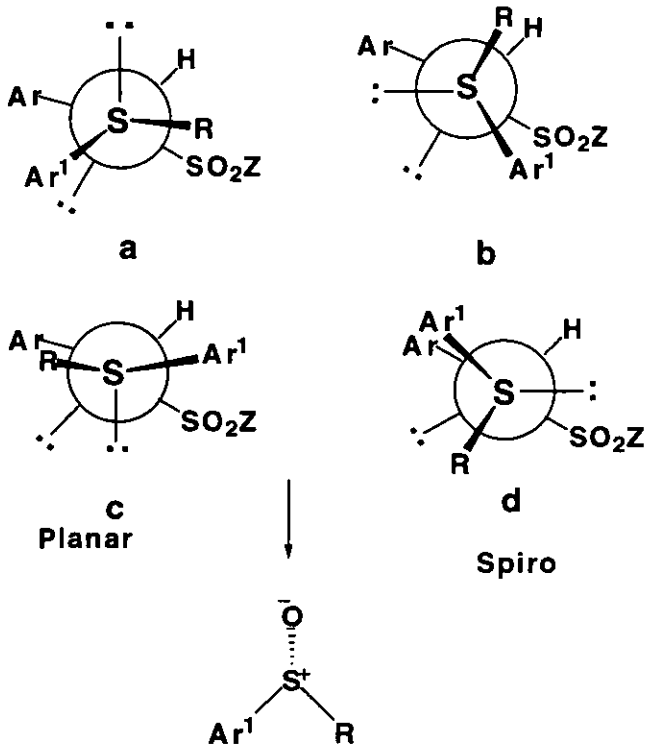
Scheme 63

When the substituent groups are in the para position the ees are not affected (Table 35).

Although more work is needed in this area, it is apparent that, when there is no substituent on the aryl group of the 2-aryl-1,3-dithiane, the ee is low. The introduction of a benzene ring at 2-position seems to improve the ees considerably. However, the introduction of a *meta*-nitrogen substituent group on the benzene seems to result in lower ees, but if the substituent is *para* then there is no effect on ee.

As shown in Tables 35 and 36, the absolute configuration of product sulfoxide was (*R*) in each case. Davis has examined the extremes of the possible transition states for the 2-sulfamyloxaziridine shown in figure 68 below, with the common feature being the approach of the sulfur atom lone pair attacking in the plane of the oxaziridine ring. In one case, both lone pairs are coplanar with the three-membered ring, the spiro transition state, while in the other extreme, the plane occupied by the lone pairs of the sulfur atom is perpendicular to that of the oxaziridine ring, the planar transition state. Scheme 64 shows the possible conformations which result in the (*R*) sulfoxide configuration. The Newman

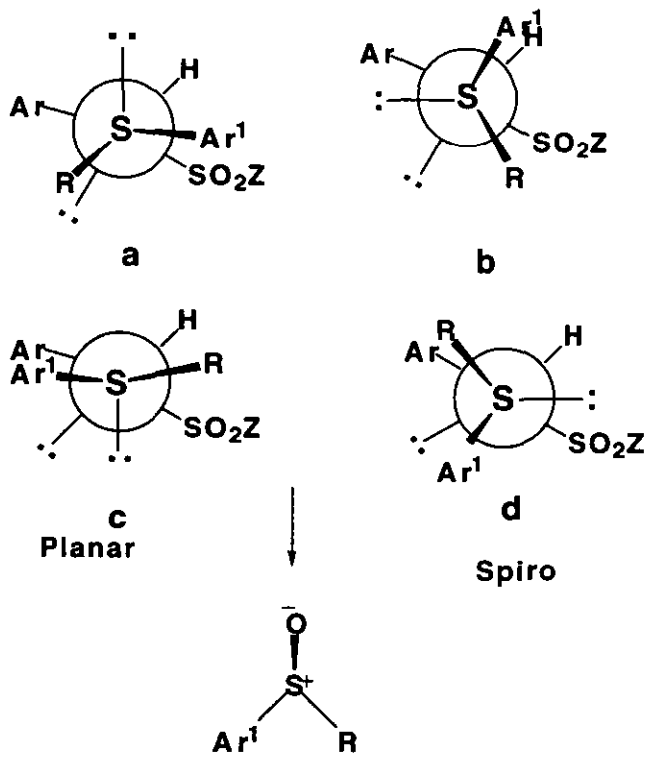
projections show the sulfur atom with its reacting lone pair colinear with the oxygen-nitrogen bond.



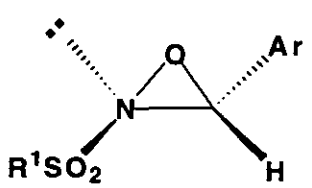
Scheme 64, Newman projections as reported by F.A.Davis

Davis[72] suggested that the most representative of the true transition states are those that show the fewest non-bonded interactions between the Ar' and ZSO_2 group of the oxaziridine and the sulfide (Ar-S-R), thus transition state (a) and (c) (Scheme 64) are favoured while (b) and (d) are disfavoured. Davis also looked at the possible transition states which result in the (*S*) configuration. These are shown in Scheme 65. He again argued that a presence of the (*S*) configuration arises from the transition state which shows the least non-bonded interactions.

The favoured transition states are the (a) and (c), while the disfavoured transition states are (b) and (d) (Scheme 65).[72,73] These transition states are again for the oxaziridine shown in figure 68 below.



Scheme 65, Newman projections as reported by F. A. Davis.



(+)-(R,R)

Fig 68

Both the spiro and planar transition states are modelled by the lone pair of sulfur attacking the oxygen of the oxaziridine ring. It is apparent from Schemes 64 and 65 that planar transition states (a, c) have fewer nonbonded interactions than do the spiro transition states (b, d), therefore Davis argued that the planar transition state is favoured. Therefore the transition states (a, c) result in product formation. The preferred diastereomeric transition state for oxidation by (*R, R*) and (*S, S*) oxaziridines is one where the sulfur atom attacks the electrophilic oxygen atom in such a way that Ar' and *R* groups of the substrate Ar'-*S*-*R* face the small and large regions of the oxaziridine three membered ring. In this case ZSO_2 is considered to be bulkier than C-Ar group.

Using similar argument to the above case the Davis oxaziridine (Figure 67) could be expected to adopt the spiro or planar transition state conformations shown in figure 69 below, again with the planar conformation resulting in the least number of interactions.

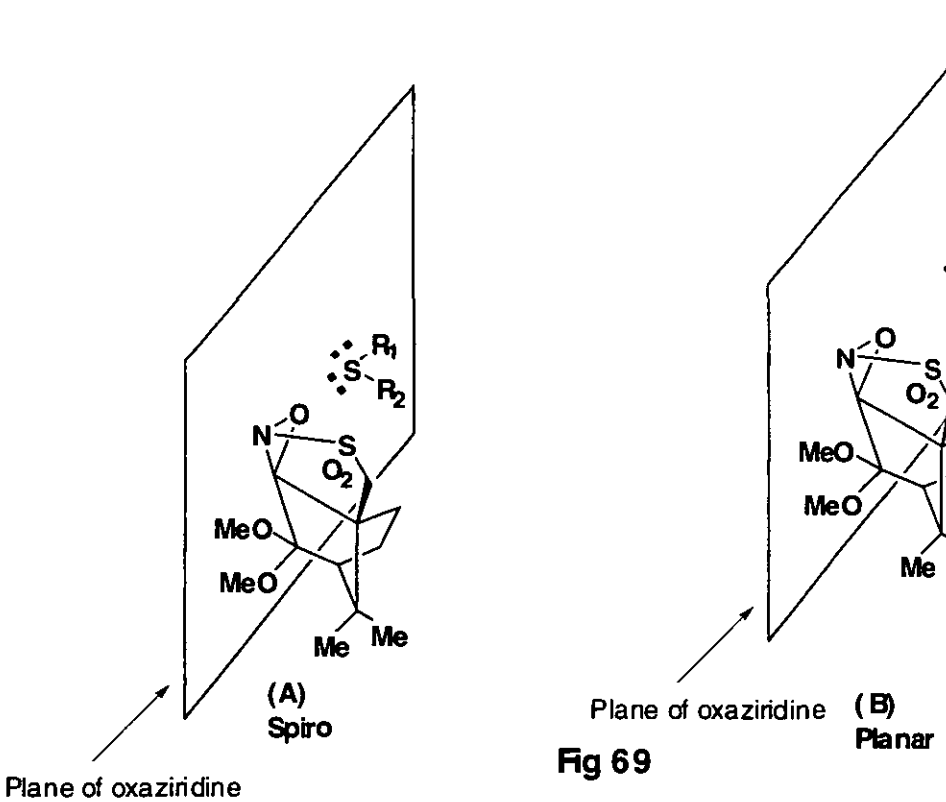
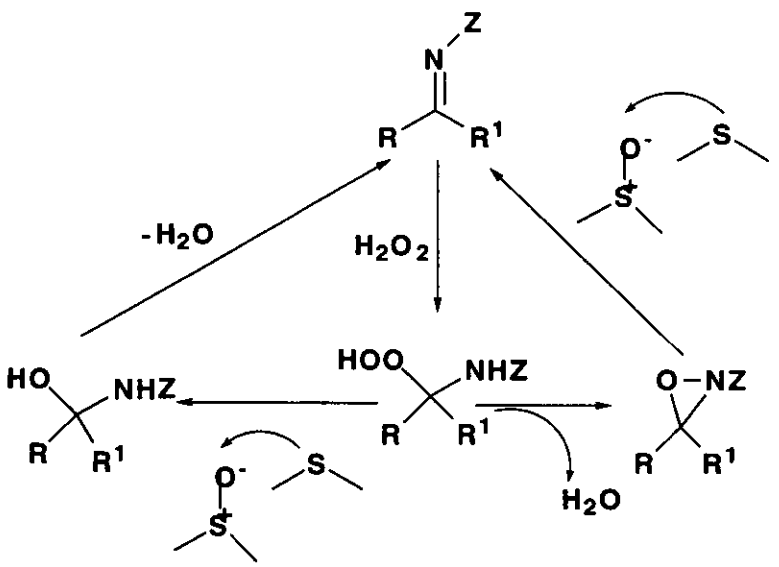


Fig 69

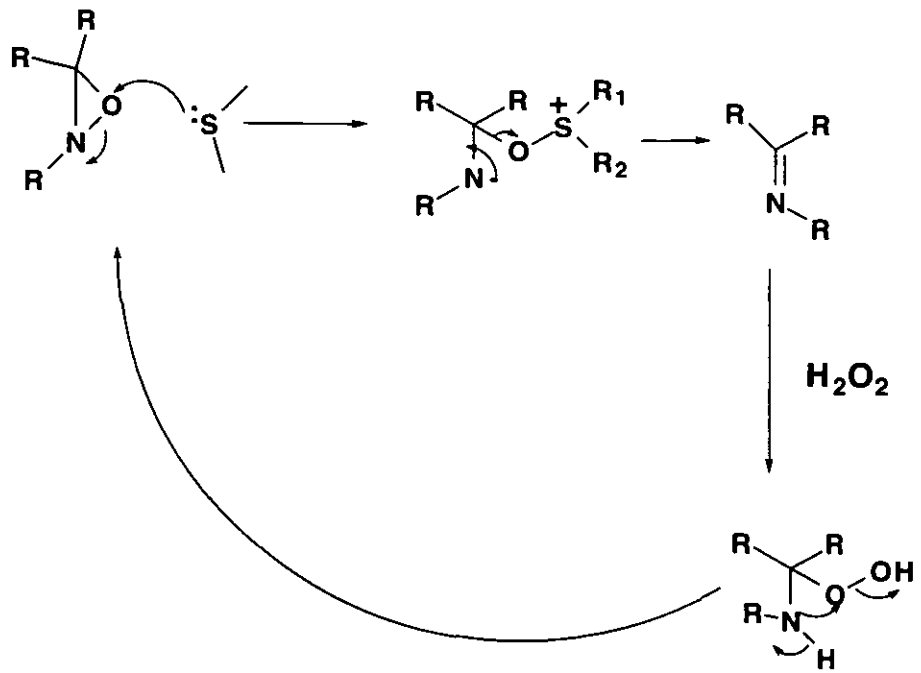
The results in Tables 35 and 36 show that there is a considerable improvement of ee when an unsubstituted phenyl group is introduced, compared to when there is no substituent on the 1,3-dithiane moiety; this perhaps is due to the steric influences in the transition state of oxygen transfer, but could also be partly due to electronic effects. However, the presence of a substituent group more electronegative than carbon at the *meta*-position of the ring has the effect of making the sulfur atom less nucleophilic and thus has the effect of reducing the ability of sulfur to donate electrons to the oxaziridine. This effect may contribute towards reducing the enantioselectivity (Table 36).

The introduction of a similar substituent group at the *para* position however, seems to have very little effect on the enantioselectivity, as the results in Tables 35, 36 show. Davis in his work had explained that although electronic effects do play some part in determining the enantioselectivity of the sulfoxidation reaction, the steric influence is the more important.[74]

The possible catalytic cycle for the sulfoxidation by oxaziridine and catalysed by the corresponding imine can be represented as in Scheme 66 below, and the mechanism of sulfoxidation using oxaziridine and H_2O_2 is shown in Scheme 67.



Scheme 66



Scheme 67

Having considered the effect of some phenylsubstituent groups on the sulfoxidation of 2-phenyl-1,3-dithiane, we wished to investigate different substituents on the oxaziridine. We decided to synthesize the diethoxy derivative shown below in figure 70. The synthesis of this compound is shown in Scheme 68. The synthesis proceeded from camphor sulfonyl chloride and reaction with ammonium hydroxide to yield the sulfonylimine, which was oxidized *in situ* using selenium dioxide to obtain the ketoimine. This was then reacted with triethylorthoformate to form the diethoxy imine which was converted to the oxaziridine derivative with hydrogen peroxide.

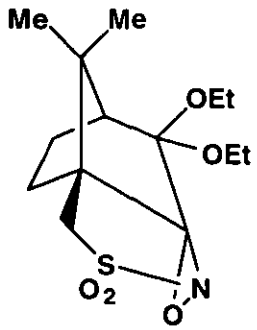
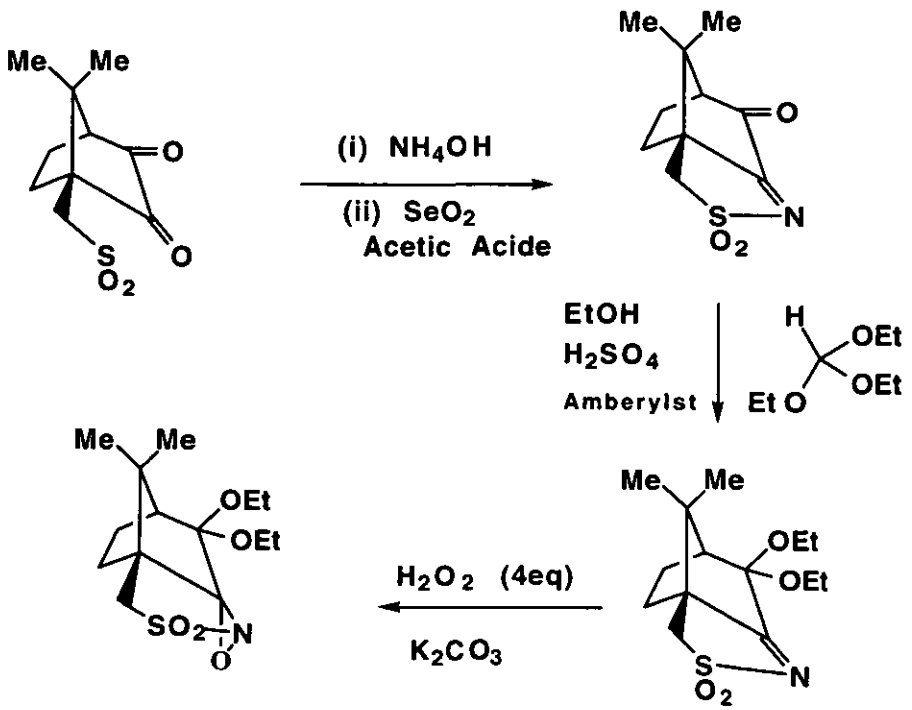


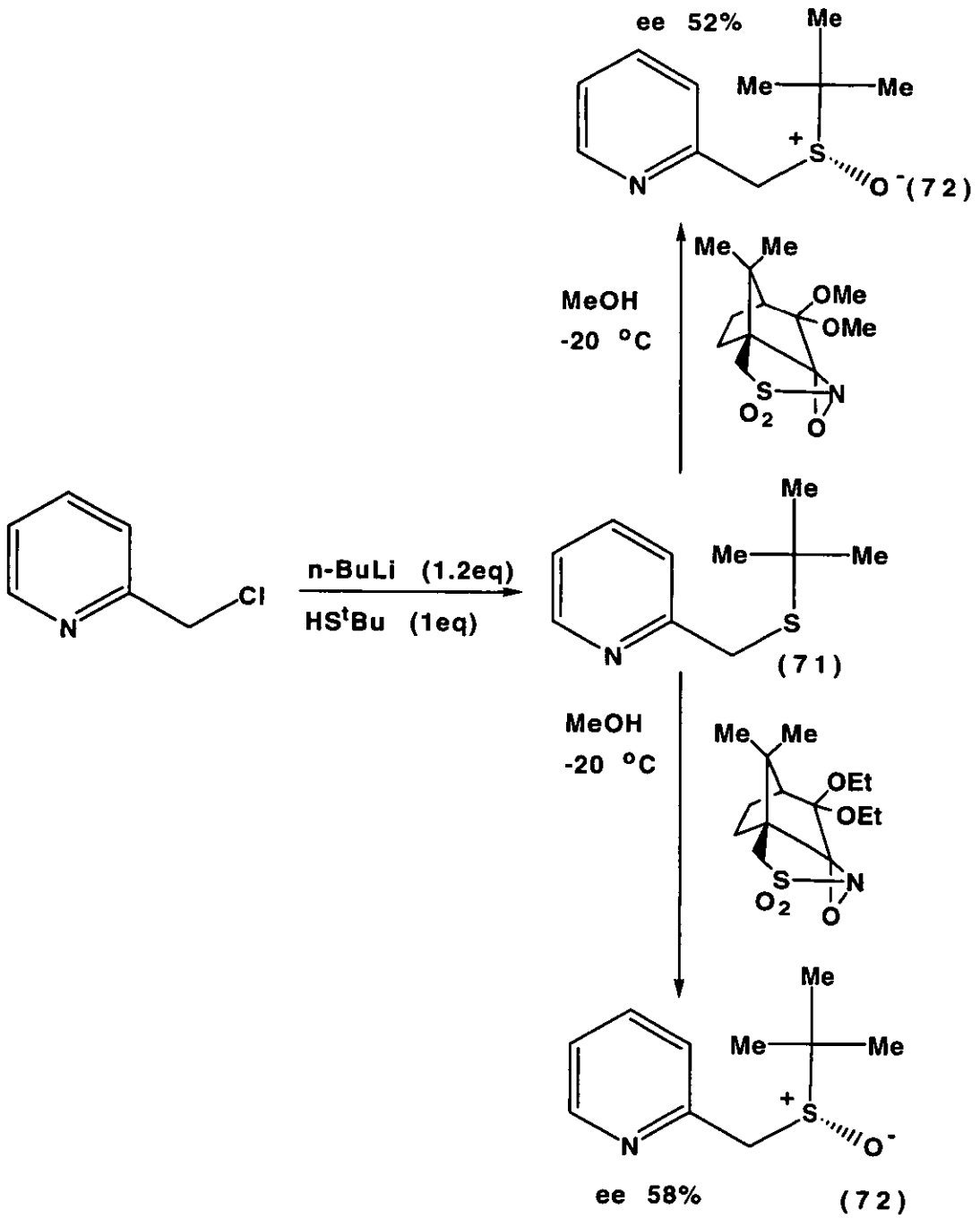
Fig70



Scheme 68

We next decided to use the diethoxy oxaziridine (Figure 70) and dimethoxy derivative Figure 67 in the sulfoxidation of sulfide 71 as shown in Scheme 69. The sulfide was synthesized from the 2-chloromethyl pyridine as shown. Using the

diethoxy oxaziridine we obtained an ee of 58% while for the case of dimethoxy oxaziridine an ee of 52% was obtained, thus an improvement of nearly by 10% was achieved using the diethoxy derivative over the dimethoxy derivative. The major product (72), a new compound is believed to have the (R) configuration on the basis of the known results from oxidation of other sulfideds with these reagents.[77]


ee 52%
Me
Me
Me
+
S
O⁻(72)
MeOH
-20 °C
Me
Me
OMe
OMe
S
N
O2
O
Cl
N
n-BuLi (1.2eq)
HS^tBu (1eq)
Me
Me
Me
S
N
(71)
MeOH
-20 °C
Me
Me
OEt
OEt
S
N
O2
O
Me
Me
Me
+
S
O⁻
N
ee 58%
(72)

Scheme 69

CHAPTER 5

Conclusion

CONCLUSION

The aim of the current work was to synthesize chiral hybrid ligands with various ligating heteroatoms including S-N and P-N types, and to examine the possibility of applying these to asymmetric catalysis. Special attention was paid to palladium catalysed allylic displacement reaction, conjugate addition of diethylzinc to enones, and the asymmetric Heck reaction.

Through our journey towards our goal of the synthesis of these ligands we were able to devise methods of synthesis of the various important intermediates, including the oxazolidines derived from aryl ketones, and the very important α-amino alcohols, achieved by diastereoselective ring-opening using DIBAL in hexanes. From there we were able to synthesize various chiral thioethers which gave respectable ees of up to 78% in the palladium catalysed allylic displacement reaction, and > 99% in the conjugate addition of diethylzinc to cyclic and acyclic enones.

In our quest to improve the enantioselectivity we were able to synthesize a series of sulfur imine ligands which performed extremely well in the palladium catalysed allylic displacement reaction, providing ees of up to 96%.

We then proceeded to the synthesis of phosphorus imine ligands, which were very poor performers in the palladium catalysed allylic displacement reaction, but proved to be very impresive in the conjugate addition of diethylzinc to cyclic

and acyclic enones, with ees up to 99%. Moreover, these ligands showed impressive results in the asymmetric Heck reaction with ees of up to 97%. Overall, we have managed to design and optimize the conditions for all three types of reaction mentioned above, and in all cases we managed to achieve stereoselectivity comparable with the best results in the literature. Further, our ligands are all structurally very simple, and are based on readily available inexpensive materials, and are prepared through extremely simple synthetic routes.

In sulfoxidation, we examined the effects of substituents on the phenyl ring of a 1,3-dithiane system. We were able to show that the presence of *para* nitrogen substituents has no effect on the absolute configuration obtained, and also that the presence of a *meta* nitrogen substituents on the benzene ring has the effect of reducing the enantioselectivity.

We have also utilized our first generation thioether ligands (4a-d) in the asymmetric Heck reaction and obtained an ee of 76%. It is hoped that further work should be carried out in this field since this type of ligand has never been used in this reaction.

It is to be hoped that the present work may contribute in a small way to the understanding of how chiral ligands are incorporated into the transition states of the reactions investigated and how stereoselectivity is achieved thereby.

EXPERIMENTAL PROCEDURES

Commercially available solvents and reagents were used without further purification. However, low grade solvents were distilled before use. Petroleum ether was distilled from calcium chloride, ethyl acetate and dichloromethane were distilled from calcium hydride. Tetrahydrofuran was distilled from the Na/benzophenone ketyl radical before use.

Air and moisture sensitive reactions were carried out under nitrogen, and all glassware was dried for 24 hours at 150 *°C* before use.

Column chromatography was carried out using either silica or alumina. Thin layer chromatography was carried out on silica plates. Compounds were visualized using a UV lamp or by permanganate dip.

Melting points were performed on Reichert hot stage apparatus.

Microanalyses were performed on a Perkin-Elmer 2400 Analyser at Loughborough University.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 88 model. Liquids were run neat, solids were run as nujol mulls.

NMR spectra were run on either a Bruker 250 MHz or 400 MHz spectrometer. Tetramethylsilane in deuteriochloroform was used as internal standard. Where needed the chiral shift reagent used to determine ees was (+) europium tris [3,-(heptafluoropropylhydroxymethylene camphorate], 10 mol % equivalent.

All other enantiomeric excesses were determined by HPLC using a Chiralcel OD column, For Pd catalysed allylic displacement reactions, the eluent used was

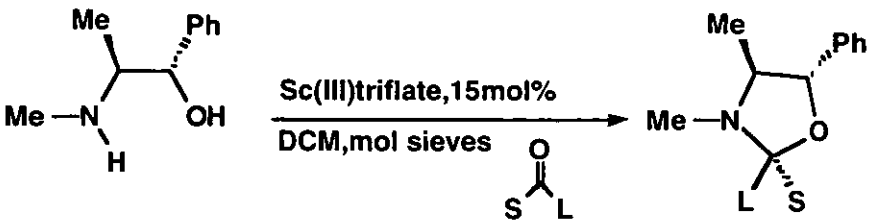
99:1 hexane:isopropanol; flow rate 0.5 ml/min, retention times were 30.5 min (*R*) and 33.7 min (*S*). For the asymetric Heck reaction using 2-phenyl cyclohex-1-ene as alkene, the eluent used was 60:40 hexane:isopropanol; retention times were 7.2min (*S*), 9.4 min (*R*).

For the conjugate addition of diethylzinc, a Perkin Elmer gas chromatograph 8700 was used, using chiral Chrompack CP7502 CP-Chirasil Dex CB 25mm 0.25 mm 1D column. For cyclohexen-1-one, the retention times were 10.5 min (*R*) and 10.6 min (*S*) at isothermal 200 °C. For cyclopenten-1-one, the retention times were 14.5 min (*R*) and 15.2 min (*S*).

Optical rotations were measured on an Optical Activity polAAr-2001 polarimeter at λ= 589 nm.

EXPERIMENTAL PROCEDURES

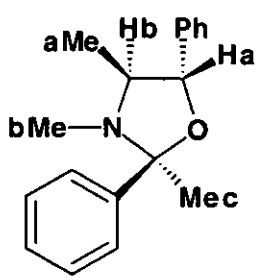
Oxazolidine Synthesis from Ketones and Pseudoephedrine



To an excess (1.5 eq) of the ketone in DCM (40 ml), scandium (III) triflate (1.34-1.4 g, 27 mmol, 15 mol %) was added, then pseudoephedrine (3.0 g, 18 mmol) was added, followed by 4Å molecular sieves (13 g). The resulting mixture was allowed to stand for two weeks. The mixture was stirred with solid sodium hydrogen carbonate for two hours, then filtered and washed with water (2 × 50 ml). The organic solutions was dried over magnesium sulfate and removal of the solvent yielded the required oxazolidine.

(4S,5S)-2,3,4-Trimethyl-2,5-diphenyl 1,3-oxazolidine (1.8 g, 74% yield)

[pseudoephedrine (1.5 g, 9.0 mmol), acetophenone (1.63 g, 13.63 mmol)]



(12h)

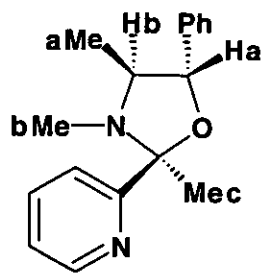
ν_{max} (neat) 4379, 3488, 3698, 2309, 1483, 1437, 1360, 1352, 1278, 1230, 1187, 1121 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 1.1 (3 H, d, *J*=4.0 Hz,Me a), 1.6 (3 H, s, Me c), 2.3 (3 H, s, Me b), 2.6-2.8 (1 H, m,Hb), 4.51 (1 H, d, *J*=4.4 Hz, Ha), 7.2-7.4 (8 H, m), 7.5-7.6 (2 H, m).

δ_C ($CDCl_3$, 100 MHz) 14.26, 20.94, 37.35, 83.96, 96.48, 124.57, 126.14, 127.16, 127.58, 128.03, 128.43, 139.77, 143.86, 145.57.

m/z FAB (Found: 268.1702 (M^++1) $C_{18}H_{22}NO$ requires: 268.1623). $[\alpha]_D$ = +67 (CCl_4, 10 mg/ml).

(4S,5S)-2- Pyridine- 2- yl- 2,3,4- trimethyl- phenyl 1,3- oxazolidine (1.79 g, 74% yield) [(pseudoephedrine(1.5 g, 9 mmol), 2- acetylpyridine(1.63 g, 13.5 mmol)]



(12k)

ν_{max} (neat) 4350, 3482, 3679, 1304, 1491, 1437, 1356, 1200, 1135, 1126 cm^{-1}.

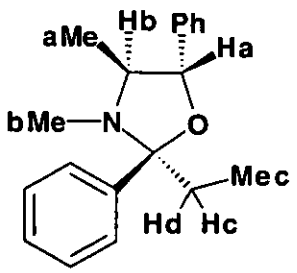
δ_H($CDCl_3$, 250 MHz) 1.15 (3 H, d, *J*=4.4 Hz,Me a), 1.83 (3 H, s,Me c), 2.30 (3 H, s,Me b), 2.57-2.60 (1 H, m,Hb), 4.41 (1 H, d, *J*=6.7 Hz, Ha), 7.1-7.2 (2 H, m), 7.2-7.4 (5 H, m), 7.62-7.80 (2 H, m), 8.52-8.65 (1 H, m).

δ_C($CDCl_3$, 250 MHz) 16.31, 18.91, 25.32, 35.76, 65.35, 86.21, 99.76, 119.85, 121.76, 125.37, 125.82, 126.76, 127.02, 135.32, 139.46, 149.26, 165.72.

m/z FAB (Found: 269.1656 (M^++1) $C_{17}H_{21}N_2O$ requires: 269.1575). $|\alpha|_D$ = +65 (CCl_4, 10 mg/ml).

(4S,5S)-2- Ethyl- 3,4 dimethyl- 3,5- diphenyl 1,3- oxazolidine (1.85 g, 79% yield)

[pseudoephedrine (1.5 g, 9 mmol), propiophenone (1.82 g, 13.5 mmol)]



(12i)

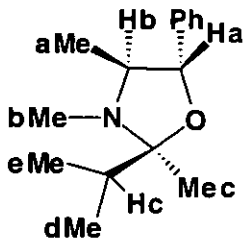
ν_{max} (neat) 4382, 3496, 3703, 2306, 1489, 1436, 1359, 1297, 1198, 1135, 1146 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.9 (3 H, d, *J*=4.4 Hz, Me a), 1.15 (3 H, t, *J*=5.0 Hz,Me c), 2.2 (3 H, s,Me b), 2.51-2.53 (1 H, m, Hb), 2.9 (2 H, q, *J*=5.0 Hz,Hc, Hd), 4.1 (1 H, d, *J*=4.2 Hz, Ha), 7.15-7.25 (2 H, m), 7.35-7.44 (5H, m), 7.62-7.85 (2 H, m).

δ_C($CDCl_3$, 100 MHz) 8.23, 15.46, 31.75, 37.43, 61.26, 101.23, 126.21, 127.03, 127.96, 128.35, 128.54, 132.85, 136.92, 142.63.

m/z FAB (Found: 282.1878(M^++1) $C_{19}H_{24}NO$ requires: 282.1799). $[\alpha]_D$ = +45.6 (CCl_4, 10 mg/ml).

(4S,5S) 2,3,4- Trimethyl- 2- (1 methyl ethyl) 5- phenyl]- 1,3- oxazolidine (35 g, 83% yield) [pseudoephedrine (3.0 g, 18.18 mmol), methyl isopropyl ketone (2.3 g, 27.27 mmol)]



(12n)

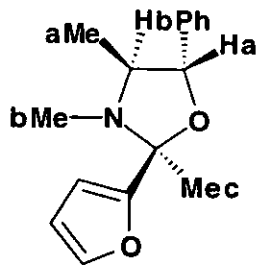
ν_{max} (neat) 43289, 3734, 3130, 2924, 2761, 1459, 1373, 1326, 1189, 1135 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.9 (3 H, d, *J*=5.0 Hz,Me a), 1.07 (6 H, d, *J*=4.2 Hz,Me d Me e), 1.12 (3 H, s,Me c), 1.8-1.9 (1 H, m,Hc), 2.1 (3 H, s,Me b), 2.21-2.23 (1 H, m,Hb), 4.21 (1 H, Ha, d, *J* = 5.0 Hz, Ha), 7.2-7.3 (5 H, m).

δ_C($CDCl_3$, 100 MHz) 7.71, 14.38, 14.56, 33.66, 36.43, 65.14, 85.39, 98.63, 126.22, 126.67, 127.00, 127.74, 140.43.

m/z FAB (Found: 234.1801,(M^++1) $C_{15}H_{24}NO$ requires: 234.1799). $[\alpha]_D$ = +39 (CCl_4, 10 mg/ml).

(4S,5S)-2- Furan- 2- yl- 2,3,4- trimethyl- 5- phenyl 1,3- oxazolidine (1.66 g72% yield) [pseudoephedrine(1.5 g, 9 mmd), 2 acetyl Furan(1.27 g, 13.5 mmd)]



(12j)

ν_{max} (neat) 4371, 3454, 2986, 2201, 1481, 1354, 1200, 1175, 1121 cm^{-1}.

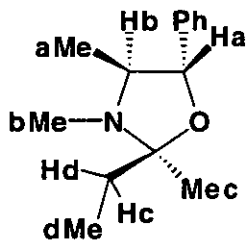
δ_H($CDCl_3$, 250 MHz) 0.90 (3 H, d, *J*=4.4 Hz,Me a), 1.71 (3H, s,Me c), 2.2 (3H, s,Me b) 2.58-2.61 (1H, m,Hb), 4.12 (1 H, d, *J*=4.3 Hz,Ha), 6.29-6.31 (1 H, m), 7.11-7.21 (1 H, m), 7.31-7.45 (5 H, m), 7.61-7.63 (1 H, m).

δ_C($CDCl_3$, 250 MHz) 14.41, 25.99, 33.45, 61.29, 77.50, 100.12, 108.50, 112.26, 126.83, 127.83, 127.32, 127.80, 142.01, 146.43, 152.89.

m/z FAB (Found: 258.1499,(M^++1) $C_{16}H_{20}NO_2$ requires: 268.1415). $[\alpha]_D$ = +37.4 (CCl_4, 10 mg/ml).

(4S,5S)–2,3,4- Trimethyl- 2- (ethyl) - 5- phenyl 1,3- oxazolidine (3.8 g, 88% yield).

[pseudoephedrine (3.0 g, 18.18 mmd), methyl ethyl ketone (1.96 g, 27.27 mmd)]



(12m)

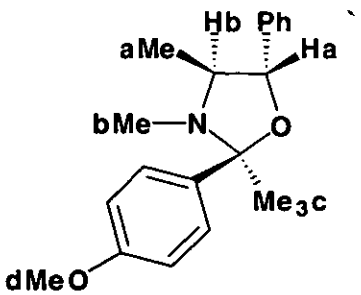
ν_{max} 3827, 3812, 2870, 2787, 1493, 1454, 1370, 1166 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.9 (3 H, d, *J*= 7.4 Hz,Me d), 1.1 (3 H, d, *J*=4.4 Hz,Me a), 1.3 (3 H, s,Me c), 1.6-1.71 (2 H, m,Hc, Hd,), 2.2 (3 H, s,Me b), 2.6-2.7 (1 H, m,Hb), 4.6 (1 d, *J*=7.6 Hz, Ha), 7.2-7.3 (5 H, m).

δ_C($CDCl_3$, 100 MHz) 7.70, 114.54, 23.86, 32.18, 32.48, 64.71, 85.71, 96.83, 126.67, 127.76, 127.85, 140.03.

m/z FAB (Found: 220.1625,(M^++1) $C_{14}H_{22}NO$ requires: 220.1623). $[\alpha]_D$ = +43 (CCl_4, 10 mg/ml).

(4S,5S)-2,3,4-Trimethyl-2-(methylphenyl)-5-phenyl 1,3-oxazolidine (1.9 g, 71% yield). [pseudoephedrine (1.5 g, 9 mmol), para-methoxyacetophenone (2.02 g, 13.5 mmol)]



(121)

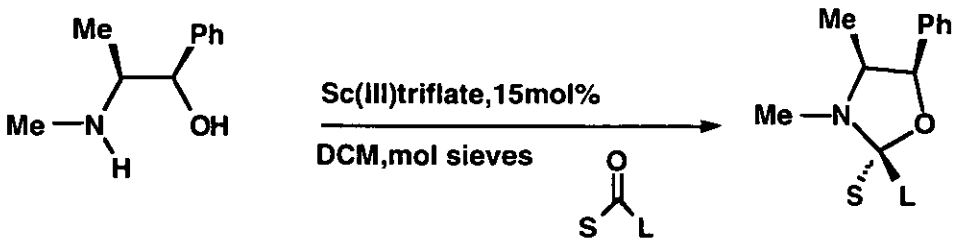
ν_{max} 4327, 3472, 2206, 1489, 1359, 1198, 1142, 1125 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.9 (3 H, d, *J*=4.4 Hz, Me a), 1.8 (3 H, s,Me c), 2.2 (3 H, s,Me b), 3.59-3.61 (1 H, m, Hb), 3.9 (3 H, s,Me d), 4.4 (1 H, d, *J*=4.3 Hz,Ha), 6.9-7.1 (2 H, m), 7.2-7.4 (5 H, m), 8.1-8.2 (2 H, m).

δ_C($CDCl_3$, 100 MHz) 15.12, 26.31, 33.56, 62.39, 77.6, 101.12, 125.31, 26.01, 126.82, 127.31, 127.82, 133.42, 147.35, 153.92.

m/z FAB (Found: 298.2012, $(M^+ + 1)$ $C_{19}H_{24}NO_2$ requires: 298.1728). $[\alpha]_D$ = +41.3 (CCl_4, 10 mg/ml).

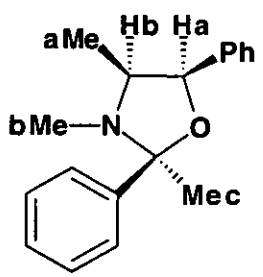
Oxazolidine Synthesis from Ketones and Ephedrine



To an excess (1.5 eq) of the ketone in DCM (40 ml), scandium (III) triflate (1.34-1.4 g, 27 mmol, 15 mol %) was added, then ephedrine (3.0 g, 18 mmol) was added, followed by 4Å molecular sieves (13 g). The resulting mixture was allowed to stand for two weeks. The mixture was stirred with solid sodium hydrogen carbonate for two hours, then filtered and washed with water (2 x 50 ml). The organic solutions were dried over magnesium sulfate and removal of the solvent yielded the required oxazolidine.

(4S,5R)-2-3,4,-Trimethyl-2,5-diphenyl-1,3-oxazolidine (1.8 g, 76% yield).

[ephedrine (1.0 g, 6.0 mmol), acetophenone (1.08 g, 9 mmol)]



(12a)

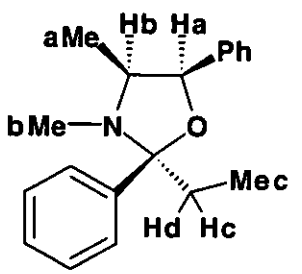
ν_{max} (neat) 4347, 3028, 2314, 1454, 1377, 1265, 1195, 1152 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.83 (3 H, d, *J*=4.7 Hz,Me a), 1.82 (3 H, s,Me c), 2.23 (3 H, s,Me b), 2.59-2.61 (1 H, m, Hb), 4.52 (1 H, d, *J*=4.6 Hz, Ha), 7.1-7.5 (8 H, m), 8.15-8.21 (2 H, m).

δ_C($CDCl_3$, 100 MHz)14.27, 18.96, 33.86, 37.78, 64.21, 81.89, 98.88, 126.15, 126.92, 127.49, , 128.28, , 137.08, 137.11, 141.89.

m/z FAB (Found: 268.1705,(M^++1) $C_{19}H_{24}NO_3$ requires: 268.1623). $[\alpha]_D$ = –4.5 (CCl_4, 10 mg/ml).

(4S,5R)–2- Ethyl- 3,4- dimethyl- 2,5- diphenyl- 1,3- oxazolidine (3.3 g, 65% yield). [ephedrine(3.0 g, 18.18 mmol), propiophenone(3.68 g, 27.27 mmol)]



(12b)

ν_{max} (neat) 4390, 3352, 2977, 1450, 1377, 1350, 1218, 1145, 1137 cm^{-1}.

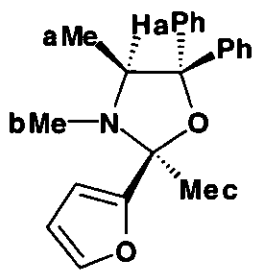
δ_H($CDCl_3$, 250 MHz) 0.8 (3 H, d, *J*=4.4 Hz,Me a), 1.03 (3H, t, *J*=4.5 Hz,Me c), 2.2 (3 H, s,Me b), 2.59-2.61 (1 H, m, Hb), 2.7 (2 H, q, *J*=4.5 Hz Hc, Hd), 4.5 (1H, d, *J*=4.3 Hz, Ha), 7.25-7.32 (8 H, m), 7.81-7.83 (2 H, m).

δ_C($CDCl_3$, 100 MHz)8.26, 14.19, 31.80, 60.45, 72.92, 96.88, 126.94, 127.07, 128.11, 128.56, 132.87, 136.98, 141.43.

m/z FAB (Found: 282.1793,(M^++1) $C_{20}H_{24}NO$ requires: 282.1796). $[\alpha]_D$ = −7.5 (CCl_4, 10 mg/ml).

(4S,5R)-2- Furan- 2yl- 2,3,4- trimethyl- 5- phenyl 1,3- oxazolidine (2.9 g ephedrine62 % yield).

[(3.0 g 18.18 mmd), 2- acetylfuran (2.0 g 27.27 mmd)]



(12c)

ν_{max} 4373, 3393, 2201, 1969, 1392, 1358, 1199, 1137 cm^{-1}.

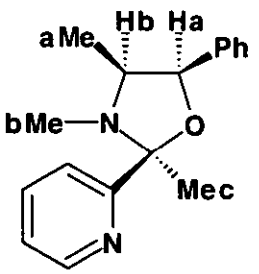
δ_H($CDCl_3$, 250 MHz) 0.93 (3 H, d, *J*=4.4 Hz,Me a), 1.75 (3 H, s, Me c), 2.35(3H,s, Me b), 2.59-2.61 (1 H, m, Hb), 4.6 (1H, d, *J*=4.3 Hz, Ha), 6.2-6.3 (1 H, m, furan), 7.1-7.2 (1 H, m, Furan), 7.3-7.4 (5 H, m), 7.6-7.7 (1 H, m, Furan).

δ_C($CDCl_3$, 100 MHz) 14.56, 26.32, 33.67, 62.14, 78.13, 99.96, 107.30, 1121.76, 126.62, 127.93, 127.92, 142.3, 146.53, 153.12.

m/z FAB (Found: 258.1501 (M^++1)$C_{17}H_{21}NO_2$ requires: 258.1415). $[\alpha]_D$ = −6.9 (CCl_4, 10 mg/ml).

(4S,5S)-2-Pyridine-2yl-2,3,4-trimethyl-phenyl 1,3-oxazolidine (2.98 g, 61% yield).

[ephedrine (3.0 g, 18.18 mmol), 2-acetylpyridine (3.3 g, 27.27 mmol)]



(12d)

ν_{max} 3294, 3085, 1585, 1493, 1454, 1358, 1327, 1238, 1196, 1136 cm^{-1}.

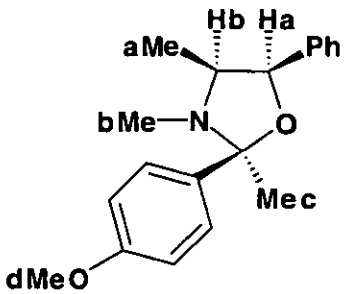
δ_H($CDCl_3$, 250 MHz) 0.98 (3 H, d, *J*=4.89 Hz,Me a), 1.32 (3 H, s,Me c), 2.63 (3 H, s, Me b), 2.65-2.66 (1 H, Hb, m, Hb), 5.22 (1 H, d, *J*=4.8 Hz, Ha), 7.25-7.91 (8 H, m), 8.52-8.53 (1 H, m).

δ_C($CDCl_3$, 100 MHz) 4.92, 24.96, 33.90, 60.19, 76.89, 82.12, 97.28, 120.65, 121.20, 127.92, 128.09, 128.39, 136.21, 137.01, 140.72, 148.75, 162.97.

m/z FAB (Found: 269.1651(M^++1) $C_{17}H_{21}N_2O$ requires: 269.1575). $[\alpha]_D$ = −3.9 (CCl_4, 10 mg/ml).

(4S,5R)-2,3,4-Trimethyl-2-(methoxyphenyl)5-phenyl-1,3-oxazolidine (3.4 g, 63% yield).

[ephedrine(3.0 g, 18.18 mmol), pmethoxy acetophenone(2.73 g, 36.36 mmol)]



(12e)

ν_{max} 4333, 3444, 2970, 1454, 1419, 1358, 1258, 1198, 1145 cm^{-1}.

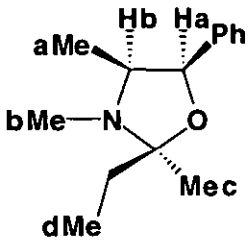
δ_H($CDCl_3$, 250 MHz) 0.83 (3 H, d, *J*=4.5 Hz,Me a), 1.92 (3H, s,Me c), 2.33 (3 H, s,Me b), 2.52-2.53 (1 H, m, Hb), 4.64 (1 H, d, *J*=4.7 Hz, Ha), 7.1-7.2 (2 H, m), 7.3-7.4 (5 H, m), 7.5-7.6 (2 H, m).

δ_C($CDCl_3$, 100 MHz) 14.25, 26.33, 33.70, 55.38, 63.42, 73.37, 88.12, 103.68, 126.18, 126.94, 127.31, 128.06, 128.39, 130.28, 130.56, 142.17.

m/z FAB (Found: 298.1808(M^++1) $C_{19}H_{24}NO_2$ requires: 298.1728). $[\alpha]_D$ = −8.6 (CCl_4, 10 mg/ml).

(4S,5R)-2,3,4-Trimethyl-2-(ethyl)-5-phenyl 1,3-oxazolidine (3.4 g, 81% yield).

[ephedrine (3.0 g, 18.8 mmol), methyl isopropyl ketone (2.35g, 27.27 mmol)]



(12f)

ν_{max} 4390, 3352, 2977, 1450, 1377, 1350, 1218, 1145, 1137 cm^{-1}.

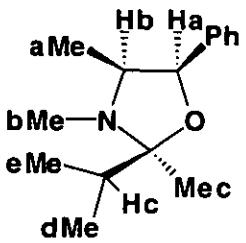
δ_H($CDCl_3$, 250 MHz) 0.8 (3 H, d, *J*=4.4 Hz, Me a), 1.03 (3 H, t, *J*=4.5 Hz,Me d), 1.07 (3 H, t,J=4.3 Hz,Me c), 1.72 (2 H, m, Hc, Hd), 2.2 (3 H, s,Me b), 4.92 (1 H, d, *J*=4.3 Hz, Ha), 7.2-7.3 (5 H, m).

δ_C($CDCl_3$, 100 MHz) 7.68, 14.55, 32.10, 32.44, 60.20, 65.11, 77.55, 96.45, 126.68, 126.74, 127.57, 127.75, 140.48.

m/z FAB (Found: 219.1698(M^++1) $C_{19}H_{21}NO$ requires: 219.1623). $[\alpha]_D$ = −10.7. (CCl_4, 10 mg/ml).

(4S,5R)- 2,3,4- Trimethyl- 2- (1- methylethyl) 5- phenyl- 1,3- oxazolidine (3.43 g, 81% yield).

[ephedrine (3.0 g, 18.18 mmol), methyl isopropyl ketone (1.34 g, 27.27 mmol)]



(12g)

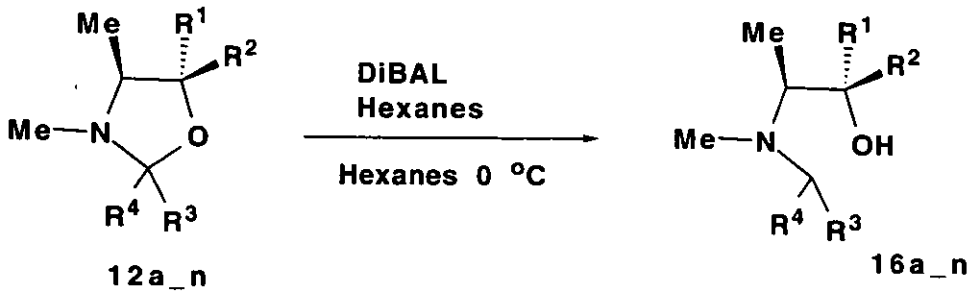
ν_{max} 4299, 3736, 3261, 2929, 2362, 1460, 1375, 1336, 1198, 1146 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.8 (3 H, d, *J*=4.8 Hz,Me a), 1.07 (6 H, d, *J*=4.5 Hz,Me d, Mee), 1.16 (3 H, s,Me c), 2.1-2.2 (1 H, m,Hc), 2.3 (3 H, s,Me b), 2.4-2.5 (1 H, m, Hb), 4.5 (1 H, d, *J*=4.6 Hz, Ha), 7.2-7.4 (5 H, m).

δ_C($CDCl_3$, 100 MHz) 8.70, 14.55, 16.30, 17.03, 18.22, 32.54, 34.00, 60.12, 80.69, 96.95, 126.47, 127.48, 128.02, 129.57, 140.64.

m/z FAB (Found: 234.1877 (M^++1) $C_{25}H_{24}NO$ requires: 234.1799). $[\alpha]_D$ = –6.1 (CCl_4, 10 mg/ml).

Ring Opening of Oxazolidines using DIBAL/ Hexanes



12a_n

16a_n

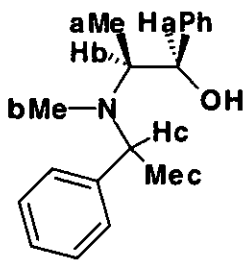
R^1=H,R^2=Ph ephedrine

R^1=Ph,R^2=H pseudoephedrine

DiBAL in hexanes (1.5eq) was added slowly to a stirred solution of the oxazolidines (12a-n) in hexanes at 0 °C under nitrogen. The resulting solution was stirred at 0 °C overnight. Ethyl acetate (30 ml), methanol (5 ml) and sodium potassium tartarate (10 ml) were added and the resulting mixture was left to stir for two hours. The solid precipitate was filtered off and washed with ethyl acetate (30 ml). The filtrate was dried over magnesium sulphate; removal of the solvent afforded the required product.

(1R,2S) - 2- (Methyl (phenyl- methyl) amino) - 1- phenyl butan- 1- ol

(0.86 g, 85% yield) [5a(1.0 g, 3.7 mmol) DIBAL (5.5 ml, 5.5 mmol)]



16a

ν_{max} (neat) 3314, 3061, 3028, 2972, 2877, 2801, 2361, 1950, 1602, 1584, 1492 cm^{-1}.

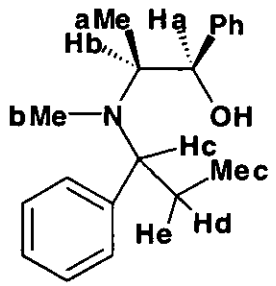
δ_H($CDCl_3$, 250 MHz) 0.86 (3 H, , d, *J*=6.4 Hz, Me a), 1.49 (3 H, d, *J*=6.4 Hz, Me c), 2.31 (1 H, br, OH), 2.43 (3 H, s, Me b), 2.74 (1 H, dq, *J*=6.4, 4.0 Hz, Hb), 4.72 (1 H, d, *J*=4.0 Hz, Ha), 4.82 (1 H, q, *J*=4 Hz, Hc), 7.26-7.51 (10 H, aromatics).

δ_C($CDCl_3$, 100 MHz) 14.25, 33.61, 46.26,70.73, 125.19, 126.21, 127.31, 128.15, 128.25, 128.35, 129.15, 137.32, 141.35, 146.26.

m/z EI (Found: 269.1809 $C_{18}H_{23}NO$ requires: 269.1796). Yielded 89%. $[\alpha]_D$ = −23.3 (CCl_4, 10 mg/ml).

(1R,2S) - 2 - (Methyl (1 - phenyl propyl) amino) - 1 - phenyl propane- 1 - ol

(1.25 g, 83% yield) [5b (1.5 g, 5.3 mmd) DIBAL (7.95 ml, 7.95 mmd)]



16b

ν_{max} (neat) 3313, 3061, 3027, 2969, 2874, 1603, 1492, 1451 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, d, *J*=6.48 Hz, Me a), 0.85 (3 H, t, *J*=7.4 Hz, Me c), 1.72-1.73 (2 H, m, He, Hd,), 2.41 (3 H, s,He, Hd,), 2.72 (1 H, dq, *J*=5.0, 6.48 Hz, Hb), 4.52 (1 H, d, *J*=5.0 Hz, Ha), 4.71 (1 H, t, *J*=2.5 Hz, Hc), 7.26-7.65 (9 H, m), 7.92-7.961 (1 H, m).

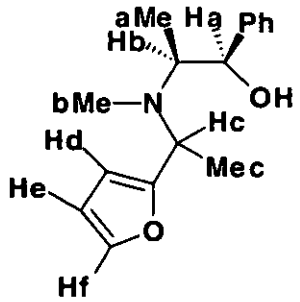
δ_C($CDCl_3$, 100 MHz) 1015, 10.83, 30.25, 31.45, 60.25, 70.65, 125.32, 126.15, 12745, 127.67, 128.35, 128.15, 141.25, 144.35.

m/z EI (Found: 283.1883 $C_{19}H_{24}NO$ requires: 283.1877).

$[\alpha]_D$ = -8.3 (CCl_4, 10 mg/ml).

(1R,2S)-2-(1-Furan-2yl ethyl)(methyl)amino)-1-phenyl propane-1-ol

(1.85 g, 87% yield) *[*5c(2.1 g, 8.17 mmd) DIBAL (12.2 ml, 12.2 mmd)]



16c

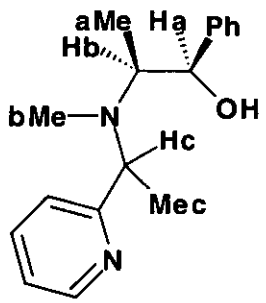
ν_{max} (neat) 3315, 2977, 1952, 1814, 1658, 1602 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.85 (3 H, d, *J*=6.6 Hz, Me a), 1.52 (3 H, d, *J*=6.4 Hz, Me c), 2.42 (3 H, , s, Me c), 2.75 (1 H, dq, *J*=4.0, 6.6 Hz, Hb), 4.72 (1 H, d, *J*=4.0 Hz, Ha), 4.82 (1 H, q, *J*=6.6 Hz, Hc), 6.22 (1 H, *J*=3.5 Hz, Hd), 6.35 (1 H, dd, *J*=1.85, 3 Hz, He), 7.26-7.45 (5 H, m), 7.42-7.53 (1 H, Hf, m).

δ_C($CDCl_3$, 100 MHz) 9.2,14.63,33.26, 42.15, 60.27, 73.26, 104.25, 110.26, 126.15, 126.52, 127.56, 128.26, 140.78, 158.26.

m/z EI (Found: 259.1568 $C_{16}H_{21}NO_2$ requires: 259.1572). Yield 80%. $[\alpha]_D$ = −3.6 (CCl_4, 10 mg/ml).

(1R,2S)-2-(Methyl-(1-pyridin-2yl-methyl)amino-1-phenyl propane-1-ol (1.39 g, 88% yield) [5d(1.85 g, 6.87 mmd), DIBAL (10.3 ml, 10.3 mmd)]



16d

ν_{max} (neat) 3313, 3062, 2973, 2879, 1952, 1608, 1595 cm^{-1}.

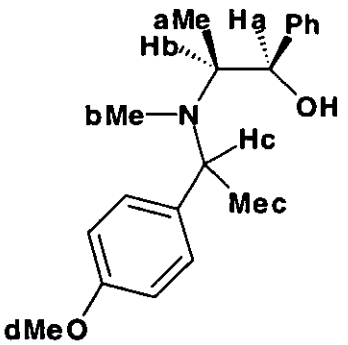
δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, d, *J*=6.5 Hz, Me a), 1.52 (3 H, d, *J*=6.6 Hz, Me c), 2.43 (3 H, s, Me b), 2.75 (1 H, dq, *J*=4.0, 6.5 Hz, Hb,), 4.92 (1 H, q, *J*=6.6 Hz, Hc), 7.26-7.46 (5 H, m), 7.22-7.35 (2 H, m), 7.62-7.72 (1 H, m), 8.42-8.51 (1 H, m).

dC($CDCl_3$, 100 MHz) 12.74,16.31, 25.25, 33.56,60.25, 69.35, 120.25, 127.11, 127.5, 128.31, 136.21, 141.35, 143.42, 148.22, 163.5.

m/z EI (Found: 270.1703 $C_{17}H_{22}N_2O$ requires: 270.1723).

$[\alpha]_D$ = –6.4 (CCl_4, 10 mg/ml).

(1R,2S) - 2- (Methyl- (1- (4- methoxy phenyl- methyl) amino- 1- phenyl- propan- 1- ol (1.25 g, 83% yield) [5b (1.5 g, 5.3 mmol) DIBAL (7.95 ml, 7.95 mmol)]



16e

ν_{max} (thin film) 3065, 3067, 2988, 2978, 1921, 1604, 1573 cm^{-1}.

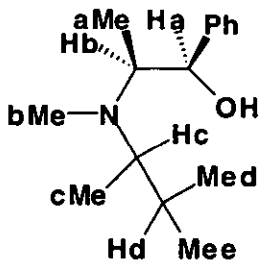
δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, d, *J*=6.4 Hz, Me a), 1.52 (3 H, d, *J*=6.4 Hz, Me c), 2.43 (3 H, s, Me b), 2.62(1 H, br, OH), 2.74 (1 H, dq, *J*=3.2, 6.4 Hz, Hb), 3.87 (3 H,s, Me d), 4.82 (1 H, d, *J*=3.0 Hz, Ha), 4.91 (1 H, q, *J*=6.4 Hz, Hc), 6.91-7.26 (4 H, m), 7.25-7.43 (5H, m).

δ_C($CDCl_3$, 100 MHz) 13.36, 25.26, 33.16, 55.27, 60.20, 72.15, 113.26, 125.62, 125.92, 126.16, 128.83, , 128.35, , 128.75, 141.26, 158.36.

m/z EI (Found: 299.1803 $C_{19}H_{25}NO_2$ requires: 299.1728).

$[\alpha]_D$=8.2 (CCl_4,10 mg/ml).

(1R,2S)-2-(1,2-Dimethyl propyl)-methyl-amino-1-phenyl propane-1-ol (3.72 g, 82% yield) [5f (2.5 g, 10.73 mmd) DIBAL (16 ml, 16.01 mmd)]



16f

ν_{max} (thin film) 3316, 3078, 2965, 2878, 1947, 1612, 1585 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, d, *J*=8.0 Hz, Me a), 0.91 (3 H, d, *J*=8 Hz, Me c), 0.98 (6 H, 2d, *J*=12, 8 Hz, Me d, Me e), 1.6 (1 H, Hd, m, Hd), 2.15 (3 H, s,Me b), 2.45 (1 H, dq, *J*=12, 4 Hz, Hb), 3.5 (1H, br, OH), 3.7 (1 H, d, *J*=4.0 Hz, Ha), 7.2-7.4 (5 H, m).

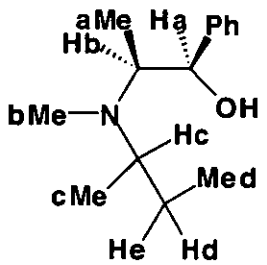
δ_C($CDCl_3$, 100 MHz) 11.04, 11.91, 14.50, 20.50, 21.00, 31.94, 53.43, 60.62, 63.47, 128.74, 125.94, 126.10, 126.94, 128.01, 128.13, 141,38.

m/z FAB (Found: 236.1937 (M^++1) $C_{15}H_{26}NO$ requires: 236.1360).

$[\alpha]_D$ = −12.5 (CCl_4, 10 mg/ml).

(1R,2S)-2-(1,2-Methyl ethyl)-methyl-amino-1-phenyl propane-1-ol

(2.6 g, 86% yield) [5g(3.0 g, 13.7 mmol) DIBAL (20.5 ml, 20.5 mmol)]



16g

ν_{max} (thin film) 3095, 2987, 2862, 1602, 1542, 1419, 1360 cm^{-1}.

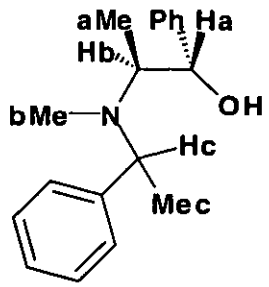
δ_H($CDCl_3$, 250 MHz) 0.86 (3 H, d, *J*=8.0 Hz, Me a), 0.91 (3 H, t, *J*=4.0 Hz, Me d), 0.94-0.96 (2 H, m, Ha Hc), 1.01 (3 H, *J*=12 Hz, Me c), 2.15 (3 H, , s, Me b), 2.65 (1 H, dq, *J*=4.0, 4.7 Hz, Hb), 4.16 (1 H, d, *J*=4.0 Hz, Ha), 5.12 (1 H, br, OH), 7.26-7.45 (5 H, m).

m/z FAB (Found: 222.1874 (M^++1) $C_{14}H_{24}NO$ requires: 222.1799).

$[\alpha]_D$ = −7.2 (CCl_4, 10 mg/ml).

(1S,2S) - 2- (Methyl- (phenyl- methyl) amino) - 1- phenyl butan- 1- ol

(1.3 g, 82% yield) [5b (1.6 g, 5.9 mmol) DIBAL (9 ml, 8.9 mmol)]



16h

ν_{max} (neat) 3402, 3091, 3030, 2982, 2890, 2798, 1960, 1605, 1588, 1497 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.82(3 H, d, *J*=6.5 Hz, Me a), 1.35 (3 H, *J*=4.5 Hz, Me c), , 2.43 (3 H, s, Me b), 2.61 (1 H, dq, *J*=6.4, 8.2 Hz, Hb), 2.91 (1H, br, OH), 4.15 (1 H, d, *J*=8.2 Hz, Ha), 4.52 (1 H, t, *J*=6.0 Hz, Hc), 7.25-7.52 (6 H, m), 7.62-7.66 (4 H, m).

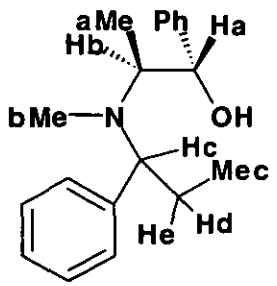
δ_C($CDCl_3$, 100 MHz) 14.26, 33.26, 61.15, 68.26, 77.36, 94.36, 125.35, 126.36, 126.76, 128.15, 128.73, 129.36, 139.67,142.36.

m/z EI (Found: 269.1802 $C_{18}H_{23}NO$ requires: 269.1796).

$[\alpha]_D$ = +67 (CCl_4, 10 mg/ml).

(1S,2S) - 2- (Methyl- (1- phenyl- propyl) amino) - 1- phenyl propane- 1- ol

(1.38 g, 86% yield) [5i (1.6 g, 5.69 mmd) DIBAL (8.5 ml, 8.5 mmd)]



16i

ν_{max} (neat) 3313, 3061, 2970, 2874, 1950, 1603, 1495, 1398 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, d, *J*=6.5 Hz, Me a), 1.35 (3 H, t, *J*=4.5 Hz, Me c), 1.78-1.92 (2 H, Hd, He, m, Hd, He), 2.43 (3 H, s, Me b), 2.61 (1 H, dq, *J*=6.5, 8.2 Hz, Hb), 2.91 (1 H, br, OH), 4.15 (1 H, d, *J*=8.2 Hz, Ha), 4.52 (1 H, t, *J*=6.0 Hz, Hc), 7.25-7.51 (6 H, m), 7.62-7.66 (4 H, m).

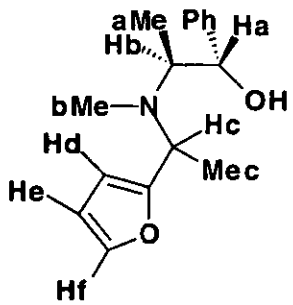
δ_C($CDCl_3$, 100 MHz) 10.26, 15.26, 31.15, 33.35, 55.67,61.27, 75.26, 127.66, 127.52, 127.75, 128.36,128.65,129.34, 142.61, 148.26.

m/z EI (Found: 283.2008 $C_{19}H_{25}NO$ requires: 283.1936).

$[\alpha]_D$ = +71 (CCl_4, 10 mg/ml).

(1S,2S)-2-(1-Furan-2yl-ethyl) methyl amino) 1-phenyl propane-1-ol

(1.34 g, 86% yield) [5j (1.60 g, 6.2 mmol) DIBAL (9.5 ml, 9.4 mmol)]



16j

ν_{max} (thin film 3317, 2979, 2285, 1952, 1603, 1584, 1492, 1395, 1319 cm^{-1}.

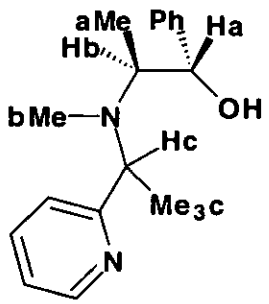
δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, d, *J*=6.5 Hz, Me a), 1.51 (3 H, d, *J*=6.45 Hz, Me c), 2.42 (3 H, s, Me b), 2.62 (1 H, dq, *J*=6.5, 8.2 Hz, Hb), 3.01 (1 H, br, OH), 4.12 (1 H, d, *J*=8.2 Hz, Ha), 4.91 (1 H, q, *J*=6.45 Hz, Hc), 6.12 (1 H, d, *J*=3.2 Hz, Hd), 6.22-6.23 (1 H, m, He), 7.25-7.51 (6 H, m).

δ_C($CDCl_3$, 100 MHz) 14.25, 20.35, 33.62, 61.50, 63.42, 77.51, 105.25, 110.35, 127.15, 127.8, 18.35, 1412.15, 142, 86 , 158.65.

m/z EI (Found: 259.1653 $C_{16}H_{21}NO_2$ requires: 259.1572).

$[\alpha]_D$ = +74 (CCl_4, 10 mg/ml).

(1S,2S)- 2- (Methyl- (1- pyridine- 2yl- methyl) amino)- 1- phenyl propane- 1- ol (1.4 g, 87% yield) [5k (1.6 g, 5.97 mmol) DIBAL (9 ml, 8.95 mmol)]



16k

ν_{max} (neat) 3315, 3078, 32888, 1955, 1876, 1610, 1597, 1487, 1391 cm^{-1}.

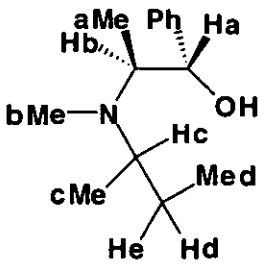
δ_H($CDCl_3$, 250 MHz) 0.82 (3 H, Me1, d, *J*=4.8 Hz), 1.22 (3 H, Me3, d, *J*=6.4 Hz), 2.43 (3 H, Me2, s), 2.73 (1 H, Hb, dq, *J*=4.00, 4.80 Hz), 3.01 (1 H, br, OH), 4.31 (1 H, Ha, d, *J*=4.9 Hz), 4.85 (1 H, Hc, q, *J*=6.4 Hz), 7.26-7.62 (5 H, m), 7.76-8.0 (2 H, m), 8.15-8.32 (2 H, m).

δC($CDCl_3$, 100 MHz) 16.75, 17.34,25.55, 60.37, 69.42, 74.26, 120.42, 127.10, 127.50, 128.00, 128.30, 136.75, 141.45, 148.60, 163.75.

m/z EI (Found: 270.1723 $C_{17}H_{22}NO$ requires: 270.1732).

$[\alpha]_D$ = +64 (CCl_4, 10 mg/ml).

v (1S,2S) - 2- (1,2- Dimethyl propyl) (methyl amino) - 1- phenyl propane- 1- ol (3.15 g, 98% yield) [5m (3.2 g, 13.79 mmol) DIBAL (21 ml, 20.6 mmol)]



16m

ν_{max} 3389, 3256, 2878, 2647, 1645, 1542, 1396, 1327 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.85 (3 H, d, *J*=7.2 Hz, Me a), 0.92 (3 H, Me d, t, *J*=8 Hz, Me d), 0.93 (2 H, m, Hd, Hc), 0.96 (3 H, d, *J*=6.5 Hz, Me c), 1.2-1.21 (1 H, m, Hc), 2.15 (3 H, s, Me b), 2.65 (1 H, dq, *J*=4.7, 4.0 Hz, Hb), 4.16 (1 H, d, *J*=4.0 Hz, Ha), 5.12 (1 H, br, OH), 7.28-7.45 (5 H, m).

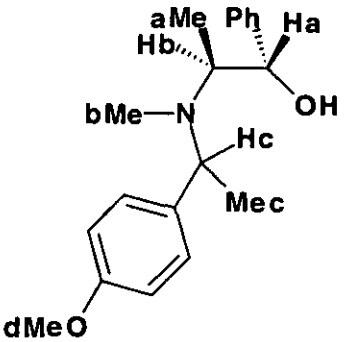
δC($CDCl_3$, 100 MHz) 11.22, 18.47, 27.63, 27.86, 59.80, 61.54, 76.65, 125.91, 126.11, 127.43, 142.67.

m/z FAB (Found: 223.1881(M^++1) $C_{14}H_{24}NO$ requires: 223.1877).

$[\alpha]_D$ = +58 (CCl_4,

(1S,2S) - 2- (Methyl (1- (4- methoxyphenyl) amino) 1- phenyl propane- 1- ol

(1.47 g, 81% yield) [5l (1.8 g, 6.27 mmol) DIBAL (9.8 ml, 9.4 mmol)]



16l

ν_{max} (neat) 3146, 3332, 2879, 1950, 1678, 1600, 1454, 1419, 1359 cm^{-1}.

δ_H($CDCl_3$, 250 MHz) 0.83 (3 H, Me a, d, *J*=6.48 Hz, Me a), 1.42 (3 H, d, *J*=6.25 Hz, Me c), 2.43 (3 H, s, Me b), 2.51 (1 H, dq, *J*=6.48, 8.3 Hz, Hb), 3.00 (1 H, br, OH), 3.72 (3 H, Me c, s, Me c), 4.12 (1 H, d, *J*=8.3 Hz, Ha), 4.8 (1 H, Hc, q, *J*=6.25 Hz), 6.85-7.0 (4 H, m), 7.35-7.56 (5 H, m).

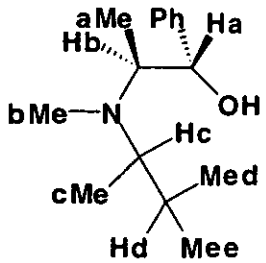
δC($CDCl_3$, 100 MHz) 16.15, 17.67,25.25, 35.42, 61.00, 70.25, 115.16, 127.35, 127.70, 127.85, 128.35, 128.56, 139.54, 146.78,160.35.

m/z EI (Found: 299.1342 $C_{19}H_{25}NO_2$ requires: 299.1455).

$[\alpha]_D$ = +39 (CCl_4, 10 mg/ml).

(1S,2S) - 2- (1,2- Methyl ethyl) (methyl) amino) 1- phenyl propane- 1- ol

(2.7 g, 89% yield) [5n (3.0 g, 13.69 mmd) DIBAL (21 ml, 20.5 mmd)]



16n

ν_{max} 3335, 3256, 2873, 2470, 1604, 1493, 1453, cm^{-1}.

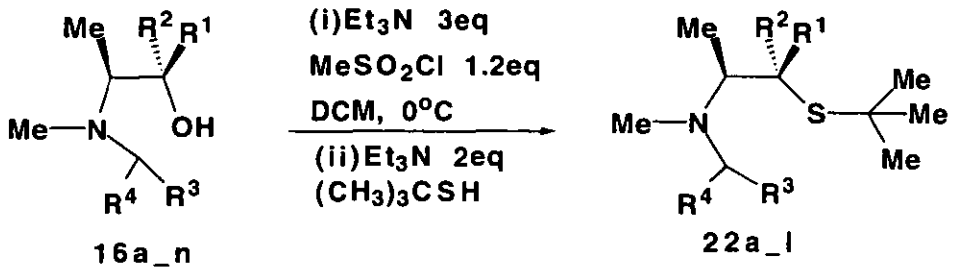
δ_H($CDCl_3$, 250 MHz) 0.86 (3 H, d, *J*=6,6 Hz, Me a), 0.92 (3 H, Me c, t, *J*=6.6Hz, Me c), 1.02_1.06 (6 H, 2d, J=6.07,6,6Hz, Me d,Me e,), 1.72_1.78 (1H, m, Hd), 2.15 (3 H, s, Me b), 2.34 (1 H, m, Hc), 2.66 (1 H, dq, *J*=6.6,9.0 Hz, Hb), 4.15 (1H, d, J=9.0Hz, Ha), 5.12 (1H,br,OH), 7.28-7.45 (5 H, m).

δC($CDCl_3$,100MHz)11.17,13.26,19.16,21.27,27.35,32.62,65.21,66.26,75.35 ,127.26.127.65,128.15,142.36.

m/z FAB (Found: 236.1936.1881 (M^++1) $C_{15}H_{26}NO$ requires: 236.1936).

$[\alpha]_D$ = +86 (CCl_4, 10 mg/ml).

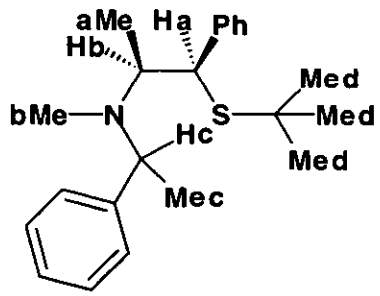
General Procedure for the Synthesis of Sulfides



To a solution of the amino alcohol 6a-n (1 eq) in DCM (30 ml) at 0 °C, triethylamine (2 eq) was added and the reaction was stirred for 10 minutes, methanesulfunyl chloride (1.2 eq) was added and the resulting mixture was left to stir for 1 hour. Triethylamine (2 eq) was added followed by t-butylthiol (2 eq) and the resulting mixture was stirred overnight. The solvent was evaporated and the residue washed with diethyl ether (3 × 30 ml). The combined ether layers were dried over magnesium sulfate. The solvent was evaporated and the residue chromatographed in 10% ethyl acetate, 90% petrol to yield the title compounds as yellow oils.

N- {(1R,2S) - 2- (1,1) - Dimethyl ethyl thiol}1- methyl- 2- phenyl ethyl–N- (1- methyl N- (1- phenyl ethyl amine)

(0.65 g, 65% yield) [6a(10.8 g, 2.97 mmol), t- butylthiol (0.6 ml, 5.94 mmol), triethylamine (1.5 ml, 4 eq)]



22a

ν_{max} 3597, 2995, 2467, 2312, 1419, 1270, 1216, 1197 cm^{-1}.

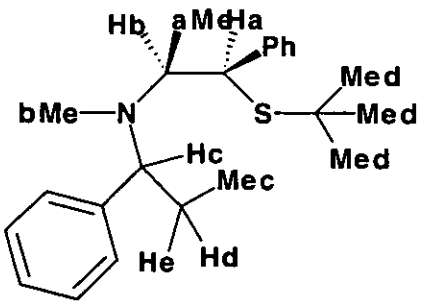
δ_H($CDCl_3$, 250 MHz) 1.1 (3 H, d, *J*=7.5 Hz, Me a), 1.25 (9 H, s, Me d), 2.53 (3 H, d, *J*=8.7 Hz, Me c), 2.63 (3 H, s, Me b), 3.22 (1 H, dq, *J*=6.5 Hz, 7.4 Hz, Hb), 4.23 (1 H, d, *J*=7.4 Hz, Ha), 5.17 (1 H, q, *J*=8.5 Hz, Hc), 7.16-7.46 (10 H, m, aromatics).

δC ($CDCl_3$, 100 MHz) 9.2, 9.89, 15.70, 38.52, 39.87, 46.52, 58.98, 125.67, 127.30, 128.52, 128.79, 129.79, 131.20, 140.36,142.26.

m/z FAB (Found: 342.2262 (M^++1) $C_{22}H_{32}NS$ requires: 342.2177). $[\alpha]_D$ = – 33.5 (CCl_4, 10 mg/ml).

N- {(1R,2S) - 2- [(1,1) - Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl –N- methyl N- (1- phenyl propyl amine)

(0.65 g, 65% yield) 6b (0.8 g, 2.83 mmol), t- butylthiol (0.65 ml, 5.66 mmol), triethylamine (1.50 ml, 4 eq)]



22b

ν_{max} 3422, 3033, 2935, 2526, 1335, 1227, 1198 cm^{-1}.

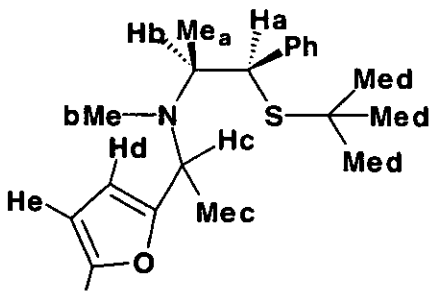
δ_H ($CDCl_3$, 250 MHz) 0.95 (3 H, d, *J*=6.67 Hz, Me a), 1.21 (9 H, s, Me d), 1.25 (3 H, t, *J*=7.0 Hz, Me c), 1.52 (2 H, m, Hd, He), 2.43 (3 H, s, Me b), 2.51 (1 H, t, *J*=7 Hz, Hc), 2.91-2.92 (1 H, m, Hb), 4.3 (1 H,d, *J*=7.4 Hz, Ha).

δC ($CDCl_3$, 100 MHz) 9.21, 9.81, 15.72, 20.52, 38.64, 39.95, 46.92, 59.22, 125.87, 126.21, 127.22, 127.87, 128.15, 129.06, 129.72, 133.15.

m/z FAB (Found: 356.2423 (M^++1) $C_{23}H_{34}NS$ requires: 356.2333). $[\alpha]_D$ = – 19.2 (CCl_4, 10 mg/ml).

N- {(1R,2S) - 2- [(1,1) - Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl} –N- (1- furyl- 2- ethyl) amine

(1.0 g, 55% yield) *[*6c(1.5 g, 5.8 mmd), t- butylthiol (1.3 ml, 11.6 mmd), triethylamine(13.0 ml, 4 eq)]



22 c

ν_{max} 3379, 3298, 2981, 2507, 1654, 1454, 1346, 1191, 1138 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.21 (3 H, d, *J*=6.4 Hz, Me c), 1.30 (3 H, d, *J*=6.7 Hz, Me a), 1.31 (9 H, s, Me d), 2.41 (3 H , s, Me b), 3.92 (1 H, dq, *J*=4.6, 6.4 Hz, Hb), 4.26 (1 H, q, *J*=6.7 Hz, Hc), 4.91 (1 H, Ha, d, *J*=4.6 Hz, Ha), 6.21-6.22 (1H , m, He), 6.23-6.24 (1 H, m, Hd), 7.24-7.26 (6 H, m,5 ar,1Hf)

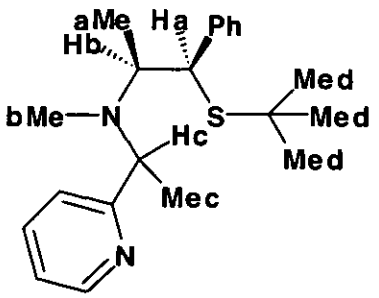
δC ($CDCl_3$, 100 MHz) 7.61, 1435, 18.25, 31.26, 31.71, 39.42, 61.21, 75.26, 105.21, 106.76, 127.35, 127.82, 127.98, 128.62, 142.02, 158.10.

m/z FAB (Found: 332.2054 (M^++1) $C_{20}H_{30}NO$ *S* requires: 332.2048).

$[\alpha]_D = -13.2$ (CCl_4, 10 mg/ml).

N- {(1R,2S)- 2- [(1,1)- Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl}–N- (1- pyridin- 2- yethyl amine)

(0.63 g, 45% yield) [6d(1.1 g, 4.07 mmd), t- butylthid (0.95 ml, 8.14 mmd), triethylamine(2 ml, 4 eq)]



22 d

ν_{max} 3436, 2987, 2941, 1459, 1331, 1197, 1179, 1139 cm^{-1}.

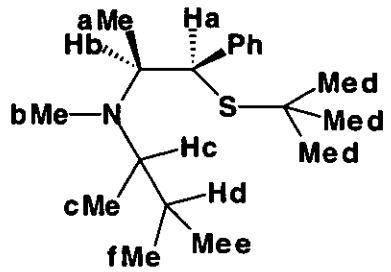
δ_H ($CDCl_3$, 250 MHz) 1.00 (3 H, d, *J*=6.4 Hz, Me a), 1.32 (9 H, s, Me d), 1.45 (3 H, d, *J*=6.6 Hz, Me c), 2.42 (3 H, s, Me b), 3.22 (1 H, q, *J*=6.8 Hz, Hc), 3.51 (1 H, dq, *J*=4.6, 6.4 Hz, Hb), 4.15 (1 H, d, *J*=4.6 Hz, Ha), 7.16-7.23 (7 H, m), 7.46-7.48 (1 H, m), 8.42-8.43 (1 H, m).

δC($CDCl_3$, 100 MHz) 11.79, 20.01, 31.33, 31.95, 54.06, 60.21, 64.06, 120.21, 121.97, 125.81, 126.82, 128.46, 129.68, 136.25, 136.79, 149.21,158.15.

m/z FAB (Found: 343.2203 (M^++1) $C_{21}H_{30}N_2S$ requires: 343.2129). $[\alpha]_D$ = – 17.2 (CCl_4, 10 mg/ml).

N- {(1R,2S) - [(1,1) - Dimethyl ethyl thio] 1 - methyl- 2 - phenyl ethyl}–N- (1,2- dimethyl propyl- N- methyl amine)

(2.4 g, 76% yield) [6f (2.5 g, 10.6 mmd), t- butylthiol (2.4 ml, 21.2 mmd), triethylamine (6.0 ml, 4 eq)]



22 e

ν_{max} 3752, 2989, 2309, 1435, 1269, 1196 cm^{-1}.

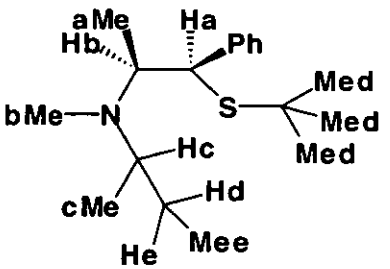
δ_H ($CDCl_3$, 250 MHz) 0.95 (6H, 2d,J=6.4,6.7 Hz, Me e, Me f), 0,96 (6H, 2 d, *J*= 6.7, 8.2 Hz, Me a, Me c), 1.15 (9 H, s, Me c), 1.83-1.84 (1 H, m, Hc), 2.43-2.45 (1 H, m, Hd), 3.00 (3 H, s, Me b), 3.22 (1 H, dq, *J*=6.4, 6.7 Hz, Hb), 7.15-7.26 (5 H, m).

δC ($CDCl_3$, 100 MHz) 8.75, 29.31, 30.26, 31.35, 41.75, 54.72, 64.75, 125.48, 125.92, 126.95, 127.98,136.12, 142.31, 165.82.

m/z FAB (Found: 308.2411 (M^++1) $C_{19}H_{34}NS$ requires: 308.2333). $[\alpha]_D$ = – 24.2 (CCl_4, 10 mg/ml.

N- {(1R,2S) - [(1,1) - Dimethyl ethyl thio] 1 - methyl - 2 - phenyl ethyl}–N- (1 - methylethyl) - N- methyl amine

(2.58 g, 78% yield) [6g(2.5 g, 11.31 mmd), t- butylthid (2.5 ml, 22.32 mmd), triethylamine(6 ml, 4 eq)]



22 f

ν_{max} 3672, 2898, 2401, 1426, 1269, 1201, 1198 cm^{-1}.

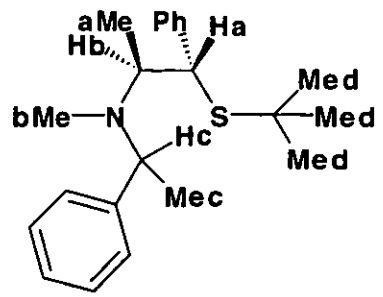
δ_H ($CDCl_3$, 250 MHz) 0.95 (3 H, d,*J*=7.5 Hz, Me e), 0.98 (3 H, d, *J*=6.7 Hz, Me a), 1.0 (3 H, d, *J*=6.4 Hz, Me a), 1.42 (9 H, s, Me d), 1.52-1.54 (2 H, m, Hd , He), 2.46 (3 H, s, Me b), 3.0 (1 H, dq, *J*=6.7, 7.2 Hz, Hb), 3.91 (1 H, d, *J*=6.7 Hz, Ha), 7.15-7.35 (5 H, m).

δC ($CDCl_3$, 100 MHz) 8.82, 13.91,27.35, 30.54, 31.54, 31.62, 45.89, 60.82, 62.46, 126.35, 120.49, 127.38, 127.85, 134.65.

m/z FAB (Found: 294.2253 (M^++1) $C_{18}H_{32}NS$ requires: 294.2255). $[\alpha]_D$ = – 13.6 (CCl_4, 10 mg/ml).

N- (1S,2S) - 2- [(1,1) - Dimethyl ethyl thio] 1 - methyl- 2 - phenylethyl}–N- methyl- N- (1phenylethyl amine)

(0.9 g, 71% yield) [6h (1.0 g, 3.72 mmd), t- butylthid (1.7 ml, 7.44 mmd)]



22g

ν_{max} 3651, 2898, 2471, 2309, 1418, 1269, 1211, 1198 cm^{-1}.

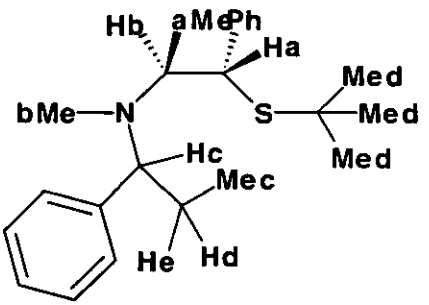
δ_H ($CDCl_3$, 250 MHz) 1.20 (3 H, d, *J*=7.4 Hz, Me a), 1.21 (9 H, Me d, s, Me d), 2.53 (3 H, d, *J*=9.3 Hz, Me c), 2.61 (3 H, s, Me b). 3.22 (1 H, dq, *J*=6.7, 7.4 Hz, Hb), 4.51 (1 H, d, *J*=7.4 Hz, Ha), 4.8 (1 H, q, *J*=9.3 Hz, Hc), 7.15-7.52 (10 H, m).

δC ($CDCl_3$, 100 MHz) 8.93, 9.69, 15.50, 16.69, 31.42, 38.42, 39.74, 46.47, 59.07, 125.72, 127.40, 128.68, 128.77, 129.73, 131.06.

m/z FAB (Found: 342.2258 (M^++1) $C_{22}H_{32}NS$ requires: 342.2177). $[\alpha]_D$ = +72 (CCl_4, 10 mg/ml).

N- {(1S,2S)- 2- [(1,1)- Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl}–N- methyl- N- (1phenyl propyl amine)

(0.65 g, 65% yield) [6i (1.0 g, 3.5 mmol), t- butylthiol (0.8 ml, 7 mmol), triethylamine (2.0 ml, 4 eq)]



22 h

ν_{max} 3414, 3028, 2898, 2511, 1323, 1219, 1195 cm^{-1}.

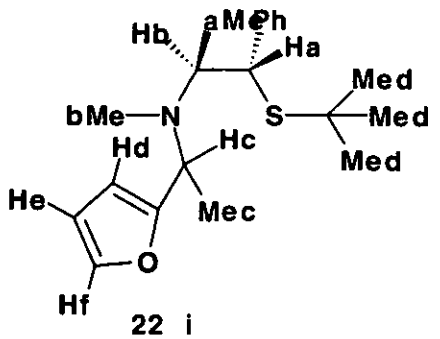
δ_H ($CDCl_3$, 250 MHz) 0.91 (3 H, d, *J*=6.4 Hz, Me a), 1.0 (9 H, s, Me d), 1.22 (3 H, d, *J*=7.0 Hz, Me c), 1.53-1.54 (2 H, m, Hd, He), 2.3 (3 H, s, Me b), 2.52 (1 H, t, *J*=7.0 Hz, Hc), 3.0-3.05 (1 H, m, Hb), 4.51 (1 H, d, *J*=6.4 Hz, Ha), 7.0-7.25 (10 H, m).

δC ($CDCl_3$, 100 MHz) 8.98, 9.79, 15.60, 20.15, 38.42, 39.84, 46.97, 59.18, 125.92, 126.25, 127.31, 127.92, 128.98, 129.01, 129.62, 133.12.

m/z FAB (Found: 356.2407 (M^++1) $C_{23}H_{34}NS$ requires: 356.2333). $[\alpha]_D$ = +66 (CCl_4, 10 mg/ml).

N- [(1S,2S) - 2- [(1,1) - Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl} –N- (1- furyl- 2- yethyl] amine

(0.86 g, 61% yield) [6j (1.1 g, 4.25 mmd), t- butylthid (1.00 ml, 8.5 mmd), triethylamine(2.5 ml, 4 eq)]



22 i

ν_{max} 3379, 3050, 2938, 2928, 1350, 1220, 1198 cm^{-1}.

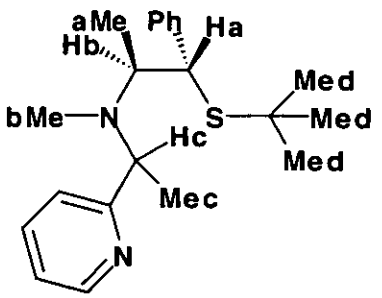
δ_H ($CDCl_3$, 250 MHz) 1.20 (3 H, d, *J*=6.4 Hz, Me a), 1.21 (9 H, s, Me d), 1.92 (3 H, d, *J*=8.0 Hz, Me c), 2.4 (3 H, s, Me b), 3.21 (1 H, dq, *J*=6.4, 8.0 Hz, Hb), 4.23 (1 H, q, *J*=8.0 Hz, Hc), 4.51 (1 H, d, *J*=8.0 Hz, Ha), 6.22 (1 H, d, *J*=4.0 Hz, Hd), 6.21-6.22 (1 H, m, He), 7.15 (1 H, d, *J*=4.0 Hz, Hf), 7.25-7.56 (5 H, m).

δC ($CDCl_3$, 100 MHz) 7.66, 14.27, 28.21, 31.12, 31.17, 39.39, 60.39, 75.14, 105.01, 106.98, 127.32, 127.76, 127.88, 128.57, 141.78, 157.92.

m/z FAB (Found: 332.2054 (M^++1) $C_{20}H_{30}NO$ *S* requires: 332.2048). $[\alpha]_D$ = +82 (CCl_4, 10 mg/ml).

N- {(1S,2S) - 2- [(1,1) - Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl}–N- (1- pyridin- 2- yethyl amine)

(0.77 g, 55% yield) [6k (10.1g, 4.07 mmd) , t- butylthid (1.0 ml, 8.15 mmd) , triethylamine (2.1ml, 4 eq)]



22 j

ν_{max} 3425, 2981, 2939, 1454, 1327, 1191, 1176, 1138 cm^{-1}.

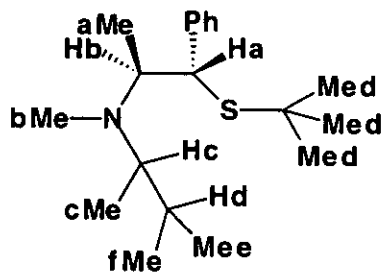
δ_H ($CDCl_3$, 250 MHz) 0.91 (3 H, d, *J*=6.6 Hz, Me a), 1.22 (9 H, s, Me d), 1.45 (3 H, d, *J*=6.6 Hz, Me c), 2.16 (3 H, s, Me b), 3.35 (1 H, q, *J*=6.5 Hz, Hc), 3.45 (1 H, dq, *J*=4.6, 6.6 Hz, Hb), 3.91 (1 H, d, *J*=4.6 Hz, Ha), 7.16-7.28 (5H, m), 7.32-7.33 (2 H, m), 8.35-8.36 (2 H, m).

δC ($CDCl_3$, 100 MHz) 11.41, 19.09, 31.24, 31.80, 53.08, 59.35, 63.97, 119.72, 121.81, 125.79, 126.79, 128.36, 136.50, 144.86,148.37, 148.46, 165.10.

m/z FAB (Found: 343.2213 (M^++1) $C_{21}H_{31}N_2S$ requires: 343.2129). $[\alpha]_D$ = +69 (CCl_4, 10 mg/ml).

N- {(1S,2S) - [(1,1) - Dimethyl ethyl thio]- 1- methyl 2- phenyl ethyl}–N- (1,2 dimethyl, propyl) N- methyl amine

(02.87 g, 88% yield) [6m (2.5 g, 10.64 mmd), t- butylthid (2.4 ml, 21.28 mmd), triethylamine (6 ml, 4 eq)]



22 k

ν_{max} 3748, 2984, 2305, 1420, 1265, 1194 cm^{-1}.

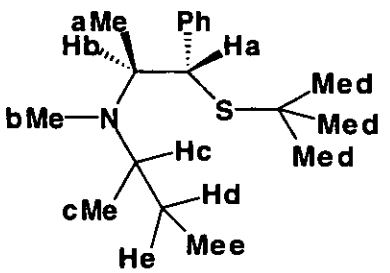
δ_H ($CDCl_3$, 250 MHz) 1.10 (6 H, 2 d, *J*=6.7, 6.4 Hz, Me e, Me f), 1,12 (6H,,2d,J=7.0,7.6 Hz, Me a, Me c), 1.12 (9 H, s, Me d), 1.83-1.85 (1 H, m, Hd), 2.42-2.43 (1 H, m, Hc), 3.0 (3 H, s, Me b), 3.12 (1 H, dq, *J*=6.7, 6.4 Hz, Hb), 4.2 (1 H, d, *J*=6.4 Hz, Ha), 7.15-7.36 (5 H, m).

δC ($CDCl_3$, 100 MHz) 8.67, 29.31, 30.21, 31.33, 41.67, 54.64, 64.56, 66.02, 125.48, 125.90, 126.94, 127.84,129.56, 143.45.

m/z FAB (Found: 304.2412 (M^++1) $C_{19}H_{34}NS$ requires: 304.2333). $[\alpha]_D$ = +92 (CCl_4, 10 mg/ml).

N- {(1S,2S) - [(1,1) - Dimethyl ethyl thio] 1- methyl 2- phenyl ethyl}–N- (1,methylethyl) N- methyl amine

(2.4 g, 91% yield) [6n (2.0 g, 9.0 mmd), t- butylthid (2.0 ml, 18.0 mmd), triethylamine (5 ml,4 eq)]



22 I

ν_{max} 3650, 2897, 2406, 1421, 1267, 1201, 1197 cm^{-1}.

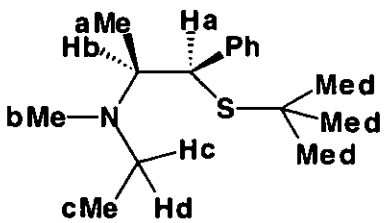
δ_H ($CDCl_3$, 250 MHz) 0.9 (3 H, t, *J*=7.15 Hz, Me e), 0.96 (3 H, d, *J*=6.45 Hz, Me a), 0.98 (3 H, d, *J*=6.0 Hz, Me c), 1.42 (9 H, s, Me d), 1.53-1.54 (2 H, m, Hd, He), 2.15 (3 H, s, Me b), 3.0 (1 H, dq, 6.0, 6.7 Hz, Hd), 3.2-3.3 (1 H, d, m, Hc), 3.92 (1 H, d, *J*=6.7 Hz, Ha), 7.0-7.25 (5 H, m).

δC ($CDCl_3$, 100 MHz) 8.72, 13.80, 15.93, 27.35,31.39, 31.54, 45.86, 60.72, 62.44, 126.27, 126.42, 127.28, 127.72, 134.45.

m/z FAB (Found: 294.2252 (M^++1) $C_{18}H_{32}NS$ requires: 294.2255). $[\alpha]_D$ = +63 (CCl_4, 10 mg/ml).

N- (1R,2S) - [(1,1) - Dimethyl ethyl thiol] 1- methyl- 2- phenyl ethyl –N- methyl ethyl amine

(1.3 g, 65% yield) [3a(1.5 g, 7.7 mmol), t- butylthiol (1.74 ml, 15.4 mmol), triethylamine(4.0 ml, 4 eq)]



11 a

ν_{max} 3698, 2867, 2327, 1445, 1273, 1196 cm^{-1}.

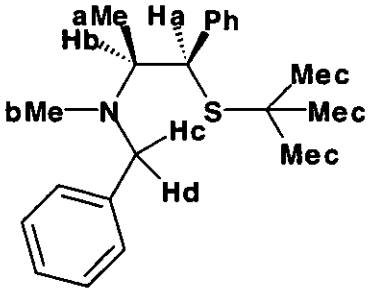
δ_H ($CDCl_3$, 250 MHz) 0.99 (3 H, d, *J*=8.0 Hz Me a), 1.15 (9 H, s, Me d), 1.45 (3 H, t, *J*=7.6 Hz, Me c), 2.5 (3 H, s, Me b), 3.31 (2 H, q, *J*=8.0 Hz, Hc , Hd), 3.24-3.26 (1 H, m, Hb), 4.12 (1 H, d, *J*=8.6 Hz, Ha), 7.15-7.52 (5 H, m).

δC ($CDCl_3$, 100 MHz) 8.21, 8.67, 9.21, 29.56, 49.21, 55.26, 67.34,125.47, 126.42, 127.62, 127.83, 141.29.

m/z FAB (Found: 266.1997 (M^++1) $C_{16}H_{28}NS$ requires: 266.1864). $[\alpha]_D$ = – 34.7 (CCl_4, 10 mg/ml).

N- (1 R,2S) - (1 ,1) - Dimethyl ethyl thiol 1 - methyl- 2- phenyl ethyl –N- 1 - phenyl ethyl amine

(0.74 g, 63% yield) [3b (1.2 g, 3.6 mmol) , t- butylthiol (0.8 ml, 7.2 mmol) , triethylamine (2 ml, 4 eq)]



11b

ν_{max} 3666, 2892, 2334, 1440, 1280, 1199 cm^{-1}.

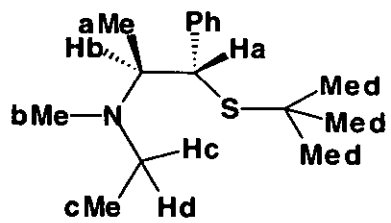
δ_H ($CDCl_3$, 250 MHz) 1.19 (9 H, s, Me d), 1.23 (3 H, d, *J*=8.0 Hz, Me a), 2.2 (3 H, s, Me b), 3.11 (2 H, s,Hc, Hd,), 3.49-3.51 (1 H, m, Hb), 3.91 (1 H, d, *J*=8.0 Hz, Ha), 6.85-7.75 (10 H, m).

δC ($CDCl_3$, 100 MHz) 11.40, 30.57, 36.56, 52.65, 58.26, 63.33, 125.98, 126.47, 127.81, 127.86, 128.34, 128.46, 140.01, 145.51.

m/z EI (Found: 328.2017 $C_{21}H_{30}NS$ requires: 328.2014). $[\alpha]_D = -37$ (CCl_4, 10 mg/ml).

N- {(1S,2S) - [(1,1) - Dimethyl ethyl thio) 1 - methyl - 2 - phenyl ethyl–N- methyl} ethyl amine

(0.69 g, 62% yield) [3c(1.4 g, 4.2 mmd), t- butylthid (0.9 ml, 8.4 mmd), triethylamine (2.5 ml, 4 eq)]



11 c

ν_{max} 3696, 2884, 2331, 1440, 1268, 1194 cm^{-1}.

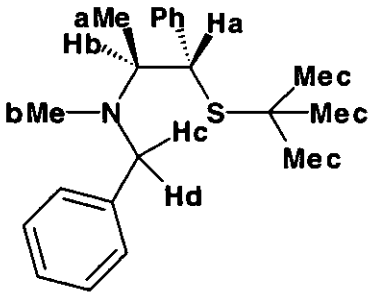
δ_H ($CDCl_3$, 250 MHz) 1.04 (3 H, d, *J*=8.0 Hz, Me a), 1.24 (9 H, Me d, s, Me d), 1.35 (3 H, t, *J*=8.2 Hz, Me c), 2.5 (3 H, s, Me b), 3.12 (2 H, q, *J*=8.0 Hz, Hc, Hd,), 3.16-3.18 (1 H, m, Hb), 3.91 (1 H, d, *J*=8.0 Hz, Ha), 7.15-7.52 (5 H, m).

δC ($CDCl_3$, 100 MHz) 7.62, 7.67, 8.77, 29.75, 46.51, 51.77, 126.43, 127.49, 128.29, 129.03, 139.29, 143.77.

m/z FAB (Found: 266.1990 (M^++1) $C_{16}H_{28}NS$ requires: 266.1864). $[\alpha]_D$ = +61 (CCl_4, 10 mg/ml).

N- (1S,2S) - [(1,1) - Dimethyl ethyl thio] 1- methyl- 2- phenyl ethyl–N- 1- phenyl ethyl amine

(1.0 g, 69% yield) [3d(1.5 g, 4.5 mmd), t- butylthid (1.0 ml, 9 mmd), triethylamine(2.5 ml, 4 eq)]



11 d

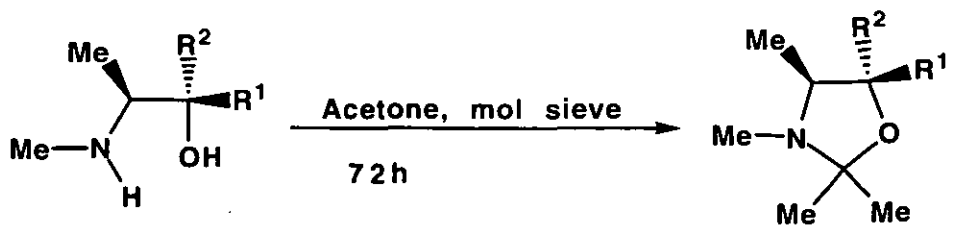
ν_{max} 3652, 2897, 2311, 1436, 1270, 1199 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.83 (3 H, d, *J*=6.8 Hz, Me a), 1.12 (9 H, s, Me d), 2.15 (3 H, s, Me b), 2.43 (2 H, s, Hc, Hd,), 3.16 (1 H, dq, *J*=6.8, 9.6 Hz, Hb), 3.91 (1 H, d, *J*=9.6 Hz, Ha), 7.15-7.52 (10 H, m).

δC($CDCl_3$, 100 MHz) 8.37, 10.30, 31.20, 32.10, 35.75, 51.68, 63.02, 126.72, 126.82, 127.40, 128.02, 128.08, 128.22, 141.89, 143.77

m/z FAB (Found: 328.2099 (M^++1) $C_{21}H_{30}NS$ requires: 328.2020). $[\alpha]_D$ = +63 (CCl_4, 10 mg/ml).

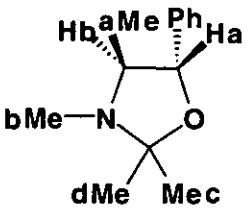
Synthesis of Oxazolidines from Acetone Ephedrine and Pseudoephedrine



Ephedrine or pseudoephedrine (3.0 g, 18 mmol) was dissolved in acetone (50 ml), 4Å molecular sieve added, and the mixture allowed to stand at room temperature for 3 days. The solvent was evaporated to leave the product.

(4S,5S)-2,3,4-Tetramethyl-5-phenyl-1,3-oxazolidine

(3.0 g, 82% yield) [pseudoephedrine (3.0 g, 18.18 mmol)]



ν_{max} (neat) 3443, 3030, 2474, 2795, 1645, 1450, 1250 cm^{-1}.

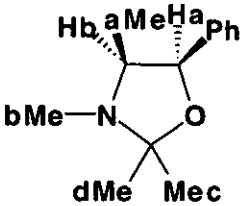
δ_H (250 MHz $CDCl_3$) 1.16 (3 H, d, *J*=7.0 Hz, Me a), 1.33 (6 H, s, Me c, Me d), 2.30 (3 H, s, Me b), 2.60-2.61 (1 H, m, Hb), 4.50 (1 H, d, *J*=7.5 Hz, Ha).

δC ($CDCl_3$, 100 MHz) 14.25, 21.35, 28.25, 32.15, 62.25, 83.65, 95.16, 126.5, 127.11, 128.15, 140.25.

m/z (EI) (Found: 205.1466 $C_{13}H_{19}NO$ requires: 205.1466). $[\alpha]_D$ = +35.6 (CCl_4, 10 mg/ml).

(4R,2S) - 2,3,4- Tetramethyl- 5- phenyl- 1,3- oxazolidine

(3.2 g, 85% yield) [ephedrine(3.0 g, 18.18 mmol)]



(Found: C 75.57, H 9.24, N 6.79, $C_{13}H_{19}NO$. requires: C 76.01, H 9.27, N 6.83%

ν_{max} (slurry) 3422, 2976, 2932, 2800, 2796, 1607, 1592, 1492 cm^{-1}.

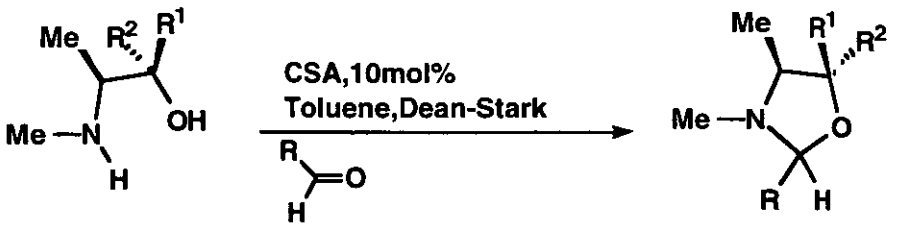
δ_H (250 MHz $CDCl_3$) 0.63 (3 H, d, *J*=5.0 Hz, Me a), 1.22 (3 H, s, Me c), 2.25 (3 H, Me d, s), 3.60-3.61 (1 H, Hb, m), 5.0 (1 H, Ha, d, *J*=7.0 Hz), 7.26-7.54 (5 H, m).

δC ($CDCl_3$, 100 MHz) 14.25, 19.35, 35.25, 60.35, 81.25, 95.15, 127.35, 127.5, 127.7, 128.3, 140.15.

m/z (EI) (Found: 205.1463 $C_{13}H_{19}NO$ requires: 205.1466).

$[\alpha]_D$ = +49 (CCl_4, 10 mg/ml).

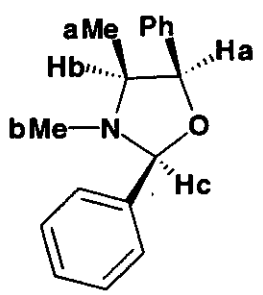
Synthesis of Oxazolidines using Aldehydes, Ephedrine or Pseudoephedrine under Dean-Stark Conditions



Ephedrine or pseudoephedrine (3.0 g, 18.0 mmol) was dissolved in toluene (50 ml), then the aldehyde was added (2 eq), followed by CSA (10 mol %). The resulting mixture was heated under Dean-Stark conditions. The solvent was removed, and DCM (30 ml) added, and the solution was washed with aqueous sodium hydrogen carbonate (3 × 20 ml). The organics were dried over magnesium sulfate. Removal of the solvent yielded the title compound.

(4R,5S)-3,4-Dimethyl-2,5-phenyl-1,3-oxazolidine

(3.5 g, 76% yield) [pseudoephedrine (3.0 g, 18.18 mmd)]



9 b

(Found: C 81.0, H 7.51, N 5.53; $C_{17}H_{19}NO$, requires: C 81.17, H 7.65, N 5.45 %)

ν_{max} (slurry) 3448, 2968, 2794, 2719, 1605, 1495, 1456, 1191 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.81 (3 H, Me1, d, *J*=5.0 Hz), 2.22 (3 H, Me2, s), 3.0-3.01 (1 H, Hb, m), 4.71 (1 H, Hc, s), 5.22 (1 H, Ha, d, *J*=5.0 Hz), 7.10-7.62 (10 H, m).

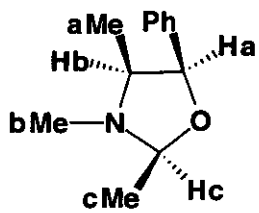
δC ($CDCl_3$, 100 MHz) 14.25, 35.15, 65.32, 100.21, 127.75, 128.12, 128.4, 130.0, 130.15, 131.21, 131.45, 132.15, 139.8.

m/z EI (Found: 253.1468 $C_{17}H_{19}NO$ requires: 253.1468).

$[\alpha]_D$ = –55 (CCl_4, 10 mg/ml).

(4R,5S)-2,3,4-Trimethyl-5-phenyl-1,3-oxazolidine

(2.85 g, 82% yield) [ephedrine (3.0 g, 18.18 mmd)]



9 a

δ_H ($CDCl_3$, 250 MHz) 0.65 (3 H,d, *J*=7.0 Hz, Me a), 1.45 (3 H, d, *J*=5.0 Hz, Me c), 2.25 (3 H, s, Me b), 2.74-2.75 (1 H, m, Hb), 3.91 (1 H, q, *J*=5.0 Hz, Hc), 5.0 (1 H, d, *J*=6.0 Hz, Ha), 7.24-7.43 (5 H, m).

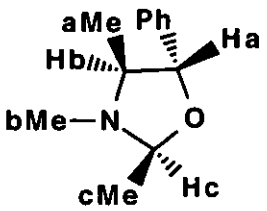
δC ($CDCl_3$, 100 MHz) 14.19, 36.64, 65.12, 82.25, 94.75, 127.15, 127.40, 127.60, 128.1, 129.35.

m/z EI (Found: 191.1308 $C_{12}H_{17}NO$ requires: 191.1310).

$[\alpha]_D$ = –21.2 (CCl_4, 10 mg/ml).

(4S,5S)-2,3,4-Trimethyl-5-phenyl-1,3-oxazolidine

(1.43 g, 62% yield) [pseudoephedrine (2.0 g, 12.12 mmol) acetaldehyde (1.1 g, 24.24 mmol)]



9 c

ν_{max} 3485, 2713, 2803, 1608, 1492, 1362 cm^{-1}.

$_H$ ($CDCl_3$, 250 MHz) 1.15 (3 H, d, *J*=6.4 Hz, Me a,), 1.42 (3 H, d, *J*=6.8 Hz, Me c), 2.24 (3 H, s, Me b), 2.31-2.34 (1 H, m, Hb), 4.22 (1 H, q, *J*=6.9 Hz, Hc), 4.52 (1 H, d, *J*=6.8 Hz, Ha), 7.26-7.45 (5 H, m).

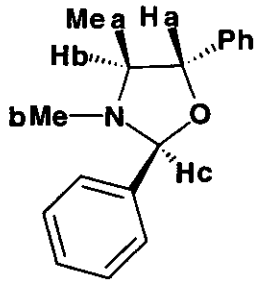
δ_C ($CDCl_3$, 100 MHz) 14.25, 19.35, 36.25, 64.51, 82.50, 94.75, 127.15, 128.7, 128.85, 141.25.

m/z EI (Found: 191.1308 $C_{12}H_{17}NO$ requires: 191.1310).

$[\alpha]_D$ = +22 (CCl_4, 10 mg/ml).

(4S,5S)- 3,4- Dimethyl- 2,5- diphenyl- 1,3- oxazolidine

(2.1 g, 69% yield) [pseudoephedrine(2.0 g, 12.12 mmol) benzaldehyde(2.5 g, 24.24 mmol)]



9 d

(Found: C 80.83, H 7.61, N 5.65. requires: C 80.63, H 7.51, N 5.57 %)

ν_{max} 3482, 2908, 2792, 1604, 1485, 1395 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.22 (3 H, d, *J*=6.0 Hz, Me a), 2.23 (3 H, s, Me b), 2.61-2.63 (1 H, m, Hb), 4.75 (1 H, d, *J*=6.5 Hz, Ha), 4.95 (1 H, s, Hc), 7.26-7.46 (10 H, m).

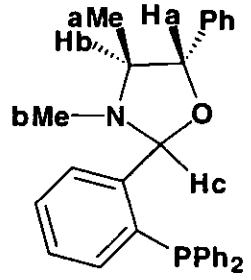
δ_C ($CDCl_3$, 100 MHz) 14.65, 35.45, 65.82, 84.75, 101.45, 127.85, 128.32, 128.64, 130.05, 130.25, 131.65, 131.72, 141.25.

m/z EI (Found: 253.1469 $C_{17}H_{19}NO$ requires: 253.1468).

$[\alpha]_D$ =+46 (CCl_4, 10 mg/ml).

(4S,5S) - 2- [2- (1,1- Diphenyl phosphenyl) phenyl] 3,4- dimethyl- 5- phenyl- 1,3- oxazolidine (4.10 g, 78% yield) mp 233_236 °C

[pseudoephedrine (2.0 g, 12.12 mmol) diphenyl phosphinebenzaldehyde (3.5 g, 24.24 mmol)]



31 c

ν_{max} (slurry,thin film) 3460, 2970, 1100, 1037, 1026 cm^{-1}.

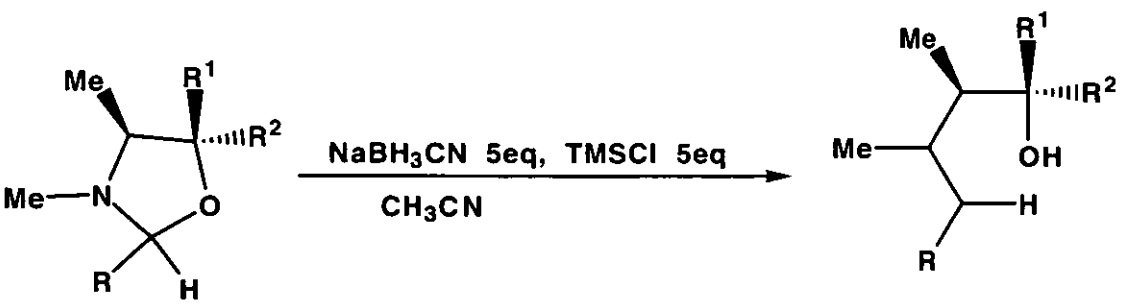
δ_H ($CDCl_3$, 250 MHz) 0.95 (3 H, Me a, d, *J*=6.5 Hz, Me a), 2.52 (3 H, s, Me b), 2.73-2.79 (1 H, m, Hb), 4.22 (1 H, d, *J*=8.0 Hz, Ha), 5.72 (1 H, s, Hc), 7.26-7.91 (19 H, m).

δ_C ($CDCl_3$, 100 MHz) 14.15, 65.25, 85.22, 95.75, 126.5, 128.3, 129.11, 130.25, 130.46, 130.74, 130.89, 131.25, 131.45, 131.75, 132.55, 133.45,133.77, 134.77, 140.65.

m/z EI (Found: 437.1902 $C_{29}H_{28}NOP$ requires: 437.1908).

$[\alpha]_D$ = +82.5 (CCl_4, 10 mg/ml).

Ring Opening of Oxazolidines using $NaBH_3CN$/TMSCl

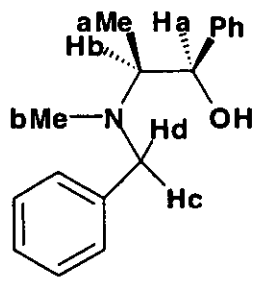


1,3-Oxazolidine derived from ephedrine, pseudoephedrine or isoquinolinol (1.0 g), was dissolved in acetonitrile (40 ml); sodium cyanoborohydride (5 eq) was added, and then TMSCl (5 eq) was added to the vigorously stirred mixture at room temperature.

After 15 minutes the solvent was removed, DCM (30 ml) added and the solution was washed with water (2 × 15 ml). The organic solvents were removed and methanol (30 ml) added followed by potassium carbonate (5 eq) and the mixture stirred at room temperature overnight. The solid residue was filtered off, the filtrate evaporated to dryness, DCM (50 ml) added, and the organic solvents were washed with water (3 × 30 ml). The organic layer was dried over magnesium sulphate. Removal of the solvents gave the desired compound.

(1R,2S)-2-[Methyl(phenylmethyl)amino1-phenylpropane-1-ol (1.4 g, 96% yield)

[2b(1.5 g, 5.9 mmol), $NaBH_3CN$(1.86 g, 29.52 mmol), TMSCl (3.63 g, 29.52 mmol)]



10 b

ν_{max} (neat) 3419, 3084, 3017, 2416, 1602, 1493, 1451, 1386 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.0 (3 H, d, *J*=6.0 Hz, Me a), 2.21 (3 H, Me b, s, Me b), 2.91 (1 H, dq, Hb), 3.61 (1 H, br, OH), 3.62 (2 H, s, Hc, Hd,), 4.8 (1 H, Ha, d, *J*=4.0 Hz), 7.26-7.42 (10 H, m).

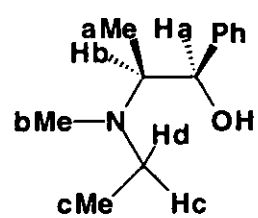
δ_C ($CDCl_3$, 100 MHz) 10.12, 39.26, 59.15, 65.26, 74.26, 126.76, 126.92, 127.15, 127.91, 128.26, 128.63, 140.26, 142.35.

m/z (EI) (Found: 255.1619 $C_{17}H_{21}NO$ requires: 255.1623).

$[\alpha]_D$ = –31 (CCl_4, 10 mg/ml).

(1R,2S)-2-[Ethyl(methyl)amino]-1-phenylpropane (1.32 g, 87% yield)

[2a(1.5 g, 3.85 mmol), $NaBH_3CN$(2.47 g, 39.25 mmol), TMSCl (4.83 g, 39.25 mmol)]



10 a

ν_{max} (neat) 3399, 3086, 2970, 1685, 1602, 1493, 1450, 1379 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.85 (3 H, d, *J*=3 Hz, Me a), 1.0 (3 H, Me c, t, *J*=6 Hz, Me c), 2.25 (3 H, s, Me b), 2.55 (2 H, q, *J*=6.0 Hz, Hc, Hd,), 2.83 (1 H, dq, *J*=3.4 Hz, Hb), 4.80 (1 H, d, *J*=4. Ha), 7.20-7.30 (5 H, m).

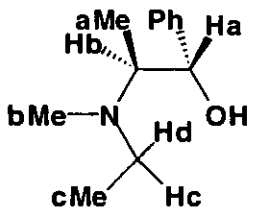
δ_C ($CDCl_3$, 100 MHz) 10.41, 14.25, 37.25, 62.51, 72.86, 125.6, 126.1, 126.81, 127.9, 142.10.

m/z (EI) (Found: 193.1464 $C_{12}H_{19}NO$ requires: 193.1466).

$[\alpha]_D$ = –32 (CCl_4, 10 mg/ml).

(1S,2S) - 2- [Ethyl- methyl amino]- 1phenyl propane 1- ol (1.1 g, 94% yield)

[2c(1.2 g, 6.28 mmol), $NaBH_3CN$(1.98 g, 31.41 mmol), TMSCl (3.86 g, 31.41 mmol)]



10 c

ν_{max} (neat) 3405, 3112, 2985, 1692, 1610, 1496, 1385 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.75 (3 H, d, *J*=6.5 Hz, Me a), 1.15 (3 H, t, *J*=7.0 Hz, Me c), 2.25 (3 H, s, Me b), 2.65 (2 H, m, Hc, Hd), 2.4 (1 H, Hb, m, Hb), 4.2 (1 H, d, *J*=7.0 Hz, Hb), 7.26-7.42 (5 H, m).

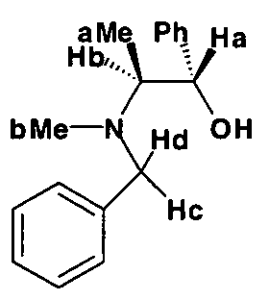
δ_C ($CDCl_3$, 100 MHz) 9.53, 14.25, 37.61, 49.21, 62.65, 72.15, 126.15, 126.70, 126.85, 142.15.

m/z (EI) (Found: 193.1463 $C_{12}H_{19}NO$ requires: 193.1466).

$[\alpha]_D$ = +56 (CCl_4, 10 mg/ml).

(1S,2S) - 2- [Methyl (phenyl methyl) amino]- 1phenyl propane 1- ol (1.58 g, 92% yield)

[2d(1.7 g, 6.72 mmol), $NaBH_3CN$(2.12 g, 33.60 mmol), TMSCl (4.13 g, 33.60 mmol)]



10 d

ν_{max} (neat) 3425, 3091, 3025, 1615, 1466, 1391 cm^{-1}.

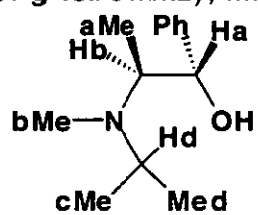
δ_H ($CDCl_3$, 250 MHz) 0.86 (3 H, d, *J*=6.5 Hz, Me a), 2.22 (3 H, Me b, s, Me b), 2.83 (1 H, m, Hb), 3.45 (1 H, d, *J*=13 Hz, Hc,), 3.72 (1 H, d, *J*=9.7 Hz, Hd), 4.33 (1 H, d, *J*=9.7 Hz, Ha), 4.92 (1 H, br, OH), 7.27-7.63 (10 H, m).

δ_C ($CDCl_3$, 100 MHz) 9.26, 35.36, 54.25, 58.16, 75.26, 120.15, 123.6, 124.15, 124.62, 126.21, 126.83, 131.91, 140.25.

m/z (EI) (Found: 255.1619 $C_{12}H_{21}NO$ requires: 255.1623). $[\alpha]_D$ = +42 (CCl_4, 10 mg/ml).

(1S,2S)-2-{Methyl(1-methyl ethyl) amino} 1-phenyl propane-1-ol (1.92 g, 95% yield)

[2e(2.0 g, 9.76 mmd), $NaBH_3CN$ (3.07 g, 48.78 mmd), TMSCl (6.0 g, 48.78 mmd)]



ν_{max} (neat) 3299, 3857, 2971, 2616, 2398, 2361, 2251, 1604, 1493, 1457, 1342 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.83 (3 H, d, *J*=4.0 Hz, Me a), 1.16 (6 H, dd, *J*=7.0, 7.0 Hz, Me c,Me d,), 2.38 (6H, d, *J* =6.0Hz, Me c,Me d,), 2.83 (1 H, m, Hd), 3.0 (1 H, dq, *J*=4.10, 9.70 Hz, Hb), 4.16 (1 H, d, *J*=10.0, Ha), 5.32 (1 H, br, OH), 7.26-7.42 (5 H, m).

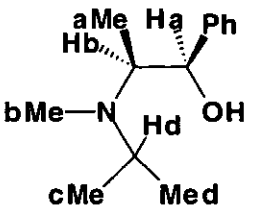
δ_C ($CDCl_3$, 100 MHz) 10.99, 19.91, 20.16, 30.27, 54.25, 62.16,127.12, 127.28, 127.62, 128.34, 141.26.

m/z (EI) (Found: 207.1678 $C_{13}H_{21}NO$ requires: 207.1673).

$[\alpha]_D$ = +72.5 (CCl_4, 10 mg/ml).

(1R,2S)-2-Methyl {1-methyl (1-methyl ethyl) amino} 1-phenyl propane-1-ol (2.2 g, 88% yield)

[2f (2.5 g, 12.2 mmd), $NaBH_3CN$ (3.84 g, 360.98 mmd), TMSCl (75 g, 60.98 mmd)]



δ_H ($CDCl_3$, 250 MHz) 0.86 (3 H, d, *J*=7 Hz, Me a), 1.05 (6 H, 2d, *J*=7.0, 7.0 Hz, Me c, Me d), 2.15 (3 H, s, Me b), 2.86-2.92 (1 H, m, Hd), 3.15-3.26 (1 H, m, Hb), 3.66 (1 H, br, OH), 4.82 (1 H, d, *J*=6.0 Hz, Ha), 7.26-7.42 (5 H, m).

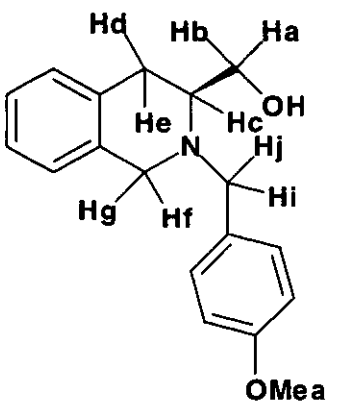
δ_C ($CDCl_3$, 100 MHz) 11.21, 18.61, 18.92, 31.51, 51.25, 61.51, 72.15, 120.15, 127.25, 127.65, 141.52.

m/z (EI) (Found: 207.1621 $C_{13}H_{21}NO$ requires: 207.1623).

$[\alpha]_D$ = –86 (CCl_4, 10 mg/ml).

(3S)-2-{[4-(Methyloxy) phenyl] methyl} 1,2,3,4-tetrahydro isoquinolin-3-yl) methanol (1.38 g, 92% yield)

[2h (1.5 g, 5.3 mmd), $NaBH_3CN$ (1.68 g, 26.69 mmd), TMSCl (3.28 g, 26.69 mmd)]



8c

ν_{max} (thin film), 3357, 2931, 2834, 1611, 1511, 1249 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.4-2.5 (1 H, dd, *J*=5.0, 5.0 Hz, Ha), 2.8-2.9 (1 H, dd, *J*=6.0, 6.0 Hz, Hb), 3.1-3.2 (1 H, m, Hc), 3.5-3.6 (4 H, m. Hi, Hj, Hf, Hg), 3.7 (1H,OH , s), 3.9 (3 H,s, Me a), 6.9-7.2 (8 H, m).

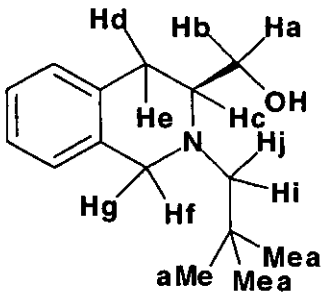
δ_C ($CDCl_3$, 100 MHz) 26.10, 50.25, 58.15, 59.00, 62.15, 115.16, 126.72, 126.89, 127.15, 129.32, 130.52, 130.61, 131.21, 14.06, 134.70, 160.12.

m/z (EI) (Found: 283.1570 $C_{18}H_{21}NO_2$ requires: 283.1572).

$[\alpha]_D$ = –39 (CCl_4, 10 mg/ml).

(3S) - 2- (2,2- Dimethyl propyl) - 1,2,3,4 tetrahydro isoquinolin- 3- yl] methanol (0.76 g, 92% yield)

[2g(1.0 g, 3.56 mmd), $NaBH_3CN$(1.1 g, 13.74 mmd), TMSCl (2.2 g, 17.79 mmd)]



8 d

ν_{max} (neat) 3364, 3021, 2952, 2417, 2254, 1643, 1495, 1479, 1360, 1188, 1035 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.92 (9 H, s, Me a), 2.26 (2 H, q, *J*=12 Hz, Hc, Hd), 3.16 (2 H, AB, *J*=12 Hz, He, Hf,), 3.42 (2 H, q, *J*=4.0 Hz, Hi, Hj,), 3.65-3.67 (1 H, m, Hc), 4.21 (1 H, d, *J*=12 Hz, Ha, Hb,), 5.27 (1 H, br, OH), 7.16-7.23 (5 H, m).

δ_C ($CDCl_3$, 100 MHz) 25.26, 27.61, 51.26, 60.26, 63.35, 65.36, 126.26, 126.35, 126.90, 129.33, 134.62.
m/z (EI) (Found: 233.18041 $C_{15}H_{23}NO$ requires: 233.17996). $[\alpha]_D$ = –41 (CCl_4, 10 mg/ml).

(3S)-1,2,3,4-Tetrahydro-3-isoquinoline-3-methanol

8 a

Lithium aluminium hydride (4.0 g, 10.54 mmol, 2 eq) was suspended in dry diethyl ether (150 ml). (*S*)-1,2,3,4-Tetrahydroisoquinoline 3-carboxylic acid (10 g, 57 mmol) was added The mixture was stirred overnight at room temperature. Water (30 ml) was added carefully, then sodium hydroxide (20%) solution (40 ml) was added slowly. The solid precipitate was filtered off and the organic solutions extracted. The aqueous layer was extracted with diethyl ether (3 × 50 ml). The solid precipitate was dissolved in water (100 ml) and extracted with DCM (3 × 30 ml). The combined organic solutions were dried over magnesium sulphate. The solvent was removed to give an orange solid (8 g, 87%) mp 112-114 °C. [76]

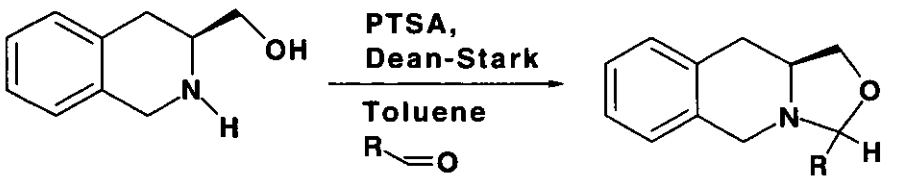
(Found: C, 73.30, H, 7.53, N, 8.10, $C_{10}H_{13}NO$. requires: C, 73.57, H, 7.87, N, 8.38%).

δ_H ($CDCl_3$, 250 MHz) 2.5-2.8 (4 H, , m, Hd, He, Hf, Hg), 2.95-3.10 (1 H, m, Hc), 3.45 (1 H, dd, *J*=8.0 Hz, Ha), 3.7 (1 H, dd, *J*=4.0 Hz, Hb), 4.0 (2 H, br, OH), 7.0-7.1 (4 H, m).

δ_C ($CDCl_3$, 100 MHz) 31.16, 48.26, 55.26, 66.18, 120.16, 125.32, 130.16, 137.35, 168.26.

m/z EI (Found: 163.0996 $C_{10}H_{13}NO_2$ requires: 163.0997). $[\alpha]_D$ = –96.5 (CCl_4, 10 mg/ml).

Synthesis of Oxazolidines derived from Isoquinoline



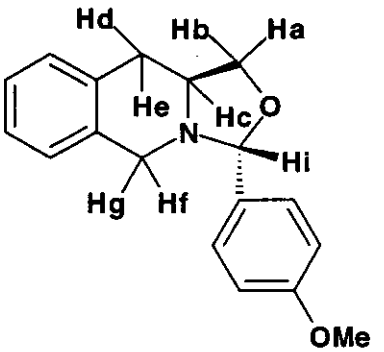
8a-b

(3S),1,2,3,4-Tetrahydroisoquinoline-3-methanol was dissolved in toluene (50 ml). Then the required aldehyde (1 eq) was added, followed by PTSA (10 mol %). The mixture was heated under Dean Stark conditions overnight. Sodium hydrogen carbonate (30 ml) was added. The organic solution was evaporated to result in the required oxazolidine.

R=(MeOPh)

8a- (3R,10aS)-3-[4-(Methoxy-phenyl]-1,5,10 10a-tetrahydro[1,3]-oxazolo[3,4-b] isoquinoline (1.87 g, 88%) 1g- (1.2 g, 7.3 mmd)

[p-MeO benzaldehyde (0.88 g, 7.3 mmd)]



8a

(Found: C, 76.38, H, 6.65, N, 4.92, $C_{18}H_{19}NO_2$. requires: C, 76.46, H, 6.76, N, 4.98%).

ν_{max} (slurry) 3421, 2937, 1612, 1512, 1242, 1167 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.85-3.10 (3 H, m, Hf, Hg, He), 3.4 (1 H, d, *J*=15, Ha), 3.7 (1 H, d, *J*=15, Hb), 3.8 (3 H, s, Me), 3.85 (1 H, d, *J*=8 Hz, Hd), 4.25-4.8 (1 H, m, Hc), 4.75 (1 H, s, Hi), 6.8-7.5 (8 H, m).

δ_C ($CDCl_3$, 100 MHz) 47.26, 55.26, 71.35, 72.16, 113.28, 114.26, 126.18, 127.35, 128.61, 129.31, 130.21, 137.35, 137,56, 161.26, 164.35.

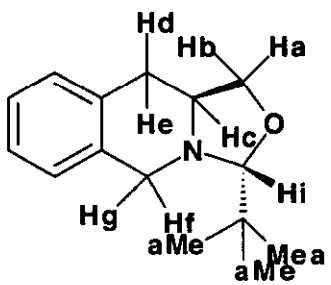
m/z (EI) (Found: 281.1410 $C_{18}H_{19}NO_2$ requires: 281.1416).

$[\alpha]_D$ = –92 (CCl_4, 10 mg/ml), mp 186-188°.

R=(C(Me)$_3$)

8b - (3R,10aS) - 3- (1,1- Dimethyl (ethyl) - 1,5- 10,10a tetrahydro[1,3] oxazolo[3,4,6] isoquinoline (2.3 g82%) (1 g(2.0 g 12.27 mmd)

[t- butyl- acetaldehyde(1.1 g 12.27 mmd)]



8 b

(Found: C 77.98, H 8.86, N 6.19, $C_{18}H_{21}NO_2$. requires: C 77.92, H 9.09, N 6.06%).

ν_{max} (slurry) 3063, 2956, 1642, 1483, 1452, 1329, 1192 cm^{-1}.

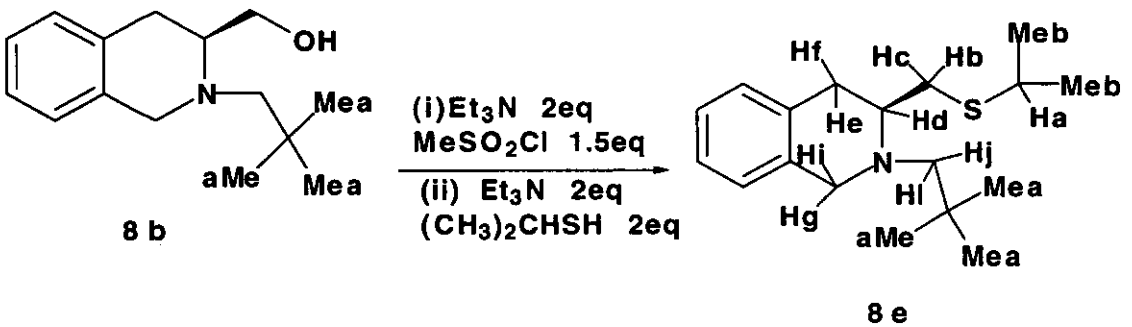
δ_H ($CDCl_3$, 250 MHz) 1.01 (9 H, Me1, s), 2.6 AB(3 H, He, Hf, Hg, m), 3.52 (1 H, Ha, d, *J*=7.0 Hz), 3.6 (1 H, Hb, d, *J*=7.0 Hz), 4.05 (2 H, , Hd, Hi, m), 4.16 (1 H, Hi, s), 7.00-7.26 (4 H, m).

δ_C ($CDCl_3$, 100 MHz) 25.16, 30.26, 52.15, 57.52, 70.14, 103.25, 105.15, 121.25, 125.15, 126.26, 126.90, 127.1, 127.6, 129.07, 134.14, 135.01, 136.2.

m/z EI (Found: 231.1625 $C_{15}H_{21}NO$ requires: 231.1623).

$[\alpha]_D$ = –96 (CCl_4, 10 mg/ml).

(3S)-2-(2,2-Dimethyl propyl)-1,2,3,4 [tetrahydroisoquinolin-3-yl]methyl (1-methyl ethyl)sulfide



(3S)-2-(2,2-Dimethylpropyl)-1,2,3,4-[tetrahydroisoquinolin-3-yl]-methanol (1.5 g, 6.43 mmol) was dissolved in DCM (10 ml). The solution was cooled to 0 °C, triethylamine (0.11 g, 1.05 mmol, 3.5 eq) was added, then methylsulfonyl chloride (0.04 g, 0.027 mmol, 0.35 ml, 1.2 eq) was added followed by 2-propanthiol (0.068 g, 0.082 ml, 0.9 mmol, 3 eq), and the resulting solution was left to stir overnight. The solvent was removed and the residual oil subjected to flash chromatography using 95% petrol 5% ethyl acetate as eluent to yield the product as an oil (1.29 g, 69%).

ν_{max} (neat) 2957, 2867, 1655, 1604, 1582, 1442, 1414, 1364, 1161, 1141 cm^{-1}.

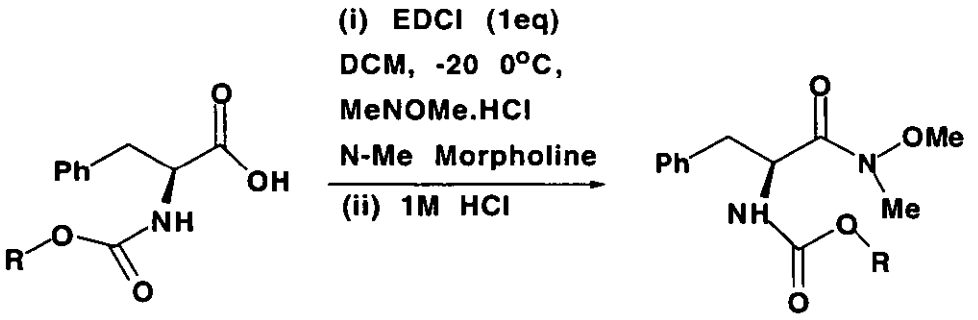
δ_H ($CDCl_3$, 100 MHz), 0.82 (9 H, s, Me b), 1.12 (1 H, m, Ha), 1.35 (6 H, d, *J*=7.0 H, Me az), 1.46 (2 H, d *J*=8.0 Hz, Hb, Hc), 2.0 (2 H, s, HI, Hj), 2.31-2.33 (2 H, m, He, Hf), 2.61-2.73 (1 H, m, Hd), 3.16-3.72 (2 H, m, Hi, Hg), 7.52-7.53 (4 H, m,).

δ_C (100 MHz, $CDCl_3$) 23.16, 25.26, 28.35, 51.26, 60.15, 65.32, 125.16, 126.30, 126.90, 133.60, 134.25.

(*m/z*) (EI) (Found: 291.2018 $C_{18}H_{29}NS$ requires: 291.2020).

$[\alpha]_D$ = +75 (CCl_4, 10 mg/ml).

Phenyl methyl N-(1S)-2-[methyl(methoxy)amino]-2 oxo –1-Me-(phenyl methyl)(ethyl)ethyl)carbamate



27a-b

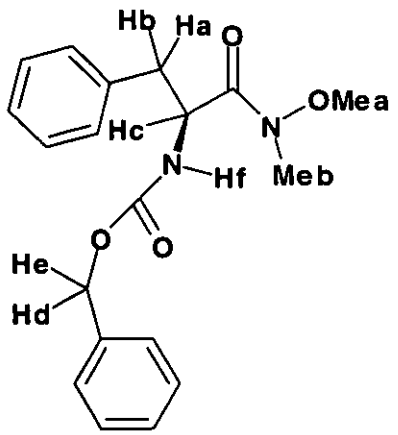
R=$CH_2(C_6H_5)$, $C(CH_3)_3$

N-tert-butoxycarbonyl-L-phenylalanine (10 g, 40.16 mmol) OR N-(carbobenzyloxy)-L-phenylanaline (10g, 33.4 mmol) was dissolved in DCM (150 ml) and the solution cooled to –20 °C. N-O Dimethyl hydroxylamine hydrochloride (1 eq) was added, followed by *N*-methyl morpholine (1 eq). EDCI (1 eq) was added in portions over a period of 1 hour at –20 °C. The reaction was allowed to stir for a further 1 hour at –20°C. The reaction was allowed to stir for a further 1 hour. Ice cooled 1M HCl was added (30 ml) and the mixture extracted with DCM, and the aqueous layer was re-extracted with DCM (3 × 10 ml). The combined organic solutions were washed with aqueous sodium hydrogen carbonate (30 ml) and brine (30 ml). The combined aqueous was washed with DCM (3 × 15 ml) and the combined organic solutions dried over magnesium sulphate. Removal of the solvent and purification by chromatography yielded the desired compound

R=(Ph CH_2) =27a

Phenyl methyl N- (1S) - 2- [methyl(methoxy) amino]- 2- oxo-1- phenyl methyl ethyl carbamate (11 g, 80% yield)

[Cbz- L- phenylalaine(10 g, 40.16 mmd), N, O- Dimethyl hydroxylamine(3.9 g, 40.1 mmd), N- methylmorphdine(4.1 g, 40.16 mmd), EDCI (7.8 g, 40.16 mmd)]



27a

ν_{max} (neat) 3405, 2843, 1660, 1670, 1341, 1134 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.7 (1 H, d, *J*=6.0 Hz, Ha), 2,8 (1H, d, *J*=6.0Hz, Hb), 3.1 (3 H, s, Me b), 3.6 (3 H, s, Me a), 3.6 (1 H, Hc, t, *J*=6.0Hz, Hc) , 5.0 (2 H, s, He, Hd), 7.2-7.5 (10 H, aromatics).

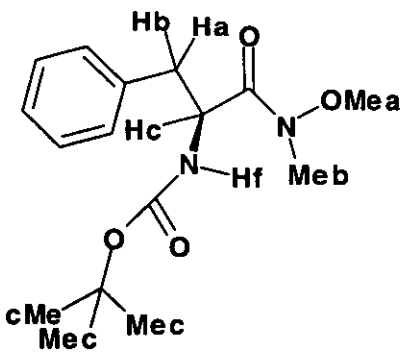
δ_C ($CDCl_3$, 100 MHz) 32.16, 35.26, 42.52, 52.21, 61.26, 126.46, 127.91, 128.43, 128.72, 128.16, 129.21, 129.40, 129.64, 155.26, 171.21.

m/z EI (Found 342.1749 $C_{19}H_{22}N_2O_4$ required 342.1746).

R=C(CH$_3$)$_3$=27b

1,1-Dimethyl-N-[(1S)-2-[methyl-(methoxy)amino]-2-oxo-1-(phenyl methyl ethyl) carbamate (9.5 g, 92% yield)

[BOC-L-phenylanaline(10 g, 33.4 mmol), N,O-dimethyl hydroxylaminehydrochloride(3.26 g, 33.4 mmol), N-methylmorpholine(3.38 g, 33.4 mmol), EDC (6.4 g, 40.16 mmol)]. mp 186-189 °C



27b

ν_{max} (neat) 3411, 2872, 2695, 1672, 1346, 1145 cm^{-1}.

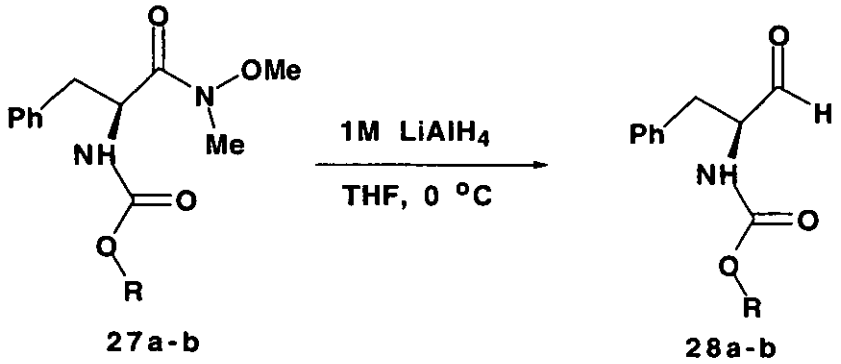
δ_H ($CDCl_3$, 250 MHz) 1.43 (9 H, s, Me c), 3.15 (1 H, d, *J*=7.5 Hz, Ha), 3.16 (1H ,d, *J*=7.5Hz, Hb), 2.82-2.83 (1 H, t, *J*=7.7Hz, Hc), 3.26 (3 H, s, Me b), 3.72 (3 H, s, Me a), 7.26-7.51 (5 H, m).

δ_C ($CDCl_3$, 100 MHz) 28.15, 32.62, 38.16, 51.26, 61.52, 126.25, 126.62, 127.15, 128.2, 137.26, 155.25, 172.23.

m/z EI (Found: 308.1739 $C_{16}H_{24}N_2O_4$ requires: 308.1736).

$[\alpha]_D$ = –32 (CCl_4, 10 mg/ml).

Phenyl methyl N-[(1S)-1 formyl-2-phenyl ethyl] carbamate



27a-b

28a-b

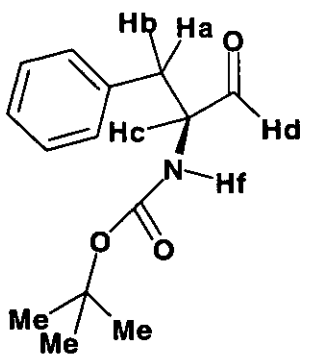
R=CH_2Ph,$C(CH_3)_3$

N-BOC substituted carbamate (1 eq) or (1b) N-Cbz substituted carbamate (1 eq) was dissolved in dry THF (30 ml). The solution was cooled to 0 °C in an ice bath. Then $LiAlH_4$ in THF 1.0M (1/2 eq) was added dropwise. The solution was left to stir for 30 minutes, then cooled to –15 °C and saturated aqueous potassium hydrogen sulphate (20 ml) was added carefully, the mixture was diluted with diethyl ether (50 m), and stirred vigorously for further 30 minutes. The mixture was allowed to reach room temperature and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 × 15 ml). The combined organic solutions were dried over magnesium sulphate. Removal of solvent at temperature no greater than 30 °C yielded the required material which was recrystallized from methanol to yield the required material.

R=C(CH$_3$)$_3$=28b

1,1- Dimethyl- N- [(1S) - 1 formyl- 2- phenyl ethyl carbamate (1.15 g, 97% yield)

[N- BOC- L- phenyl carbamate (1.5 g, 4.8 mmd), LiAlH$_4$ (2.4 ml, 2.4 mmd)]



28 b

(Found: C, 66.68, H, 7.74, N, 5.58, $C_{14}H_{19}NO_3$, Requires: C, 67.74, H, 7.26, N, 5.56%. $[\alpha]_D$ = –34 (CCl_4, 10 mg/ml). mp 174-177 °C

ν_{max} (CH_2Cl_2 solution) 3425, 2817, 1687, 1472, 1315, 1192 cm^{-1}.

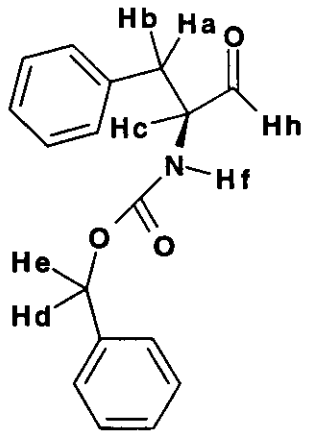
δ_H ($CDCl_3$, 250 MHz) 1.42 (9 H, s, Me a), 3.18 (1 H, d, *J*=7.4 Hz, Ha), 3.2 (1H, d, *J*=7.6Hz, Hb), 3.16-3.17 (1 H, m, Hc,), 7.16-7.26 (5 H, m), 9.82 (1 H, Hd, s).

δ_C ($CDCl_3$, 100 MHz) 28.15, 35.25, 60.15, 127.15, 128.4, 129.25, 130.15 135.15, 192.35, 196.15.

R=(CH_2Ph) =28a

Phenyl methyl- N- [(IS) - 1- formyl- 2- phenyl ethyl] carbamate (0.94 g, 95% yield)

[N- Cbz- L- phenyl carbamate(1.2 g, 3.5 mmd) , $LiAlH_4$ (2.0 ml, 1.75 mmd)]



28 a

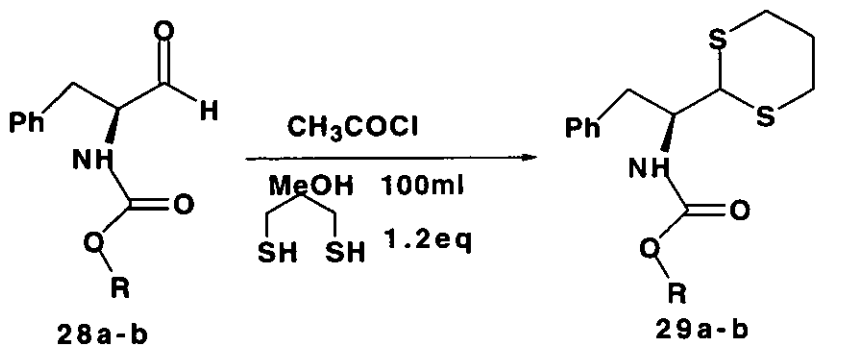
ν_{max} (slurry) 3407, 2843, 1750, 1680, 1198 cm^{-1}

δ_H ($CDCl_3$, 250 MHz) 2.63 (2 H, d, *J*=12.0 Hz, Ha, Hb,), 3.16 (1 H, m, Hc), 4.16 (1H, br, NH), 5.52 (2 H, s, He, Hf,), 7.16-7.31 (10 H, m), 9.8 (1 H, s, Hh).

δ_C ($CDCl_3$, 100 MHz) 39.15, 39.26, 120.21, 123.6, 124.2, 131.25, 134.21, 136.26, 138.26, 140.35, 168.26, 171.21.

m/z EI (Found: 283.1203 $C_{17}H_{17}NO_3$ requires: 283.1208). $[\alpha]_D$ = –12 (CCl_4, 10 mg/ml).

Phenyl methyl N-[(1S)-1-(1,3-dithiane-2yl)-2-phenyl] carbamate



28a-b

29a-b

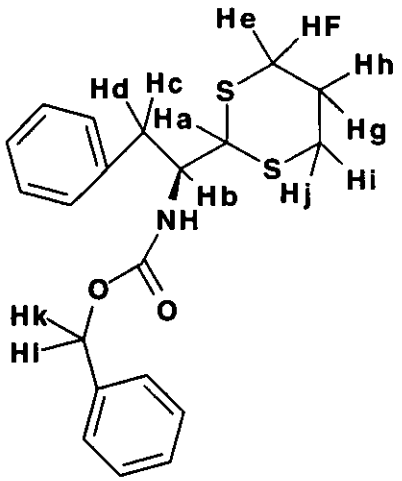
R=CH_2Ph,$C(CH_3)_3$

Methanol (50 ml) was cooled to 0 °C, and acetyl chloride (5 ml) was added. The solution was stirred for 10 minutes under nitrogen. The carbamate (28a-b) (1 eq) was added as a solution in methanol (10 ml) and DCM (10 ml) to help solubility. The resulting solution was stirred overnight. The solvent was removed and the resulting solid recrystallized from methanol to yield the title compound.

R=(CH_2Ph) =29a

Phenyl methyl N- [(1S) - 1 - (1,3- dithiane- 2yl) - 2- phenyl] carbamate (0.72 g, 92% yield)

[28a- (0.6 g, 2.12 mmd), propane1,3 dithid (0.34 g, 3.18 mmd) acetylchloride(5 ml)]



29 a

ν_{max} (slurry) 3328, 3028, 1713, 1510, 1453 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.31-1.44 (1 H, m, Hb), 1.82-1.83 (2 H, m, Hc, Hd), 2.85-2.35 (6 H, m, He-j,Hm), 4.22 (1 H, d, *J*=3.0 Hz, Ha), 5.1 (2 H, s, Hk, Hl), 7.2-7.4 (10 H, m).

δ_C ($CDCl_3$, 100 MHz) 23.16, 25.26, 45.32, 47.61, 62.16, 127.12, 127.18, 128.32, 128.43, 128.82, 128.94, 129.21, 129.47, 129.65, 129.74

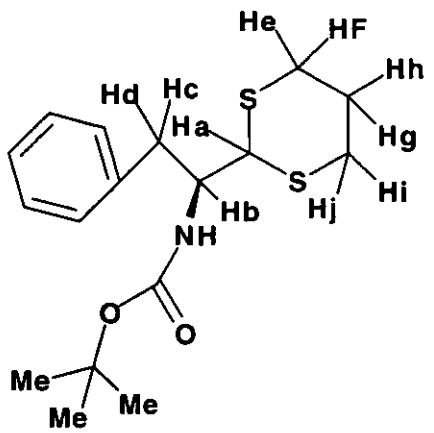
m/z (EI), (Found: 373.1164 $C_{20}H_{27}NO_2S_2$ requires: 373.1170).

$[\alpha]_D$ = −14 (CCl_4, 10 mg/ml). Mp 143-146 °C

R=(CH_3)$_3$=29b

1,1- Dimethyl ethyl- N- [(1S)- 1- (1,3- dithiane- 2- yl)- 2- phenyl ethyl] carbamate (1.03 g, 97% yield)

[28b- (0.8 g, 3.22 mmd), propane1,3 dithiol (0.51 g, 4.82 mmd) acetylchloride(5 ml)]



29 b

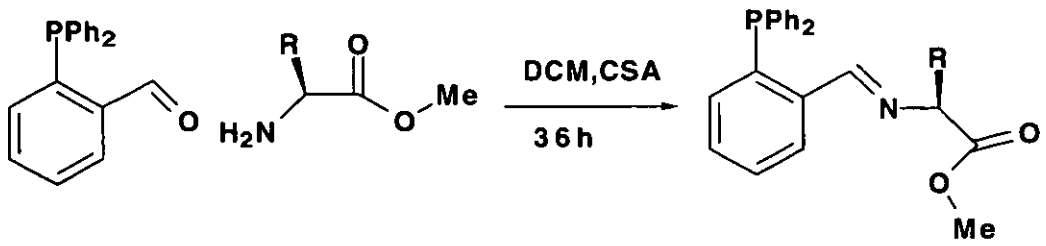
(Found: C 60.20, H 7.34, N 4.2, $C_{17}H_{15}NO_2S_2$. requires: C 60.18, H 7.37, N 4.2%). $[\alpha]_D$ = −39.5 (CCl_4, 10 mg/ml). Mp 165-168 °C

ν_{max} (slurry,nujol mull) 3428, 3072, 2969, 1723, 1515, 1462 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.42 (9 H, , s, Me), 2.10-2.21 (1 H, m, Hb), 2.9-3.4 (6 H, He, m, He-j, Hm), 4.12 (2 H, d, *J*=9.0 Hz, Hc, Hd), 4.22 (1 H, br, NH), 4.83 (1 H, d, *J*=7.5 Hz, Ha), 7.26-7.41 (5 H, m).

δ_C ($CDCl_3$, 100 MHz) 5.25, 28.10, 30.26, 38.15, 50.25, 55.15, 80.25, 122.15, 126.5, 127.1, 129.21, 140.15, 158.15.

Synthesis of Phosphorus Imine Ligands

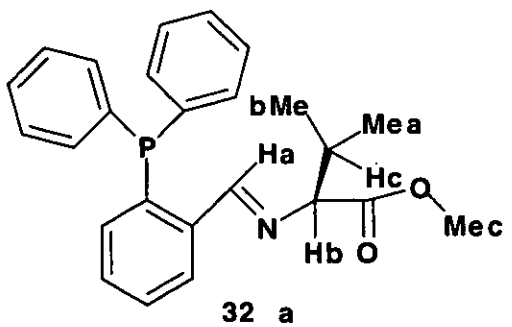


To a stirred solution of the phosphine aldehyde (1.2 eq) in DCM (30 ml), the L amine ester hydrochloride salt (1 eq) was added, followed by CSA (10 mol %). 4Å Molecular sieve (2.0 g) was added and the resulting mixture allowed to stand for 72 hours. The molecular sieve was removed by filtration and the solution washed with sodium bicarbonate (3 x 20 ml). The organic solutions were dried and the crude mixture subjected to column chromatography using 1% triethylamine, 19% ethyl acetate and 80% petrol as eluent to yield the desired product (32a-c) as coloured oils.

R=CH(CH_3) $_2$

(32a) Methyl- 2- {(E) - 1- [2- (1,1- diphenyl phosphanyl) phenyl] methylidene} –(3S) - methyl butanoate (3.45 g, 72% yield)

[Phosphinealdehyde (4.15 g, 14.33 mmol) , L-valinemethyl (2.0 g, 11.94 mmol)]



32 a

ν_{max} 3033, 2960, 2872, 2831, 1732, 1633, 1435, 1194 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.62 (3 H, d, *J*=6.7 Hz, Me a), 0.86 (3 H, d, *J*=6.8 Hz, Me b), 2.15-2.16 (1H, m, Hc), 3.42 (1 H, d, *J*=7.2 Hz, Hb), 3.61 (3 H, s, Me c), 7.25-7.54 (14 H, m), 8.7 (1 H, s, Ha).

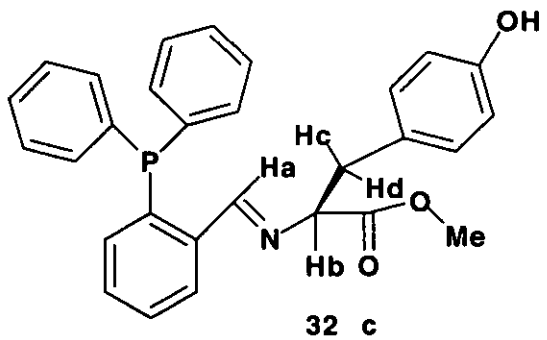
δ_C ($CDCl_3$, 100 MHz) 17.67, 18.51, 30.09, 52.13, 77.02, 128.36, 128.42, 128.98, 129.09, 129.19, 129.33, 134.62, 134.65, 136.68, 162.13, 172.60.

m/z FAB (Found: 404.1729 (M^++1) $C_{25}H_{27}NO_2P$ requires: 404.1651). $[\alpha]_D$ = +20.2 (CCl_4, 10 mg/ml).

R=CH_2 (C_6H_4p( ) H)

(32c) Methyl- 2- {[(E) - 1 - [2- (1,1- diphenyl phosphanyl) phenyl] methylidene} amino] - 1--3- (2S- hydroxyphenyl) propanoate (2.65 g, 66% yield)

[L- Tyrosinemethyl ester HCl (2.0 g, 8.64 mmol), phosphinealdehyde (3.0 g, 10.37 mmol)]



32 c

ν_{max} 3055, 1739, 1516, 1437, 1263, 1170 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.15 (1 H, dd, *J*=5.9, 10.5 Hz, Hc), 3.16 (1 H, dd, *J*=5.9, 10.5 Hz, Hd), 3.52 (3 H, s, Me), 4.16 (1 H, dd, *J*=10.5, 10.5 Hz, Hb,), 5.25 (1 H, br, OH), 6.95-7.8 (18 H, m).

δ_C ($CDCl_3$, 100 MHz) 39.4, 52.46, 75.28, 115.72, 128.35, 128.42, 128.92, 128.96, 129.03, 129.18, 129.22, 130.99, 131.12, 137.73, 134.18, 134.28, 155.05, 162.76, 172.92.

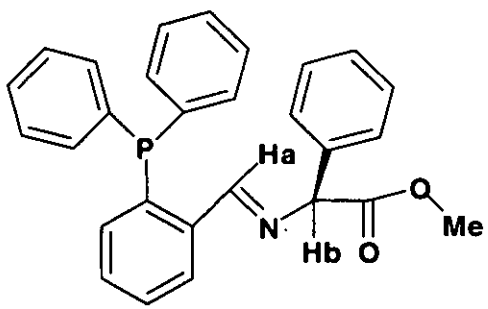
m/z FAB (Found: 468.1729 (M^++1) $C_{29}H_{27}NO_2P$ requires: 468.1651).

$[\alpha]_D$ = +62 (CCl_4, 10 mg/ml).

R=Ph

(32b) Methyl- 2- {(E)- 1- [2- (1,1- diphenyl phosphanyl) phenyl] methylidene amino} –2S- phenyl ethanoate (4.27 g, 70% yield)

[L- Phenylanaline methyl ester (3.0 g, 13.95 mmol), diphenyl phosphinealdehyde (4.86 g, 16.74 mmol)]



32 b

ν_{max} (Neat) 3070, 2983, 2875, 1739, 1645, 1462, 1438, 1197 cm^{-1}.

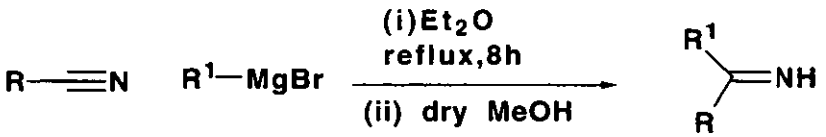
δ_H ($CDCl_3$, 250 MHz) 3.62 (3 H, s, Me), 5.00 (1 H, s, Hb), 7.16-7.83 (20 H, m), 8.2 (1 H, s, Ha).

δ_C ($CDCl_3$, 100 MHz) 52.25, 70.31, 128.21, 128.30, 128.53, 128.06, 129.06, 129.18,129.25,131.24,132.38,132.46,133.15,133.35,133.62,133.75, 162.6171.60.

. *m/z* FAB (Found: 438.1618 (M^++1) $C_{28}H_{25}NO_2P$ requires: 438.1545).

$[\alpha]_D$ = +19.5 (CCl_4, 10 mg/ml).

Synthesis of Imines from Nitriles

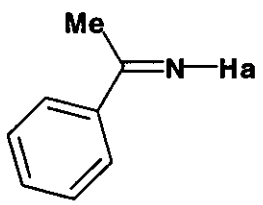


To a stirred solution of the Grignard reagent (1.5 eq) in ether under nitrogen, the nitrile (1 eq) was added slowly as a solution in ether, then heated under reflux and the reaction was followed by TLC. When all the starting nitrile had reacted, the reaction was quenched by the addition of dry methanol (20 eq) carefully into the cooled reaction mixture at –15 °C - –20 °C. The solid precipitate was filtered off and the crude product used for the next step.

R=Ph, R^1=Me

(23a) Methylphenyl imine (4.9 g, 85% yield)

[Benzonitrile (5.9 g, 48.5 mmd), methyl magnesium bromide (27 ml, 1.5 eq)]



23 a

ν_{max} (neat) 3560, 2982, 2800, 1600 cm^{-1}.

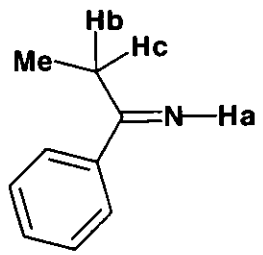
δ_H ($CDCl_3$, 250 MHz) 2.42 (3 H, s, Me,), 7.25-7.46 (5 H, m),7.92 (1 H, d, *J*=4.25 Hz, Ha).

m/z EI (Found: 119.0746, C_8H_9N, requires: 119.0668).

R=Ph, R^1 = Et

(23c) Ethylphenyl imine (5.5 g, 86% yield)

[Benzonitrile (5.0 g, 48.5 mmol), methyl magnesium bromide (32 ml, 1.5 eq)]



23 c

ν_{max} (neat) 3570, 2982, 2811, 1607 cm^{-1}.

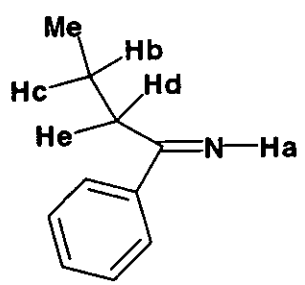
δ_H ($CDCl_3$, 250 MHz) 1.15 (3 H, t, *J*=7.4 Hz, Me), 2.43 (2 H, q, *J*=7.8 Hz, Hh, Hc), 7.26-7.47 (5 H, m), 7.92 (1 H, d, *J*=4 Hz, Ha,).

m/z EI (Found: 133.0813, $C_9H_{11}N$, requires: 133.0891).

R^1=propyl, R=Ph

(23b) Propylphenyl imine (6.10 g, 85% yield)

[Benzonitrile (5.0 g, 48.5 mmol), propyl magnesium chloride (36.5 ml, 1.5 eq)]



23 b

ν_{max} (neat) 3530, 2982, 2885, 2822, 1610 cm^{-1}.

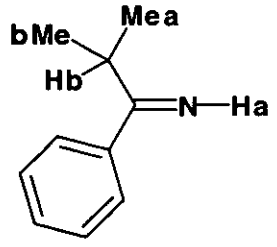
δ_H ($CDCl_3$, 250 MHz) 0.93 (3 H, t, *J*=4.6 Hz, Me), 1.82 (2 H, dq, *J*=4.57,4,5 Hz, Hb, Hc), 2.93 (2 H, t, *J*=4.5 Hz, Hd, He), 7.26-7.46 (5H, m), 7.92 (1 H, s, Ha).

m/z EI (Found: 147.1126, $C_{10}H_{13}N$, requires: 147.1048).

R^1=iPr, R=Ph

(23f) Isopropylphenyl imine (7.2 g, 92% yield)

[Benzonitrile (5.0 g, 48.5 mmd), isopropyl magnesium chloride (36.4 ml, 1.5 eq)]



23 f

ν_{max} (neat) 3555, 2982, 2887, 1622 cm^{-1}.

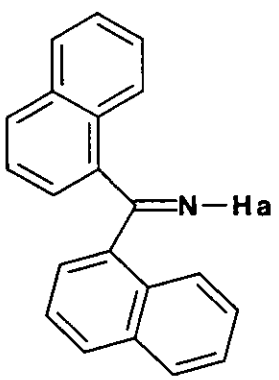
δ_H ($CDCl_3$, 250 MHz) 1.10 (6 H, d, *J*=6.8 Hz, Me a, Me b), 3.0 (1 H, m, Hb), 7.2-7.4 (5 H, m), 7.9 (1 H, d, *J*=6.8 Hz, Ha).

m/z EI (Found: 161.1126, $C_{11}H_{15}N$, requires: 161.1204).

R^1=1- NaPh, R=1- NaPh

(23g) 1,1- Dinaphthalene- imine (9.1 g, 65% yield)

[1- Cyanonaphlene (7.6 g, 50 mmol), 1- bromonaphthalene (20.7 ml, 100 mmol) magnesium (2.43 g, 100 mmol)]



23 g

ν_{max} (neat) 3555, 2982, 2887, 1630 cm^{-1}.

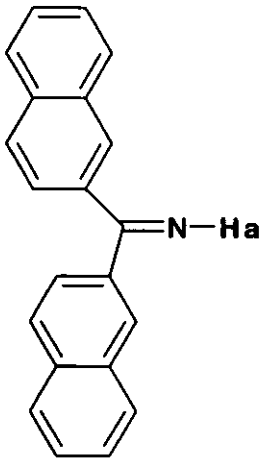
δ_H ($CDCl_3$, 250 MHz) 7.1-8.0 (14 H, m), 8.1 (1 H, s, Ha).

m/z EI (Found: 281.1283, $C_{21}H_{15}N$, requires: 281.1204).

R^1=2- Naph, R=2- Naph

2,2- Dinaphthalene- imine (4.36 g, 62% yield)

(23h) [2- Cyanonaphthalene (2.14 g, 25 mmol), 2- bromonaphthalene (10.83 g, 50 mmol), magnesium (1.215 g, 50 mmol)]



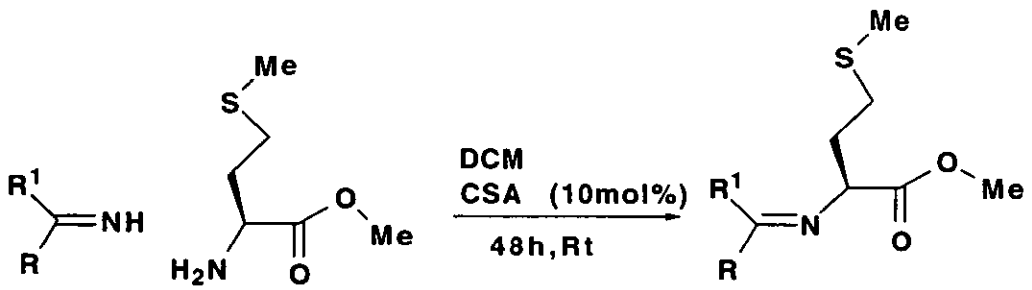
23 h

ν_{max} (neat) 3561, 2979, 2892, 1640 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 7.1-8.0 (14 H, m), 8.1 (1 H, s, Ha).

m/z EI (Found: 281.1282, $C_{21}H_{15}N$, requires: 281.1204).

Synthesis of Sulfur Imine Ligands

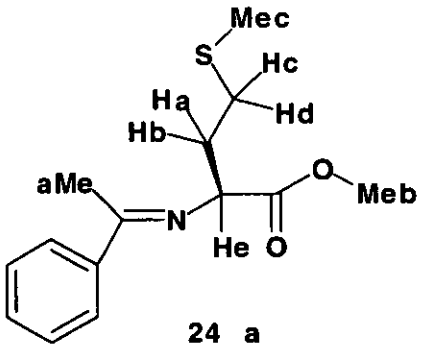


To a stirred solution of the imine (1 eq) in dry DCM, L-methinonine methyl ester hydrochloride (1 eq) was added, then CSA 10 mol %, followed by dry 4Å molecular sieves . The reaction mixture was allowed to stand at room temperature for 48 hours. The molecular sieve was then filtered off and the mixture washed with saturated aqueous sodium bicarbonate (3 × 20 ml). The organic solutions were dried over magnesium sulfate and removal of the solvents yielded the crude product which was purified by column chromatography using 1% triethylamine, 15% ethyl acetate, 84% hexane.

R=Ph, R^1=Me

(24a) Methyl (2 s)- 2- [(diphenyl methylidene) amino 3- 4- methyl thio] butanoate (4.49 g, 76% yield)

[methylphenyl imine(2.6 g, 21.85 mmd), L- methioninemethyl ester HCl (3.86 g, 21.85 mmd)]



24 a

ν_{max} 3598, 2961, 2841, 2827, 1635 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.1 (3 H, s, Me a), 2.3 (3 H, s, Me c), 2.3-2.31 (2 H, , m, Ha, Hb), 2.45-2.46 (2H, m, Hc, Hd), 3.6 (3 H, s, Me b), 4.5 (1 H, t, *J*=5.2 Hz, He), 7.1-7.4 (5 H, m).

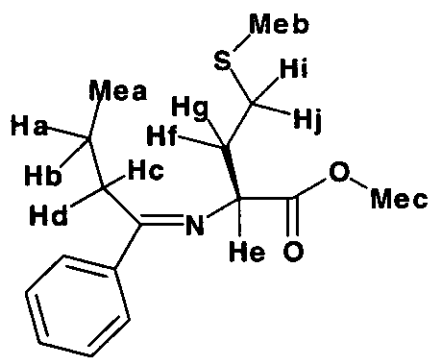
δ_C ($CDCl_3$, 100 MHz) 14.50, 15.73, 29.87, 30.73, 52.34, 62.54, 126.28, 127.38, 127.59, 144.45, 168.84, 172.73.

m/z EI (Found: 265.1219 $C_{14}H_{19}NO_2S$ requires: 265.1136).

R- Ph, R^1 = propyl

(24b) Methyl (2 s)- 2- [(z)- 2- {(z) 1phenyl butylidene} amino]- 4- (methyl thiol) butanoate (11.34 g, 81% yield)

[Propylphenyl imine(7.0 g, 47.62 mmd), L- methoninemethyl ester (5.7 g, 47.62 mmd)]



24 b

ν_{max} 3588, 2941, 2871, 2825, 1625 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.9 (3 H, t, *J*=4.5 Hz, Me a), 1.51 (2 H, d q, *J*=4.6,4.8Hz, Ha, Hb), 2.1 (3 H, s, Me b), 2.2 (2 H, t, *J*=4.8 Hz, Hc, Hd,), 2.3-2.4 (2 H, m, Hg, Hf), 2.5-2.6 (2 H, m, Hi, Hj), 3.6 (3 H, s, Me c), 4.5 (1 H, t, *J*=3.3 Hz, He). 7.2-7.6 (5H,m)

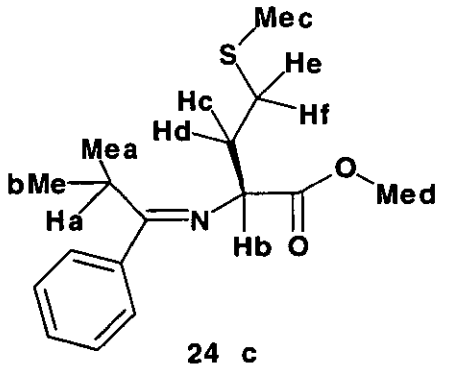
δ_C ($CDCl_3$, 100 MHz) 16.25, 20.51, 20.64, 28.37, 32.89, 39.51, 52.10, 63.62, 126.71, 126.83, 127.02, 127.16 140.89, 172.62.

m/z EI (Found: 293.1530 $C_{16}H_{23}NO_2S$ requires: 293.1528).

R=Ph, R^1=i Pr

(24c) Methyl (2 s)-2-[(z)(methyl-1-phenyl, propylidene amino)]-3-4-methyl thio] butanoate (7.27 g, 73% yield)

[isopropyl-phenyl-imine (5.0 g, 34 mmd), L-methioninemethylest HCl (6.8 g, 34 mmd)]



24 c

ν_{max} 3598, 2961, 2841, 2827, 1635 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.1 (3 H, d, *J*=4.5, Hz, Me a), 1.1(3H,d, *J*=4.6Hz, Me b), 2.1 (3 H, s, Me c), 2.2-2.3 (2 H, m, Hc, Hd,), 2.4-2.41 (2 H, m, He, Hf), 2.6 (1 H, m, Ha), 3.6 (3 H, s, Me d,), 3.91 (1 H, t, *J*=4.7 Hz, Hb), 7.2-7.4 (5 H, m).

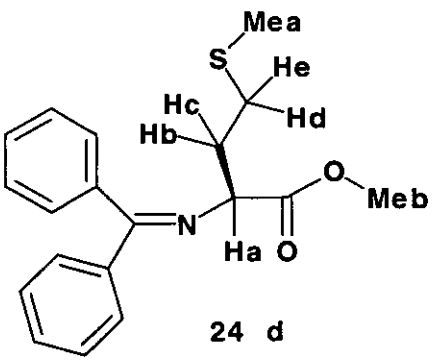
δ_C ($CDCl_3$, 100 MHz) 15.56, 20.14, 20.52, 28.27, 32.79, 39.41, 52.05, 63.43, 126.44, 126.61, 126.92, 129.15, 140.72, 172.48.

m/z EI (Found: 293.1529 $C_{16}H_{23}NO_2S$ requires: 293.1527).

R=Ph, R^1=Ph

(24d) Methyl (2 s)-2-{(diphenyl methylidene) amino 3-4-methyl thiol}butanoate (1.18 g, 72% yield)

[Benzophenoneimine (0.91 g, 5 mmol), L-methioninemethyl ester HCl (0.8 g, 5 mmol)]



24 d

(Found: C 69.72, H 6.51, N 4.19, requires: C 69.72, H 6.42, N 4.28%).

ν_{max} 3610, 2979, 2835, 2822, 1840 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.92 (3 H, s, Me a), 2.15 (2 H, t, *J*=6.7 Hz, Hd, He), 2.45-2.46 (2 H, m, Hc, Hb), 3.61 (3 H, s, Me b), 4.22 (1 H, t, *J*=6.2 Hz, Ha,), 7.1-7.5 (10 H, m).

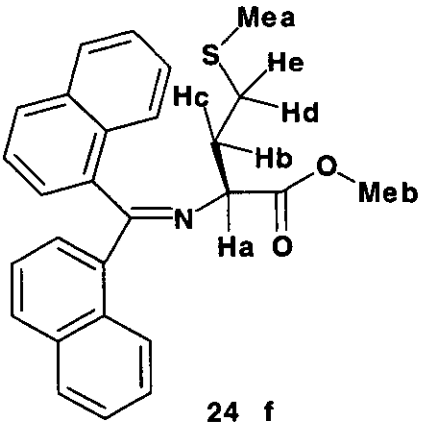
δ_C ($CDCl_3$, 100 MHz) 15.33, 30.54, 33.59, 64.10, 127.82, 128.12, 128.57, 128.77, 130.99, 136.26, 171.23.

m/z EI (Found: 327.1293 $C_{19}H_{21}NO_2S$ requires: 327.1293).

R^1=1- Naph, R=1- Naph

(24f) (2 s)- 2- [(1,t) Dinaphthalene- 2- ylmethylidene] amino- 4- (methyl thiol) butanoate (5.0 g, 52% yield)

[1,1- Dinaphthalene- imine(6.36 g, 22.6 mmd), L- methioninemethylester HCl (4.5 g, 22.6 mmd)]



24 f

ν_{max} 3610, 2979, 2962, 2835, 2822, 1645 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.15 (3 H, s, Me a), 2.26-2.27 (2 H, m, He, Hd), 2.43-2.46 (2 H, m, Hb, Hc), 3.52 (1 H, t, *J*=4.7 Hz, Ha), 3.6 (3 H, s, Me b), 7.1-7.9 (14 H, m).

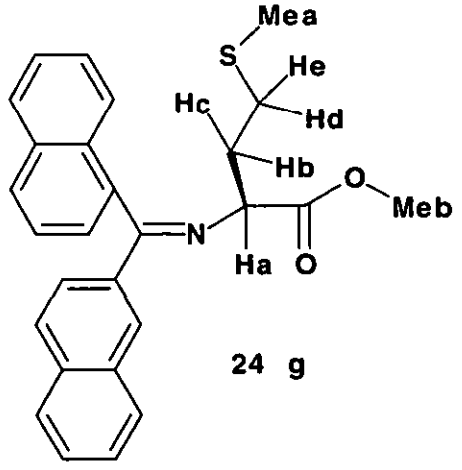
δ_C ($CDCl_3$, 100 MHz) 15.79, 30.89, 34.36, 53.81, 123.21, 125.32, 125.58, 126.19, 127.09, 127.49, 127.56, 128.31, 128.69, 130.29, 133.29, 176.62.

m/z EI (Found: 427.1687 $C_{27}H_{25}NO_2S$ requires: 427.1684).

R=2- Naph, R^1=2- Naph

(24g) (2 s)- 2- [(1,t) Dinaphthalene- 2- ylmethylidene] amino- 4- (methyl thiol) butanoate (7.38 g, 54% yield)

[2,2- Dinaphthalene- imine(9 g, 32 mmd), L- methioninemethylester HCl (6.37 g, 32 mmd)]



24 g

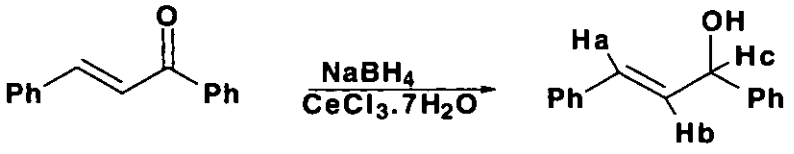
ν_{max} 3615, 2982, 2965, 2880, 2815, 1615 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.17 (3 H, s, Me a), 2.36-2.37 (2 H, m, He, Hd), 2.61-2.62 (2 H, m, Hb, Hc), 3.52 (1 H, t, *J*=4.7 Hz, Ha), 3.6 (3 H, s, Me b), 7.1-7.9 (14 H, m).

δ_C ($CDCl_3$, 100 MHz) 15.28, 25.16, 33.85, 52.08, 53.22, 64.26, 125.03, 125.44, 125.87, 126.22, 126.89, 127.22, 127.59, 128.45, 128.95, 130.54, 143.36, 171.27.

m/z EI (Found: 427.1685 $C_{27}H_{25}NO_2S$ requires: 427.1684).

E-1,3-Diphenyl-3-hydroxy-1-propene



Cerium (III) chloride heptahydrate (19.8 g, 53.2 mmol) was dissolved in methanol (250 ml) and chalcone (10g, 48 mmol) added. The resulting solution was cooled to 0 *°C*. Sodium borohydride (2.0 g, 53.2 mmol) was added to the solution in small portions over a period of 5 minutes such that effervescence was kept to a minimum. The reaction was stirred for a further 3 hours, water (100 ml) added, and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 100 ml), the combined organic extracts dried over magnesium sulphate and the solvent removed to yield an oil which turned to a white solid on standing, this was recrystallized from hexane to give needle-like crystals (9.9 g, 94%) mp 53-55 *°C*.[76]

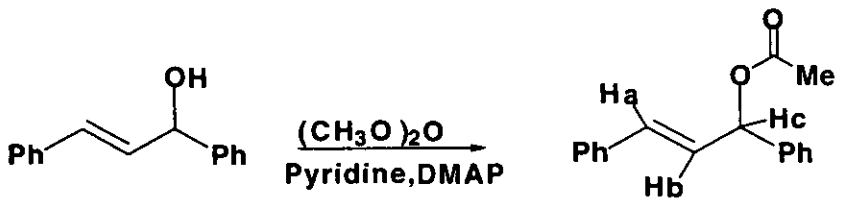
(Found: C 85.62, H 6.75, $C_{15}H_{14}O$ requires: C 85.68, H 6.71%)

ν_{max} (CH_2Cl_2 solution) 3348, 3033, 1501, 1450, 968 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 2.71 (1 H, br, OH), 5.2 (1 H, d, *J*=6.4 Hz, Hc), 6.40 (1 H, dd, *J*=6.4, 16 Hz, Hb), 6.62 (1 H, d, *J*=16.0 Hz, Ha), 7.26-7.52 (10 H, m).

δ_C ($CDCl_3$, 100 MHz), 79.16, 125.25, 126.15, 126.32, 127.52, 128.23, 130.26, 131.62, 136.26, 141.26, 141.37.

E-1,3-Diphenyl-3-acetoxy-1-propane



1, 3-Diphenyl-2-propan-1-ol (0.3 g, 1.43 mmol) was dissolved in DCM (20 ml) and pyridine (0.23 ml, 286 mmol, 2 eq) added. To the resulting clear solution was added 4-dimethylaminopyridine (100 mg, 0.82 mmol) and acetic anhydride (0.15 ml, 1.5 mmol, 1.05 eq), and the reaction was stirred for 3 hours. The mixture was concentrated, diethylether (100 ml) was added, and the solution was washed with aqueous copper sulphate (3 × 30 ml). The organic solutions were extracted and washed with sodium hydrogen carbonate solution (3 × 10 ml). The organic solution was dried over magnesium sulphate and the solvent removed to yield a colourless oil (0.3 g, 83%).[76]

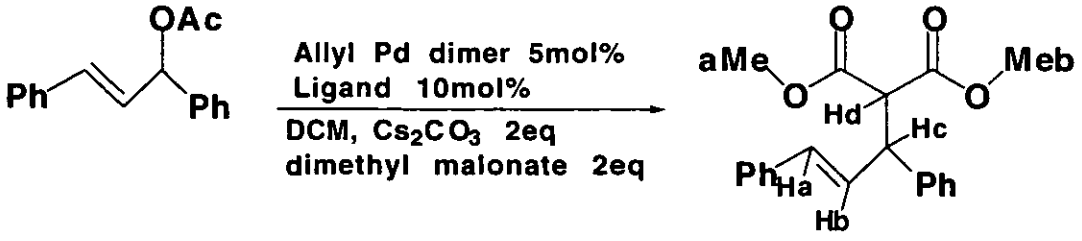
(Found: C 80.90, H 6.41, $C_{17}H_{16}$ 02 requires: C 80.92, H 6.40%)

ν_{max} (neat film) 3029, 1739, 1501, 1375, 1239 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 2.11 (3 H, s, Me), 6.34 (1 H, dd, *J*=16, 7 Hz, Hb), 6.45 (1 H, d, *J*=7.0 Hz, Hc), 6.63 (1 H, d, *J*=16 Hz, Ha), 7.18-7.43 (10 H, m).

δC ($CDCl_3$, 100 MHz), 22.16, 76.72, 127.53, 127.82, 128.26, 129.42, 129.52, 129.73, 133.26, 136.16, 140.26, 171.26.

Dimethyl-2--1,3-diphenyl prop-2-enyl propandioate



Allyl palladium chloride (22 mg, 0.06 mmol, 5% mol) was added to a solution of *anti*-2- (S)- (2-pyridyl)-1,3-dithiane 1-oxide (25 mg, 0.119 mmol, 10%) in DCM (1 ml) was added. The resulting solution was stirred for 30 minutes. 1, 3-Diphenylprop-2-enyl acetate (0.300g, 1.19 mmol) was added as a solution in DCM (5 ml), a catalytic amount of potassium acetate was added, and the resulting solution stirred for a further 30 minutes. Caesium carbonate (0.53 g, 2.38 mmol, 2 eq) and dimethyl malonate (0.31 g, 2.38 mmol, 2 eq) were added and the resulting solution stirred for 24 hours. The solution was filtered through Celite, the solvents removed and the residue purified by column chromatography using 5% ethyl acetate, 95% petroleum ether as eluent to yield the compound as a white solid (0.18 g, 93%), mp 123-124 °C.

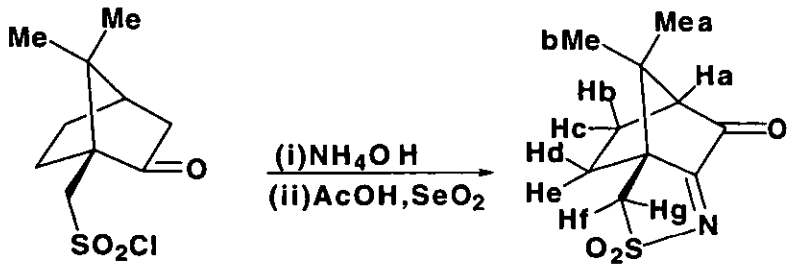
(Found: C 73.59, H 6.18, $C_{20}H_{20}O_4$ requires: C 74.06, H 6.21%).[76]

ν_{max} ($CHCl_3$ solution) 3031, 2965, 1756, 1437 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 3.42 (3 H, s, Me a), 3.65 (3 H, s, Me b,), 4.0 (1 H, d, *J*=16.0 Hz, Hd), 4.21 (1 H, dd, *J*=16 , 8Hz, Hc), 6.31 (1 H, dd, *J*=16, 8 Hz, Hb), 6.95 (1 H, d, *J*=16 Hz, Ha), 7.15-7.30 (10 H, m).

δ_C ($CDCl_3$, 100 MHz), 52.20, 52.50, 57.60, 126.42, 127.16, 127.62, 127.83, 128.82, 129.16, 132.19, 137.27, 140.26, 168.37, 168.26

(-)-(Oxo camphor sulfonyl) imine



Reagent grade ammonium hydroxide (500 ml) was cooled to 0 °C. A solution of (+)-10-Camphorsulphonyl chloride (50 g 199.5 mmol) in DCM (500 ml) was added slowly to the stirred ammonium hydroxide solution. The mixture was stirred at 0 °C for 4 hours and allowed to reach room temperature. The organic layer was removed and the aqueous layer extracted with DCM (3 × 100 ml). The combined organic extracts were dried over magnesium sulphate and evaporated to dryness to yield the crude (+)-(1S)-10-camphorsuphonamide (35g, 76%), which was judged sufficiently pure for use in the preparation of (-)-(oxocamphorsulphonyl) imine.

The crude (+)-(1S)-camphorsulphonamide was added slowly to acetic acid (750 ml) and selenium dioxide (25 g, 225 mmol) at 0° in a 3 l flask. The reaction was heated to reflux overnight. The reaction was allowed to cool and filtered to remove the precipitated selenium. Water (250 ml) was added to the filtrate in a separating funnel, and the organic layer separated. The aqueous layer was extracted with DCM (3 × 125 ml) and the combined organic extracts dried over magnesium sulphate. Evaporation to dryness under reduced pressure yielded the crude product which was subsequently recrystallized from chloroform to yield the pure material as pale yellow crystals (23 g, 52%), mp 197-199 *°C*.[75]

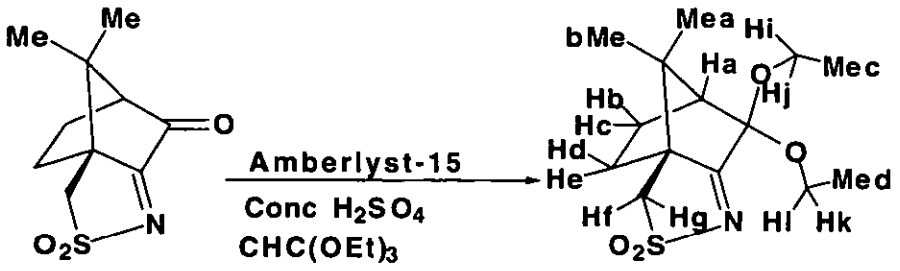
(Found: C, 52.90; H, 5.68; N, 6.30 C_{10} H_{13} NO_3S. requires: C, 52.86, H, 5.73, N, 6.18%). $[\alpha]_D$ = −179° (CCl_4, 10 mg/ml).

ν_{max} (slurry) 2957, 1772, 1359, 1169 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.99 (3 H, Me a, s, Me a), 1.17 (3 H, s, Me b), 1.8 – 2.1 (2 H, m, Hd, He), 2.2 – 2.4 (2 H, m, Hb, Hc,), 2.78 (1 H, d, *J*=5.0 Hz,Ha), 3.24 (1 H, d, *J*=13.6 Hz, Hf), 3.45 (1 H, d, *J*=13.6 Hz, Hg).

δ_C ($CDCl_3$, 100 MHz) 18.25, 20.14, 22.26, 27.95, 44.67, 50.67, 60.03, 62.95, 181.7, 198.26.

(+)-[(8,8-Diethoxy camphoryl)sulfonyl] imine



(–)–(Oxocamphorsulphonyl)imine (2.0 g, 9 mmol) was dissolved in dry ethanol (60 ml). To this was added triethyl orthoformate (6.5 g, 7.3 ml, 43.95 mmol, 5 eq), concentrated hydrochloric acid (1 ml) and amberylst-15 ion exchange resin (1.0 g), and the reaction heated to reflux. After refluxing overnight, the reaction was allowed to cool to room temperature, water (30 ml) added and the organic layer separated. The aqueous layer was extracted with DCM (3 × 100 ml), the combined organic extract dried over magnesium sulphate, and the solvent removed. Recrystallization of the crude solid from methanol-water (1:2) gave the title material as a white crystalline solid (2.5 g, 65%), mp 144-146 °C.

(Found: C 55.92; H 7.72, N 4.72, $C_{14}H_{23}NO_4S$. requires: C 55.79, H 7.71, N 9.65%).

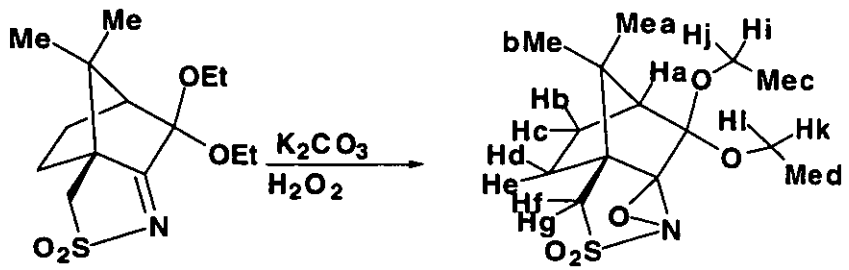
ν_{max} (CH_3Cl_2 solution) 1662, 1345, 1169 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.03 (3 H, s, Me a), 1.08 (3 H, s, Me b), 1.21 (3 H, t, *J*=7.0 Hz, Me c), 1.23 (3 H, t, *J*=7.0 Hz, Me d), 1.76 – 2.05 (4 H, , m,Hb, Hc, Hd, He), 2.1 (1H, d, *J*=5.0 Hz,Ha), 2.81 (1 H, d, *J*=13.5 Hz, He), 2.82 (1 H, d, *J*=13.5 Hz, Hj), 2.87 (2 H,q, *J*=7.0 Hz, Hh, Hi), 2.90 (2 H, q, *J*=7.2 Hz, Hj,

Hk).

δ_C ($CDCl_3$, 100 MHz) 14.80, 15.12, 20.82, 20.91, 20.99, 29.56, 46.28, 49.15, 53.02, 58.73, 58.92, 64.53, 103.26.

(+) -[8,8 -Diethoxy camphoryl sulphonyl] oxaziridine



Commercial aqueous hydrogen peroxide (0.6 ml, 5.12 mmol, 30% eq w/v) was added to a stirred suspension of potassium carbonate (0.37 g, 2.7 mmol) in methanol (15 ml) at room temperature. (+(-[(8,8-Diethoxycamphoryl) sulphonyl] imine (0.35 g, 1.16 mmol) was added, and the reaction allowed to stir at room temperature for 8 hours. After this time, saturated brine (20 ml) and DCM (20 ml) was added and the organic later separated. The aqueous layer was extracted with DCM (2 × 20 ml) and the combined organic extracts washed with aqueous sodium sulphite solution (20 ml, 5% w/v) and dried over magnesium sulphate. Removal of the solvent with a bath temperature below 40 °C, followed by recrystallization from methanol furnished the title compound as a colourless crystalline solid (0.24 g, 65%), mp 117-119°C.

(Found: C 52.78, H 7.24, N 4.49. requires: C 52.80, H 7.16, N 4.39%).

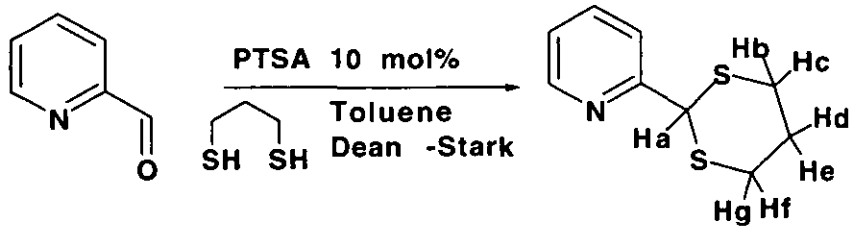
ν_{max} (slurry) 1370, 1162, 1069 cm^{-1}.

δ_H ($CDCl_3$ 250 MHz) 1.04 (3 H, s, Me a,), 1.24 (3 H, t, *J*=6.0 Hz, Me c), 1.34 (3

H, s, Me b), 1.42 (3 H, t, *J*=6.2 Hz, Me d,), 1.78-1.98 (4 H, m, Hb, Hc, Hd, He), 3.10 (1 H, d, *J*=14.0 Hz,Ha), 3.29 (1 H, d, *J*=14.0 Hz, Hf), 3.43 (1 H, d, *J*=14.0 Hz, Hq), 3.55 (1 H, Hi, Hj, q, *J*=7.0 Hz), 3.65 (2 H, Hk, Hl, q, *J*=7.2 Hz).

δ_C ($CDCl_3$ 100 MHz) 14.95, 15.20, 20.70, 21.80, 28.30, 45.33, 47.65, 53.50, 54.65, 58.50, 59.10, 97.90, 102.52.

2-(2-Pyridyl)-1,3-dithiane



Distilled pyridine-2-carboxaldehyde (2.38 g, 22.2 mmol) and 1,3-propanedithiol (2.48 g, 23.15 mmol, 1.05 eq) were dissolved in toluene (100 ml), and p-toluene sulphonic acid (0.25 g) was added. The mixture was heated to reflux for 48 hours with a Dean-Stark trap attached, then allowed to cool to room temperature. The mixture was washed with 1.0 M sodium hydroxide (2 × 25 ml) and the organic portion extracted and dried over magnesium sulphate. The solvent was removed and the residue subjected to flash column chromatography with gradient elution from 10% ethyl acetate to 30% ethyl acetate in petroleum ether, to yield the title compound as a pale yellow oil (2.9 g, 66%). [75]

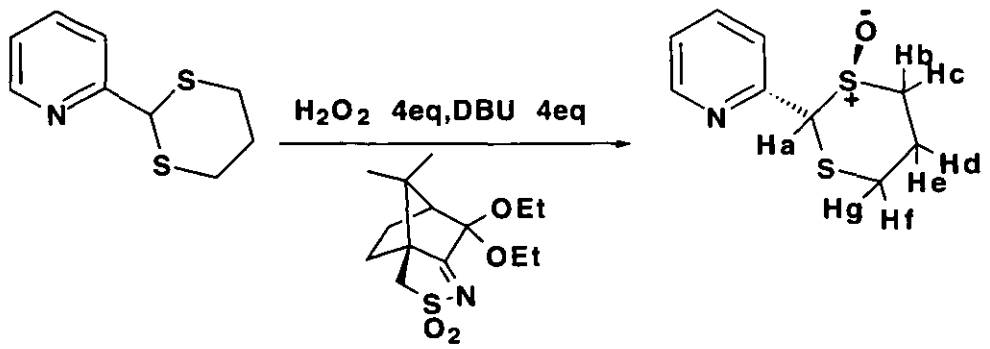
(Found: C 54.82, H 5.58, N 7.17, $C_9H_{11}NS_2$ requires: C 54.79, H 5.62, N 7.10%).

ν_{max} (neat) 2902, 1469, 1432, 1221, 1049 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.8-2.26 (2 H, m, Hd, He), 2.9-3.15 (4 H, m, Hb, Hc, Hf, Hg), 5.36 (1 H, s, Ha), 7.18-7.72 (3 H, m), 8.45-8.60 (1 H, m).

δ_C ($CDCl_3$, 100 MHz) 25.37, 31.26, 53.26, 53.65, 121.62, 123.46, 137.62, 150.27, 157.52.

Anti-2-(2-Pyridyl)-1,3 dithiane 1-(*S*)-oxide



DCM (30 ml) was cooled to –20 °C and 30% aqueous hydrogen peroxide (0.94 ml 8.12 mmol, 4 eq) added, followed by diazabicycloundec-7-ene (DBU) (1.27 g, 8.12 mmol, 4 eq). After five minutes (+)-[8,8-(Diethoxycamphoryl)] sulfonylimine (0.67 g, 2.23 mmol, 1.1 eq) was added and the solution stirred for 20 minutes. 2-(2-Pyridyl)-1,3-dithiane (0.4 g, 2.03 mmol, 1 eq) was added as a solution in DCM (5 ml) dropwise over 5 minutes. The reaction was allowed to stir for 3 hours, then quenched by the addition of saturated aqueous sodium sulfide solution (10 ml) and allowed to reach room temperature. The organic layer was separated and the aqueous layer extracted with DCM (3 × 50 ml). The combined organic extracts were washed with 0.1 M hydrochloric acid and the acid washings extracted with DCM (2 × 30 ml). The combined organic extracts were dried over magnesium sulphate and evaporated. The residue was subjected to flash chromatography with gradient elution from 100% DCM to 2% methanol in DCM to yield first (+)-[(8,8-diethoxycamphoryl) sulphonylimine (0.55 g, 82%) and the title material (0.4 g, 92%) as a white solid mp 123-126 °C

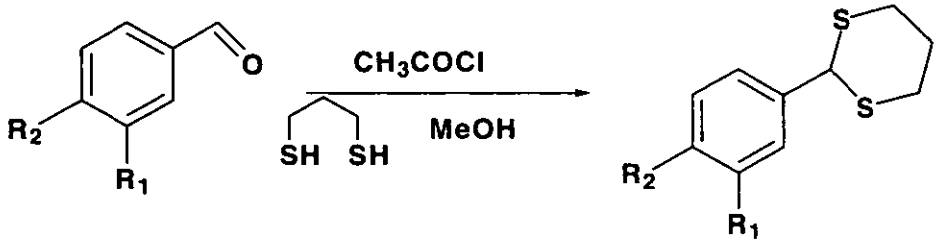
(Found: C 50.59, H 5.2, N 6.53, $C_9H_{11}NOS_2$ requires: C 50.68, H 5.20, N 6.57%). $[\alpha]_D = 54$ (CCl_4, 10 mg/ml). ee 98%.

ν_{max} (slurry), 3050, 1586, 1434, 1035 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 2.20-2.89 (5 H, m), 3.6-3.75 (1 H, m), 4.75 (1 H,Ha, s, Ha), 7.26-7.72 (3 H, m), 8.6 (1 H, d, J=5 Hz).

Absolute stereochemistry confirmed by X-ray as *trans* (Andrew Lund thesis)[75]

Synthesis of 1,3-Dithianes from Para and Meta Nitro Substituted Benzaldehyde



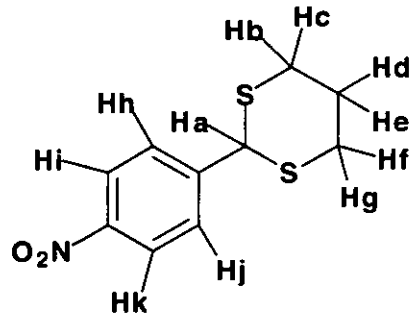
R1=H,R2=NO_2 61a
R1=NO2,R2=H 61b

Propane -1, 3-dithiol (1.1 eq) was added at 0 °C to a stirred solution of the aldehyde. The solution was stirred for two minutes and acetyl chloride (10 ml) added. After stirring overnight, the solution was evaporated and the residue recrystallized from methanol to yield the required compound. [76a]

R_2=NO_2 R_1=H

2-(4-Nitrophenyl)-1,3-dithiane (5.91 g, 93%)

(paranitrobenzaldehyde (4.0 g, 26.5 mmol), propane 1,3-dithiol (3.15 g, 29.15 mmol)



61a

(Found: C 49.58, H 4.51, N 5.71, $C_{10}H_{11}NO_2S_2$ requires: C 49.79, H 4.56, N 5.30%). mp 120-122 °C

ν_{max} (slurry) 2935, 1451, 1392, 1276 cm^{-1}.

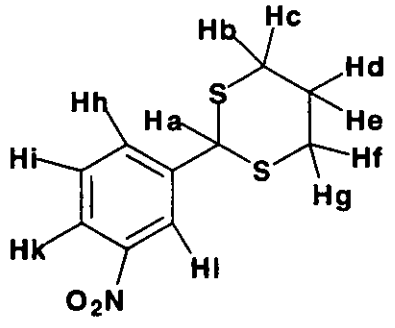
δ_H ($CDCl_3$, 250 MHz), 2.0 (2 H, m, Hf, Hg), 2.72 (4 H, m, Ha, Hb, Hf, Hg), 5.22 (1 H, s), 7.4-7.5 (2 H, m, Hl, Hj), 8.2-8.9 (2 H, m, Hi, Hk).

δ_C ($CDCl_3$, 100 MHz) 24.76, 31.76, 50.37, 123.94, 128.01, 140.13, 147.61.

R_1=NO_2 R_2=H

2-(3-Nitrophenyl)-1,3-dithiane (5.8 g, 91%)

(metanitrobenzaldehyde (4.0 g, 26.5 mmd), propane1,3-dithid (3.15 g, 29.15 mmd)



61 b

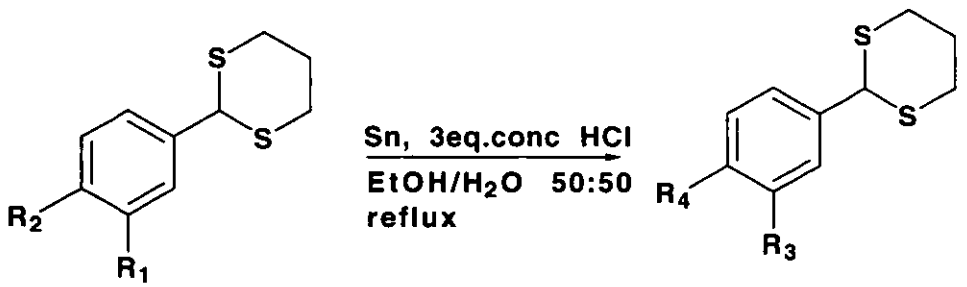
(Found: C 50.13, H 4.55, N 5.78, $C_{10}H_{11}NO_2S_2$ requires: C 49.79, H 4.56, N 5.80%). mp 146-148 °C.

ν_{max} (solution DCM) 2942, 1462, 1341, 1281 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 2.0-2.7 (1 H,m, Hb, Hc), 3.16-3.20 (4 H, m, Hd, He, Hf, Hg), 5.22 (1 H,s, Ha), 7.50-7.52 (1 H, m, Hh, Hi), 7.92-7.93 (1 H, m, Hk), 8.30-8.36 (1 H, m, Hl).

δ_C ($CDCl_3$, 100 MHz) 25.01, 31.21, 51.26, 122.31, 131.26, 135.41, 141.27, 149.62.

Synthesis of Benzaldehyde Amine Derivatives from the Corresponding Nitro



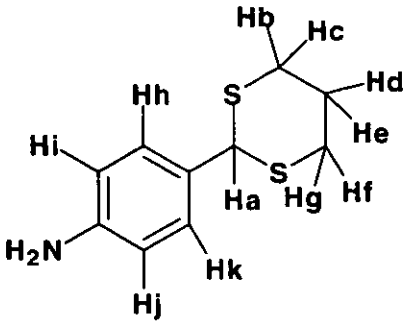
61a,61b **61c,61d**

To a stirred mixture of (25a) or (25b) in a mixture of 50:50 ethanol and water, tin (3 eq) was added and the resulting mixture stirred for 10 minutes. Concentrated HCl (7 ml) was added, and the resulting mixture heated under reflux overnight. After cooling, sodium hydroxide pellets were added until the solution was basic. The mixture was separated and the aqueous later extracted with DCM (3 × 30 ml). The combined organic solutions were dried over magnesium sulphate. The solvent was removed and residue purified by column chromatography in petrol 80% ethyl acetate 20%, to yield the desired compound as a yellow solid.

R_4=NH_2 R_3=H

2- (4- Aminophenyl) - 1,3- dithiane (1.7 g, 87%)

(p- nitro- 1,3 dithiane(2.0 g, 8.3 mmd) , Sn (28 g, 23.17 mmd)



61 c

(Found: C 56.81, H 6.18, N 6.44, $C_{10}H_{13}NS_2$ requires: C 56.87, H 6.13, N 6.6%). mp 142-144 *°C*.

ν_{max} (slurry) 3456, 2986, 1595, 1491, 1392 cm^{-1}.

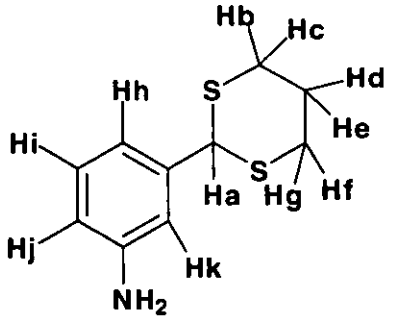
δ_H ($CDCl_3$, 250 MHz), 2.0-2.05 (2 H, m, Hd, He), 2.83-2.85 (4 H, m, Hb, Hc,Hf,Hg), 3.43 (2 H, br, NH_2), 5.22 (1 H, s, Ha), 6.8 (2 H, d, *J*=6.95 Hz, Hk, Hj), 7.36 (2 H, d, *J*=6.65 Hz, Hh, Hi).

δ_C ($CDCl_3$, 100 MHz) 25.23, 32.14, 51.26, 115.72, 127.76,128.35, 146.32.

R_4=H, R_3=NH_2

2-(3-Aminophenyl)-1,3-dithiane (1.7 g, 97%)

(3-nitro-1,3 dthiane(2.0 g, 8.3 mmd), Sn (2.5 g, 23.17 mmd)



61d

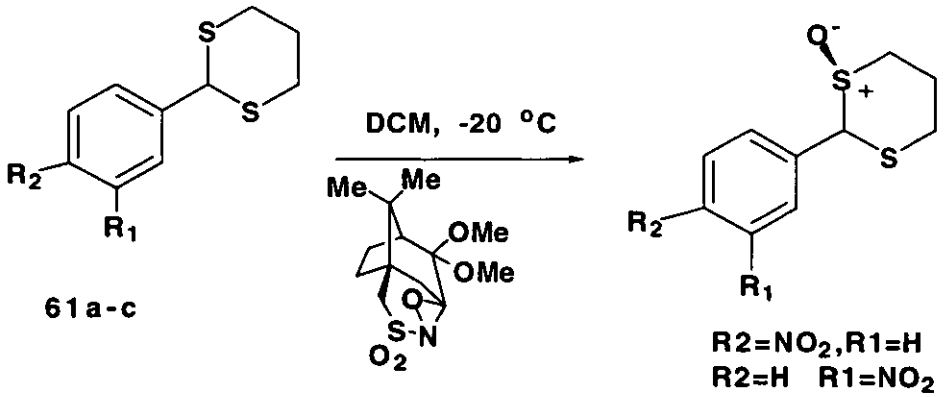
(Found: C 56.73, H 5.99, N 6.41, $C_{10}H_{13}NS_2$ requires: C 50.87, H 6.13, N 6.6%). mp 138-140 °C.

ν_{max} (slurry) 3492, 2965, 1592, 1497, 1398 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 2.1 (2 H, Hd, He, m), 3.26-3.29 (4 H, Hb, Hc, Hf, Hg, m), 3.52 (2 H, br, NH_2), 5.16 (1 H, s, Ha), 6.52-6.54 (1 H, Hh, m), 6.81-6.83 (1 H, Hi, m), 7.16-7.18 (1 H, Hj, m), 7.3 (1 H, Hk, s).

δ_C ($CDCl_3$, 100 MHz) 29.25, 32.14, 51.26, 114.25, 115.62, 118.15, 130.25, 140.25, 149.29

Synthesis of 1,3-Dithiane oxides from corresponding NO_2 and NH_2 derivatives



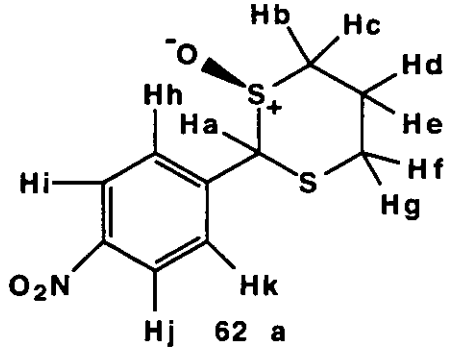
R2=NO_2,R1=H 62a
R2=H R1=NO_2 62b
R2=NH_2,R1=H 62c
R2=H, R1=NH_2 62d

To a stirred solution of (25a-b) or (26a-b) in DCM, (+)-[(8, 8-dimethoxy camphoryl) sulphonyl oxaziridine (1.1 eq) was added at –20 °C and the resulting solution stirred for 24 hours. The solution was concentrated and the residue chromatographed in 10% petrol 90% ethyl acetate as eluent to yield the sulfoxide.

R_2=NO_2 - R_1=H

2-(4-Nitrophenyl)-1,3-dithiane 1-oxide (0.26 g, 82%)

(25a(0.3 g, 1.24 mmd), oxaziridne(0.4 g, 1.37 mmd))



62 a

(Found: C 46.69, H 4.28, N 5.45, $C_{10}H_{11}NO_3S_2$ requires: C 46.69, H 4.22, N

5.39%). mp 145-147 °C.

ν_{max} (slurry) 2985, 1591, 1492, 1392, 1195 cm^{-1}.

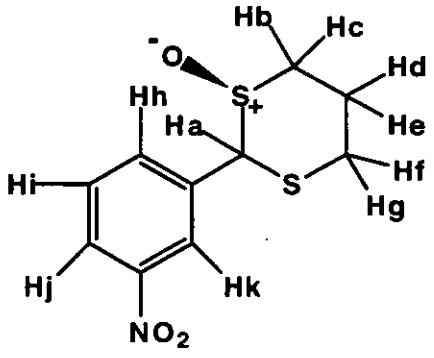
δ_H ($CDCl_3$, 250 MHz), 2.51-2.6 (2 H, m, Hd, He), 2.72-3.65 (2 H, m, Hf Hg), 3.7-4.4(2H, m, Hb, Hc), 4.62 (1 H, s, Ha), 7.5 (2 H, d, *J*=8.0 Hz, Hh, Hk), 8.2 (2 H, d, *J*=8.0 Hz, Hi, Hj).

δ_C ($CDCl_3$, 100 MHz) 29.01, 31.06, 55.12, 70.25, 125.21, 129.32, 140.15, 148.32.

R_1=NO_2 R_2=H

2-(3-Nitrophenyl)-1,3-dithiane-1-oxide (0.31 g 97%)

(26b(0.3 g 1.24 mmd), oxaziridne(0.4 g 1.37 mmd))



62e

(Found: C 46.55, H 4.19, N 5.38, $C_{10}H_{11}NO_3S_2$ requires: C 46.69, H 4.28, N 5.45%). mp 166-168 °C.

ν_{max} 2979, 1598, 1496, 1393, 1196 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 2.51-2.58 (2 H, m, Hd, He), 2.73-3.65 (2 H, m, Hf, Hg), 3,72-4.62 (2H, m, Hb, Hc), 4.82 (1 H, s, Ha), 7.52-7.55 (1 H, m, Hi), 7.8 (1

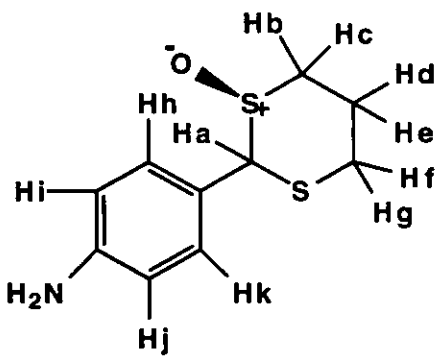
H, d, J=8.0 Hz, Hn), 8.2 (1 H, d, J=8.0 Hz, Hj), 8.7 (1 H, s, Hk).

δ_C ($CDCl_3$, 100 MHz) 29.21, 31.25, 59.32, 69.25, 124.25, 125.32, 136.25, 148.35.

R_2=NH_2 R_1=H

2-(4-Aminophenyl)-1,3-dithiane-1-oxide (0.2 g, 92%)

(26a(0.21 g, 0.96 mmd), oxaziridine(0.39 g, 1.34 mmd))



62b

(Found: C 52.89, H 5.71, N 5.98, $C_{10}H_{13}NS_2O$ requires: C 52.86, H 5.72, N 6.17% mp 132-134 °C. ν_{max} 3425, 2985, 1586, 1496, 1398, 1176 cm^{-1}.

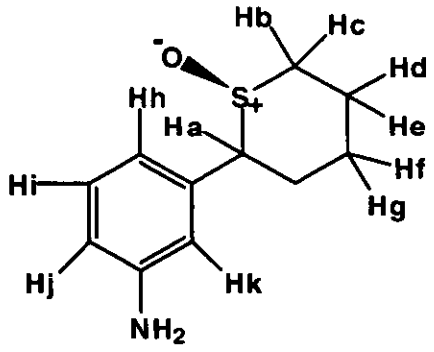
δ_H ($CDCl_3$, 250 MHz), 2.52-2.55 (2 H, m, Hd, He), 2.73-3.52 (4 H, m, Hb, Hc, Hf,Hg), 3.75 (2 H, br, NH_2), 4.62 (1 H, s, Ha), 6.52 (2 H, d, J=8.0 Hz, Hh, Hk), 7.44 (2 H, d, J=8.2 Hz, Hi, Hj).

δ_C ($CDCl_3$, 100 MHz) 29.21, 31.25, 55.16, 69.27, 115.26, 122.35, 129.27, 147.25.

R_1=H R_1=NH_2

2-(3-Aminophenyl)-1,3-dithiane-1-oxide (0.24 g, 93%)

(26b (0.24g, 1.1 mmd), oxaziridne (0.35 g, 1.21 mmd))



62 f

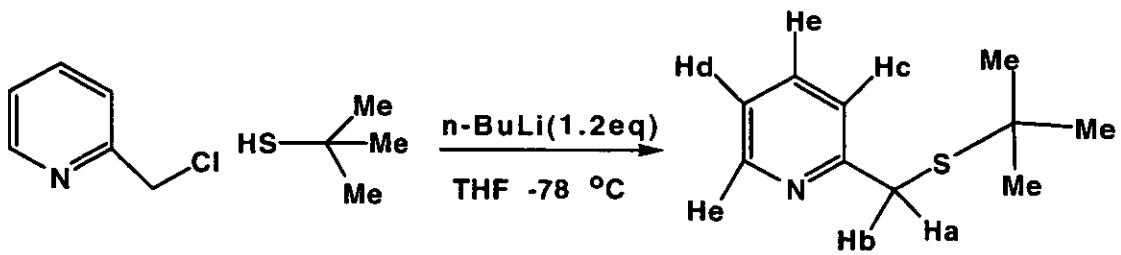
(Found: C 52.92, H 5.76, N 5.94, $C_{10}H_{13}NS_2O$ requires: C 52.86, H 5.72, N 6.17%). mp 159-165 °C.

ν_{max} 3435, 2976, 1572, 1496, 1392, 1162 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 2.32-2.34 (2 H, m, Hd, He), 2.43-2.63 (4 H, m, Hb, Hc, Hf,Hg), 3.62 (2 H, br, NH_2), 4.85 (1 H, s, Ha), 6.92-6.96 (2 H, m, Hi), 7.25-7.28 (2 H, m, Hh, Hj), 7.8 (1 H,s, Hk).

δ_C ($CDCl_3$, 100 MHz) 29.36, 32.15, 56.25, 69.76, 116.26, 122.75, 131.25, 148.25.

2-{[1,1-Dimethylthio]methyl}pyridine



2-Methyl-2-propanthiol (2.0 g, 22.2 mmol) was dissolved in dry THF (15 ml) and the solution was cooled to –78 *°C*. *N*-butyllithium (19.4 ml, 31.04 mmol) was added slowly, and the resulting mixture left to stir for one hour. Purified 2-chloromethyl pyridine (3.6 g, 22 mmol) was added dropwise at –78 *°C*. The resulting mixture left to stir for 3 hours. Water (30 ml) was added and the organic solution extracted with DCM (2 × 40 ml). The solvent was removed and the residue chromatographed in petrol ethyl acetate 70/30 as eluent to yield the required compound (2.3 g, 58%).

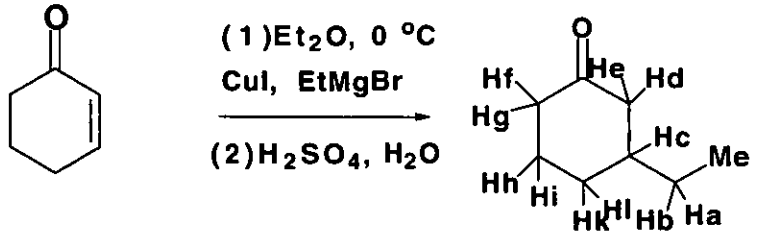
(Found: C 66.10, H 7.87, N 7.20, $C_{10}H_{15}NS$ requires: C 66.29, H 8.29, N 7.73%). mp 159-165 *°C*.

ν_{max} (neat) 2960, 2898, 1590, 1568, 1475, 1459 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.43 (9 H, s, Me), 3.9 (2 H, s, Hb), 7.1-7.16 (7 H, m, He), 7.4-7.42 (1 H, m, Hc), 7.6-7.65 (1 H, m, Hd,), 8.5-8.53 (1 H, Hf, m, Hf).

δ_C ($CDCl_3$, 100 MHz) 8.24, 26.32 53.35,126.32, 139.35,139.64,140.21, 149.26.

3 -Ethyl cyclohexan -1 -one



Ethyl magnesium chloride in diethyl ether 1M (20 ml) was added to copper iodide (0.52 g, 2.93 mmol) under nitrogen and the resulting mixture stirred for 15 minutes at 0° C. Cyclohex-2-enone (1.9 g, 20.75 mmol) was added and the mixture stirred for 50 minutes. The mixture was added to ice cold 10% sulfuric acid, and left to stir for 30 minutes. The mixture was extracted with diethyl ether (3 × 30 ml), and the organic solution dried over magnesium sulfate. The organic solution was evaporated to dryness and the resulting yellow oil distilled under a pressure of 0.43 m bar to yield the product as a colourless oil (1.1 g, 42%).

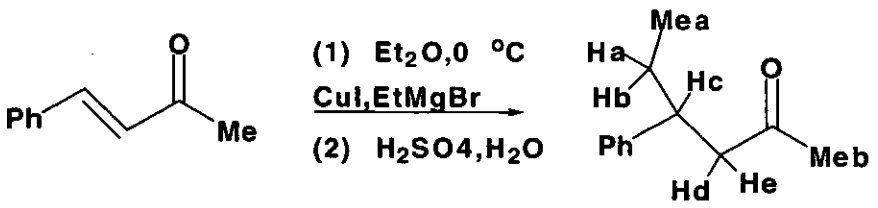
ν_{max} 3506, 2935, 1712, 1454, 1313, 1226 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 0.82 (3 H, , J=7.4 Hz, Me), 1.26-1.28 (4 H, m, Hh, Hi, Hj, Hk), 1.65-1.66 (2 H, m, Hb), 2.16-2.18 (3 H, m, Hc, He, Hd), 2.7.2.73 (4 H, m, Hd, He, Hf, Hg,).

δ_C ($CDCl_3$, 100 MHz) 11.12, 23.52, 25.39, 25.45, 20.23, 35.97, 38.15, 211.15

m/z EI (Found: 126.1041 $C_8H_{14}O$ requires: 126.1044).

4-Phenyl-hexan-2-one



Copper iodide (0.25 g, 1.3 mmol) was suspended in diethyl ether (30 ml) and cooled to 0 °C. Ethyl magnesium bromide 1M (9 ml, 8.2 mmol) was added and the reaction stirred for 15 minutes. *Trans*-4-phenylbut-3-en-2-one (1.5 g, 7.1 mmol) was added and the resulting solution stirred overnight. The reaction mixture was added to a mixture of ice cooled water (100 ml) and 10% sulphuric acid (30 ml) and stirred for 2 hours. The mixture was extracted with diethyl ether (3 × 30 ml), the solvent removed and the crude product chromatographed over silica in 9:1 petroleum ether ethylacetate to yield the required product (1.2 g, 95%).

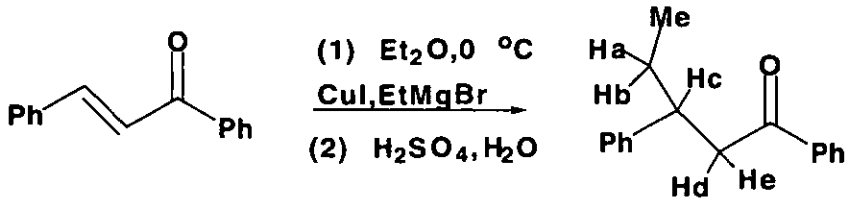
ν_{max} (neat) 2963, 1716, 1495, 1412m 1356, 1163 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.73 (3 H, t, *J*=7.6 Hz, Me a), 1.62-1.63 (2 H, m, Hb), 2.0 (3 H, s, Me b), 2.62-2.64 (2 H, m, He, Hd,), 3.16-3.18 (1 H, m, Hc).

δ_C ($CDCl_3$, 100 MHz) 11.95, 29.34, 30.47, 42.42, 50.42, 126.30, 127.53, 128.37, 128.41, 207.59.

m/z FAB (Found 177.1239, (M^++1) $C_{12}H_{17}O$, requires 177.1201).

1,3 -Diphenylpentan -1 -one



Copper iodide (0.25 g, 1.3 mmol) was suspended in diethyl ether (30 ml) and the mixture cooled to 0 *°C*. Ethylmagnesium bromide 1.0M (9 ml, 8.2 mmol) was added and the reaction was stirred for 15 minutes. Chalcone (1.5 g, 7.1 mmol) was added and the resulting solution stirred overnight. The reaction mixture was added to a mixture of ice cooled water (100 ml) and 10% sulphuric acid (30 ml), and stirred for 2 hours. The mixture was extracted with diethyl ether (3 × 30 ml), the solvent removed and chromatographed over silica in 9:1 petroleum ether ethylacetate to yield the product (1.60 g, 95%).

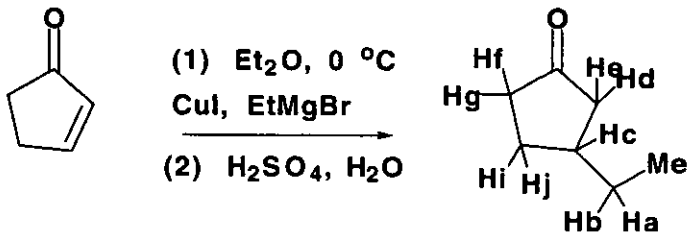
ν_{max} (neat) 2955, 1680, 1600, 1448, 1408 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.75 (1 H , m, Hc), 0.82 (3 H, t, *J*=7.4 Hz, Me), 1.63-1.64 (2 H,m, Hb), 3.16-3.18 (2 H, m, Hd, He), 7.2-7.9 (10 H, m).

δ_C ($CDCl_3$, 100 MHz) 11.81, 29.09, 36.11, 41.39, 125.64, 126.64, 126.28, 127.97, 128.26, 128.42, 137.33, 144.70, 199.15.

m/z FAB (Found 239.1430, $(M^+ + 1)$ $C_{17}H_{19}O$, requires 239.1435).

3-Ethyl cyclopentan-1-one



Copper iodide (0.25 g, 1.3 mmol) was suspended in diethyl ether (30 ml) and cooled to 0 °C. Ethylmagnesium bromide 1M (9 ml, 8.2 mmol) was added and the reaction was stirred for 15 minutes. Cyclopenten-2-enone (1.5 g, 7.1 mmol) was added and the resulting solution stirred overnight. The reaction mixture was added to a mixture of ice cooled water (100 ml) and 10% sulphuric acid (30 ml) and stirred for 2 hours. The mixture was extracted with diethyl ether (3 × 30 ml), the solvent removed and the crude product chromatographed over silica in 9:1 petroleum ether ethylacetate to yield the required product (0.73 g, 95%).

ν_{max} 1675, 1435, 1406, 1321, 1198 cm^{-1}.

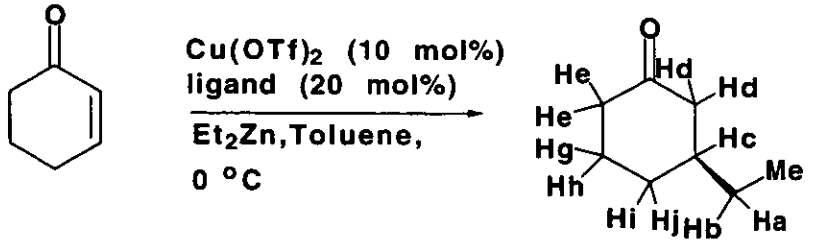
δ_H ($CDCl_3$, 250 MHz) 0.83 (2 H,q, *J*=6.4 Hz, Hb), 0.92 (3 H, t, *J*=6.4 Hz,Me), 1.25-1.26 (1 H, m, Hc), 1.62-1.65 (2 H,m, Hh, Hi), 2.16-2.20 (4 H, m, Hd, He,Hf, Hg).

δ_C ($CDCl_3$, 100 MHz) 12.53, 28.54, 28.91, 38.55, 38.95, 41.52, 219.99.

m/z EI (Found 112.0885, $C_7H_{12}O$, requires 112.0888).

General procedure for conjugate addition of diethyl zinc to cyclohexenone

(S)-3-Ethyl-cyclohexanone



To a stirred solution of copper triflate (0.0045 g, 12 mmol, 10 mol %) and chiral ligand (20 mol %) at 0 °C in toluene, enone (0.097 g,1.1mmol,1eq) and diethylzinc (3ml, 3 eq) were added sequentially. The resulting solution was stirred for 2 hours, then poured into 1 M HCl (20 ml), and the mixture extracted with ethyl acetate (3 × 40 ml). The organic layer was dried over magnesium sulfate and the solvent removed to leave the required product as a yellow oil, which was purified by chromatography to yield the title compound as a colourless oil.

ν_{max} 3506, 2935, 1712, 1454, 1313, 1226 cm^{-1}.

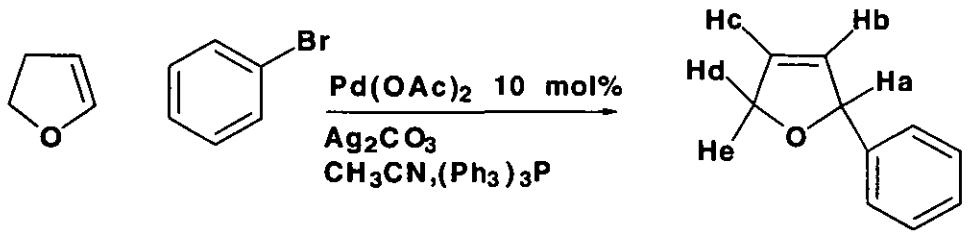
δ_H ($CDCl_3$, 250 MHz) 0.86 (3 H, t, *J*=7.4 Hz, Me), 1.26-1.29 (2 H,m, Hb, Ha), 1.61-1.63 (2 H, m, Hj, Hi), 2.16 (1 H, m, Hc), 2.26-2.30 (6 H, m, Hd, He, Hg).

δ_C ($CDCl_3$, 100 MHz) 11.12, 23.52, 25.45, 26.33, 35.97, 38.15, 211.10.

m/z EI (Found: 126.1041, $C_8H_{14}O$, requires: 126.1044).

$[\alpha]_D$ = 69° (CCl_4, 10 mg/ml).

2 -Phenyl 2,5 - dihydrofuran



Bromobenzene (79 mg, 0.5 mmol), 2,3 -dihydrofuran (175 mg, 2.5 mmol), Pd $(OAc)_2$ (30 mg, 5 mol %), triphenylphosphine (20 mg, 15 mol %) and silver carbonate (300 mg, 1.78 mmol), were added to acetonitrile (25 ml) and the reaction heated at 80 °C for 3 days. The solvent was removed and the residue chromatographed in ethyl acetate to yield the product as a pale yellow oil (0.05 g, 68%).

ν_{max} neat 2100, 1550, 1200, 1100 cm^{-1}.

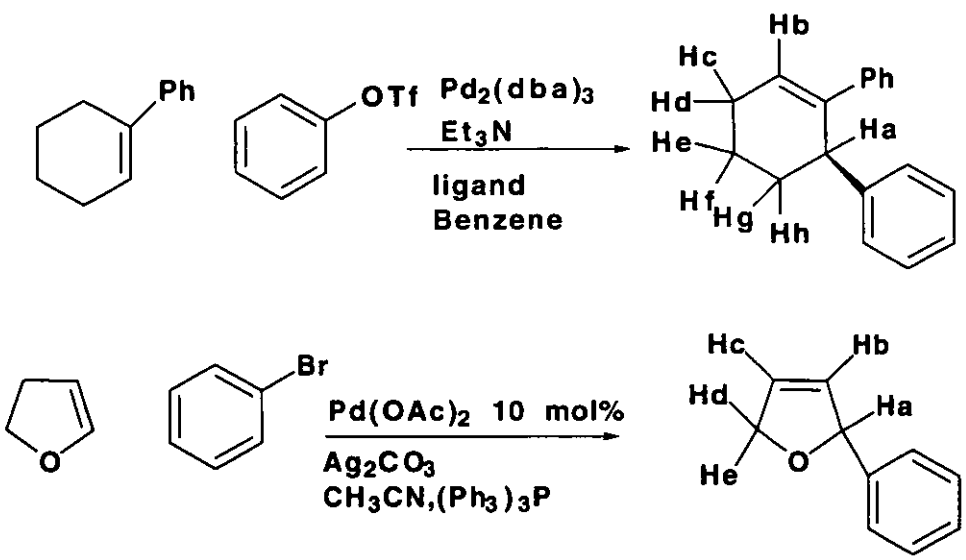
δ_H ($CDCl_3$, 250 MHz) 4.4-4.6 (2 H, m, Hc, Hb), 5.6-5.8 (2 H, m, Hd, He), 5.6 (1 H, d, J=4.8 Hz,Ha), 7.5-7.8 (5 H, m).

δ_C($CDCl_3$,100MHz),67.68,100.43,103.15,118.51,128.03,128.35,129.45,

130.55

m/z EI (Found 146.0731, $C_{10}H_{10}O$, requires 146.0731).

General Procedure for the Asymmetric Heck Reaction



To a stirred solution of Pd2 $(dba)_3$ (10 mmol%), benzene (30 ml) and triethylamine (10 ml) were added and the mixture stirred for 10 minutes, then the ligand (20% mmol) was added and the mixture heated at 40 °C for 2 hours.

Phenyltriflate (1 eq) and alkene (5 eq) were added and the mixture heated to 40°C for 3 days. The solvent was removed and the residue chromatographed in 7:3 mixture of ethyl acetate-petroleum ether to yield the product (60 mg, 70%).

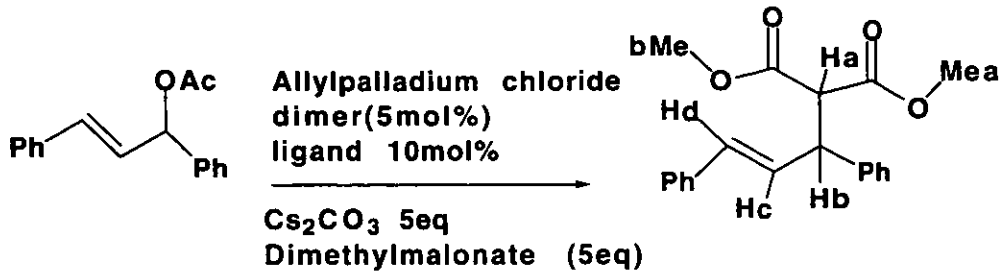
ν_{max} 2800, 2750, 2250, 1100, 1050 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 1.52 (1 H, t, *J*=10.3 Hz, Ha), 1.63-1.64 (2 H, m, Hf, Hg,), 1.72-1.73 (2 H, m, Hf, He), 2.26-2.18 (2 H, m, Hc, Hd), 6.16 (1 H, d, *J*=2.4 Hz,Hb,), 7.2-7.4 (10 H, m).

δ_C ($CDCl_3$, 100 MHz) 22.18, 22.43, 22.86, 24.86, 121.35, 124.76, 124.96, 125.46, 128.39, 128.41, 128.75, 128.86, 142.71, 143.33.

m/z EI (Found 234.1411, $C_{18}H_{18}O$, requires 234.1408).

General procedure for the palladium catalysed allylic displacement reaction



To a stirred solution of the ligand (10 mol) in DCM (30 ml) at 0°C, allylpalladium chloride dimer (5 mol %) was added and the mixture stirred for 10 minutes.

1,3-Diphenyl-2-propylacetate (1 eq) was added and the resulting mixture stirred for 0.5 hour. Cesium carbonate (5 eq) and dimethylmalonate (5 eq) were added sequentially and the resulting mixture stirred for 24 hours at 0 °C. The solvent was filtered through celite, the celite was washed with DCM (3 × 30 ml), the combined organic solutions were evaporated and the residue chromatographed in 9:1 petroleum ether diethyl ether mixture, to yield the products.

(Found: C 73.92, H 6.18. $C_{20}H_{25}NO_4$ requires: C 74.06, H 6.21%). mp 118-123 °C.

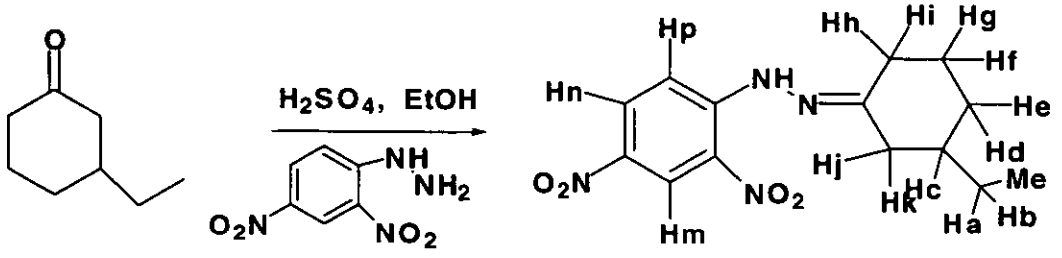
ν_{max} 3031, 2952, 1735, 1452 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 3.45 (3 H, s, Me b), 3.66 (3 H, s, Me a), 3.99 (1 H, d, *J*=10.0 Hz, Ha), 4.26 (1 H, dd, *J*=8.0, 10.0 Hz, Hb), 6.31 (1 H, dd, *J*=8, 16 Hz, Hc), 6.48 (1 H, d, *J*=16.0 Hz, He), 97.20-7.35 (10 H, m).

δ_C ($CDCl_3$, 100 MHz) 49.10, 52.31, 52.49, 126.21, 127.01, 127.42, 127.75,

128.35, 128.75, 129.01, 132.15, 136.72, 140.01, 167.72, 168.21.

3-Ethyl cyclohexanone 2,4 - dinitrophenyl hydrazone



To a stirred solution of 3-ethyl cyclohexan-1-one (1 eq) in ethanol (30 ml), 2 or 3 drops of sulfuric acid were added followed by 2, 4 -dinitrophenylhydrazine (1 eq) and the solution was stirred for 20-30 minutes. The mixture was washed with sodium hydrogen carbonate (2 × 10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic solutions were dried over magnesium sulfate and the solvent removed to yield the crude product as an oil which was chromatographed in petroleum ether -ethyl acetate 80:20 to yield an orange solid.

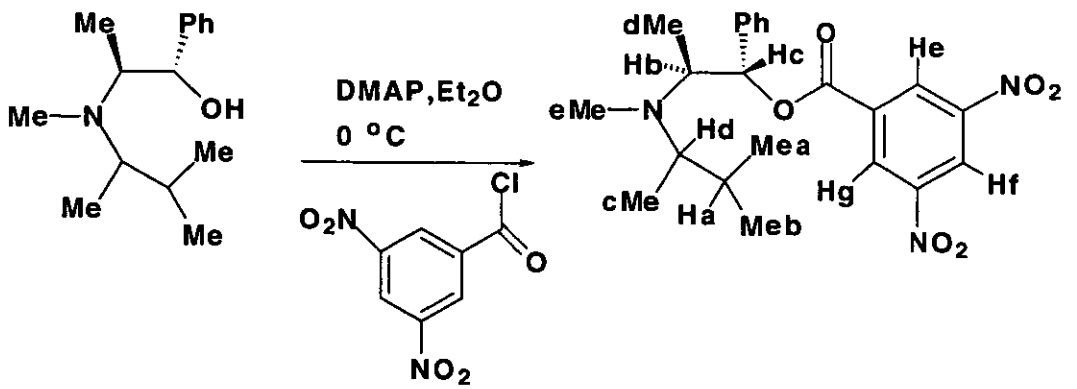
ν_{max} 3425, 2950, 1618, 1589, 1517, 1334, 1309 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz), 0.93 (3 H, t, *J*=7.5 Hz, Me), 1.43-144 (3 H,, m, Hb, Hc), 1.63-1.64 (2 H, m, Hd, He), 2.16-2.18 (3 H, m, Hf, Hg), 3.24-3.30 (4 H, m, Hh, Hi, Hk, Hl), 7.92 (1 H, d, *J*=4.0 Hz,Hp), 8.1 (1 H, d, *J*=4.0 Hz, Hn), 9.16 (1 H, s,Hm).

δ_C ($CDCl_3$, 100 MHz) 11.68, 25.21, 26.19, 27.37, 29.53, 29.60, 40.77, 116.60, 124.01, 130.33, 145.72, 161.75.

m/z FAB (Found: 307.1406 (M^++1) $C_{14}H_{19}N_4O_4$ requires: 307.1328).

(1S,2S)-2-[1,2-Dimethyl propyl (methyl) amino] -1-phenyl propyl -3,5-dinitrobenzoate



To a solution of 3,5-dinitrobenzoyl chloride (160 mg, 0.7 mmol, 1.2 eq), in diethyl ether (20 ml) at 0°C amino alcohol (1S,2S)-2[1,2-dimethyl-propyl(methyl) amino)-1-phenyl propan -1-ol (150 mg, 0.64 mmol) was added, followed immediately by DMAP (76 mg, 0.64 mmol). An immediate white precipitate appeared. After one hour the solid precipitate was collected and purified by column chromatography using petroleum ether- ethyl acetate-triethylamine (80:19:1) as eluent to yield the product as an oil (150 mg, 55%). Appendix 5

ν_{max} 2970, 2461, 1739, 1542, 1458, 1346, 1265, 1157 cm^{-1}.

δ_H ($CDCl_3$, 250 MHz) 0.70 (3 H, d, *J*=8.0 Hz, Me a), 0.77 (3 H, d, *J*=8.0 Hz, Me b), 0.80 (3 H, d, *J*=12.0 Hz, Me c), 1.00 (3 H, d, *J*=8.0 Hz, Me d), 1.60 (1 H, septet, *J*=8.0, 8.0 Hz, Ha), 2.15 (3 H, s, Me e), 2.38 (1 H, dq, *J*=8.0, 12.0 Hz, Hb), 7.2-7.5 (5 H, m), 9.15 (2 H, d, *J*=4.0 Hz, He, Hg), 9.20 (1 H, s,Hf).

δ_C ($CDCl_3$, 100 MHz) 22.18, 12.96, 19.52, 20.96, 27.80, 32.00, 62.27, 66.21, 80.19, 122.09, 127.68, 128.68, 129.44, 134.78, 138.19, 148.56,

161.73.

m/z FAB (Found: 430.1972, (M^++1) $C_{22}H_{18}N_3O_6$ requires 430.1899).

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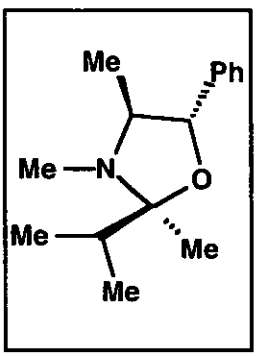
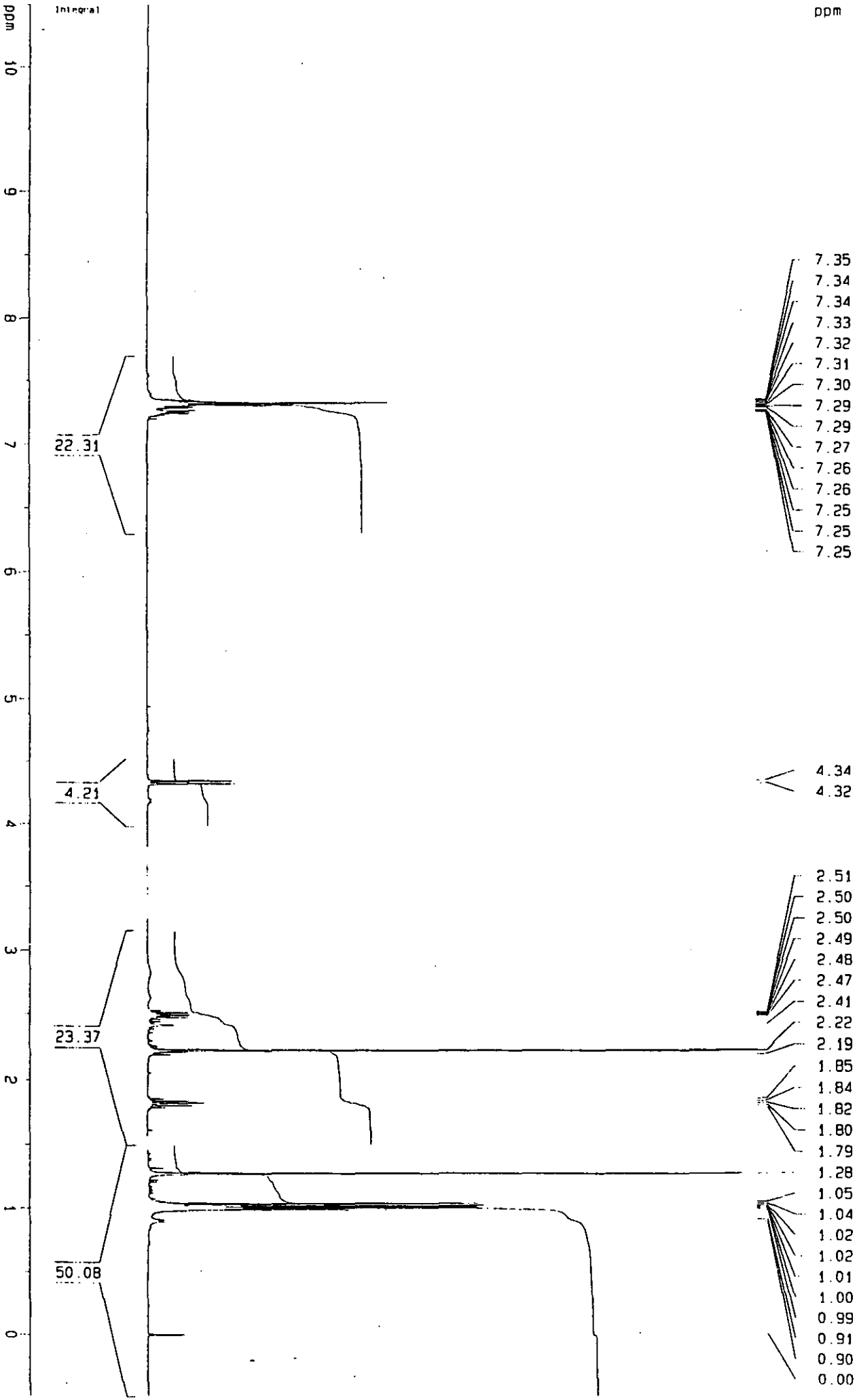
APPENDICES

APPENDIX 1

nOe Studies on Oxazolidines

(4S,5S)-2,3,4-trimethyl-2-(1-methyl ethyl)
5-phenyl-1,3-oxazolidine

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7.29
7.29
7.27
7.26
7.26
7.25
7.25
7.25
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4.32
2.51
2.50
2.50
2.49
2.48
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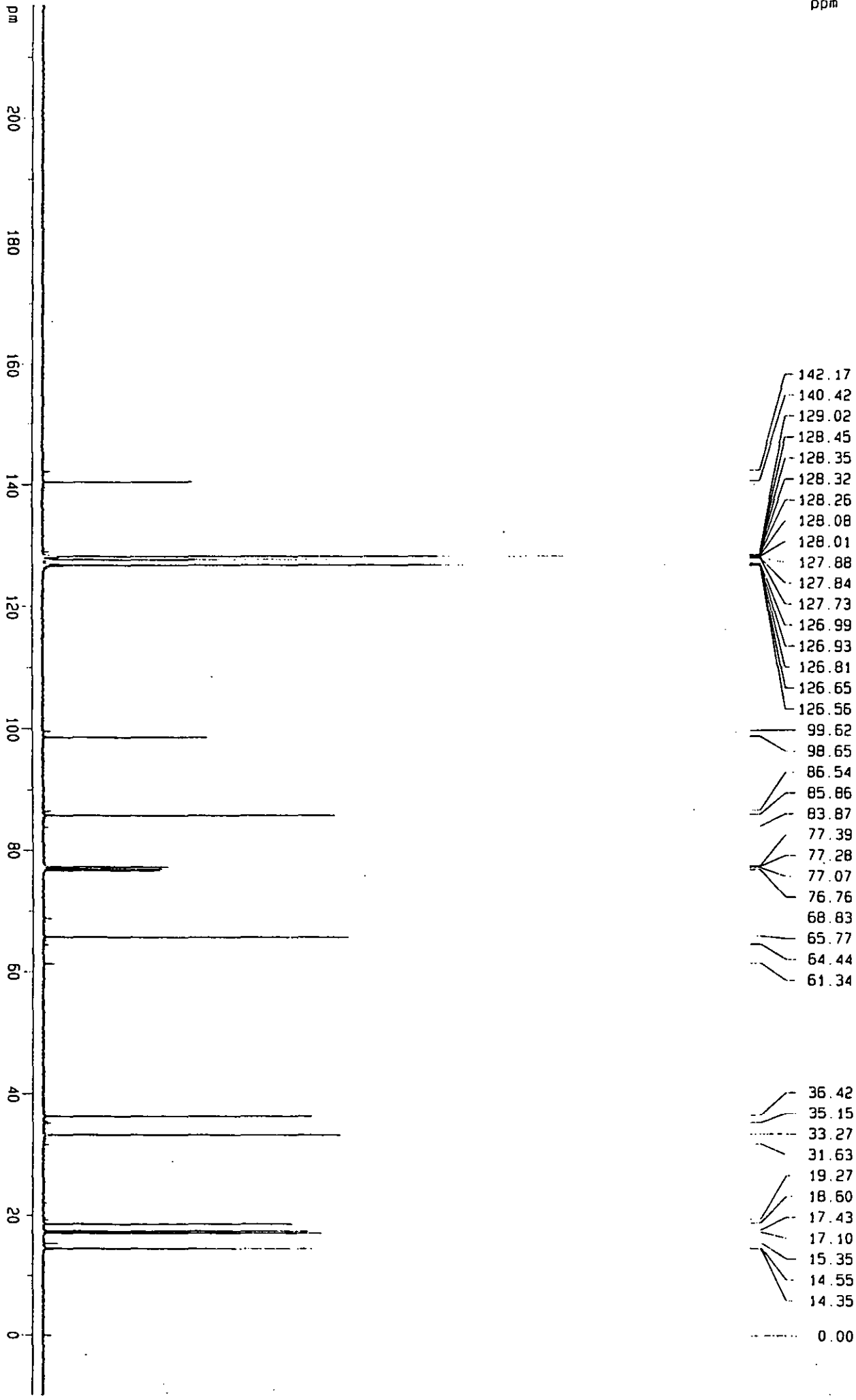
0.90
0.00

SAT 221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128.26
128.08
128.01
127.88
127.84
127.73
126.99
126.93
126.81
126.65
126.56
99.62
98.65
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77.28
77.07
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65.77
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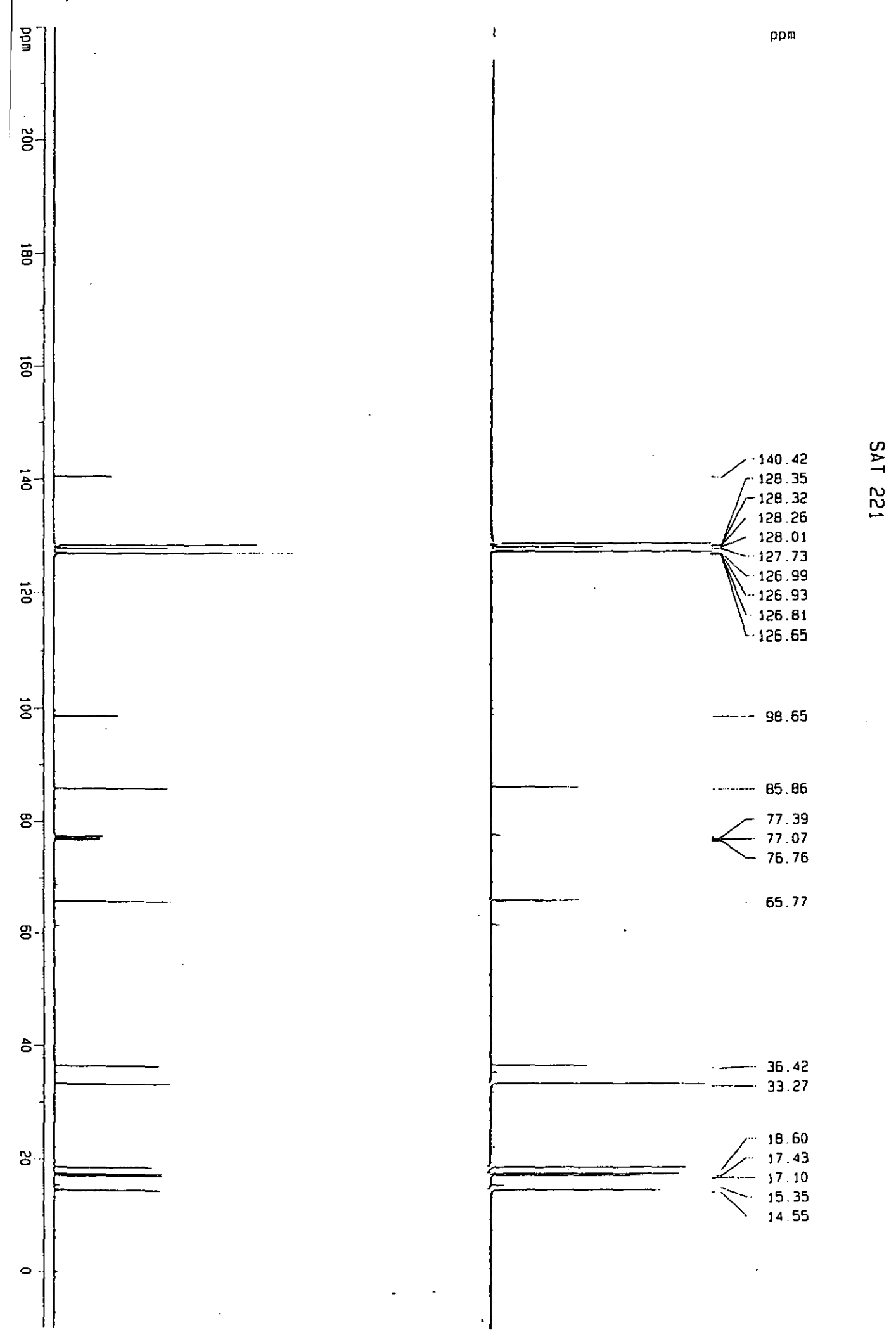
SAT 221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ppm
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128.32
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128.01
127.73
126.99
126.93
126.81
126.65
98.65
85.86
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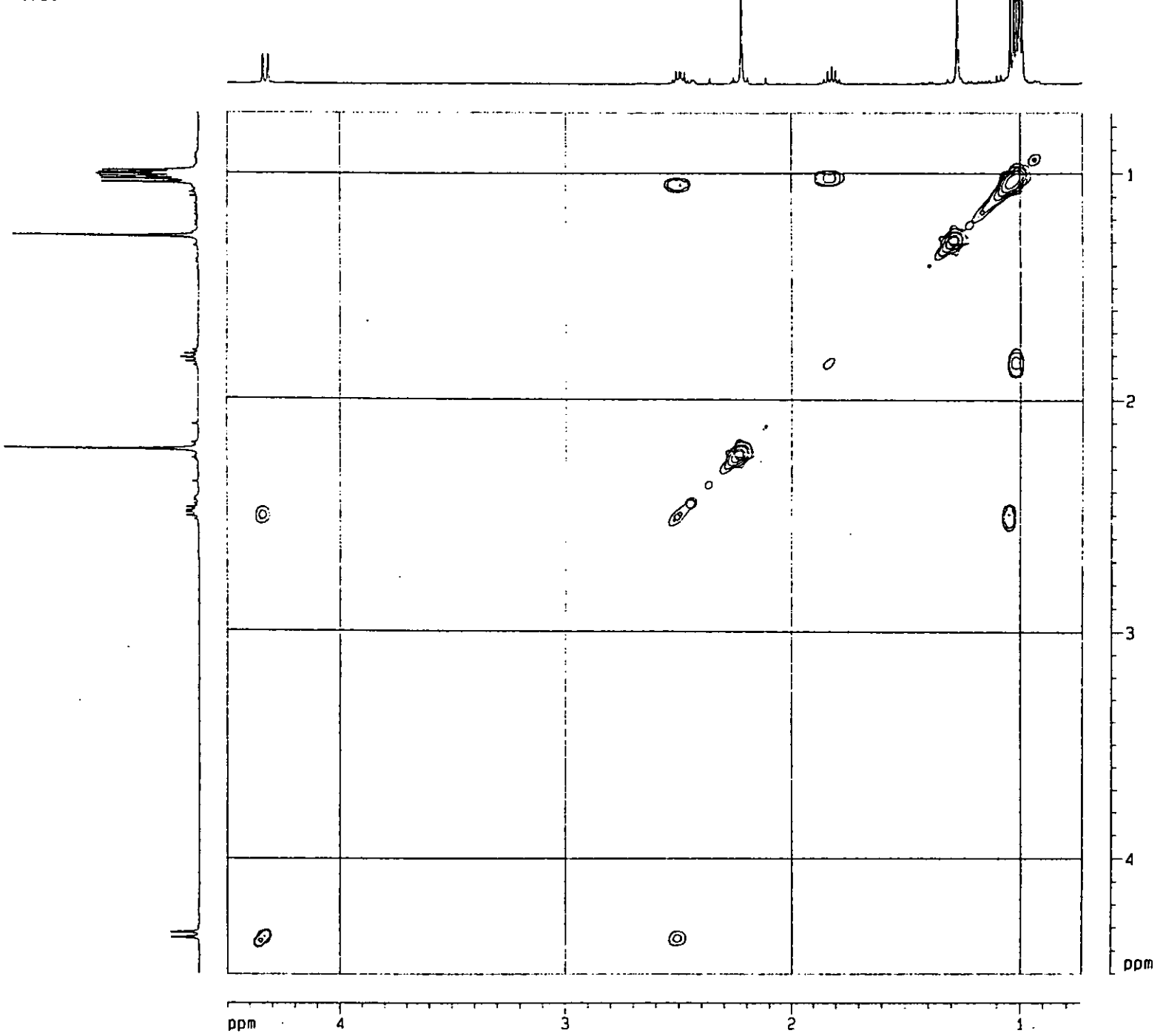
SAT 221



F2 - Acquisition Parameters

Date_	20010604
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PULPROG	cosy45
TD	1024
SOLVENT	CDCl3
NS	8
DS	16
SWH	3396.739 Hz
FIDRES	3.317128 Hz
AQ	0.1507828 sec
RG	35.9
DW	147.200 usec
DE	7.50 usec
TE	300.0 K
D1	2.00000000 sec
P1	15.00 usec
SFO1	400.1315265 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00029440 sec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	400.1315 MHz
FIDRES	13.268512 Hz
SW	8.489 ppm

F2 - Processing parameters

SI	512
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

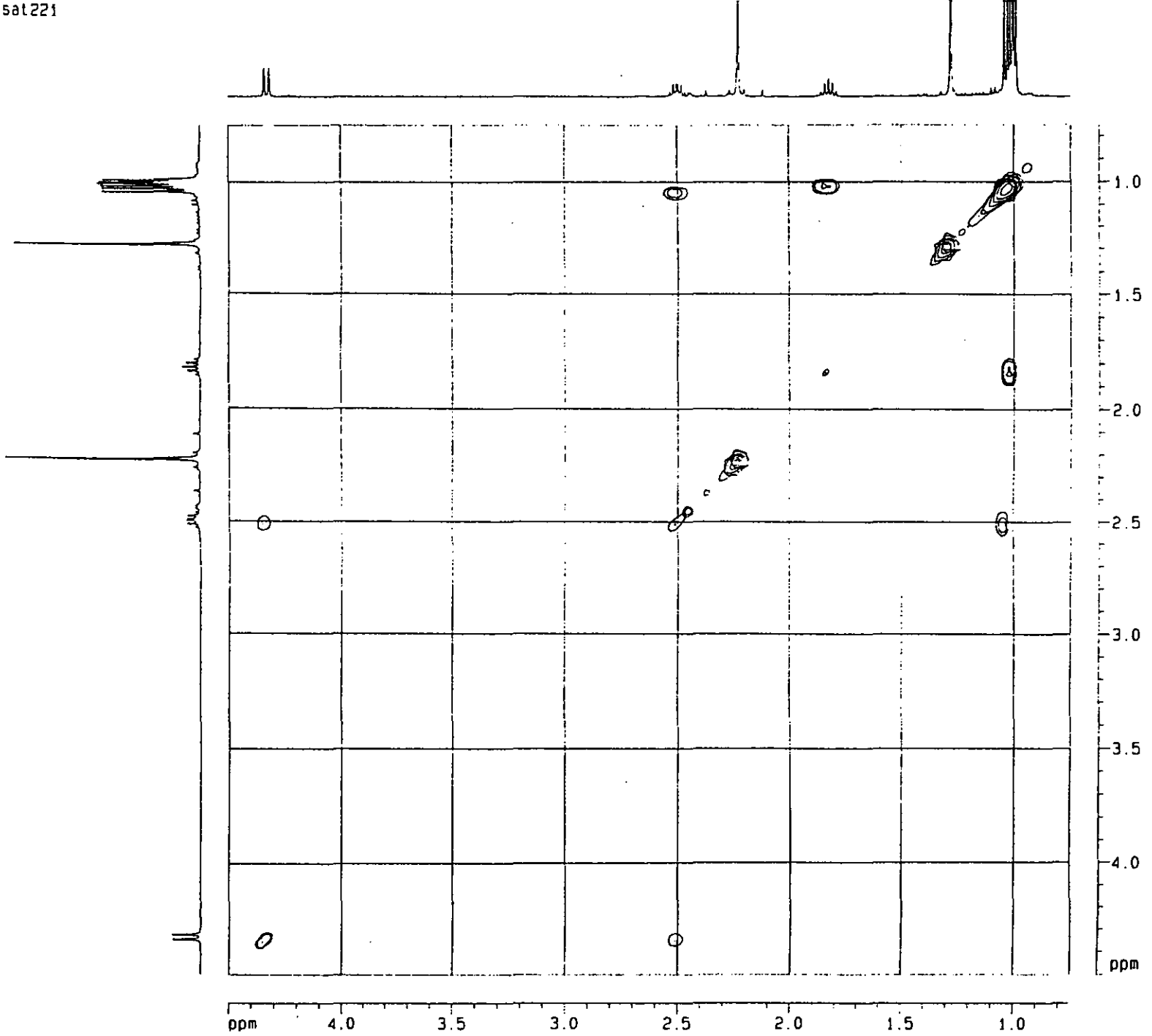
F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.502 ppm
F2LO	1801.20 Hz
F2PHI	0.738 ppm
F2HI	295.22 Hz
F1PLO	4.502 ppm
F1LO	1801.20 Hz
F1PHI	0.738 ppm
F1HI	295.22 Hz
F2PPMCM	0.25091 ppm/cm
F2HZCM	100.39841 Hz/cm
F1PPMCM	0.25091 ppm/cm
F1HZCM	100.39841 Hz/cm

sat221



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SOLVENT	CDCl3
NS	8
DS	16
SWH	3395.739 Hz
FIDRES	3.317128 Hz
AQ	0.1507828 sec
RG	35.9
DW	147.200 usec
DE	7.50 usec
TE	300.0 K
D1	2.00000000 sec
P1	15.00 usec
SFO1	400.1315265 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00029440 sec

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	400.1315 MHz
FIDRES	13.268512 Hz
SW	8.489 ppm

F2 - Processing parameters

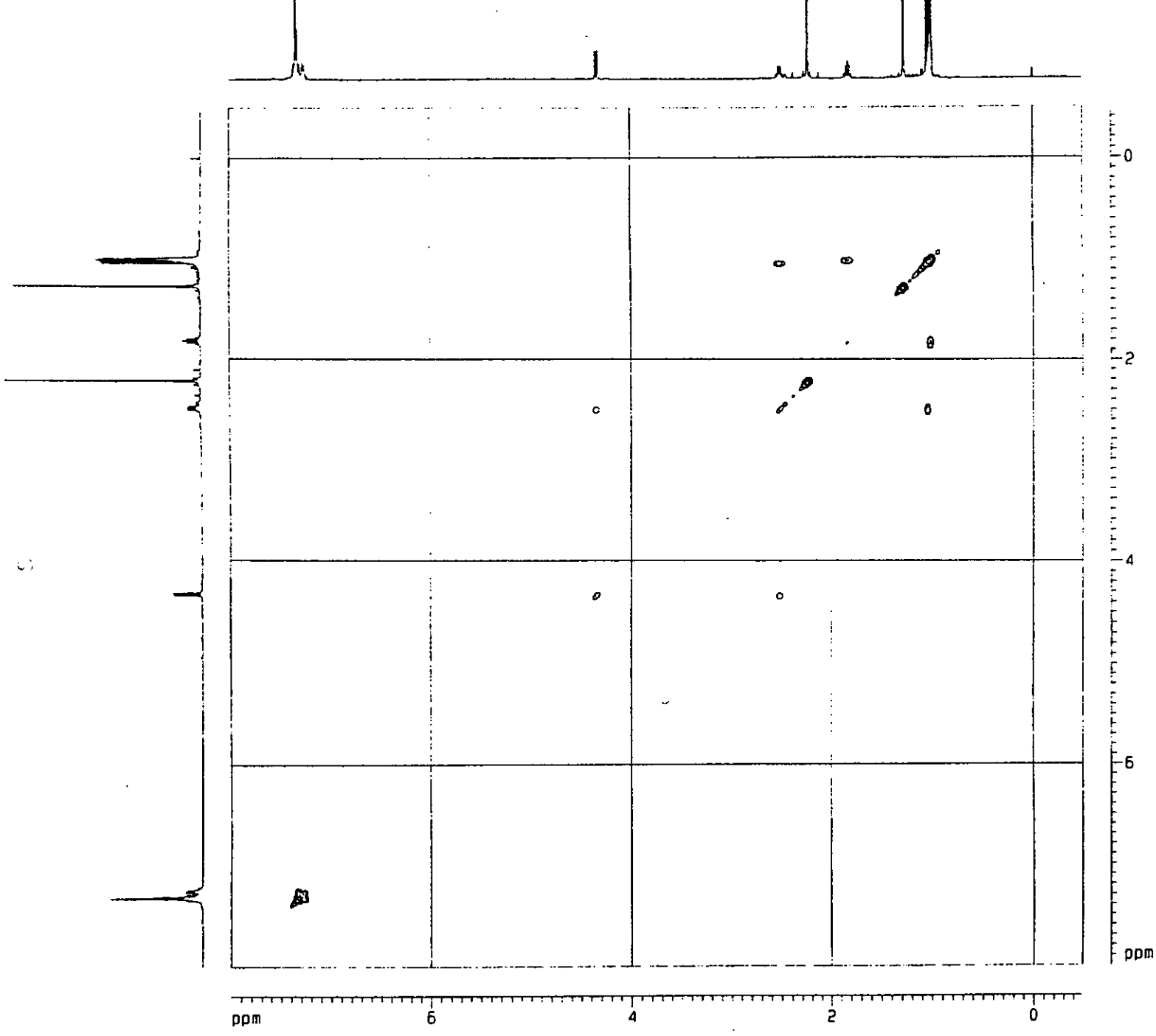
SI	512
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.500 ppm
F2LO	1800.59 Hz
F2PHI	0.750 ppm
F2HI	300.10 Hz
F1PLO	4.500 ppm
F1LO	1800.59 Hz
F1PHI	0.750 ppm
F1HI	300.10 Hz
F2PPMCM	0.25000 ppm/cm
F2HZCM	100.03251 Hz/cm
F1PPMCM	0.25000 ppm/cm
F1HZCM	100.03251 Hz/cm



F2 - Acquisition Parameters

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PULPROG	cosy45
TD	1024
SOLVENT	CDCl3
NS	8
DS	16
SWH	3396.739 Hz
FIDRES	3.317128 Hz
AQ	0.1507828 sec
RG	35.9
DW	147.200 usec
DE	7.50 usec
TE	300.0 K
D1	2.00000000 sec
P1	15.00 usec
SFO1	400.1315265 MHz
NUC1	1h
PL1	-6.00 dB
DO	0.00000300 sec
IN0	0.00029440 sec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	400.1315 MHz
FIDRES	13.268512 Hz
SW	8.489 ppm

F2 - Processing parameters

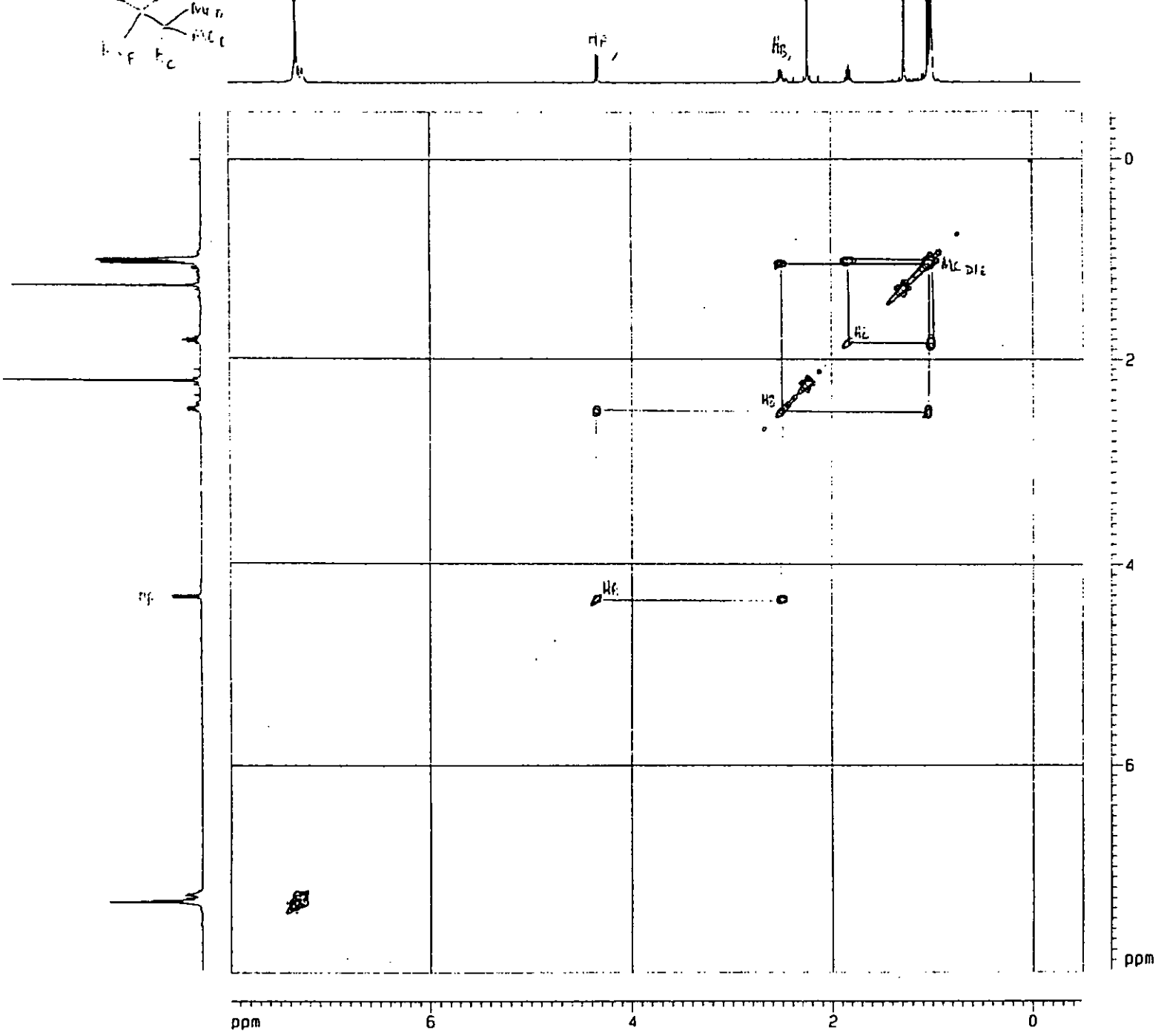
SI	512
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	8.000 ppm
F2LO	3201.03 Hz
F2PHI	-0.489 ppm
F2HI	-195.71 Hz
F1PLO	8.000 ppm
F1LO	3201.03 Hz
F1PHI	-0.489 ppm
F1HI	-195.71 Hz
F2PPMCM	0.56594 ppm/cm
F2HZCM	226.44928 Hz/cm
F1PPMCM	0.56594 ppm/cm
F1HZCM	226.44928 Hz/cm



F2 - Acquisition Parameters

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DS	16
SWH	3396.739 Hz
FIDRES	3.317128 Hz
AQ	0.1507828 sec
RG	35.9
DW	147.200 usec
DE	7.50 usec
TE	300.0 K
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P1	15.00 usec
SFO1	400.1315265 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00029440 sec

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	400.1315 MHz
FIDRES	13.268512 Hz
SW	6.489 ppm

F2 - Processing parameters

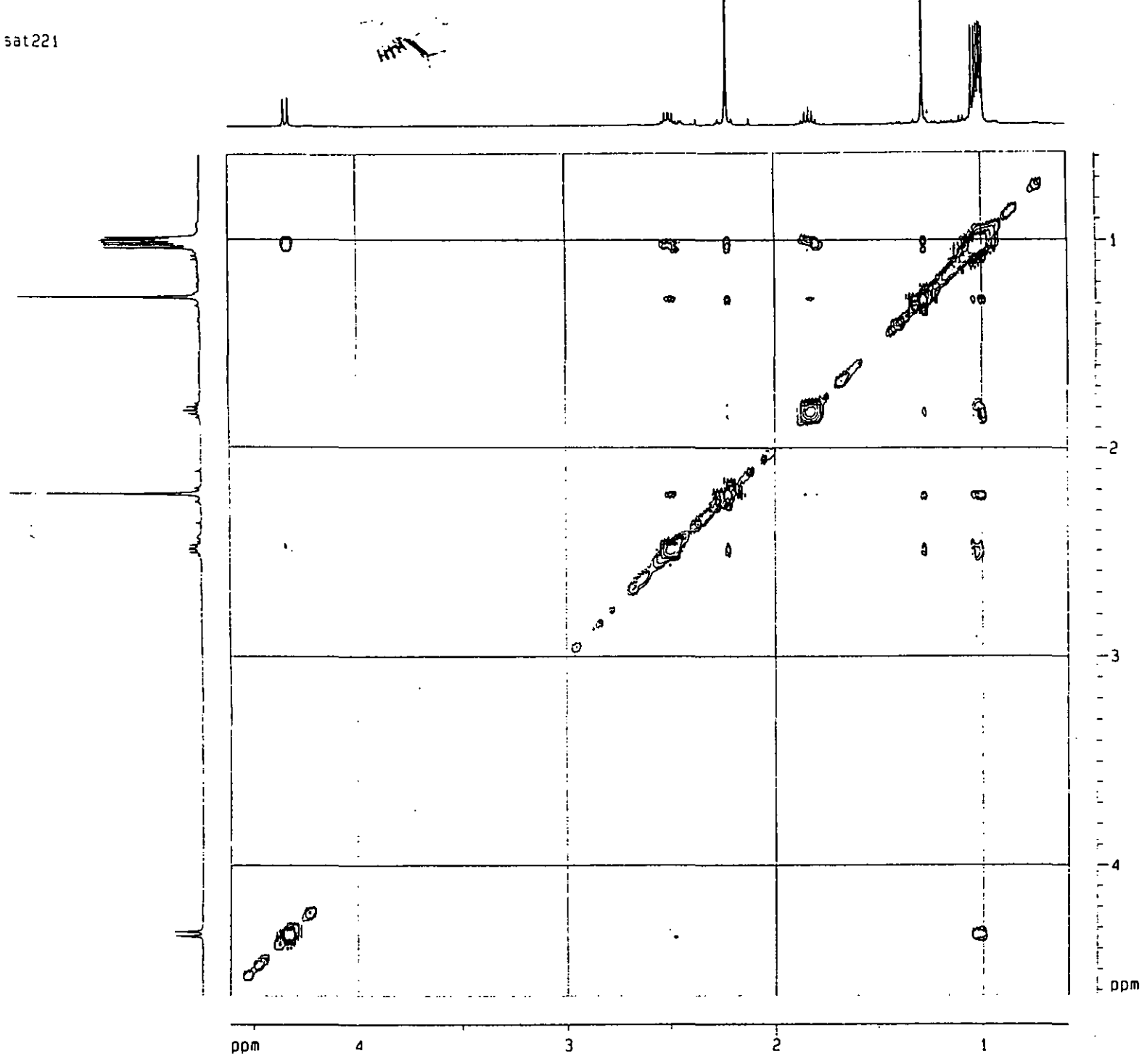
SI	512
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300239 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	7.995 ppm
F2LO	3198.87 Hz
F2PHI	-0.495 ppm
F2HI	-197.87 Hz
F1PLO	8.021 ppm
F1LO	3209.26 Hz
F1PHI	-0.469 ppm
F1HI	-187.48 Hz
F2PPMCM	0.56594 ppm/cm
F2HZCM	226.44928 Hz/cm
F1PPMCM	0.56594 ppm/cm
F1HZCM	226.44930 Hz/cm



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AQ	0.1507828 sec
RG	143.7
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DE	7.50 usec
TE	300.0 K
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SFO1	400.1315265 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
D8	0.99999999 sec
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F1 - Acquisition parameters

NDO	2
TD	256
SFO1	400.1315 MHz
FIDRES	13.255512 Hz
SW	5.489 ppm

F2 - Processing parameters

SI	1024
SF	400.1300262 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

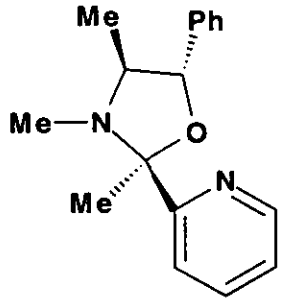
F1 - Processing parameters

SI	512
MC2	TPPI
SF	400.1300262 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

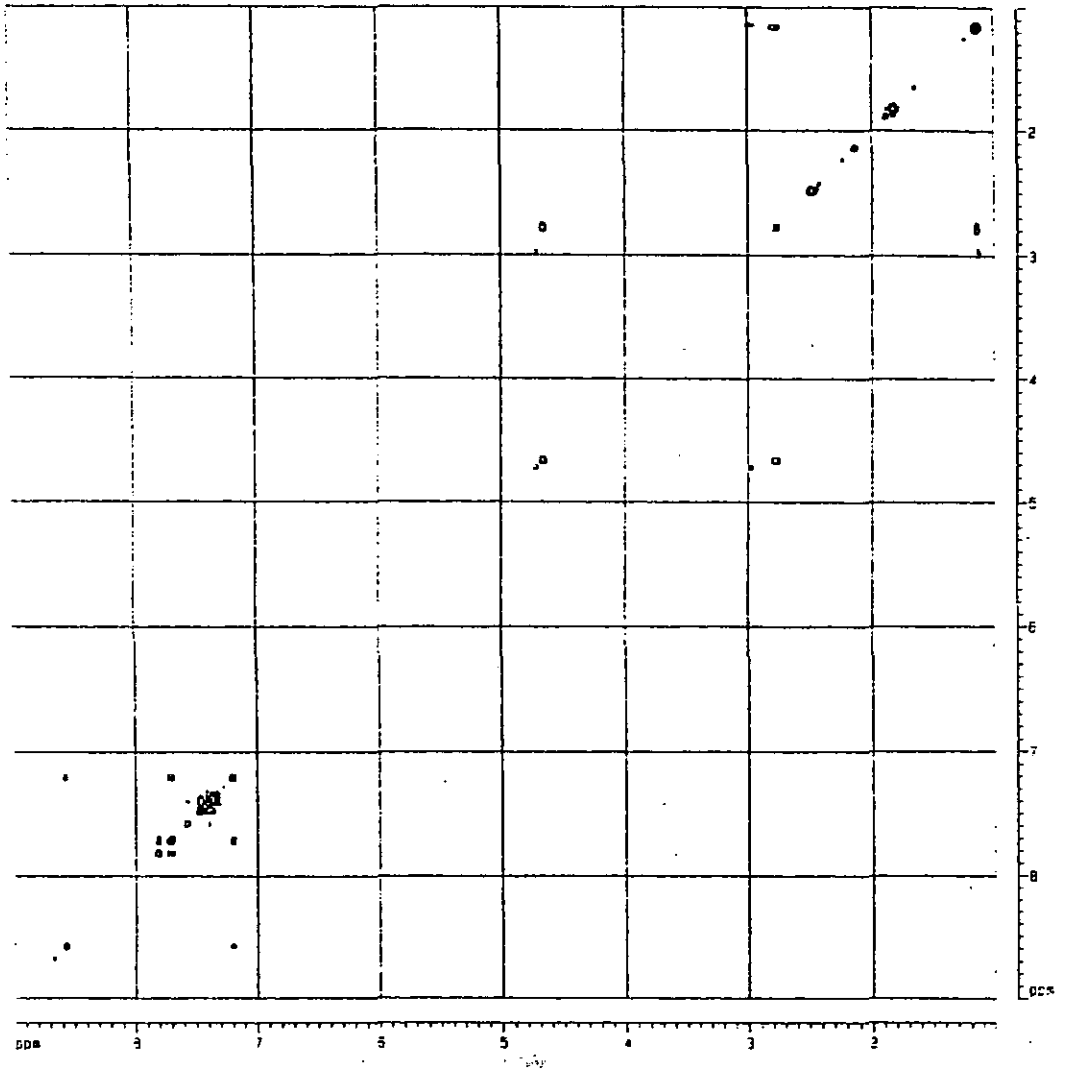
2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.612 ppm
F2LO	1845.33 Hz
F2PHI	3.591 ppm
F2HI	236.52 Hz
F1PLO	4.528 ppm
F1LO	1851.97 Hz
F1PHI	3.583 ppm
F1HI	233.21 Hz
F2PPMCM	0.26805 ppm/cm
F2HZCM	107.25391 Hz/cm
F1PPMCM	0.25971 ppm/cm

(4S,5S)-2,3,4-trimethyl-5-phenyl-2 pyridin yl 1,3-oxazolidine



CASS Analysis 0950: Structure and Stereochemistry of ST84254-027A1 (CDCl3)



Current Data Parameters

NAME	CASS_0950
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20010406
Time	14.51
INSTRUM	qnp400
PROBHD	5mm BBO ATMA
PULPROG	zg30
TD	2048
SOLVENT	CDCl3
NS	2
DS	16
SWH	3581.054 Hz
FIDRES	1.753884 Hz
AQ	0.2851316 sec
RG	812.7
DW	139.200 usec
DE	6.00 usec
TE	300.0 K
D0	3.00000300 sec
D1	2.00000000 sec
D12	0.00020300 sec
D16	0.00015000 sec
DA3	0.00027840 sec

CHANNEL f1

NUC1	1H
P0	10.50 usec
P1	10.50 usec
PL1	3.00 dB
SFO1	400.1320007 MHz

GRADIENT CHANNEL

P16	1500.00 usec

F1 - Acquisition parameters

NDO	1
TD	128
SFO1	400.132 MHz
FIDRES	28.062146 Hz
SW	8.977 ppm

F2 - Processing parameters

SI	1024
SF	400.1299988 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

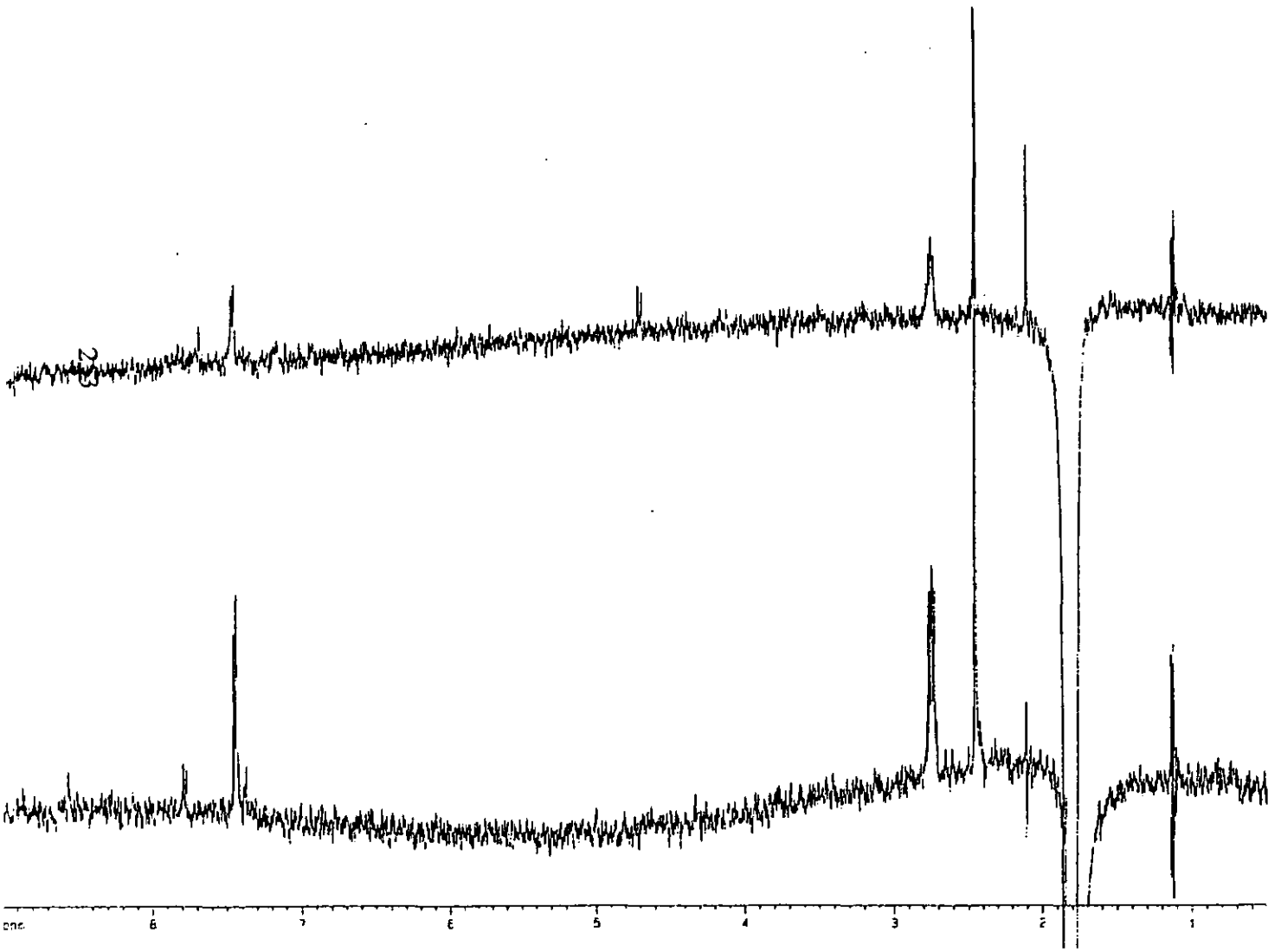
F1 - Processing parameters

SI	1024
MC2	QF
SF	400.1299988 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	28.00 cm
CY1	20.00 cm
F2PLO	9.000 ppm
F2LO	3601.17 Hz
F2PH1	1.000 ppm
F2H1	400.13 Hz
F1PLO	9.000 ppm
F1LO	3601.17 Hz
F1PH1	1.000 ppm
F1H1	400.13 Hz
F2PPCM	0.40000 ppm/cm
F2HZCM	160.05208 Hz/cm
F1PPCM	0.40000 ppm/cm
F1HZCM	160.05208 Hz/cm

CASS Analysis 0950: Structure and Stereochemistry of ST84254-027A1 (CDCl3)



Current Data Parameters

NAME	CASS_0950
EXPNO	8
PROCNO	1

F2 - Acquisition Parameters

Date_	20010405
Time	10.39
INSTRUM	ora400
PROBHD	5 mm TXI 31P
PULPROG	sa1ngqp.3
TD	65536
SOLVENT	DMSO
NS	512
DS	4
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	2048
DW	60.400 usec
DE	6.00 usec
TE	300.0 K
D1	2.00000000 sec
D8	0.50000000 sec
D1E	0.00010000 sec
d20	0.24890000 sec

---------- CHANNEL f1 ----------

NUC1	1H
P1	8.40 usec
p2	16.80 usec
P12	90000.00 usec
PL0	120.00 dB
PL1	0.00 dB
SFO1	400.1307158 MHz
SP1	69.00 dB
SPNAM1	gaus1.1k
SPOFF1	0.00 Hz

---------- GRADIENT CHANNEL ----------

GPNAM1	sine.100
GPNAM2	sine.100
GPNAM3	sine.100
GPNAM4	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPX4	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPY4	0.00 %
GPZ1	11.00 %
GPZ2	17.00 %
GPZ3	40.00 %
GPZ4	-40.00 %
P16	1000.00 usec

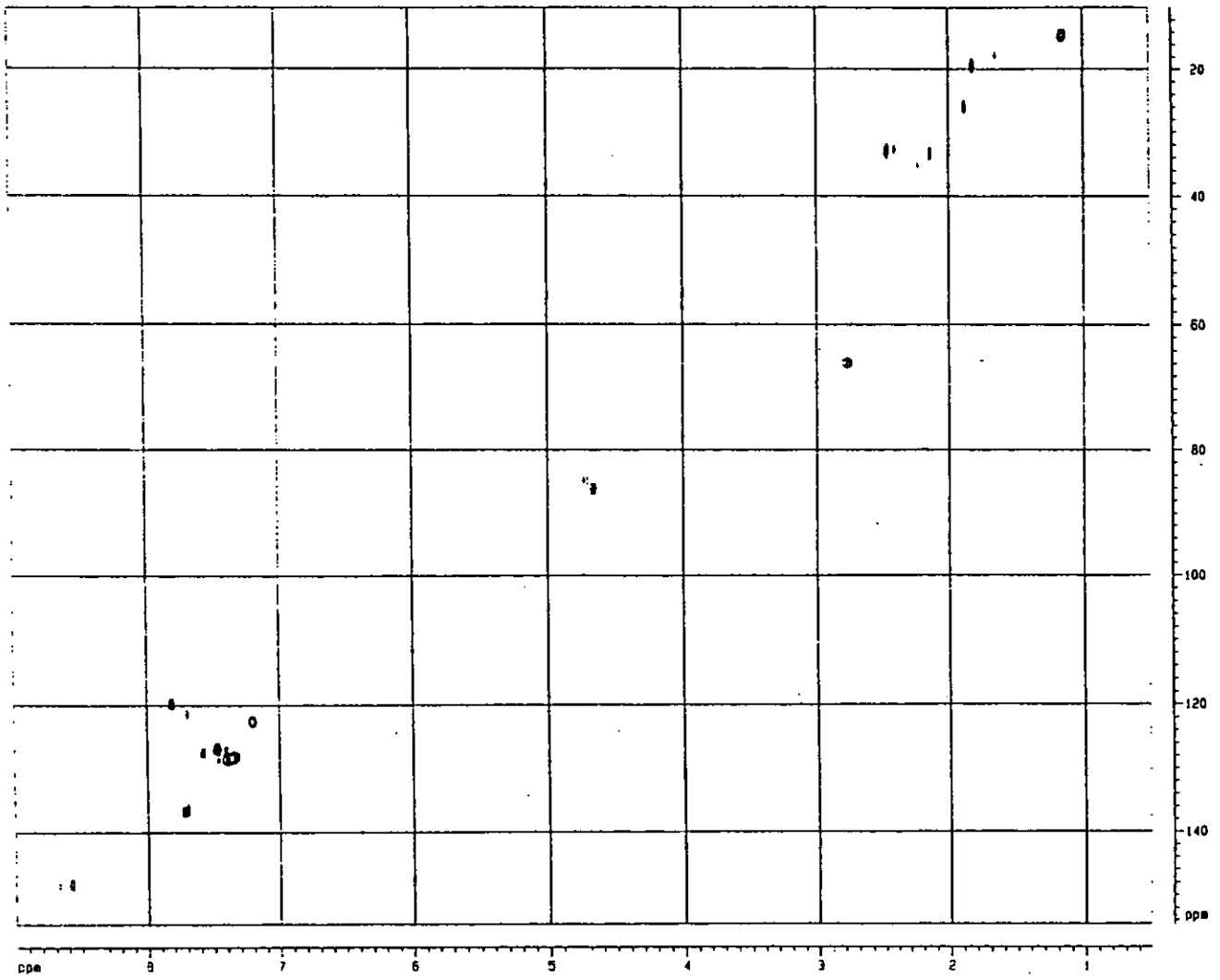
F2 - Processing parameters

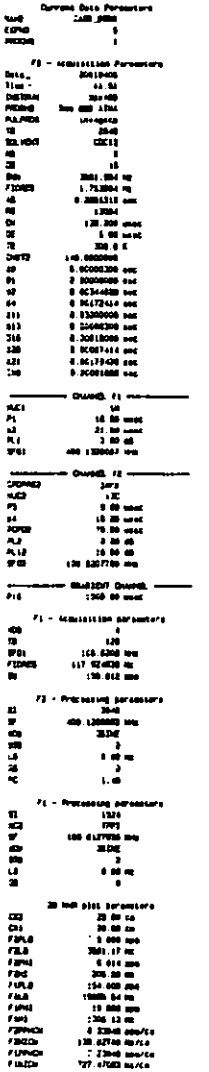
SI	32768
SF	400.1300106 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

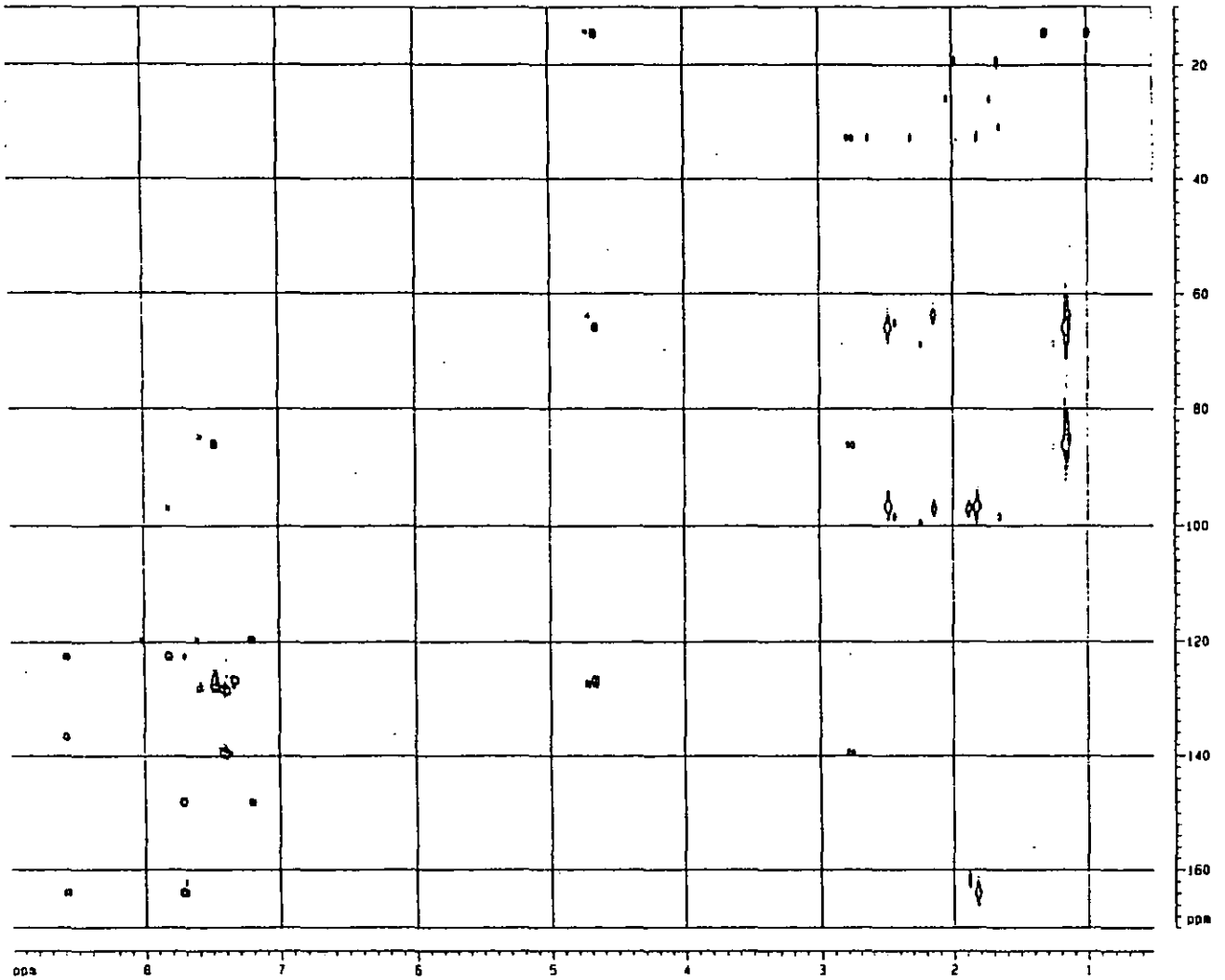
CY	30.00 cm
F1P	8.000 ppm
F1	3501.17 Hz
F2P	0.500 ppm
F2	205.07 Hz
PPMCM	0.28333 ppm/cm
HZCM	113.37017 Hz/cm

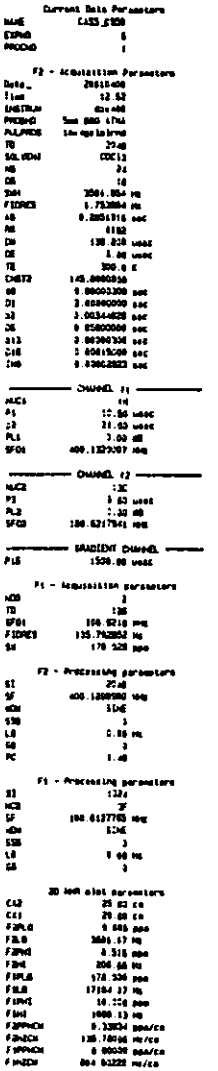
CASS Analysis 0950: Structure and Stereochemistry of ST84254-027A1 (CDCl3)



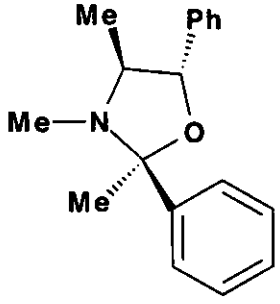


CASS Analysis 0950: Structure and Stereochemistry of ST84254-027A1 (CDCl3)

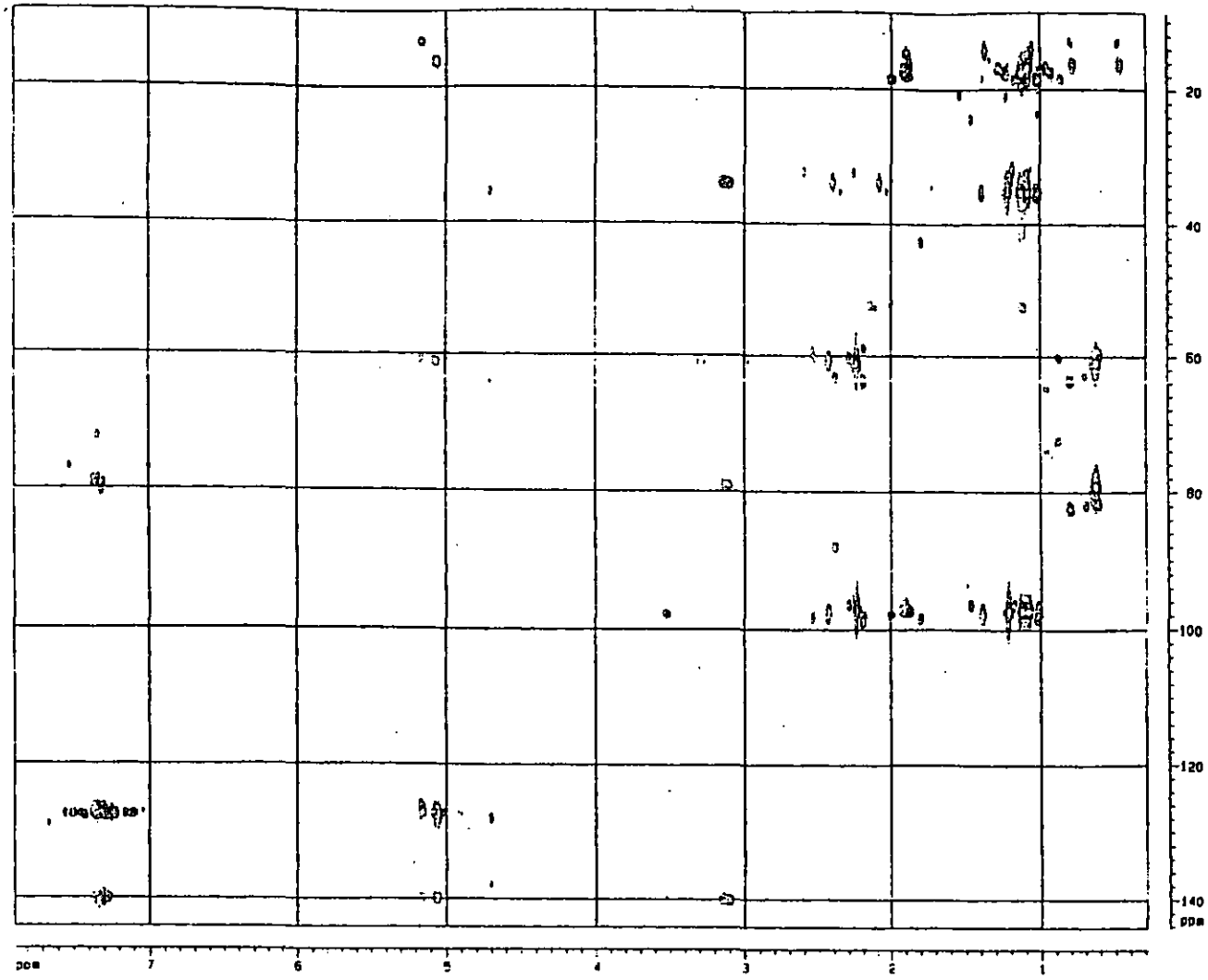




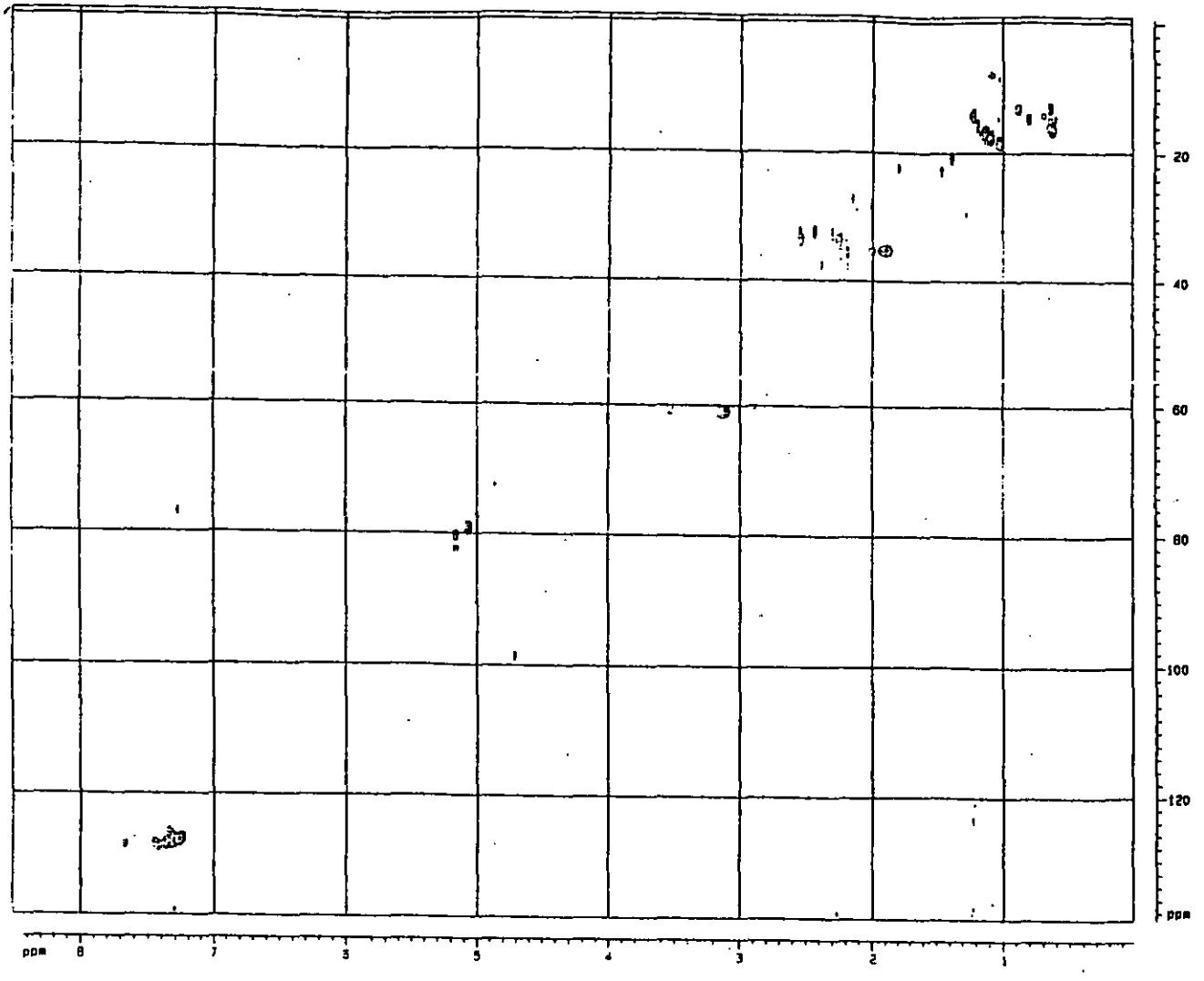
(4S,5S)-2,3,4-trimethyl-2,5-diphenyl-1,3-oxazolidine



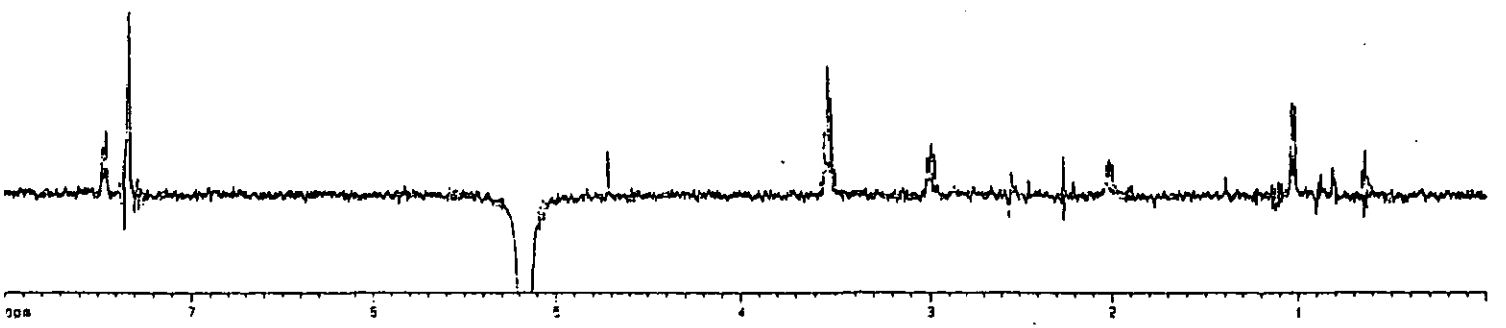
,S 0992 Stereochemistry of STB4254-006 in CDCl3



S 0992 Stereochemistry of ST84254-006 in CDCl3



CASS 0992 Stereochemistry of ST84254-006 in CDCL3



Current Data Parameters

NAME	CASS_0992
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20010425
Time	9.12
INSTRUM	dr=400
PROBHD	5 mm TXI 31P
PULPROG	seinogp.3
TD	65538
SOLVENT	CDCl3
NS	150
DS	4
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	512
DW	60.400 usec
DE	6.00 usec
TE	333.6 K
D1	2.00000000 sec
D3	0.50000000 sec
D16	0.00010000 sec
D20	0.24583000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	7.80 usec
p2	15.20 usec
P12	50000.00 usec
PL0	120.00 dB
PL1	0.00 dB
SFO1	400.1320719 MHz
SP1	89.00 dB
SPNAM1	gaus1.1k
SPOFF1	0.00 Hz

========== GRADIENT CHANNEL ==========

SPNAM1	sine.100
SPNAM2	sine.100
SPNAM3	sine.100
SPNAM4	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPX4	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPY4	0.00 %
GPZ1	11.00 %
GPZ2	17.00 %
GPZ3	40.00 %
GPZ4	-40.00 %
P18	1000.00 usec

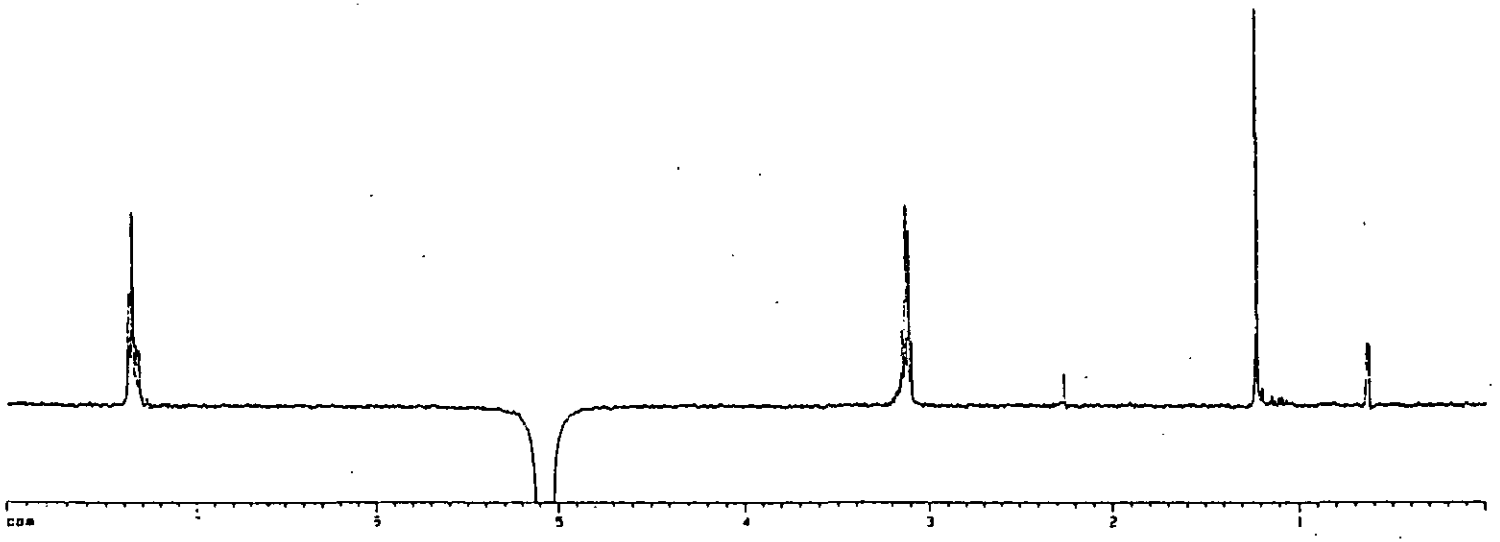
F2 - Processing parameters

SI	32768
SF	400.1300024 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

10 NMR plot parameters

CX	20.00 cm
F1P	8.000 ppm
F1	3201.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.20667 ppm/cm
HZCM	108.70133 Hz/cm

CASS 0992 Stereochemistry of ST84254-006 in CDCL3



Current Data Parameters

NAME	CASS_0992
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20010425
TICs	0.57
INSTRUM	drs400
PROBHD	5 mm TXI 31P
PULPROG	selnogp.3
TD	65536
SOLVENT	DMSO
NS	94
DS	4
SWH	6278.146 Hz
FIDRES	0.128314 Hz
AQ	3.9584243 sec
RG	512
DW	80.400 usec
DE	6.00 usec
TE	330.0 K
D1	2.00000000 sec
D3	0.50000000 sec
D16	0.00010000 sec
D20	0.24850000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	7.80 usec
p2	15.20 usec
P12	50000.00 usec
PLW	120.00 dB
PL1	0.00 dB
SFO1	400.1320327 MHz
SP1	90.00 dB
SPNAM1	gaus1.1k
SPOFF1	0.00 Hz

========== GRADIENT CHANNEL ==========

SPNAM1	sine.100
SPNAM2	sine.100
SPNAM3	sine.100
SPNAM4	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPX4	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPY4	0.00 %
GPZ1	11.00 %
GPZ2	17.00 %
GPZ3	40.00 %
GPZ4	-40.00 %
PIE	1000.00 usec

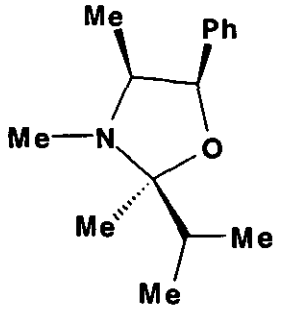
F2 - Processing parameters

SI	32768
SF	400.1300024 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

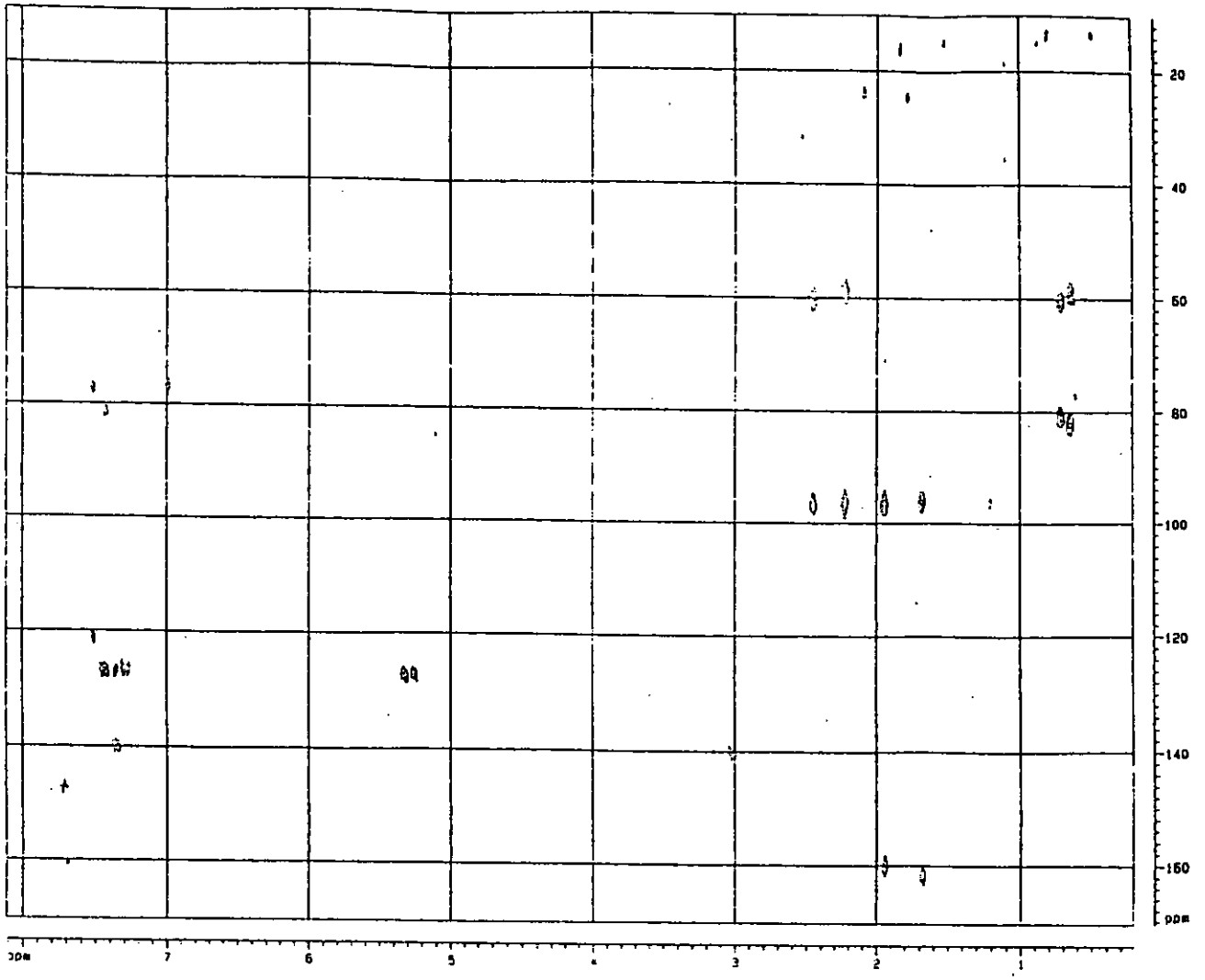
1D NMR plot parameters

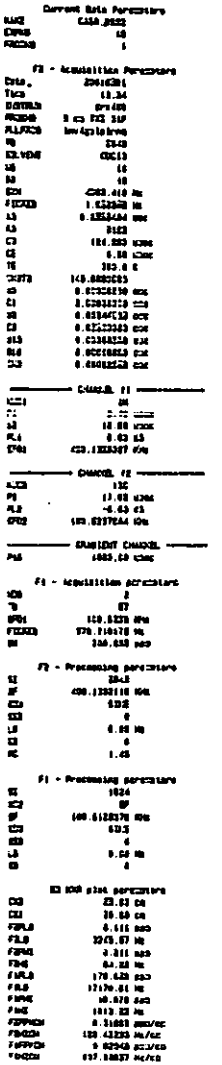
CX	13.00 cm
F1P	0.000 ppm
F1	3201.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.26667 ppm/cm
HZCM	105.75133 Hz/cm

(4S,5R)-2,3,4-trimethyl-5-phenyl-2-pyridyl 1,3-oxazolidine

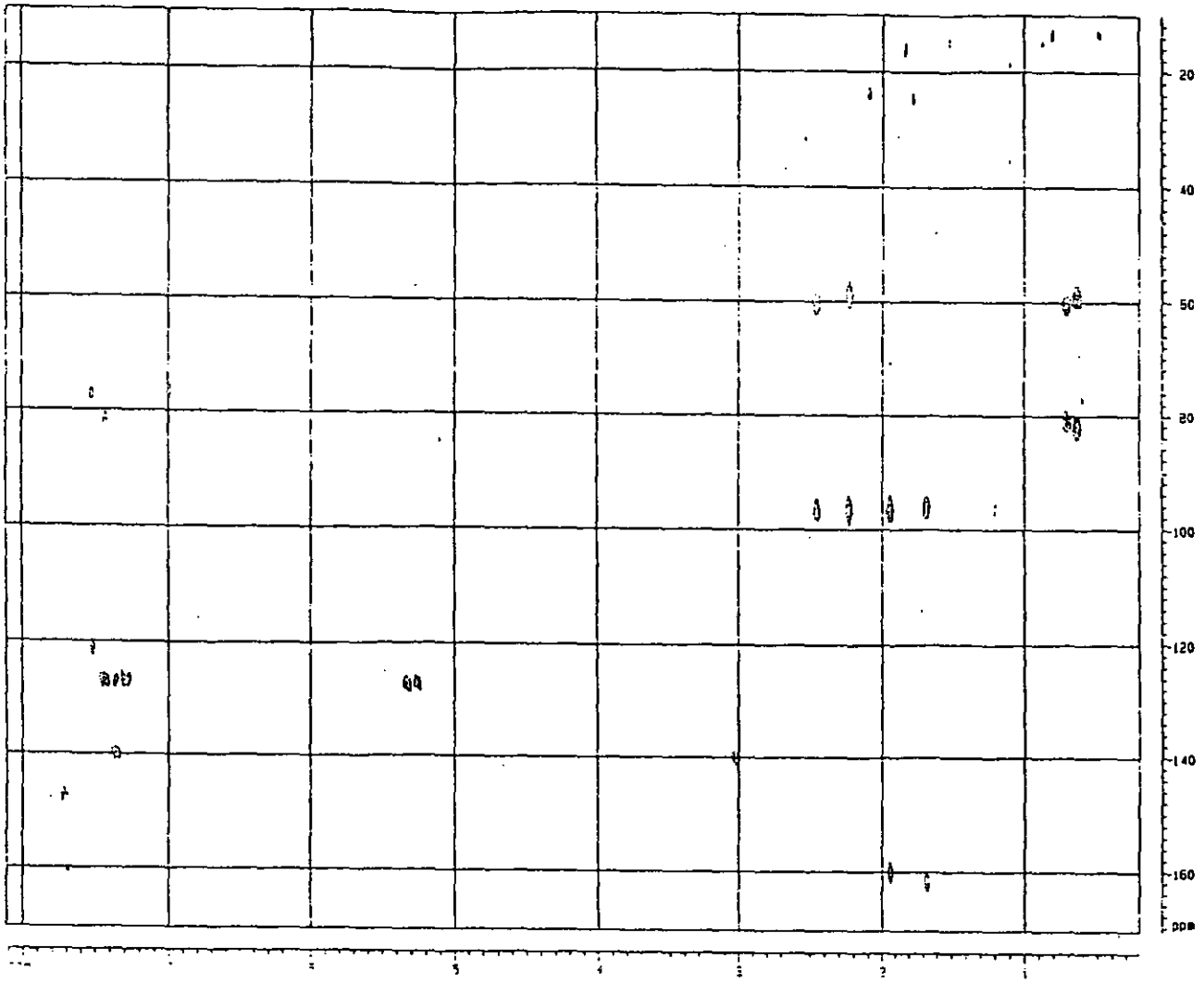


.SS 0991 Stereochemistry of ST84254-002 in COCL3

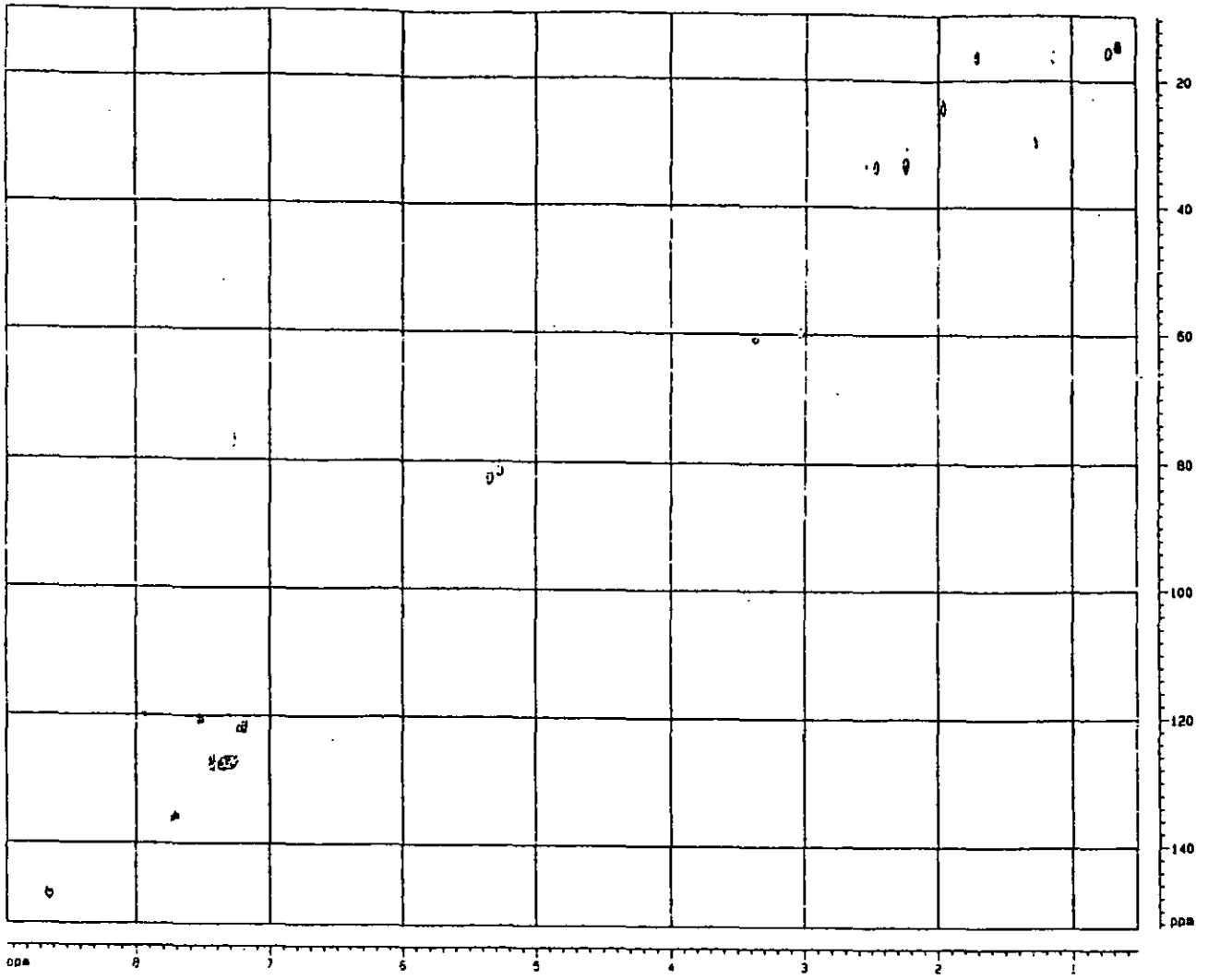




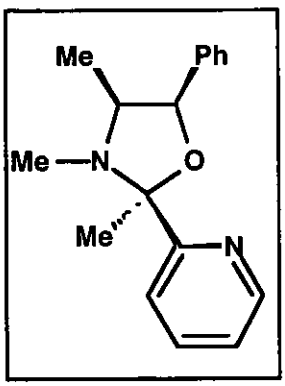
ASS 0991 Stereochemistry of ST84254-002 in CDCL3



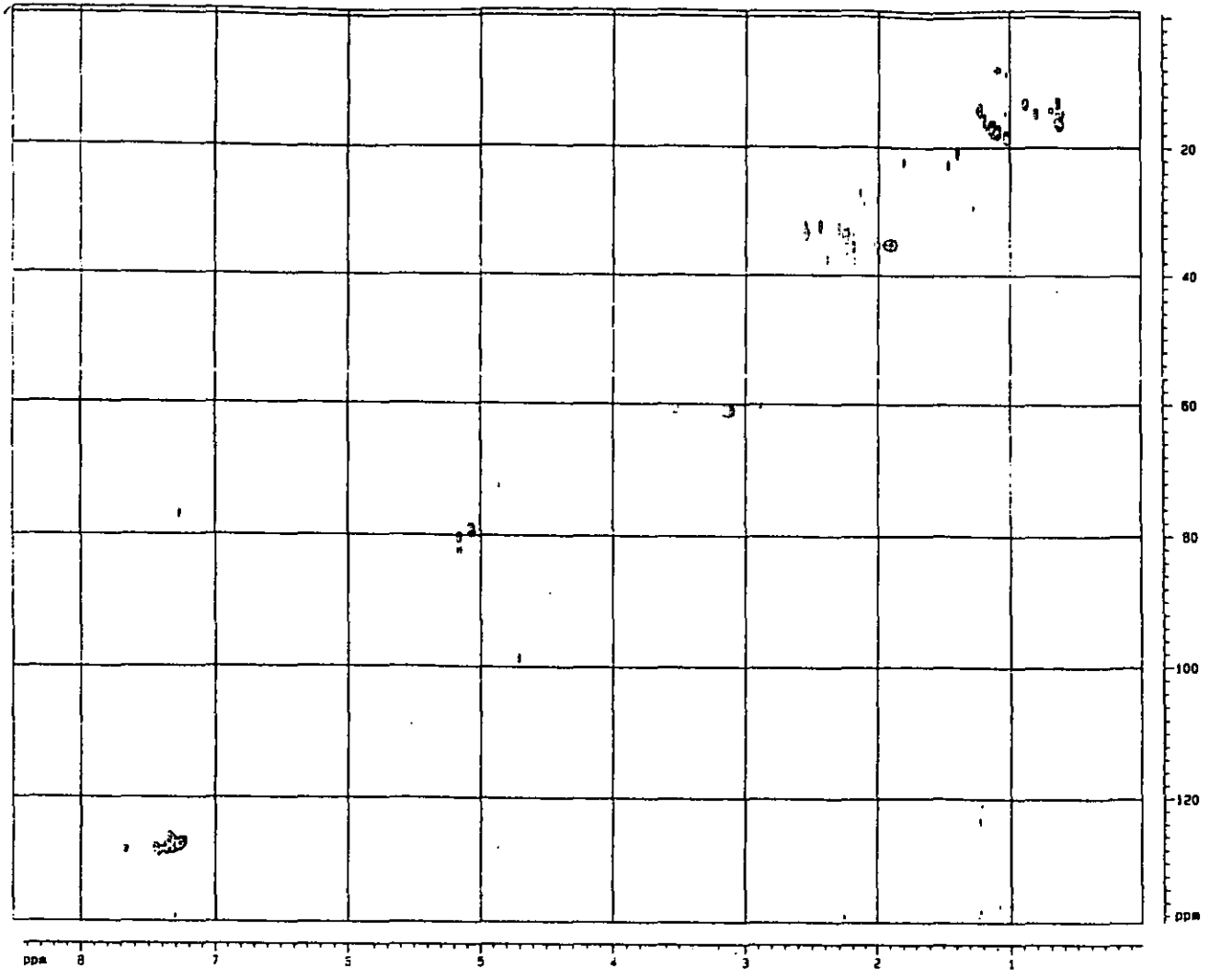
ASS 0991 Stereochemistry of ST84254-002 in CDCL3



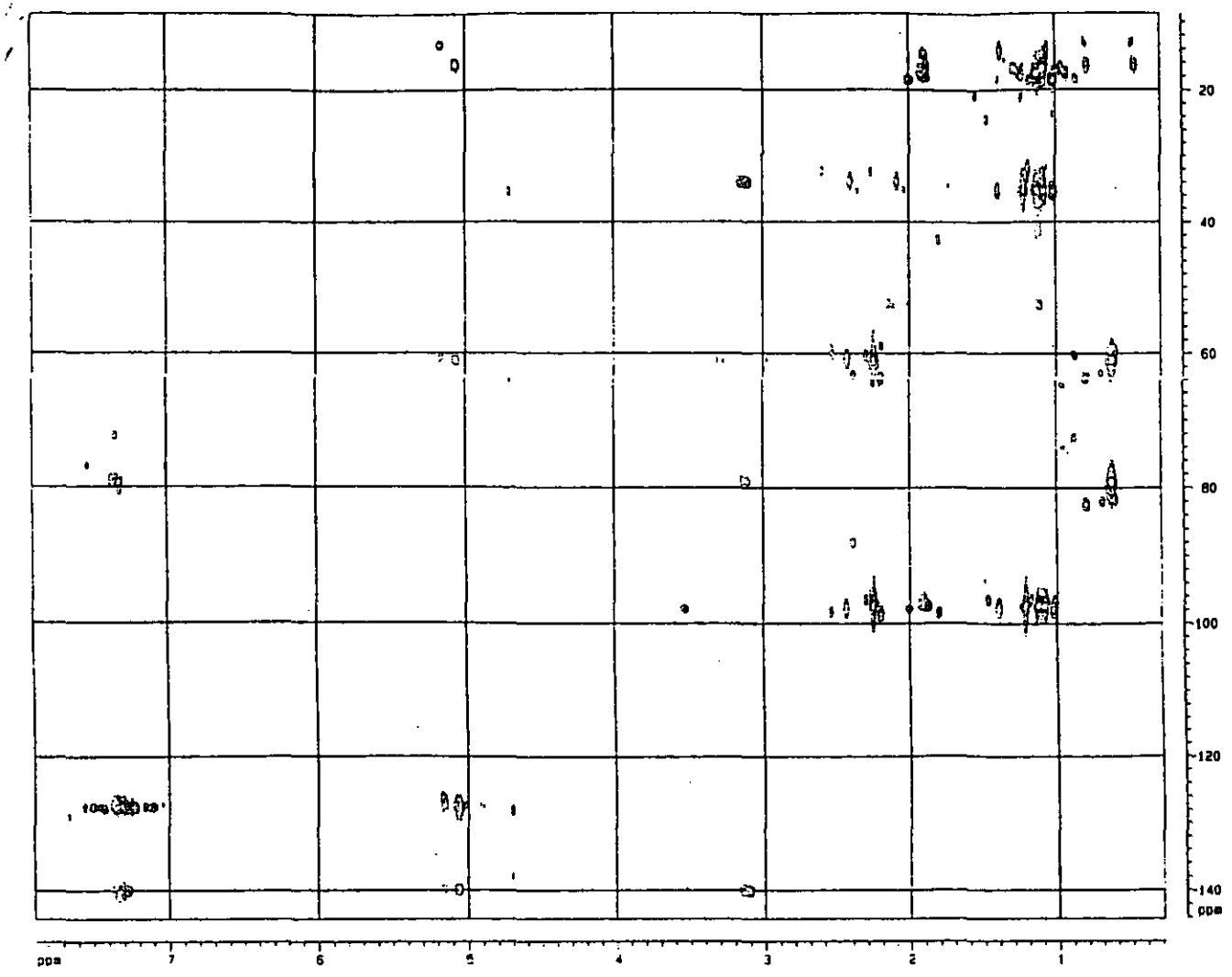
(4S,5R)-2,3,4-trimethyl-2-(1-methyl ethyl)
5-phenyl-1,3-oxazolidine

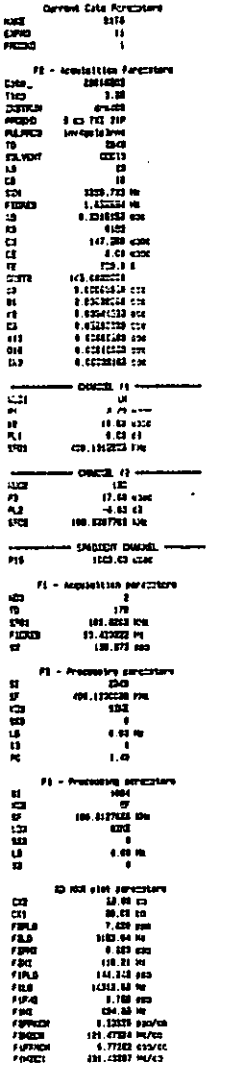


/S 0992 Stereochemistry of ST84254-006 in CDCl3

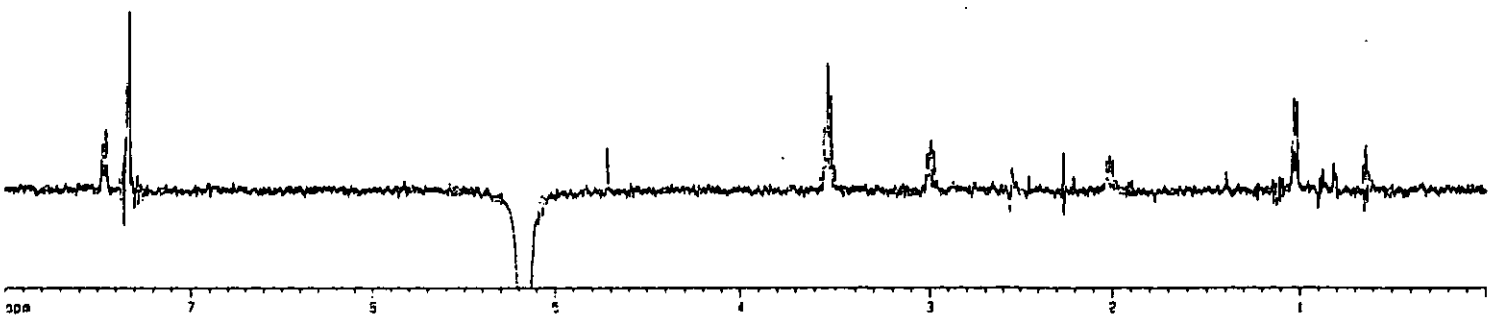


/S 0992 Stereochemistry of ST84254-006 in CDCl3





CASS 0992 Stereochemistry of ST84254-006 in CDCL3



Current Data Parameters

NAME	CASS_0992
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20010425
Time	9.12
INSTRUM	drx400
PROBHD	5 cm TXI 31P
PULPROG	selnogp.3
TD	95536
SOLVENT	CDCl3
NS	150
DS	4
SWH	6278.148 Hz
FIDRES	0.128314 Hz
AQ	3.9584243 sec
RG	512
DW	80.400 usec
DE	6.00 usec
TE	323.0 K
D1	2.00000000 sec
D8	0.50000000 sec
D16	0.00010000 sec
D20	0.24580000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	7.80 usec
p2	15.20 usec
P12	50000.00 usec
PL0	120.00 dB
PL1	0.00 dB
SFO1	400.1320719 MHz
SP1	89.00 dB
SPNAM1	gaus1.1k
SPOFF1	0.00 Hz

========== GRADIENT CHANNEL ==========

SPNAM1	sine.100
SPNAM2	sine.100
SPNAM3	sine.100
SPNAM4	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPX4	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPY4	0.00 %
GPZ1	11.00 %
GPZ2	17.00 %
GPZ3	40.00 %
GPZ4	-40.00 %
P16	1000.00 usec

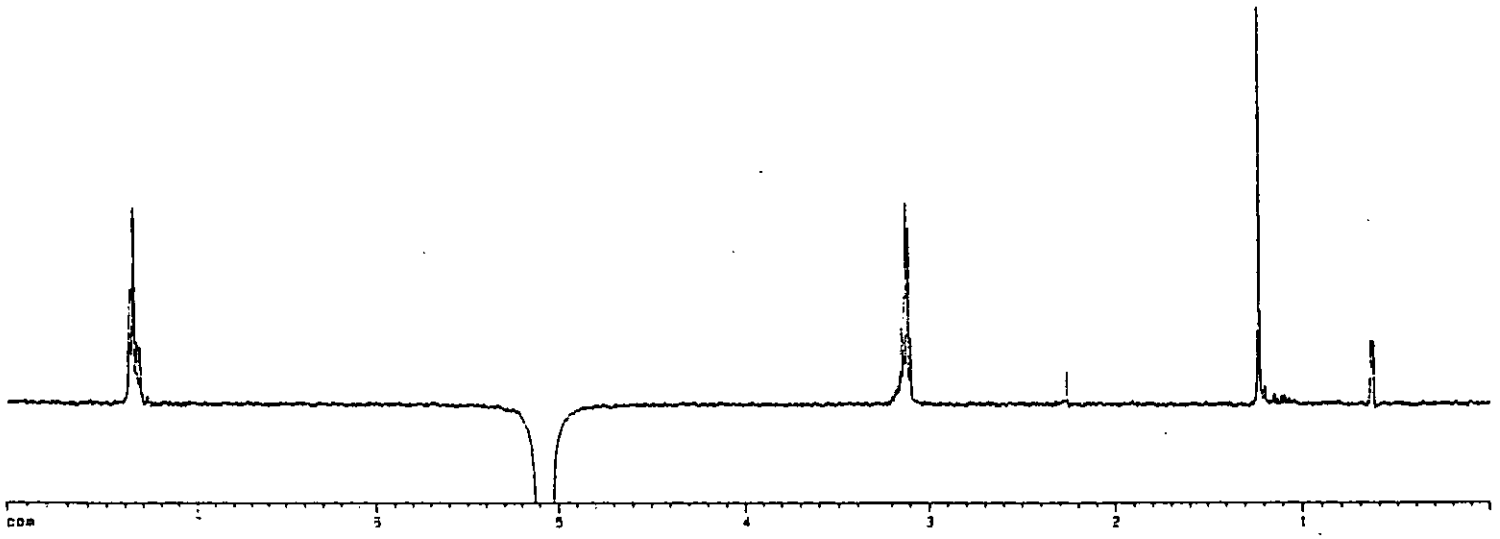
F2 - Processing parameters

SI	32768
SF	400.1300024 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	30.00 cm
F1P	8.000 ppm
F1	3201.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.26867 ppm/cm
HZCM	106.70133 Hz/cm

CASS 0992 Stereochemistry of ST84254-006 in CDCL3



Current Data Parameters

NAME	CASS_0992
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20010425
Time	9.57
INSTRUM	drx400
PROBHD	5 mm TXI 31P
PULPROG	selnogp.3
TD	65536
SOLVENT	CDCL3
NS	94
DS	4
SWH	8278.148 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	512
DW	60.400 usec
DE	6.00 usec
TE	330.0 K
D1	2.00000000 sec
D3	0.50000000 sec
D16	0.00010000 sec
D20	0.24850000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	7.80 usec
p2	15.20 usec
P12	50000.00 usec
PL0	120.00 dB
PL1	0.00 dB
SFO1	400.1320327 MHz
SP1	60.00 dB
SPNAM1	gaus1.1k
SPOFF1	0.00 Hz

========== GRADIENT CHANNEL ========

SPNAM1	sine.100
SPNAM2	sine.100
SPNAM3	sine.100
SPNAM4	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPX4	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPY4	0.00 %
GPZ1	11.00 %
GPZ2	17.00 %
GPZ3	40.00 %
GPZ4	-40.00 %
P16	1000.00 usec

F2 - Processing parameters

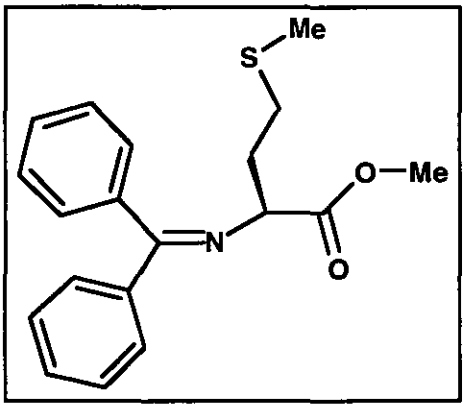
SI	32768
SF	400.1300024 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	30.00 cm
F1P	0.000 ppm
F1	3201.04 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.26687 ppm/cm
HZCM	105.70133 Hz/cm

APPENDIX 2

Methyl (2S)-2-[diphenyl methylidene) amino]-4-methyl thiol butanoate



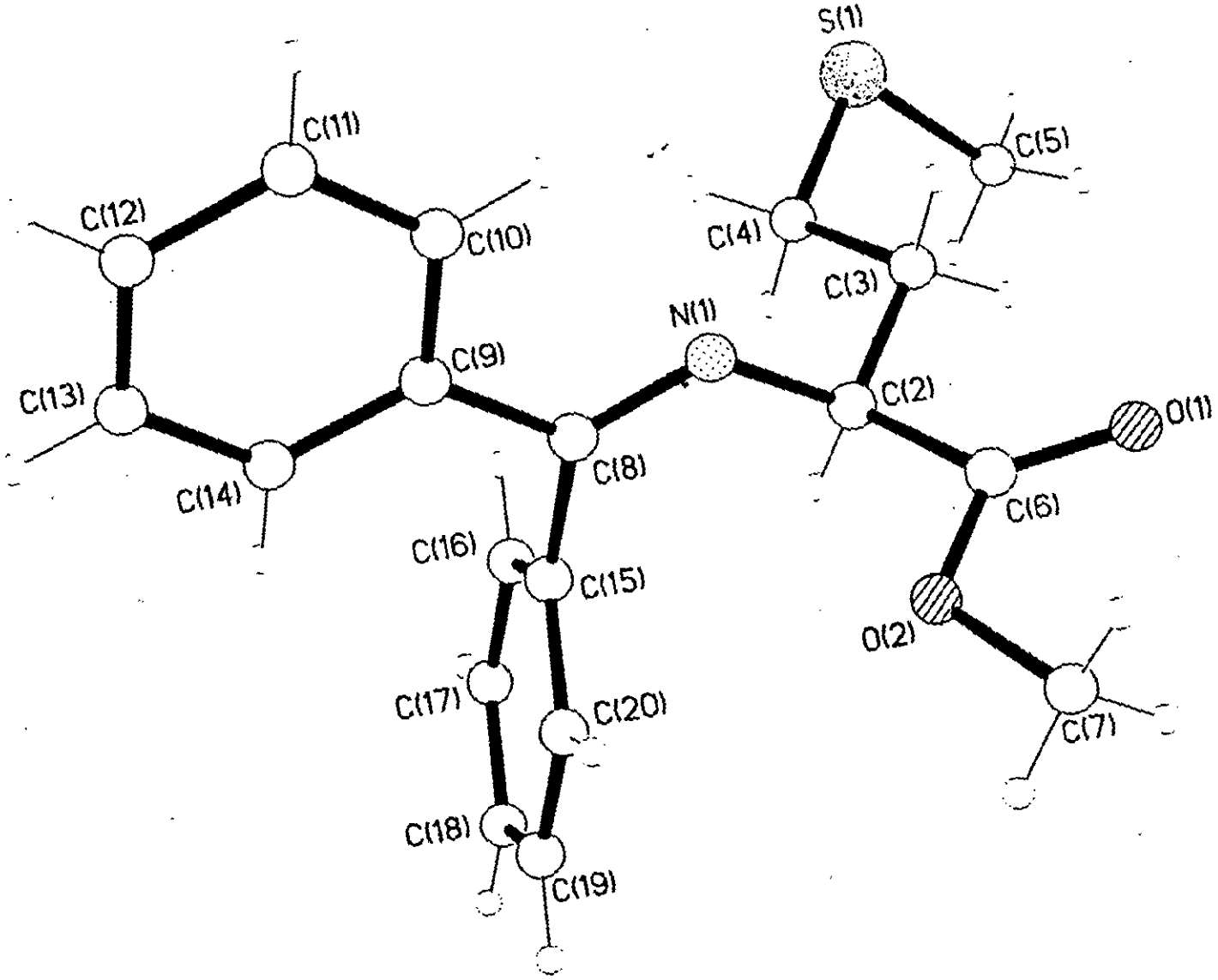

S(1)
C(5)
C(4)
C(3)
C(11)
C(12)
C(10)
N(1)
C(9)
C(2)
O(1)
C(13)
C(8)
C(14)
C(6)
C(16)
C(15)
O(2)
C(17)
C(20)
C(7)
C(18)
C(19)

Table 1. Crystal data and structure refinement for pcb1.

Identification code	pcb1	
Chemical formula	$C_{19}H_{21}NO_2S$	
Formula weight	327.43	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 9.8599(7) Å	α = 90°
	b = 9.0747(7) Å	β = 101.609(2)°
	c = 10.1733(7) Å	γ = 90°
Cell volume	891.64(11) $Å^3$	
Z	2	
Calculated density	1.220 g/cm^3	
Absorption coefficient μ	0.190 mm^{-1}	
F(000)	348	
Crystal colour and size	colourless, 0.93 × 0.79 × 0.55 mm^3	
Reflections for cell refinement	6985 (θ range 2.63 to 28.60°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω-rotation with narrow frames	
θ range for data collection	2.04 to 28.60°	
Index ranges	h −12 to 12, k −11 to 11, l −13 to 13	
Completeness to θ = 26.00°	99.6 %	
Intensity decay	0%	
Reflections collected	7527	
Independent reflections	3942 (R_{int} = 0.0125)	
Reflections with $F^2>2\sigma$	3854	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.843 and 0.903	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0572, 0.1265	
Data / restraints / parameters	3942 / 1 / 211	
Final R indices [$F^2>2\sigma$]	R1 = 0.0311, wR2 = 0.0842	
R indices (all data)	R1 = 0.0317, wR2 = 0.0846	
Goodness-of-fit on F^2	1.030	
Absolute structure parameter	−0.03(6)	
Extinction coefficient	0.009(3)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.381 and −0.200 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for pcb1. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.83218(11)	0.48875(12)	0.64871(11)	0.0248(2)
C(2)	0.85380(12)	0.33241(15)	0.62404(12)	0.0249(2)
C(3)	0.88564(13)	0.31405(16)	0.48399(13)	0.0284(2)
C(4)	0.76099(16)	0.35105(18)	0.37638(14)	0.0362(3)
S(1)	0.78674(4)	0.32516(5)	0.20723(3)	0.04072(11)
C(5)	0.7977(2)	0.1278(2)	0.1981(2)	0.0524(5)
C(6)	0.97535(14)	0.27720(15)	0.72971(15)	0.0284(3)
O(1)	1.07541(11)	0.21585(15)	0.70680(12)	0.0425(3)
O(2)	0.95356(11)	0.30059(15)	0.85253(11)	0.0436(3)
C(7)	1.0596(2)	0.2458(3)	0.96163(19)	0.0561(5)
C(8)	0.72551(13)	0.53156(13)	0.69198(12)	0.0217(2)
C(9)	0.71317(13)	0.69263(14)	0.71632(13)	0.0227(2)
C(10)	0.81242(15)	0.78902(16)	0.68554(16)	0.0328(3)
C(11)	0.80393(17)	0.93833(18)	0.70879(19)	0.0415(4)
C(12)	0.69649(17)	0.99478(17)	0.76277(18)	0.0383(3)
C(13)	0.59750(16)	0.90065(16)	0.79336(17)	0.0332(3)
C(14)	0.60447(14)	0.75031(15)	0.76987(15)	0.0284(3)
C(15)	0.61405(12)	0.43313(14)	0.72357(13)	0.0227(2)
C(16)	0.50245(15)	0.38865(17)	0.62460(15)	0.0314(3)
C(17)	0.40009(14)	0.29896(19)	0.65773(15)	0.0375(3)
C(18)	0.40759(14)	0.25346(16)	0.78822(16)	0.0330(3)
C(19)	0.51787(14)	0.29726(15)	0.88694(14)	0.0310(3)
C(20)	0.62088(14)	0.38714(15)	0.85487(14)	0.0263(3)

Table 3. Bond lengths [Å] and angles [°] for pcb1.

N(1)–C(8)	1.2796(16)	N(1)–C(2)	1.4638(18)
C(2)–C(6)	1.5246(18)	C(2)–C(3)	1.5286(17)
C(3)–C(4)	1.5101(19)	C(4)–S(1)	1.8046(14)
S(1)–C(5)	1.798(2)	C(6)–O(1)	1.1959(17)
C(6)–O(2)	1.3268(18)	O(2)–C(7)	1.451(2)
C(8)–C(9)	1.4915(17)	C(8)–C(15)	1.5003(17)
C(9)–C(10)	1.3943(18)	C(9)–C(14)	1.3980(17)
C(10)–C(11)	1.381(2)	C(11)–C(12)	1.386(2)
C(12)–C(13)	1.379(2)	C(13)–C(14)	1.3891(19)
C(15)–C(20)	1.3881(18)	C(15)–C(16)	1.3934(19)
C(16)–C(17)	1.390(2)	C(17)–C(18)	1.378(2)
C(18)–C(19)	1.382(2)	C(19)–C(20)	1.3916(18)
C(8)–N(1)–C(2)	120.76(11)	N(1)–C(2)–C(6)	108.58(10)
N(1)–C(2)–C(3)	109.26(11)	C(6)–C(2)–C(3)	109.98(10)
C(4)–C(3)–C(2)	111.20(10)	C(3)–C(4)–S(1)	114.34(9)
C(5)–S(1)–C(4)	101.56(9)	O(1)–C(6)–O(2)	123.66(14)
O(1)–C(6)–C(2)	125.30(13)	O(2)–C(6)–C(2)	110.99(11)
C(6)–O(2)–C(7)	115.95(13)	N(1)–C(8)–C(9)	117.05(11)
N(1)–C(8)–C(15)	125.53(11)	C(9)–C(8)–C(15)	117.40(11)
C(10)–C(9)–C(14)	118.71(12)	C(10)–C(9)–C(8)	119.55(11)
C(14)–C(9)–C(8)	121.74(11)	C(11)–C(10)–C(9)	120.51(13)
C(10)–C(11)–C(12)	120.54(14)	C(13)–C(12)–C(11)	119.52(14)
C(12)–C(13)–C(14)	120.52(14)	C(13)–C(14)–C(9)	120.20(13)
C(20)–C(15)–C(16)	119.12(12)	C(20)–C(15)–C(8)	119.30(11)
C(16)–C(15)–C(8)	121.58(11)	C(17)–C(16)–C(15)	120.05(13)
C(18)–C(17)–C(16)	120.55(13)	C(17)–C(18)–C(19)	119.73(12)
C(18)–C(19)–C(20)	120.19(13)	C(15)–C(20)–C(19)	120.36(12)

Table 4. Anisotropic displacement parameters ($Å^2$) for pcb1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

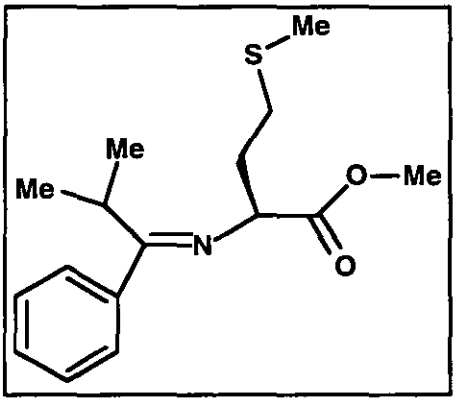
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	0.0240(5)	0.0248(5)	0.0274(5)	-0.0005(4)	0.0094(4)	-0.0004(4)
C(2)	0.0226(5)	0.0247(6)	0.0291(6)	-0.0020(5)	0.0092(4)	-0.0010(5)
C(3)	0.0261(6)	0.0312(6)	0.0297(6)	-0.0018(5)	0.0099(4)	0.0031(5)
C(4)	0.0349(7)	0.0467(9)	0.0285(6)	0.0003(6)	0.0099(5)	0.0123(6)
S(1)	0.0419(2)	0.0538(2)	0.02698(17)	-0.00052(16)	0.00826(13)	0.00927(18)
C(5)	0.0538(11)	0.0485(11)	0.0534(11)	-0.0166(8)	0.0077(9)	0.0028(8)
C(6)	0.0236(6)	0.0264(6)	0.0356(7)	0.0004(5)	0.0068(5)	-0.0038(5)
O(1)	0.0275(5)	0.0559(7)	0.0437(6)	-0.0032(5)	0.0065(4)	0.0108(5)
O(2)	0.0357(5)	0.0635(8)	0.0315(5)	0.0041(5)	0.0067(4)	0.0129(5)
C(7)	0.0471(10)	0.0807(15)	0.0363(9)	0.0089(9)	-0.0012(7)	0.0128(10)
C(8)	0.0215(6)	0.0250(6)	0.0192(5)	0.0008(4)	0.0050(4)	-0.0013(4)
C(9)	0.0214(5)	0.0248(6)	0.0224(6)	0.0007(4)	0.0055(4)	-0.0004(5)
C(10)	0.0312(7)	0.0271(7)	0.0451(8)	-0.0007(5)	0.0200(6)	-0.0013(5)
C(11)	0.0401(8)	0.0278(7)	0.0637(11)	-0.0007(7)	0.0274(8)	-0.0060(6)
C(12)	0.0447(9)	0.0232(6)	0.0519(9)	-0.0006(6)	0.0215(7)	0.0016(6)
C(13)	0.0329(7)	0.0304(7)	0.0407(8)	0.0017(6)	0.0179(6)	0.0054(5)
C(14)	0.0266(6)	0.0283(6)	0.0331(7)	0.0018(5)	0.0127(5)	0.0003(5)
C(15)	0.0199(5)	0.0241(5)	0.0258(6)	-0.0015(5)	0.0087(4)	0.0001(4)
C(16)	0.0272(6)	0.0410(7)	0.0259(6)	-0.0014(5)	0.0055(5)	-0.0041(5)
C(17)	0.0238(6)	0.0484(9)	0.0396(8)	-0.0067(6)	0.0042(5)	-0.0094(6)
C(18)	0.0247(6)	0.0317(7)	0.0468(8)	-0.0013(6)	0.0169(6)	-0.0039(5)
C(19)	0.0320(6)	0.0330(7)	0.0323(7)	0.0035(5)	0.0164(5)	-0.0005(5)
C(20)	0.0249(6)	0.0296(6)	0.0250(6)	-0.0006(5)	0.0067(5)	-0.0022(5)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for pcb1.

	x	y	z	U
H(2)	0.7685	0.2755	0.6304	0.030
H(3A)	0.9636	0.3794	0.4748	0.034
H(3B)	0.9142	0.2111	0.4722	0.034
H(4A)	0.7352	0.4551	0.3873	0.043
H(4B)	0.6823	0.2889	0.3896	0.043
H(5A)	0.8855	0.0944	0.2534	0.079
H(5B)	0.7932	0.0980	0.1048	0.079
H(5C)	0.7205	0.0833	0.2313	0.079
H(7A)	1.0747	0.1406	0.9482	0.084
H(7B)	1.0296	0.2600	1.0469	0.084
H(7C)	1.1460	0.2998	0.9635	0.084
H(10)	0.8864	0.7517	0.6483	0.039
H(11)	0.8723	1.0029	0.6876	0.050
H(12)	0.6911	1.0976	0.7786	0.046
H(13)	0.5240	0.9389	0.8308	0.040
H(14)	0.5352	0.6865	0.7903	0.034
H(16)	0.4963	0.4197	0.5344	0.038
H(17)	0.3243	0.2688	0.5898	0.045
H(18)	0.3372	0.1922	0.8102	0.040
H(19)	0.5234	0.2659	0.9770	0.037
H(20)	0.6963	0.4172	0.9232	0.032

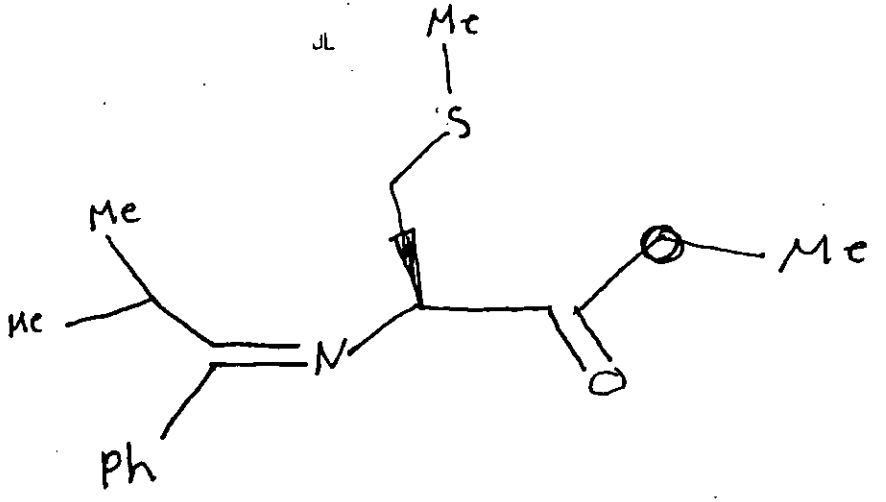
APPENDIX 3

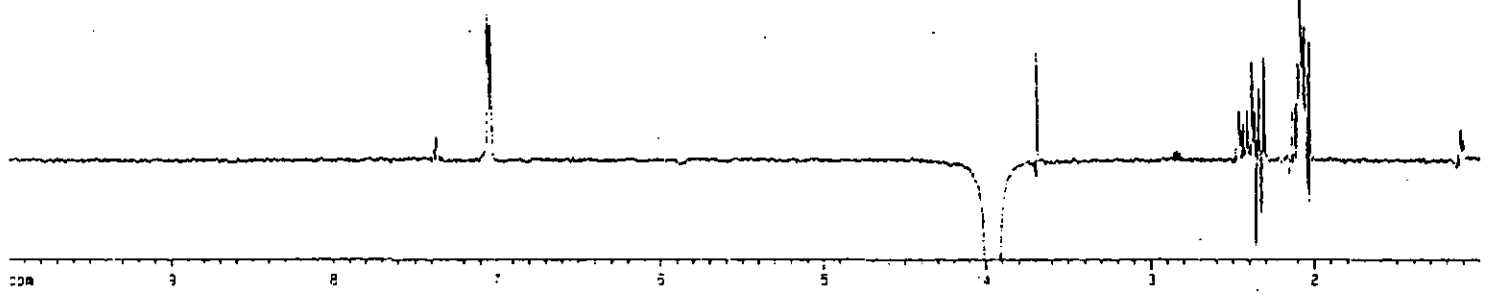
Methyl (2S)-2-{(E)-2-methyl-1-phenyl propylidene amino]-4-(methyl thiol) butanoate



NOE

JL



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NS                      36
DS                       4
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FIDRES           0.126314 Hz
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DE                   6.00 usec
TE                  300.0 K
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P2                 15.20 usec
P12              30000.00 usec
PL0                120.00 dB
PL1                  0.00 dB
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SP1                 59.00 dB
SPNAM1            gauss.1k
SPOFF1               0.00 Hz

============ GRADIENT CHANNEL ========
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GPNAM2            sine.100
GPNAM3            sine.100
GPNAM4            sine.100
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GPX3                 0.00 %
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GB                      0
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1D NMR plot parameters
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F1                4001.30 Hz
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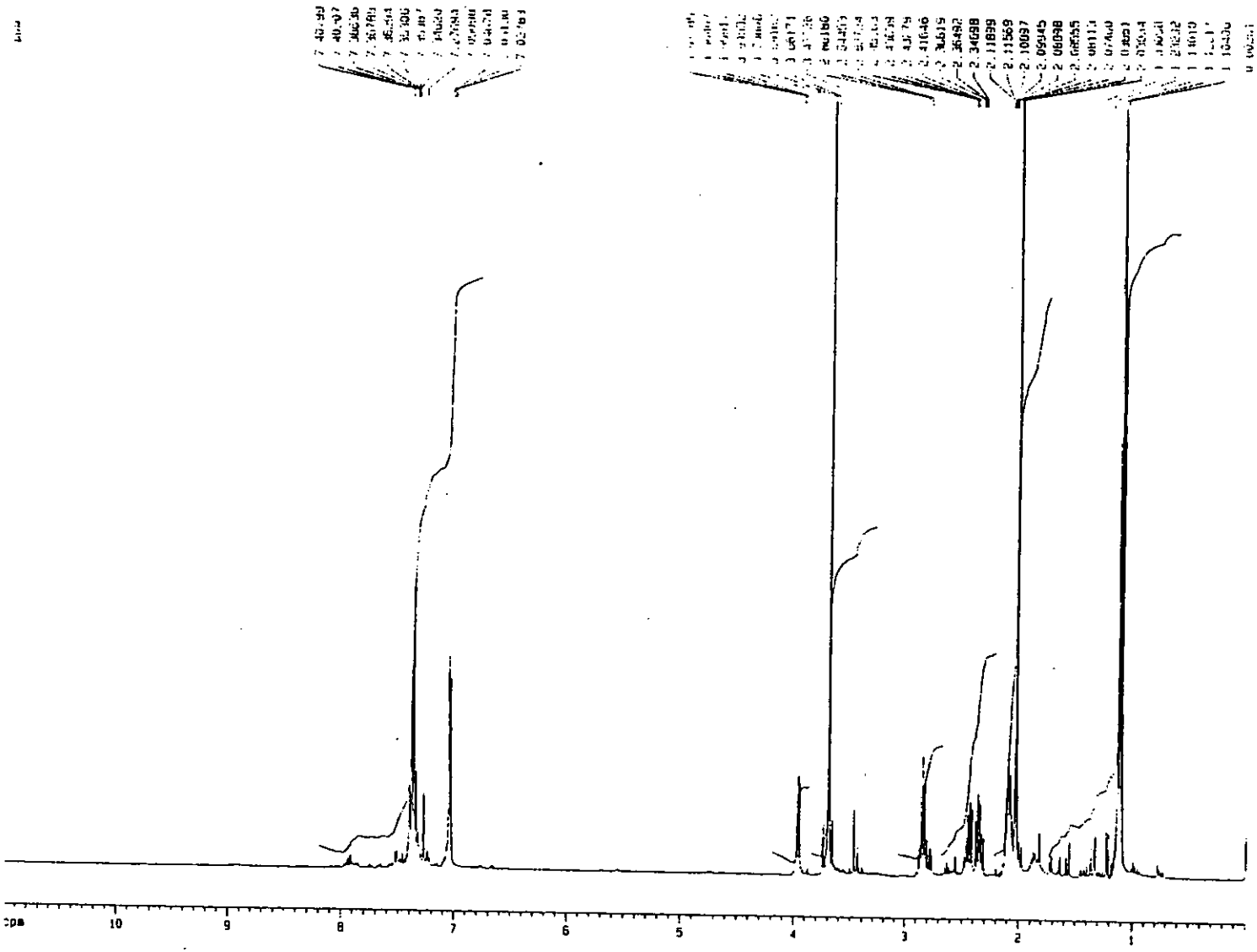
JL



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TE 300.0 K
D1 2.00000000 sec

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F2 - Processing parameters
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
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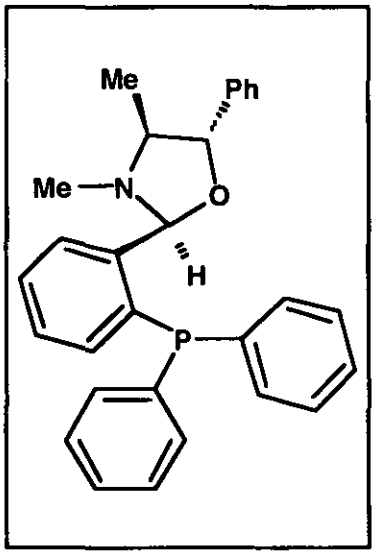
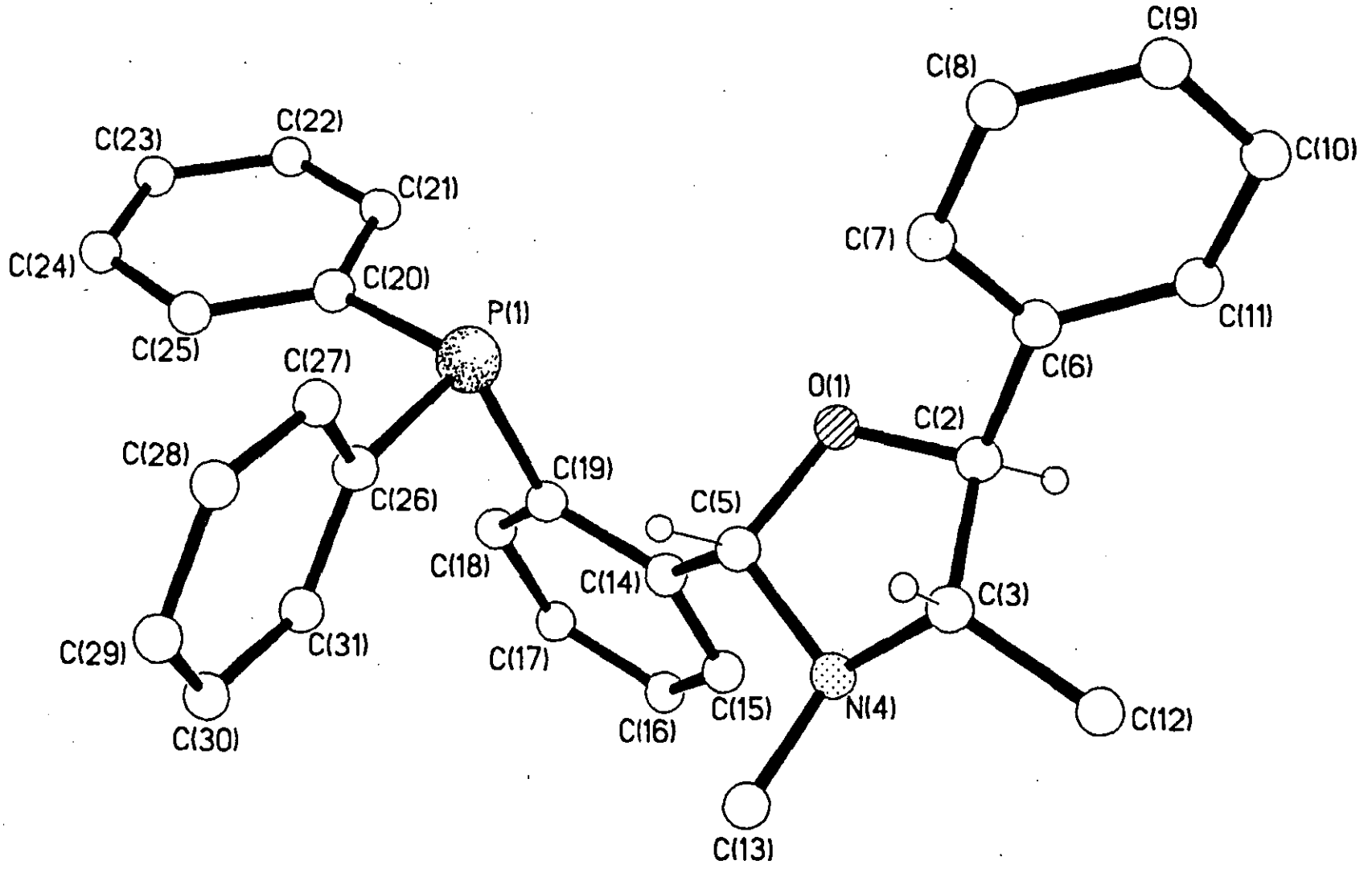
F1 4401.43 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.36667 ppm/cm
HZCM 146.71434 Hz/cm

APPENDIX 4

(4S,5S)-2-[2-(1,1-diphenyl phosphenyl]
3,4-dimethyl-5-phenyl-1,3-oxazolidine

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C(31)
C(17)
C(15)
N(4)
C(12)
C(30)
C(16)
C(13)

Table 1. Crystal data and structure refinement for pcbp3.

Identification code	pcbp3	
Chemical formula	$C_{29}H_{28}NOP$	
Formula weight	437.49	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 7.2969(5) Å	α = 90°
	b = 10.9083(7) Å	β = 95.113(2)°
	c = 15.2493(10) Å	γ = 90°
Cell volume	1208.97(14) $Å^3$	
Z	2	
Calculated density	1.202 g/cm^3	
Absorption coefficient μ	0.135 mm^{-1}	
F(000)	464	
Crystal colour and size	colourless, 0.59 × 0.32 × 0.30 mm^3	
Reflections for cell refinement	8635 (θ range 1.29 to 28.61°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.34 to 28.77°	
Index ranges	h −9 to 9, k −14 to 14, l −19 to 20	
Completeness to θ = 26.00°	100.0 %	
Intensity decay	0%	
Reflections collected	10256	
Independent reflections	5378 (R_{int} = 0.0245)	
Reflections with $F^2>2\sigma$	5093	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.925 and 0.961	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0787, 0.1322	
Data / restraints / parameters	5378 / 1 / 291	
Final R indices [$F^2>2\sigma$]	R1 = 0.0408, wR2 = 0.1073	
R indices (all data)	R1 = 0.0425, wR2 = 0.1090	
Goodness-of-fit on F^2	1.030	
Absolute structure parameter	−0.07(7)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.367 and −0.333 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for pcbp3. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	0.77962(16)	0.64964(15)	0.58090(8)	0.0357(3)
C(2)	0.8328(2)	0.65321(18)	0.49268(11)	0.0282(3)
C(3)	1.0265(2)	0.7090(2)	0.50152(11)	0.0324(4)
N(4)	1.09393(19)	0.66605(17)	0.58954(10)	0.0331(3)
C(5)	0.9358(2)	0.67950(18)	0.64062(11)	0.0293(4)
C(6)	0.6968(2)	0.72449(18)	0.43251(11)	0.0312(4)
C(7)	0.6252(3)	0.8350(2)	0.45898(16)	0.0449(5)
C(8)	0.5075(3)	0.9026(3)	0.3994(2)	0.0664(9)
C(9)	0.4626(3)	0.8587(3)	0.3150(2)	0.0688(9)
C(10)	0.5314(3)	0.7497(3)	0.28944(14)	0.0590(7)
C(11)	0.6482(3)	0.6819(2)	0.34791(13)	0.0419(5)
C(12)	1.1449(3)	0.6666(3)	0.43057(14)	0.0519(6)
C(13)	1.2555(3)	0.7318(3)	0.62786(14)	0.0522(7)
C(14)	0.9448(2)	0.59548(16)	0.71993(10)	0.0257(3)
C(15)	1.0545(2)	0.49067(17)	0.72113(11)	0.0299(3)
C(16)	1.0667(2)	0.41161(16)	0.79257(12)	0.0299(3)
C(17)	0.9683(2)	0.43636(16)	0.86440(12)	0.0285(3)
C(18)	0.8584(2)	0.54093(15)	0.86409(11)	0.0260(3)
C(19)	0.8456(2)	0.62188(15)	0.79308(11)	0.0235(3)
P(1)	0.69434(5)	0.75805(4)	0.78798(2)	0.02506(11)
C(20)	0.5830(2)	0.74279(16)	0.89086(11)	0.0254(3)
C(21)	0.4401(2)	0.65714(18)	0.89216(12)	0.0314(4)
C(22)	0.3447(2)	0.64429(19)	0.96677(13)	0.0353(4)
C(23)	0.3862(3)	0.71889(19)	1.03921(13)	0.0367(4)
C(24)	0.5253(3)	0.8051(2)	1.03836(12)	0.0355(4)
C(25)	0.6243(2)	0.81640(17)	0.96446(11)	0.0296(3)
C(26)	0.8612(2)	0.88031(16)	0.81642(11)	0.0251(3)
C(27)	0.8157(2)	0.99829(17)	0.78670(11)	0.0301(3)
C(28)	0.9335(3)	1.09611(17)	0.80809(13)	0.0344(4)
C(29)	1.1002(3)	1.07663(19)	0.85779(13)	0.0364(4)
C(30)	1.1469(3)	0.95938(19)	0.88650(14)	0.0386(4)
C(31)	1.0291(3)	0.86236(17)	0.86596(13)	0.0339(4)

Table 3. Bond lengths [Å] and angles [°] for pcbp3.

O(1)–C(5)	1.432(2)	O(1)–C(2)	1.434(2)
C(2)–C(6)	1.506(2)	C(2)–C(3)	1.533(2)
C(3)–N(4)	1.465(2)	C(3)–C(12)	1.516(3)
N(4)–C(5)	1.456(2)	N(4)–C(13)	1.457(3)
C(5)–C(14)	1.514(2)	C(6)–C(11)	1.387(3)
C(6)–C(7)	1.388(3)	C(7)–C(8)	1.403(3)
C(8)–C(9)	1.385(5)	C(9)–C(10)	1.361(5)
C(10)–C(11)	1.391(3)	C(14)–C(15)	1.395(2)
C(14)–C(19)	1.413(2)	C(15)–C(16)	1.386(3)
C(16)–C(17)	1.389(3)	C(17)–C(18)	1.394(2)
C(18)–C(19)	1.394(2)	C(19)–P(1)	1.8481(17)
P(1)–C(26)	1.8319(18)	P(1)–C(20)	1.8374(17)
C(20)–C(25)	1.391(2)	C(20)–C(21)	1.402(2)
C(21)–C(22)	1.393(3)	C(22)–C(23)	1.384(3)
C(23)–C(24)	1.385(3)	C(24)–C(25)	1.397(2)
C(26)–C(31)	1.394(2)	C(26)–C(27)	1.395(2)
C(27)–C(28)	1.391(3)	C(28)–C(29)	1.391(3)
C(29)–C(30)	1.385(3)	C(30)–C(31)	1.382(3)

C(5)–O(1)–C(2)	108.89(12)	O(1)–C(2)–C(6)	111.52(14)
O(1)–C(2)–C(3)	104.65(14)	C(6)–C(2)–C(3)	113.63(15)
N(4)–C(3)–C(12)	112.98(16)	N(4)–C(3)–C(2)	100.69(13)
C(12)–C(3)–C(2)	113.33(18)	C(5)–N(4)–C(13)	112.79(16)
C(5)–N(4)–C(3)	103.91(13)	C(13)–N(4)–C(3)	113.83(16)
O(1)–C(5)–N(4)	105.11(13)	O(1)–C(5)–C(14)	110.22(14)
N(4)–C(5)–C(14)	112.73(15)	C(11)–C(6)–C(7)	119.3(2)
C(11)–C(6)–C(2)	119.57(18)	C(7)–C(6)–C(2)	121.04(18)
C(6)–C(7)–C(8)	119.5(2)	C(9)–C(8)–C(7)	120.0(3)
C(10)–C(9)–C(8)	120.4(2)	C(9)–C(10)–C(11)	120.1(2)
C(6)–C(11)–C(10)	120.6(2)	C(15)–C(14)–C(19)	119.38(15)
C(15)–C(14)–C(5)	119.38(15)	C(19)–C(14)–C(5)	121.25(15)
C(16)–C(15)–C(14)	121.14(16)	C(15)–C(16)–C(17)	119.82(17)
C(16)–C(17)–C(18)	119.61(16)	C(19)–C(18)–C(17)	121.31(15)
C(18)–C(19)–C(14)	118.74(15)	C(18)–C(19)–P(1)	122.70(13)
C(14)–C(19)–P(1)	118.47(12)	C(26)–P(1)–C(20)	101.48(8)
C(26)–P(1)–C(19)	101.14(7)	C(20)–P(1)–C(19)	101.48(8)
C(25)–C(20)–C(21)	118.77(16)	C(25)–C(20)–P(1)	123.79(13)
C(21)–C(20)–P(1)	117.30(14)	C(22)–C(21)–C(20)	120.35(18)
C(23)–C(22)–C(21)	120.22(17)	C(22)–C(23)–C(24)	120.03(17)
C(23)–C(24)–C(25)	119.96(18)	C(20)–C(25)–C(24)	120.64(17)
C(31)–C(26)–C(27)	118.55(16)	C(31)–C(26)–P(1)	124.01(14)
C(27)–C(26)–P(1)	117.44(13)	C(28)–C(27)–C(26)	120.50(16)
C(29)–C(28)–C(27)	120.18(17)	C(30)–C(29)–C(28)	119.48(18)
C(31)–C(30)–C(29)	120.35(17)	C(30)–C(31)–C(26)	120.92(17)

Table 4. Anisotropic displacement parameters ($Å^2$) for pcbp3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

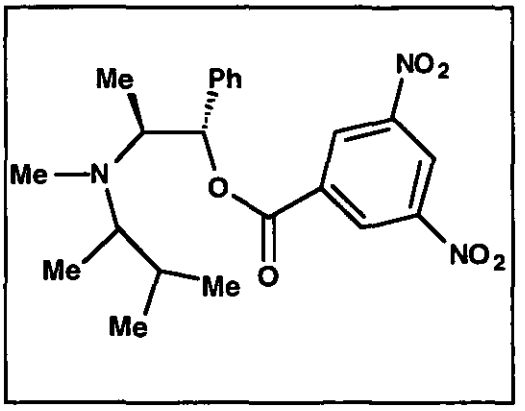
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0231(6)	0.0599(9)	0.0244(6)	0.0084(6)	0.0038(4)	−0.0049(6)
C(2)	0.0256(7)	0.0353(9)	0.0240(7)	0.0027(7)	0.0030(6)	−0.0010(7)
C(3)	0.0261(8)	0.0474(10)	0.0240(7)	0.0073(7)	0.0036(6)	−0.0035(7)
N(4)	0.0211(7)	0.0526(10)	0.0257(7)	0.0076(7)	0.0028(5)	−0.0056(6)
C(5)	0.0270(8)	0.0371(10)	0.0244(8)	0.0028(7)	0.0049(6)	−0.0029(7)
C(6)	0.0217(8)	0.0420(10)	0.0301(8)	0.0099(7)	0.0035(6)	−0.0030(6)
C(7)	0.0347(10)	0.0431(11)	0.0578(13)	0.0087(10)	0.0101(9)	0.0036(8)
C(8)	0.0364(11)	0.0552(15)	0.110(3)	0.0338(16)	0.0198(13)	0.0126(10)
C(9)	0.0327(11)	0.099(2)	0.0739(18)	0.0587(18)	−0.0001(11)	−0.0009(13)
C(10)	0.0329(10)	0.103(2)	0.0393(10)	0.0307(14)	−0.0048(8)	−0.0164(14)
C(11)	0.0309(9)	0.0647(14)	0.0301(9)	0.0096(9)	0.0017(7)	−0.0094(9)
C(12)	0.0330(10)	0.0924(19)	0.0320(10)	0.0089(11)	0.0132(8)	0.0060(11)
C(13)	0.0327(9)	0.083(2)	0.0391(10)	0.0146(11)	−0.0050(8)	−0.0218(11)
C(14)	0.0267(8)	0.0287(8)	0.0216(7)	−0.0006(6)	0.0013(6)	−0.0040(6)
C(15)	0.0289(8)	0.0324(9)	0.0294(8)	−0.0018(7)	0.0072(6)	−0.0004(7)
C(16)	0.0265(8)	0.0263(8)	0.0373(9)	−0.0014(7)	0.0048(6)	−0.0002(6)
C(17)	0.0303(8)	0.0256(8)	0.0296(8)	0.0037(6)	0.0027(6)	−0.0022(6)
C(18)	0.0272(8)	0.0273(8)	0.0234(7)	−0.0008(6)	0.0021(6)	−0.0019(6)
C(19)	0.0221(7)	0.0247(8)	0.0236(7)	−0.0018(6)	0.0003(6)	−0.0019(6)
P(1)	0.02449(19)	0.02588(19)	0.02435(18)	0.00130(16)	−0.00044(13)	0.00078(16)
C(20)	0.0217(7)	0.0249(8)	0.0293(7)	0.0016(7)	0.0005(5)	0.0029(6)
C(21)	0.0264(8)	0.0310(9)	0.0361(9)	0.0039(7)	−0.0001(7)	−0.0009(7)
C(22)	0.0250(8)	0.0353(9)	0.0458(10)	0.0125(8)	0.0047(7)	−0.0007(7)
C(23)	0.0290(9)	0.0477(11)	0.0345(9)	0.0117(8)	0.0081(7)	0.0048(7)
C(24)	0.0365(9)	0.0414(10)	0.0289(9)	−0.0003(7)	0.0046(7)	0.0023(8)
C(25)	0.0266(8)	0.0317(9)	0.0307(8)	0.0006(7)	0.0038(6)	−0.0012(7)
C(26)	0.0262(7)	0.0267(8)	0.0231(8)	0.0006(6)	0.0053(6)	−0.0004(6)
C(27)	0.0298(8)	0.0303(8)	0.0302(8)	0.0029(7)	0.0022(6)	0.0023(7)
C(28)	0.0440(10)	0.0239(8)	0.0364(10)	0.0026(7)	0.0096(8)	−0.0012(7)
C(29)	0.0371(10)	0.0352(10)	0.0378(10)	−0.0030(8)	0.0080(8)	−0.0101(8)
C(30)	0.0284(9)	0.0404(10)	0.0463(11)	−0.0015(8)	−0.0016(8)	−0.0027(8)
C(31)	0.0304(9)	0.0285(9)	0.0419(10)	0.0044(7)	−0.0025(7)	0.0027(7)

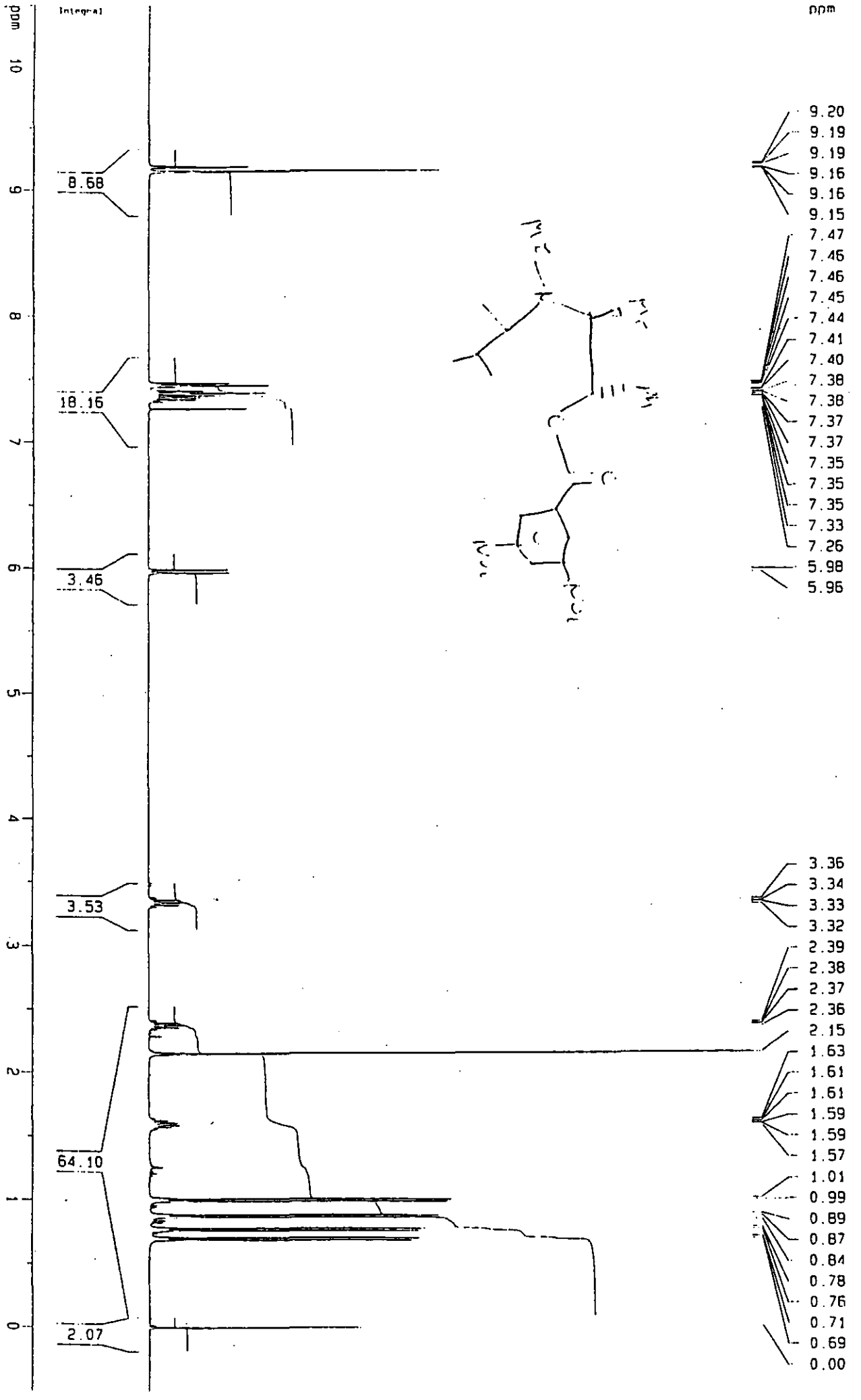
Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for pcbp3.

	x	y	z	U
H(2)	0.8401	0.5674	0.4701	0.034
H(3)	1.0180	0.8005	0.5012	0.039
H(5)	0.9264	0.7666	0.6603	0.035
H(7)	0.6558	0.8646	0.5170	0.054
H(8)	0.4586	0.9786	0.4170	0.080
H(9)	0.3832	0.9048	0.2748	0.083
H(10)	0.4996	0.7199	0.2315	0.071
H(11)	0.6952	0.6056	0.3298	0.050
H(12A)	1.1542	0.5770	0.4318	0.078
H(12B)	1.2681	0.7024	0.4412	0.078
H(12C)	1.0890	0.6931	0.3728	0.078
H(13A)	1.2953	0.6968	0.6856	0.078
H(13B)	1.2248	0.8185	0.6347	0.078
H(13C)	1.3550	0.7243	0.5891	0.078
H(15)	1.1219	0.4732	0.6721	0.036
H(16)	1.1422	0.3407	0.7924	0.036
H(17)	0.9759	0.3823	0.9135	0.034
H(18)	0.7909	0.5573	0.9133	0.031
H(21)	0.4081	0.6076	0.8419	0.038
H(22)	0.2509	0.5841	0.9679	0.042
H(23)	0.3193	0.7109	1.0896	0.044
H(24)	0.5533	0.8566	1.0880	0.043
H(25)	0.7208	0.8749	0.9645	0.036
H(27)	0.7034	1.0119	0.7516	0.036
H(28)	0.9001	1.1765	0.7887	0.041
H(29)	1.1813	1.1432	0.8719	0.044
H(30)	1.2605	0.9456	0.9205	0.046
H(31)	1.0629	0.7823	0.8859	0.041

APPENDIX 5

(1R,2S)-2-[1,2-dimethyl propyl) methyl amino]-1, -phenyl propyl-3,-5-dinitro-benzene-1-carboxylate

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7.46
7.46
7.45
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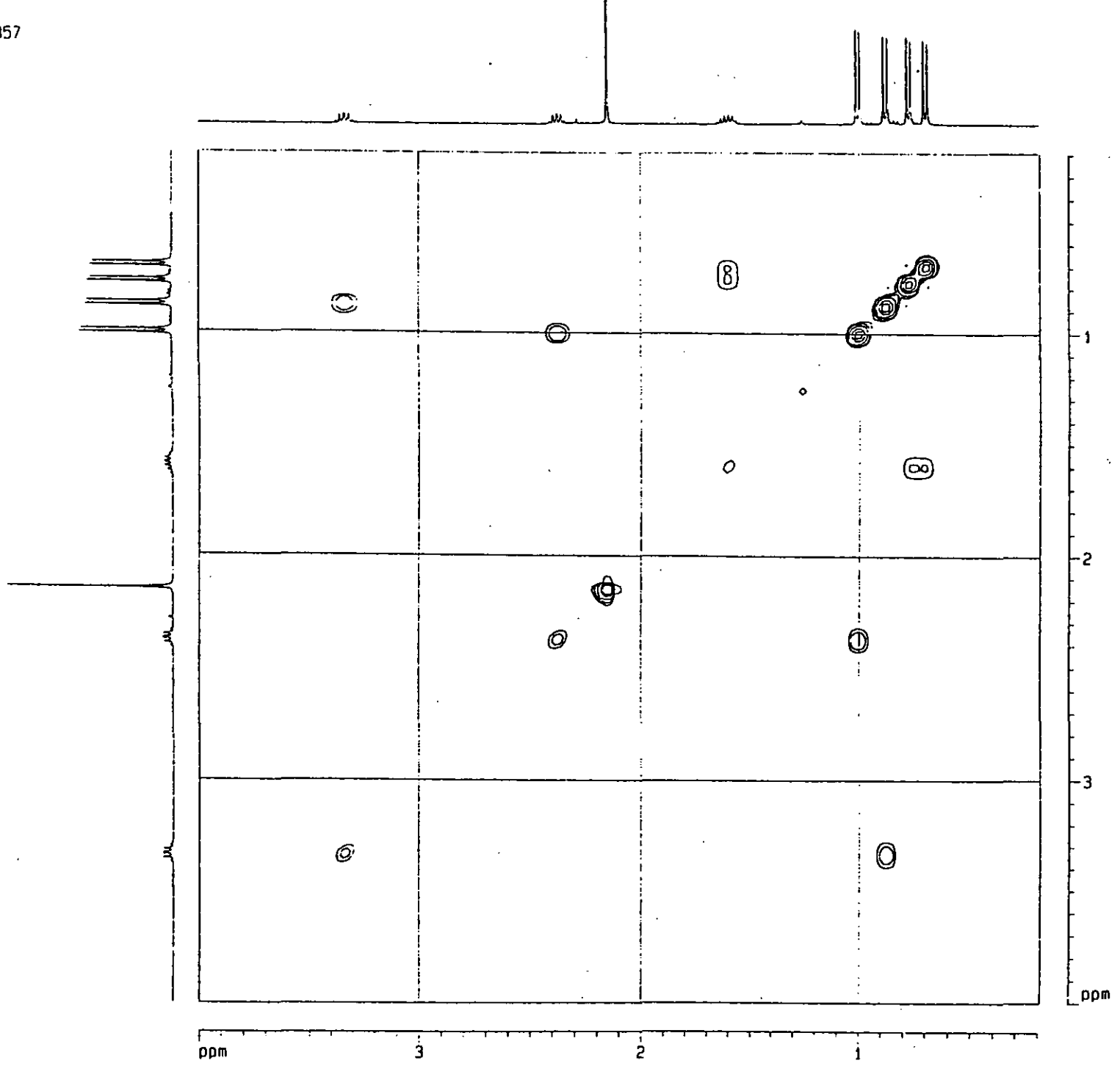
Sa357

Sa357



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F2 - Acquisition Parameters

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SOLVENT	D2O
NS	28
DS	16
SWH	4194.631 Hz
FIDRES	4.096319 Hz
AQ	0.1221108 sec
RG	287.4
DW	119.200 usec
DE	7.50 usec
TE	300.0 K
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P1	15.00 usec
SFO1	400.1319304 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00023840 sec

F1 - Acquisition parameters

ND0	1
TD	243
SFO1	400.1319 MHz
FIDRES	17.261856 Hz
SW	10.483 ppm

F2 - Processing parameters

SI	512
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

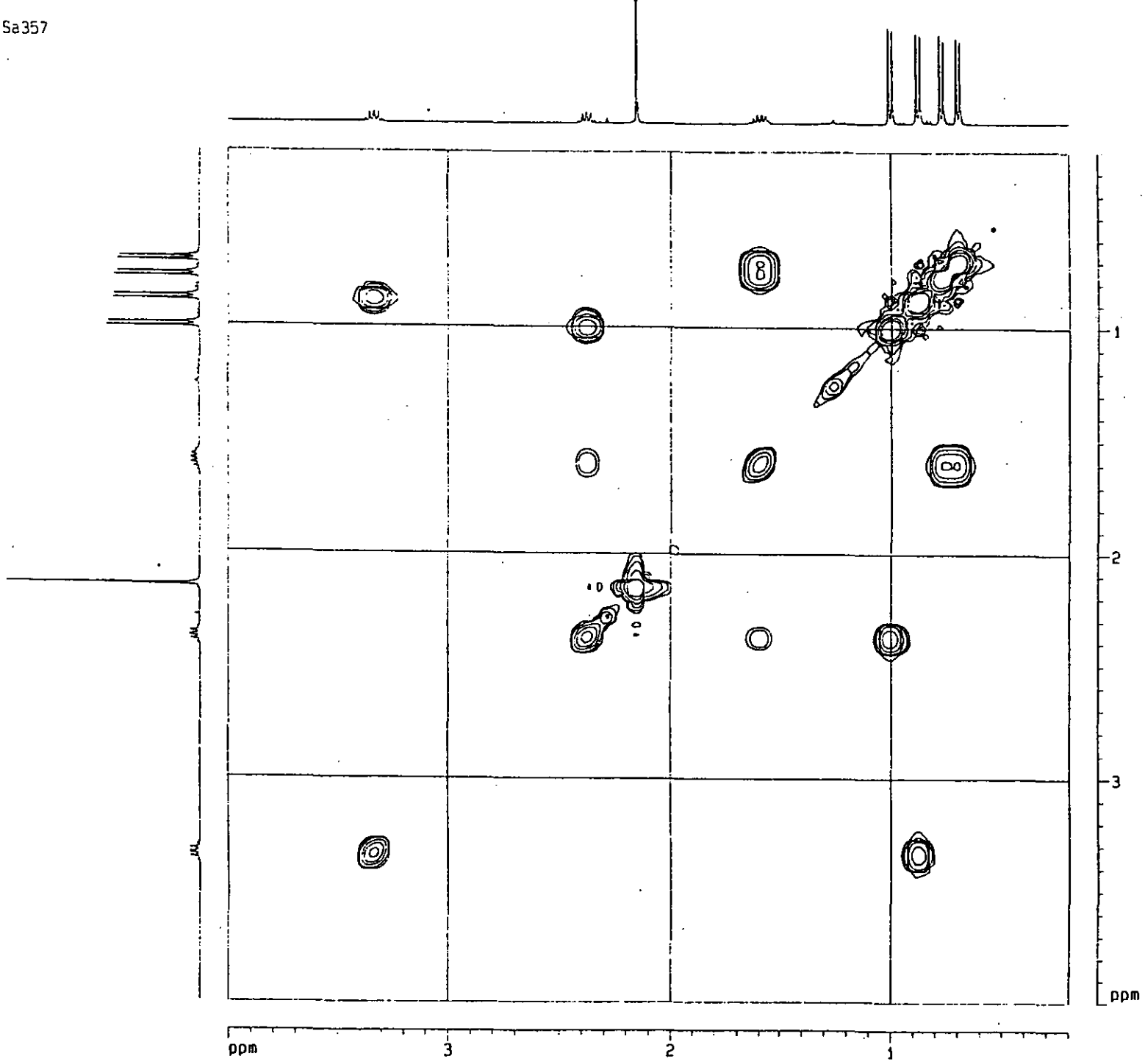
F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.002 ppm
F2LO	1601.13 Hz
F2PHI	0.193 ppm
F2HI	77.30 Hz
F1PLO	4.002 ppm
F1LO	1601.13 Hz
F1PHI	0.193 ppm
F1HI	77.30 Hz
F2PPMCM	0.25389 ppm/cm
F2HZCM	101.58871 Hz/cm
F1PPMCM	0.25389 ppm/cm
F1HZCM	101.58871 Hz/cm

Sa357



EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

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PULPROG	cosy45
TD	1024
SOLVENT	D2O
NS	26
DS	16
SWH	4194.631 Hz
FIDRES	4.095319 Hz
AQ	0.1221108 sec
RG	287.4
DW	115.200 usec
DE	7.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	15.00 usec
SFO1	400.1319304 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00023840 sec

F1 - Acquisition parameters

NDO	1
TD	243
SFO1	400.1319 MHz
F1DRES	17.261856 Hz
SW	10.483 ppm

F2 - Processing parameters

SI	512
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

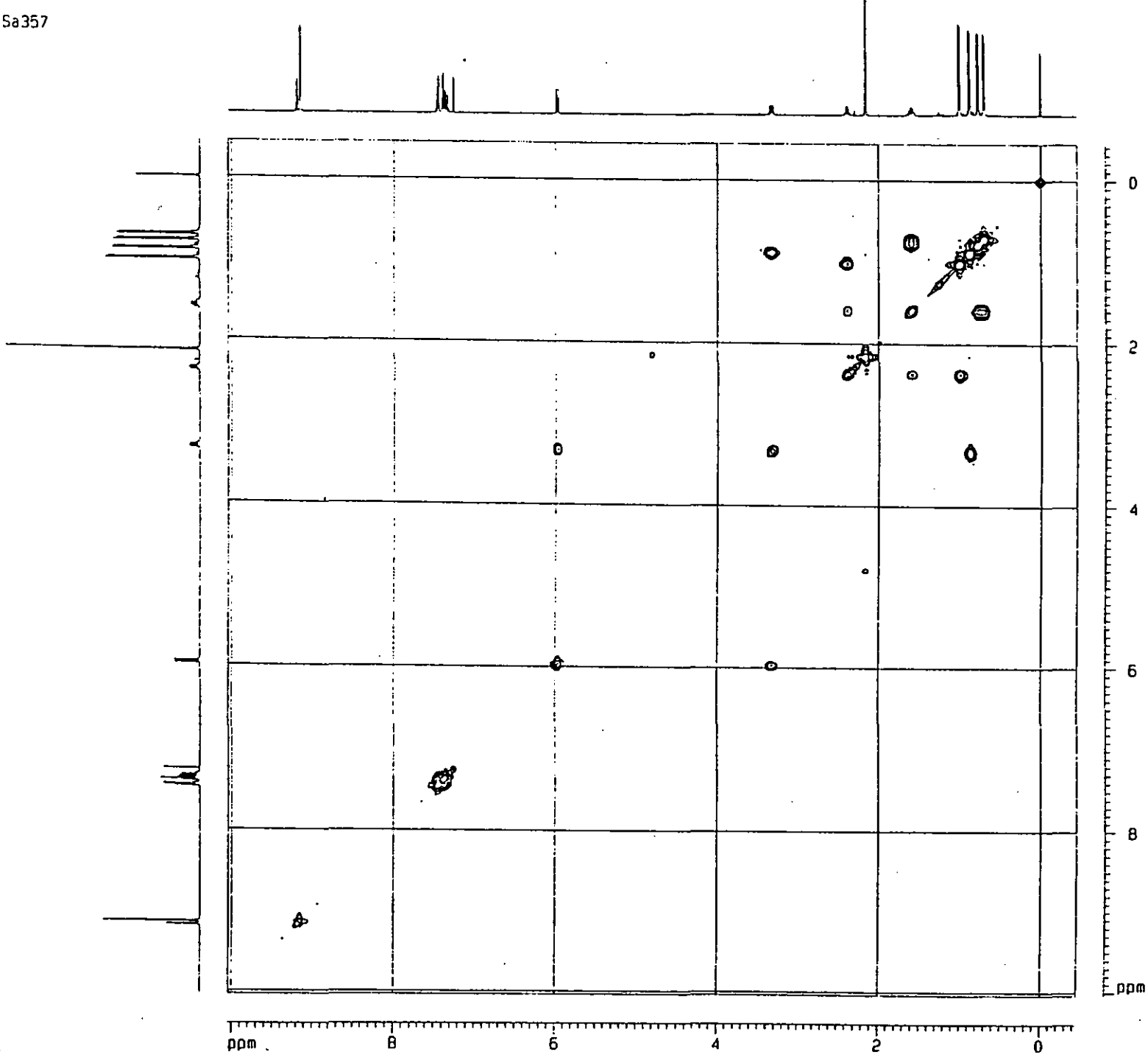
F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.000 ppm
F2LO	1600.52 Hz
F2PHI	0.200 ppm
F2HI	80.03 Hz
F1PLO	4.000 ppm
F1LO	1600.52 Hz
F1PHI	0.200 ppm
F1HI	80.03 Hz
F2PPMCM	0.25333 ppm/cm
F2HZCM	101.36626 Hz/cm
F1PPMCM	0.25333 ppm/cm
F1HZCM	101.36626 Hz/cm

Sa357



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PROCNO	1

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TD	1024
SOLVENT	D20
NS	28
DS	16
SWH	4194.631 Hz
FIDRES	4.096319 Hz
AQ	0.1221108 sec
RG	287.4
DW	119.200 usec
DE	7.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	15.00 usec
SFO1	400.1319304 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00023840 sec

F1 - Acquisition parameters

NDO	1
TD	243
SFO1	400.1319 MHz
FIDRES	17.261856 Hz
SW	10.483 ppm

F2 - Processing parameters

SI	512
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

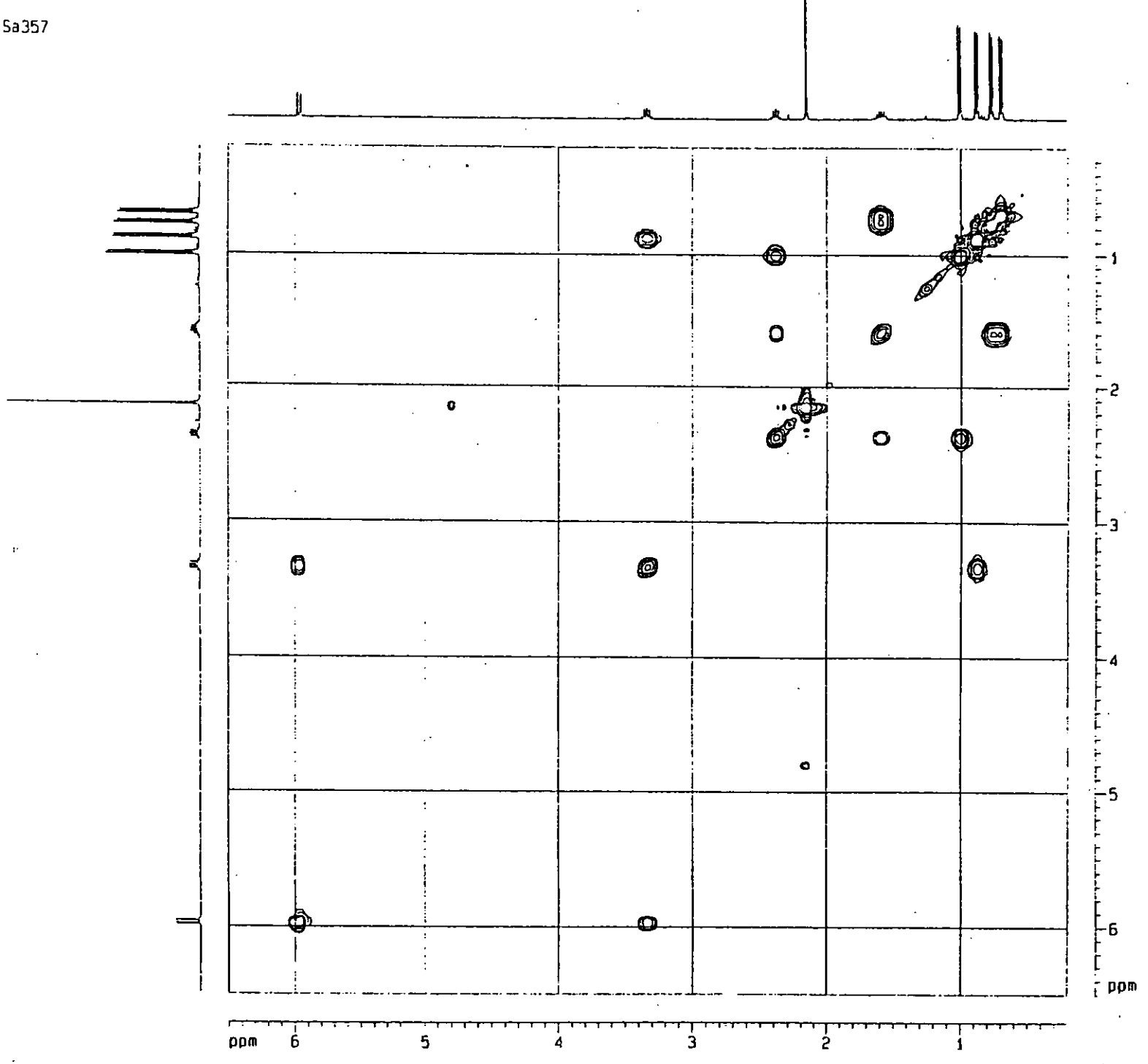
F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	10.042 ppm
F2LO	4017.96 Hz
F2PHI	-0.442 ppm
F2HI	-176.67 Hz
F1PLO	10.042 ppm
F1LO	4017.96 Hz
F1PHI	-0.442 ppm
F1HI	-176.67 Hz
F2PPMCM	0.69888 ppm/cm
F2HZCM	279.64206 Hz/cm
F1PPMCM	0.69888 ppm/cm
F1HZCM	279.64206 Hz/cm

Sa357



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PROCNO	1

F2 - Acquisition Parameters

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PULPROG	cosy45
TD	1024
SOLVENT	D2O
NS	26
DS	16
SWH	4194.631 Hz
FIDRES	4.096319 Hz
AQ	0.1221108 sec
RG	267.4
DW	119.200 usec
DE	7.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	15.00 usec
SFO1	400.1319304 MHz
NUC1	1H
PL1	-6.00 dB
D0	0.00000300 sec
IN0	0.00023840 sec

F1 - Acquisition parameters

NDO	1
TD	243
SFO1	400.1319 MHz
FIDRES	17.261856 Hz
SW	10.483 ppm

F2 - Processing parameters

SI	512
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	QF
SF	400.1300097 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	6.500 ppm
F2LO	2600.84 Hz
F2PHI	0.200 ppm
F2HI	80.03 Hz
F1PLO	6.500 ppm
F1LO	2600.84 Hz
F1PHI	0.200 ppm
F1HI	80.03 Hz
F2PPMCM	0.42000 ppm/cm
F2HZCM	168.05461 Hz/cm
F1PPMCM	0.42000 ppm/cm
F1HZCM	168.05461 Hz/cm